NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Bristol-Myers Squibb

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Guts UK
   b. NCRI-ACP-RCP-RCR

4. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**
   a. Appendix

7. **Technical engagement responses and statements from experts:**
   a. Prof. Wasat Mansoor, Consultant Medical Oncologist – clinical expert, nominated by Bristol-Myers Squibb
   b. Dr Elizabeth Smyth, Consultant in Gastrointestinal Oncology – clinical expert, nominated by the Royal College of Physicians *(*see item 8b)*

8. **Technical engagement responses from consultees and commentators:**
   a. Association of Cancer Physicians
   b. NCRI-ACP-RCP-RCR

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

February 2021

File name	Version	Contains confidential information	Date
		Yes	

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Tables and figures

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Abbreviations

1L	First-line
5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
BICR	Blinded independent central review
BSC	Best supportive care
CapeOX	Capecitabine and oxaliplatin
CF	Cisplatin/fluorouracil
CHEMO	Fluoropyrimidine- and platinum-containing chemotherapy
CI	Confidence interval
CNS	Central nervous system
CPS	Combined positive score
CR	Complete response
CT	Computerised tomography
CVAD	Central venous access device
CX	Cisplatin/capecitabine
DBL	Database lock
DC	Discontinuation
DFS	Disease-free survival
DIC	Deviance information criterion
DOR	Duration of response
DRR	Durable response rate
DSU	Decision Support Unit
EAC	Oesophageal adenocarcinoma (US abbreviation)
EAMS	Early Access to Medicines Scheme
ECF	Epirubicin, cisplatin, fluorouracil
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
ECX	Epirubicin, cisplatin, capecitabine
EMA	European Medicines Agency
EOF	Epirubicin, oxaliplatin, fluorouracil
EOX	Epirubicin, oxaliplatin, capecitabine

EQ-5D	EuroQol 5-dimensions
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric
FOLFOX	Folinic acid, 5-fluorouracil, oxaliplatin
GaCS	Gastric cancer subscale
GC	Gastric cancer
GEJ	Gastroesophageal junction (US abbreviation)
GERD	Gastroesophageal reflux disease
GOJ	Gastroesophageal junction
GP	General Practitioner
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
HR	Hazard ratio
HS	Health state
HTA	Health Technology Appraisal
ICER	Incremental cost-effectiveness ratio
IgG4	Immunoglobulin antibody
IPD	Individual patient data
IPI	Ipilimumab
IMAEs	Immune-mediated adverse event
IRRC	Independent RECIST Review Committee
ITC	Indirect treatment comparison
IV	Intravenous
LYs	Life years gained
MID	Minimal important difference
MONO	Monotherapy
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stable
MUGA	Multigated acquisition scan
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NR	Not reached

OAC	Oesophageal adenocarcinoma
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
OSPP	Overall survival post-progression
PAS	Patient Access Scheme
PBO	Placebo
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFS2	Progression-free survival 2
PICOS	Population-Intervention-Comparators-Outcomes-Study
PSA	Probabilistic sensitivity analysis
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	Rest of world
S-1	Tegafur, gimeracil, oteracil
SAE	Serious adverse event
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOX	Oxaliplatin and S-1
TA	Technology Assessment
TBC	To be confirmed
ToT	Time on treatment

TPS	Tumour proportion score
TRAE	Treatment related adverse event
TSD	Technical support document
TTR	Time to recurrence
TTSD	Time to symptom deterioration
UI	Utility index
US	United States
VAS	Visual analogue scale
WHO	World Health Organisation
WTP	Willingness to pay
XELOX	Capecitabine and oxaliplatin

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

B.1.1 Decision problem

The submission covers the technology's proposed marketing authorisation for this indication ([redacted]). The technology is nivolumab in combination with chemotherapy (XELOX or FOLFOX), hereafter referred to as NIVO+CHEMO. The decision problem that this submission addresses is presented in Table 1.

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 untreated locally advanced or metastatic gastric or gastroesophageal junction or oesophageal adenocarcinoma	[redacted]	NA
Intervention	Nivolumab in combination with chemotherapy.	Nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy.	As specified in draft SmPC
Comparator(s)	• Chemotherapy without nivolumab, such as: ○ Doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin ○ Triplet treatment with fluorouracil or capecitabine in combination plus cisplatin or oxaliplatin plus epirubicin. • For people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma ○ Trastuzumab with cisplatin plus capecitabine or fluorouracil	• Chemotherapy without nivolumab, such as: ○ Doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin ○ Triplet treatment with fluorouracil or capecitabine in combination plus cisplatin or oxaliplatin plus epirubicin. • For people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma • Trastuzumab with cisplatin plus capecitabine or fluorouracil	Evidence is provided versus all relevant comparators. However, based on clinical expert opinion, capecitabine plus oxaliplatin (XELOX) and fluorouracil, folinic acid plus oxaliplatin (FOLFOX) can be considered the main standard of care in this patient population. As such, the submission applies direct trial evidence versus these comparators as base case analysis evidence. An ITC has been undertaken versus additional comparators to ensure all evidence is available to inform decision making. Additionally, clinical advice indicates that use of epirubicin is extremely limited in the UK for first-line treatment of gastro-oesophageal cancers.[1] Hence, this should not be considered a comparator. However, comparative effectiveness is explored for completeness.

Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	NA
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 intervention, comparator and subsequent treatment technologies will be taken into account.	As NICE reference case	NA
Subgroups to be considered	If evidence allows subgroups by PD-L1 status will be considered.	Predefined subgroups provided, including PD-L1 status.	NA
Special considerations including issues related to equity or equality	NA	No equality issues have been identified or are anticipated.	NA

HER2: human epidermal growth factor receptor 2; NHS: National Health Service; PD-L1: programmed death-ligand 1.

B.1.2 Description of the technology being appraised

A description of the technology being appraised in this submission (NIVO+CHEMO), is presented in Table 2. The draft summary of product characteristics (SmPC) and the draft European Public Assessment Report (EPAR) are presented in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Nivolumab (Opdivo®) + Chemotherapy (XELOX or FOLFOX)
Mechanism of action	PD-1 is an immune checkpoint involved in T-cell differentiation and function, specifically inhibiting T-cell destruction of healthy 'self-cells' at the effector (later) stage of the immune response. Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 to limit the activity of T-cells at the tumour site. Nivolumab is a fully human, monoclonal immunoglobulin antibody (IgG4) that acts as a checkpoint inhibitor of PD-1. It potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell); this results in destruction of the tumour through pre-existing, intrinsic processes.[2]
Marketing authorisation/CE mark status	A Type II variation for a new indication in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indication: [redacted]
Method of administration and dosage	The anticipated recommended dose is: • 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks **or** • 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine and platinum-based chemotherapy administered every 2 weeks. Dosing does not depend upon body weight. Nivolumab should be given first, followed by chemotherapy on the same day. Treatment is recommended until disease progression or unacceptable toxicity. The maximum treatment duration for nivolumab is 24 months.[2]
Additional tests or investigations	No additional testing or investigation is required.

List price and average cost of a course of treatment	List price: Acquisition cost: 10 mg/ml concentration for solution for infusion, 4 ml vial: £439.00; 10 ml: £1097.00; 24 ml: £2,633.00. Average cost per cycle (excluding XELOX/FOLFOX costs): Nivolumab plus XELOX: £3,950 for 360 mg nivolumab dose (total cost per cycle: £4,334.30 including administration costs) Nivolumab plus FOLFOX: £2,633 for 240 mg nivolumab dose (total cost per cycle: £3,018.55 including administration costs) Patient Access Scheme (PAS) price: Acquisition cost: 10 mg/ml concentration for solution for infusion, 4 ml vial: [redacted]; 10 ml: [redacted]; 24 ml: [redacted]. Average cost per cycle (excluding XELOX/FOLFOX costs): Nivolumab plus XELOX: [redacted] for 360 mg nivolumab dose (total cost per cycle: [redacted] including administration costs) Nivolumab plus FOLFOX: [redacted] for 240 mg nivolumab dose (total cost per cycle: [redacted] including administration costs)
Patient access scheme (if applicable)	There is a confidential simple discount PAS for nivolumab which applies to all current and future indications.

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

B.1.3.1 Disease Background

Epidemiology

Cancer of the stomach, known as gastric cancer (GC) is the fifth most common cancer worldwide, and the third leading cause of cancer death, with an estimated 783,000 deaths in 2018 (equating to 1 in every 12 cancer deaths globally). Over a million new cases of GC are diagnosed, worldwide, each year.[3,4] The cumulative risk of developing GC from birth to age 74 is 1.87% in males and 0.79% in females worldwide.[4] Over the past few years there has been a rapid increase in incidence of tumours at the junction of the oesophagus and stomach, arising from changes in the lining of the oesophagus and leading to adenocarcinoma of the lowest part of the oesophagus, the gastroesophageal junction (GOJ).[3] In the UK, GC accounted for 2% of all new cancer cases in 2017,[5] making it a significant ongoing risk to health in the UK, with 6,600 new cases reported every year (2015-2017).[6]

GC is almost twice as common in men, with approximately 3,378 cases diagnosed in men, and 1,764 cases in women in England in 2017.[5] In the UK, GC is most common in Black people, then White people, and least common in Asian people.[6] However, there may be an environmental component as migrant studies have documented regional variations in incidence rates, with elevated levels observed in Eastern Asia: Mongolia, Japan and the Republic of Korea.[4] Most GCs are sporadic, but there may be a genetic predisposition towards developing the disease in nearly 10% of patients.[3,7] Dietary factors increase risk; foods preserved by salting, low fruit intake, alcohol consumption and active tobacco smoking are established risk factors.[4] Cancers of the gastric cardia (GOJ cancers) have epidemiological characteristics similar to oesophageal adenocarcinoma (OAC), and risk factors associated exclusively with cardia GC include obesity and gastroesophageal reflux disease (GERD).[3] Incidence of GC in the UK is strongly related to age, with the highest incidence in older people. In the UK in 2015-2017, on average each year around half of new cases (51%) were in people aged 75 and over.[5]

Pathophysiology and clinical presentation

Ninety-five percent of cancers of the stomach are adenocarcinomas (other types include lymphomas, sarcomas and carcinoid tumours),[3,8] and are divided into cardia and non-cardia subtypes based on their anatomical site.[3,5] Non-cardia arise from the glandular cells of the stomach lining,[3,8] whilst cardia arise in the gastro-oesophageal junction where the centre of the cancer is less than 5 cm above or below where the stomach meets the oesophagus.[4,9] Both subtypes are treated and managed in a similar fashion.[10,11] *Helicobacter pylori* is the main risk factor for gastric adenocarcinomas, with almost 90% of new cases of non-cardia GC attributed to this bacterium.[4] Success in preventing and treating these infections may account for a recent reduction in incidence of non-cardia GC; however, the incidence of the cardia

subtype is increasing rapidly, especially in the developed world.[3,7] For the purposes of this submission, the term gastric cancer will include both cardia and non-cardia subtypes (gastric/GOJ cancer), and OAC.

The most common symptoms of GC include: dysphagia, weight loss, dyspepsia, a feeling of stomach fullness, vomiting, and anaemia.[12] Patients presenting with early GC cancer can achieve complete remission through surgical or endoscopic resection of tumours. However, initial symptoms can be quite vague and similar to other stomach conditions, such as stomach ulcers, meaning that the chance of early detection is often missed.[12] Most patients are therefore diagnosed at an advanced stage (Figure 1), where symptoms become more obvious but also when prognosis is poor, with few effective treatment options available.[5,13]

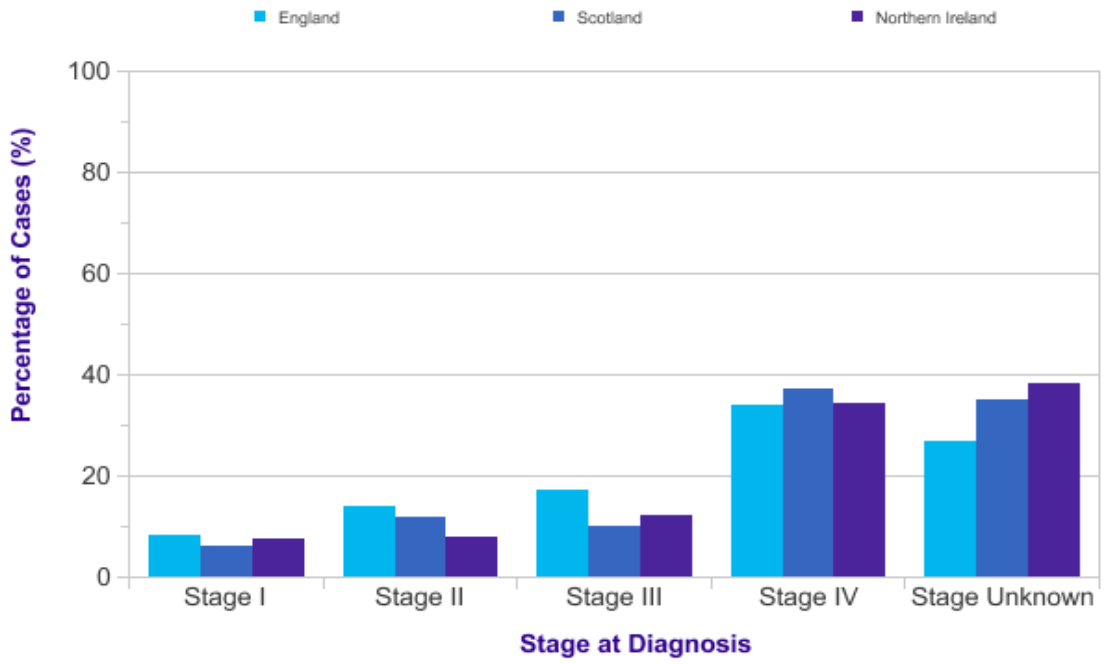


Figure 1. Proportion of gastric cancer cases diagnosed at each stage, all ages, England 2014, Scotland 2014 and Northern Ireland 2010-2014.[5]

Prognosis and unmet need

All-stage five-year survival rates for GC are extremely poor compared with other cancers such as breast cancer, where 85% of women are alive at 5 years.[14] Survival is strongly related to stage of the disease at diagnosis, with one-year net survival falling from 88.5% at Stage 1 to 21.4% at Stage 4 (Table 3).[14,15]

Table 3. Age-standardised one-year and five-year net survival, adults (Aged 15-99), England, 2013-2017[14]

Stage at diagnosis	Number of patients	One-year age-standardised survival (%)	Five-year age-standardised survival (%)
All stages	26,763	47.4	21.6
Stage 1	2,493	88.5	65.3
Stage 2	3,619	71.4	36.0
Stage 3	4,473	63.2	23.5
Stage 4 (metastatic)	9,733	21.4	4*

*There are no centrally gathered UK five-year survival statistics available for Stage 4 gastric cancer, due to poor survival rates at this stage. A UK retrospective study showed a 5-year overall survival of 4%.[16]

NA. Not available.

There are no centrally gathered UK-specific 5 -year survival statistics for Stage IV GC available, as most people do not survive to 5 years after diagnosis.[12] However, a UK retrospective study in 511 patients with advanced gastro-oesophageal adenocarcinoma showed a 5-year OS of 4%.[16] In the UK, 46-51% of GC cases are diagnosed at stage III or IV with about 27-38% of the patients with an unknown staging at diagnosis (Figure 1).[5] Understandably, this is associated with poor survival expectations.

In these newly diagnosed, late-stage patients, chemotherapy or radiation can improve symptoms and may improve survival,[17,18] but the aim of treatment for this patient population is primarily palliative: to prolong the time to progression, extend survival and relieve symptoms with minimal adverse effects.[19] Despite receiving palliative treatment, it was shown in a UK retrospective study that a small number of patients may survive for a number of years with a proportion of patients surviving past eight years.[16] Additionally, the ATTRACTION-2 study, which enrolled Asian GC patients who had previously received at least two prior therapies and had therefore a worse prognosis, reported that 5.6% of patients receiving nivolumab were alive at three years. However, despite this, overall survival remains low, particularly where patients are receiving standard chemotherapy regimens. Therefore, there is an important need for novel therapies in the management of metastatic or advanced GC.

B.1.3.2 Clinical pathway of care

The aim of treatment in advanced or metastatic GC unsuitable for radical or surgical treatment is primarily palliative, with first-line chemotherapy recommended to prevent progression, extend survival and relieve symptoms with minimal adverse effects. NICE technology appraisal 191 (TA191) recommends capecitabine in combination with a platinum-containing agent as an option for inoperable untreated advanced gastric cancer.[20] NICE clinical guideline 83 (NG83) recommends chemotherapy combination regimens for people who have a performance status 0 to 2 and no significant comorbidities.[21] Chemotherapy regimens include:

- doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin

- triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic GC who have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (TA208).[22] NICE recommends that HER2 testing is offered to people with metastatic GC to ensure that an appropriate treatment pathway can be followed.

The NICE palliative management pathway for people with metastatic GC is shown in Figure 2, together with an indication of the proposed place of nivolumab + chemotherapy in therapy. Subsequent therapies are second-line palliative chemotherapy or best supportive care.[21]

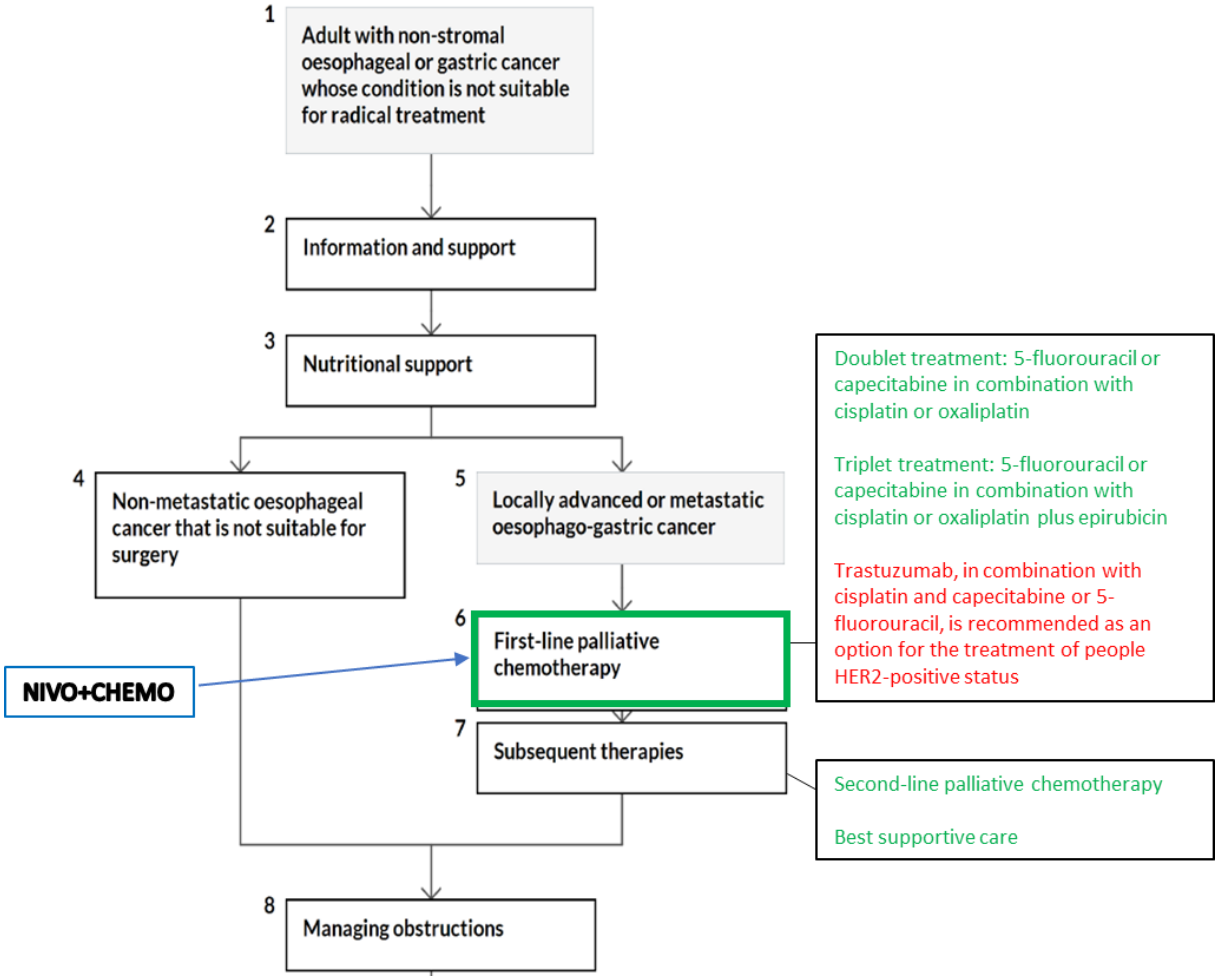


Figure 2. NICE palliative management pathway

Clinical advisors confirmed that in cases of inoperable metastatic GC, preferred first-line treatment is FOLFOX or XELOX. Trastuzumab is added if HER2 status is positive.[1] Clinical advice indicates that epirubicin is not used in the UK for first-line treatment of gastro-

oesophageal cancers, and that recent guidelines have actively removed epirubicin from the treatment options.[1,23]

NICE guidelines for the management of GC state that the benefits of first-line chemotherapy, including improved overall and disease-free survival with accompanying symptom relief, must be carefully balanced against the putative side effects and potential lack of efficacy.[21] Given the poor survival rates from currently available treatments for advanced or metastatic GC (only 21.4% are alive at one-year [Table 3]), there is a clear unmet need for an effective and well-tolerated treatment to improve survival outcomes for patients with GC.

B.1.3.3 Role of nivolumab in therapy

The technology being appraised in this submission is nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Immunotherapy has been at the forefront of therapeutic development in oncology since the discovery that cancer cells evade destruction by exploiting the signalling pathways that control the immune system. The typical immune response to foreign cells or antigens in the body is the activation of T-cells that can then destroy those foreign cells or antigens. T--cells proliferate and differentiate through various pathways, with T-cell activation regulated through a complex balance of positive and negative signals provided by co-stimulatory and co-inhibitory receptor interactions on the T--cell surface (Figure 3). Healthy, non-foreign cells ('self'-cells) avoid T--cell destruction by stimulating inhibitory receptors, known as checkpoints, to suppress the T--cell response; cancer cells can use these same inhibitory receptors to escape destruction by T--cell activity. Antibodies designed to bind to and block these checkpoints (so called 'checkpoint inhibitors') can prevent tumour-driven T-cell suppression, as depicted in Figure 3, and increase immune activity against cancer cells.

PD-1 is an immune checkpoint protein receptor expressed at high levels on activated T-cells, which has been shown to control the inhibition of T-cell response at the effector stage of the immune response, in the setting of human malignancy.[24-27] Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 with its ligands (programmed death ligand-1 [PD-L1] and programmed death ligand-2 [PD-L2]) to limit the activity of T-cells at the tumour site.

A recent publication has reported that PD-L1 is expressed in 59.3 % of Asian GC patients and is associated with microsatellite instability and Epstein-Barr virus positivity.[28] Further, it has been demonstrated that where PD-1 and its ligands are upregulated in GC tissues and tumour-infiltrating immune cells, it is correlated with poor prognosis and clinical parameters, including tumour size, depth of infiltration, metastasis and survival.[29-31] Hence, through exploitation of the PD-1 immune checkpoint inhibitor pathway, GC cells are able to escape immune surveillance. PD-1 and its ligands may therefore be considered as therapeutic targets for immune-mediated therapies in GC.

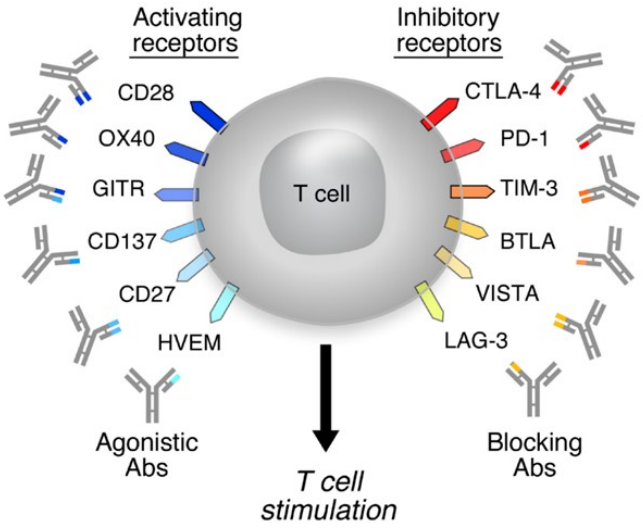


Figure 3. Receptors involved in the regulation of the T-cell immune response (from Mellman, 2011[32])

Mechanism of action of nivolumab

Nivolumab is a fully human, monoclonal immunoglobulin G4 antibody (IgG4 HuMAb) that acts as a PD-1 checkpoint-inhibitor, blocking the interaction of PD-1 with PD-L1 and PD-L2 (Figure 4). Through interruption of PD-1 binding to PD-L1 and PD-L2, nivolumab stops the evasion of immune-mediated tumour destruction and restores T-cell activity by stimulating the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes.

Nivolumab is currently approved as OPDIVO® in the European Union (EU), United States (US), Japan, Australia, Canada and several other countries. Initial and subsequent approvals in the EU now include indications for specific types of melanoma, second-line squamous cell oesophageal cancer, non-small-cell lung carcinoma, renal-cell carcinoma, squamous cell cancer of the head and neck, classical Hodgkin lymphoma and urothelial carcinoma. Clinical development of nivolumab remains actively ongoing in a broad and extensive programme. Development and registration planning continues in expanded patient populations in the currently indicated tumours as well as other solid tumours and haematologic malignancies.

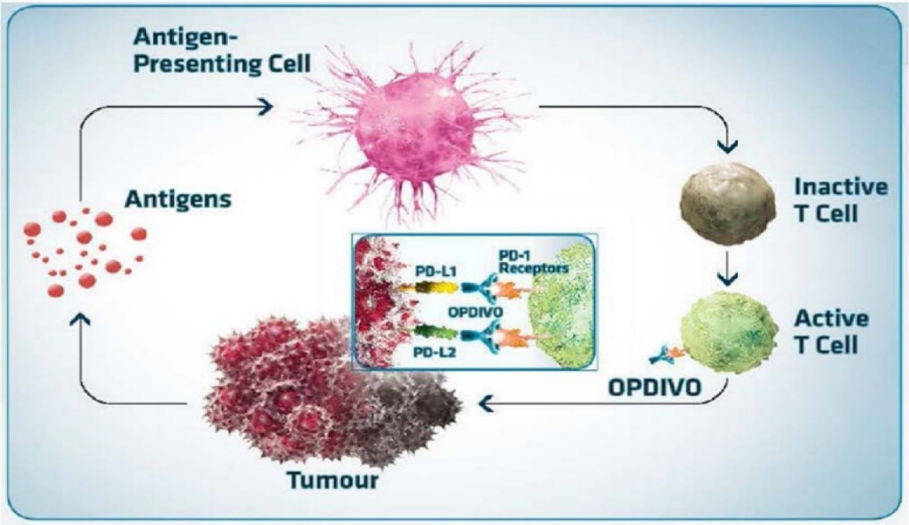


Figure 4. Nivolumab stimulation of immune-mediation tumour destruction

The benefit of currently available first-line treatment options for GC is limited, highlighting the unmet medical need for more effective therapies. Nivolumab with chemotherapy (5-fluorouracil, folinic acid and oxaliplatin [FOLFOX] or capecitabine and oxaliplatin [XELOX]), if recommended by NICE, would be the first immunotherapeutic treatment option for patients with GC, providing an alternative to the standard chemotherapy treatment options. It is anticipated to provide significant and durable clinical benefit for these patients, addressing the unmet need that exists in the current care pathway.

B.1.4 Equality considerations

No equality issues have been identified or are anticipated.

B.2 Clinical effectiveness

Key points

- Patients with previously untreated advanced or metastatic gastric/GOJ cancer, including oesophageal adenocarcinoma (OAC), have a poor prognosis (1-year survival 21.4%[14]) and limited treatment options.
- In CheckMate 649, NIVO+CHEMO demonstrated statistically significant improved survival (both PFS and OS) versus CHEMO alone (median OS:13.83 vs 11.56 months [HR 0.80; 99.3% CI: 0.68-0.94]); median PFS: 7.66 vs 6.93 months [HR 0.77; 95% CI: 0.68 0.87]).
- The benefit of NIVO+CHEMO on survival was sustained for a continued duration demonstrating a significant inhibitory effect of nivolumab on disease progression.
- Benefit was observed in all randomised patients, and in subgroups comprising patients whose tumours expressed PD-L1 CPS ≥5 and CPS ≥1.
- NIVO+CHEMO is well-tolerated, with a similar safety profile to chemotherapy treatments currently used to treat gastric cancer. Further, the safety profile of nivolumab is well-established based on that observed in other indications.
- Patients in both treatment arms reported improved HRQoL compared with baseline at most on-treatment visits, on both the EQ-5D-3L generic health status measure, and the gastric cancer-specific FACT-Ga health status measure.
- Nivolumab meets the end-of-life criteria in the patient group that would be eligible for treatment under the proposed indication.

B.2.1 Identification and selection of relevant studies

B.2.1.1 Systematic literature review

A systematic literature review (SLR) was undertaken to identify the clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of gastric/GOJ cancer/OAC. Full details of the methods and processes employed to identify and select the relevant clinical evidence are summarised in Appendix D. An initial search was undertaken in 2018 and an update in 2019 and this report is provided as Appendix D1. This was updated a second time in October 2020, which is provided as Appendix D2.

B.2.2 List of relevant clinical effectiveness evidence

Two studies providing information on NIVO+CHEMO in this indication were identified and are described below.

Evidence to describe the effectiveness of NIVO+CHEMO for the treatment of previously untreated gastric and GOJ cancer, including OAC, is primarily derived from CheckMate 649, a Phase III randomised, open-label study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine in patients with previously untreated advanced or metastatic gastric/GOJ cancer/OAC (Table 4).[33] The focus of this submission will be on the cohort of patients with untreated gastric/GOJ cancer/OAC that received combination treatment with NIVO+CHEMO. The estimated study completion date is October 6, 2022.[33]

Evidence is also presented from ATTRACTION-4, a multi-centre, phase II/III trial in HER2 negative patients with previously untreated advanced or recurrent gastric/GOJ cancer/OAC. This study has a number of important differences from CheckMate 649 which limit its relevance to UK clinical practice. ATTRACTION-4 was conducted in an exclusively Asian population and 64.1% of patients received chemotherapy that would not be considered relevant to UK practice (tegafur, gimeracil, oteracil [S-1] and oxaliplatin [SOX/XELOX]). There are well recognised differences in the characteristics of GC between Asian and Western populations. In general, although Asian patients have a higher incidence of GC, they also have higher survival rates due to the impact of screening programmes, tumours at a more distal site, diagnosis at earlier tumour stages and at younger ages, and more aggressive treatment schemes;[34] this is borne out by the fact that the control arm in ATTRACTION-4 had a much longer PFS (8.34) and OS (17.15 months) than seen in CheckMate 649[35]. In addition, in ATTRACTION-4, there was also significantly greater use of immunotherapies in subsequent treatment lines for the control arm (27.4%, vs 8.1% in CheckMate 649), making the comparison of treatment with and without nivolumab more difficult.

By contrast, CheckMate 649 was conducted in a predominantly non-Asian population (75%) and used chemotherapy that is considered standard of care in a UK setting (XELOX and FOLFOX); hence it is directly relevant to the UK population and UK clinical practice. It is also a much larger study, with approximately twice as many NIVO+CHEMO patients as ATTRACTION-4 (N=1,581 vs N=724). Lastly, patients enrolled into CheckMate 649 had to have confirmed histological predominance of adenocarcinoma, whereas histological confirmation was not required in ATTRACTION-4.

For the reasons given above, CheckMate 649 can be directly extrapolated to the UK population and is used as the primary source for comparative effectiveness in the submission; however, information on ATTRACTION-4 is provided for completeness (Section B.2.8.1). A similar patient population in the ATTRACTION-2 trial for GC, was not considered by the EMA. This was due to similar generalisability issues with an Asian population.[36]

B.2.2.1 Rationale for design of CheckMate 649[37]

Gastric cancer, including GOJ cancer and OAC, is a heterogeneous disease with several established risk factors, including environmental, genetic and behavioural risks. Current evidence suggests that OAC shares similar disease and molecular characteristics[38] with gastric/GOJ adenocarcinomas, and are managed and treated similarly.[39] They were therefore included within the study population of CheckMate 649.

Cancer therapeutics such as chemotherapy may modulate tumour/immune-system interactions in favour of the immune system. The combination of NIVO+CHEMO was chosen as an experimental arm with the rationale that nivolumab, which acts against evasion of immune-mediated tumour destruction and restores T-cell activity, could have enhanced clinical activity in untreated gastric/GOJ cancer/OAC compared with chemotherapy alone.[40] Pre-clinical and clinical data suggest that nivolumab in combination with oxaliplatin and fluoropyrimidine may bring clinical benefits to advanced gastric/GOJ cancer/OAC patients with manageable safety.[41]

The study was designed as an open-label trial to overcome the difficulties associated with different dosing schedules and unique characteristic drug-related AEs. In addition, the correct management of frequent AEs such as diarrhoea might require a process of unblinding which may delay appropriate supportive care for management of AEs. Further, it should be noted that there is an ethical issue in conducting double-blind trials for infusional drugs, where administration of the placebo arm will use up hospital resources, including clinic space and nurse time, that could have been used on treating other patients. This is of particular relevance in studies with endpoints unlikely to be impacted by open-label study design, such as OS and PFS.

B.2.2.1.1 Role of PD-L1 expression in study design and analysis

CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%). However, the two primary endpoints evaluated the benefit NIVO+CHEMO in patients with PD-L1 combined positive score (CPS) ≥5. PD-L1 CPS is a scoring method that evaluates the number of PD-L1 positive cells (tumour, lymphocytes and macrophages) divided by the total number of tumour cells, multiplied by 100[42]. Hence, it is a composite score that allows the capture of PD-L1 positive tumour and immune cells in a single reading.[43] This is preferred over tumour PD-L1 score, which only reflects the percentage of tumour cells that are positive for PD-L1 expression.

[redacted] Reflecting the study design, the submission contains subgroup analyses for the PD-L1 subgroups; however, the population of interest is the overall population.

Table 4. Clinical effectiveness evidence: CheckMate 649[37]

<table>
<tr><th>Study</th><th colspan="5">Checkmate 649</th></tr>
<tr><td>Study design</td><td colspan="5">Ongoing Phase III, randomised, open-label, multi-centre of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs SoC (oxaliplatin plus fluoropyrimidine).</td></tr>
<tr><td>Population</td><td colspan="5">Patients with previously untreated advanced or metastatic gastric or GOJ cancer/OAC.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">NIVO+CHEMO (XELOX [oxaliplatin and capecitabine] or FOLFOX [folinic acid, 5-fluorouracil, oxaliplatin]) combination therapy.

A cohort within CheckMate 649 assessed the safety and efficacy of nivolumab with ipilimumab as combination therapy, but <u>this is not relevant to the indication under consideration</u>.</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">XELOX (oxaliplatin and capecitabine) or FOLFOX (folinic acid, 5--fluorouracil, oxaliplatin).</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Source of direct comparative evidence evaluating the efficacy of NIVO+CHEMO combination therapy versus SoC chemotherapy.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Overall survival
• Progression-free survival
• Response rate
• Adverse effects of treatment
• Health-related quality of life.</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">Pharmacokinetic, biomarker, and immunogenicity data were also collected.</td></tr>
<tr><td colspan="6">CHEMO: chemotherapy; FOLFOX: folinic acid, 5-fluorouracil, oxaliplatin; GOJ: gastroesophageal junction; NIVO: nivolumab; OAC: oesophageal adenocarcinoma; SoC: standard of care; XELOX: oxaliplatin and capecitabine.</td></tr>
</table>

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

A summary of methodology for CheckMate 649 is provided in Table 5.

Table 5. Summary of trial methodology: CheckMate 649

Trial acronym	CheckMate 649
Trial design	Ongoing Phase III, open-label, multi-centre trial.
Eligibility criteria for participants	Adults (≥18 years), with previously untreated, inoperable metastatic or advanced gastric or GOJ cancer or distal oesophageal cancer and have histologically confirmed predominant adenocarcinoma. Previously untreated with systemic treatment (including HER2 inhibitors). Prior adjuvant or neoadjuvant chemo/radio or chemoradiotherapy were permitted as long as the last administration occurred at least 6 months prior to randomisation. Palliative radiotherapy was allowed if completed 2 weeks before randomisation. ECOG performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1). Patients with known HER2 positive status and patients with untreated central nervous system (CNS) metastases were excluded.
Settings and locations where the data were collected	This study was conducted at 175 sites in 29 countries across Europe, USA, and Asia, including the UK [redacted]
Intervention	NIVO+XELOX: Nivolumab 360mg (30-minute intravenous [IV] infusion) on day 1 of each treatment cycle every 3 weeks, plus XELOX: oxaliplatin (130 mg/m^2) IV and capecitabine (1000 mg/m^2) orally twice daily on days 1 and 14 of each treatment cycle, every 3 weeks. OR NIVO+FOLFOX: 240mg (30-minute IV infusion) on day 1 of each treatment cycle every 2 weeks, plus FOLFOX: oxaliplatin (85 mg/m^2), folinic acid (400 mg/m^2) and fluorouracil (400 mg/m^2) IV on day 1 of each treatment cycle and fluorouracil (1200 mg/m^2) IV continuous infusion over 24 hours on days 1 and 2 of each treatment cycle, every 2 weeks.
Comparator	Chemotherapy: XELOX: oxaliplatin (130 mg/m^2) IV and capecitabine (1000 mg/m^2) orally twice daily on days 1 and 14 of each treatment cycle, every 3 weeks. OR FOLFOX: oxaliplatin (85 mg/m^2), folinic acid (400 mg/m^2) and fluorouracil (400 mg/m^2) IV on day 1 of each treatment cycle, and fluorouracil (1200 mg/m^2) IV continuous infusion over 24 hours on days 1 and 2 of each treatment cycle, every 2 weeks.
Permitted and disallowed Concomitant medications	Permitted medications: 1) Inhaled or topical steroids, and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Trial acronym	CheckMate 649
	2) Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). 3) Adrenal replacement steroid doses including doses >10 mg daily prednisone. 4) A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen). 5) Use of marijuana and its derivatives are permitted if attained by prescription or if its use has been legalised locally. 6) Supportive care for disease-related symptoms to all patients on the trial. Disallowed medications: 1) Immunosuppressive agents (except to treat a drug-related adverse event). 2) Immunosuppressive doses of systemic corticosteroids (except as stated under *Permitted medications*, or to treat a drug-related adverse event). 3) Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines). 4) Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in *Permitted medications* or standard or investigational agents for treatment of cancer). Concomitant medications were collected within 14 days prior to first dose and through the study treatment period.
Primary outcome	• Progression-free survival (PFS) by BICR determination in patients with PD-L1 CPS ≥ 5 (PFS population) • Overall survival (OS) in patients with PD-L1 CPS ≥ 5
Other outcomes used in the economic model/specified in the scope	• OS • PFS • Response rate • Adverse effects of treatment • Health-related quality of life
Pre-planned subgroups	• Region (Asia vs US vs Rest of World [ROW]) • ECOG performance status (0 vs 1) • Chemotherapy regimen (XELOX vs FOLFOX) • TPS* PD-L1 (≥1% vs <1% [including indeterminate]) Subgroups are described further in Section 0.
BICR: blinded independent central review; CPS: combined positive score; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; NIVO: nivolumab; OS: overall survival; PD-L1: programmed cell death ligand-1; PFS: progression-free survival; TPS: tumour proportion score; US: United States. **TPS stratification was changed to CPS stratification in a protocol amendment 23 dated 14-Sep-2018. However, both sets of data are presented*	

B.2.3.1 CheckMate 649

B.2.3.1.1 Study design

CheckMate 649 (NCT02872116) is a Phase III, open-label, randomised, multi-centre trial initiated by Bristol-Myers Squibb in 2016 to examine whether nivolumab in combination with chemotherapy (NIVO+CHEMO) demonstrates improved progression-free survival and overall survival (co-primary endpoints) compared with chemotherapy alone, in patients with untreated advanced and metastatic gastric/GOJ cancer/OAC with PD-L1 CPS ≥5. A hierarchically tested secondary objective was to compare OS in patients with advanced or metastatic gastric or GOJ cancer with PD-L1 CPS ≥1 or all randomised patients.

Treatment arms in CheckMate 649:[37]

- Nivolumab plus ipilimumab (not considered in this submission)
- NIVO+CHEMO (nivolumab in combination with chemotherapy: XELOX or FOLFOX)
- Chemotherapy alone (XELOX or FOLFOX)

Patients were randomised in an open-label fashion, with a 1:1:1 ratio, until the nivolumab plus ipilimumab arm was closed to enrolment on 05 June 2018, after which patients were randomised in a 1:1 ratio. The nivolumab plus ipilimumab cohort will not be described in this submission.

The multi-centre study comprised of study locations in 29 countries (Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Taiwan, Turkey, United Kingdom, and United States).

As stated above, CheckMate 649 also included a cohort who received nivolumab plus ipilimumab which is outside the scope of the proposed indication. As such, results are only presented for the cohorts relevant to the proposed indication: the NIVO+CHEMO and chemotherapy only arms of the CheckMate 649 study. The study schematic is shown in Figure 5.

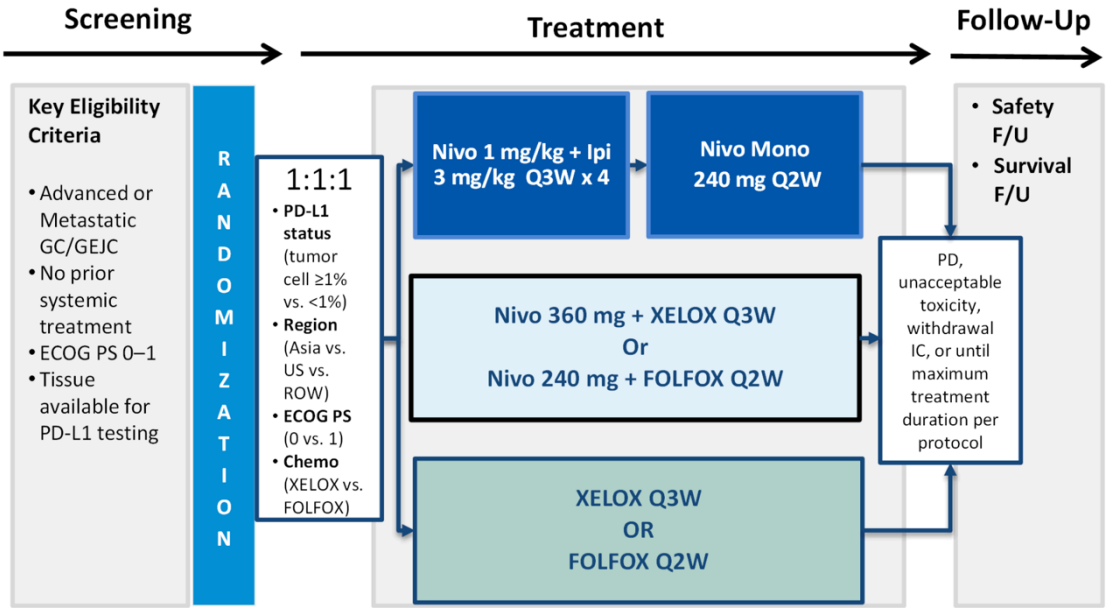


Figure 5. CheckMate 649: study schematic

Chemo: chemotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFOX: folinic acid, 5-fluorouracil, oxaliplatin; GC: gastric cancer; GOJC = gastroesophageal junction cancer (US abbreviation), Ipi: ipilimumab; Mono: monotherapy; Nivo: nivolumab; Q2W: every 2 weeks; Q3W: every 3 weeks; PD: progressive disease; PD-L1: programmed death-ligand 1; ROW: rest of world; XELOX: capecitabine plus oxaliplatin.

B.2.3.1.2 Eligibility criteria

The key inclusion criteria for CheckMate 649 were as listed below:[37]

- Adults ≥18 years of age with inoperable, advanced or metastatic gastric/GOJ, or distal oesophageal carcinoma, who have histologically confirmed predominant adenocarcinoma.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
- Previously untreated with systemic treatment (including HER2 inhibitors) given as primary therapy for advanced or metastatic disease.
- At least one measurable lesion or evaluable disease by CT or MRI per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria. Radiographic tumour assessment should be performed within 28 days prior to randomisation.
- Willingness to provide tumour tissue (archival or fresh biopsy specimen), including possible pre-treatment biopsy, for PD-L1 expression analysis and other biomarker correlative studies.

Key exclusion criteria included:[37]

- Known HER2 positive status
- Patients with untreated known central nervous system (CNS) metastases. Patients are eligible if CNS metastases are adequately treated and neurologically returned to

baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomisation
- Patients with ascites which cannot be controlled with appropriate interventions
- Prior malignancy active within the previous 3 years except for locally curable cancers
- Active, known, or suspected autoimmune disease
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration
- 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.

B.2.3.1.3 Study medications

All patients who met eligibility criteria and were enrolled into the NIVO+CHEMO arm received either: [37]

- **Nivolumab plus XELOX**: nivolumab 360 mg (30-minute IV infusion) on day 1 of each treatment cycle every 3 weeks, plus XELOX: oxaliplatin (130 mg/m^2) administered IV, and capecitabine (1000 mg/m^2) administered orally twice daily on days 1 and 14 of each treatment cycle, every 3 weeks.

OR

- **Nivolumab plus FOLFOX**: nivolumab 240 mg (30-minute IV infusion) on day 1 of each treatment cycle every 2 weeks, plus FOLFOX: oxaliplatin (85 mg/m^2), folinic acid (400 mg/m^2) and fluorouracil (400 mg/m^2) administered IV on day 1 of each treatment cycle and fluorouracil (1200 mg/m^2) IV continuous infusion over 24 hours on days 1 and 2 of each treatment cycle, every 2 weeks.

All patients who met eligibility criteria and were enrolled into the chemotherapy arm received either:[37]

- **XELOX**: oxaliplatin (130 mg/m^2) administered IV and capecitabine (1000 mg/m^2) administered orally twice daily on days 1 and 14 of each treatment cycle, every 3 weeks.

OR

- **FOLFOX**: oxaliplatin (85 mg/m^2), folinic acid (400 mg/m^2) and fluorouracil (400 mg/m^2) administered IV on day 1 of each treatment cycle and fluorouracil (1200 mg/m^2) IV continuous infusion over 24 hours on days 1 and 2 of each treatment cycle, every 2 weeks.

Choice of chemotherapy regimen (FOLFOX versus XELOX) was decided on an individual patient basis by the treating physician prior to randomisation in both treatment arms, on the

basis of personal clinical preference (there were no protocol-defined criteria for the choice). No cross-over was allowed between XELOX and FOLFOX in this study.

Treatments were given until disease progression, discontinuation due to toxicity, death, withdrawal of consent, or study end. Treatment with nivolumab could be given for up to 24 months in the absence of disease progression or unacceptable toxicity.[2] Chemotherapy was given as per the study dosing schedule. Dose reduction of nivolumab was not permitted. Dose reduction for chemotherapy was permitted according to local standard or local package insert. Dose delays of <6 weeks were permitted for all treatment related adverse events (TRAEs) according to pre-specified criteria. If toxicity was not resolved within 6 weeks, that component was discontinued unless it was determined by the treating investigator that the patient might benefit from continuation of the component. The assessments for discontinuation of nivolumab and/or chemotherapy were made separately. Continuation of nivolumab alone when chemotherapy had been discontinued due to toxicity was permitted. Chemotherapy doublet or single drug was allowed to continue if the discontinuation criteria for nivolumab were met.

B.2.3.1.4 Study endpoints and assessments

The primary, secondary, and exploratory endpoints of CheckMate 649 are provided in Table 6. Assessments also included biomarker analysis, immunogenicity, and patient-reported outcomes. The primary analysis population was changed to subjects with PD-L1 CPS ≥5 rather than PD-L1 ≥1% (Revised Protocol 07) in order to reflect the stronger predictive effect of PD-L1 CPS for immune-oncology therapies.

Table 6. Study endpoints in CheckMate 649[37]

CheckMate 649 study outcomes	
Primary endpoint	• PFS by BICR in patients with PD-L1 CPS ≥5 (PFS population) • OS in patients with PD-L1 CPS ≥5.
Secondary endpoints	• OS in patients with PD-L1 CPS ≥1, and in all randomised patients • OS in patients with PD-L1 CPS ≥10 • PFS by BICR in patients with PD-L1 CPS ≥10, 1 or all randomised patients • ORR by BICR in patients with PD-L1 CPS ≥10, 5, 1 or all randomised patients.
Exploratory endpoints	• PFS by BICR in patients with CPS across cut-offs (all randomised population) • ORR, PFS by investigator in patients with PD-L1 CPS ≥10, 5, 1 or all randomised patients • OS, PFS[a], ORR[a], in patients with TPS across cut-offs • OS rates at 18, 24, and 36 months • PFS2 or TSST of next line treatment • DOR[a] • DRR[a] • TTSD in patients with PD-L1 CPS ≥10, 5, 1, or all randomised patients • Biomarkers.
[a]By BICR and by investigator. *BICR: Blinded Independent Central Review; CPS: combined positive score; DOR: duration of response; DRR: durable response rate; ORR: objective response rate; OS: overall survival; PD-L1: performance death ligand-1; PFS: progression-free survival; PFS2: second disease progression; TPS: tumour proportion score; TSST: time to second subsequent therapy; TTSD: time to symptom deterioration.*	

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

B.2.4.1 Statistical analyses

Sample size calculations of the primary endpoints were based on simulations in the statistical analysis software EAST (version 6.4.1).[37]

Progression-free survival: the target average HR of 0.62 was modelled as a 2-piece hazard ratio, a delayed effect with a HR of 1 versus chemotherapy for the first 1.5 months followed by a constant HR of 0.56. A total of 228 PFS events was required to provide approximately 90% power with a Type I error of 2% (two-sided). To ensure a reasonable minimum follow-up of approximately 8 months for all patients, the 228 events had to be observed in the first 298 patients with PD-L1 CPS ≥5. The number of events was expected to be reached after approximately 23.2 months from first patient randomised in 1:1:1 under the assumption of 35% prevalence of CPS ≥5. The PFS population in all comers was adjusted accordingly based on final estimation of the prevalence of the CPS ≥5 in order to maintain the 298 PD-L1 CPS ≥5.

Overall survival: the target average HR of 0.69 was modelled as a 2-piece hazard ratio with a delayed effect of a HR of 1 versus chemotherapy for the first 3 months followed by a constant HR of 0.65. A total of 354 OS events was required to provide approximately 90% power with a Type I error of 3% (two-sided). Approximately 420 patients with PD-L1 CPS ≥5 were needed to contribute to the OS analysis. The final analysis was projected to occur approximately 47.4 months from first patient randomised in 1:1:1 and 27.5 months from last patient randomised to these arms under the assumption of 35% prevalence of CPS ≥5. OS sample size determination accounted for two interim analyses at 70% and 85% of all events.

B.2.4.2 Sample size and power calculation

The original CheckMate 649 study design (before Amendment 08) had 2 arms, with 83 patients being randomised in a 1:1 ratio to the nivolumab plus ipilimumab or to the chemotherapy (XELOX or FOLFOX) arms. Amendment 08 added the new NIVO+CHEMO arm, when the IRT switched to a 1:1:1 randomisation. It was planned to randomise an additional 1,266 patients into the three arms of the study. Amendment 19 was approved to allow additional 300 patients to be randomised under 1:1:1 ratio for a total additional sample size of 1,566 to the 3 treatment arms (1,649 including the 83 already randomised in the 1:1 stage of the study).

Given the prevalence of CPS ≥5 (estimated 27%) was lower than the original estimate of 35%, enrolment was extended to approximately 2005 to ensure that the study was appropriately powered for PFS and OS primary endpoints in the CPS ≥5 population. Given the uncertainty about the CPS ≥5 prevalence, sample size was adjustable over the study. Randomisation is shown in Figure 6.

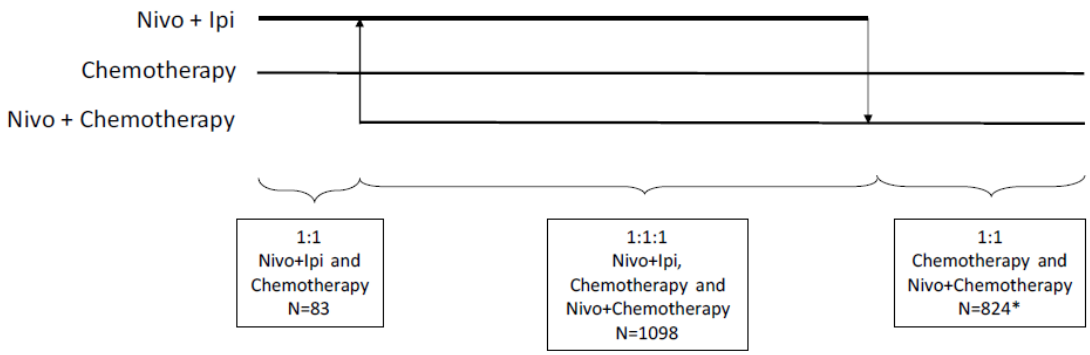


Figure 6. Randomisation schema
CPS: combined positive score; Ipi: ipilimumab; Nivo: nivolumab.

For the comparison of NIVO+CHEMO and CHEMO, only patients who were randomised to those 2 arms concurrently were used. This means patients randomised to receive CHEMO before the NIVO+CHEMO arm was introduced were not included in the analysis of this comparison.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of the pivotal CheckMate 649 RCT was conducted using the University of York, Centre for Reviews and Dissemination (2008)[44] checklist as shown in Table 7. There were no quality issues of note.

Table 7. Quality assessment results for CheckMate 649

Study questions	Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A
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?	N/A
Were there any unexpected imbalances in drop-outs 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
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination[44] *ITT: intention-to-treat; N/A: not applicable.*	

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 CheckMate 649

B.2.6.1.1 Patient disposition summary

By the time of database lock (DBL) for this CSR, the median follow-up (date of randomisation to the last known date alive or death date) was [redacted] months for the NIVO+CHEMO arm and [redacted] months for the CHEMO arm. A total of [redacted] subjects were concurrently randomised in the NIVO+CHEMO and CHEMO arms: [redacted] to the NIVO+CHEMO arm and [redacted] to the CHEMO arm. [redacted] subjects were treated: [redacted] with NIVO+CHEMO and [redacted] with CHEMO. [redacted] subjects were randomised but not treated ([redacted] in the NIVO+CHEMO arm and [redacted] in the chemo arm). Of the [redacted] treated subjects, [redacted] subjects were continuing in the treatment period at the time of DBL: [redacted] NIVO+CHEMO subjects and [redacted] CHEMO subjects (Table 8).

The overall rates of discontinuation were [redacted] in the NIVO+CHEMO and CHEMO arms, respectively. The primary reason for not continuing the treatment period was disease progression in both treatment arms ([redacted] subjects, [redacted] NIVO+CHEMO -treated subjects and [redacted] CHEMO -treated subjects.

Subjects who discontinued due to study drug toxicity were similar between treatment arms; [redacted] and [redacted] subjects in the NIVO+CHEMO and CHEMO arms, respectively. This is further described in Section B.2.11.1.5.

Subjects who discontinued study therapy due to AEs are further described in (Section B.2.11). [redacted] subjects overall withdrew consent and did not complete the treatment period: [redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm.

Table 8. Patient disposition at end of treatment period

	NIVO+CHEMO N=789	CHEMO N=792	Total
Enrolled [a]			[redacted]
Randomised	[redacted]	[redacted]	[redacted]
Treated [b]	[redacted]	[redacted]	[redacted]
Not treated [b]	[redacted]	[redacted]	[redacted]
Reason for not being treated			
Disease progression	[redacted]	[redacted]	[redacted]
AE unrelated to study drug	[redacted]	[redacted]	[redacted]
Subject request to discontinue study treatment	[redacted]	[redacted]	[redacted]
Subject withdrew consent	[redacted]	[redacted]	[redacted]
Subject no longer meets study criteria	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Continuing in the treatment period [c]	[redacted]	[redacted]	[redacted]
Not continuing in the treatment period [c]	[redacted]	[redacted]	[redacted]
Reasons for not continuing in the treatment period [c]			
Disease progression	[redacted]	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
AE unrelated to study drug	[redacted]	[redacted]	[redacted]
Subject request to discontinue study treatment	[redacted]	[redacted]	[redacted]
Subject withdrew consent	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Maximum clinical benefit	[redacted]	[redacted]	[redacted]
Poor/ non-compliance	[redacted]	[redacted]	[redacted]
Subject no longer meets study criteria	[redacted]	[redacted]	[redacted]
Completed treatment as per protocol	[redacted]	[redacted]	[redacted]

Other	[redacted]	[redacted]	[redacted]
Continuing in the study [c d e]	[redacted]	[redacted]	[redacted]
Not continuing in the study [c d]	[redacted]	[redacted]	[redacted]
Reason for not continuing in the study [c d]			
Death	[redacted]	[redacted]	[redacted]
Subject withdrew consent	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

AE: adverse event; CHEMO: chemotherapy; NIVO: nivolumab.
[a] Enrolled population contains all concurrently randomised subjects to nivo+chemo and chemo as well as subjects enrolled as of the start of the 1:1:1 randomisation and not randomized to any of the treatment arms
[b] Percentages based on subjects randomised.
[c] Percentages based on subjects treated.
[d] Subject status at end of treatment
[e] Includes subjects still on treatment and subjects off treatment continuing in the follow-up period.

B.2.6.1.2 Baseline demographics

Baseline and disease characteristics in all randomised patients were well balanced between the NIVO+CHEMO and the CHEMO arms and were representative of patients with previously untreated advanced or metastatic gastric/GOJ cancer/OAC (Table 9). Overall, the median age of all randomised patients was [redacted]. Most patients were white [redacted] male [redacted] and had an ECOG PS of 1 [redacted] The majority of primary tumour locations were gastric [redacted] Most patients had Stage IV disease at initial diagnosis [redacted] In total, [redacted] and [redacted] of patients had liver metastases and signet ring cell, respectively.

Per protocol, patients with known HER2 positive status were excluded. As HER2 test is a routine diagnostic procedure in first line gastric/GOJ cancer/OAC across regions, this was not included as a mandatory study procedure in the protocol. A total of [redacted] randomised patients did not report HER2 test results with the number of patients with unknown HER2 status being balanced between the two treatment arms.

Table 9. Baseline characteristics: CheckMate 649[41]

	NIVO+CHEMO N=789	CHEMO N=792
Median age, years (range)	[redacted]	[redacted]
Sex, male (%)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Region, n (%)		
Asia	[redacted]	[redacted]

US	[redacted]	[redacted]
Rest of world	[redacted]	[redacted]
Initial diagnosis, n (%)		
Gastroesophageal junction cancer	[redacted]	[redacted]
Gastric cancer	[redacted]	[redacted]
Oesophageal adenocarcinoma	[redacted]	[redacted]
Disease stage at initial diagnosis, n (%)		
Stage I	[redacted]	[redacted]
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Disease status classification, n (%)		
Locally recurrent	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]
Locally advanced	[redacted]	[redacted]
Lauren classification, n (%)		
Intestinal type	[redacted]	[redacted]
Diffuse type	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
WHO histologic classification, n (%)		
Adenosquamous carcinoma	[redacted]	[redacted]
Mucinous adenocarcinoma	[redacted]	[redacted]
Papillary serous adenocarcinoma	[redacted]	[redacted]
Signet ring cell	[redacted]	[redacted]
Tubular adenocarcinoma	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Liver metastases, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Peritoneal metastases, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Microsatellite instability, n (%)		
MSI-H	[redacted]	[redacted]
MSS	[redacted]	[redacted]
Invalid	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
HER2 status, n (%)		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

Not reported	[redacted]	[redacted]
ECOG PS		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
CHEMO: chemotherapy; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability-high; MSS: microsatellite stable; NIVO: nivolumab; PS: performance status; WHO: World Health Organisation.		

B.2.6.1.3 Results

Results presented within this report are based on a database lock (DBL) on 10th July 2020, providing an overall minimum follow-up of 12.1 months.

In patients with previously untreated advanced or metastatic gastric/GOJ cancer/OAC, NIVO+CHEMO provided statistically significant and clinically meaningful improvements in PFS per BICR and OS in all randomised patients with PD-L1 CPS ≥5, as well as OS in patients with PD-L1 CPS ≥1 and all randomised patients.

These results were supported by improvements in PFS, ORR and duration of response (DOR) per BICR in all randomised patients and across PD-L1 CPS populations (≥10, ≥5, and ≥1). Results for PFS per investigator assessment were consistent with those for PFS per BICR.

OS and PFS curves for all randomised patients are shown in Figure 7 and all randomised patients with PD-L1 CPS ≥5 in Figure 8. A summary of key efficacy results is provided in Table 11.

It needs to be noted that a long plateau in the OS curve was seen in both arms of the CheckMate 649 trial. Although median OS was reached relatively quickly, the hazard decreased over time (Table 10), with zero events observed following month 30 (Figure 7). This indicates the potential for long-term survival in this small proportion of the population.

Table 10. Summary of CheckMate 649 survival outcomes

	NIVO+CHEMO	CHEMO
Median OS (months)	13.83	11.56
OS at one year (%)	55.0	47.9
OS at two years (%)	[redacted]	[redacted]
OS at three years (%)	[redacted]	[redacted]
Median BICR-assessed PFS (months)	7.66	6.93
BICR-assessed PFS at one year (%)	[redacted]	[redacted]
BICR-assessed PFS at two years (%)	[redacted]	[redacted]

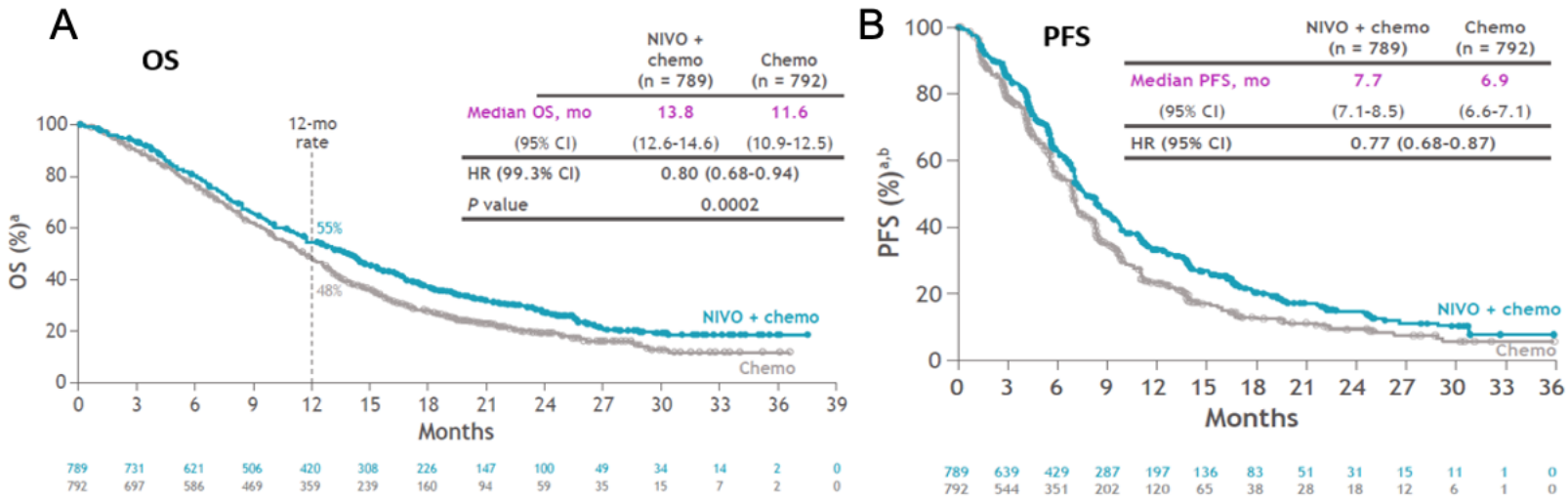


Figure 7. A) Overall survival (OS) and B) progression-free survival (PFS; per BICR) for all randomised patients[45]

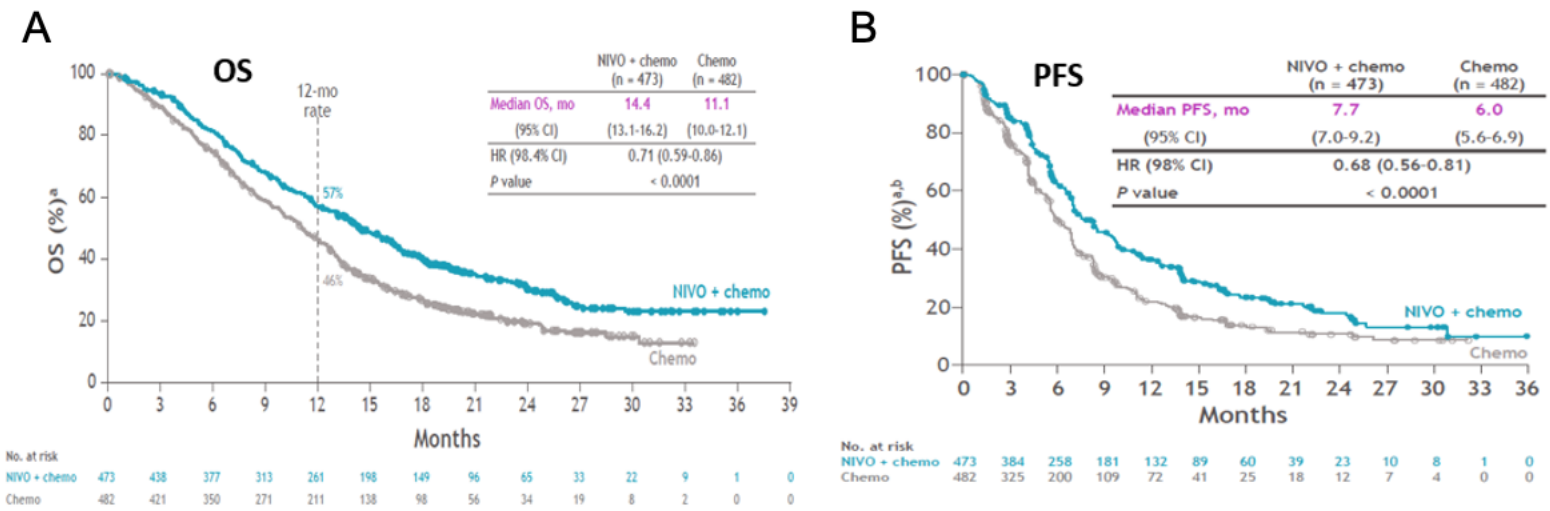


Figure 8. A) Overall survival (OS) and B) progression-free survival (PFS; per BICR) for all randomised patients with PD-L1 CPS ≥5[45]

Table 11. CheckMate 649 key efficacy results (10 July 2020 DBL)[41,45]

Endpoint	All randomised patients		All randomised patients with PD-L1 CPS ≥5		All randomised patients with PD-L1 CPS ≥1	
	NIVO+CHEMO (N=789)	CHEMO (N=792)	NIVO+CHEMO (N=473)	CHEMO (N=482)	NIVO+CHEMO (N=641)	CHEMO (N=655)
OS						
Median OS [95% CI][a], months	13.83 [12.55, 14.55]	11.56 [10.87, 12.48]	14.39 [13.11, 16.23]	11.10 [10.02, 12.09]	13.96 [12.55, 14.98]	11.33 [10.64, 12.25]
HR (CI)[b]	0.80 (99.3% CI: 0.68, 0.94)		0.71 (98.4% CI: 0.59, 0.86)		0.77 (99.3% CI: 0.64, 0.92)	
p-value[c]	0.0002		<0.0001		<0.0001	
PFS per BICR						
Median PFS [95% CI][a], months	7.66 [7.10, 8.54]	6.93 [6.60, 7.13]	7.69 [7.03, 9.17]	6.05 [5.55, 6.90]	7.49 [7.03, 8.41]	6.90 [6.08, 7.03]
HR (CI)[b]	0.77 (95% CI: 0.68, 0.87)		0.68 (98% CI: 0.56, 0.81)		0.74 (95% CI: 0.65, 0.85)	
p-value[c]	Not tested		<0.0001		Not tested	
ORR per BICR (CR+PR) in all randomised patients						
N responders, n/N (%)	[redacted]		[redacted]		[redacted]	
95% CI[d]	[redacted]		[redacted]		[redacted]	
Difference of ORR [95% CI][e]	[redacted]		[redacted]		[redacted]	
ORR per BICR (CR+PR) in patients with measurable disease						
N responders, n/N (%)	[redacted]		[redacted]		[redacted]	
95% CI[d]	[redacted]		[redacted]		[redacted]	
Difference of ORR (95% CI)[e]	[redacted]		[redacted]		[redacted]	
DOR per BICR in patients with measurable disease						
N events/N responders (%)	[redacted]		[redacted]		[redacted]	
Median (95% CI)[a], months	[redacted]		[redacted]		[redacted]	

[a]based on Kaplan Meier estimates; [b]Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo; [c]2-sided p-value using a stratified log-rank test. Stratified by region (Asia vs. US vs ROW), ECOG (0 vs 1), Tumour Cell PD-L1 (≥ 1% vs <1% [including indeterminate]) and chemotherapy (XELOX vs FOLFOX); [d]Confirmed CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method; [e]The difference in response rate (Nivo+Chemo vs Chemo) is not the simple difference between the rates but is adjusted for the stratification factors based on the DerSimonian and Laird methodology.

BICR: blinded independent central review; CHEMO: chemotherapy; CI: confidence interval; CPS: combined positive score; CR: complete response; DOR: duration of response; EGOG: Eastern Cooperative Oncology Group; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; NIVO: nivolumab; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand-1; PFS: progression-free survival; PR: partial response; ROW: rest of world; US: United States; XELOX: capecitabine plus oxaliplatin.

B.2.6.1.3.1 PD-L1

All randomised patients had a baseline tumour tissue sample tested for PD-L1. Overall, 789 randomised patients in the NIVO+CHEMO arm and 787 randomised patients in the CHEMO arm had quantifiable tumour cell PD-L1 expression at baseline.

In all randomised patients with PD-L1 quantifiable at baseline, [redacted] and [redacted] had a baseline tumour cell PD-L1 ≥5% in the NIVO+CHEMO and CHEMO arms, respectively. Further, [redacted] and [redacted] had a baseline tumour cell PD-L1 ≥1% in the NIVO+CHEMO and CHEMO arms, respectively.

Data from three immuno-oncology therapy trials suggested that PD-L1 measured by CPS might be a better predictor of efficacy than tumour cell PD-L1 expression for checkpoint inhibitors in GC and was therefore applied to CheckMate 649 according to revised Protocol 07. All randomised patients had their PD-L1 stained slides rescored for CPS using a CPS algorithm. Of the patients randomised to the NIVO+CHEMO and CHEMO arms, [redacted] and [redacted] patients had quantifiable CPS PD-L1 expression at baseline, respectively.

In all randomised patients with PD-L1 CPS quantifiable at baseline, [redacted] and [redacted] had a baseline PD-L1 CPS ≥5 in the NIVO+CHEMO and CHEMO arms, respectively. In all randomised patients with PD-L1 CPS quantifiable at baseline, [redacted] and [redacted]) had a baseline PD-L1 CPS ≥1 in the NIVO+CHEMO and CHEMO arms, respectively.

By the time of DBL, for all randomised patients with PD-L1 CPS ≥5, median follow-up was [redacted] for the NIVO+CHEMO arm and [redacted] for the CHEMO arm. A total of [redacted] patients with PD-L1 CPS ≥5 were concurrently randomised in the NIVO+CHEMO and CHEMO arms. Patient disposition at the end of the treatment period for patients with PD-L1 CPS ≥5 is shown in Table 12.

Results for the PD-L1 based subgroups are provided in Figure 8, Table 11 and Figure 11. As can be observed, outcomes are improved in the PD-L1 positive subgroups; however, significant benefits are observed.

Table 12. CheckMate 649: Patient disposition at the end of the treatment period (all enrolled, randomised and treated patients with PD-L1 CPS ≥5)[41]

	NIVO+CHEMO n (%)	CHEMO n (%)
Patients randomised	[redacted]	[redacted]
Patients treated	[redacted]	[redacted]
Patients continuing in the treatment period	[redacted]	[redacted]
Patients not continuing in the treatment period	[redacted]	[redacted]
Patients continuing in the study	[redacted]	[redacted]
Patient not continuing in the study	[redacted]	[redacted]
Reason for not continuing in the treatment period (discontinuing treatment)		
Disease progression	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]
Death	[redacted]	[redacted]
Adverse event related to study drug	[redacted]	[redacted]
Patient request to discontinue study treatment	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]
Maximum clinical benefit	[redacted]	[redacted]
Poor/non-compliance	[redacted]	[redacted]
Patient no longer meets study criteria	[redacted]	[redacted]
Completed treatment as per protocol	[redacted]	[redacted]
Other	[redacted]	[redacted]
Reason for not continuing in the study		
Death	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]
Other	[redacted]	[redacted]

CHEMO: chemotherapy; CPS: combined positive score; NIVO: nivolumab; PD-L1: programmed death ligand-1.

B.2.6.1.4 Health-related quality of life (HRQoL)

B.2.6.1.4.1 EQ-5D-3L

Mean baseline EQ-5D-3L utility index (UI) scores in all randomised patients were similar in the NIVO+CHEMO ([redacted]) and CHEMO ([redacted]) arms. Patients in the NIVO+CHEMO arm had improvement in mean UI scores at all on-treatment assessments after baseline through Week 103. The mean change from baseline met or exceeded the minimum important difference (MID: ≥ 0.08 points[46]) at Weeks 91, 97, and 103. Patients in the CHEMO arm had improvement in mean UI scores at most on-treatment assessments, with the mean change from baseline

exceeding the minimal important difference (MID) at Week 97. There was a decrease from baseline (worsening) that approached or exceeded the MID for both arms at most follow-up visits.

Mean baseline EQ-5D-3L visual analogue scale (VAS) scores in all randomised patients were similar in the NIVO+CHEMO and CHEMO arms ([redacted]. Overall, the mean EQ-5D-3L VAS scores in all randomised patients increased (improved) over time in both arms. The mean change from baseline in the NIVO+CHEMO arm met or exceeded MID (≥7 points) at all the time points where there were ≥10 patients eligible to respond, starting at Week 85. The mean change from baseline did not meet or exceed the MID for the CHEMO arm.

B.2.6.1.4.2 FACT-Ga

Mean baseline FACT-Ga total scores for all randomised patients were similar for the NIVO+CHEMO [redacted] and CHEMO ([redacted] arms. There was an increase from baseline (improvement) in the mean FACT-Ga scores in both treatment arms at all on-treatment assessments where there were ≥ 10 evaluable patients (through Week 103 for NIVO+CHEMO and through Week 109 for CHEMO).

Mean baseline scores for the gastric cancer subscale (GaCS) for all randomised patients were similar for the NIVO+CHEMO ([redacted] and CHEMO [redacted] arms. Increases in mean score from baseline were observed for both treatment arms, with changes for the NIVO+CHEMO arm meeting or exceeding the MID (≥ 8.2 points[47]) for all time points during the treatment period where there were ≥10 patients, starting at Week 31. Although there were improvements in the CHEMO arm at all the time points during the treatment period, the MID was never met. FACT-Ga plots are presented in [redacted]Figure 9 and **Figure 10.

[redacted]Figure 9. Mean changes in FACT-Ga from baseline - all randomised patients
[redacted]Figure 10. Mean changes in FACT-Ga GaCS from baseline - all randomised patients
[1]Horizontal reference line indicates minimum important difference (MID) in score.

B.2.7 Subgroup analysis

Overall Survival: In a subgroup analysis for all randomised patients with PD-L1 CPS ≥5, OS HRs (95% CIs) for most subgroups favoured (HR <1) NIVO+CHEMO over CHEMO alone (Figure 11), including:

- Region: Asia (HR=0.64), North America (US and Canada; HR=0.67), and ROW (HR=0.74)
- Tumour location: GC (HR=0.66), GOJ (HR=0.84), and OAC (HR=0.78)
- Histology, presence of signet ring: yes (HR=0.71) and no (HR=0.69)
- Lauren classification: intestinal type (HR=[redacted]), diffuse type (HR=[redacted]), mixed (HR=[redacted]), and unknown (HR=[redacted])

- Peritoneal metastases, yes (HR=[redacted]) and no (HR=[redacted])
- Liver metastases, yes (HR=0.63) and no (HR=0.76)
- MSI status: high (HR=0.33), stable (HR=0.73), and not reported (HR=[redacted])
- Tumour cell PD-L1 expression: < 1% (HR=0.75) and ≥ 1% (HR=0.56)
- HER2 status: negative (HR=[redacted]) and not reported (HR=[redacted]).

Note that the HRs for 2 subgroups were > 1.0: Asia (without China): HR = 1.03 (95% CI: 0.58-1.83) and subjects who received prior radiotherapy (HR = 1.34, 95% CI: 0.82-2.20). For these groups, the sample sizes and event counts were small with wide CIs.

Subgroup analyses for the overall population are provided in [redacted]Figure 12, [redacted]Figure 13 and [redacted]Figure 14. These outcomes are broadly supportive of analyses in the PD-L1 CPS ≥5 population.

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 955)		14.4	11.1	0.70	
Age, years	< 65 (n = 552)	14.8	11.0	0.69	
	≥ 65 (n = 403)	14.3	11.2	0.72	
Sex	Male (n = 680)	14.4	10.8	0.67	
	Female (n = 275)	14.4	12.1	0.78	
Race	Asian (n = 236)	16.1	11.5	0.63	
	White (n = 655)	14.0	11.1	0.71	
	Other (n = 64)	9.8	10.6	0.93	
Region	Asia (n = 228)	15.6	11.8	0.64	
	US/Canada (n = 137)	16.8	12.6	0.67	
	ROW (n = 590)	13.6	10.4	0.74	
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79	
	1 (n = 557)	12.6	8.8	0.63	
Primary tumor location	GC (n = 667)	15.0	10.5	0.66	
	GEJC (n = 170)	14.2	13.1	0.84	
	EAC (n = 118)	11.2	11.3	0.78	
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75	
	≥ 1% (n = 230)	16.2	8.8	0.56	
Liver metastases	Yes (n = 408)	13.1	9.8	0.63	
	No (n = 518)	15.5	12.0	0.76	
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71	
	No (n = 814)	15.1	11.3	0.69	
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73	
	MSI-H (n = 34)	Not reached	8.8	0.33	
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71	
	XELOX (n = 454)	15.0	11.0	0.69	

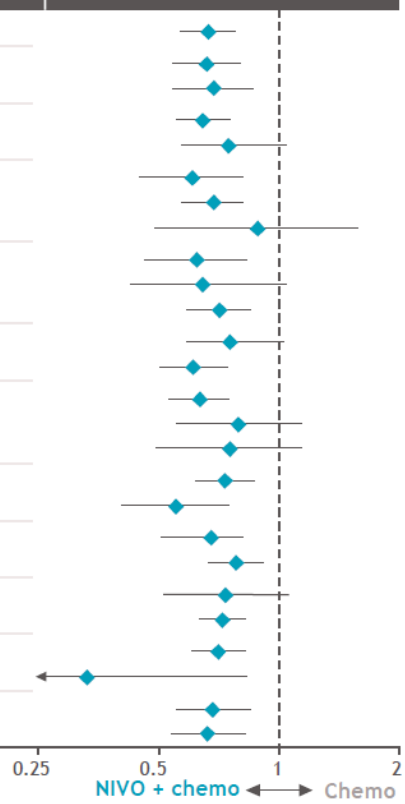


Figure 11. Overall survival subgroup analysis: PD-L1 CPS ≥5[45]

[a]Not reported, n=1; [b]Unknown, n=1; [c]Not reported/invalid, n=75

CI: confidence interval; EAC: oesophageal adenocarcinoma (US abbreviation); ECOG PS: Eastern Cooperation Oncology Group Performance Status; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; GC: gastric cancer; GEJC: gastroesophageal junction cancer (US abbreviation); HR: hazard ratio; MSI: microsatellite instability; MSS: microsatellite stable; MSI-H: microsatellite instability high; OS: overall survival; PD-L1: performance death ligand-1; ROW: rest of world; US: United States; XELOX: capecitabine plus oxaliplatin.

Figure 12. Overall survival subgroup analysis: overall population
Figure 13. Overall survival subgroup analysis: overall population continued

Figure 14. Overall survival subgroup analysis: overall population continued

Progression-free survival: In a subgroup analysis for all randomised patients with PD-L1 CPS ≥5, PFS (primary definition) HRs (95% CI) for most subgroups favoured (HR <1) NIVO+CHEMO over CHEMO, including:

- Region: Asia (HR = [redacted]), North America (US and Canada; HR=[redacted]), and ROW (HR=0.70)
- Tumour location: GC (HR=[redacted]), GOJ (HR = [redacted]), and OAC (HR=[redacted])
- Histology, presence of signet ring: yes (HR=[redacted]) and no (HR=[redacted])
- Lauren classification: intestinal type (HR=[redacted]), diffuse type (HR=[redacted]), mixed (HR=[redacted]), and unknown (HR=[redacted])
- Peritoneal metastases, yes (HR=[redacted]) and no (HR=[redacted])
- Liver metastases, yes (HR= [redacted]) and no (HR=[redacted])
- MSI status: high (HR=[redacted]), stable (HR=[redacted]), and not reported (HR=[redacted])
- Tumour cell PD-L1 expression: < 1% (HR=[redacted]) and ≥ 1% (HR=[redacted])
- HER2 status: negative (HR=[redacted]) and not reported (HR=[redacted]).

Note that the PFS HRs for the following subgroups were > 1.0: Asia (without China): HR = 1.08 (95% CI: 0.61-1.93) and subjects who received prior radiotherapy (HR = 1.61, 95% CI: 0.98-2.66). For these groups, the sample sizes and event counts were small with wide CIs.

B.2.8 Additional studies

B.2.8.1 ATTRACTION-4

B.2.8.1.1 Trial methodology

ATTRACTION-4 (NCT02746796) is a multi-centre, phase II/III trial in HER2 negative patients with previously untreated advanced or recurrent gastric/GOJ cancer, conducted in Asia.[48] An overview of methodology is provided in Table 13.

Table 13. ATTRACTION-4: methodology overview[35,48,49]

	Part 1 (Phase II)	Part 2 (Phase III)
Design	Multi-centre, open-label, randomised study.	Multi-centre, double-blind, randomised, controlled study.
Key eligibility criteria	Adults (≥20 years) with previously untreated, unresectable advanced or recurrent gastric/GOJ cancer that has been histologically confirmed to be adenocarcinoma ECOG performance status of 0 or 1 and measurable disease per RECIST, v1.1 No prior chemotherapy (except neoadjuvant or adjuvant completed >180 days before randomisation) Patients with known HER2 positive status or indeterminate GC were excluded.	
Trial settings	13 centres in Japan and South Korea.	130 sites in Japan, South Korea, and Taiwan.
Intervention	NIVO+CHEMO (SOX or XELOX, randomly allocated 1:1).	NIVO+CHEMO (SOX or XELOX [1:1] chosen in the best interests of the patient).
	Nivolumab 360 mg every 3 weeks. 2 doses counted as one cycle. SOX: oxaliplatin 130 mg/m^2 every 3 weeks and S-1 80 mg/m^2 for 14 days (40 mg/m^2, twice daily), followed by 7 days off. XELOX: oxaliplatin 130 mg/m^2 every 3 weeks and oral capecitabine 2000 mg/m^2 for 14 days (1000 mg/m^2, twice daily), followed by 7 days off.	
Comparator	No comparator.	PBO+CHEMO (either SOX or XELOX, chosen in the best interests of the patient). Placebo administered IV over 30 mins every 3 weeks. SOX/XELOX dosage as above.
Primary objectives	To evaluate the tolerability and safety of NIVO+CHEMO in a HER2 negative population.	To evaluate the efficacy of NIVO+CHEMO versus PBO+CHEMO in a HER2 negative population based on the primary endpoints of IRRC-assessed OS and PFS, and OS.
Secondary objectives	To evaluate the efficacy of NIVO+CHEMO in an exploratory manner in a HER2 negative population.	To evaluate the efficacy and safety of NIVO+CHEMO versus PBO+CHEMO from various perspectives in a HER2 negative population.

CHEMO: chemotherapy; GC: gastric cancer; GOJ: gastroesophageal junction; HER2: human epidermal growth factor receptor 2; IRRC: Independent RECIST Review Committee; NIVO: nivolumab; OS: overall survival; PBO: placebo; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours; SOX: S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin; XELOX: capecitabine plus oxaliplatin.

B.2.8.1.2 Summary of results

B.2.8.1.2.1 Part 1 (Phase II)[49]

Of 40 randomised patients, 39 (NIVO+SOX: 21; NIVO+XELOX: 18) and 38 (21 and 17, respectively) comprised the safety and efficacy populations, respectively. The median age was 62.5 years; 67.5% were male.

Most frequent (>10%) grade 3/4 TRAEs were neutropenia (14.3%) in the NIVO+SOX group, and neutropenia (16.7%), anaemia, peripheral sensory neuropathy, decreased appetite, type 1 diabetes mellitus, and nausea (11.1% each) in the NIVO+XELOX group. No treatment-related deaths occurred. Objective response rate was 57.1% (95% CI: 34.0–78.2) with NIVO+SOX and 76.5% (95% CI: 50.1–93.2) with NIVO+XELOX. Median OS was not reached in both groups. Median PFS was 9.7 months (5.8–NR) and 10.6 months (5.6–12.5), respectively (Figure 15).

In the Phase II trial section of ATTRACTION-4, NIVO+SOX/XELOX was well tolerated and demonstrated encouraging efficacy for unresectable advanced or recurrent HER2 negative gastric/GOJ cancer.

B.2.8.1.2.2 Part 2 (Phase III)[35]

Of 724 patients: 362 received NIVO+CHEMO and 362 received PBO+CHEMO. Baseline characteristics were similar across groups.

At final analysis (31 January 2020), median OS for NIVO+CHEMO of 17.45 months vs 17.15 months PBO+CHEMO was not significant (p=0.257). At interim analysis (31 October 2018), median PFS for NIVO+CHEMO was 10.45 months vs 8.34 months for PBO+CHEMO (p=0.0007), with 1-year PFS of 45.4% and 30.6%, respectively. (Figure 16).

At final analysis, the ORR for NIVO+CHEMO was 57.5% vs 47.8% for PBO+CHEMO (p=0.0088), with a median DOR of 12.91 months and 8.67 months, respectively. Grade 3-4 TRAEs were reported in 57.1% of NIVO+CHEMO patients, compared with 48.6% of PBO+CHEMO patients.

In the Phase III trial section of ATTRACTION-4, NIVO+CHEMO demonstrated a statistically significant improvement in PFS but not OS, with higher overall response rates, more durable responses, and a manageable safety profile.

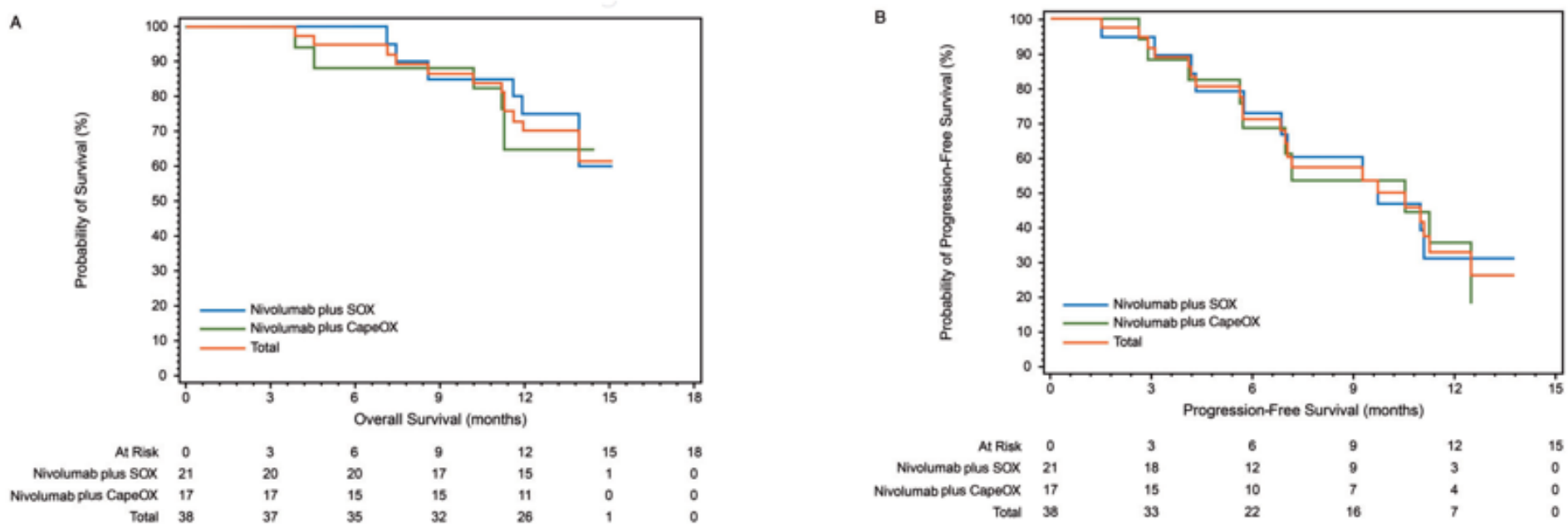


Figure 15. ATTRACTION-4: OS and PFS* in Part 1 (Phase II)

*Kaplan-Meier curves for OS and PFS for NIVO+SOX/XELOX (described as CapeOX in figure)

CapeOX: capecitabine plus oxaliplatin; PFS: progression-free survival; OS: overall survival; SOX: S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin.

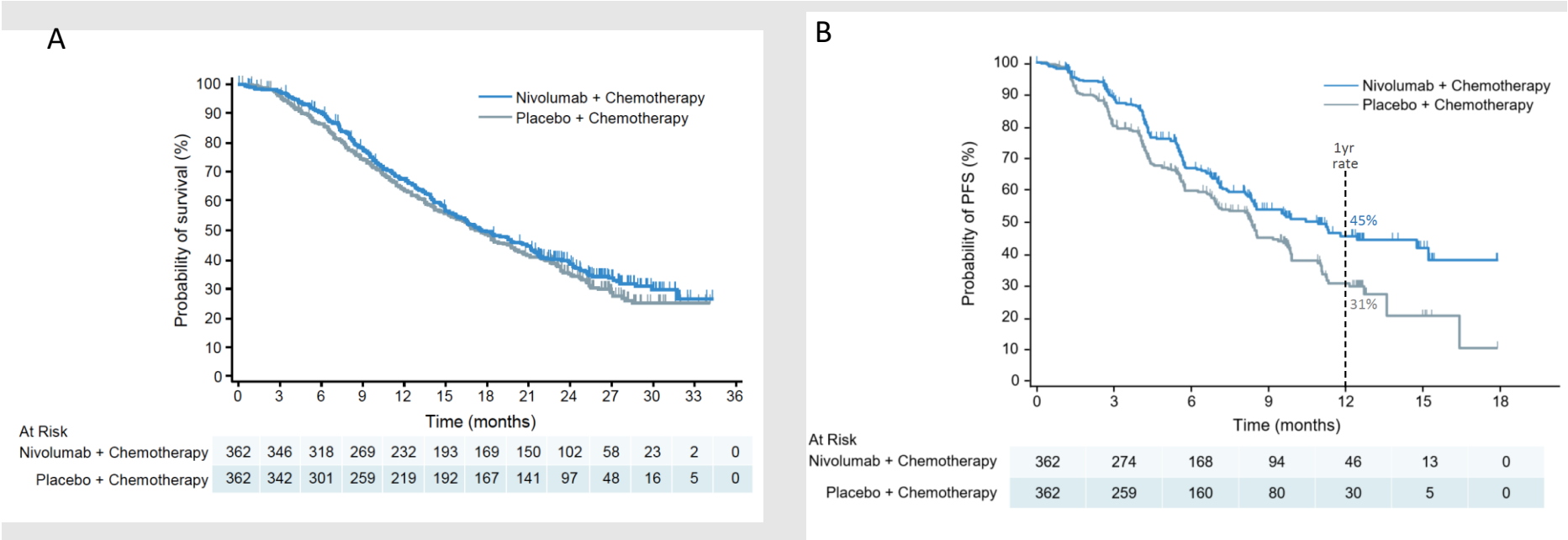


Figure 16. ATTRACTION-4: OS and PFS in Part 2 (Phase III)

A. Overall survival (database lock 31 Jan 2020); B: Progression-free survival (database lock 31 Oct 2018).
PFS: progression-free survival; OS: overall survival.

B.2.9 Meta-analysis

Direct evidence for comparative efficacy of NIVO+CHEMO vs CHEMO may be drawn from the CheckMate 649 study, so that no meta-analysis is required. Indirect treatment comparisons deriving comparative efficacy using CheckMate 649 are presented in Section B.2.10.

B.2.10 Indirect and mixed treatment comparisons

Key points

- The results of the NMA indicate that XELOX/FOLFOX is less effective in terms of extending OS and PFS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab, but more efficacious than 5-fluorouracil + cisplatin.
- Epirubicin-based triplet therapies were not included in the NMA due to lack of published relative efficacy measures. However, clinical advice indicates that epirubicin is not used in the UK for first-line treatment of gastro-oesophageal cancers.

B.2.10.1 Identification of evidence

As described in B.2.1.1, a systematic literature review (SLR) was undertaken to identify the clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of gastric/GOJ cancer/OAC. Full details of the methods and processes employed to identify and select the relevant clinical evidence are summarised in Appendix D. This SLR and associated updates were used to inform the indirect comparison outlined below. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D. An overview of comparator efficacy is shown in Table 14

Table 14. ITC summary inputs

Treatment	Number of studies	Number of comparisons	Median OS (Months)		Median PFS (Months)	
			Minimum reported	Maximum reported	Minimum reported	Maximum reported
FP	10	10	6.6	9.7	3.9	5.5
XP	18	19	7.9	11.8	4.1	7.2
XP or FP	1	2	10.7	11.2	5.4	5.7
FOLFOX	12	12	6.37	14.5	2.24	7.1
CapeOx/XELOX	5	6	6.3	11.3	5.27	7.1
XELOX or FOLFOX	1	1	NR	11.6	NR	NR
ECF	10	10	5	12	NR	7.4
ECX	7	10	6	12.2	5	7.1
EOF	2	2	9.3	9.5	NR	NR
EOX	3	3	8.4	15	4.8	8
Nivo + Chemo	2	2	13.8	17.5	NR	10.5
XP+Trast	3	3	NR	10.6	5.6	6.7
FP+Trast	1	1	NR	14.2	NR	7
XFP+Trast	1	1	NR	14.2	NR	NR

CapeOX: Capecitabine, oxaliplatin; CF = Cisplatin, fluorouracil, CX = Cisplatin, capecitabine; ECF = Epirubicin, cisplatin, fluorouracil; ECX = Epirubicin, cisplatin, capecitabine; EOF = Epirubicin, oxaliplatin, fluorouracil,; EOX= Epirubicin, oxaliplatin, capecitabine; FOLFOX = Fluorouracil, oxaliplatin, folinic acid; FP: Fluorouracil, cisplatin; NIVO: nivolumab; OS: overall survival; PFS: progression free survival; trast: Trastuzumab; XELOX = Capecitabine, oxaliplatin; XFP; Oxaliplatin, fluorouracil, cisplatin; XP: Oxaliplatin, cisplatin.

B.2.10.2 Study Selection for the NMA

Studies used to inform the NMA were identified in a clinical SLR originally performed in 2018 and updated in 2020. The scope of the clinical SLR was wider than for the NMA and therefore articles were screened for inclusion. Articles that reported OS or PFS data for potential comparators of interest were considered for inclusion in the NMA, namely:

Chemotherapy without nivolumab, such as:

- Doublet treatment with 5-fluorouracil or capecitabine plus cisplatin or oxaliplatin
- Triplet treatment with 5-fluorouracil or capecitabine in combination plus cisplatin or oxaliplatin plus epirubicin.

For people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma

- Trastuzumab with cisplatin plus capecitabine or fluorouracil.

Clinical advice indicates that epirubicin is not used in the UK for 1L treatment of gastro-oesophageal cancers,[1] hence it was not used in this analysis.

Of the 136 unique studies that reported either OS or PFS in the SLR, 42 studies reported at least one treatment of interest for this NMA. Studies were restricted to those reporting relative outcomes in the form of HR, or Kaplan-Meier data that could be used to estimate comparative outcomes including at least two potential comparators that could be used to form a network. Studies reporting only absolute outcomes were not considered. Only studies forming part of a complete network including XELOX or FOLFOX were included in the NMA, with XELOX and FOLFOX assumed to have equivalent efficacy in line with assumptions for cost-effectiveness analysis and CheckMate 649 trial design.

In total, four studies[50-53] in addition to CheckMate 649 were identified that could form a complete network. These studies were examined for their suitability for inclusion in terms of population, treatment, inclusion and exclusion criteria, and availability of outcomes. These studies and their prognostic factors are shown in Table 15.

No studies were identified that could incorporate epirubicin-containing triplet regimens in the NMA using relative measures of outcomes. One study was identified that compared an eprirubicin-containing triplet regimen (epirubicin plus FOLFOX) versus FOLFOX.[54] However, limited data were available to inform comparative efficacy and there was a paucity of data to describe the patient population, so that the appropriateness and validity of an NMA considering absolute values could not be assessed. Further, as outlined in Table 14, the efficacy of epirubicin-containing therapies appears similar to doublet regimens. Hence, these therapies are not assessed further.

Table 15: Prognostic factors of patients in studies included in the network meta-analysis from Checkmate 649

	CheckMate 649[41]		Al-Batran et al[50]		Kang et al[53]		Bang et al[51]		Chen et al[52]	
Treatment	**NIVO+CHEMO**	**XELOX/FOLFOX**	**FOLFOX**	**5-fu + cisplatin**	**Capecitabine + cisplatin**	**5-fu + cisplatin**	**Trastuzumab + capecitabine + cisplatin**	**Capecitabine + cisplatin**	**Capecitabine + cisplatin**	**5-fu + cisplatin**
N	789	792	112	108	160	156	298	296	62	64
Dose	Nivolumab 360 mg plus XELOX Q3W or nivolumab 240 mg plus FOLFOX Q2W	oxaliplatin 130mg/m^2 + capecitabine 1,000 mg/m^2 b.i.d. Q3W OR oxaliplatin 85 mg/m^2 5FU 2,800 mg/m^2 Q2W	oxaliplatin 85 mg/m^2 + 5FU 2,600 mg/m^2 Q2W	cisplatin 50 mg/m^2 Q2W 5FU 2,000 mg/m^2 Q1W	capecitabine 1,000 mg/m^2 b.i.d. cisplatin 80 mg/m^2	cisplatin 80 mg/m^2 5FU 800 mg/m^2/day by continuous infusion days 1–5 Q3W	trastuzumab 8 mg/kg cisplatin 80mg/m^2 capecitabine 1,000mg/m^2 b.i.d.[2] 5FU 800mg/m^2	capecitabine 1,000 mg/m^2, b.i.d. cisplatin 80 mg/m^2	capecitabine 1,000 mg/m^2 b.i.d. cisplatin 80 mg/m^2	cisplatin 80 mg/m^2 5FU 800 mg/m^2/day by continuous infusion days 1–5 Q3W
Study Design	Randomised open label		Randomised, multicentre, phase III		Randomised, open-label, phase III, international, multicentre		Randomised, open-label, phase III multicentre, international,		Randomised, open label phase III trial	
ECOG 0 %	[redacted]	[redacted]	NA	NA	NR	NR	NA	NA	NR	NR
ECOG 1 %	[redacted]	[redacted]	NA	NA	NR	NR	NA	NA	NR	NR
ECOG 0-1 %	[redacted]	[redacted]	92.0	89.8	NR	NR	90	91	NR	NR
ECOG 2 %	[redacted]	[redacted]	8.0	10.2	NR	NR	10	9	NR	NR
Med Age	[redacted]	[redacted]	64	64	56	56	59.4	58.5	55.5	55.5
Caucasian	[redacted]	[redacted]	NR	NR	19	19	39	36	0	0
Asian	[redacted]	[redacted]	NR	NR	66	67	51	54	100	100
Hispanic	[redacted]	[redacted]	NR	NR	11	10	NA	NA	NA	NA
African American/ Black	[redacted]	[redacted]	NR	NR	NR	NR	<1	1	NA	NA
Other / Not reported	[redacted]	[redacted]	NR	NR	4	4	9	9	NA	NA

B.2.10.3 Study heterogeneity

The four studies identified were assessed for heterogeneity comparing prognostic characteristics and trial design. Reported patient age, the proportion of patients randomised with ECOG score 0 or 1 and the proportion of Asian patients are presented in **Figure 17, **Figure 18 and **Figure 19, respectively.

Figure 17. Age by study and treatment arm

As can be seen in Figure 17, median age was consistent across all the studies identified that could potentially form a network to include XELOX/FOLFOX, with a mean age across the network of 59 years at baseline and no studies deviating significantly from the overall mean.

Figure 18. Proportion of patients with ECOG performance status 0-1 disease by study and treatment arm

In contrast, when considering ECOG score at baseline (Figure 18) CheckMate 649 enrolled only patients with ECOG 0 or 1, while studies conducted by Al-Batran et al.[50] and Bang et al.[51] also included patients with an ECOG score of 2. As ECOG score is a strong predictor of patient prognosis when treated, this could bias comparisons between XELOX/FOLFOX as assessed in CheckMate 649, as those patients with ECOG score 2 at baseline are likely to experience significantly poorer outcomes. However, more than 90% of patients enrolled in both trials had an ECOG score of 0 or 1, limiting the potential impact of any bias. Additionally, studies conducted by Chen et al. and Kang et al.[53] did not report patient ECOG score at baseline, meaning that it is not possible to assess the extent of any heterogeneity between these trials and other trials included in the network with respect to baseline ECOG score.

Figure 19. Proportion of Asian patients by study and treatment arm

The proportion of Asian patients in each trial was also assessed, as it has previously been established that prognosis for GC is better for Asian than Caucasian patients.[34] There was significant heterogeneity between trials with respect to the proportion of Asian patients randomised, with approximately half of the enrolled patients in studies conducted by Bang et al. and Kang et al.[53] and all patients reported by Chen et al.[52] being of Asian ethnicity in comparison with approximately one quarter of patients in CheckMate 649 (Figure 19). Patient ethnicity was not reported by Al-Batran et al.[50] so no assessment of heterogeneity with respect to ethnicity could be made.

In addition to differences in patient baseline characteristics, the similarity of dosing regimens used in linked treatments was assessed. Table 16 shows the comparator treatments included in each study along with the reported dosing regimen.

In general, dosing regimens for each of the treatments were comparable. For this analysis, XELOX and FOLFOX were assumed to have equivalent efficacy, in line with the results of

CheckMate 649 and their application within cost-effectiveness analysis. The dosing regimen of FOLFOX in CheckMate 649 and Al-Batran et al.[50] were similar, with patients in CheckMate 649 receiving a slightly higher dose of 5-fluorouracil. Dosing regimens of 5-fluorouracil + cisplatin were also generally comparable, with Kang et al.[53] and Chen et al.[52] reporting the same dosing regimen, and Al-Batran et al.[50] reporting higher doses of 5-fluorouracil. Dosing regimens of capecitabine + cisplatin were consistent across all studies, while capecitabine + cisplatin + trastuzumab only used in one study.

Table 16. Reported dosing regimens

Study	XELOX/FOLFOX	5-fluorouracil + cisplatin	capecitabine + cisplatin	capecitabine + cisplatin + trastuzumab
CheckMate 649	oxaliplatin 130 mg/m^2 + capecitabine 1,000 mg/m^2 b.i.d. Q3W OR oxaliplatin 85mg/m^2 5FU 2,800 mg/m^2 Q2W	NA	NA	NA
Al-Batran et al[50]	oxaliplatin 85 mg/m2 + 5FU 2,600 mg/m2 Q2W	cisplatin 50 mg/m2 Q2W	NA	NA
Kang et al[53]	NA	cisplatin 80 mg/m^2 5FU 800 mg/m^2/day by continuous infusion days 1–5 Q3W	cisplatin 80 mg/m^2 capecitabine 1,000 mg/m^2 b.i.d.	NA
Bang et al[51]	NA	NA	cisplatin 80 mg/m^2 capecitabine 1,000 mg/m^2 b.i.d.[2]	trastuzumab 8 mg/kg capecitabine 1,000 mg/m², b.i.d. 5FU 800 mg/m² cisplatin 80 mg/m²
Chen et al[52]	NA	cisplatin 80 mg/m^2 5FU 800 mg/m^2/day by continuous infusion days 1–5 Q3W	cisplatin 80 mg/m^2 capecitabine 1,000 mg/m^2 b.i.d.	NA

b.i.d.: twice a day; FOLFOX: folinic acid, 5-fluorouracil, oxaliplatin; NA: not applicable; Q2W: once every 2 weeks; Q3W: once every 3 weeks; XELOX: capecitabine and oxaliplatin; 5FU: 5-fluorouracil

B.2.10.4 Evidence Network

Combining the four studies from the clinical SLR with the CheckMate 649 data enabled a network to be constructed for OS (Figure 20).

Based on the results of the assessment of heterogeneity between trials, it was decided that all available evidence would be included in the NMA network, as where data were reported,

patient age, ECOG performance status and dosing regimens were comparable. Although there was more heterogeneity in the proportion of patients of Asian ethnicity, all studies excluding Chen et al.[52] had significant non-Asian populations. The robustness of results to the inclusion of the study by Chen et al.[52] is explored in sensitivity analysis. Furthermore, the impact of these differences should be reduced by the decision to only include studies reporting comparative treatment effects, as such the analysis only assumes that trials are balanced with respect to treatment effect modifying covariables, even if significant imbalances in characteristics prognostic of OS or PFS are present. The base case NMA network is presented in Figure 20.

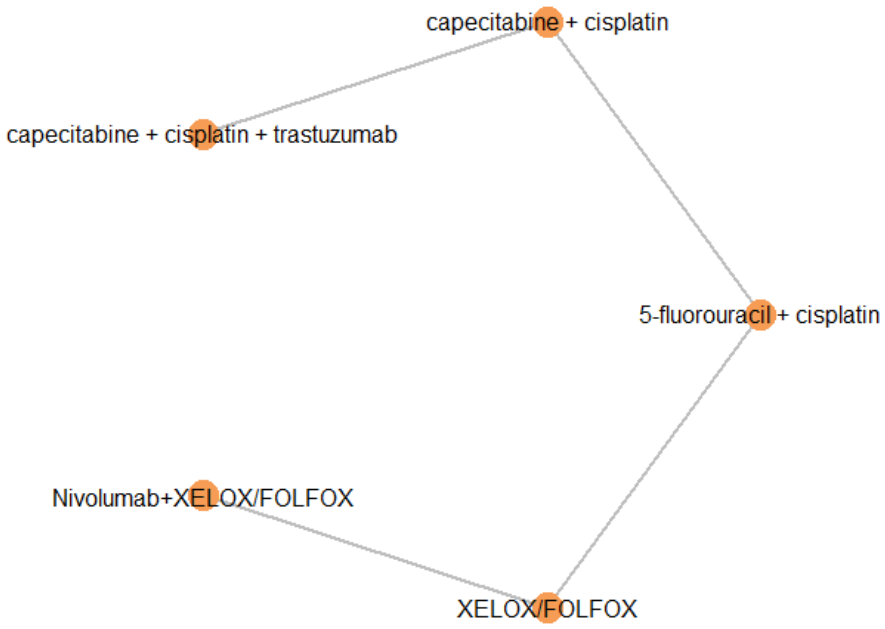


Figure 20: Network Geometry for indirect treatment comparison

The resulting HRs estimated by the model from these networks will be applied to the XELOX/FOLFOX arm of the CheckMate 649 study. This is appropriate because the CheckMate 649 PLD is available, therefore reconstruction does not require assumptions. Methods of Analysis

The Technical Support Document (TSD) 2 outlines methods that can be used to conduct an NMA, which informed the methods used.[55] Additionally, TSD3 was used to support assessments of heterogeneity in line with recommendations by NICE for good practice.[56]The Technical Support Document (TSD) 2 outlines methods that can be used to conduct an NMA, which informed the methods used.[55] Additionally, TSD3 was used to support assessments of heterogeneity in line with recommendations by NICE for good practice.[56]

While an NMA of survival analysis endpoints may often use other method, e.g. fractured polynomials, this was not deemed necessary for this analysis because this is more useful where the proportional hazards assumption is violated. As this is not the case, adopting a more complex approach where unnecessary can add to uncertainty and detract from the usefulness. Therefore, adopting the method proposed in TSD2 for estimating differences with HRs was deemed appropriate. This if further outlined in Section B.2.10.4.2.

B.2.10.4.1 Software Used

To facilitate and validate the inputs to the NMA any available KM data from literature that was to be used in the network were digitised using DigitizeIt Version 2.3.3. Median times for OS and PFS were calculated in R Version 3.5.1 with the Survival package (version 2.43-3) and compared to reported values. Additionally, cox proportional hazard models were used to estimate the hazard ratio (HR) between treatments. For CheckMate 649, as PLD was available, it was used to calculated outcomes and HRs. This practice allowed for validation of the published findings and for the generation of HRs. The HRs were used as the treatment effect input to the NMA.

Where an HR was reported, this value was used. Only if there was no HR reported, the reconstructed value was used. This is because the reported values in the literature were calculated with PLD and are therefore considerably more accurate than HRs calculated with digitised data.

Analysis was run using the BUGSnet R package (1.0.4), a package that has been developed to conduct NMA using the models outlined in TSD 2.[55] The package has been previously published and validated to the examples presented in TSD 2.[57] As the input data was given as HRs, these were log transformed and assessed as continuous outcomes with a normal distribution as recommended. Reference treatments were assumed to have a value of zero on the log scale (i.e. a HR of 1) and assumed to have arbitrarily small standard deviations.

B.2.10.4.2 Model used

A Bayesian approach was taken as this is promoted in TSD 2.[55]

Analysis was run in BUGSnet R using the model outline in TSD2. As the input data was given as HRs, these were log transformed and assessed as continuous outcomes with a normal distribution as recommended.

This model can assume that even if underlying data is skewed, the sample means are approximately normally distributed. The likelihood function can therefore be assumed as:

$$Y_{ik} \sim N(\theta_{ik}, se^2_{ik})$$

This can be directly interpreted so the identify link can be used where the parameter of interest (Θ_{ik}) can used for the linear model directly.

Only studies reporting HRs or allowing a reconstructed estimate of a HR to be generated were included. Although this reduces the number of studies that can be included in the network, it allows simpler assumptions around study homogeneity to be made. Specifically, using relative treatment effects means that the model must only assume homogeneity of treatment effect modifying covariables, and not all variables that may be prognostic of outcome.

Model fit was assessed as directed by TSD 2, with the use of the deviance information criterion (DIC) and examination of residuals.[55] A fundamental assumption of NMA is the assumption of transitivity, or that the difference in the effects between two treatments can be estimated by subtracting the differences relative to a common comparator, as this can only be assessed where closed loops are present within the NMA network, which is not the case in this analysis, no formal assessment of consistency was undertaken.

As nivolumab has a different mechanism of action, survival profile and distribution of events to other arms in the network, a point estimate HR may not be fully capable to describe the time to event in this arm. For example, applying a point estimate HR to fluorouracil + cisplatin to estimate nivolumab would assume the same distribution and would see the “new” nivolumab arm lose the tail that it is known for. As such, XELOX/FOLFOX was used as the standard reference treatment for this NMA, with the comparison between nivolumab plus XELOX/FOLFOX versus XELOX/FOLFOX alone being informed by analysis of individual patient data from CheckMate 649 and not the results of the NMA.

B.2.10.4.3 Choice of model

Both random and fixed effects models were run. This is because of the differing assumptions; namely fixed effect model assume that the treatment effects can be estimated directly from the included population and that it represents the whole population. A random effects model assumes the treatment effects are from a section of the population and that there will be an additional parameter equal to the between-study variance.

In practice, a random effects model is often most appropriate because there will be differences between trials in the interventions, dosing, schedule, population characteristics, treatment mechanisms, and study design. Additionally, the population included is a subgroup of the whole population to consider.

B.2.10.4.4 Assessment of fit

Model fit was assessed as directed by TSD2, with the use of the DIC and examination of residuals.[55]

Given the difference between the studies and populations, it was considered that random effects models may be the more suitable; however, the analysis indicated the fixed effects model to fit best. It is important to note that assessment of heterogeneity is difficult with such low study numbers.

B.2.10.5 Results

B.2.10.5.1 Overall Survival

The base case analysis shows that, in line with all included studies, XELOX/FOLFOX is less efficacious in terms of extending OS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab, but more efficacious than 5-fluorouracil + cisplatin. Treatment with capecitabine + cisplatin + trastuzumab was nominally superior to all other included treatments. Results, displayed as HR and 95% credible intervals, for each treatment and comparator combination are presented in Table 17 for both fixed and random effects analysis. Results for fixed and random effects analysis were consistent.

Goodness of fit and leverage diagnostics are presented in Figure 21. The fixed effects model provided a better fit to the data when assessed through the DIC, and there were no significant outliers in leverage plots for either the fixed or random effects models.

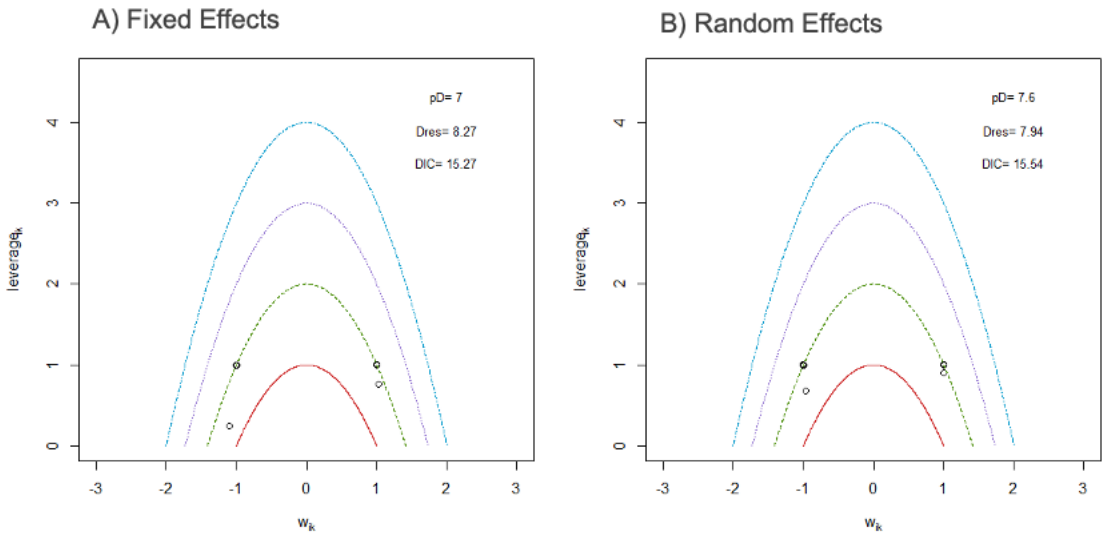


Figure 21. Goodness of fit and leverage diagnostics for overall survival

Table 17. Overall survival results

Data are HR (95% credible interval), with bold values indicating that the credible interval does not include unity.

	Fixed Effects				Random Effects			
Treatment / Comparator	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**
XELOX/FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-FU + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab+ capecitabine + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5-FU: 5-fluorouracil; FOLFOX: folinic acid, 5-FUand cisplatin; XELOX: capecitabine, oxaliplatin.

B.2.10.5.2 Progression free survival

Results for PFS were entirely consistent with those for OS, indicating that XELOX/FOLFOX is less efficacious in terms of extending PFS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab, but more efficacious than 5-fluorouracil + cisplatin. Treatment with capecitabine + cisplatin + trastuzumab was nominally superior to all other included treatments. Results, displayed as HR and 95% credible intervals, for each treatment and comparator combination are presented in Table 18 for both fixed and random effects analysis.

Goodness of fit and leverage diagnostics are presented in Figure 22. The fixed effects model provided a better fit to the data when assessed through DIC, and there were no significant outliers in leverage plots for either the fixed or random effects models. However, both models produced very consistent outcomes for all treatment comparisons.

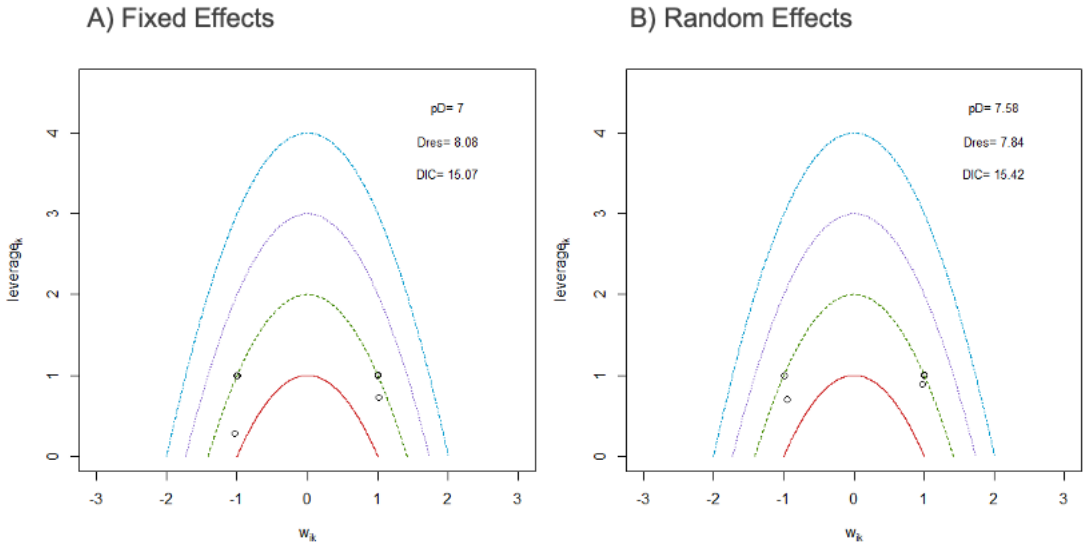


Figure 22. Goodness of fit and leverage diagnostics for progression free survival

Table 18. Progression free survival results

Data are HR (95% credible interval), with bold values indicating that the credible interval does not include unity.

	Fixed Effects				Random Effects			
Treatment / Comparator	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**
XELOX/FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-FU + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab+ capecitabine + cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5-FU: 5-fluorouracil; FOLFOX: folinic acid, 5-FUand cisplatin; XELOX: capecitabine, oxaliplatin.

Results for OS and PFS were consistent with the included studies with capecitabine + cisplatin + trastuzumab showing nominal superiority to all other treatments included in the NMA. Capecitabine + cisplatin was found to be more efficacious than XELOX/FOLFOX, and XELOX/FOLFOX superior to 5-fluorouracil + cisplatin. However, caution should be taken in the interpretation of these results as, with the exception of capecitabine + cisplatin + trastuzumab, the credible intervals around the median treatment effect included one, which in the context of an open network with multiple unconnected comparisons should be regarded as indicative rather than definitive.

B.2.10.5.3 Assessment of heterogeneity

TSD3 describes that the use of vague priors, despite this being the recommendation in TSD2, can result in counter-intuitive or unrealistic heterogeneity parameters. This is a documented issue and TSD3 recommends the use of deviance statistics and knowledge of the inputs studies to determine the most appropriate model.

While the statistical indication of heterogeneity is used to determine the model type used for these analyses, it is recognised that there may be some uncertainty in the values. Qualitative assessment of the included studies, examination of the log cumulative hazard profiles, proportional hazards and the between study variance calculated in the analysis all were used to assess the most appropriate model and the interpretation of results.

The fit statistics indicate that the fixed effects model and its assumptions are suitable. The difference between the model results are minimal, although the random effects model reports much wider credible intervals indicating greater uncertainty.

B.2.10.6 Validation

In order to validate the results of this ITC, derived HRs were applied in the cost-effectiveness model developed for the health economic evaluation of nivolumab in addition to chemotherapy. HRs for each of the included HTA comparators versus XELOX/FOLFOX were applied to the XELOX/FOLFOX arm of the model (as derived from analysis of CheckMate 649 patient data) to estimate median modelled OS. Model output was then compared with median OS reported by individual studies for each relevant comparator;and outcomes are presented in Figure 23.

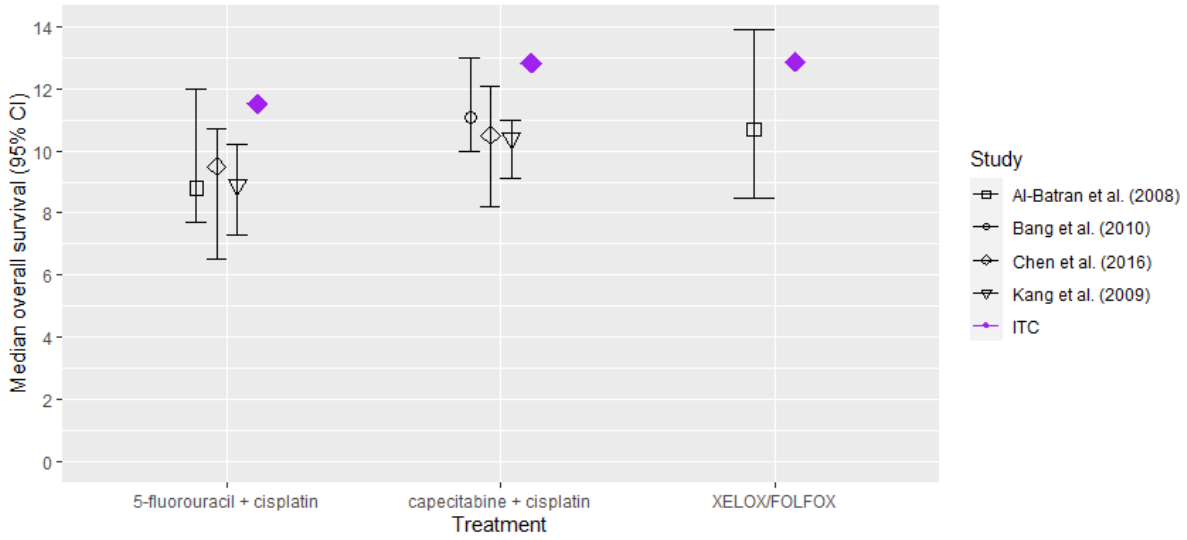


Figure 23. Comparison of model predicted OS based on results of the ITC in comparison with reported OS from individual publications.

Predicted results from the model were generally higher than any of the individual point estimates from the included studies, however all estimations were within 95% confidence intervals reported by each study. Increased survival in the CheckMate 649 population is consistent with expectations, as patients enrolled in the trial had ECOG performance status of 0 or 1, however studies conducted by Al-Batran et al. and Bang et al. also included patients with ECOG performance status of 2, suggesting a poorer overall prognosis for the patients in these trials in comparison with CheckMate 649. Kang et al. and Chen et al. did not report ECOG performance status, however given trial inclusion and exclusion criteria did not exclude patients with ECOG performance status > 1 and the consistency in outcomes between the included trials, it is likely that they also included patients with ECOG scores of 2 or greater. This difference in prognosis is not anticipated to significantly bias the results of this ITC as a result of the decision to only include relative treatment effects, meaning that only imbalances in treatment-effect modifying covariables will bias estimates. With respect to relative treatment effects, the results of the model and ITC are consistent with the findings of the individual studies, capecitabine + cisplatin and XELOX/FOLFOX having comparable survival outcomes, and with both treatments showing nominal superiority to 5-fluorouracil + cisplatin.

B.2.10.7 Conclusions

The results of the NMA indicate that XELOX/FOLFOX is more efficacious than 5-fluorouracil + cisplatin, but less effective in terms of extending OS and PFS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab. However, there are uncertainties due to the limited number of reports that were able to be included into the NMA. Validation of model output based on the ITC showed consistency with included studies with respect to relative treatment effects, and differences in OS are likely due to the inclusion of patients with ECOG performance status > 1 in published studies, in contrast with CheckMate 649.

Given the difference between the studies and populations, it was considered that random effects models may be the more suitable; however, the analysis indicated the fixed effects model to fit best. It is important to note that assessment of heterogeneity is difficult with such low study numbers.

B.2.10.8 Uncertainties in the indirect treatment comparisons

There are several marked limitations of this analysis. Notably, with the exception of the comparison between 5-fluorouracil + cisplatin and capecitabine + cisplatin, only one study informs each comparison, and with no closed loops in the network, uncertainty and heterogeneity in the included studies will be compounded across the network. In addition, without closed loops in the network, no assessment of consistency can be made.

Having only one study to inform a comparison increases uncertainty and relies on the study populations being the same, which is not upheld entirely, particularly with respect to ethnicity and ECOG performance status, where heterogeneity was observed in the included studies. Furthermore, not all studies reported complete patient baseline characteristics meaning the degree of any heterogeneity cannot be assessed. However, these studies were included to enable the inclusion of as many comparators as possible, even if they limit the generalisation of the results.

Finally, the application of a HR derived from this NMA to the outcomes of patients treated with XELOX/FOLFOX in CheckMate 649 assumes the same underlying hazard distribution between the two treatments. It is uncertain how valid this assumption can be considered, particularly given the observed Kaplan-Meier data. It is important to note also that, while median values are available for all the studies, the follow up times are different. This is important because an incomplete or heavily censored KM curve may give a different HR value than if the data were complete.

B.2.11 Adverse reactions

Key points

- Based on available evidence, the safety profile of NIVO+CHEMO in patients with metastatic/advanced gastric/GOJ cancer can be considered manageable and reflective of the known safety profiles of the nivolumab and chemotherapy components.
- This safety profile of nivolumab is well-established based on that observed in other indications.

B.2.11.1 CheckMate 649

Safety data from CheckMate 649 were taken from the 10 July 2020 DBL.

The safety profile of NIVO+CHEMO (nivolumab 360 mg + XELOX Q3W or nivolumab 240 mg + FOLFOX Q2W) in patients with previously untreated advanced or metastatic gastric/GOJ cancer/OAC in CheckMate 649 was manageable and reflective of the known safety profiles of the nivolumab and chemotherapy components.

- No new safety signals or toxicities were identified with NIVO+CHEMO, relative to each agent as monotherapy or in combination.

- Deaths attributed to study drug toxicity were reported in [redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm. Per Investigator assessment in the NIVO+CHEMO arm, [redacted] were due to nivolumab, [redacted] were due to nivolumab and chemotherapy and the remaining [redacted] were due to chemotherapy. In addition, [redacted] attributed as "other" in the NIVO+CHEMO arm were assessed as related to nivolumab per Investigator.

- The overall frequencies of all-causality and TRAEs were similar between the 2 arms; however, frequencies of Grade 3-4 AEs (all-causality and treatment-related) were numerically higher with NIVO+CHEMO compared with CHEMO.

- The frequencies of all-causality and treatment-related SAEs and AEs leading to discontinuation were numerically higher in NIVO+CHEMO compared with CHEMO.

- Select AEs, immune-mediated adverse events (IMAEs) and other events of special interest (OESIs) occurred more commonly in the NIVO+CHEMO arm and the frequency was consistent with that of nivolumab monotherapy. Most select AEs and IMAEs were Grade 1-2, except in the following categories of IMAEs (hepatitis, nephritis and renal dysfunction, and diarrhoea/colitis), in which some IMAEs were Grade 3-4. OESIs occurred at a low rate in both the NIVO+CHEMO arm and chemo arms.

- The safety profile of NIVO+CHEMO across subgroups of age, gender, race and geographic region was generally similar.

- The safety profile of NIVO+CHEMO in treated patients with PD-L1 CPS ≥5 was consistent with the safety profile in all treated patients and reflective of the known safety profiles of the nivolumab and chemotherapy components.

- Laboratory abnormalities (haematology, liver tests, kidney function tests, and electrolytes) were similar and primarily Grade 1-2 in both treatment arms.

B.2.11.1.1 Extent of exposure

Overall, the median (min, max) duration of therapy was [redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm.[41] Among all treated patients, [redacted] and [redacted] had a duration of therapy >6 months in the NIVO+CHEMO and CHEMO arms, respectively. In the NIVO+CHEMO arm, the median (min–max) duration of

therapy was [redacted] months with NIVO+XELOX and [redacted] months with NIVO+FOLFOX.

In the CHEMO arm, the median (min–max) duration of therapy was [redacted] months with XELOX and [redacted] months with FOLFOX. The median (min–max) number of doses received by all treated patients was as follows.

NIVO+CHEMO arm:

- NIVO+XELOX: [redacted]) doses for nivolumab, [redacted] doses for oxaliplatin, and [redacted] doses for capecitabine.
- NIVO+FOLFOX: [redacted]) doses for nivolumab, [redacted] doses for oxaliplatin, [redacted] doses for folinic acid, [redacted] doses for 5-FU bolus, and [redacted] doses for 5-FU continuous.

CHEMO arm:

- XELOX: [redacted] doses for oxaliplatin and [redacted] doses for capecitabine.
- FOLFOX: [redacted] doses for oxaliplatin, [redacted] doses for folinic acid, [redacted] doses for 5-FU bolus, and [redacted] doses for 5-FU continuous.

NIVO+CHEMO arm:

- NIVO+XELOX: [redacted] for nivolumab, [redacted] for oxaliplatin, and [redacted] for capecitabine.
- NIVO+FOLFOX: [redacted] for nivolumab, [redacted] for oxaliplatin, [redacted] for folinic acid, [redacted] for 5-FU bolus, and [redacted] for 5-FU continuous.

Chemo arm:

- XELOX: [redacted] for oxaliplatin and [redacted] for capecitabine.
- FOLFOX: [redacted] for oxaliplatin, [redacted] for folinic acid, [redacted] for 5-FU bolus, and [redacted] for 5-FU continuous.

Extent of exposure to study drugs is shown in Table 19 (NIVO+CHEMO), and Table 20 (CHEMO).

Table 19. CheckMate 649: extent of exposure to study drugs (NIVO+CHEMO)[41]

Variable	NIVO+CHEMO (n=782)							
	NIVO+XELOX (n=360)			NIVO+FOLFOX (n=422)				
	NIVO (n=360)	Oxaliplatin (n=360)	Capecitabine (n=360)	NIVO (n=422)	Oxaliplatin (n=422)	Folinic acid (n=422)	5-Fluorouracil (n=420)	5-Fluorouracil continuous (n=422)
Number of doses received Mean (SD)	[redacted]							
Median (Range)	[redacted]							
Duration of therapy (months) Mean (SD)	[redacted]							
Median (Range)	[redacted]							
Cumulative dose (mg/kg) Mean (SD)	[redacted]							
Median (Range)	[redacted]							
Relative dose intensity (n) > = 110%	[redacted]							
90% to <110%	[redacted]							
70% to <90%	[redacted]							
50% to <70%	[redacted]							
<50%	[redacted]							

CHEMO: chemotherapy; FOLFOX: folinic acid, oxaliplatin and 5-FU; NIVO: nivolumab; SD: standard deviation; XELOX: oxaliplatin and capecitabine.

Table 20. CheckMate 649: extent of exposure to study drugs (CHEMO)[41]

Variable	CHEMO (n=767)					
	XELOX (n=361)		FOLFOX (n=406)			
	Oxaliplatin (n=361)	Capecitabine (n=361)	Oxaliplatin (n=406)	Folinic acid (n=406)	5-Fluorouracil (n=402)	5-Fluorouracil continuous (n=406)
Number of doses received Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of therapy (months) Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative dose (mg/kg) Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity (n) > = 110%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

90% to <110%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70% to <90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% to <70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO: chemotherapy; FOLFOX: folinic acid, oxaliplatin and 5-FU; SD: standard deviation; XELOX: oxaliplatin and capecitabine.						

B.2.11.1.2 Overall adverse events

The overall frequencies of any-grade AEs and TRAEs were similar between the NIVO+CHEMO and CHEMO arms; however, the overall frequencies of Grade 3-4 AEs and TRAEs were numerically higher with the NIVO+CHEMO arm compared with the CHEMO arm.[41]

Adverse Events

Any-grade AEs (regardless of causality) were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most frequently reported AEs were:

- NIVO+CHEMO: nausea [redacted] diarrhoea [redacted] and anaemia [redacted]
- CHEMO: nausea [redacted] diarrhoea [redacted] and anaemia [redacted]

Grade 3-4 AEs (regardless of causality) were reported in [redacted]) patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most frequently reported Grade 3-4 AEs were:

- NIVO+CHEMO: neutropenia [redacted] decreased neutrophil count [redacted] and anaemia [redacted]
- CHEMO: neutropenia [redacted] decreased neutrophil count [redacted] and anaemia [redacted]

When incidence rates were exposure-adjusted, AE incidence rates (per 100 person-years) were [redacted] with NIVO+CHEMO and [redacted] with CHEMO [5% cut-off]. A list of AEs reported in ≥15% of patients is shown in Table 21.

Table 21. AEs reported in ≥15% of patients: CheckMate 649[41]

	NIVO+CHEMO		CHEMO	
	Any grade (%)	**Grade 3-4 (%)**	**Any grade (%)**	**Grade 3-4 (%)**
All-causality SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related SAEs	[redacted]	[redacted]	[redacted]	[redacted]
All-causality AEs leading to DC	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related AEs leading to DC	[redacted]	[redacted]	[redacted]	[redacted]
All-causality AEs	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs (≥15% of patients in any treatment group)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse event; CHEMO: chemotherapy; DC: discontinuation; NIVO: nivolumab; SAEs: serious adverse events; TRAEs: treatment-related adverse events.

B.2.11.1.3 Serious adverse events

The overall frequencies of SAEs (all-causality and treatment-related) were numerically higher with NIVO+CHEMO than with CHEMO.

Any Grade SAEs (regardless of causality) were reported in [redacted] patients in the NIVO+CHEMO arm vs [redacted] patients in the CHEMO arm. Grade 3-4 SAEs were reported [redacted] patients in the NIVO+CHEMO arm and [redacted] patients in the CHEMO arm.

The most frequently reported SAEs (regardless of causality) were:

- NIVO+CHEMO: malignant neoplasm progression [redacted] vomiting [redacted] and anaemia [redacted]
- CHEMO: malignant neoplasm progression [redacted], vomiting ([redacted], and dysphagia [redacted]

Any-grade treatment-related SAEs were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm. Grade 3-4 treatment-related SAEs were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most frequently reported treatment-related SAEs were:

- NIVO+CHEMO: diarrhoea [redacted] pneumonitis [redacted], and febrile neutropenia [redacted]
- CHEMO: vomiting [redacted], diarrhoea ([redacted]), and decreased appetite [redacted]

B.2.11.1.4 Treatment-related adverse events

Any grade TRAEs were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arms.

The most frequently reported TRAEs were:

- NIVO+CHEMO: nausea [redacted] diarrhoea [redacted], and peripheral neuropathy [redacted]
- CHEMO: nausea [redacted] diarrhoea [redacted]), and peripheral neuropathy [redacted]

Grade 3-4 TRAEs were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most frequently reported Grade 3-4 TRAEs were:

- NIVO+CHEMO: neutropenia [redacted] decreased neutrophil count [redacted] and anaemia ([redacted]
- CHEMO: neutropenia [redacted] decreased neutrophil count [redacted] and diarrhoea and vomiting [redacted]

A list of TRAEs with potential immunologic aetiology is provided in Table 22. Grade 3–4 select TRAEs events occurred in ≤ 5% of patients and there were no grade 5 events.[45]

Table 22. TRAEs with potential immunologic aetiology[45]

Select TRAEs[b,c], n (%)	All treated[a]			
	NIVO+CHEMO N=782		CHEMO N=767	
	Any grade	Grade 3-4[d]	Any grade	Grade 3-4
Endocrine	107 (14)	5 (<1)	3 (<1)	0
Gastrointestinal	262 (34)	43 (5)	207 (27)	25 (3)
Hepatic	203 (26)	29 (4)	134 (17)	16 (2)
Pulmonary	40 (5)	14 (2)	4 (<1)	1 (<1)
Renal	26 (3)	6 (<1)	8 (1)	1 (<1)
Skin	214 (27)	26 (3)	105 (14)	6 (<1)

[a]Patients who received ≥1 dose of study drug; Treatment-related select AEs are those with potential immunologic aetiology that require frequent monitoring/intervention; [c]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [d]The most common grade 3–4 select TRAEs (≥ 2%) in the NIVO+CHEMO arm were diarrhoea (n=35), increased aspartate aminotransferase (n=12), and pneumonitis (n=12).
AEs: adverse events; CHEMO: chemotherapy; NIVO: nivolumab; TRAEs: treatment-related adverse events.

B.2.11.1.5 Discontinuation due to adverse events

AEs leading to discontinuation were defined as events when 1 or more study drugs of a multidrug regimen were discontinued, even if the patient remained on treatment or in follow-up. The overall frequencies of all-causality and TRAEs leading to discontinuation were numerically higher in the NIVO+CHEMO arm compared with the CHEMO arm.

Any-grade AEs leading to discontinuation (regardless of causality) were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm (see also Table 8). Grade 3-4 AEs leading to discontinuation were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most common AEs leading to discontinuation (regardless of causality) were:

- NIVO+CHEMO: neuropathy peripheral [redacted] malignant neoplasm progression [redacted] and peripheral sensory neuropathy [redacted]
- CHEMO: neuropathy peripheral [redacted], peripheral sensory neuropathy [redacted] and malignant neoplasm progression [redacted].

Any-grade TRAEs leading to discontinuation were reported in [redacted]) patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm. Grade 3-4 AEs leading to discontinuation were reported in [redacted] patients in the NIVO+CHEMO arm, and [redacted] patients in the CHEMO arm.

The most common TRAEs leading to discontinuation were:

- NIVO+CHEMO: neuropathy peripheral [redacted] and peripheral sensory neuropathy [redacted]
- CHEMO: neuropathy peripheral [redacted] and peripheral sensory neuropathy [redacted]

B.2.12 Ongoing studies

CheckMate 649 is an ongoing study [redacted].

B.2.13 Innovation

Nivolumab is a checkpoint inhibitor immunotherapy agent with an innovative mechanism of action that utilises the body's own immune system to destroy cancer cells (see Section B.1.3.3). In July 2014, nivolumab was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world, and is currently approved in more than 65 countries, including the United States, the European Union, Japan and China.[58] Based on the innovative nature of nivolumab treatment, an application for Promising Innovative Medicine designation in GC was submitted on 10th May 2017, which has since been granted by the MHRA on 10th July 2017 as being a promising candidate for the Early Access to Medicines Scheme (EAMS) in the treatment, diagnosis or prevention of life-threatening or seriously debilitating conditions with unmet need.

Nivolumab is considered by physicians to be a 'breakthrough' in GC treatment, showing the first major survival benefit in non-HER2-positive oesophagogastric cancer for 10 years.[1]

The addition of nivolumab to chemotherapy would change the first-line treatment paradigm for patients with advanced cancer, for whom survival is poor. It can thus be considered a 'step change' in the management of this stage of the disease. The benefits of nivolumab plus chemotherapy include:

- **Improved survival outcomes**: Treatment options for patients with previously untreated advanced or metastatic gastric/GOJ cancer, are limited to chemotherapy alone. The addition of nivolumab to chemotherapy demonstrated a significant extension in OS in all randomised patients compared with standard chemotherapy.

- **Improved health-related quality of life**: As described in Section B.2.6.1.4, HRQoL was improved from baseline with nivolumab plus chemotherapy on both the EQ-5D-3L generic health status measure, and the gastric cancer-specific FACT-Ga health status measure.

- **Manageable toxicity**: The safety profile of nivolumab is well-established based on that observed in other indications.[2] The overall frequencies of any-grade adverse events and treatment-related adverse events following treatment with nivolumab plus chemotherapy were similar to chemotherapy alone. The most common any-grade treatment-related adverse events (≥ 25%) were nausea, diarrhoea, and peripheral

neuropathy across both arms. No new safety signals were identified for nivolumab plus chemotherapy.

- **Additional treatment option**: Current first-line treatment options for advanced or metastatic gastric/GOJ cancer are limited to chemotherapy, with putative side effects and potential lack of efficacy,[21] with only 21.4% alive at one year.[14] The addition of nivolumab to chemotherapy would provide an alternative treatment option, with a different mechanism of action to chemotherapy alone.

The lack of immunotherapy treatment options in this indication has recently been identified as a significant unmet need by UK clinical advisors consulted during this submission process, who consider checkpoint inhibitor immunotherapy to be more efficacious than the current standard of care.

The addition of nivolumab to chemotherapy would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need in the management of this life-threating condition. NIVO+CHEMO represents a new potential standard first line treatment for patients with advanced or metastatic gastric/GOJ cancer.

B.2.14 Interpretation of clinical effectiveness and safety evidence

B.2.14.1 Principal findings from clinical evidence

CheckMate 649 is the largest randomised global Phase III study (N = 1,581 received either NIVO+CHEMO or CHEMO alone) of immune checkpoint inhibitor-based therapies in the first-line (1L) setting for patients with advanced or metastatic gastric/GOJ cancer, and the first global study in over a decade to demonstrate improvement in survival over standard of care therapies in the first-line setting. NIVO+CHEMO has shown a statistically significant and clinically meaningful improvement in PFS and OS versus standard of care chemotherapy (XELOX or FOLFOX) in all randomised patients, and in patients whose tumours expressed PD-L1 CPS ≥5 and CPS ≥1 (Section B.2.6.1.3). The safety profile of NIVO+CHEMO was manageable and acceptable, with no new safety signals identified (Section B.3.3.2.2).

Clinical trial data presented within this submission (CheckMate 649) demonstrates significant survival improvements for patients treated with nivolumab in addition to chemotherapy and demonstrates the novel survival profile associated with immunotherapy agents HR: 0.80 (99.3% CI: 0.68-0.94) (Table 11). The results further demonstrate that the effect of nivolumab in addition to chemotherapy on patients who have responded to the treatment is likely to be sustained for a continued duration (Figure 7). This is in line with the long treatment effect of nivolumab already demonstrated in other indications. Therefore, the clinical significance of nivolumab in prolonging survival and the inhibitory effect on disease progression shown in this study is significant. Although there are reduced patient numbers available in the longer-term follow-up, the CheckMate 649 NIVO+CHEMO arm is observed to have significantly reduced hazard, demonstrating the beneficial impact of this combination therapy.

In addition, a favourable tolerability profile was observed in nivolumab and none of the AEs were detected as a newly identified risk of treatment with nivolumab.

Overall, combination therapy with nivolumab plus chemotherapy offers a favourable benefit-risk profile for patients with previously untreated advanced or metastatic gastric/GOJ cancer.

B.2.14.1.1 Long-term benefits of nivolumab

Prognosis is notably poor for patients with locally advanced or metastatic GC. However, a small proportion of patients demonstrate improved outcomes versus the overall cohort.

Despite receiving standard chemotherapy, it was shown in a UK retrospective study that a small number of patients may survive for a number of years with a proportion of patients surviving past eight years.[16] As can be seen in Figure 24, median OS is 11.48 months and less than 20% of patients remain alive at two years. However, this initial high hazard is observed followed by low hazard from approximately 36 months, so that there are limited events between 48 months and 96 months, despite a median age at diagnosis of 66 years. This indicates the potential for prolonged survival and/or long-term remission in a small proportion of patients.

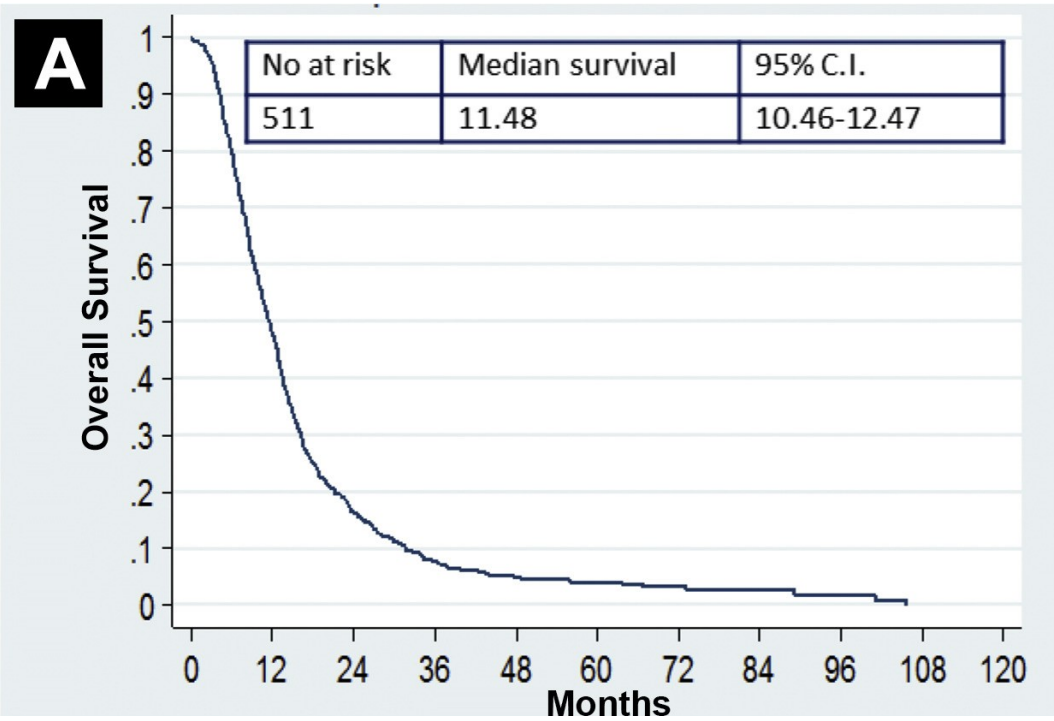


Figure 24. Overall survival for patients receiving chemotherapy for gastro-oesophageal adenocarcinoma at the Royal Marsden Hospital[16]

Another UK-based study, COUGAR-2 demonstrated similar poor median OS with prolonged survival in a small proportion of patients.[59] This randomised, controlled trial assessed docetaxel versus active symptom control in previously treated UK patients with advanced gastro-oesophageal adenocarcinoma. Median OS was 5.2 months in patients receiving

docetaxel and 3.6 months in patients receiving active symptom control. However, a small proportion of patients demonstrated prolonged survival, as illustrated in Figure 25, although this is limited by lack of follow-up.

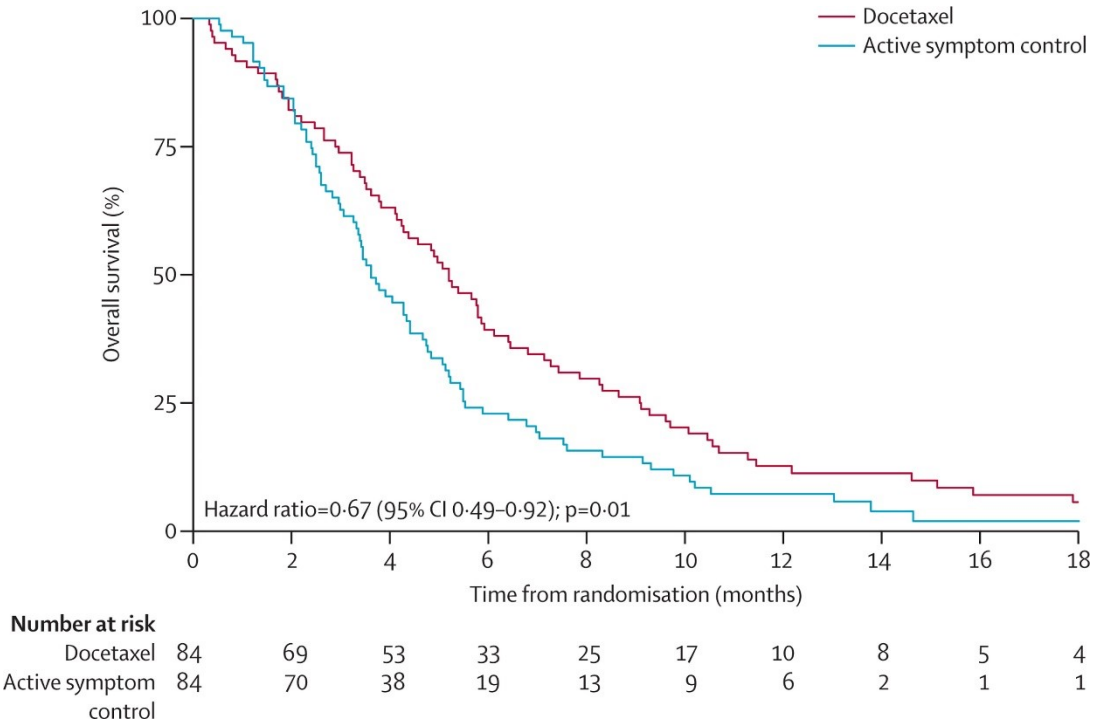


Figure 25. Overall survival during COUGAR-2[59]

A third publication from 4 RCTs assessing fluoropyrimidine ± platinum.based chemotherapy reported a re-analysis of data from 1,775 UK and Australian patients.[60] The median OS was 9.5 months in advanced OAC, 9.3 months in GOJ, and 8.7 months in GC. However, it showed that overall survival is extended to 12 years, with a plateau starting around 3 years (Figure 26).

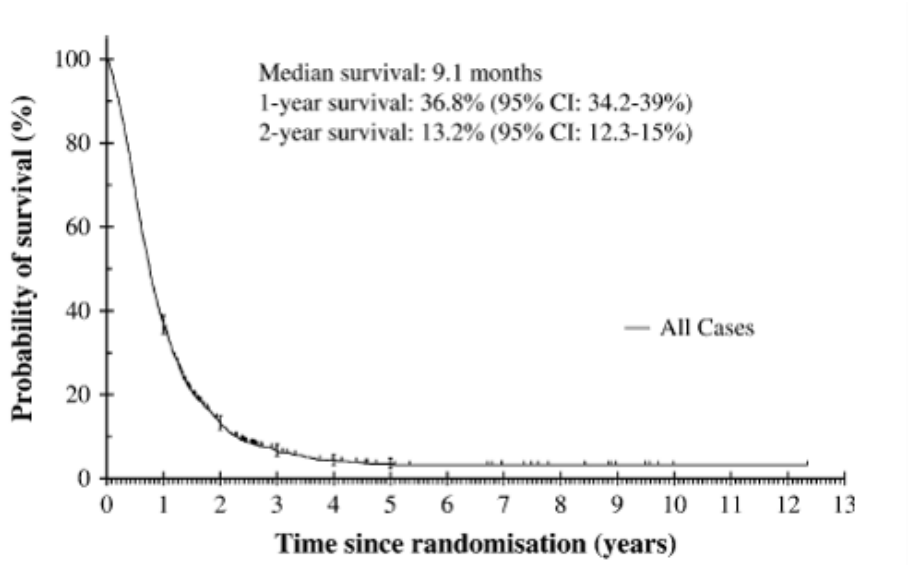


Figure 26. Overall survival from Chau et al.[60]

Similarly, a retrospective observational database study assessed OS in adult patients diagnosed with advanced or metastatic GC, GEJC or oesophageal adenocarcinoma and receiving first line treatment.[61] Median OS from start of first-line therapy was 9.5 months and 14.8% were alive at 24 months. However, a proportion remained alive at five years, indicating some benefit in a small proportion of patients.

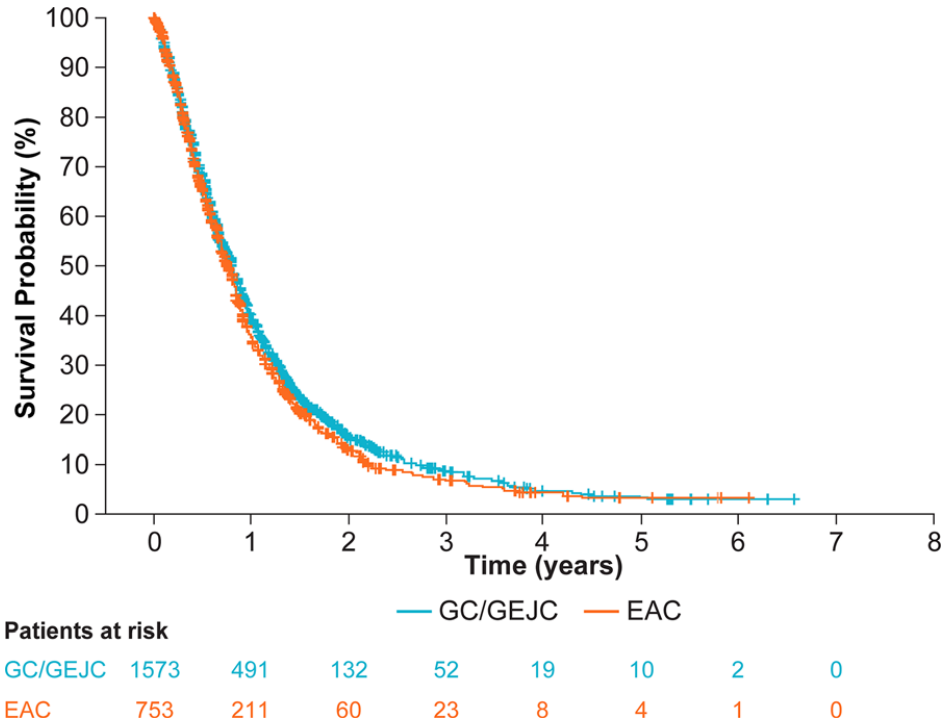


Figure 27. Survival outcomes from start of 1L in patients with adv/met GC/GEJC and adv/met EAC (reproduced from Shankaran et al 2021)[61]

Additionally, the ATTRACTION-2 study, which enrolled Asian GC patients who had previously received at least two prior therapies, reported that 3.2% of patients were alive at two years and 1.6% of patients were alive at three years, indicating that these patients may have a lower long-term risk of death.[62,63] However, this benefit was optimised in the nivolumab arm, with 10.6% of patients surviving at two years[63] and 5.6% alive at three years.[62]

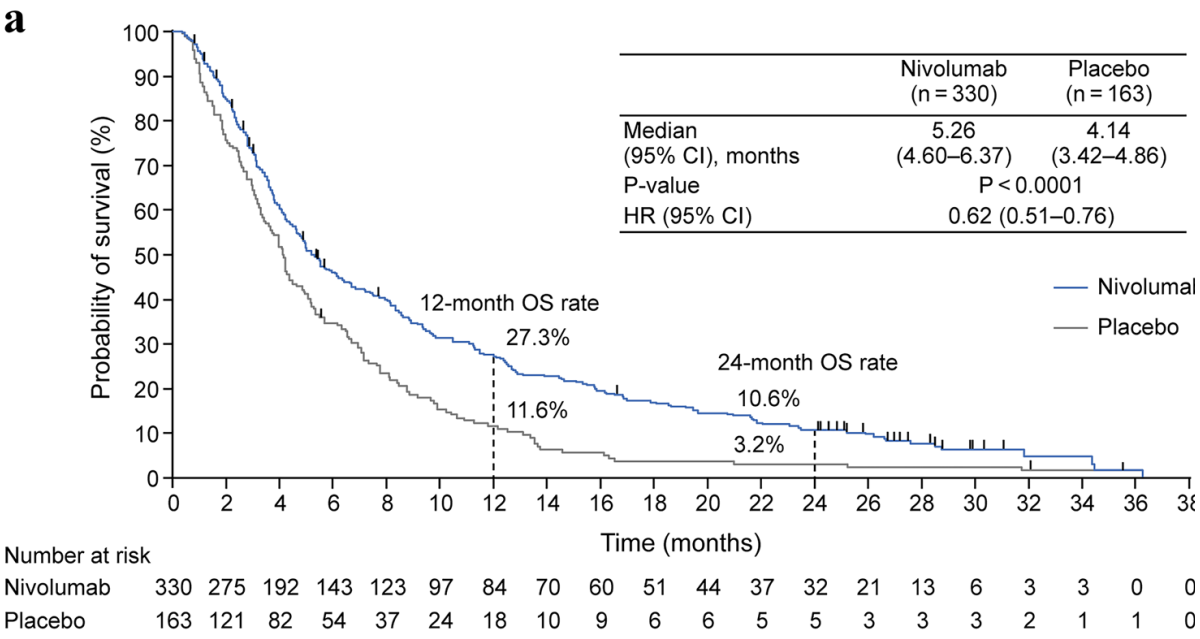


Figure 28. Overall survival outcomes from ATTRACTION-2[63]

Aligned with this evidence, CheckMate 649 reported short median OS (11.6 months) for patients receiving chemotherapy (XELOX/FOLFOX). However, as outlined in Figure 7, a small proportion of patients have prolonged survival, evidenced by very low hazard during the long-term follow-up. Patients receiving standard chemotherapy demonstrated 47.9% OS at one year, [redacted] surviving at two years and [redacted] surviving at three years. The observed Kaplan-Meier data indicate that a proportion of patients may enter long-term remission in clinical practice, with no death events observed following 30 months.

Patients receiving NIVO+CHEMO demonstrated extended median OS benefit (13.8 months versus 11.6 months). However, importantly, the proportion of patients with prolonged survival is increased in the NIVO+CHEMO arm: OS at one year was 55.0% (versus 47.9% for CHEMO), [redacted] at two years (versus [redacted] for CHEMO) and [redacted] at three years (versus [redacted] for CHEMO). These patients with prolonged survival indicate that NIVO+CHEMO increases the proportion of patients entering long-term remission, which can be considered a vital potential benefit for NIVO+CHEMO therapy.

B.2.14.2 Strengths and limitations of study evidence

The main limitations of the clinical evidence base are set out in Section B.2.14.2.1, whilst the strengths are outlined in Section B.2.14.2.2. The limitations should be viewed within the context of both the study strengths and the high unmet need in this patient population.

B.2.14.2.1 Limitations of study evidence

Nivolumab clinical efficacy is informed using the CheckMate 649 pivotal trial and the ATTRACTION-4 phase II/III trial. Inherent limitations within the study designs are:

- **Open-label study design**: The open-label study design of CheckMate 649 means that there is a possibility the knowledge of the treatment might have influenced patient responses with regards to health-related quality of life. However, an open-label design was considered appropriate because of the differences in the dosing regimens and associated toxicities for each treatment group. The primary endpoint of overall survival is an objective measure, which would not be affected by the open-label nature of the study. Furthermore, involvement of an independent data monitoring committee for safety assessments ensured anonymity of the treatment groups during data review.

- **Population of interest**: The two primary endpoints were evaluating benefit in a narrower population of patients than addressed in this submission, i.e., patients with PD-L1 CPS ≥5. However, CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%), and OS and PFS outcomes remained improved in the nivolumab combination therapy arm across the overall population and the PD-L1 ≥ 1 subgroup. [redacted] Reflecting this, the submission contains subgroup analyses for the PD-L1 subgroups; however, the population of interest is the overall population.

B.2.14.2.2 Strengths of study evidence

- **Study design:** CheckMate 649 is a well-designed, Phase III randomised controlled trial which provide direct comparative evidence on the clinically efficacy of nivolumab plus chemotherapy versus chemotherapy alone. The sizes of the patient cohorts were large (789 and 792 patients, respectively). Patient-reported outcome data was collected providing utility estimates which are directly attributable to the addition of nivolumab to chemotherapy. The choice of outcomes (OS and PFS) is appropriate in this patient group.

- **Relevant population**: CheckMate 649 is a study conducted in a study conducted in a patient population relevant to the UK. Of interest, 60.8% of patients were enrolled in locations excluding Asia and the USA, including 38 patients from the UK across 5 participating centres. Additionally, patient characteristics are similar between CheckMate 649 and the UK population, as outlined in Section B.2.14.4. Although data

from ATTRACTION-4 are presented in this submission, this trial is less relevant due to its exclusive enrolment of patients from Asian countries.

- **Relevant comparator:** CheckMate 649 included chemotherapy treatments relevant to the UK setting. FOLFOX and XELOX are considered to the standard therapy for this population. Although 64.1% of patients in ATTRACTION-4 received chemotherapy that would not be considered relevant to UK practice (S-1 and oxaliplatin), this study is presented for completeness only.

- **PD-L1 analyses**: A total of 59.3% of gastric cancers express PD-L1.[28] CheckMate 649 included analyses of PD-L1 CPS ≥5 and ≥1, and found a significant benefit of NIVO+CHEMO in both groups in addition to the overall population. These results increase the relevance of the results to the wider population of patients with gastric/GOJ cancer.

B.2.14.3 Relevance of the evidence base to the decision problem

The submission presents results from a pivotal study evaluating the safety and efficacy of NIVO+CHEMO in patients with previously untreated metastatic or advanced gastric/GOJ cancer, in line with the decision problem. Further, 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.

B.2.14.3.1 Benefits of nivolumab in HER2-positive patients

Per the CheckMate 649 protocol, patients with known HER2-positive status were excluded. Hence, the efficacy data presented in CheckMate 649 does not adequately reflect outcomes in patients with HER2-positive status. However, [redacted] of 1581 randomised patients ([redacted]) did not report HER2 test results, with a further [redacted] reporting that HER2 status was unknown. Those patients where HER2 status was not reported demonstrated [redacted] outcomes for NIVO+CHEMO versus CHEMO ([redacted]) compared with the patients in the HER2 negative subgroup ([redacted]). This indicates that the efficacy of NIVO+CHEMO is maintained in those patients who may have HER2 positive status.

Further, [redacted] CheckMate 649 patients ([redacted] receiving NIVO+CHEMO and [redacted] receiving CHEMO) were subsequently found to have HER2 positive status. Although this is too small to draw conclusions, it is of note that [redacted] patients receiving CHEMO had an OS event ([redacted]), compared with [redacted] patients receiving NIVO+CHEMO.

Additionally, outcomes from CheckMate 649 may be considered representative of outcomes in a HER2 positive population. A recent UK retrospective study demonstrated that the overall response rates in the first line treatment of oesophagogastric cancer were similar between

HER2-positive and -negative patients.[16] However, OS was significantly improved for HER2-positive patients versus HER2-negative patients (15.0 months versus 11.9 months), which may be related to increase use of trastuzumab-based therapies.[16] Similar outcomes were obtained in an Austrian study where median OS was 33 months for a HER2-positive population versus 16 months for a HER-2 negative population.[64]

It should be noted that PD-L1 expression is observed independent of HER2 status. PD-L1 expression is observed in HER2 positive and negative patients;[64] however, the expression of PD-L1 may occur more frequently in HER2-negative patients than HER2-positive cohorts (39.0% vs. 24.2% based on one study).[65]

In summary, there is no data to suggest differential effect of nivolumab in HER2-positive cohort. Available evidence supports equivalent effect between HER2-positive and HER2-negative patients. Despite benefit in HER2 postive patients, it is noted that HER2 testing is standard of care for gastric cancer patients in the UK and it is assumed that patients who test positive for HER2 would preferentially receive a trastuzumab-based therapy instead of nivolumab plus chemotherapy.

B.2.14.4 External validity of study results to patients in routine clinical practice

The proportion of non-Asian patients enrolled in the CheckMate 649 trial was high, thus the study can be considered representative of UK patients in terms of baseline characteristics and disease prognosis. For the same reason, results from the ATTRACTION-4 study conducted on Asian patients was not considered a suitable trial for inclusion in the health economic analyses in this submission.

CheckMate 649 broadly reflects UK patient population outcomes. As can be seen in Table 23, ATTRACTION-4 enrolled a slightly higher proportion of male patients than the Royal Marsden retrospective review[66] and the COUGAR-2[59] clinical study, both of which reflect an exclusively UK population. Baseline age broadly aligned across all sources. Fewer males were enrolled than in previous UK studies, and fewer patients with locally advanced or recurrent disease. Also, a larger proportion of patients enrolled in CheckMate 649 had gastric cancer (70.2%), while other studies enrolled more patients with GOJ cancer or OAC.

However, outcomes were broadly comparable between the chemotherapy arm of CheckMate 649 and other UK studies. Median OS from diagnosis was 11.5 months in the Royal Marsden study,[66] compared with 11.56 months in the chemotherapy arm of CheckMate 649, indicating that outcomes reflect the UK setting.

Table 23. Comparison of CheckMate 649 baseline characteristics versus those from UK-specific studies

		CheckMate 649[41]		Cougar-2[59]		Royal Marsden retrospective review[66]
		NIVO+ CHEMO	CHEMO	Docetaxel	Active symptom control	
N		789	**792**	**84**	**84**	**511**
Sex, male (%)		540 (68.4%)	560 (70.7%)	69 (82%)	67 (80%)	384 (75%)
Median age (range), years		62.0 (18–88)	61.0 (21–90)	65 (28–84)	66 (36–84)	66 (24-90)**
Eastern Cooperative Oncology Group performance status	0	349 (44.2%)	349 (44.1%)	24 (28%)	22 (26%)	64 (13%)
	1	440 (55.8%)	443 (55.9%)	46 (55%)	50 (60%)	276 (54%)
	2	0	0	14 (17%)	12 (14%)	87 (17%)
Disease status	Locally advanced or recurrent	[redacted]	[redacted]	11 (13%)	10 (12%)	68 (13%)*
	Metastatic disease	[redacted]	[redacted]	73 (87%)	74 (88%)	335 (66)*
Site of primary disease	Oesophagus	103 (13.1%)	108 (13.6%)	18 (22%)	15 (18%)	148 (29%)
	Oesophagogastric junction	132 (16.7%)	260 (16.4%)	27 (32%)	32 (38%)	173 (34%)
	Stomach	554 (70.2%)	556 70.2%)	39 (46%)	37 (44%)	190 (37%)

* 21% of patients had relapsed metastatic disease after radical treatment.
** Age at diagnosis, not study baseline

Slightly fewer patients with ECOG status of 1 were enrolled and no patients with ECOG status of 2 were enrolled. Clinical trials commonly specify performance scores as an inclusion criterion, typically based on either ECOG or Karnofsky scale. This leads to limited evidence of net clinical benefit for patients with certain performance scores, typically those with worse scores. This absence of evidence contributes to a reluctance to provide certain treatments to patients of reduced performance score. However, this is limited evidence to suggest different outcomes between patients with different performance score.

A 2017 SLR and meta-analysis of RCTs assessed clinical benefit by performance score subgroups. This identified 110 RCTs, with 66 (60%) reporting performance score subgroups for efficacy and none reporting subgroups for toxicity. For these 66 RCTs, pooled HRs for good performance score and reduced performance score subgroups were 0.65 (95% CI: 0.61-0.70) and 0.67 (95% CI: 0.62- 0.72), respectively, with no difference between the two groups (p=0.68). Sensitivity analyses based on drug or cancer type and type of endpoints (OS or PFS) demonstrated similar results.[67]

B.2.14.5 Application of NICE end-of-life criteria

NIVO+CHEMO in untreated advanced gastric or gastro-oesophageal junction cancer is considered to meet the NICE end of life criteria, as shown in Table 24.

Outcomes are known to be poor in patients with previously untreated advanced and metastatic gastric/GOJ cancer/OAC, with one-year survival rates of only 21.4% for metastatic disease.[14] Similar poor outcomes were seen in a retrospective review conducted by the Royal Marsden,[59] which reported median OS from diagnosis of advanced disease of 11.5 months. Both of these estimates correspond closely to the median OS seen in the chemotherapy arm of CheckMate 649 (see Table 24). Additionally, the results from the ITC support those results (Table 14).

These patients have very limited treatment options, with chemotherapy regimens currently the only options offered to UK patients who do not have HER2 positive disease. Existing comparator survival rates are poor in this population as can be seen in Table 14 where the maximum reported median OS was 14.5 months with FOLFOX.

NIVO+CHEMO produced a median survival gain of 2.27 months during CheckMate 649, which can be considered clinically meaningful in the context of the poor prognosis typically observed in this patient population. When survival outcomes were extrapolated for economic modelling, NIVO+CHEMO had a mean survival gain of 9.2 months. Thus, there is a high degree of unmet medical need in this end-of-life patient population, which would be addressed by the availability of NIVO+CHEMO.

Table 24. End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• One-year net survival in the UK is 21.4% at Stage 4.[15] • Median overall survival in the chemotherapy arm of the CheckMate 649 study was 11.56 months; one-year survival was 47.9%. • Royal Marsden retrospective review[59]: median OS 11.5 months	Section B.1.3.1, B.2.6.1.3 and B.2.14.4
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• NIVO+CHEMO was associated with a median OS of 13.83 months (95% CI: 12.55-14.55), compared with 11.56 months (95% CI: 10.87-12.48) months for current treatment (i.e., chemotherapy alone), indicating substantial survival benefit based on observed data. The OS data from the trial remain immature, but the extrapolation of the current data shows a mean OS of greater than 3 months, with a mean survival gain of 9.2 months predicted by model outputs.	Section B.2.6.1.3

CHEMO: chemotherapy; ITC: indirect treatment comparison; NHS: National Health Service; NIVO: nivolumab; OS: overall survival; SLR: systematic literature review

B.3 Cost effectiveness

Base case analysis

- Use of NIVO+CHEMO will result in an increased mean OS of [redacted] years versus CHEMO alone, as well as additional discounted QALYs and life years of [redacted] and [redacted], respectively.
- Discounted incremental costs were estimated to be [redacted] versus FOLFOX and [redacted] versus XELOX under base case assumptions and the resultant ICER was £47,840 per QALY versus FOLFOX and £45,172 per QALY versus XELOX, which is considered to be cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Sensitivity analysis

- In the deterministic and probabilistic sensitivity analyses, NIVO+CHEMO was cost-effective in the majority of scenarios at a willingness-to-pay threshold of £50,000 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 majority of ICERs remain below the £50,000 per QALY threshold.

B.3.1 Published cost-effectiveness studies

In line with the NICE Guide to the methods of technology appraisal 2013[68], an SLR was conducted to identify cost-effectiveness studies for the treatment of gastric/GOJ/OAC cancer. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) were conducted in March 2018, and subsequently updated in August 2019 and October 2020. Publications describing full economic evaluations of interventions aimed at managing previously untreated advanced or metastatic gastric/GOJ/OAC cancer were included. Full details of the process and methods to identify and select the relevant cost-effectiveness evidence, including PRISMA diagrams, are provided in Appendix G.

B.3.2 Economic analysis

The economic case presented in this submission is based on conventional cost-utility analysis, assessing the use of nivolumab plus chemotherapy versus chemotherapy alone for the treatment of previously untreated advanced or metastatic gastric/GOJ/OAC cancer, taking into account a simple discount in the form of a patient access scheme (PAS) for nivolumab.

A semi-Markov model structure was adopted due to the requirement to incorporate the impact of both time, and duration of progression, on the likelihood of death. Initially, a partitioned survival approach was also considered, however, partitioned survival models effectively preclude explicit consideration of the influence of time since progression on survival and so were not considered further.

The structure of the model was able to capture all important aspects of gastric cancer and the expected benefits of NIVO+CHEMO, including delayed progression, improved survival and benefits to HRQoL. The model also includes the impact of introducing a long term remission health state to capture the long plateau in the OS curve seen in both arms of the CheckMate 649 trial which can be indicative for a mixed population with a small "low-risk" fraction. The long term remission health state captures those patients still progression-free after a specified period of time and applies general population mortality rates instead of disease-specific mortality.

B.3.2.1 Patient population

The economic evaluation considers the use of [redacted], 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 649,[41] as detailed in Table 25.

Table 25. Baseline parameters

Parameter	Mean	SE	Source
Base case analysis			
Baseline age, years	60.3	12.0	CheckMate 649[41] patient-level data
Proportion of cohort male, %	68.4%	30.8%	
SE: standard error.			

B.3.2.2 Model structure

A semi-Markov model was developed with 4 health states. All patients entered the model in the progression-free survival state and remained there until death, progression or until they moved into the long term remission health state (Figure 29). Subsequent possible transitions in the model are illustrated by the arrows in and will be determined by the transition probabilities. The transition probabilities were derived from statistical analysis of the Checkmate 649 clinical trial data.[41] These health states reflect disease severity and determine use of healthcare resources, health-related quality of life and mortality rates. To reflect the nature of gastric cancer and available evidence, the model assumes that gastric cancer phases are consecutive, which means patients are not able to revert to pre-progression from more advanced phases of the disease.

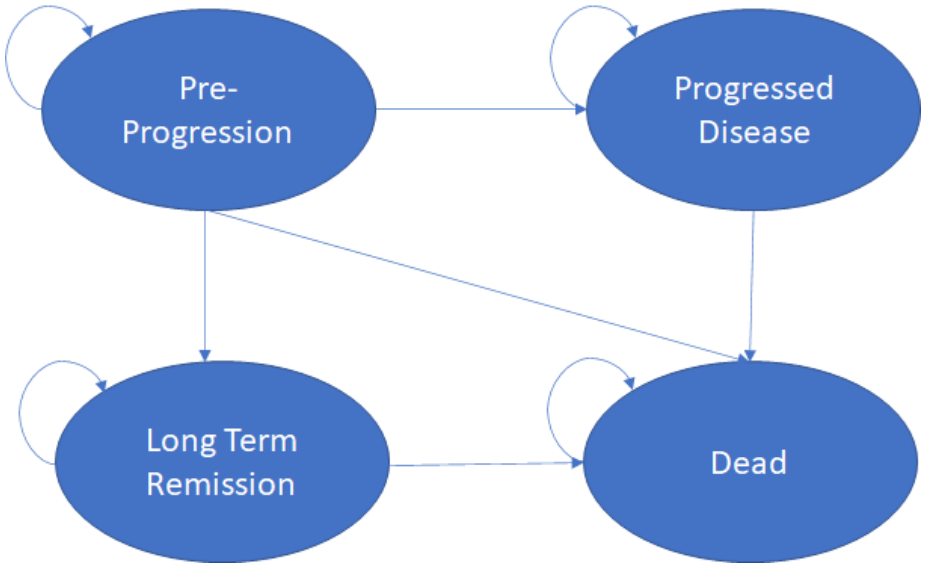


Figure 29. Base case Markov model with 4 health states

The model was designed to capture the relevant benefits of treatment with NIVO+CHEMO and represent improvements in PFS, OS and health utility as observed in CheckMate 649.

Using a fortnightly cycle length, the model predicts the proportion of the population who experience a progression or death event. Fortnightly cycles were considered appropriate for this evaluation because it enables the model to reflect the timings of drug administrations associated with both nivolumab and comparator therapies. Fortnightly cycles further capture a realistic minimum time during which the symptoms or responses can change in UK clinical practice.

Half-cycle corrections are not required in economic models where the cycle length is short and where treatment costs are applied at specific intervals. The economic model has a weekly cycle length, which can be considered fairly short. Additionally, treatment costs are applied every two to three weeks. Hence, a half-cycle correction is not required in the economic model.

The clinical inputs informing progression through the model include PFS, the likelihood of death upon progression and overall survival post-progression (OSPP):

- PFS (Primary objective of CheckMate 649): The time-dependent likelihood of investigator-assessed progression (where time is measured from the start of the trial period)

- Death on progression (Component part of primary objective of CheckMate 649): The time-dependent likelihood that a BICR-assessed progression event results in death (where time is measured from the start of the trial period).

- OSPP (Component part of primary objective of CheckMate 649): The time-dependent likelihood of death from the progressed health state (where time is measured from the incidence of progression, i.e., time is measured as the duration of progression)

Time on treatment (ToT) survival curves were used to determine the duration of treatment, in addition to the treatment stopping rule applied in CheckMate 649 and reflected in the SmPC.

These values were calculated from the individual patient data (IPD) in CheckMate 649 for the NIVO+CHEMO and base case comparator arms. Further inputs were taken from the indirect treatment comparison (ITC). External sources for these values were used to calibrate and validate those values used in the model.

To determine the transition of patients from PFS to long term remission, it was assumed that all patients progression-free at a set timepoint could be classified as in long term remission (Table 26).

Table 26. Long term remission parameters

Parameter	Mean	SE	Source
Intervention arm (NIVO + CHEMO)			
Proportion of patients moving to long term remission	100%	NA	All patients in pre-progression at 30 months are assumed to move to long-term remission
Time (weeks)	130*	NA	
Control arm (CHEMO)			
Proportion of patients moving to long term remission	100%	NA	All patients in pre-progression at 30 months are assumed to move to long-term remission
Time (weeks)	130*	NA	
SE: standard error. **equivalent to 30 months*			

B.3.2.2.1 Rationale for inclusion of long-term remission

As outlined in Section B.2.14.1.1, despite poor prognosis for the average patient, a small proportion of patients with locally advanced or metastatic GC demonstrate improved outcomes versus the overall cohort. This effect is demonstrated in several studies of patients receiving standard chemotherapy or symptom control.[16,59,62,63] Further, it has been demonstrated that this proportion of patients is increased in patients receiving nivolumab.[62,63]

CheckMate 649 patients receiving NIVO+CHEMO demonstrated the same reduction in long-term hazard observed in patients receiving standard chemotherapy, with no death events observed following 30 months. However, importantly, the proportion of patients with prolonged survival is increased in the NIVO+CHEMO arm: OS at one year was 55.0% (versus 47.9% for CHEMO), [redacted] at two years (versus [redacted] for CHEMO) and [redacted] at three years (versus [redacted] for CHEMO). These patients with prolonged survival indicate that NIVO+CHEMO increases

the proportion of patients entering long-term remission, which can be considered a vital potential benefit for NIVO+CHEMO therapy.

In support of this, analysis of CheckMate 649 data indicates that modelling of long-term remission may be the most accurate way of capturing this change in hazard profile, which is observed in both treatment arms. Figure 30 demonstrates that there are [redacted] PFS events by 18 months in the NIVO+CHEMO arm, but only [redacted] events between 24 months and 30 months, with [redacted] events in the subsequent six months. Similarly, in the CHEMO arm, there are [redacted] events by 18 months, followed by [redacted] events in the subsequent 12 months. This rapid change in hazard profile can be difficult to model, particularly with few events in the tail. Figure 31 demonstrates a similar profile in the OS Kaplan-Meier. In the NIVO+CHEMO arm, there were [redacted] events by 24 months, with only [redacted] events in the subsequent 12 months. Similarly, in the CHEMO arm, there were [redacted] events by 24 months with only [redacted] events in the subsequent 12 months. For both treatment arms and both outcomes, there were very few events after month 30.

When exploring the hazard profiles (Figure 32 to Figure 35), the sharp change in hazard can be observed across all treatments and outcomes. However, it is of note that this change of hazard cannot be adequately described by standard spline models. Table 27 discusses potential approaches to modelling the data, and the potential impact of each approach.

Table 27. Potential approaches to modelling data

Approach	Comments
Parametric functions	Unable to characterise the hazard profile in the tail of the data
Semi-parametric functions	Models with sufficient data to inform secondary parameters (shape) do not conform well to observed tail; models limited to the tail have insufficient data to inform secondary parameters
Spline functions	Smooth characterisation of hazard of observed data, but extrapolation only dependent on gradient considerations, not statistical plausibility
Mixture cure model with long-term remission state	Characterises the data and provides rationale for long-term survival outcomes

In view of the clinical setting and the observed data, a long-term remission state is the most appropriate method for capturing the long-term outcomes for patients with locally advanced or metastatic GC.

[redacted]

Figure 30. CheckMate 649 BICR-assessed PFS

[redacted]

Figure 31. CheckMate 649 OS

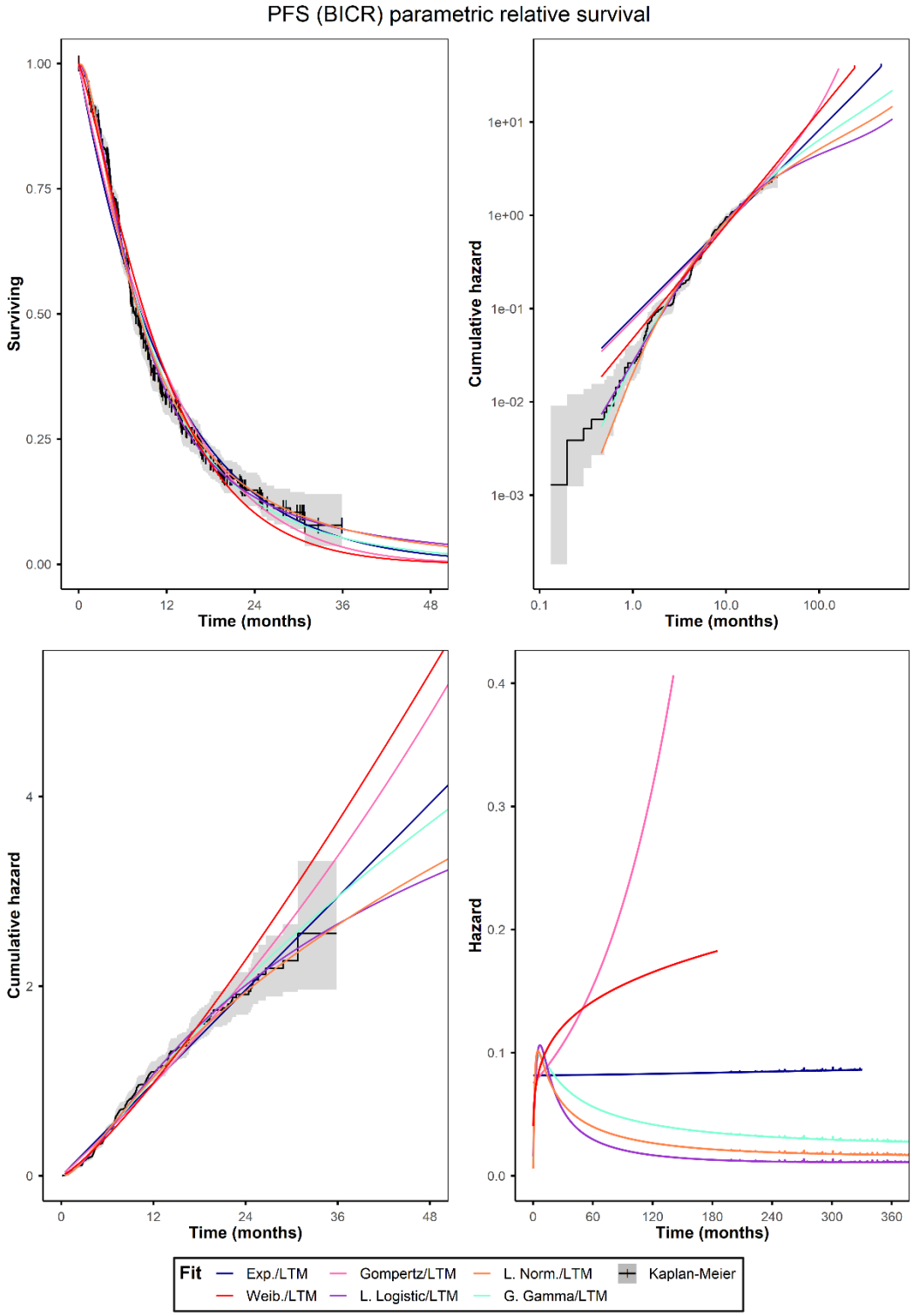


Figure 32. CheckMate 649 NIVO+CHEMO BICR-assessed PFS hazard profile

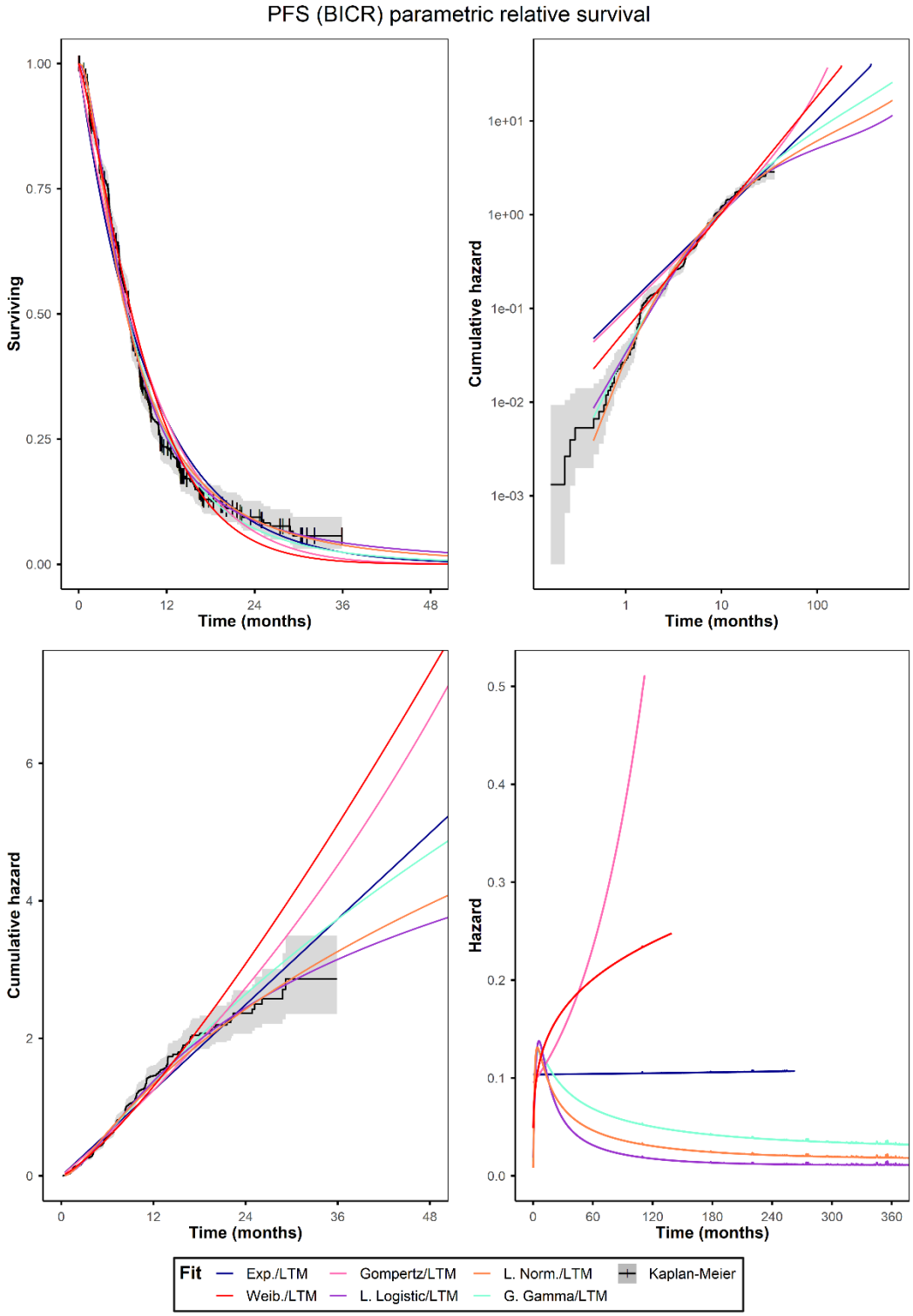


Figure 33. CheckMate 649 CHEMO BICR-assessed PFS hazard profile

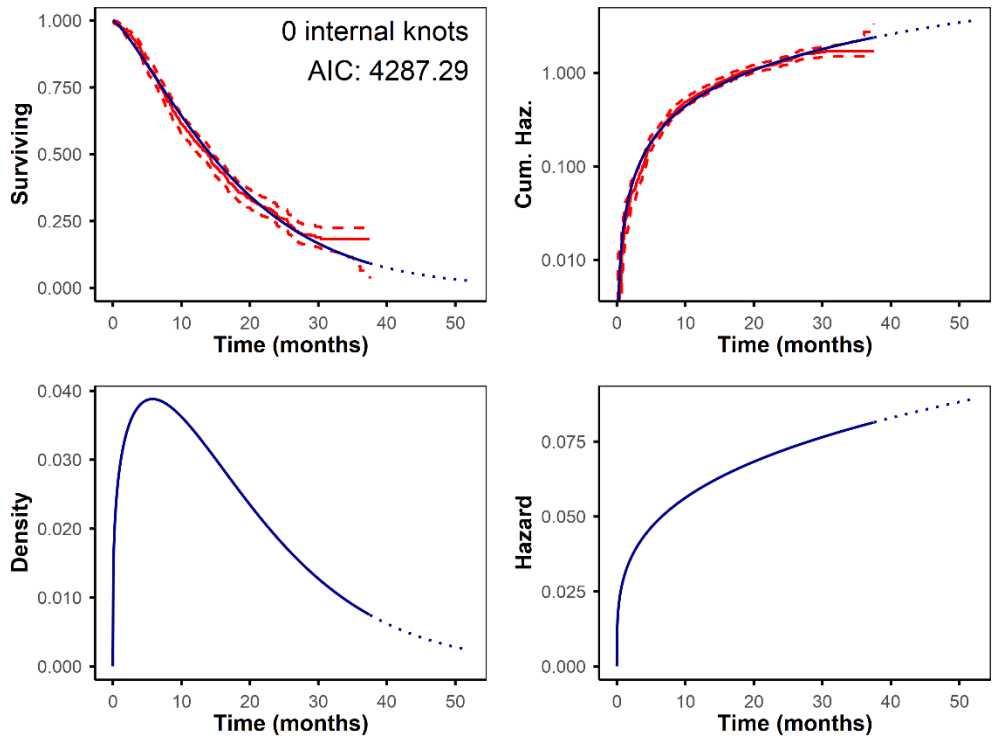


Figure 34. CheckMate 649 NIVO+CHEMO OS hazard profile

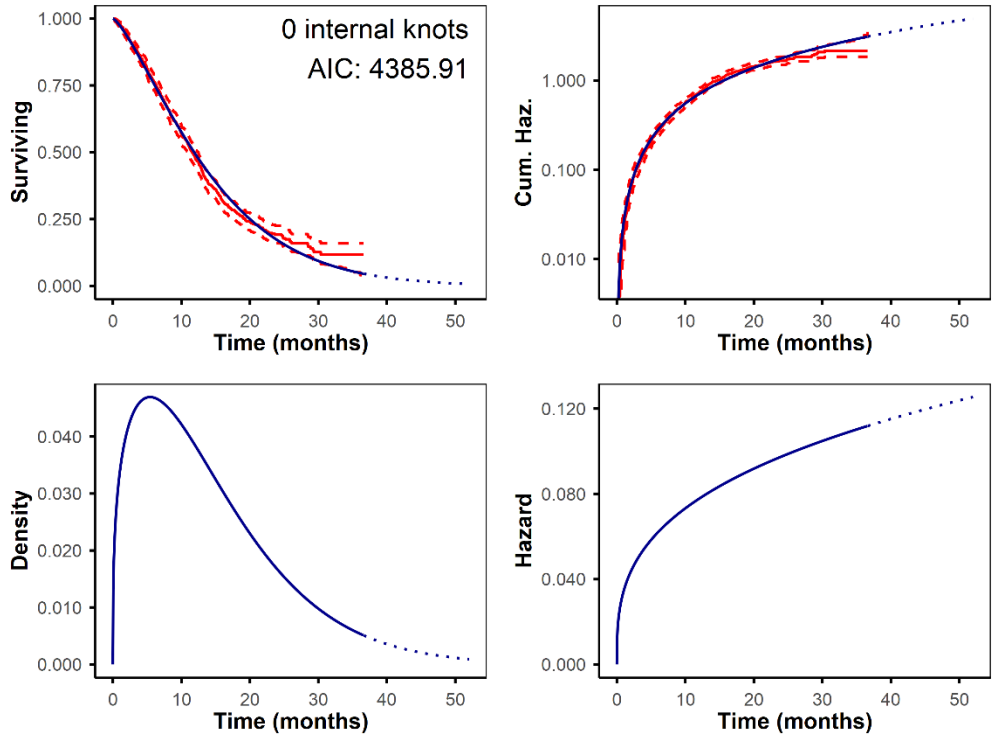


Figure 35. CheckMate 649 NIVO+CHEMO OS hazard profile

B.3.2.2.2 Derivation of health state occupancy estimates

Health state occupancy is defined by treatment specific PFS and overall survival post-progression (OSPP) extrapolations, alongside treatment specific estimates of death at the point of progression. Derivation of these estimates from available data are described in Section B.3.3.1.

In brief, patients remain in the progression-free health state based on transition probabilities derived from the PFS extrapolations. Upon the incidence of progression, patients are stratified in to progressed and death health states based on the time- and treatment-dependent probability of death on progression. Subsequently, patients that have progressed and did not die immediately upon progression may transition to the death health state based on transition rates derived from OSPP extrapolations that depend on the duration of progression.

As these survival data implicitly include the effects of any subsequent treatment that may have been administered, the need to explicitly incorporate the survival effects of these subsequent treatments is negated.

For NIVO+CHEMO, parametric curves for PFS and OSPP were fitted using patient-level data from the relevant patient cohort in CheckMate 649; methods for deriving these curves are provided in Section B.3.3.1. Estimates for the probability of death upon progression are also derived from patient-level data and take the form of a time-dependent logistic model. Data for relevant comparators is derived from the SLR and ITCs described in Section B.2.10.

B.3.2.2.2.1 Definition of progression events

Conventional anti-cancer therapies typically aim to reduce the tumour burden through disruption of cell proliferation or induction of apoptosis. By contrast, due to their mechanism of action, immuno-oncology therapies demonstrate a varied pattern of response, including the appearance that the tumour has enlarged (which is due to the increased immune cell activity in the tumour environment). This pattern of response is a well-recognised challenge associated with immuno-oncology therapies, and can result in dissociated responses, delayed responses and pseudo-progressions, where patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment.[69]

With this in mind, the cost-effectiveness model was designed such that a proportion of patients may receive treatment with NIVO+CHEMO after progression, in line with observations from CheckMate 649. For the purposes of modelling, progression events were based on BICR-assessed outcomes from CheckMate 649 and were defined as in this study.BICR-assessed outcomes were considered more suitable than investigator assessed outcomes as this was the primary definition for PFS for CheckMate 649. Further, treatment discontinuation related to progression during CheckMate 649 required BICR-based confirmation of progression, so that BICR-assessed outcomes materially impacted on treatment practises during this study. Results for PFS per investigator assessment were consistent with those for PFS per BICR but

were slightly more optimistic.[41] Hence, BICR-assessed PFS was considered the more appropriate basis for modelling in the base case.

B.3.2.2.3 Derivation of treatment line occupancy

Patients enter the model following diagnosis of untreated, advanced, gastric, gastro-oesophageal junction or oesophageal adenocarcinoma and can receive NIVO+CHEMO or a comparator treatment. Following treatment cessation, patients are assumed to receive a final line of therapy, as detailed in Section B.3.3.2.1.1. As a simplifying assumption, it is assumed that patients may not discontinue this final line of therapy and therefore remain on this until death or the end of the modelled time horizon.

In the base case analysis, the proportion of patients on initial or subsequent treatment lines is based on the following criteria:

- Observed time on treatment data as informed by CheckMate 649[41]
- Treatment cessation (where treatment duration is specified, for example in set treatment durations or stopping rules)

B.3.2.2.4 Treatment sequences

Patients enter the model following diagnosis of untreated, advanced, gastric, gastro-oesophageal junction or oesophageal adenocarcinoma and can receive NIVO+CHEMO or a comparator treatment. Following treatment cessation or progression, patients can receive a subsequent therapy (comprising of a one-off cost on the first cycle), as detailed in Section B.3.3.2.1.1; however, as a simplifying assumption, it is assumed that patients may not discontinue this final line of therapy, as it is assumed to include palliative care.

B.3.2.2.5 Outcome measures

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per QALY gained. Additionally, the model provides an overview of other outcomes, such as LYs gained, and clinically relevant outcomes, such as predicted median OS and PFS. An overview of the key features of the economic analysis are provided in Table 19.

Table 28. Features of the economic analysis

Factor	Current appraisal		Previous appraisal
	Chosen values	**Justification**	**TA208[22]**
Time horizon	Lifetime (up to 50 years)	This ensures that all events have occurred, and all patients are accounted for. Also, there is no stopping rule for subsequent treatment therefore they can be considered lifetime interventions.	Lifetime (8 years)
Source of utilities	Checkmate 649 provides EQ-5D-3L data that can be used to derive utility inputs for use in nivolumab and comparator arms.	Checkmate 649 collected utility data using the EQ-5D-3L. In line with the NICE reference case, trial utilities collected as part of Checkmate 649 (baseline and every 6 weeks until the end of the treatment phase and subsequently ever 12 weeks during the follow-up phase) have been applied in the base case analysis for both treatments.	ToGA clinical trial pre-progression. TA179 post-progression
Source of costs	Intervention and comparator costs sourced from electronic market information tool (eMIT) whereas possible (actual price paid by hospitals). Otherwise, as per TA208 (either from the newer version of sources or inflated using PSSRU indices)	TA is relevant to the same population (untreated advanced or metastatic gastric cancer), applying the same values/sources facilitates cross-comparison.	Intervention and comparator acquisition costs, sourced from BNF. Administration costs sourced from NHS reference costs. Monitoring/healthcare resource use costs sourced from PSSRU. Further costs: adverse events, one-off terminal care, HER2 testing.

EQ-5D 3L: EuroQol 5 dimensions quality of life index; HER2: human epidermal growth factor receptor 2; PSSRU: personal social services research unit; TA: technology assessment; ToGA: trastuzumab for gastric cancer trial.

B.3.2.3 Intervention technology and comparators

Based on available NICE guidance, the following would be considered the most appropriate comparators for the present indication [redacted]:

- FOLFOX (5-fluorouracil, folinic acid and oxaliplatin),

- 5-Fluorouracil plus cisplatin
- XELOX (capecitabine and oxaliplatin)
- Capecitabine plus cisplatin
- Fluorouracil plus oxaliplatin plus epirubicin
- Fluorouracil plus cisplatin plus epirubicin
- Capecitabine plus oxaliplatin plus epirubicin
- Capecitabine plus cisplatin plus epirubicin
- Trastuzumab with cisplatin plus capecitabine or fluorouracil

Clinical advisors to this submission confirmed that in cases of inoperable metastatic GC, preferred first-line treatment is FOLFOX or XELOX. Further, clinicians suggest that FOLFOX the preferred treatment as it is generally better tolerated, but XELOX would have benefits in terms of administration. However, it is suggested the choice of therapy would not be impacted by addition of nivolumab (i.e., a patient who would have received XELOX would receive NIVO+XELOX as opposed to NIVO+FOLFOX). As these therapies represent standard of care and there is direct comparative evidence (CheckMate 649), the following comparisons represent the base case analysis:

- NIVO+FOLFOX versus FOLFOX
- NIVO+XELOX versus XELOX

Additional comparators are assessed through scenario analysis using outputs from the ITC described in Section B.2.10. These scenario analysis comparisons are provided for the following comparators:

- Fluorouracil plus cisplatin
- Capecitabine plus cisplatin

However, there is limited evidence to inform comparative efficacy for other comparators. In particular, there is no ITC network that can be formed with the epirubicin-based triplet therapies, due to lack of published relative efficacy measures. Clinical advice indicates that epirubicin is not used in the UK for first-line treatment of gastro-oesophageal cancers, and that recent guidelines have actively removed epirubicin from the treatment options.[1,23] Hence, these comparators cannot be considered relevant to the decision problem. Further, evidence versus trastuzumab combination therapy is subject to several limitations. For this reason, no cost-effectiveness analysis has been undertaken versus this comparator.

B.3.3 Clinical parameters and variables

B.3.3.1 Parameterisation of progression and survival transition rates

B.3.3.1.1 Nivolumab plus chemotherapy

Clinical data to inform NIVO+CHEMO progression and survival transition rates is derived from CheckMate 649. However, follow-up was less than the maximum time horizon of the model;

mean CheckMate 649 follow-up was 13.08 months for the NIVO+CHEMO arm and 11.06 months for the CHEMO arm, which does not align with the lifetime horizon required for the model. Therefore, parametric 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)[70] and Bagust and Beale (2014).[71]

A full description of methods used to undertake parametric extrapolation is provided in Appendix M. In brief, parametric functions that inform survival curves for PFS and OSPP were developed using patient-level data from the NIVO+CHEMO treatment arm of CheckMate 649 based on the 10th July 2020 DBL.[41]

Progression events were based on BICR-assessed outcomes from CheckMate 649 and were defined as in this study. Death events from CheckMate 649 were used to inform survival modelling. Parametric survival functions were fitted to the extracted data using the R statistics environment, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions. Additionally, semi-parametric models were considered, assessing the impact of different split points and subsequent parametric functions. Logistic models were used to estimate the proportion of progression events that resulted in death, informing the cyclic probability of death on progression incidence.

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 to assessment of goodness-of-fit statistics, the appropriateness of the parametric extrapolation was by visual inspection of the fit over the observed period and consideration of the log cumulative hazard plots.

It is worth noting that while the above methods for validating the extrapolation of progression and death events are appropriate, they are also necessarily constrained by derivation from observed data, which is, as previously indicated, limited by the availability of follow-up data. Therefore, the plausibility of the extrapolation was assessed through consideration of the long-term hazard profile and the extrapolated mean survival estimates. Additionally, clinical expert opinion was sought to ensure that the survival extrapolation approach can be considered appropriate.

Kaplan-Meier plots describing PFS and OSPP in the NIVO+CHEMO arm demonstrate a high initial hazard, with a significant number of events occurring quickly after study entry, perhaps reflecting the poor prognosis in this patient population. This was followed by a lower hazard in the longer-term. Parametric models did not adequately reflect this change in hazard for PFS. Hence, for PFS, a semi-parametric approach was considered appropriate as it reflected the high initial hazard but applied the maximuminves amount of data to inform the long-term extrapolation.

Applying Kaplan-Meier data until 6.44 months followed by parametric extrapolation enabled the initial PFS hazard to be modelled appropriately and captured the high rate of events

between study entry and 6 months. Switching to parametric extrapolation from 6.44 months used the maximum number of events to inform long-term extrapolation and describe the lower long-term hazard. This semi-parametric approach was applied for PFS only. In contrast, fully parametric models offered a reasonable representation of the changes in OSPP hazard over time.

In order to model PFS for NIVO+CHEMO, Kaplan-Meier data was applied until 6.44 months followed by parametric extrapolation using the log-logistic distribution to provide an appropriate fit. In contrast, a fully parametric approach was used for modelling OSPP, where parametric extrapolation using the log-logistic distribution was utilised. These approaches were deemed appropriate as they provided an adequate fit to the data.

A full description of methods used to undertake parametric extrapolation is provided in Appendix M. A summary of the selected extrapolation approaches is provided in Table 29.

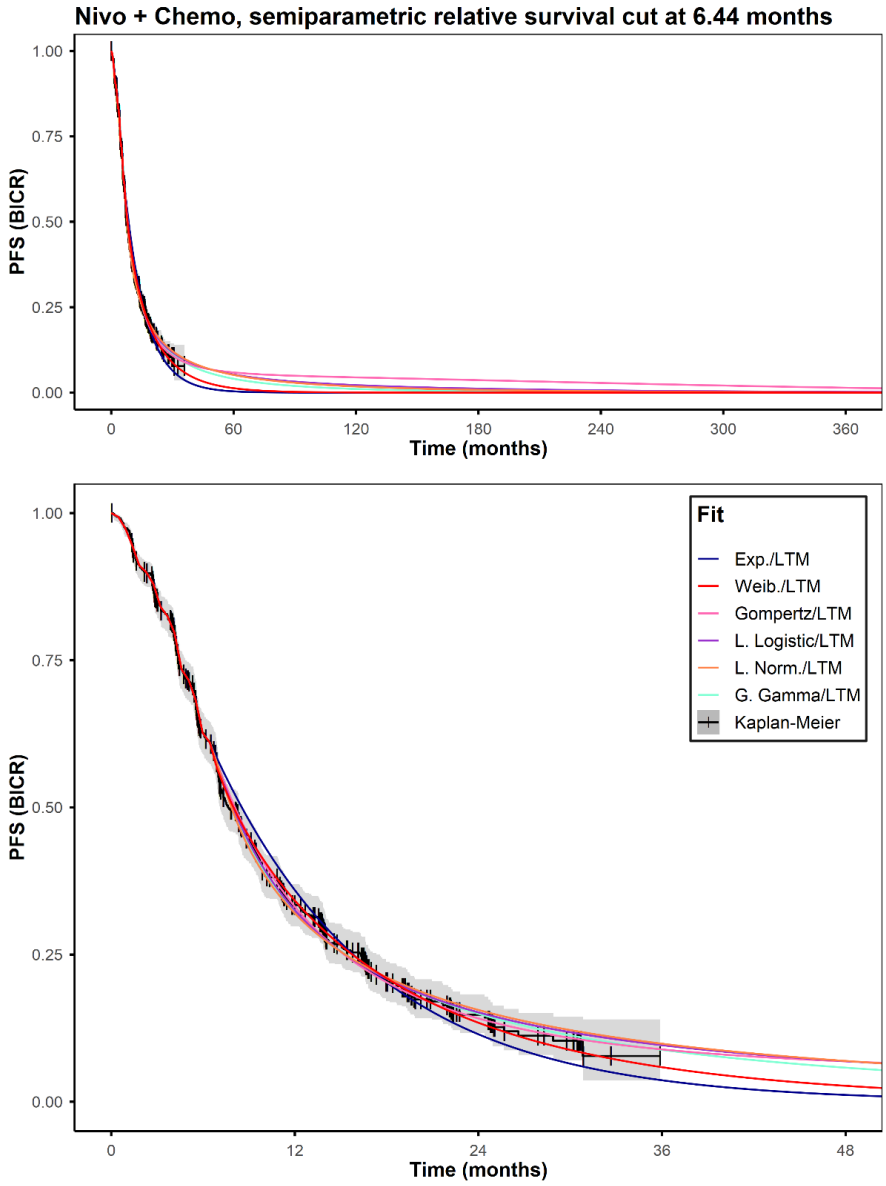
Table 29. Extrapolation of survival outcomes from CheckMate 649 NIVO+CHEMO

	PFS	OS
Extrapolation method	Semi-parametric: Kaplan-Meier to 6.44 months Log-logistic fitting	Fully parametric Log-logistic

B.3.3.1.1.1 Progression-free survival

Standard parametric functions were assessed, as outlined in Appendix M. However, none of the standard parametric functions were capable of approximating the survival function to a suitable degree. Given the expectation of heterogeneity of response to immuno-oncology therapies, alternative models capable of representing this population heterogeneity were sought.

By contrast, models fitted from 6.44 months, as presented in Figure 36 did not deviate substantially from the data and provided a relatively close range of survival extrapolations. Log-logistic, Gompertz, generalised gamma and lognormal survival functions all provided a reasonable fit to the data. The log-logistic function was selected for use in the base case given its decreasing hazard profile, strong goodness of fit profile and observed long-term survival profile, which provided a mean progression-free survival estimate in between those of the Gompertz and generalised gamma profiles.



Fit Name	AIC	BIC	Parameters for excess hazard	All-cause median (Months)
Exp./LTM	1826.12	1830.16	rate: 0.0937	8.84 (8.02, 9.57)
Weib./LTM	1814.26	1822.33	shape: 0.8319; scale: 10.8915	8.20 (7.59, 9.01)
Gompertz/LTM	1812.54	1820.60	shape: -0.0522; rate: 0.1248	8.41 (7.68, 9.06)
L. Logistic/LTM	1811.29	1819.35	shape: 1.0605; scale: 6.4050	8.14 (7.63, 8.87)
L. Norm./LTM	1806.31	1814.38	meanlog: 1.8331; sdlog: 1.6236	7.88 (7.55, 8.74)
G. Gamma/LTM	1807.26	1819.36	mu: 1.9847; sigma: 1.5345; Q: 0.2491	8.00 (7.56, 8.80)

Figure 36. CheckMate 649 NIVO+CHEMO BICR-assessed progression-free survival extrapolation

B.3.3.1.1.2 Death on progression

Upon progression, incident progression events need to be stratified into those characterised by disease progression and those characterised by death. The likelihood of death on

progression is extremely time-dependent with a very high initial hazard. Subsequently, patients that progressed in the first month observed a high likelihood of death upon progression. This initial hazard reduced significantly in the first 2 months and then began to rise again more slowly in the final months of the trial period. Notably, few events were observed in last months of follow-up. The likelihood of death on progression follows a similar pattern in each arm.

Given this event likelihood profile, a number of logistic models were considered. Multiple transformations for time were considered, both independently and within multivariable models, including log and square transformations. A complete breakdown of this methodology and the corresponding results may be found in Appendix M. The final model selected was a logistic model including covariates for time and the natural logarithm of time.

Separate models were fitted to each arm and are presented in Figure 37, with parameterisations described in Table 30. As observed in the figure, the model fit (thin coloured lines) deviates from the smoothed observed value (thick coloured lines). However, this must be considered within the context of the PFS profile where there are few patients left in a progression-free state at the point of deviation (and thus few observed events). Further, both models lie comfortably within the observed confidence intervals, which are naturally large towards the final months of follow-up.

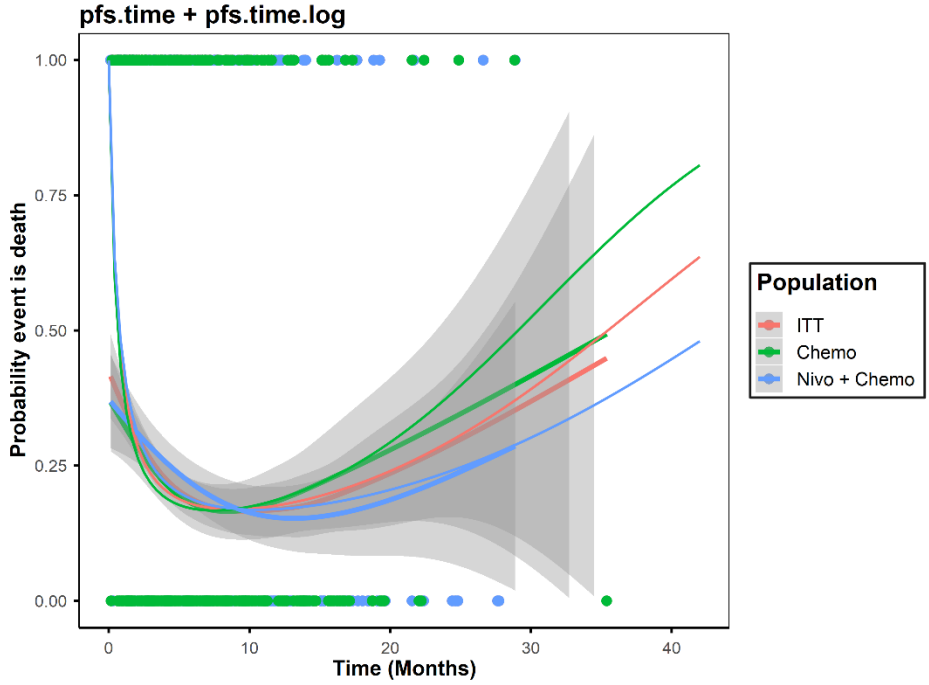


Figure 37. CheckMate 649 probability of death on incidence of BICR-assessed progression

Heavier lines denote smoothed observed values; thin lines depict fitted models; grey areas present confidence intervals.

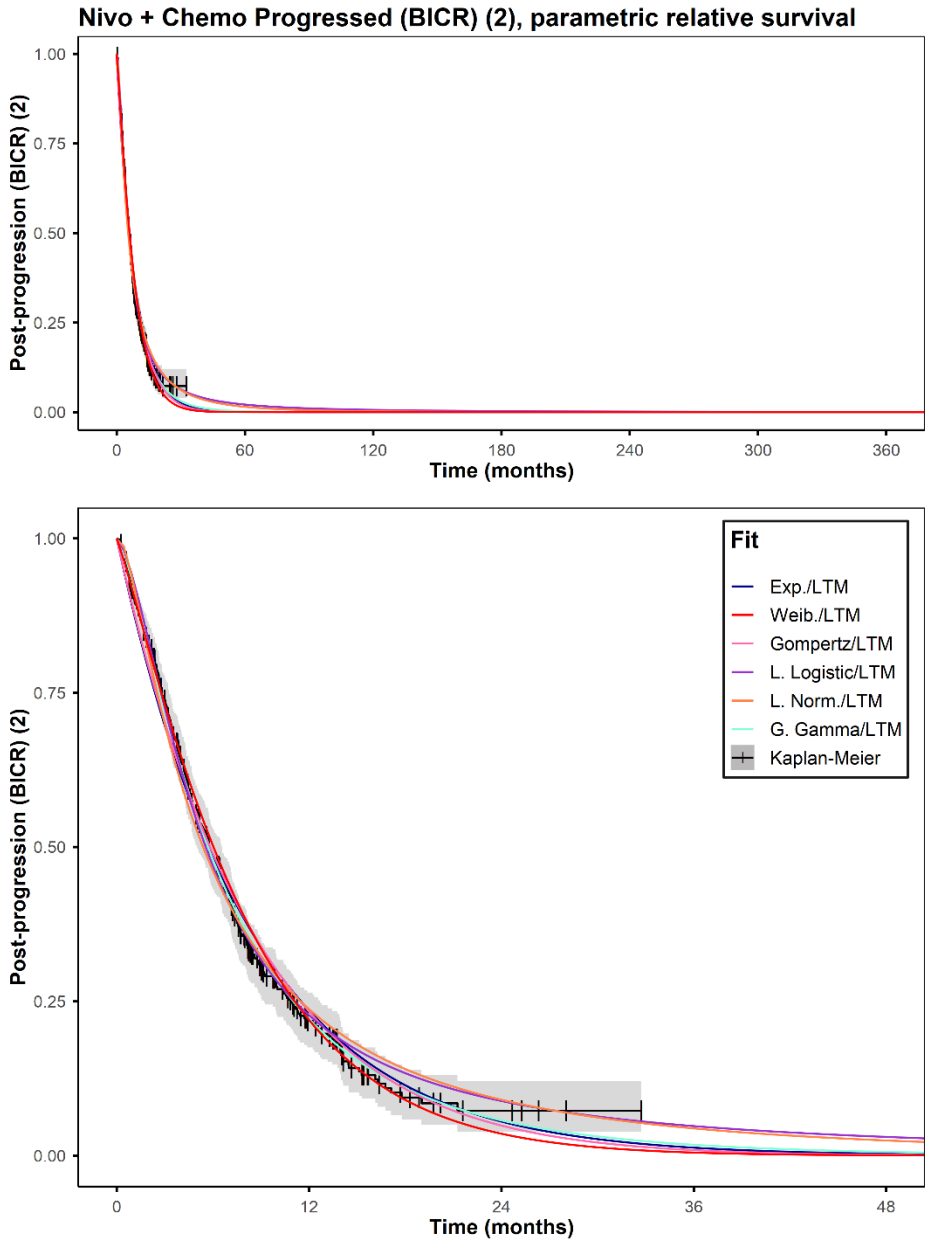
Table 30: Probability of death on incidence of investigator-assessed progression – Model parameterisations

Arm	Intercept	Coefficient 1 (time)	Coefficient 2 (natural logarithm of time)
NIVO + CHEMO	-0.30927	0.08991	-0.94883
CHEMO	-0.56083	0.13964	-1.03879

B.3.3.1.1.3 Overall survival post-progression

Importantly, the generation of overall survival post-progression relies on time since progression and not time from trial initiation. Of the standard statistical models assessed, only the log-logistic and lognormal survival functions gave a satisfactory fit, as outlined in Appendix M. Given a lack of visual differentiation between the two models and their consistency with the available data, the log-logistic model was utilised in base case analyses in line with its preferential goodness-of-fit statistics.

Semi-parametric functions were evaluated but failed to offer improvement on the initial fully parametric functions and so were not selected for use in the base case analysis.



Fit Name	AIC	BIC	Parameters for excess hazard	All-cause median (Months)
Exp./LTM	2008.83	2073.48	rate: 0.1193	6.03 (5.39, 6.70)
Weib./LTM	2002.83	2071.54	shape: 1.1400; scale: 8.4137	6.11 (5.67, 6.94)
Gompertz/LTM	2010.56	2079.26	shape: 0.0062; rate: 0.1155	6.20 (5.44, 6.89)
L. Logistic/LTM	1996.29	2064.99	shape: 1.5771; scale: 5.6028	5.59 (5.17, 6.47)
L. Norm./LTM	2003.59	2072.30	meanlog: 1.6943; sdlog: 1.1251	5.78 (5.08, 6.38)
G. Gamma/LTM	1995.78	2068.55	mu: 1.9222; sigma: 1.0010; Q: 0.5061	5.90 (5.29, 6.63)

Figure 38. CheckMate 649: NIVO+CHEMO overall survival post-progression extrapolation

B.3.3.1.1.4 Clinical rationale and validation of survival extrapolation

The selected extrapolation for PFS maintains an excess hazard of progression due to disease at all times, but as a log-logistic model, this decreases to a minimal value above matched general population mortality in the long term. Per clinical expert advice, a decreasing hazard is expected. The log-logistic model is thus considered consistent with expert advice whilst respecting the primacy of the observed trial data.

In a similar fashion to the selected PFS model, the selected extrapolation for OSPP maintains an excess hazard of death due to disease at all times, but as a generalised gamma model with the profile observed in this study, this decreases to a minimal value above matched general population mortality in the long term.

Sensitivity analyses were performed using a variety of plausible models for each outcome.

B.3.3.1.1.5 Validation of survival curves applied in the economic evaluation

There are no other prospective studies with which to validate the results for extrapolation of the NIVO+CHEMO arm other than the informing trial, CheckMate 649.

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 results for PFS and OSPP can be seen in Table 31 and Table 32, respectively.

Importantly, for PFS the semi-parametric models show no little variation in the estimates at early times. This is particularly important with reference to the median values as there are more events initially and these incur cost which need to be well represented in cost-effectiveness analysis.

Table 31. Observed and predicted estimates of progression-free survival (NIVO+CHEMO)

Excess Hazard Distribution (PFS)	Observed*	Semi-parametric**	Observed*	Semi-parametric**	Observed*	Semi-parametric**
	Survival at 6-Months		Survival at 1-Year		Survival at 2-Years	
Exponential	[redacted]	62.8%	[redacted]	36.3%	[redacted]	11.7%
Generalised Gamma		62.8%		32.8%		15.2%
Gompertz		62.8%		33.5%		14.5%
Log-Logistic		62.8%		32.9%		15.5%
Log-Normal		62.8%		32.3%		15.9%
Weibull		62.8%		34.5%		13.7%
*Kaplan-Meier, PFS per BICR, CheckMate 649; **Linear interpolation of CEM trace upon base case patient						

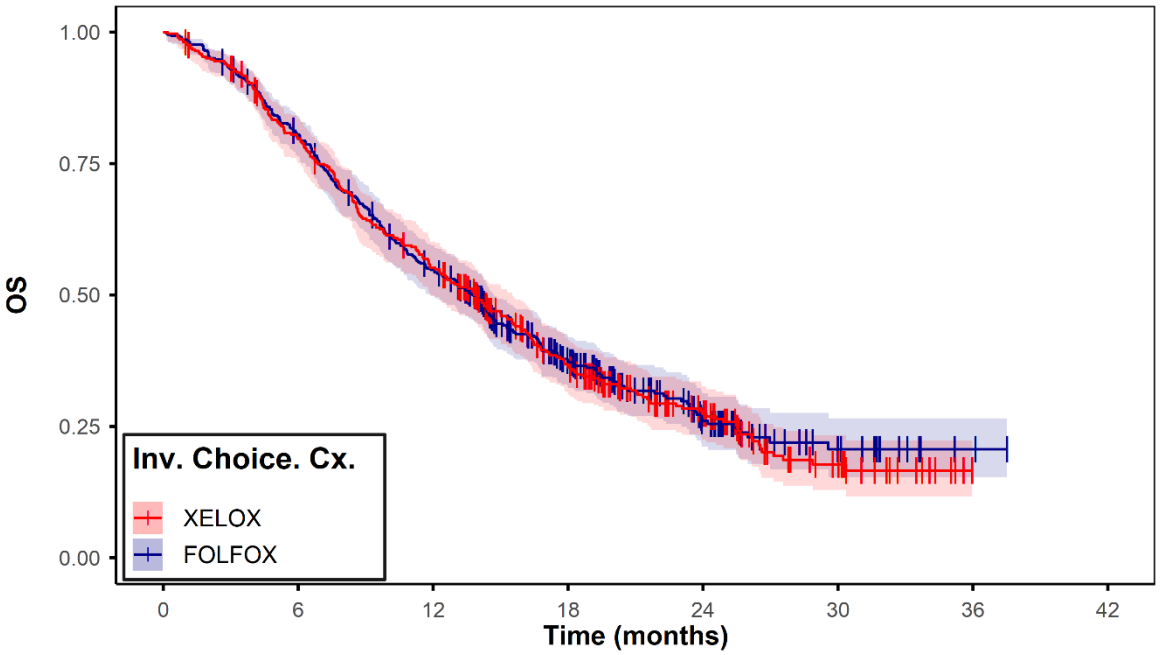
Table 32. Observed and predicted estimates of post-progression survival (NIVO+CHEMO)

Excess Hazard Distribution (PPS)	Observed*	Parametric	Observed*	Parametric	Observed*	Parametric
	Survival at 6-Months		Survival at 1-Year		Survival at 2-Years	
Exponential	[redacted]	48.7%	[redacted]	23.7%	[redacted]	5.6%
Generalised Gamma		48.7%		22.2%		5.3%
Gompertz		49.2%		23.6%		5.0%
Log-Logistic		47.1%		23.0%		9.0%
Log-Normal		46.4%		23.9%		9.2%
Weibull		50.5%		22.2%		3.6%
*Kaplan-Meier, PPS per BICR including subsequent therapy, CheckMate 649; **Linear interpolation of CEM PPS profile upon base case patient from model start						

B.3.3.1.2 Comparators

As described previously, clinicians suggest that the preferred first-line treatments for first-line GC are FOLFOX or XELOX. As these therapies represent standard of care and there is direct comparative evidence (CheckMate 649), FOLFOX and XELOX are considered to represent the comparators in the base case analysis.

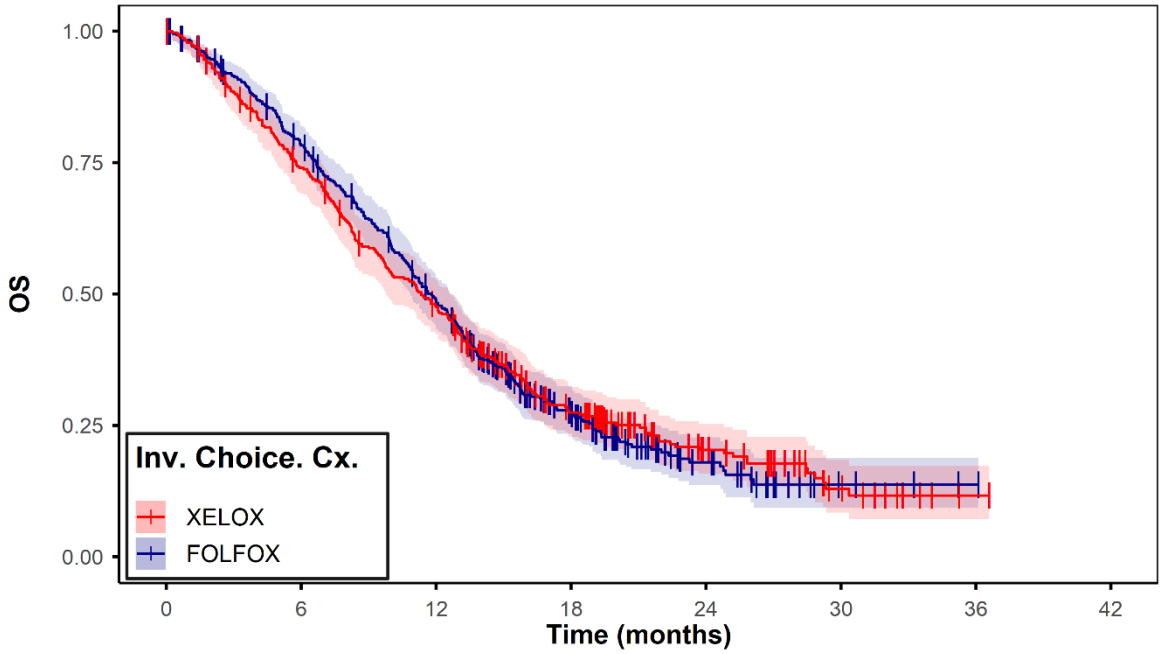
The CheckMate 649 study comparator arm specified a combined FOLFOX/XELOX chemotherapy arm and was powered to show differences in efficacy for NIVO+CHEMO against this combined chemotherapy arm, as opposed to FOLFOX and XELOX separately. Low patient numbers receiving individual treatments may impact on outcomes, particularly during later periods of follow-up. As efficacy is not anticipated to vary by fluoropyrimidine therapy, it is more appropriate to use the combined arm to inform the efficacy of treatment, with costs derived for each arm specifically. Further, outcomes for FOLFOX and XELOX are similar, regardless of treatment arm, as seen in Figure 39 and Figure 40.



NAR (Cumulative Events)

XELOX	365 (0)	284 (73)	195 (160)	110 (220)	56 (243)	19 (258)	0 (259)	0 (259)
FOLFOX	424 (0)	337 (82)	225 (189)	116 (253)	44 (279)	15 (285)	2 (285)	0 (285)

Figure 39. CheckMate 649 OS for nivolumab plus FOLFOX versus nivolumab plus XELOX



NAR (Cumulative Events)

XELOX	370 (0)	268 (95)	169 (190)	78 (255)	34 (270)	11 (279)	1 (280)	0 (280)
FOLFOX	422 (0)	318 (89)	190 (209)	82 (283)	25 (306)	4 (311)	1 (311)	0 (311)

Figure 40. CheckMate 649 OS for FOLFOX versus XELOX

Clinicians suggest the choice of therapy would not be impacted by addition of nivolumab (i.e. a patient who would have received XELOX would receive NIVO+XELOX as opposed to NIVO+FOLFOX). As these therapies represent standard of care and there is direct comparative evidence (CheckMate 649), the following comparisons represent the base case analysis:

- NIVO+FOLFOX versus FOLFOX
- NIVO+XELOX versus XELOX

The efficacy of additional comparators is informed by an NMA based on studies identified from the SLR (Section B.2.10 and Appendix L). These scenario analysis comparisons include the following comparators:

- Fluorouracil plus cisplatin
- Capecitabine plus cisplatin

In addition, the following comparators are listed within the final scope for this appraisal:

- Fluorouracil plus oxaliplatin plus epirubicin

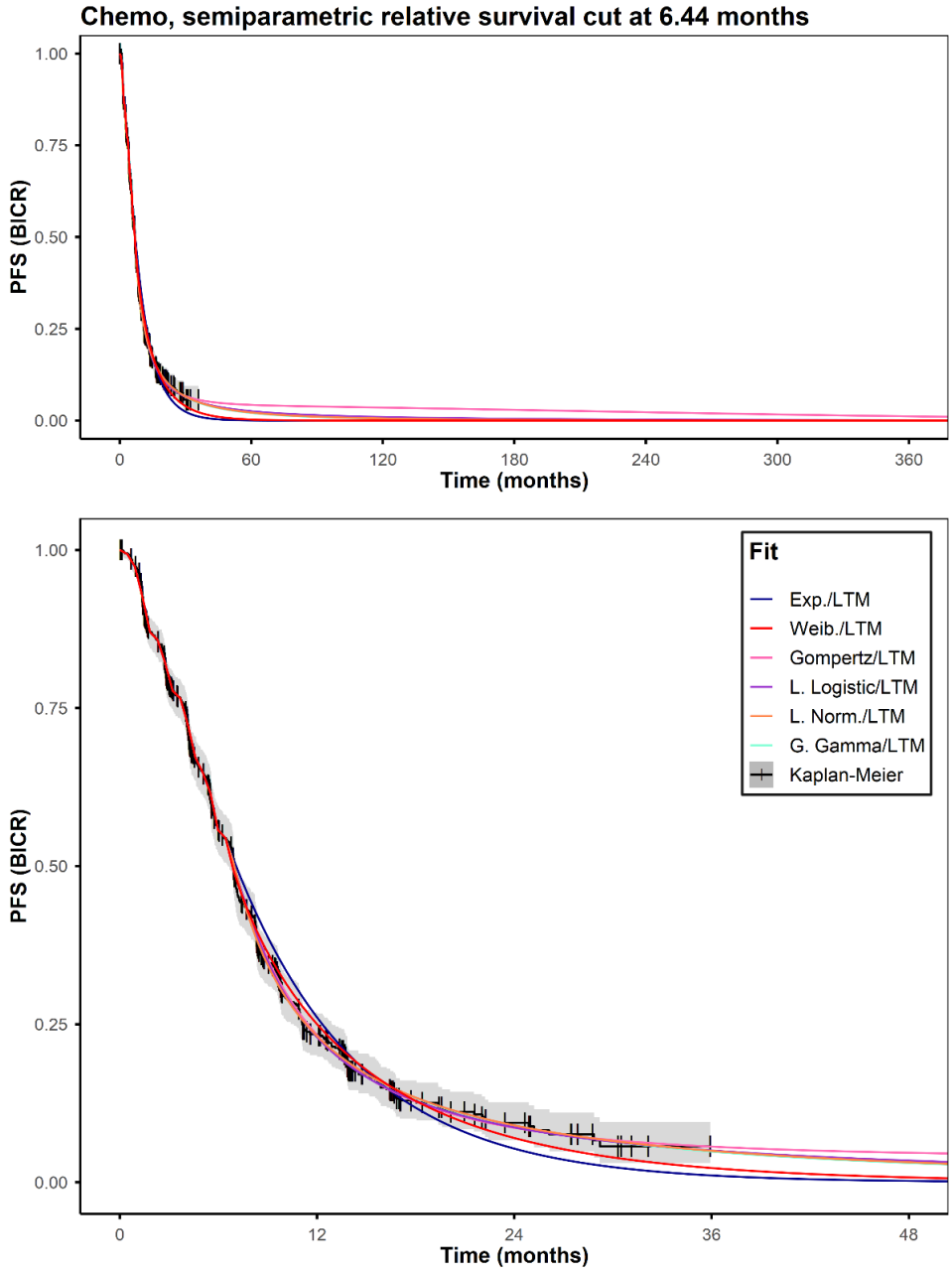
- Fluorouracil plus cisplatin plus epirubicin
- Capecitabine plus oxaliplatin plus epirubicin
- Capecitabine plus cisplatin plus epirubicin
- Trastuzumab with cisplatin plus capecitabine or fluorouracil

However, there is limited evidence to inform these comparisons. In particular, there is no ITC network that can be formed with the epirubicin-based triplet therapies, due to lack of published relative efficacy measures. Clinical advice indicates that epirubicin is not used in the UK for first-line treatment of gastro-oesophageal cancers, and that recent guidelines have actively removed epirubicin from the treatment options.[1,23] Hence, these comparators cannot be considered relevant to the decision problem. Further, evidence versus trastuzumab combination therapy is subject to several limitations. For this reason, no cost-effectiveness analysis has been undertaken versus this comparator.

B.3.3.1.2.1 CheckMate 649 comparator efficacy

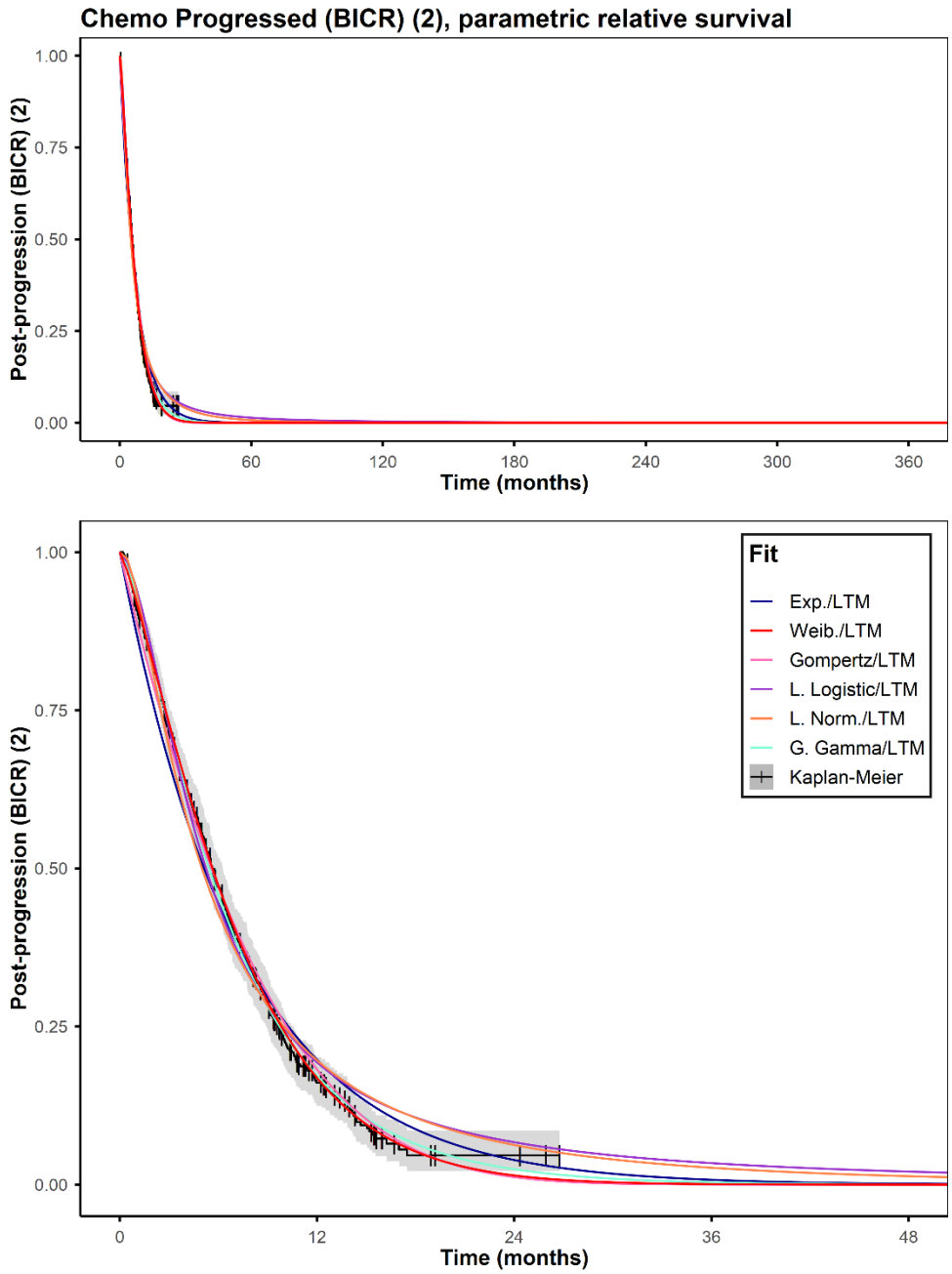
Survival data for XELOX and FOLFOX were derived using the same process as described for the NIVO+CHEMO arm, using data from the CheckMate 649 study. Complete survival analysis methodology and results are described in Appendix M.

Following consideration of both fully parametric and semi-parametric survival functions for PFS and OSPP, a semi-parametric log-logistic survival function with a split point at 6.44 months was chosen for PFS, whilst a fully parametric log-logistic function was selected for OSPP (both of which are consistent with the NIVO+CHEMO arm). Graphical representations of the choice of parameterisation for comparator (XELOX and FOLFOX) PFS and OSPP are presented in Figure 41 and Figure 42. Death on progression was modelled based on a logistic model, as described in Section B.3.3.1.1.2 and Figure 37, with the same profile utilised across all comparators.



Fit Name	AIC	BIC	Parameters for excess hazard	All-cause median (Months)
Exp./LTM	1458.47	1462.30	rate: 0.1308	7.30 (6.65, 7.92)
Weib./LTM	1448.41	1456.07	shape: 0.8404; scale: 7.5915	7.33 (6.57, 7.65)
Gompertz/LTM	1436.28	1443.95	shape: -0.0735; rate: 0.1841	6.91 (6.59, 7.72)
L. Logistic/LTM	1433.36	1441.02	shape: 1.1536; scale: 4.2760	7.03 (6.61, 7.79)
L. Norm./LTM	1429.20	1436.86	meanlog: 1.4468; sdlog: 1.4865	7.06 (6.62, 7.74)
G. Gamma/LTM	1431.17	1442.66	mu: 1.4694; sigma: 1.4782; Q: 0.0370	7.05 (6.63, 7.74)

Figure 41. CheckMate 649 CHEMO BICR-assessed progression-free survival extrapolation



Fit Name	AIC	BIC	Parameters for excess hazard	All-cause median (Months)
Exp./LTM	2138.83	2203.56	rate: 0.1339	5.21 (4.85, 6.02)
Weib./LTM	2116.54	2185.33	shape: 1.2509; scale: 7.6262	5.79 (5.36, 6.49)
Gompertz/LTM	2130.76	2199.56	shape: 0.0396; rate: 0.1099	5.65 (5.24, 6.50)
L. Logistic/LTM	2126.86	2195.66	shape: 1.7162; scale: 5.2812	5.46 (4.90, 6.09)
L. Norm./LTM	2131.62	2200.42	meanlog: 1.6170; sdlog: 1.0297	5.47 (4.69, 5.92)
G. Gamma/LTM	2115.14	2188.00	mu: 1.9135; sigma: 0.8703; Q: 0.6958	5.88 (5.10, 6.38)

Figure 42. CheckMate 649: CHEMO overall survival post-progression extrapolation

B.3.3.1.2.2 NMA efficacy

Bayesian network meta-analysis was conducted in line with the Technical Support Document (TSD) 2 written by the NICE Decision Support Unit (DSU).[72] Clinical evidence for NIVO+CHEMO was based on the results of the Checkmate-649 clinical trial, with comparator evidence derived systematically through a literature review of the available evidence, consistent with the requirements of NICE. Relevant comparators for inclusion in the ITC were aligned to recommendations for systemic anti-cancer regimens as reported in different guidelines*, and the availability of data identified through the SLRs, and included:

- CF (Cisplatin + Fluorouracil)
- CX (Cisplatin + Capecitabine)

Outcomes of interest for the ITC were OS and PFS. Analysis results are reported in line with the recommendations made in TSD2,[72] TSD3[73] and TSD7.[74]

A full description of the NMA methodology and results is provided in Appendix L. The NMA was undertaken using median survival estimates for PFS and OS, based on exponential approximations and using the chemotherapy arm of the CheckMate 649 trial as the reference treatment. Consequently, PFS HRs are applied directly to chemotherapy survival data derived from the CheckMate 649 trial in order to inform PFS for CF and CX regimens. A similar process was undertaken for OS. A summary of the HRs for each comparator are presented in Table 33.

Subsequently, the overall survival outcome from the economic model is dependent upon all three transition rates. To derive HR estimates for OSPP, the model was calibrated to the indirectly compared treatments. Initially, the Kaplan-Meier estimator of the XELOX/FOLFOX OS outcome from the CheckMate 649 trial was scaled by the NMA-derived hazard ratio. These weights were used to determine the log-likelihood of the OS predicted by the model.

The state transition model was replicated in the statistical programming language R and configured for the XELOX/FOLFOX arm of CheckMate 649. The PFS transition was scaled by the hazard ratio derived from the ITC, and the modelled proportion of patients dying upon exiting the pre-progression state was maintained as in the base case. The post-progression disease specific survival was then scaled by a hazard ratio, and the log-likelihood evaluated. This hazard ratio was then varied until maximum log-likelihood of OS was reached, and the final value was taken. Resultant HRs are described in Table 34.

Table 33. Parameters describing exponential extrapolation of profession-free and overall survival for comparators

Comparator	PFS HR (95% CI)	OS HR (95% CI)
CF	0.808 (0.406-1.614)	0.866 (0.444-1.685)
CX	1.180 (0.548-2.714)	1.141 (0.513-2.677)
CF: Cisplatin + fluorouracil; CI: confidence interval; CX: cisplatin + capecitabine; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.		

Table 34. Scaled OSPP HR parameters for comparators

Comparator	OSPP HR (95% CI)
CF	1.006 (0.393-11.109)
CX	0.990 (0.246-26.753)
CF: Cisplatin + fluorouracil; CI: confidence interval; CX: cisplatin + capecitabine; HR: hazard ratio; OSPP: overall survival post-progression	

B.3.3.1.3 All-cause mortality

In order to have plausibility of long-term survival estimates, the development of mortality hazard was assumed bounded at the lower side by that of the matched general population, as determined by contemporary national life tables. This was reflected in the survival analysis by considering relevant survival models in a relative survival context, with an additive disease-specific hazard applying over a non disease-specific baseline population hazard equivalent to that of the general population.

Individuals randomised into clinical trials are likely to be slightly younger and healthier than the overall UK patient population comprising those with previously untreated advanced or metastatic gastric or gastroesophageal junction or oesophageal adenocarcinoma. A total of 473/789 (59.9%) patients in the NIVO+CHEMO arm of the CheckMate 649 were under the age of 65 years, with a median age of 62.0 years increasing the likelihood that most deaths observed over the trial period were cancer-related.[41] However, the identified disease was not assumed to be protective from general population mortality events and so the relative survival model structure was assumed to apply at all times. Similarly, removal of deaths due to advanced gastric and gastro-oesophageal cancer from national life tables was assumed to make negligible difference to the population marginal hazard, and so the equivalence of life table hazard and non-disease-specific mortality hazard was assumed.

For evaluation of the economic model age and gender-adjusted general population probability of mortality based on information from UK life tables,[75] described in Table 35, are included. These values are included in every cycle in addition to the assumed life table independent disease-related mortality values, with hazards applied additively. While some form of double counting occurs due to the presence of gastric and gastro-oesophageal-specific cancer deaths within the general population, this effect applies equally to all comparators and is likely to have a minimal impact on predicted survival (and hence cost-effectiveness).

Table 35. Excerpt from England and Wales life tables[75]

Age	Probability of mortality*	
	Males	Females
50	0.003379	0.002169
51	0.003606	0.002358
52	0.003907	0.002557

53	0.004125	0.002697
54	0.004478	0.002914
55	0.004760	0.003194
-		
95	0.261012	0.228210
96	0.286714	0.250765
97	0.304113	0.267058
98	0.325892	0.291260
99	0.369540	0.309526
100	0.384386	0.343363
**Defined as the probability that a person aged x exact will die before reaching the age (x+1)*		

B.3.3.2 Therapy effects

B.3.3.2.1 Treatment discontinuation

The economic model incorporates a time on treatment curve (described in Section B.3.3.2.1.2) to inform the proportion of patients discontinuing treatment due to progression and AEs. The timing of discontinuations was assumed to impact on treatment costs and resource use.

B.3.3.2.1.1 Subsequent therapies

Second-line palliative chemotherapy is recommended for patients who have progressed on the first-line therapy; however, there is uncertainty around composition of therapy. Specific chemotherapy regimens are not defined in the NICE clinical guidelines in the second line setting.[76-78] Similar to UK guidance, guidelines from the European Society for Medical Oncology (ESMO) recommend palliative chemotherapy in the management of advanced or metastatic GC.[19] Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1. However, ramucirumab is not recommended by NICE for use in England.[79]

In the economic model, patients receive a subsequent therapy following discontinuation, as outlined in Table 36. As a simplifying assumption, it is assumed that all patients receive single agent taxane as subsequent therapy in the base case. BSC is defined as 50% of patients receiving paclitaxel and the other 50% receiving docetaxel. This aligns to a previously published study of UK clinical practice, which identified that more than half (54%) of patients receiving second-line therapy receive single agent treatment and the most common second-line treatment is paclitaxel (35% of use).[66]

Table 36. Subsequent therapy applied in model

Treatment arm	Base case analysis (pre-progression and post-progression)
NIVO+CHEMO*	Single agent taxane
FOLFOX/ XELOX	Single agent taxane
CF / CX	Single agent taxane
**Applied to both NIVO+FOLFOX and NIVO+XELOX* *Abbreviations: FOLFOX = Fluorouracil, oxaliplatin, folinic acid; XELOX = Capecitabine, oxaliplatin; CF = Cisplatin, fluorouracil, CX = Cisplatin, capecitabine*	

Impact of subsequent therapies in CheckMate 649

Among all randomised patients, subsequent cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by [redacted] ([redacted]%) patients in the NIVO+CHEMO treatment arm compared to [redacted] ([redacted]%) in the CHEMO arm. Subsequent systemic therapy was received by [redacted] ([redacted]%) patients in the NIVO+CHEMO treatment arm and [redacted] ([redacted]%) subjects in the CHEMO arm. The proportion of patients receiving subsequent chemotherapy was comparable ([redacted], respectively); this was most commonly paclitaxel ([redacted] respectively) or fluorouracil ([redacted]). Further, a similar percentage of patients received targeted therapies ([redacted] for NIVO+CHEMO versus [redacted] for CHEMO), which was most frequently ramucirumab ([redacted]). However, subsequent immunotherapy was received by a lower percentage of patients in the NIVO+CHEMO arm compared with CHEMO alone ([redacted]), and this was most commonly nivolumab ([redacted], respectively) or pembrolizumab ([redacted]) in both patient groups.[41]

Use of paclitaxel reflects around [redacted] of subsequent treatment use, which is aligned to UK clinical practice. However, use of targeted therapies, such as ramucirumab, and immunotherapies does not reflect the UK patient pathway. However, it should be noted that the form of systemic subsequent therapy used has limited impact on survival outcomes. As shown in Figure 43 for second line therapy which included targeted agents, the composition of second line therapy does not seem to have an impact on overall survival after progression on first line therapy. In addition, subsequent therapies involving either immunotherapies or chemotherapies as a component or as monotherapy did not appear to improve survival outcome versus those who received therapies without these components. Hence, composition of subsequent treatment is unlikely to impact on outcomes in the economic model.

[redacted]

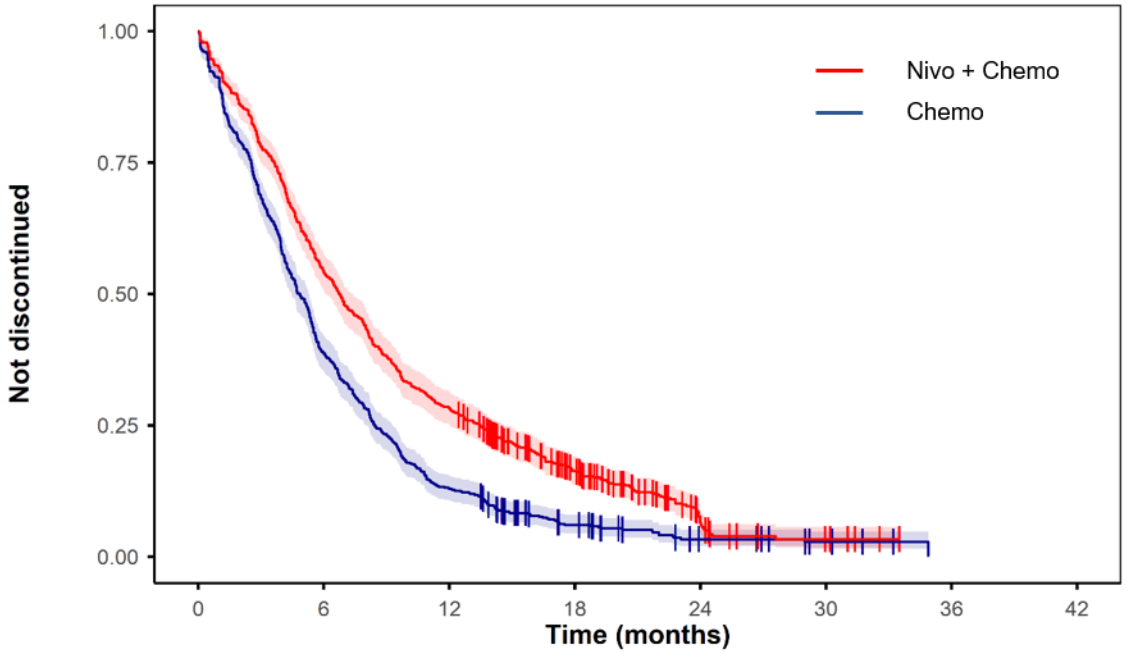
Figure 43. CheckMate 649 CHEMO arm OS following progression stratified by second line therapy (targeted therapy)

B.3.3.2.1.2 Time on treatment

Nivolumab plus chemotherapy

Patient-level data from CheckMate 649 were obtained describing discontinuation due to progression, study drug toxicity, AEs unrelated to study therapy and withdrawal of patient consent. Kaplan-Meier estimates of ToT were complete at the end of the trial follow-up period, in that the number of patients at risk of discontinuation at the end of follow-up was 0. As such the Kaplan-Meier curves themselves were used in the model to estimate ToT, ensuring complete consistency with the clinical trial data.

Kaplan-Meier data for ToT for both arms is summarised in Figure 44.



NAR (Cumulative Events)

Nivo + Chemo								
Chemo	767 (0)	297 (470)	99 (668)	33 (715)	10 (726)	4 (727)	0 (728)	0 (728)
Nivo + Chemo	782 (0)	425 (357)	221 (561)	99 (646)	22 (689)	5 (698)	0 (698)	0 (698)

Figure 44. Time on treatment: CheckMate 649 NIVO+CHEMO – parametric extrapolations

Comparators

CheckMate 649 is a randomised parallel assignment phase 3 trial. Therefore, to provide an unbiased assessment of the time on treatment of standard of care, the base case analysis applies comparator time on treatment information derived directly from the trial data.

The chemotherapy arm of the trial was made up of the following regimens:

- XELOX (Oxaliplatin + Capecitabine)
- FOLFOX (Oxaliplatin + Folinic acid + 5-Fluorouracil)

Time on treatment for both chemotherapy regimens were statistically similar. Therefore, time on treatment information for XELOX and FOLFOX has been derived using pooled data from the entire chemotherapy arm of the CheckMate 649 study and forms the base case analysis in this submission.

Adopting the same approach as for the NIVO+CHEMO arm, the Kaplan-Meier curves themselves were used in the model to estimate ToT, ensuring complete consistency with the clinical trial data. Kaplan-Meier data for ToT for both arms is summarised in Figure 44.

The ToT for additional comparators in scenario analysis was assumed to be the same as the chemotherapy arm of the CheckMate 649 study.

B.3.3.2.1.3 Discontinuation due to maximal clinical benefit

The SmPC for nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy specifies that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[2] In terms of immunotherapies, this means that treatment may be discontinued in patients with limited clinical benefit.

A formal stopping rule was applied during CheckMate 649, with the maximum treatment duration specified as 24 months in the absence of disease progression or unacceptable toxicity. In further support of this, clinical experts are aware of the use of a nivolumab stopping rule in other indications and considered it clinical practice within the context of this indication.

Previously, stopping rules have not always been applied to nivolumab indications. During the undertaking of TA483[80] and TA484,[81] the NICE Appraisal Committee noted that a 2-year stopping rule was not included in the pivotal trial or described in the SmPC and so queried whether clinicians would follow a stopping rule, especially if the patient was still benefiting from the treatment. When discussing the stopping rule however, the committee noted comments on the second ACD that a two-year stopping rule is acceptable to both patients and clinicians and would be implementable.[80] However, in this case, CheckMate 649 includes the stopping rule, so clinical data reflect this clinical reality.

Given this evidence and to remain consistent with the underlying trial data, it is considered appropriate to apply a stopping rule in the base case analysis. Patients still receiving treatment at two years are assumed to discontinue NIVO+CHEMO treatment and receive no further cost until progression. A scenario analysis is explored whereby no stopping rule is applied; however, it should be noted that this scenario is presented to assess the uncertainty around the impact of the stopping rule, but does not reflect potential clinical practice.

B.3.3.2.2 Adverse events

Treatment-related 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.

AEs were selected on the basis of relevance to NIVO+CHEMO treatment. Grade 3-4 treatment-related AEs from CheckMate 649 were assessed if occurring in more than two patients, as outlined in Table 36.

The AEs were applied in the model as a one-off cost in the first cycle only. Therefore, the proportion of the cohort demonstrated in Table 36 receives the costs and utility decrements associated with that AE.

Table 37. Grade 3-4 treatment-related adverse events applied in the economic model

Adverse event	NIVO+CHEMO*	FOLFOX/ XELOX	CF / CX
	CheckMate 649[41]	CheckMate649[41]	TA208[22]
Anaemia	6.00%	2.70%	10.34%
Diarrhoea	4.50%	3.10%	3.79%
Fatigue	3.80%	2.20%	2.41%
Nausea	2.60%	2.50%	7.24%
Neutropenia	15.10%	12.10%	30.34%
Vomiting	2.20%	3.10%	7.59%

**Applied to both NIVO+FOLFOX and NIVO+XELOX*

Abbreviations: FOLFOX = 5-Fluorouracil, oxaliplatin, folinic acid; XELOX = Capecitabine, oxaliplatin; CF = Cisplatin, 5-fluorouracil, CX = Cisplatin, capecitabine

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life studies

In line with the NICE guidelines to the methods of technology appraisal 2013[68], studies describing health-related quality-of-life for patients with gastric/GOJ cancer were identified systematically. This search was undertaken as part of the SLR conducted for cost-effectiveness studies, described within Appendix G.

B.3.4.2 Health-related quality-of-life data from clinical trials

CheckMate 649 included assessment of health-related quality of life during the study, which can be used to derive utilities for modelling analysis. Assessments of EQ-5D status in CheckMate 649 were carried out every 6 weeks during the treatment phase and every 12 weeks in the follow-up phase. Ultimately, patient-assessed HRQoL data was collected with varying frequency through the trial, dependent upon treatment status, and progression status.

In the NIVO+CHEMO arm, 789 patients were assessed, of which 741 patients had patient-reported outcome data. Similarly, in the CHEMO arm, 792 patients were assessed, of which 734 patients had patient-reported outcome data. Completed questionnaires were sourced from the 10th July 2020 DBL for the overall population of CheckMate 649. Patient-reported outcomes from the trial are summarised in Section B.2.6.1.4. Patients in both treatment arms reported improvements over baseline at most on-treatment visits; baseline scores were similar between groups, at [redacted] in the NIVO+CHEMO group and [redacted] in the CHEMO group.

As data were limited for patients who had discontinued treatment or experienced a progression event, an additional analysis was conducted assessing utility in patients receiving NIVO+CHEMO prior to discontinuation. Each EQ-5D-3L questionnaire was converted to utility using the UK EQ-5D-3L tariff and stratified by date of treatment discontinuation. If the questionnaire was prior to treatment discontinuation, it informed the on-treatment utility. Further details are available within Appendix N.

The mean on-treatment utility value was [redacted] for the pre-progression health state and [redacted] for the progressed health state. Age-related utilities were applied for patient in the long term remission health state.

Further, utility decrements were applied based on age-dependent values, and within the last 6 months before death. Age-dependent disutility values were applied using data reported by Janssen et al.[82] The time-to death disutility was 0.406 and was implemented using a quadratic model since this improved the goodness-of-fit versus linear models.

B.3.4.3 Mapping

EQ-5D-3L was collected alongside CheckMate 649; therefore, no mapping algorithms were used between patient-reported outcomes and EQ-5D to derive utilities.

B.3.4.4 Adverse reactions

Disutilities were applied to patients in the first modelled cycle only, based on the incidence of events reported in CheckMate 649. Adverse event inputs are summarised in Table 38 below.

Table 38. Summary of adverse event disutility values for cost-effectiveness analysis

Adverse event	Utility value mean	Utility value (SE)	Source
Anaemia	-0.115	0.023	Swinburn et al.[83] (2010)
Diarrhoea	-0.0468	0.009	Doyle et al.[84] (2008)
Fatigue	-0.119	0.024	Lloyd et al.[85] (2006)
Nausea	-0.103	0.021	Assumed equal to vomiting
Neutropenia	-0.08973	0.015	Nafees et al.[86] (2008)
Vomiting	-0.103	0.021	Swinburn et al.[83] (2010)
Thrombocytopenia	-0.11	0.022	Tolley et al.[87] (2013)
Where SE values were not reported in the literature, these are 20% of the mean values			

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The health utility of patients is dependent upon their disease state and so consequently, during each cycle, patients are assigned the health utility value equivalent to their current disease state.

B.3.4.5.1 Summary of health-related quality of life data applied in the economic model

Table 39 and Table 40 summarises the health state health-related quality of life values applied in the economic model.

Table 39. Summary of utility values for cost-effectiveness analysis

Health state	Utility value mean (SE)	Source
Progression-free	[redacted]	Checkmate 649[41]
Progressed disease	[redacted]	Checkmate 649[41]
Time-to-death disutility	[redacted]	Checkmate 649[41]

Table 40. Excerpt from age-dependent utility decrements for cost-effectiveness analysis

Age (years)	Utility value
50	0.153
51	0.153
52	0.153
53	0.153
54	0.153
55	0.201
…	..
95	0.274
96	0.274
97	0.274
98	0.274
99	0.274
100	0.274
Source: Janssen et al.[82]: Table 3.6	

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

B.3.5.1 Resource identification, measurement and valuation studies

In line with the NICE guidelines to the methods of technology appraisal 2013[68], studies describing costs and healthcare resource use for patients with gastric/GOJ cancer were identified systematically. This search was undertaken as part of the SLR conducted for cost-effectiveness studies, described within Appendix G.

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Nivolumab plus chemotherapy costs

The costs of nivolumab, including drug procurement and administration, are applied each cycle, based on acquisition costs detailed in Table 41, Table 43, Table 44.Treatment modifiers were applied to the acquisition and administration costs, which accounted for missed doses during CheckMate 649 (0.883 for NIVO + XELOX, 0.877 for NIVO + FOLFOX). The total cyclical costs for NIVO + CHEMO arms were the costs of nivolumab and chemotherapy.

Table 41. Nivolumab dosing and acquisition cost

	With XELOX	With FOLFOX
Dosing	One IV infusion per three-week cycle, 360 mg	One IV infusion per two-week cycle, 240 mg
Dose per cycle	360 mg	240 mg
Cost per dose (excluding PAS)	£3,950.00	£2,633.00
Cost per cycle	£3,950.00	£2,633.00
Administration costs per cycle	£385.28	£385.28
Total with treatment modifier	£3,828.66	£2,645.56
Total	£4,335.28	£3,018.28
Source: CheckMate 649 PLD[41] [data on file]		

The costs of the chemotherapy including drug procurement and administration, are applied each cycle, based on acquisition costs detailed in Table 42, Table 43, Table 44.

Table 42. Chemotherapy dosing and acquisition cost

	Component 1	Component 2	Component 3
FOLFOX: Cycle length two weeks, total cost per cycle £2,338.54 (first cycle), £1,630.82 (subsequent cycles)			
Component	Oxaliplatin	5-Fluorouracil	Folinic acid
Dosing	One IV infusion per two-week cycle, 85 mg/m^2	One 400 mg/m^2 IV infusion per two-week cycle Two 1200 mg/m^2 IV infusion per two-week cycle	One IV infusion per two-week cycle, 400 mg/m^2
Single dose	149.6 mg	704 mg (400 mg/m^2) 2,112 mg (1200 mg/m^2)	704 mg
Dose per cycle	149.6 mg	4,928 mg	704 mg
Cost per cycle (excluding PAS)	£15.16	£816.95	£46.08
Administration costs per cycle	£385.28	£707.72*+ +£362.35	None - included in oxaliplatin
Total (FOLFOX)	£405.44	£1,887.02 (first cycle) £1,179.30 (subsequent cycles)	£46.08
XELOX: Cycle length three weeks, total cost per cycle £430.26			
Component	Oxaliplatin	Capecitabine	-

Dosing	One IV infusion per three-week cycle, 130 mg/m^2	Twice daily oral tablet, 1000 mg/m^2, for first 14 days of cycle only	-
Single dose	228.8 mg	1,760 mg	
Dose per cycle	228.8 mg	49,280 mg	-
Cost per cycle (excluding PAS)	£23.19	£21.79	
Administration costs per cycle	£385.28	£0.00	-
Total (XELOX)	£408.47	£21.79	
Source: CheckMate 649 PLD[41] [data on file] *One off cost applied at first cycle only, for central venous access device installation. Body surface area = 1.76 m^2 (according to CheckMate 649)			

Table 43. Unit drug cost per mg

Drug	Cost per mg	Source
Capecitabine	£0.00044	eMIT database[88]
Cisplatin	£0.08082	eMIT database[88]
Epirubicin	£0.11239	eMIT database[88]
Fluorouracil	£0.16578	eMIT database[88]
Folinic acid	£0.06546	eMIT database[88]
Oxaliplatin	£0.10135	eMIT database[88]
Nivolumab*	£10.97194	BNF[89]
All values except those indicated with * are a weighted average		

Table 44. Unit administration costs

Details	Day case value	Source
Oral tablets	£0.00	-
First intravenous infusion per cycle	£385.28	NHS reference costs (SB14Z)[90]
Subsequent intravenous infusion per cycle	£362.35	NHS reference costs (SB15Z)[90]
CVAD pump price and installation	£707.72	TA208[22]

B.3.5.2.1.1 Patient Access Scheme

A Patient Access Scheme (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 as an add-on to SoC chemotherapy, the economic evaluation presented in this submission applies the PAS in the base case analysis.

Table 45. Acquisition cost of nivolumab following application of PAS

	240mg (24 ml) vial	Cost per cycle	
		Cycle 1-4	Cycle 5+
No PAS	£2,633.00	£3,018.00	£3,018.00
PAS	[redacted]	[redacted]	[redacted]
PAS: patient access scheme			

B.3.5.2.2 Comparators

Costs of comparator treatments are based on the costs required for each of the components:

- Drug costs
- Administration costs
- Subsequent therapy costs (composition detailed in Section B.3.3.2.1.1).

For each component, the intervention cost, comprising acquisition cost, and administration cost was calculated on a per cycle basis. This was subsequently converted to a weekly cost over the course of each regimen (Table 46).

Table 46. Comparator costs per cycle

Regimen	Components	Dosing instructions	Single dose	Total dose	Acquisition cost per dose	Admin cost per dose	Acquisition cost per treatment cycle	Administration cost per treatment cycle	Cycle length
XELOX	Oxaliplatin	Day 1 of 3-week cycle 2-hour IV infusion, 130 mg/m^2	222.8 mg	228.8 mg	£23.19	£385.28	£44.98	£385.28	3 weeks
	Capecitabine	Twice daily for 2 weeks Oral, 1000 mg/m^2	2,112 mg	49,280 mg	£21.79	£0.00			
FOLFOX	Oxaliplatin	Day 1 of 2-week cycle 2-hour IV infusion, 85 mg/m^2	149.6 mg	149.6 mg	£15.16	£385.28	£878.19	£1,840,63**	2 weeks
	Fluorouracil (first dose)	Day 1 of 2-week cycle, 2-hour IV infusion, 400 mg/m^2	704 mg	704 mg	£116.71	£385.28			
	Fluorouracil (subsequent doses)	Two days of 2-week cycle, continuous infusion, 1200 mg/m^2	2,112 mg	4,224 mg	£700.24	£362.35			
	Folinic acid	Day 1 of 2-week cycle 2-hour IV infusion, 400 mg/m^2	704 mg	704 mg	£46.08	-*			

Dosing based on 1.76 m^2 body surface area (as per *CheckMate 649*[41] trial)
*Cost not applicable, assuming administered with cisplatin/oxaliplatin infusion
**Also includes one-off cost of installation of the CVAD pump for infusion at £707.72
Abbreviations: FOLFOX = Fluorouracil, oxaliplatin, folinic acid; XELOX = Capecitabine, oxaliplatin

B.3.5.3 Health-state unit costs and resource use

Progression-free resource use was aligned to TA208 and used to inform accrual of costs.[22] Resource use in the progressed disease is based on that applied in NICE CG81,[91] which is aligned to TA208.[22] Costs were sourced as per TA208,[22] either using more recent versions of the same sources (e.g. NHS reference costs/PSSRU),[92] or inflating from TA208[22] where the source was not available. Where required, costs were inflated to 2019-2020 costs using PSSRU indices.[93] Progressed disease health state costs also include the costs of subsequent therapies (as described in Section B.3.3.2.1.1).

Table 47. Health state cyclical costs

Health state	Mean cost (SE)	Source
Progression-free	[redacted]	See Table 40
Progression-free (post-treatment cessation)	[redacted]	
Progressed disease	[redacted]	See Table 49
SE: standard error SE assumed to be 20% of the mean value		

Table 48. Progression free healthcare resource use

Healthcare resource	Details	Frequency	Frequency source	Unit cost	Cost details and source
Oncologist consultation	During treatment	1 per 3 weeks	Expert opinion used in TA208[22]	£128.00	NHS reference costs: 370,[90] Medical Oncology, consultant led, outpatient
	After treatment	1 per 6 weeks			
Cardiac monitoring	All other treatments	1 per 3 months		£227.16	33% MUGA scan, remaining ECG, costs inflated from TA208 (2010)
CT scan	At diagnosis & progression Cost not included (cancels out between regimens)			-	-

Table 49. Progressed disease healthcare resource use

Healthcare resource	Frequency	Frequency source	Unit cost	Cost source
Nurse, home visit	20 min, 1 per week	NICE CG81[91]	£12.60	PSSRU[92]
Clinical nurse specialist	1 hr per week		£50.00	
GP	1 home visit every fortnight		£39.00	

Therapist	1 hr every fortnight		£48.00	

Table 50. Subsequent therapy costs applied in progressed disease health state

Intervention	Dosing regime	Unit size	Unit cost per dose	Administration cost per dose	Total cost per 2 weeks*
Docetaxel	1 per 3 weeks, 75 mg/m^2	160 mg/8 mL	£20.96	£362.35	£241.57
Paclitaxel	3 per 4 weeks, 80 mg/m^2	150 mg/25 mL	£18.88	£362.35	£543.53
Dosing regime source: TA378[94] (assuming body surface area of 1.76m^2) Unit size and cost source: eMIT[88] Administration cost source: NHS reference costs[90] (intravenous infusion) *Within progressed disease, assumed an equal split between docetaxel and paclitaxel					

Table 51. End of life costs

	Costs	Inflated to
	Mean	Mean (SE)
End-of-life costs	£4,000	£5,387.03 (£1,077.41)
SE: standard error SE assumed to be 20% of the mean value End-of-life cost sourced from TA208[22]		

B.3.5.4 Adverse reaction unit costs and resource use

In order to provide an assessment of the costs associated with AEs, costs were sourced from recent NICE appraisals where possible, where costs were agreed with the ERG, and inflated to 2019-2020 costs.[93] These costs are summarised in Table 52.

Table 52. Adverse events costs

Adverse event	Costs	SE	Source
Anaemia	£1,853.55	£370.71	Copley-Merriman et al.[95] 2018 (using data from Wehler et al.[96] 2017)
Diarrhoea	£3,160.87	£632.17	Copley-Merriman et al.[95] 2018 (using data from Wehler et al.[96] 2017)
Fatigue	£693.53	£138.71	TA378[94]
Nausea	£1,216.39	£243.28	Assumption: equal to vomiting
Neutropenia	£1,522.82	£304.56	Copley-Merriman et al.[95] 2018 (using data from Wehler et al.[96] 2017)
Vomiting	£1,216.39	£243.28	Copley-Merriman et al.[95] 2018 (using data from Wehler et al.[96] 2017)
Thrombocytopenia	£783.27	£156.65	NHS reference costs, SA12G-K[90]
Where appropriate, costs inflated from using PSSRU indices All standard errors assumed to be 20% of mean value			

B.3.5.5 Miscellaneous unit costs and resource use

All costs and resource use has been detailed in Sections B.3.5.1 to B.3.5.4.

Further information about how relevant cost and healthcare resource data were identified can be found in Appendix I.

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

B.3.6.1 Summary of base-case analysis inputs

Table 53. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Section
Baseline parameters			
Baseline parameters	Table 25	SE (age: normal; sex: beta)	B.3.2.1
Survival and progression functions			
Overall survival	Table 29	Described in Section B.3.3.1	B.3.3.1
Progression-free survival			
All-cause mortality	Table 35	None	B.3.3.1.3
Clinical parameters			
Discontinuations	Figure 44	Described in Section B.3.3.2.1	B.3.3.2.1
AE prevalence	Table 37	SE (beta)	B.3.3.2.1.3
Utilities			
Health state utilities	Table 39	SE (beta)	B.3.4.5
Costs			
Medication costs	Table 41, Table 42, Table 46	Not applicable	B.3.5.1
Health state costs	Table 47	SE (gamma)	B.3.5.3
AE costs	Table 52	SE (gamma)	B.3.5.4
Subsequent therapy costs	Table 50	Not applicable	B.3.5.3
AE: adverse events; SE: standard error.			

B.3.6.2 Assumptions

A summary of the main assumptions within the economic model is provided within Table 54.

Table 54. Assumptions applied within the economic model

Assumption	Rationale	Section
After 30 months patients in the pre-progression state within both arms move into a long-term remission state, to which age-related mortality is applied instead of disease-specific mortality	The long term remission health state was introduced to capture the long plateau in the OS curve seen in both arms of the CheckMate 649 trial which was an indication for a mixed population with a small “low-risk” fraction.	3.2
Baseline parameters are derived from Checkmate 649 cohort, which is assumed to be reflective	Although there may be differences between characteristics in Checkmate 649 and GC patients in UK clinical practice, Checkmate 649 isrepresentative of the types of patients who will be considered for treatment in clinical practice.	B 3.2.2

Assumption	Rationale	Section
of patients seen in UK clinical practice.		
To reflect the nature of GC and available evidence, the model assumes that GC phases are consecutive, so that patients cannot revert to pre-progression from more advanced phases of the disease	This assumption has been validated by clinicians and is line with other HTAs and economic analyses assessing the GC population.	B 3.2.3
Identification of most appropriate survival curves describing PFS, OS and time on treatment	Extensive analyses have been undertaken to identify appropriate and conservative survival curves describing nivolumab efficacy, with reference to the guidance from the NICE Decision Support Unit (DSU) and Bagust and Beale (2014).[70,71] The approach and identified survival extrapolations have been validated by clinical and health economic experts.	B.3.3.1
Source of adverse events for comparator treatments	Adverse events were sourced from Checkmate 649 for NIVO+CHEMO, FOLFOX and XELOX, whereas for the comparators of interest, estimates were derived from the systematic literature review. Immune-related adverse events were not modelled, due to the low incidence of grade 3-4 events and low cost of management. Further, evidence was not available to describe these events for comparators.	B 3.3.3.2
Utility values from Checkmate 649 reflect the on-treatment utility in the NIVO+CHEMO arm and the CHEMO arms	As data were limited for patients who had discontinued treatment or experienced a progression event, utility values are split by on-treatment and off-treatment in the NIVO+CHEMO arm. This was deemed appropriate to reflect the improvement in quality-of-life associated with NIVO+CHEMO.	B.3.4.5.1
Medical resource use is derived from evidence presented during TA208	Robust estimates of medical resource use for patients in this setting are not publicly available, given the lack of alternative treatments available for which evidence may have previously been gathered. In order to provide relevant economic evaluations and facilitate comparison between these appraisals, medical resource use from TA 208 is applied.	B 3.5.2

B.3.7 Base-case results

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

Total discounted costs associated with NIVO+CHEMO (with PAS), accrued over the modelled time horizon, were predicted to be [redacted] for NIVO+FOLFOX and [redacted] for NIVO+XELOX. By comparison, total discounted costs associated with comparators were notably lower. Incremental discounted costs for NIVO+FOLFOX were predicted to be [redacted] (versus FOLFOX), and for NIVO+XELOX were predicted to be [redacted] (versus XELOX), under base case assumptions. The resulting ICER estimates for NIVO+CHEMO were £47,840 per QALY (NIVO+FOLFOX versus FOLFOX) to £45,172 per QALY gain (NIVO+XELOX versus XELOX).

The results of the base-case analysis are summarised in Table 55 and Table 56.

Table 55. NIVO+FOLFOX base-case results

	NIVO+FOLFOX	FOLFOX
Patient level survival (undiscounted)		
Median ToT (years)*	[redacted]	0.422
Mean ToT (years)*	[redacted]	0.580
Median PFS (years)	[redacted]	0.613
Mean PFS (years)	[redacted]	2.224
Median OS (years)	[redacted]	1.073
Mean OS (years)	[redacted]	2.803
Patient-level progression		
Time in pre-progression (years)	[redacted]	0.782
Time in long term remission (years)	[redacted]	1.441
Time in post-progression (years)	[redacted]	0. 579
Costs (with PAS)		
HS costs	[redacted]	£10,821
Treatment costs	[redacted]	£18,116
AE costs for initial therapy	[redacted]	£429
Discontinuation costs	[redacted]	£43
Death costs	[redacted]	£4,972
Total costs	[redacted]	£33,950
Health benefits		
HS QALYs	[redacted]	1.664
Age-dependent utility	[redacted]	0.000
Adverse event utility	[redacted]	-0.001
Time-to-death utility	[redacted]	-0.059
Total QALYs	[redacted]	1.604
Total LYs (undiscounted)	[redacted]	2.802
Incremental results		
Incremental total costs	-	[redacted]
Incremental QALYs	-	[redacted]
Incremental LYs (undiscounted)	-	[redacted]
Cost/QALY	**-**	**£47,840**

AE: adverse event; HS: health state; LY: life year; OS: overall survival; PFS: progression free survival; QALY: quality-adjusted life year; ToT: Time on Treatment.

Table 56. NIVO+XELOX base-case results

	NIVO+XELOX	XELOX
Patient level survival (undiscounted)		
Median ToT (years)*	[redacted]	0.422
Mean ToT (years)*	[redacted]	0.580
Median PFS (years)	[redacted]	0.613
Mean PFS (years)	[redacted]	2.224
Median OS (years)	[redacted]	1.073
Mean OS (years)	[redacted]	2.803
Patient-level progression		
Time in pre-progression (years)	[redacted]	0.782
Time in long term remission (years)	[redacted]	1.441
Time in post-progression (years)	[redacted]	0.579
Costs (with PAS)		
HS costs	[redacted]	£10,821
Treatment costs	[redacted]	£4,155
AE costs for initial therapy	[redacted]	£429
Discontinuation costs	[redacted]	£43
Death costs	[redacted]	£4,972
Total costs	[redacted]	£19,990
Health benefits		
HS QALYs	[redacted]	1.664
Age-dependent utility	[redacted]	0.000
Adverse event utility	[redacted]	-0.001
Time-to-death utility	[redacted]	-0.059
Total QALYs	[redacted]	1.604
Total LYs (undiscounted)	[redacted]	2.802
Incremental results		
Incremental total costs		[redacted]
Incremental QALYs		[redacted]
Incremental LYs (undiscounted)		[redacted]
Cost/QALY		**£45,172**

AE: adverse event; HS: health state; LY: life year; OS: overall survival; PFS: progression free survival QALY: quality-adjusted life year; ToT: Time on Treatment.

B.3.8 Sensitivity analyses

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses 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.

B.3.8.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), a non-parametric bootstrapping approach will be 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, 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.

In order to enable the model results to converge to a sufficient degree of accuracy, 1000 simulations of the model were required.

B.3.8.1.1 PSA results

The ICER scatterplots for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 45 and Figure 46, while the cost-effectiveness acceptability curves (CEAC) are presented in Figure 47 and Figure 48.

Figure 45. ICER scatterplot: Nivolumab + FOLFOX versus FOLFOX

Figure 46. ICER scatterplot: Nivolumab + XELOX versus XELOX

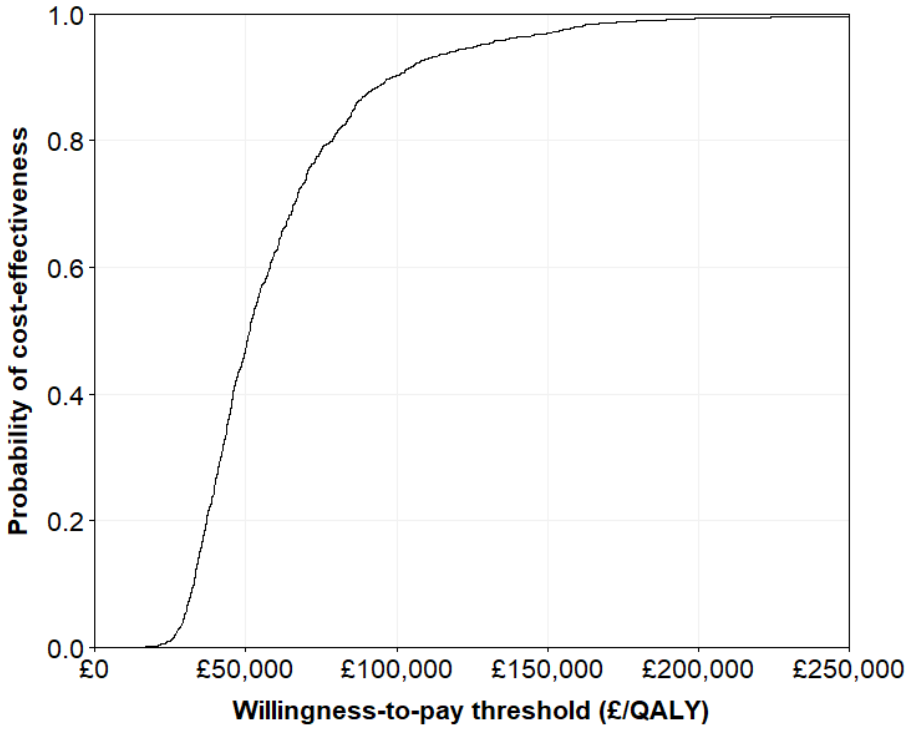


Figure 47. Cost-effectiveness acceptability curve: Nivolumab + FOLFOX versus FOLFOX

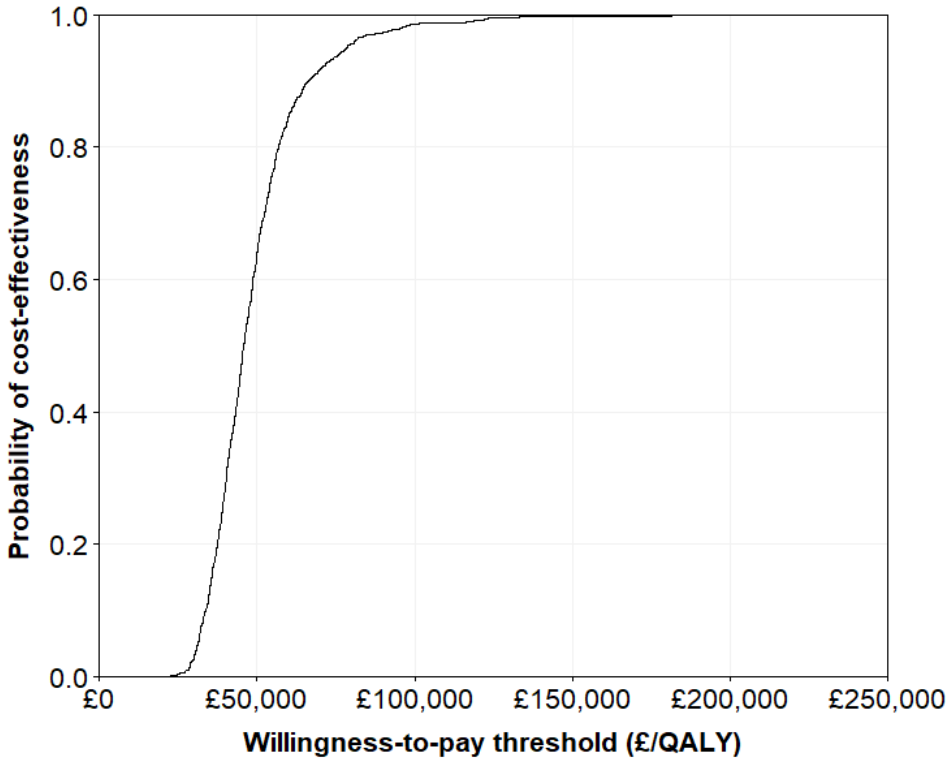


Figure 48. Cost-effectiveness acceptability curve: Nivolumab + XELOX versus XELOX

Based on this analysis, the probability that nivolumab + FOLFOX is cost-effective versus FOLFOX is estimated to be [redacted] at a willingness-to-pay threshold of £50,000 per QALY, and the same probability for nivolumab + XELOX versus XELOX is estimated to be [redacted]%. The base case results are presented in Table 57 and Table 58.

Table 57. Base case results (probabilistic): Nivolumab + FOLFOX versus FOLFOX

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,041
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 58. Base case results (probabilistic): Nivolumab + XELOX versus XELOX

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,305
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

B.3.8.2 Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, regarding the following assumption and parameters:

- Time horizon (32 and 48 years)
- Discounting: costs (0% and 6%)
- Discounting: benefits (0% and 6%)
- Baseline characteristics: age (± 20%, impacting on all-cause mortality)
- Baseline characteristics: sex (0% and 100% male, impacting on all-cause mortality)
- Life table mortality rates (± 20%)
- Health state costs: pre-progression and post-progression (± 20%)
- Health state costs: death (± 20%)
- Adverse event costs (± 20%)
- Health state utility: pre-progression and post-progression (± 20%)

- Adverse event disutility (± 20%)

Note; where (± 20%) is specified, the mean value is multiplied by 0.8 or 1.2 so to assess the impact of a 20% change in a value.

Results of the deterministic sensitivity analysis are presented in Figure 49 and Figure 50. These figures demonstrate the impact of specific parameters on ICER estimates. In both cases, the factors with the greatest impact on the ICER were baseline age of patients, discounting, and age-dependent utilities.

In the majority of scenarios, the ICER for NIVO+CHEMO versus FOLFOX stayed near the £50,000 per QALY willingness-to-pay threshold; scenarios where the ICER exceeded the £50,000 threshold included the value increasing the benefits discounting, as well as increasing the baseline age of patients and the age-dependent utility decrements.

In the majority of scenarios, the ICER for NIVO+CHEMO versus XELOX stayed near the £50,000 per QALY willingness-to-pay threshold; scenarios where the ICER exceeded this threshold included increasing the benefits discounting, baseline age of patients and the age-dependent utility decrements.

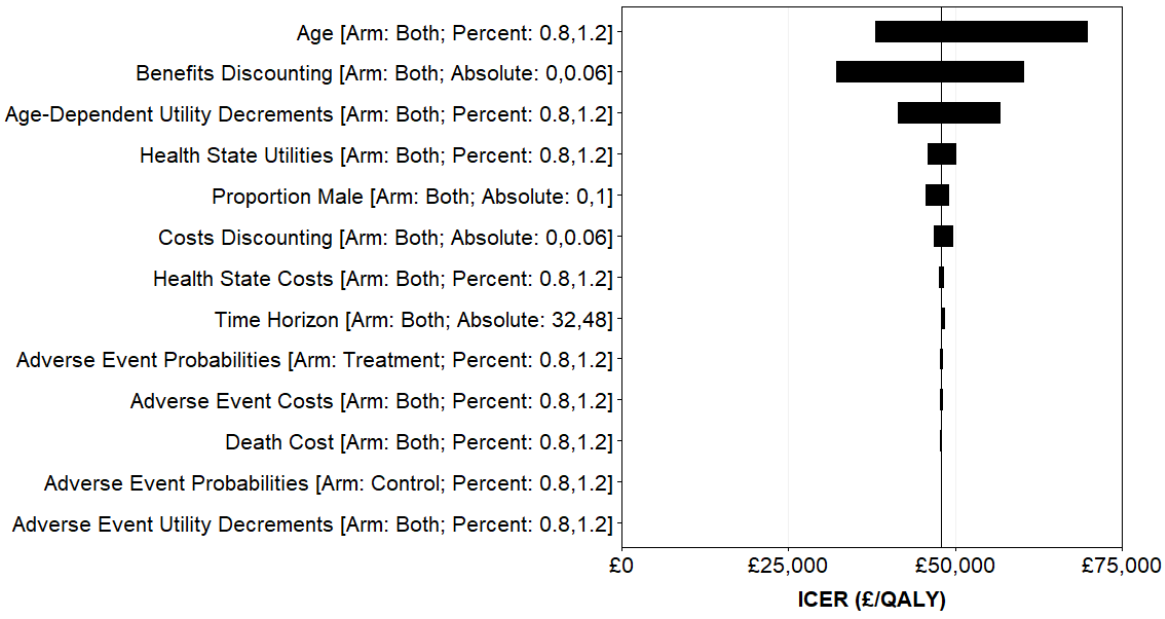


Figure 49. Deterministic sensitivity analysis for nivolumab + FOLFOX versus FOLFOX: impact on ICER

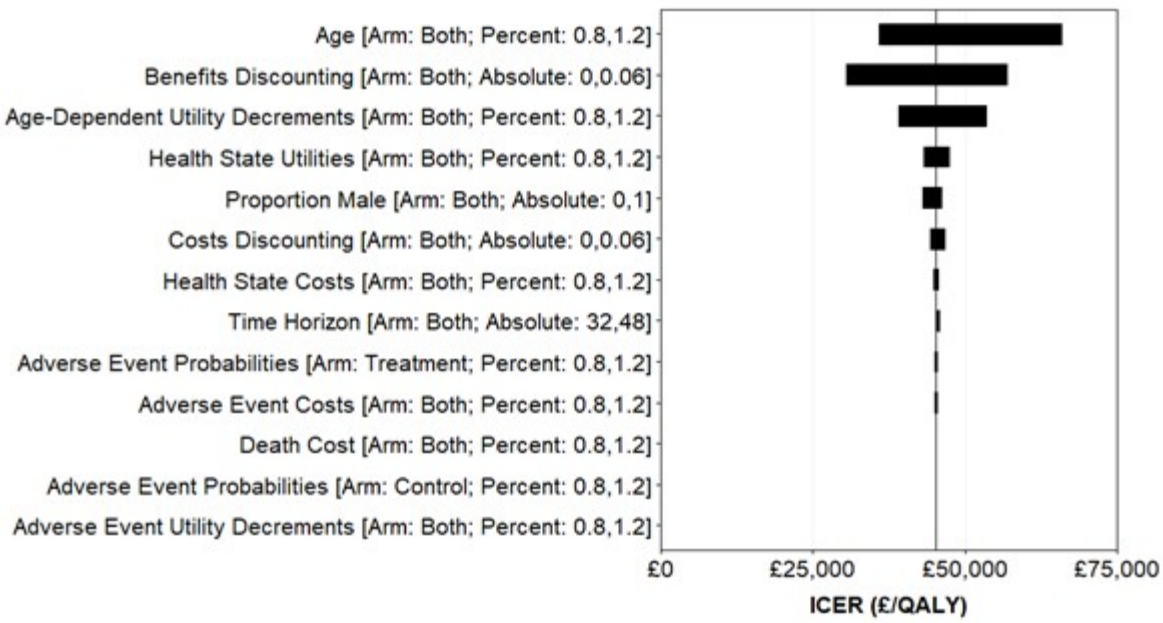


Figure 50. Deterministic sensitivity analysis for nivolumab + XELOX versus XELOX: impact on ICER

B.3.8.3 Scenario analysis

B.3.8.3.1 Removal of the long-term remission state

The base case analysis informed by CheckMate 649 utilised a long-term remission state in both the treatment and comparator arm to reflect the long tail seen in the results of the survival analysis. A scenario was conducted removing this state and allowing patients who have not progressed to remain in the progression-free state, increasing their mortality risk and keeping them at risk of progression. Results are shown in Table 59.

Removing the long-term remission state had little impact on incremental costs (an increase from [redacted] in the base case to [redacted] for NIVO+CHEMO vs FOLFOX and from [redacted] to [redacted] vs XELOX) however the total QALYs dropped for both arms (from [redacted] in the base case to [redacted] for NIVO+CHEMO and from [redacted] to [redacted] for FOLFOX and XELOX). The ICERs increased compared to the base case, with the NIVO+CHEMO vs FOLFOX ICER increasing from £47,840 per QALY to £99,456 and the NIVO+CHEMO vs XELOX ICER increasing from £45,172 per QALY to £94,075.

Table 59. Scenario analysis: impact of not using a long-term remission state

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£99,456**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£94,075**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.3.2 Impact of the treatment modifier

A treatment modifier was used in the base case to reflect doses that were missed during CheckMate 649. To explore the impact of this on the ICER, a scenario was run without the treatment modifier and results are displayed in Table 60. The removal of the treatment modifier increased both ICERs; to £56,018 from the base case of £47,840 for NIVO+CHEMO vs FOLFOX and to £51,067 from the base case of £45,172 for NIVO+CHEMO vs XELOX.

Table 60. Scenario analysis: impact of removing treatment modifier

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£56,018**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,067**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.3.3 Impact of alternative utilities

In the base case analysis, time to death utilities were implemented from six months prior to death. A scenario exploring the impact of not using time to death utilities was conducted. Results are displayed in Table 61, where the removal of time to death utilities resulted in an ICER estimate of £47,962 for NIVO+CHEMO vs FOLFOX and £45,287 for NIVO+CHEMO vs XELOX, which represented minimal increases from the base case estimates (£47,840 per QALY and £45,172 per QALY respectively).

Table 61. Scenario analysis: impact of removing time to death utilities

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,962**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,287**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.3.4 Efficacy by PD-L1 CPS subgroup

CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%). However, the two primary endpoints evaluated the benefit NIVO+CHEMO in patients with PD-L1 CPS ≥5. This allowed for the evaluation of the benefit of NIVO+CHEMO in three subgroups determined by CPS score: ≥1 (Table 62) and ≥5 (Table 63). The results demonstrated a reduction in ICERs for both comparisons that increased the higher the CPS score threshold.

Table 62. Scenario analysis: results in ≥1 CPS subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,370**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,438**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

Table 63. Scenario analysis: results in ≥5 CPS subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,157**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,973**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.3.5 Removal of stopping rule

The base case assumes a stopping rule of two years for the NIVO+CHEMO treatments, aligned to the CheckMate 649 study design and the draft SmPC for nivolumab. As this limits the costs in the treatment arm and not the control arm, a scenario was undertaken exploring the impact of not using the stopping rule; however, it should be noted that this scenario is presented to assess the uncertainty of the stopping rule application, but does not reflect clinical practice.

Results from this analysis are shown in Table Table 64. The removal of the stopping rule increased both ICERs; from £47,840 in the base case to £50,368 for NIVO+CHEMO vs FOLFOX and from £45,172 in the base case to £46,943 for NIVO+CHEMO vs XELOX.

Table 64. Scenario analysis: removal of NIVO+CHEMO stopping rule

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,368**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,943**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.3.6 Alternative comparators

The base case analysis informed by CheckMate 649 compares NIVO+CHEMO versus chemotherapy, either XELOX or FOLFOX. As outlined in Section B.2.10.2, this can be considered clinically appropriate based on current guidelines, clinical evidence and expert opinion.

However, in order to inform decision-making, a comparison of NIVO+CHEMO against other potential comparators has been provided as a scenario analysis, specifically cisplatin + 5FU (CF) and cisplatin + capecitabine (CX). Hazard ratios estimated in the ITC (Section 2.10.5) were applied to the CHEMO arm to determine health state occupancy for CF and CX. The NIVO+CHEMO arm consisted of 50% NIVO+XELOX and 50% NIVO+FOLFOX.

As described in Table 65, predicted discounted incremental QALYs ranged from 0.956 (versus CX) to 1.150 (versus CF), with variation in discounted incremental costs from £40,794 to £34,363, versus CX and CF, respectively. The resultant ICER estimate for NIVO+CHEMO versus CX was £56,470 per QALY and for NIVO+CHEMO versus CF was £29,871 per QALY.

Table 65. Scenario analysis: impact of alternative comparators

	CF	CX
Incremental QALYs	1.150	0.733
Incremental life years	1.660	0.956
Incremental costs	£34,363	£40,794
ICER (£/QALY)	**£29,871**	**£56,470**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year		

B.3.8.3.7 Only NIVO+CHEMO patients enter the long-term remission state

The base case analysis informed by CheckMate 649 utilised a long-term remission state in both the treatment and comparator arm to reflect the long tail seen in the results of the survival

analysis. To demonstrate that this was a conservative assumptiom, a scenario was conducted where only patients in the treatment arm could enter this state. Results are shown in Table 66.

Allowing only NIVO+CHEMO patients to enter the long-term remission state had little impact on incremental costs (a decrease from [redacted] in the base case to [redacted] for NIVO+CHEMO vs FOLFOX and from [redacted] to [redacted] vs XELOX) however the incremental QALYs increased for both comparisons (from [redacted] in the base case to [redacted]). The ICERs decreased greatly compared to the base case, with the NIVO+CHEMO vs FOLFOX ICER decreasing from £47,840 per QALY to £27,517 and the NIVO+CHEMO vs XELOX ICER decreasing from £45,172 per QALY to £25,947.

Table 66. Scenario analysis: impact of only NIVO+CHEMO patients entering long-term remission

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,517**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,947**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

B.3.8.4 Summary of sensitivity analyses results

Several sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model, In the deterministic analysis, in the majority of scenarios NIVO+CHEMO remained cost-effective at a willingness-to-pay threshold of £50,000 per QALY. Similarly, in the PSA, the probability that NIVO+CHEMO was cost-effective versus FOLFOX is [redacted] and versus XELOX is [redacted] at a willingness-to-pay threshold of £50,000 per QALY.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Section 3.8.3; again, the majority of these scenarios resulting in cost-effective ICERs at the £50,000 per QALY threshold.

B.3.8.5 Subgroup analysis

All available subgroup analyses are provided in Section B.3.8.3.

B.3.9 Validation

B.3.9.1 Validation of cost-effectiveness analysis

In general, where no evidence has been identified to validate the results of the cost-effectiveness analysis, simple assumptions have been made based on independent sources, such as published literature, GC guidelines or previous NICE appraisals in the field of GC. These assumptions will be assessed for clinical plausibility; uncertainty will be characterised through the use of sensitivity analyses. Extensive sensitivity analyses will also be undertaken to ascertain at which threshold the ICERs will remain under.

A technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

B.3.9.2 Validation of survival extrapolation

As described in B.3.3.1.1.5, there are no other studies with which to validate the results for extrapolation of the CheckMate 649 NIVO+CHEMO arm, other than ATTRACTION-4, which cannot be considered representative of UK clinical practice.

However, as shown in Figure 51. Overall survival for patients receiving chemotherapy for gastro-oesophageal adenocarcinoma at the Royal Marsden Hospital16, the median OS reported for patients of a UK retrospective study receiving chemotherapy was broadly similar with that of the CHEMO arm of CheckMate 649, but slightly underestimated outcomes throughout (median OS: 11.48 months and 12.88 months, respectively).[16] This suggests that modelled outcomes are for CHEMO are conservative compared with clinical practice.

Figure 51. Overall survival for patients receiving chemotherapy for gastro-oesophageal adenocarcinoma at the Royal Marsden Hospital[16]

Despite the lack of real-world data, it was possible to validate the survival extrapolation for nivolumab against longer-term survival data from studies evaluating other indications using immunotherapy agents. Available long-term data are presented in Table 67 for nivolumab in various other indications. As can be seen, there is typically an initial high rate of mortality followed by a lower rate of mortality over long-term follow-up. Long term survivorship without the need for prolonged treatment has been observed for immunotherapies in other indications. Long term survivorship without the need for prolonged treatment has been observed for immunotherapies in other indications. For example, nivolumab therapy can lead to five-year survival in 13% of NSCLC patients, as presented in Table 67.[97]

Table 67. Survival rates for immunotherapies with available long-term follow-up

Study	CheckMate 649	CheckMate 025	CheckMate 017/057	CheckMate 017/057/063/003	CheckMate 003	Schadendorf et al., 2015[98]	CheckMate 067
Reference		Plimack et al., 2016[99]	Vokes 2018[97], Gettinger 2019[100]	Antonia 2019	Hodi et al., 2016[101]		Hodi 2018[102], Wolchok 2017[103], Larkin 2019[104]
Drug	Nivolumab + chemotherapy	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Ipilimumab	Nivolumab plus ipilimumab
Indication	GC	RCC	NSCLC	NSCLC	Melanoma	Melanoma	Melanoma
n	789	410	427	664	107	1,861	314
12 month OS	55.0%	76%	48%		63%	~27%	73%
24 month OS	-	52%	27%		48%	~47%	64%
36 month OS	-	~35%	17%		42%	22%	58%
48 month OS	-	-	-		35%	~21%	-
60 month OS	-	-	13.4%	14%	34%	~20%	-
120 month OS	-	-	-		-	~18%	52%

ACM: all cause mortality; NSCLC: non-small cell lung cancer; OS: overall survival; RCC: renal cell carcinoma
~ numbers approximated from visual inspection of Kaplan Meier curves

B.3.10 Interpretation and conclusions of economic evidence

Base case analysis

- Use of NIVO+CHEMO will result in an increased mean OS of [redacted] years versus CHEMO alone, as well as additional discounted QALYs and life years of [redacted] and [redacted], respectively.
- Discounted incremental costs were estimated to be [redacted] versus FOLFOX and [redacted] versus XELOX under base case assumptions and the resultant ICER was £47,840 per QALY versus FOLFOX and £45,172 per QALY versus XELOX, which is considered to be cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Sensitivity analysis

- In the deterministic and probabilistic sensitivity analyses, NIVO+CHEMO was cost-effective in the majority of scenarios at a willingness-to-pay threshold of £50,000 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 majority of ICERs remain below the £50,000 per QALY threshold.

As previously noted, this analysis has been conducted where there is a paucity of evidence necessitating several pragmatic assumptions, which have been made based on independent sources, such as published literature, gastric cancer guidelines or previous NICE appraisals. These assumptions have been assessed through sensitivity analysis and scenario analysis in order to assess the impact of uncertainty. Further, the modelling approach has been chosen to reflect the most important treatment outcomes for most gastric cancer patients: survival, side effects and quality of life.

In the base case analysis, it was estimated that NIVO+CHEMO use would result in [redacted] discounted QALYs and [redacted] discounted LYs. Further, it was estimated that patients receiving NIVO+CHEMO would spend [redacted] years in the pre-progression state (versus [redacted] years for patients receiving chemotherapy alone), with a subsequent [redacted] years in the post-progression state (versus [redacted] years for chemotherapy along) or a subsequent [redacted] years in the long term remission state (versus [redacted] years for chemotherapy along), indicating that NIVO+CHEMO is associated with incremental benefit across all health states. Discounted incremental costs were estimated to be [redacted] over FOLFOX and [redacted] over XELOX under base case

assumptions and the resultant ICERs were £47,840 and £45,172 respectively, which can be considered cost-effective at a willingness-to-pay threshold of £50,000 per QALY

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis and PSA, NIVO+CHEMO was cost-effective in the majority of scenarios at a WTP threshold of £50,000/QALY. Similarly, when plausible alternative inputs and assumptions were assessed as scenario analyses within Section B.3.8.3, the majority of ICERs remain below the £50,000/QALY threshold. This indicates that the ICER is relatively stable across analyses.

The addition of nivolumab to standard chemotherapy for adults with untreated gastric cancer would provide an opportunity to make a significant and substantial impact on health-related benefits, address a current unmet need, and would represent a further, significant advance in the management of this end-of-life condition.

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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 (original)	Provided as a separate document
	D2: Identification, selection and synthesis of clinical evidence: systematic literature review report (update)	Provided as a separate document
E	Subgroup analysis	Provided in the main body of the report
	E1: CheckMate 649 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 (original)	Provided as a separate document
	G2: Published cost-effectiveness studies: systematic literature review (update)	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	Indirect treatment comparison report	Provided as a separate document
M	Survival analysis report	Provided as a separate document
N	Utility analysis report	Provided as a separate document

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

Clarification questions

February 2021

File name	Version	Contains confidential information	Date
		Yes	17 March 2021

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.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

CheckMate 649 trial

A1. Priority question: Please provide the statistical analysis plan for the analyses based on the database lock (DBL) of 10th July 2020.

The statistical analysis plan is provided as Appendix A1.

A2. Priority question: Please provide results of any tests or analyses conducted to explore the proportional hazards assumption for the following outcomes:

a) **Overall survival (OS) for all randomised patients**

b) **Progression free survival (PFS) by blinded independent central review (BICR) for all randomised patients**

c) **OS for all randomised patients with programmed cell death ligand (PD-L1) combined positive score CPS≥5**

d) **PFS by BICR for all randomised patients with PD-L1 CPS≥5**

e) **OS for all randomised patients with PD-L1 CPS≥1**

f) **PFS by BICR for all randomised patients with PD-L1 CPS≥1**

If no tests or analyses have been conducted to explore the proportional hazards assumption, please provide log cumulative hazard plots, Schoenfeld residuals plots and Schoenfeld test p-values for each of the outcomes listed.

These figures and values are provided as Appendix A2.

Over the observed period, the assumption of proportional hazards was not violated. However, as outlined in Section B.3.2.2.1 of Company submission Document B, there is significant evidence for a proportion of the population in both arms experiencing long-term remission. This evidence is partly reflected as a hazard plateau in the data provided in Appendix A2. For patients achieving long-term remission, disease-related outcomes are likely to be comparable. However, the increasing influence of a long-term remission population that is potentially unequal between the arms is not consistent with the assumption of proportional hazards. The existence of this fraction is acknowledged among conventional therapies (see question and response to B3 and B4), and whilst small in proportion to the treated population, as a fraction among survivors they necessarily become dominant at some time within extrapolation. By definition, these long-term responders must be at the

same hazard regardless of therapy, and so the time-varying hazard ratio between arms must tend to 1 in long term extrapolation. If the arms were to be modelled according to proportional hazards, but respecting the existence of an LTR fraction, this would imply that based upon the <1 hazard ratio applied to NIVO+CHEMO, as the hazard upon the CHEMO arm approached the LTR hazard, the NIVO+CHEMO hazard would drop below the LTR hazard. This hazard may be reasonably assumed to be that of the matched general population, and so the proportional hazards model lacks face validity in extrapolation as, when applied to a scenario with an acknowledged LTR fraction, the marginal hazard of mortality is reduced to below the general population. This lack of face validity of the model structure precludes the use of proportional hazards models in extrapolation and there is limited value in using a proportional hazards model during the observed period.

A3. Please provide the following supplementary tables to the primary Clinical Study Report (CSR) based on the 10th July 2020 database lock:

a) For all randomised patients with PD-L1 CPS≥5:

i. PFS per investigator: Table S.5.22.2 (primary definition)

ii. Objective response rate (ORR) per investigator: Table S.5.9.4 (all responders), Table S.5.9.2 (all measurable responders)

b) For all randomised patients with PD-L1 CPS≥1:

i. PFS per investigator: Table S.5.221.1 (primary definition)

ii. ORR per investigator: Table S.5.9.8 (all responders), Table S.5.9.6 (all measurable responders)

c) For all randomised patients:

i. PFS rates per investigator: Table S.5.23.17 (primary definition)

ii. ORR per investigator: Table S.5.9.16 (all responders), Table S.5.9.14 (subjects with measurable disease).

These tables are included in Appendix A3.

Table	Appendix A3 Page number
All randomised patients with PD-L1 CPS≥5	
PFS per investigator: [redacted] (primary definition)	Page 8
Objective response rate (ORR) per investigator: [redacted] (all responders)	Page 3

Objective response rate (ORR) per investigator: [redacted] (all measurable responders)	Page 1
All randomised patients with PD-L1 CPS≥1	
PFS per investigator: [redacted] (primary definition)	Page 10
ORR per investigator: [redacted] (all responders)	Page 5
ORR per investigator: [redacted] (all measurable responders)	Page 4
For all randomised patients	
PFS rates per investigator: Table [redacted] (primary definition)	Page 9
ORR per investigator: [redacted] (all responders)	Page 7
ORR per investigator: [redacted] (subjects with measurable disease)	Page 6

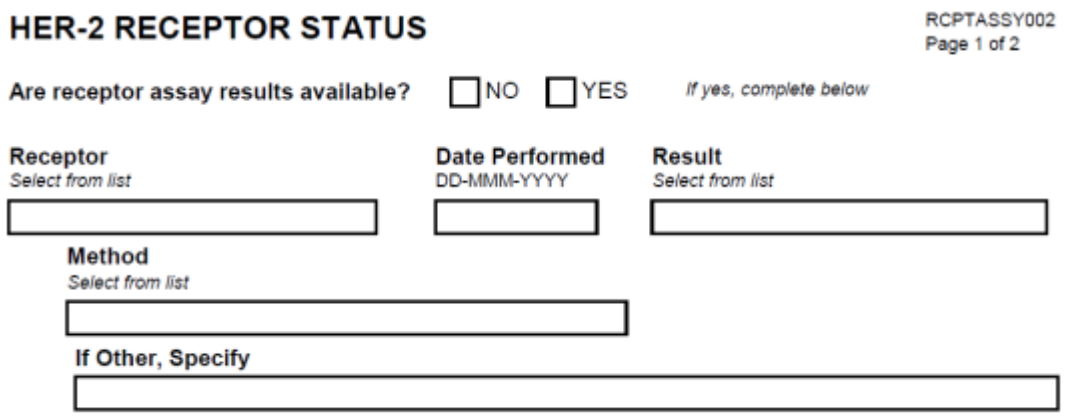
A4. The HER2 status of patients in the CheckMate 649 trial is listed in Table 9 of the company submission (CS). Please explain the difference between HER2 status that is 'unknown' and HER2 status that is 'not reported'.

Per the CheckMate 649 protocol, patients with known HER2-positive status were excluded. Please explain why some patients with positive HER2 status were randomised in the trial?

Where HER2 testing was undertaken but the results were inconclusive, the CheckMate 649 study captured the result as "unknown". By contrast, "not reported" referred to patients where HER2 test results were not reported or not performed, as this testing was not routine practice in some regions.

To explain further, Figure 1 shows the electronic case report form (eCRF) page below:

- Patients where HER2 status was designated "not reported" indicates that the site checked that the receptor assay results available as NO.
- Patients where HER2 status was designated "unknown" indicates that the lead question below would be YES, but with the results marked as UNKNOWN due to the test being inconclusive or there being no report available.


HER-2 RECEPTOR STATUS

RCPTASSY002
Page 1 of 2

Are receptor assay results available? ☐ NO ☐ YES *If yes, complete below*

Receptor
Select from list

Date Performed
DD-MMM-YYYY

Result
Select from list

Method
Select from list

If Other, Specify

Clarification questions

Figure 1. eCRF page with HER2

Although HER2 positive status at baseline was reason for exclusion from CheckMate 649, some patients who were enrolled at baseline with unknown HER2 status but may have been tested during the study. However, these patients are still relevant to ITT analysis.

In the 10th July 2020 DBL, there were ▌ subjects with HER2 positive status:

- ▌ subjects had HER2 positive status available prior to randomisation, both were reported as significant protocol deviation.
- ▌ subjects had HER2 positive result available after randomisation

However, after the DBL, the site confirmed that ▌ of the ▌ subjects with confirmed HER2 positive status was actually negative and that the data was entered incorrectly. This subject data will be updated in next DBL and the report will reflect a total of ▌ HER2 positive subjects.

A5. Patients in the NHS with untreated advanced gastric or gastro-oesophageal junction cancer are routinely tested for dihydropyrimidine dehydrogenase (DPD) deficiency prior to treatment with fluoropyrimidine chemotherapy agents. Were patients in the CheckMate 649 trial tested for DPD deficiency prior to enrolment?

DPD tests were not required for inclusion in the trial. However, some country specific protocols did require a DPD test before 5-FU infusion, with the following exclusion criteria applied in those protocols:

- To be eligible a systematic search for DPD deficiency has to be performed before any administration of 5-fluorouracil/capecitabine, in compliance with INCa/HAS recommendations,
- For total deficiency of DPD, defined as blood uracil level ≥150 ng/mL, the subject should be excluded.

Indirect treatment comparisons

A6. Priority question: The Chen *et al* study (reference 52 of the CS) is a re-analysis of the 126 Chinese patients randomised into the ML17032 trial (Kang *et al* 2009).

Please clarify whether these 126 patients have been included in the NMAs twice, i.e., results from both the Chen *et al* and Kang *et al* studies are used in the NMAs.

a. **If the 126 patients have been included twice, please repeat the NMAs for OS and PFS including only the results from the Kang *et al* study**

OR

b. If the Chen *et al* and Kang *et al* studies do not have any overlap of patients, please confirm the reference for the Chen *at al* study and please provide the results of a sensitivity analysis designed to explore the robustness of the NMA results to the inclusion of the study by Chen *et al*, conducted solely within an Asian population (CS, page 66 [Section B.2.10.4])

Given that there is uncertainty around the overlap for patients within these two publications, both sets of data were included in the base case NMA, with sensitivity analyses undertaken excluding Chen et al, as provided in Appendix A of the ITC report (Appendix L). In general, NMA results excluding Chen et al. are consistent in effect with previously provided analysis including Chen et al.

The sensitivity analysis shows that, in line with previous analysis, XELOX/FOLFOX is less efficacious in terms of extending OS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab, but more efficacious than 5-fluorouracil + cisplatin. Treatment with capecitabine + cisplatin + trastuzumab was nominally superior to all other included treatments. Results, displayed as HR and 95% credible intervals, for each treatment and comparator combination are presented in Table 1 for both fixed and random effects analysis. Results for fixed and random effects analysis were consistent.

Results of the sensitivity analysis for PFS were entirely consistent with those for OS, indicating that XELOX/FOLFOX is less efficacious in terms of extending PFS than capecitabine + cisplatin and capecitabine + cisplatin + trastuzumab, but more efficacious than 5-fluorouracil + cisplatin. Treatment with capecitabine + cisplatin + trastuzumab was nominally superior to all other included treatments. Results for each treatment and comparator combination are presented in Table 2 for both fixed and random effects analysis.

Table 1. Overall survival results

Data are HR (95% credible interval), with bold values indicating that the credible interval does not include unity.

	Fixed Effects				Random Effects			
Treatment / Comparator	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**
XELOX/FOLFOX	1.00 (1.00-1.00)	0.99 (0.63-1.55)	1.16 (0.82-1.65)	0.73 (0.44-1.20)	1.00 (1.00-1.00)	0.98 (0.50-1.92)	1.16 (0.71-1.91)	0.73 (0.33-1.60)
Capecitabine + cisplatin	1.01 (0.64-1.59)	1.00 (1.00-1.00)	1.18 (0.88-1.56)	**0.74 (0.60-0.91)**	1.02 (0.52-1.98)	1.00 (1.00-1.00)	1.18 (0.74-1.86)	0.74 (0.49-1.12)
5-FU + cisplatin	0.86 (0.61-1.23)	0.85 (0.64-1.13)	1.00 (1.00-1.00)	**0.63 (0.44-0.90)**	0.87 (0.52-1.42)	0.85 (0.54-1.34)	1.00 (1.00-1.00)	0.63 (0.34-1.17)
Trastuzumab+ capecitabine + cisplatin	1.37 (0.83-2.25)	**1.35 (1.10-1.67)**	**1.59 (1.12-2.26)**	1.00 (1.00-1.00)	1.38 (0.62-3.01)	1.35 (0.89-2.05)	1.59 (0.86-2.94)	1.00 (1.00-1.00)

5-FU: 5-fluorouracil; FOLFOX: folinic acid, 5-FU and cisplatin; XELOX: capecitabine, oxaliplatin.

Table 2. Progression free survival results

Data are HR (95% credible interval), with bold values indicating that the credible interval does not include unity.

	Fixed Effects				Random Effects			
Treatment / Comparator	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**	**XELOX/FOLFOX**	**Capecitabine + cisplatin**	**5-FU + cisplatin**	**Trastuzumab+ capecitabine + cisplatin**
XELOX/FOLFOX	1.00 (1.00-1.00)	1.00 (0.66-1.52)	1.23 (0.88-1.72)	0.71 (0.45-1.12)	1.00 (1.00-1.00)	1.00 (0.49-2.04)	1.23 (0.73-2.08)	0.71 (0.31-1.66)
Capecitabine + cisplatin	1.00 (0.66-1.52)	1.00 (1.00-1.00)	1.23 (0.96-1.59)	**0.71 (0.59-0.86)**	1.00 (0.49-2.04)	1.00 (1.00-1.00)	1.23 (0.76-2.00)	0.71 (0.45-1.13)
5-FU + cisplatin	0.81 (0.58-1.13)	0.81 (0.63-1.04)	1.00 (1.00-1.00)	**0.58 (0.42-0.79)**	0.81 (0.48-1.37)	0.81 (0.50-1.32)	1.00 (1.00-1.00)	0.58 (0.30-1.12)
Trastuzumab+ capecitabine + cisplatin	1.41 (0.89-2.22)	**1.41 (1.16-1.70)**	**1.74 (1.27-2.38)**	1.00 (1.00-1.00)	1.41 (0.60-3.27)	1.41 (0.89-2.22)	1.74 (0.89-3.37)	1.00 (1.00-1.00)

5-FU: 5-fluorouracil; FOLFOX: folinic acid, 5-FUand cisplatin; XELOX: capecitabine, oxaliplatin.

A7. Priority question: It is stated in the CS, page 69 (Section B.2.10.4.2), that "as nivolumab has a different mechanism of action, survival profile and distribution of events to other arms in the network, a point estimate HR may not be fully capable to describe the time to event in this arm."

Please clarify how the differences between nivolumab and the other drugs in the network do not violate the fundamental assumption of transitivity that underpins NMAs (i.e., it is equally likely that any patient in the network could have been given any of the treatments in the network).

If the assumption of transitivity has been violated by including nivolumab + chemotherapy in the network, please repeat the NMAs excluding the CheckMate 649 trial data and present NMA results only for the comparators to nivolumab + chemotherapy. If appropriate, please provide updated cost effectiveness scenario analyses based on the updated NMA results.

Nivolumab has a different mechanism of action, survival profile and distribution of events in comparison with other arms of the network. To account for this, all HRs as estimated from the conducted NMA were applied as effects to the XELOX/FOLFOX arm of CheckMate 649; as such an assumption of transitivity applies only to the network and the control arm of CheckMate 649. As all included comparators treatments are chemotherapy regimens, they will have similar survival profiles, although with varying degrees of efficacy. Presented NMA analysis did not include study data from CheckMate 649 in the network, and as such the requested sensitivity analysis already forms the basis for the submission.

A8. Priority question: Please clarify which published results for OS and PFS from the Al-Batran *et al*, Bang *et al,* and Kang *et al* studies (and Chen *et al* if appropriate) have been included in the NMAs. Specifically, for each study:

a. **Have HRs and 95% CIs have been extracted or have Kaplan-Meier curves been digitised?**

b. **Which population results have been included? (i.e., intention to treat, per protocol etc.)**

c. Have unadjusted / non-stratified or adjusted / stratified results been included?

d. For PFS outcomes, have BICR or investigator results been included?

Please see below for a summary of results included in the NMA for each study.

- Al-Batran et al.[1] analysis was based on digitised Kaplan-Meier estimates of OS and PFS, based on an intention to treat population, and as such, results are unadjusted. Per the methodology described by Al-Batran et al., *"responses were classified according to WHO criteria. Computed tomography or magnetic resonance imaging scans of target areas were performed before the start of the treatment and were repeated every 6 weeks in both arms. Patients who discontinued the study were evaluated every 2 months. PFS was measured from the date of random assignment until disease progression or death of any cause."*

- Bang et al.[2] analysis was based on reported HRs and 95% CIs for OS and PFS based on an analysis population that included only patients who received a randomised treatment. NMA analysis was based on stratified results, however, point estimates of PFS were the same in both stratified and un-stratified analysis. PFS was assessed as the time to the first of progressive disease or death, with progressive disease defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as a reference the smallest sum of the longest diameter of lesion recorded since the treatment started, or the appearance of one or more lesions. For non-target lesions, progressive disease was defined as an unequivocal progression of existing non-target lesions.

- Kang et al.[3] analysis was based on reported HRs and 95% CIs for OS and PFS based on the per-protocol study population. Reported results were based on stratified analysis which included geographical region and other unreported prognostic factors. PFS, measured as time from randomisation to the date of first documented disease progression or death, whichever occurred first.

- Chen et al.[4] analysis was based on reported HRs and 95% CIs for OS and PFS based on the per-protocol study population. Results included in the NMA were not adjusted for patient characteristics. PFS, measured as time from randomisation to the date of first documented disease progression or death, whichever occurred first.

A9. Priority question: It is stated in the CS, page 67 (Section B.2.10.4), that the method proposed in Technical Support Document 2 for estimating differences with HRs is deemed appropriate as the proportional hazard assumption is not violated. Please provide evidence that this assumption is not violated for the Al-

Batran *et al*, Bang *et al,* and Kang *et al* studies (and Chen *et al* if appropriate) for the outcomes OS and PFS.

Results reported by Bang et al.,[2] Kang et al.[3] and Chen et al.,[4] all reported HRs and 95% CI as derived from Cox proportional hazards regression models. As individual patient data are not available for the patients enrolled in these studies, the authors are best placed to assess the validity of proportional hazards assumptions, however from visual inspection of the reported Kaplan-Meier data, there is little evidence of violations of these assumptions. The study conducted by Al-Batran et al.[1] does not report results of Cox proportional hazards models, and as such, presented Kaplan-Meier data were digitised in order to derive an estimate of relative treatment efficacy. Analysis of simulated patient level data based on digitised Kaplan-Meier data indicate that the proportional hazards assumption is not violated for the OS outcome, with non-significant results from the Schoenfeld individual test, and parallel lines for each treatment arm when plotting log(-log(S(t))) vs. log(t) (Figure 2).

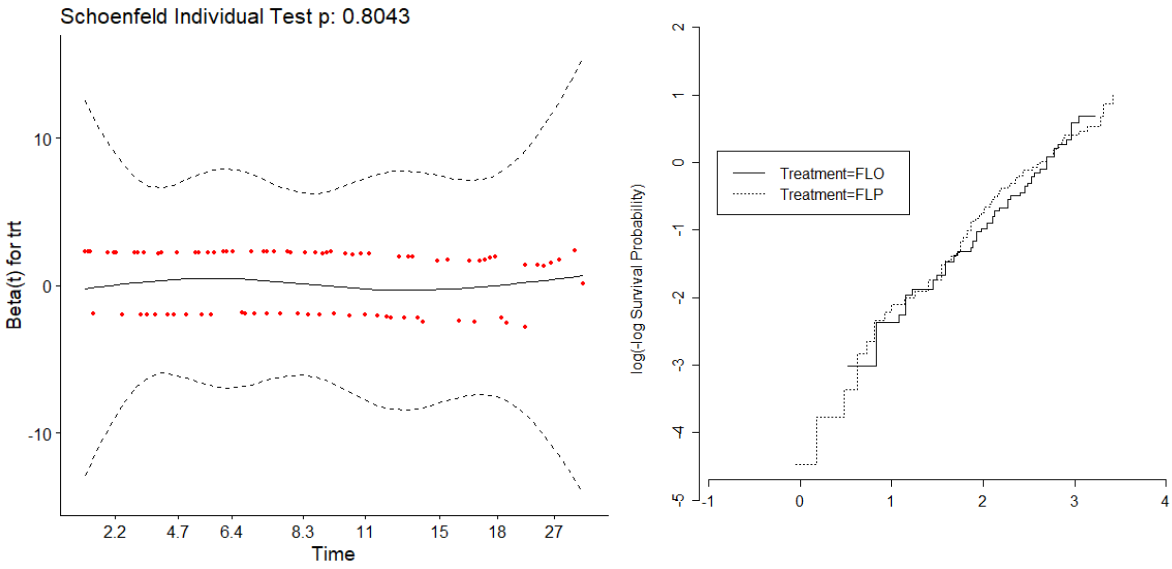


Figure 2. Schoenfeld residuals (left) and log(-log(S(t))) vs. log(t) plot (right) for simulated OS data based on the results of Al-Batran et al.[1]

However, in this study there is evidence that the proportional hazards assumption is violated with respect to study arm for PFS outcomes, where Kaplan-Meier estimates cross after approximately 12 months. This conclusion is supported by examination of Schoenfeld residuals and log(-log(S(t))) vs. log(t) plot, with statistically significant time interaction on treatment effect, and non-parallel lines (Figure 3).

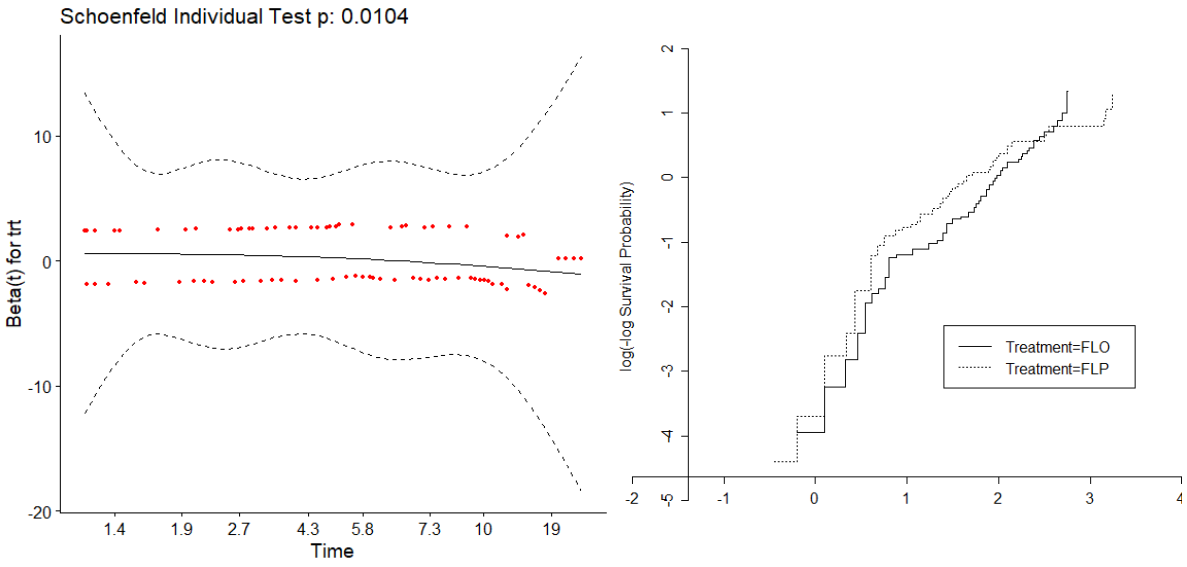


Figure 3. Schoenfeld residuals (left) and log(-log(S(t))) vs. log(t) plot (right) for simulated PFS data based on the results of Al-Batran et al.[1]

However, it is important to note that without inclusion of PFS data from Al-Batran et al.,[1] it is not possible to form a network for comparison of outcomes for XELOX/FOLFOX and any of the identified potential comparators. As such, PFS estimates generated from the NMA should be interpreted as indicative, however, they remain the most informative estimate of comparative efficacy between treatments available based on currently published data.

A10. Please clarify the following statement on page 68, Section B.2.10.4.1 (Software used): "Reference treatments were assumed to have a value of zero on the log scale (i.e., a HR of 1) and assumed to have arbitrarily small standard deviations."

Does this statement relate to prior distributions assumed or extracted data input into the NMA?

If this statement does not relate to prior distributions assumed for the NMAs, please provide details of the prior distributions assumed.

This statement relates to the extracted data used as input for the NMA. The NMA is based on vague or non-informative priors. Prior distributions included within the analysis are aligned to those described by Béliveau et al[5] in Table 3 below.

Table 3. Priors implemented by default in BUGSnet[5]

Parameters	Consistency model		Inconsistency model	
	Random effect	Fixed effect	Random effect	Fixed effect
μ1, …, μM	iid N(0,(15u) ^{2}) Except when a log link is used with a binomial family, in which case: μi = log(pi), pi ~ iid U(0,1) as per Warn et al.[6]			
d1, 2, …. ,d1, T	iid N(0,(15u)^2)		NA	
d1, 2, …. ,d1, T, …, dT − 2, T − 1, dT − 2, T, dT − 1, T	NA		iid N(0,(15u)^2)	
σ	U(0,u)	NA	U(0,u)	NA
β(1, 2), …, β(1, K) (meta-regression only)	Unrelated: iid t(0, u^2 , df = 1) Exchangeable: iid N(b, γ^2), b~ t(0, u^2, df = 1), γ~U(0, u) Equal: β2 = … = βT = B, B~ t(0, u^2 , df = 1)			

ATTRACTION-4 trial

A11. Please provide the baseline patient characteristics for the phase II and phase III trial populations, including median age and range (if available, please provide proportion of patients by age group), sex, race, number of patients with measurable disease, ECOG performance status, PD-L1 expression status, disease status classification and HER2 status.

ATTRACTION-4 is presented in the submission for completeness. It should be emphasised that there are a number of important differences from CheckMate 649 that limit its relevance to UK clinical practice. ATTRACTION-4 was conducted in an exclusively Asian population and 64.1% of patients received chemotherapy that would not be considered relevant to UK practice (tegafur, gimeracil, oteracil [S-1] and oxaliplatin [SOX/XELOX]). By contrast, CheckMate 649 was conducted in a predominantly non-Asian population (75%) and used chemotherapy that is considered standard of care in a UK setting (XELOX and FOLFOX). In addition, in ATTRACTION-4, there was also significantly greater use of immunotherapies in subsequent treatment lines for the control arm (27.4%, vs 8.1% in CheckMate 649), making the comparison of treatment with and without nivolumab more difficult in ATTRACTION-3.

Clarification questions

Table 4 shows the baseline characteristics for the Phase II of ATTRACTION 4 and Table 5 the baseline characteristics for Phase III. All patients enrolled in ATTRACTION 4 were HER2 negative as per inclusion criteria. The CSR for ATTRACTION 4 is not available to provide the more granular data for proportion of patients by age group.

Table 4. ATTRACTION 4 baseline characteristics for Phase II[7]

		Nivo + SOX N=21	Nivo + CapeOx N=19
Gender n (%)	Male	12 (57.1%)	15 (78.9%)
Age	Median	61.0	65.0
	Range	37-77	39-80
BMI kg/m^2	Mean (SD)	21.5 (4.21)	22.3 (4.07)
Country	Japan	10 (47.6%)	10 (52.6%)
	South Korea	11 (52.4%)	9 (47.4%)
ECOG PS	0	10 (47.6%)	10 (52.6%)
	1	11 (52.4%)	9 (47.4%)
Prior surgery n (%)		7 (33.3%)	10 (52.6%)
Organs with metastases ≥2 n (%)		15 (71.4%)	14 (73.7%)
Tumour PD-L1	<1%	15 (78.9%)	16 (88.9%)
	≥ 1%	4 (21.1%)	2 (11.1%)

BMI: body mass index; CapeOx: capecitabine plus oxaliplatin; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: programmed death ligand 1; SOX: S-1 (tegafur–gimeracil–oteracil potassium) plus oxaliplatin.

Table 5. ATTRACTION 4 baseline characteristics for Phase III[8]

		Nivo + chemo N= 362	Placebo + chemo N=362
Gender n (%)	Male	253 (69.9%)	270 (74.6%)
Age	Median	63.5	65.0
	Range	25-86	27-89
Country n (%)	Japan	198 (54.7%)	197 (54.4%)
	Taiwan	16 (4.4%)	22 (6.1%)
	South Korea	148 (40.9%)	143 (39.5%)
Disease status n (%)	Advanced	280 (77.3%)	279 (77.1%)
	Recurrent	82 (22.7%)	83 (22.9%)
ECOG PS n (%)	0	195 (53.9%)	194 (53.6%)
	1	167 (46.1%)	168 (46.4%)
Perioperative chemotherapy n (%)		68 (18.8%)	59 (16.3%)
Organs with metastases n (%)	≤ 1	108 (29.8%)	105 (29.0%)
	≥2	254 (70.2%)	257 (71.0%)
Tumour PD-L1 n (%)	<1%	304 (84.0%)	306 (84.5%)
	≥ 1%	58 (16.0%)	56 (15.5%)
Chemotherapy regimen n (%)	SOX	232 (64.1%)	232 (64.1%)
	CapeOx	130 (35.9%)	130 (35.9%)
Histology n (%)	Intestinal	139 (38.4%)	154 (42.5%)
	Diffuse	192 (53.0%)	176 (48.6%)
	Others	11 (3.0%)	12 (3.3%)
	Unknown	20 (5.5%)	20 (5.5%))

Clarification questions

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide the following Kaplan-Meier analyses:

A. **Time to death from any cause (OS)**

B. **Time to progression (based on central assessment by independent review) or death from any cause (PFS)**

C. **Time to study treatment discontinuation (TTD)**

Please use the following specifications:

Trial data set: **CheckMate 649**

Format: **Please present analysis outputs using the format used in the sample table below**

Populations: **(i) The population with PD-L1 CPS≥1 including all patients lost to follow-up or withdrawing from the trial**

(ii) The population with PD-L1 CPS≥5 including all patients lost to follow-up or withdrawing from the trial

(iii) The population with PD-L1 CPS<1 including all patients lost to follow-up or withdrawing from the trial

(iv) The population with PD-L1 CPS<5 including all patients lost to follow-up or withdrawing from the trial

Trial arms: **(i) Nivolumab + chemotherapy (XELOX or FOLFOX)**

(ii) Chemotherapy (XELOX or FOLFOX)

These outputs are provided as Appendix B1.

In all randomised patients with PD-L1 CPS quantifiable at baseline, [redacted] and [redacted]) had a baseline PD-L1 CPS ≥1 in the NIVO+CHEMO and CHEMO arms, respectively. Hence, there are only [redacted] patients in the NIVO+CHEMO arm and [redacted] patients in the CHEMO arm with baseline PD-L1 CPS <1. This subgroup is insufficiently powered to detect differences in outcomes and the small patient numbers would not provide informative data.

Clarification questions

Similarly, [redacted] and [redacted] had a baseline PD-L1 CPS ≥5 in the NIVO+CHEMO and CHEMO arms, respectively. Although there are more patients with baseline PD-L1 CPS <5 than with CPS <1 ([redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm), this subgroup remains insufficiently powered to detect differences in outcomes.

For this reason, KM data for these subgroups are not provided. However, the OS and PFS hazard ratios (HRs) for the PD-L1 CPS<1 and PD-L1 CPS<5 populations are provided below in Figure 4. Time to study treatment discontinuation (TTD) is not available for the CPS<1 and CPS<5 populations.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Figure 4. OS, PFS and ORR hazard ratios for the PD-L1 CPS<1 and PD-L1 CPS<5 populations

B2. Priority question: Please provide cost effectiveness scenario analyses results for the CPS<5 and CPS<1 populations. Please provide a version of the cost effectiveness model where these scenarios are selectable options.

As outlined in the response to Question B1, these subgroups are insufficiently powered to detect differences in outcomes and the small patient numbers would not provide informative data. For this reason, data for these subgroups are not provided.

B3. Priority question: Please confirm that patients who are still in PFS at 30 months (classed as being in long-term remission) have the same mortality hazard as the general population of the same age. Please provide further justification as to why this is plausible.

Patients who have not yet progressed at month 30 are assumed to be in long-term remission, which is assumed to have similar mortality hazard as the general population of the same age. This key assumption can be broken down into three aspects:

1. **Long-term remission is plausible in the advanced gastric cancer population**: evidence to support the plausibility of long-term remission in this patient cohort is primarily derived from the published literature, as outlined below. However, this is supported by clinical experts, including those advising the ERG, as noted in Question B4. Further supporting evidence is found in CheckMate 649.

2. **Patients in long-term remission have a mortality hazard similar to the general population**: evidence to support specific outcomes for patients in long-term remission is sparse. However, supporting evidence for this assumption is provided in the published literature, where few death events are observed during long-term follow-up. This effect is independent of treatment received. Further, although follow-up is limited, a short amount of supporting evidence is provided in CheckMate 649.

3. **Patients reach long-term remission at 30 months**: this assumption is primarily supported by CheckMate 649, as this study has large patient numbers and patient-level data is available so that it is possible to assess the precise hazard profile and identify the hazard turning point. However, supporting evidence is available from the published literature. Several studies outlined below demonstrate survival plateaus that start at approximately 36 months.

Published evidence to support long-term remission cohort in advanced gastric cancer

Prognosis is notably poor for patients with locally advanced or metastatic GC. However, a small proportion of patients demonstrate improved outcomes versus the overall cohort,

achieving long-term remission. This long-term remission cohort is observed across multiple real-world studies, detailed in Section B.2.14.1.1 of Document B. This includes a UK retrospective study by the Royal Marsden Hospital, which reflected NHS patients comparable to CheckMate 649.[9] Median OS is 11.48 months and less than 20% of patients remain alive at two years. However, this initial high hazard is observed followed by low hazard from approximately 36 months for this study, despite a median age at diagnosis of 66 years. At 60 months (five years), OS was 4% and there are very few events before 96 months, so that patients remained alive beyond 100 months. This indicates the potential for prolonged survival and/or long-term remission in a small proportion of patients.

Another UK study, COUGAR-2, demonstrated similar poor median OS with prolonged survival in a small proportion of patients.[10] This randomised, controlled trial assessed docetaxel versus active symptom control in previously treated UK patients with advanced gastro-oesophageal adenocarcinoma. Median OS was 5.2 months in patients receiving docetaxel and 3.6 months in patients receiving active symptom control. Although follow-up is limited to 18 months, OS was 6% in the docetaxel arm and 2% in patients assigned to active symptom control, indicating that a small proportion of patients demonstrated prolonged survival. Similarly a retrospective database study in the US assessed OS in adult patients receiving first line treatment or advanced or metastatic GC, GEJC or oesophageal adenocarcinoma.[11] Although median OS was short (9.5 months), Kaplan-Meier data plateaued from three years and 3% remained alive at five years.

Similarly, Chau et al.,[12] reviewed the data from four RCTs conducted in the UK and Australia and demonstrated a five-year survival rate of 4% in patients with gastric primary lesion sites and 3% in patients with GEJ primary lesion sites. Maximum follow-up was beyond 110 months for these patients, and OS remained at 4% and 3% respectively. Hence, this benefit is also observed in clinical trials, across therapies.[10,12-14]

Nivolumab RCT evidence to support long-term remission cohort

CheckMate 649 patients in both treatment arms demonstrated a similar profile, with the same reduction in long-term hazard observed and no death events observed following 30 months. Further, there are [redacted] PFS events by 18 months in the NIVO+CHEMO arm, but only [redacted] events between 24 months and 30 months, with [redacted] events in the subsequent six months. Similarly, in the CHEMO arm, there are [redacted] events by 18 months, followed by [redacted] events in the subsequent 12 months. This rapid change in hazard profile can be difficult to model, particularly with few events in the tail. A similar profile in the OS Kaplan-Meier. In the NIVO+CHEMO arm, there were [redacted] events by 24 months, with only [redacted] events in the subsequent 12 months. Similarly, in the CHEMO arm, there were [redacted] events by 24 months with only [redacted] events in the subsequent 12 months. For both treatment arms and both outcomes, there were very few events after month 30.

As noted above, during CheckMate 649 there were no deaths observed among patients who had not progressed from month 30. Whilst follow-up from this point is limited, hazard conditional upon landmark progression status was observed to reduce dramatically over time. Figure 5 shows the evolution of this hazard from patients who are progression free at 12 months to patients who are progression free at 18 months. Due to both selection

pressure and therapeutic effect, the marginal hazard would be expected to continue to decline towards background mortality at further landmarks. As can be seen, the OS hazard was predicted by several estimators to reduce to approximately match the general population in the full ITT population (Figure 6), indicating that patient numbers and follow-up in this region were sufficient to indicate a plateauing of survival from this point.

Figure 5. OS conditional upon PFS to 12 and 18 months; CheckMate 649, NIVO+CHEMO

Figure 6. OS hazard from first treatment; CheckMate 649, NIVO+CHEMO ITT

B4. Priority question: In the company model, at baseline, the median age of patients is 62 years and approximately 7% of patients treated with chemotherapy achieve long-term remission. Clinical advice to the ERG is that patients treated in the NHS are 75 years old and fewer than 1% of patients who are treated with chemotherapy will ever achieve long-term remission. Please, further justify the assumptions on long-term remission in the company base case and their plausibility to observed long-term remission rates in NHS clinical practice. In addition, please carry out cost effectiveness analyses for a population that reflects the characteristics of patients treated in the NHS.

Generalisability of CheckMate 649 to UK clinical practice

It is acknowledged that age at diagnosis reflects the patient characteristics set out by clinicians contacted by the ERG. Based on 6,594 patients diagnosed in the UK from 2015-2017, 3,264 were aged ≤74 years and 3,330 were aged ≥75 years.[15] However, not all these patients would be considered for first-line treatment of advanced gastric cancer. In particular, older patients may have more comorbidities, such as poor renal function, and poorer fitness, which may prohibit intensive chemotherapies such as FOLFOX and XELOX.

CheckMate 649 broadly reflected the baseline characteristics for patients starting chemotherapy for advanced gastric in clinical practice. As noted in the submission, median baseline age (62 years in the NIVO+CHEMO arm and 61 years in the CHEMO arm) was similar but slightly younger that for the Royal Marsden retrospective review[16] (median age: 66 years) and the COUGAR-2[10] clinical study (median age: 65 years in the docetaxel arm and 66 years in the active symptom control arm). Patients in the UK REAL-2 clinical study had similar baseline age (median age: 65 years in arm 1, 64 years in arm 2, 61 years in arm 3 and 62 years in arm 4).[17]

Of note, data collected by the NHS, produced by the Cancer Research UK – Public Health England Partnership and provided by the National Cancer Registration and Analysis Service (CRUK dataset) show that 75 years is over the median age at diagnosis for patients with

stomach cancer treated with chemotherapy, and that the majority are below 70 years (Table 6).[18] Of the 5,840 patients who received chemotherapy for gastric cancer in this dataset, 3,357 (57.5%) were aged ≤69 years and 2,483 (42.5%) were aged ≥70 years. It is not possible to identify median age due to the broad categories of age reported; however, it is clear that median age is below 70 years.

Aligned with the UK data sources outlined above, NHS patients would need to be fit and eligible for treatment with chemotherapy in order to receive treatment with nivolumab combination therapy therefore only patients with better performance scores were included in the clinical trial. The evidence clearly demonstrates that the focus should be on baseline characteristics of patients who are treated with chemotherapy and not the full population diagnosed with gastric cancer, as they would be significantly older than the diagnosed population. More patients eligible for treatment in UK clinical practice are in the age range closer to the CheckMate 649 trial population. Hence, when considering the model and patients eligible for nivolumab; the analysis is reflective of the Checkmate 649 median baseline age and this is validated by relevant UK data sources.

Alternative age scenario

Although the CheckMate 649 baseline age is considered most appropriate for the base case, a scenario analysis was undertaken to assess the impact of adjusting the data to reflect the CRUK dataset. Using the method of moments (as in a matching-adjusted indirect comparison [MAIC]),[19,20] the weighted proportion of patients in each age subgroup within CheckMate 649 was matched to that in the CRUK dataset. This resulted in an increase in mean age from [redacted] years to 64.15 years and a reduction of effective sample size from 1581 to 1226.29.

The influence of these weights upon the survival outcomes was minimal (Figure 7, Figure 8), indicating that marginal disease-specific hazards were not affected by this difference in age distribution and that use of the disease-specific hazards obtained from the unweighted ITT population would provide appropriate estimation of outcomes in the cost-effectiveness model.

However, in order to assess the impact of altering the modelled age on cost-effectiveness outcomes, the outcome from the adjustment (i.e. 64.15 years) was applied in the cost-effectiveness model. The results of this analysis are shown in Table 7 and Table 8. When patient age is increased to 64.15 years, fewer patients are able to achieve long-term remission due to the impact of all-cause mortality in months 0-30. This has minimal impact on incremental QALYs, which [redacted] slightly from the base case analysis to this scenario analysis. Overall, this resulted in a [redacted].

The proportion of patients achieving long-term remission on the chemotherapy arm under this scenario is [redacted], which is more aligned to the outcomes suggested by the ERG's clinical advisors.

Clarification questions

Table 6. Age distribution of patients with stomach cancer treated with chemotherapy - England (CRUK)[18] and CheckMate 649

Variable	Cancer research UK (2013-2015) – stomach cancer, chemotherapy-receiving	CheckMate 649	
		Unadjusted	Age-adjusted*
N/ESS	5840	1581	1226.29
Age (years) - mean	NR	[redacted]	64.15
Age (years) - sd	NR	[redacted]	[redacted]
Age (years) - < 50 (%)	10.00%	[redacted]	[redacted]
Age (years) - 50-59 (%)	16.5%	[redacted]	[redacted]
Age (years) - 60-69 (%)	31.0%	[redacted]	[redacted]
Age (years) - 70-79 (%)	35.0%	[redacted]	[redacted]
Age (years) - ≥ 80 (%)	7.5%	[redacted]	[redacted]

**Patient-level data weighted by method of moments to match weighted proportions within all age categories to CRUK.*
ESS: effective sample size (sum of weights)^2 / sum(weights^2)

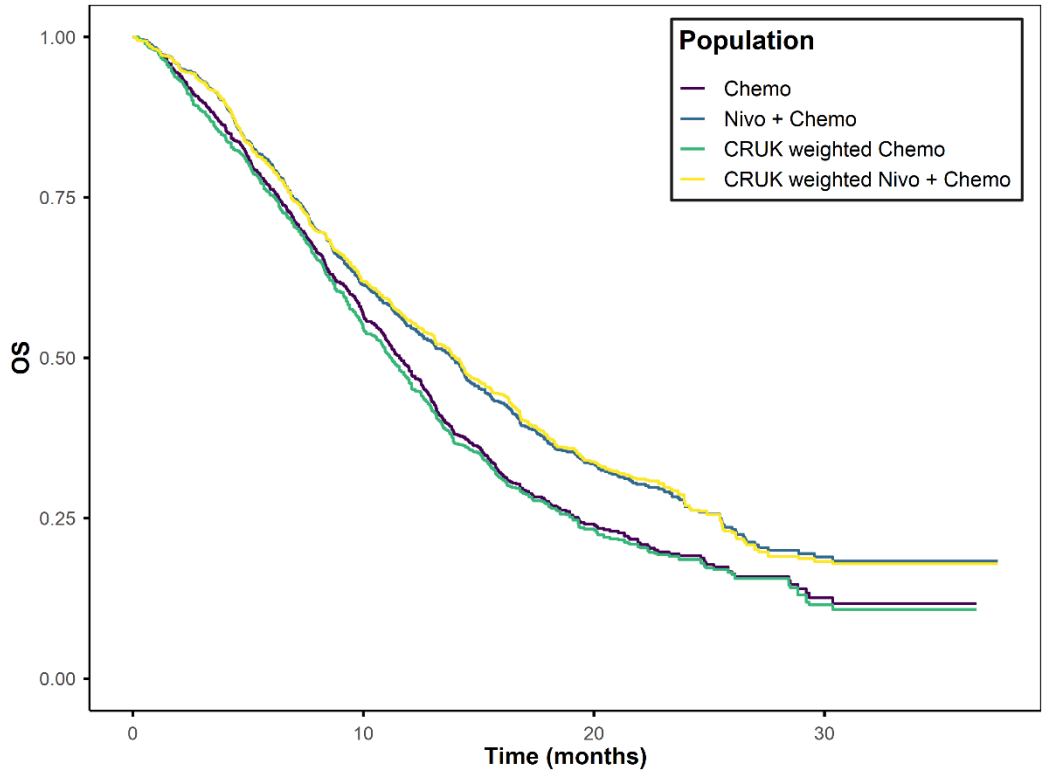


Figure 7. CRUK-weighted OS in CheckMate 649, ITT population

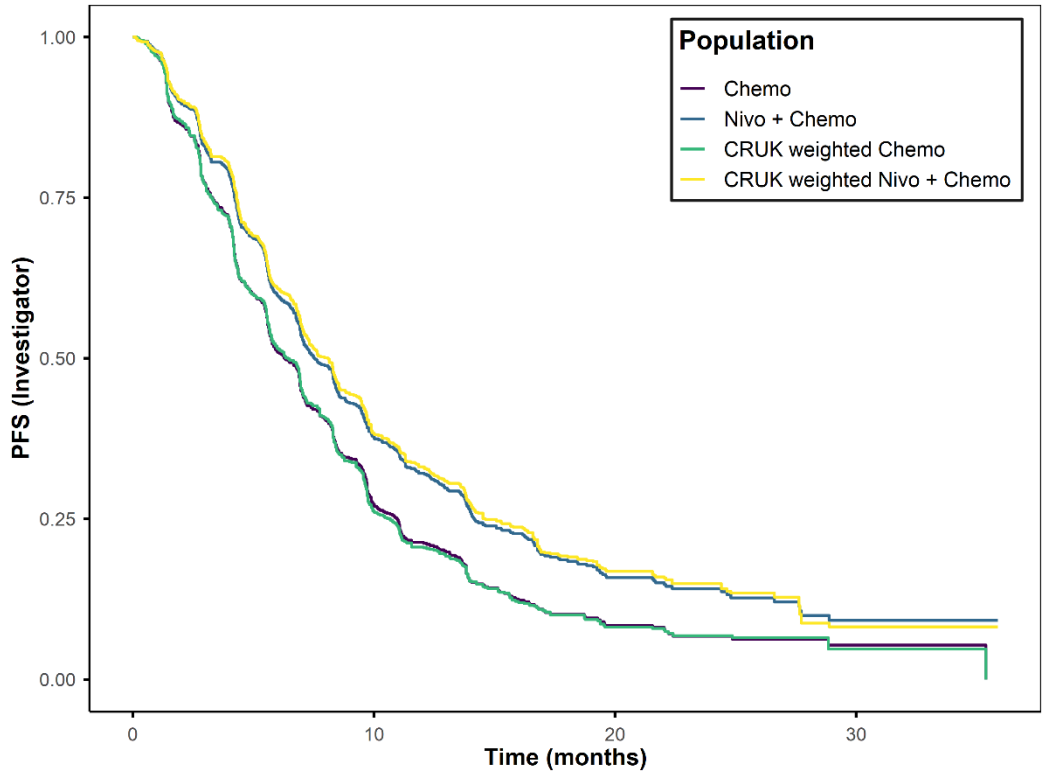


Figure 8. CRUK-weighted PFS (per investigator) in CheckMate 649, ITT population

Clarification questions

Table 7. NIVO+FOLFOX vs FOLFOX – baseline age 64.15 years

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Submission base case analysis							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£33,950	2.802	1.604	[redacted]	[redacted]	[redacted]	£44,424
Scenario analysis							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£33,915	2.566	1.513	[redacted]	[redacted]	[redacted]	£49,460
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 8. NIVO+XELOX vs XELOX – baseline age 64.15 years

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Submission base case analysis							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,990	2.802	1.604	[redacted]	[redacted]	[redacted]	£41,652
Scenario analysis							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,954	2.566	1.513	[redacted]	[redacted]	[redacted]	£46,374
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Section C: Textual clarification and additional points

C1. Please provide i) the Updated Report of the SLR (Appendix D2) and ii) the ITC Report (Appendix L)

Both reports are provided as Appendix C1.

C2. The ATTRACTION-4 trial. The text on page 25 of the CS states that histological confirmation of adenocarcinoma was not required in the ATTRACTION-4 trial. However, the text in Table 13 states that patients recruited to the ATTRACTION-4 trial had unresectable advanced or recurrent gastric/GOJ cancer that was histologically confirmed to be adenocarcinoma. Please clarify which statement is correct.

The text on page 25 is incorrect and the text in table 13 is correct. ATTRACTION-4[21] inclusion criteria did require histologically confirmed adenocarcinoma as per the inclusion criteria in the protocol: “Patients with unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer) that has been histologically confirmed to be adenocarcinoma and has not been treated with the first-line therapy with systemic antitumor agents for advanced or recurrent gastric cancer (including esophagogastric junction cancer).”

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Appendices

Appendix number	Title	Clarification question	Confidential
A1	CheckMate 649 Statistical Analysis Plan	A1	AIC
A2	Assessment of proportional hazards	A2	AIC
A3	CheckMate 649 Supplementary tables	A3	AIC
B1	CheckMate 649 Kaplan-Meier data	B1	AIC
C1A	Appendix D2 Updated clinical SLR report	C1	-
C1B	Appendix L Indirect treatment comparison report	C1	AIC
D	Updated cost-effectiveness model	-	AIC/CIC

Appendix B4

Table 9. NIVO+XELOX vs XELOX – baseline age 64.15 years

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Submission base case analysis							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,990	2.802	1.604	[redacted]	[redacted]	[redacted]	£45,172
Scenario analysis							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,954	2.566	1.513	[redacted]	[redacted]	[redacted]	£50,293
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 10. NIVO+FOLFOX vs FOLFOX – baseline age 64.15 years

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Submission base case analysis							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£33,950	2.802	1.604	[redacted]	[redacted]	[redacted]	£47,840
Scenario analysis							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£33,915	2.566	1.513	[redacted]	[redacted]	[redacted]	£53,263
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Appendix D

Table 11. Base case deterministic results

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
FOLFOX							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£33,950	2.802	1.604	[redacted]	[redacted]	[redacted]	£44,424
XELOX							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,990	2.802	1.604	[redacted]	[redacted]	[redacted]	£41,652
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465]

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]

NICE National Institute for Health and Care Excellence

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 within support groups for people living with advanced gastric cancer, 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. We also asked if anyone had experience of nivolumab in combination with other chemotherapy for untreated or advanced stomach cancer, oesophageal cancer or cancer between the stomach and gullet. This request was specifically for people diagnosed with adenocarcinoma type cancer. We have also previously developed surveys but these were not successful in getting responses. Understandably it is difficult for people with advanced cancer to input time into submissions, so we also searched for qualitative studies for quality of life and life experience of people diagnosed with these cancers to understand their experience. We also interviewed support group leaders who help people living with oesophageal cancers.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Oesophageal and gastric cancer 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. The chance of surviving beyond five years with stomach cancers is approximately 20% (ONS 2019), numbers who survive five years have tripled in the last 40 years from a very low baseline of 4% (CRUK, 2021). It still however remains one of the lower cancer survival rate statistics. Often patients and their families have limited time together, as many as 7 in 10 (Humphreys E et al 2020) people are 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. Larsen et al (2020) reported "patients with oesophageal cancer are putting their ordinary lives on hold and experiencing the meal as a battleground during treatment. Patients strive to maintain autonomy, gain control, and take ownership and their suffering was associated with symptoms and side effects of treatment, which affect their and their relatives' social world and relationships." For gastric cancer the most prominent symptoms were fatigue, pain, appetite loss and these were the symptoms most associated with changes in the tumour (Chau et al 2019) malnutrition is also common. With people who have gastric cancer that is advancing, quality of life is reduced on a global scale and symptoms of nausea and vomiting and appetite loss and a reduction in the ability to function. (Chau et al 2019) For people with oesophageal cancer swallowing problems can be severe even at times people are unable to swallow their own saliva and this is associated with pain, heartburn, reflux and indigestion. These symptoms severely affect quality of life, lead to weight loss and fatigue. Hard food containing touch fibres are problematic as these are unable to be swallowed, this can be a difficult symptom for people with advanced cancer.

	Not only does eating provoke symptoms but the diet can significantly change not only in texture but food choices are affected by the side effects of treatment. This includes stent placement and also people who have feeding tubes for nutrition, both of which can have many impacts on quality of life. Fatigue is a major symptom that patients experience. When I was told, 'You'll feel a bit of fatigue,' you automatically think, 'Ah yeah, so I'll feel a bit tired.' But fatigue is totally different— you have to explain that it's a total knackered—all over. And you haven't done anything, but suddenly you're knackered and you don't know why. And it plays on your mind, where you're saying, 'What's gone wrong now that I'm suddenly like this?' (Bennett et al 2020.) Symptoms have wider impact on quality of life and will affect social activities such as eating with family, enjoyment of food and attending social events. Sharing food and meal provision is an important aspect of family care provision and loss of weight and inability to enjoy meals is often distressing to both the person with cancer and their families and carers. With a life limiting condition it is important that people living with these cancers enjoy time with their family and controlling tumour progression can help people to participate. Awareness of a poor prognosis and the demanding treatment pathway triggered psychological distress, as patients gave expressions of their feelings of vulnerability. (Larson 2020) Non curative treatments are difficult to tolerate alongside physically debilitating symptoms make it impossible for some people to continue working or take part in social events. Bennett AE, O'Neill L, Connolly D, et al. Perspectives of Esophageal Cancer Survivors on Diagnosis, Treatment, and Recovery. *Cancers (Basel)*. 2020;13(1):100. Published 2020 Dec 31. doi:10.3390/cancers13010100 Chau I, Fuchs CS, Ohtsu A, Barzi A, Liepa AM, Cui ZL, Hsu Y, Al-Batran SE. Association of quality of life with disease characteristics and treatment outcomes in patients with advanced gastric cancer: Exploratory analysis of RAINBOW and REGARD phase III trials. Eur J Cancer. 2019 Jan;107:115-123. doi: 10.1016/j.ejca.2018.11.013. Epub 2018 Dec 14. PMID: 30557792. Larsen MK, Schultz H, Mortensen MB, Birkelund R. Patients' Experiences With Illness, Treatment, and Decision-Making for Esophageal Cancer: A Qualitative Study in a Danish Hospital Setting. *Glob Qual Nurs Res*. 2020;7:2333393620935098. Published 2020 Jun 29. doi:10.1177/2333393620935098

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are challenging to experience and they are not always effective. People with cancer feel that the treatment schedule constantly interrupts their normal everyday life and this is particularly true of chemotherapy (Larsen et al 2020). People will often defer decisions about treatment to their healthcare practitioners (Larsen et al 2020) this is possibly due to a lack of information presented in a manner that the person with cancer will understand and accept it.
8. Is there an unmet need for patients with this condition?	There are relatively few options in advanced disease and is usually chemotherapy, radiotherapy or a combination of both - Nivolumab, being immunotherapy, is a new type of treatment for these cancers.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nivolumab with chemotherapy increased survival time. Plus, immunotherapy alone takes time to have an effect so having chemotherapy with Nivolumab will provide some treatment whilst the immunotherapy has time to be effective. The additional treatment does not impact on current chemotherapy treatment time as it is given consecutively with current chemotherapy. Adverse events for chemotherapy alone include dysphagia which was not a reported serious adverse event for the chemotherapy plus nivolumab.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Immunotherapy may have different side effects to current therapy. The additional treatment does not change treatment time as it is given consecutively with current treatment. Some patients may feel that extra treatment can reduce their quality of life and wellbeing, with added side effects. The fitness of the person and their nutritional status may be a factor in deciding if this treatment is suitable.
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.	No, there are small numbers of people who are diagnosed with these cancers compared to other cancers so any differences in populations from studies should not prevent the patients from having choice in the treatment options.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Their may be a culture of some community groups not utilising primary care and going to their GP, people in this situation often present late. Also, inequalities in health in respect to cancer mean that people from the most deprived areas are more likely to be diagnosed later as people have reduced ability and opportunity to access healthcare. This is particularly true of stomach cancer.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Yes, these cancers are difficult for GPs to identify or suspect symptoms are due to cancer at an early stage. Quality of life vs treatment all depends on the patients functional fitness and nutritional status, ability to eat or if they are using a feeding tube and also family can provide peer pressure too.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • These cancers are less survivable cancers, for which there are no screening tools to identify them widely used and they are frequently diagnosed late, when treatment options are limited. • People with lived experience of these cancers strive to maintain fitness and gain control of their situation and their suffering is associated with symptoms and treatment side effects, which massively affects their quality of life, social experience and relationships with family and carers.	

- With a life limiting condition it is extremely important that people living with these cancers enjoy time with their family and this treatment could help people to participate and provide them with valuable time.
- This treatment works by a different mechanism and offers another option for treatment where there are currently few options available.
- Patients will always look for hope in new treatments, or trials for themselves and others.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465]

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).	No
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.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
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.)	In advanced gastroesophageal adenocarcinoma the aims of treatment are to prolong survival, improve symptoms and maintain quality of life. Sadly, cure is very unlikely with current chemotherapy regimens and surgery is not performed in patients with advanced disease. In most contemporary clinical trials, median overall survival has not exceeded one year. One exception to his is patients with HER2 positive cancers (which make up 15% of the population) who can be treated with trastuzumab – survival for this group is approximately 18 months. On average, response rates to chemotherapy are approximately 30-45%. Tumour shrinkage is helpful to relieve symptoms as many patients experience dysphagia and nutritional difficulties due to the primary tumour.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	As median overall survival is generally less than one year, an improvement in survival of approximately 3 months, or a reduction in the risk of death of > 25% (HR 0.75 or better) would be clinically relevant.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need. Oesophageal cancer has been identified by the government and Cancer Research UK as a disease in which more research and better treatments are required to improve outcomes. Currently used chemotherapy regimens do not lead to long term remissions or cures.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The standard first line treatment for gastroesophageal adenocarcinoma is platinum based chemotherapy (oxaliplatin/cisplatin) plus a fluoropyrimidine (infused 5FU or capecitabine tablets). Although the NICE guidelines mention triplet chemotherapy with anthracyclines, these are outdated and there has been a move away from triplet chemotherapy and anthracyclines over the past few years. There has never been a phase III trial which demonstrated that adding anthracyclines to platinum doublet improved survival. One older trial (V325 Ajani et al, JCO 2006) showed a benefit to adding docetaxel to platinum doublet, but with very increased toxicity. A recent larger trial (JCOG 1013 Yamada et al, Lancet G&H 2019) showed no benefit, and international guidelines have been updated to reflect the preference for two drug chemotherapy rather than three, and if three drugs are used, then a taxane is to be preferred. There may be some less academic centres in the UK which continue to use anthracycline triplets as a relic from previous trials, but this is gradually decreasing. In general, oxaliplatin is preferred to cisplatin as it is safer and has a shorter infusion time. Therefore, the preferred regimens for treatment of HER2 negative gastroesophageal cancers are CAPOX, FOLFOX, cisplatin-5FU, cisplatin-capecitabine, and less preferred would be EOX or ECX (Smyth et al, Lancet 2020).
• Are any clinical guidelines used in the	NICE guidelines exist but are somewhat out of date as triplet chemotherapy is recommended, and this is not recommended internationally, or used in academic centres. International guidelines which are

treatment of the condition, and if so, which?	frequently referenced are the European Society for Medical Oncology Guidelines (ESMO). (Muro et al, Annals Oncology 2018 https://www.esmo.org/guidelines/gastrointestinal-cancers/gastric-cancer/pan-asian-adapted-esmo-clinical-practice-guidelines-for-the-management-of-patients-with-metastatic-gastric-cancer)
• 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 of care is well defined. New diagnoses of cancer are routinely reviewed in a specialist multidisciplinary meeting (MDT) where a treatment plan is discussed by attending oncologists, surgeons, radiologists and other specialists. The patient is then referred for chemotherapy and treated with the chosen chemotherapy. In general, we aim to start treatment within a period of 31 days.
• What impact would the technology have on the current pathway of care?	Depending on whether the treatment is NICE supported for all patients or for PD-L1 CPS 5 patients only, assessment of PD-L1 staining could be reported at the MDT and a treatment decision could be made for chemotherapy with or without nivolumab. However, if PD-L1 staining was not available, its likely that the patient would start treatment with chemotherapy and then have nivolumab added later when that result became available. This is a model which happens for HER2 and trastuzumab in centres which do not have local HER2 testing.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nivolumab is not currently used for patients with gastroesophageal cancer in the first line setting in the NHS. However, it is used in multiple other cancer settings, although not generally with chemotherapy. Therefore, this use would be a new use for a drug with which there is significant experience.

• How does healthcare resource use differ between the technology and current care?	There would be no difference in resource use. Chemotherapy would continue the same schedule as previously. The only additional resource use would be the addition of some laboratory tests which are required for immunotherapy (thyroid function tests and cortisol).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Nivolumab plus chemotherapy would be used by oncologists experienced in the treatment of gastroesophageal adenocarcinoma in secondary care. This could occur in district general hospitals, university hospitals and cancer centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment is required to introduce nivolumab as it is already commonly used. However, if PD-L1 testing is required, provision of the means to measure this for gastroesophageal cancer patients will be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, absolutely. In the CheckMate 649 trial, a meaningful benefit in terms of overall survival was shown for the primary endpoint. Nivolumab improved overall survival by > 3 months in patients with PD-L1 CPS ≥ 5 cancers. This is considered very meaningful by the oncology community. The benefits in CPS ≥ 1 and all comer cohorts were statistically significant, but less clinically meaningful.
• Do you expect the technology to increase length of life more than current care?	Yes, nivolumab was added to standard of care chemotherapy in the CheckMate 649 trial and significantly improved survival. In the trial, the control arm chemotherapy performed as expected, so we can anticipate that these results should be generalisable.

• Do you expect the technology to increase health-related quality of life more than current care?	QoL details have not been made available for the trial, but as nivolumab increased response rates from 45% to 60%, I would anticipate that more patients will have relief from symptoms relating to their primary tumour. As this is cause of major symptoms and morbidity in gastroesophageal cancer patients, I suspect that quality of life will be improved. There was a small increase in side effects when nivolumab was added to chemotherapy, but this did not lead to patients stopping treatment, so I suspect that QoL was not impacted negatively by nivolumab treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The most convincing results in the trial are in the group of patients who express PD-L1 at a score of CPS ≥ 5. The general population who express this biomarker would be expected to have the same benefit.
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	Most oncologists are now familiar with use of immunotherapy drugs. Although there is a learning curve for all new combination therapies, nivolumab plus chemotherapy should not be more difficult than standard chemotherapy. The practical requirements are needing to screen intermittently for evidence of thyroid dysfunction and more rarely, adrenal dysfunction. Otherwise the standard safety labs will be the same as with chemotherapy.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As above, integration of PD-L1 testing into the clinical pathway will be required if approval is granted in patients with PD-L1 CPS ≥5 patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Depending on the approval, tumour PD-L1 testing may be required. In general, patients eligible for chemotherapy would be treated with nivolumab and chemotherapy. Treatment is stopped if the cancer grows on treatment or if there is significant toxicity, or if the patient would like to stop.
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?	As response rates with nivolumab are higher patients may be less likely to need oesophageal stents, or NJ/NG tubes for enteral feeding due to dysphagia. Placement of stents and NJ tubes often require hospital admission for control of stent related symptoms and tube feeding training respectively.

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 improve the way that current need is met?	Yes, the this is the first study to demonstrate a benefit with immunotherapy in the first line setting for gastroesophageal adenocarcinoma. Survival is prolonged by a substantial and clinically relevant amount of time. Additionally, long term survival (i..e one and two year survival is also improved).
• Is the technology a 'step-change' in the management of the condition?	Yes, it introduces a new form of treatment (immunotherapy) for gastroesophageal adenocarcinoma. This has not yet been used in this disease.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, the unmet need is prolonged survival and improved response rates. Both needs are met by nivolumab.
17. How do any side effects or adverse effects of the technology affect the	Side effects associated with nivolumab are noted and are slightly more common compared to chemotherapy alone. However, as oncologists we are not familiar with using immunotherapy and have standard protocols in place to manage immunotherapy toxicity. It is notable that although there were slightly

management of the condition and the patient's quality of life?	more toxicities measured in nivolumab treated patients, that these patients were not more likely to stop treatment than patients treated with chemotherapy alone.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, standard practice is treatment with a platinum and fluoropyrimidine drug. This is the common practice in the UK. Most centres now use oxaliplatin and either capecitabine tablets (CAPOX) or infusional 5FU (FOLFOX) depending on the patient. For example, if a patient has difficulty swallowing, FOLFOX would be preferred.
• If not, how could the results be extrapolated to the UK setting?	Not applicable
• What, in your view, are the most important outcomes, and were they measured in the trials?	In CheckMate 649 the most important outcome was the >3 month benefit in overall survival in the CPS ≥ 5 group. This was statistically significant and clinically meaningful. Overall survival was measured using standard statistical methods.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. There is clear evidence of efficacy of nivolumab outside the clinical trial. In the ATTRACTION-2 trial (Kang, Lancet 2017) nivolumab was superior to best supportive care in chemorefractory gastroesophageal adenocarcinoma, demonstrating single agent activity.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No

21. How do data on real-world experience compare with the trial data?	The outcome in the control arm of the trial is consistent with real world outcomes. Median overall survival in the control arm was 11.1 months. The last UK first line trial (REAL-3) had a survival in the control arm (EOX) of 11.3 months (Waddell et al, Lancet Oncol 2013). There is no reason to believe that UK patients treated with doublet chemotherapy (rather than triplet) would have worse outcomes because multiple clinical trials across countries and time show comparable survival for doublet vs triplet chemotherapy.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	Not applicable
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions	

will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

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

- Survival for patients with advanced gastroesophageal cancer is poor, and is a focus for the NHS and Cancer Research UK
- CheckMate 649 is a large, well powered global trial which shows a significant and meaningful survival benefit for nivolumab plus chemotherapy in advanced gastroesophageal cancer with a PD-L1 CPS score of ≥ 5.
- Although adding nivolumab to chemotherapy does lead to slightly higher levels of toxicity, patients did not stop treatment as a results of these side effects.
- Patients enrolled in CheckMate 649 and treatments used in the trial are otherwise in line with NHS standards of care.
-

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ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma [ID1465]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 133505

Completed 20th April 2021

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma [ID1465]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Date completed: 20th April 2021

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Declared competing interests of the authors: Within the last 3 years, Dr Madi has received consultancy fees and fees for attending a symposium from Bristol Myers Squibb.

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Contributions of authors

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Rebecca Bresnahan	Critical appraisal of the clinical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Critical appraisal of the economic evidence
Bhattacharyya Devarshi	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the clinical evidence and search strategies
Joanne McEntee	Critical appraisal of the company submission
Cheng Boon	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
BID	Twice daily
BICR	Blinded independent central review
CheckMate 649	Main trial discussed in the company submission
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical Study Report
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DBL	Database lock
DPD	dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D-3L	EuroQol 5-dimensions three levels
ERG	Evidence Review Group
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric
FOLFOX	Folinic acid, 5-fluorouracil, oxaliplatin
GaCS	Gastric cancer subscale
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
IMAE	Immune-mediated adverse event
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
LRiG	Liverpool Reviews and Implementation Group
LYs	Life years gained
MID	Minimal important difference
mg	Milligram
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NMA	Network meta-analysis
NR	Not reported
OESI	Other events of special interest
Oesophago-gastric	Overall term for gastric, gastro oesophageal and oesophageal cancer

ORR	Objective response rate
OS	Overall survival
OSPP	Overall survival post-progression
PAS	Patient Access Scheme
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PH	Proportional hazard
PPS	Post-progression survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response rates
S-1	Tegafur, gimeracil, oteracil
SAE	Serious adverse event
SD	Standard deviation
SoC	Standard of care
SOX	Oxaliplatin and S-1
TA	Technology Appraisal
ToT	Time on treatment
TPS	Tumour proportion score
TRAE	Treatment related adverse event
TSAP	Trial statistical analysis plan
UI	Utility index
VAS	Visual analogue scale
XELOX	Capecitabine and oxaliplatin

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 ERG scenarios and resulting incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained.

Section 1.1 provides an overview of the key issues identified by the ERG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on cost effectiveness results as outlined by the company. Sections 1.3 to 1.7 explain the key issues identified by the ERG in more detail. A summary of the key cost effectiveness results generated by the company and the ERG is presented in Section 1.7.

All the issues outlined in this report represent the views of the ERG and are not the opinion of NICE.

1.1 Overview of the ERG's key issues

Summary of key issues

Issue	Summary of issue	Report sections
1	Limited population and comparators included in the decision problem	Section 2.6, Section 2.6.2, Section 2.6.3, Section 2.6.4, Section 2.6.5, Section 3.2.2Table 3, Section 3.6.4, Section 3.6.5, Section 4.3.4, Section 6.2 and Section 6.9
2	Lack of generalisability of CheckMate 649 trial data	Section 2.6.2, Section 3.2.3, and Section 6.2
3	Company NMAs do not include treatment with nivolumab+chemotherapy	Section 2.6.4, Section 2.6.5, Section 3.6.1, Section 3.6.3, Section 3.6.4 and Section 3.6.5
4	Evidence does not support patients who have not progressed by 30 months only having background mortality	Section 6.4, Section 6.10 and Section 6.11
5	Company model generates OS estimates that are not in line with results from the first 12 months of the model time horizon	Section 6.2, Section 6.3 and Section 6.11
6	High utility values in the PFS and progressed disease health states	Section 6.2, Section 6.5, Section 6.10 and Section 6.11
7	Low model baseline population age	Section 6.7, Section 6.10 and Section 6.11
8	Limited cost effectiveness results for PD-L1 subgroups	Section 6.8 and Section 6.11
9	Inappropriate treatment modifier	Section 6.2 and Section 6.6
10	NICE End of life criteria	Section 7

NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life using a measure called a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Overall, nivolumab+chemotherapy is modelled to affect QALYs by:

- delaying disease progression (health-related quality of life decreases as disease progresses)
- extending life.

Overall, treatment with nivolumab+chemotherapy is not expected to reduce health care costs.

The modelling assumptions, explored by the company in sensitivity and scenario analyses, that have the greatest effect on the ICERs per QALY gained are:

- removal of the model long-term remission health state
- adjustment of model baseline patient age
- changes to the discount rate applied to benefits.

1.3 Decision problem: summary of the ERG's key issues

Issue 1 Limited population and comparators included in the decision problem

Report section	Section 2.6, Section 2.6.2, Section 2.6.3, Section 2.6.4, Section 2.6.5, Section 3.2.2Table 3, Section 3.6.4, Section 3.6.5, Section 4.3.4, Section 6.2 and Section 6.9
Description of issue and why the ERG has identified it as important	**Population** • Population considered by the company is in line with the final scope issued by NICE except for patients with known HER2-positive disease (these patients were excluded from the pivotal CheckMate 649 trial and only indirect clinical effectiveness results [trastuzumab+capecitabine+cisplatin versus FOLFOX] are available from the company NMAs). This means that the company has only considered nivolumab+chemotherapy as a treatment for patients with HER2-negative disease **Comparators** No clinical effectiveness evidence is presented in the CS for the comparison of **nivolumab+chemotherapy** versus: i) fluorouracil+cisplatin ii) capecitabine+cisplatin iii) trastuzumab+capecitabine+cisplatin No clinical effectiveness evidence is presented in the CS for the comparison of **chemotherapy** versus trastuzumab+fluorouracil+cisplatin (HER2-positive population) Clinical advice to the company and the ERG is that epirubicin is rarely used in the NHS to treat patients with oesophago-gastric adenocarcinoma. Due to the limited evidence base, the company was only able to provide a narrative summary of clinical effectiveness evidence for epirubicin-containing triplet chemotherapy combinations **Outcome** The two primary outcomes in the CheckMate 649 trial are (BICR) PFS and OS in patients with PD-L1 CPS≥5. However, [redacted]
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion

BICR=blinded independent central review; CPS=combined positive score; CS=company submission; ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HER2=human epidermal growth factor receptor 2; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; OS=overall survival; NMA=network meta-analysis; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; XELOX=capecitabine+oxaliplatin

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

Issue 2 Lack of generalisability of CheckMate 649 trial data

Report section	Section 2.6.2, Section 3.2.3 and Section 6.2
Description of issue and why the ERG has identified it as important	In the CheckMate 649 trial: • patients are younger than patients seen in NHS clinical practice (CheckMate 649 trial: mean age=[redacted] years; clinical advice to the ERG is that average age of patients treated in the NHS is 70-75 years). The Cancer Research UK dataset shows that, during 2013-2015, approximately 42% of patients diagnosed with stomach cancer treated with chemotherapy were aged ≥70 years and 57.5% were aged ≤69 years • patients are fitter than those seen in NHS clinical practice (CheckMate 649 trial: at baseline all patients had an ECOG PS of 0 or 1; clinical advice to the ERG is that, in NHS clinical practice, patients with ECOG PS 2 are routinely treated)
What alternative approach has the ERG suggested?	See issue 7 for ERG comment on age None for the other issues
What is the expected effect on the cost effectiveness estimates?	Not applicable (except for age)
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the generalisability of the CheckMate 649 trial results to NHS practice

ECOG=Eastern Cooperative Oncology Group; ERG=Evidence Review Group; NHS=National Health Service; PS=performance status

Issue 3 Company NMAs do not include treatment with nivolumab+chemotherapy

Report section	Section 2.6.4, Section 2.6.5, Section 3.6.1, Section 3.6.3, Section 3.6.4 and Section 3.6.5
Description of issue and why the ERG has identified it as important	The ERG considers that results from the company NMAs are of limited use to decision-makers: • out of the three included trials, one trial only recruited patients with HER2-positive disease and level of HER2-positive disease of patients participating in the other two trials is unknown • uncertainty around the size and direction of impact of missing data on prognostic factors (HER2 status and level of PD-L1 expression) • uncertainty around the validity of some of the OS and PFS PH assumptions for trials included in the network Furthermore, results from the company NMAs are for FOLFOX (assumed to have the same efficacy as XELOX) versus: • fluorouracil+cisplatin • capecitabine+cisplatin • trastuzumab+capecitabine+cisplatin No clinical effectiveness results have been presented for the comparison of nivolumab+chemotherapy versus these three chemotherapy regimens. The company considered that including nivolumab+chemotherapy in the network was not appropriate as nivolumab has a different mechanism of action, survival profile and distribution of events to other treatments in the network
What alternative approach has the ERG suggested?	The ERG did not suggest an alternative approach as results are not used in the company's base case cost effectiveness analysis and the ERG considers that the comparators used in the secondary cost effectiveness analyses (which rely on the results of the NMAs) are not relevant to the decision problem as they are rarely used in NHS clinical practice
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	NMA results demonstrating the clinical effectiveness of nivolumab+chemotherapy versus fluorouracil+cisplatin, versus capecitabine+cisplatin and versus trastuzumab+capecitabine+cisplatin could be generated for completeness

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HER2=human epidermal growth factor receptor 2; NHS=National Health Service; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; XELOX=capecitabine+oxaliplatin

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

Issue 4 Long-term remission health state: evidence does not support patients who have not progressed by 30 months only having background mortality

Report section	Section 6.4, Section 6.10 and Section 6.11
Description of issue and why the ERG has identified it as important	The company model results are most sensitive to the company assumption that patients who have not progressed by 30 months enter a long-term remission health state in which mortality is equal to background mortality. The ERG considers that this assumption is not supported by the evidence presented by the company
What alternative approach has the ERG suggested?	Removal of the assumption of long-term remission from the company base case analysis
What is the expected effect on the cost effectiveness estimates?	Removal of long-term remission at 30 months from the company model increases the ICER per QALY gained for the comparison of nivolumab+chemotherapy versus chemotherapy
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion about the validity of the company assumption that effectively means that patients who enter the long-term remission health state are cured

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 5 Company model generates OS estimates that are not in line with the first 12 months of the model time horizon

Report section	Section 6.2, Section 6.3 and Section 6.11
Description of issue and why the ERG has identified it as important	At 12 months, the modelled proportions of patients alive in the nivolumab+chemotherapy and chemotherapy arms are higher than the proportions of CheckMate 649 trial patients alive at this time point. As the company model does not reflect CheckMate 649 trial survival estimates over this short time frame, confidence in model long-term survival projections is limited. As model OS projections are not reliable, model cost effectiveness results cannot be reliable
What alternative approach has the ERG suggested?	None – given the complexity of the model design, making changes to address this issue was beyond the remit of the ERG
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	A model that generates 12-month survival estimates that are similar to CheckMate 649 trial 12-month survival results would be helpful

ERG=Evidence Review Group: OS=overall survival

Issue 6 High utility values in the PFS and progressed disease health states

Report section	Section 6.2, Section 6.5, Section 6.10 and Section 6.11
Description of issue and why the ERG has identified it as important	The model is populated with utility values derived from CheckMate 649 trial data. These values appear high compared to population norms, values used in previous NICE TA submissions, and published studies in advanced gastric cancer
What alternative approach has the ERG suggested?	Lower utility values for the PFS and progressed disease health states from a previous NICE TA
What is the expected effect on the cost effectiveness estimates?	Use of lower utility values slightly increased the company base case ICERs per QALY gained (nivolumab+chemotherapy versus chemotherapy)
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for additional health-related quality of life information

ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; PFS=progression-free survival; QALY=quality-adjusted life year; TA=technology appraisal

Issue 7 Low model baseline population age

Report section	Section 6.7, Section 6.10 and Section 6.11
Description of issue and why the ERG has identified it as important	The model baseline population mean age is [redacted] years (mean baseline age of CheckMate 649 trial population). This age is lower than the average age suggested by the ERG's clinical advisor and lower than the average age reported in some UK sources
What alternative approach has the ERG suggested?	An alternative mean start age of 64.15 years calculated from a company analysis of Cancer Research UK data was used in the model
What is the expected effect on the cost effectiveness estimates?	Using a baseline age of 64.15 years resulted in a moderate increase in the company base case ICERs per QALY gained. The older the patients, the less cost effective the intervention becomes. The company deterministic sensitivity analyses showed that adjusting baseline population age by ±20% was the biggest driver of cost effectiveness
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for information about the age of patients treated in the NHS

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 8 Limited cost effectiveness results for PD-L1 subgroups

Report section	Section 6.8 and Section 6.11
Description of issue and why the ERG has identified it as important	It is stated in the final scope issued by NICE that results from subgroup analyses by level of tumour PD-L1 expression would be considered if evidence allowed. Whilst the company provided results for the PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups, no clinical effectiveness or cost effectiveness results were provided for PD-L1 CPS<1 and PD-L1 CPS<5 subgroups OS HR results from the CheckMate 649 trial show that the clinical effectiveness (and cost effectiveness) of nivolumab+chemotherapy versus chemotherapy may be lower in the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups than in the PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups
What alternative approach has the ERG suggested?	The ERG requested clinical and cost effectiveness analyses for patients with PD-L1 CPS<1 and CPS<5 at clarification. Limited clinical effectiveness results and no cost effectiveness results were provided by the company as they stated that the sample sizes for these CheckMate 649 subgroups were too small
What is the expected effect on the cost effectiveness estimates?	It would be expected that, for the comparison of nivolumab+chemotherapy versus chemotherapy, the ICERs per QALY gained for the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups would be higher than for the PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups
What additional evidence or analyses might help to resolve this key issue?	The ERG considers the sample sizes for the PD-L1 CPS<1 (nivolumab+chemo: [redacted]; chemotherapy: [redacted]) and PD-L1 CPS<5 (nivolumab+chemo: [redacted]; chemotherapy: [redacted]) populations in the CheckMate 649 trial are sufficient for the company to undertake informative cost effectiveness analyses for these subgroups

CPS=combined positive score; ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; OS=overall survival; PD-L1=programmed cell death-ligand 1; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Issue 9 Inappropriate treatment modifier

Report section	Section 6.2 and Section 6.6
Description of issue and why the ERG has identified it as important	The ERG considers that it is inappropriate to apply a treatment modifier to the costs of only one of the treatments considered in the company base case analyses
What alternative approach has the ERG suggested?	Remove the treatment modifier from the company base case analysis
What is the expected effect on the cost effectiveness estimates?	The effect is to increase the company base case ICERs per QALY gained
What additional evidence or analyses might help to resolve this key issue?	The company to apply appropriate treatment modifiers to all drug acquisition and administration costs used in the base case analyses

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

1.6 Other key issues: summary of the ERG's views

Issue 10 NICE End of life criteria

Report section	Section 7
Description of issue and why the ERG has identified it as important	The ERG considers that the available data suggest that life expectancy for the population described in the final scope issued by NICE is <24 months. However, when estimating median OS, the ERG highlights that results from the CheckMate 649 trial show that a gain of ≥3 months was only evident for the PD-L1 CPS≥5 subgroup; a median OS gain of ≥3 months is not demonstrated for the whole population
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost effectiveness estimates?	The ERG identified weaknesses in the company's approach to generating OS estimates that mean that any predicted survival gain is highly uncertain. However, the ERG base case analysis predicts incremental life years exceeding 3 months. The validity of any estimates of cost effectiveness will depend on the validity of any implemented alterations to the company model
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on company long-term survival estimates

CPS=combined positive score; ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence; OS=overall survival; PD-L1=programmed cell death-ligand 1

1.7 Summary of company and ERG's cost effectiveness results

1.7.1 Company's pairwise deterministic cost effectiveness results

Table A Base case pairwise cost effectiveness results for nivolumab+FOLFOX versus FOLFOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Cost	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]				
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,840**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 55

Table B Base case pairwise cost effectiveness results for nivolumab+XELOX versus XELOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Cost	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]				
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,172**

LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin
Source: CS, Table 56

Table C Scenario analysis results in PD-L1 CPS≥1 subgroup (PAS price for nivolumab, list prices for other drugs)

Treatment	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,370**
Nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,438**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; LYs=life years; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin
Source: CS, Table 62

Table D Scenario analysis results in PD-L1 CPS≥5 subgroup (PAS price for nivolumab, list prices for other drugs)

Technologies	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,157**
Nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,973**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years; XELOX=capecitabine+oxaliplatin
Source: CS, Table 63

1.7.2 ERG's pairwise deterministic cost effectiveness results

Table E ERG revisions to company model and preferred ICER per QALY gained, whole population: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£45,172***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,503	-£669
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,075	£48,903
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,995	£823
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,067	£5,895
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,293	£5,121
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£116,712***	***£71,540***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table F ERG revisions to company model and preferred ICER per QALY gained, whole population: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£47,840***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,197	-£643
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,456	£51,616
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,711	£871
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,018	£8,178
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,263	£5,423
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£127,870***	***£80,030***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

Table G ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS ≥1: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£40,438***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,854	-£584
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£88,305	£47,867
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,195	£757
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,662	£5,224
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,016	£4,578
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£108,647***	***£68,209***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table H ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS ≥1: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£43,370***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,803	-£567
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,497	£51,127
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,183	£813
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,615	£7,245
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,279	£4,909
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£120,232***	***£76,862***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

Table I ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS ≥5: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£34,973***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,504	-£469
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,246	£33,273
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,791	£818
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,370	£4,397
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,776	£3,803
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£84,805***	***£49,832***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table J ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS ≥5: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY gained	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£38,157***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,694	-£463
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,210	£36,053
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,049	£892
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,255	£6,098
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,307	£4,150
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£95,074***	***£56,917***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of nivolumab (Opdivo) in combination with chemotherapy for untreated, advanced, gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. In the company submission (CS), the chemotherapy regimens combined with nivolumab are fluorouracil+folinic acid+oxaliplatin (FOLFOX) and capecitabine+oxaliplatin (XELOX). In this Evidence Review Group (ERG) report, references to the CS are to the company's Document B, which is the company's full evidence submission. For simplicity, in this ERG report, where appropriate, gastric, gastro-oesophageal junction and oesophageal adenocarcinomas are referred to as oesophago-gastric adenocarcinomas.

2.2 Oesophago-gastric adenocarcinoma

Oesophago-gastric cancers are located in the upper gastro-intestinal tract. Gastric tumours originate in the cells of the stomach.[1] Gastro-oesophageal junction cancers are tumours with centres that lie within 5cm of the gastro-oesophageal junction.[2] Oesophageal cancers are found in the cells that line the oesophagus[3] and approximately 83% of these cancers are found in the lower part of the oesophagus.[4] In the UK, most gastric, gastro-oesophageal junction and oesophageal cancers are of adenocarcinoma histology.[1,3] Between 10% and 15% of gastric and gastro-oesophageal junction cancers also carry the human epidermal growth factor receptor 2 (HER2) gene.[5]

In England in 2015, 5142[6] people were diagnosed with gastric and gastro-oesophageal junction cancer and 7569[7] were diagnosed with oesophageal cancer. Incidence rates were higher in men than women; 65% of gastric and gastro-oesophageal junction cancers and 70% of oesophageal cancers were diagnosed in men.[6,7] Age is a risk factor, and the highest incidence is in older people.[6,7] In the UK, almost 50% of people diagnosed with gastric and gastro-oesophageal junction cancer and 41% of people diagnosed with oesophageal cancer are aged 75 years and older (based on data from 2015 to 2017).[6,7] Other risk factors are *Helicobacter pylori* infection, being overweight or obese, smoking and excess alcohol intake.[8,9]

In England, most oesophago-gastric adenocarcinomas are diagnosed at a late stage, either Stage III (17% gastric and gastro-oesophageal junction, 29% oesophageal) or Stage IV (34% gastric and gastro-oesophageal junction and 30% oesophageal).[6,7] The 5-year age-standardised survival estimates for patients diagnosed with Stage III gastric and gastro-oesophageal junction and oesophageal cancer are 23% and 16%, respectively.[10] Insufficient data are available to calculate survival at 5 years for patients who are diagnosed with Stage IV disease as few of these patients are alive 5 years after diagnosis.[10]

2.3 Nivolumab+chemotherapy

Nivolumab, a monoclonal antibody, is a programmed cell death protein 1 (PD-1) checkpoint inhibitor that directly blocks the interaction of PD-1 with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2) with PD-1. Nivolumab is administered intravenously (IV) in combination with chemotherapy. In the CS, the chemotherapy regimens used in combination with nivolumab are FOLFOX and XELOX.

2.4 Company's overview of current service provision

2.4.1 Treatments in the pathway

The company's proposed positioning of nivolumab+chemotherapy is as a first-line treatment for patients with untreated, locally advanced or metastatic, oesophago-gastric adenocarcinoma (Figure 1).

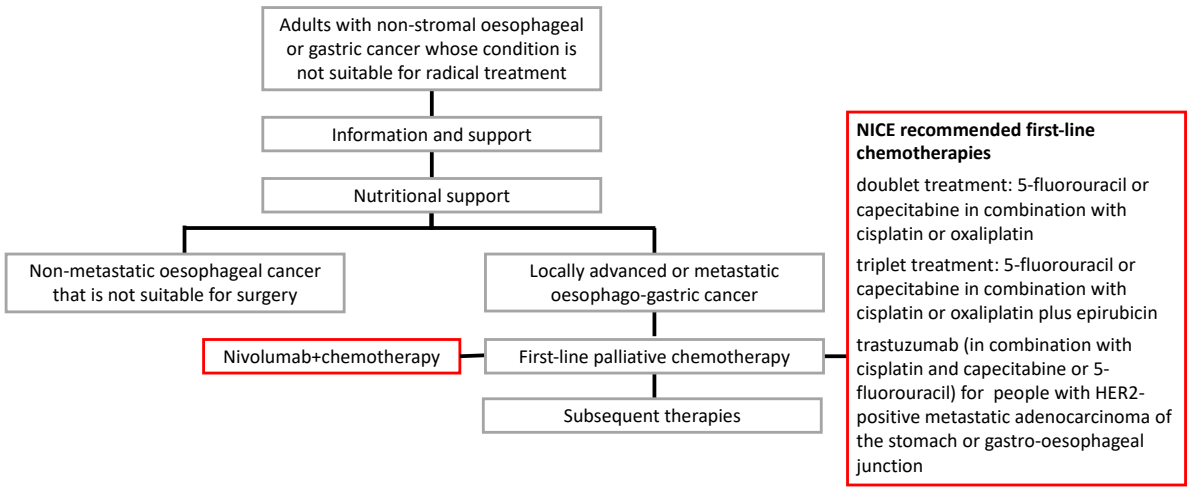


Figure 1 Treatment pathway for patients with advanced oesophago-gastric cancer

HER2=human epidermal growth factor receptor 2
Source: Adapted from CS, Figure 1

2.4.2 Chemotherapy regimens recommended by NICE

In the NICE clinical guideline for oesophago-gastric cancer (NG83[11]), it is recommended that treatment with chemotherapy should be offered to patients with untreated advanced or metastatic disease who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and no significant co-morbidities. The chemotherapy combinations suggested in NICE clinical guideline (NG83)[11] for patients with oesophago-gastric cancer are:

- fluorouracil with cisplatin
- fluorouracil with oxaliplatin
- capecitabine with cisplatin (TA191[12])

- capecitabine with oxaliplatin (TA191[12]); this combination is described as XELOX in the CS and is sometimes known as CAPOX
- fluorouracil with cisplatin or oxaliplatin plus epirubicin
- capecitabine with cisplatin or oxaliplatin plus epirubicin

Trastuzumab plus chemotherapy (fluorouracil+cisplatin or capecitabine+cisplatin) is recommended for patients with gastric or gastro-oesophageal junction adenocarcinoma that is HER2-positive. NICE guidance (TA208[13]) for the use of trastuzumab is not applicable to patients with HER2-positive adenocarcinoma of the oesophagus; the ToGA[14] trial (the trial that informed NICE TA208,[13] the appraisal of trastuzumab) did not include patients with oesophageal carcinoma.

Testing prior to treatment

Clinical advice to the ERG is that prior to treatment in the NHS, gastric or gastro-oesophageal junction adenocarcinomas are tested for HER2 status. In line with NICE guidance (TA208),[13] patients with HER2-positive adenocarcinomas are offered treatment with trastuzumab combined with chemotherapy. Clinical advice to the ERG is that patients in the NHS may wait up to 6 to 8 weeks for the results of their HER2 test and may begin treatment prior to confirmation of HER2 status.

Patients in the NHS with oesophago-gastric adenocarcinoma are also tested for dihydropyrimidine dehydrogenase deficiency (DPD). The test identifies patients who have an impaired ability (partial or complete) to metabolise fluoropyrimidines.[15] Clinical advice to the ERG is that approximately 5% of patients treated in the NHS have partial DPD. Patients with partial DPD start treatment at 50% of the standard dose of a fluoropyrimidine agent and the dose may be escalated depending on the patient's ability to tolerate treatment. Patients with complete DPD (less than 1% of patients) are not offered treatment with any fluoropyrimidine agent.

Clinical advice to the ERG is that in the NHS, oesophago-gastric adenocarcinomas are not tested for PD-L1 expression.

2.5 Number of patients eligible for treatment with nivolumab+chemotherapy

In Document A of the CS (Table 11), the company has estimated that, if recommended by NICE, 3385 patients in England with oesophago-gastric adenocarcinoma would be eligible for treatment with nivolumab+chemotherapy. The ERG considers that the company estimate is reasonable.

2.6 Critique of company's definition of the decision problem

A summary of the decision problem outlined in the final scope[16] issued by NICE and addressed by the company is presented in Table 1. Each parameter is discussed in more detail in the text following Table 1 (Section 2.6.1 to Section 2.6.8).

Table 1 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Population	Adults with untreated locally advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma	As per scope	As per the NICE scope. However, there are no cost effectiveness results presented for patients with HER2-positive disease, only (indirect) clinical effectiveness results are available for this subgroup of patients
Intervention	Nivolumab in combination with chemotherapy	As per scope Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy	As per the NICE scope In the pivotal CheckMate 649 trial, patients received treatment with nivolumab+FOLFOX or nivolumab+XELOX. The choice of chemotherapy therapy regimen was made by the treating clinician prior to randomisation Clinical advice to the company was that the FOLFOX and XELOX regimens used in the trial were standard of care in the NHS. Clinical advice to the ERG is that fewer than 10% of NHS patients are treated with FOLFOX whilst at least 80% of NHS patients are treated with XELOX

Comparator(s)	• Chemotherapy without nivolumab, such as: - doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin - triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin plus epirubicin For people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: trastuzumab with cisplatin plus capecitabine or fluorouracil	As per scope	**Direct clinical evidence in the CS** Direct evidence is available from the CheckMate 649 trial for the comparison of nivolumab+chemotherapy (FOLFOX or XELOX) versus chemotherapy (FOLFOX or XELOX) **Indirect clinical evidence in the CS** The company conducted NMAs to allow a comparison of the clinical effectiveness of chemotherapy (FOLFOX) versus: i) fluorouracil+cisplatin ii) capecitabine+cisplatin iii) trastuzumab+capecitabine+cisplatin Clinical advice to the ERG is that fluorouracil+cisplatin and capecitabine+cisplatin are rarely used to treat patients in the NHS except in combination with trastuzumab for patients with HER2-positive disease The ERG is uncertain about the impact of prognostic factors (HER2 and PD-L1) which are not accounted for in the company NMAs and also has concerns about the validity of the company's proportional hazards assumptions (see Section 3.6.5 of this ERG report) None of the trials included in the NMAs recruited patients with oesophageal adenocarcinoma (see Section 3.6.1 of this ERG report) **Narrative clinical effectiveness evidence in the CS** Clinical advice to the company and the ERG is that epirubicin is rarely used in the NHS to treat this patient population. Due to the limited evidence base, the company was unable to conduct NMAs to allow a comparison of nivolumab+chemotherapy versus triplet chemotherapy regimens that include epirubicin:

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
			However, the company has provided a narrative summary of the clinical effectiveness evidence available for epirubicin-containing triplet chemotherapy combinations **No clinical evidence in the CS** No clinical effectiveness evidence is presented in the CS for the comparison of nivolumab+chemotherapy versus: i) fluorouracil+cisplatin ii) capecitabine+cisplatin iii) trastuzumab+capecitabine+cisplatin No clinical effectiveness evidence is presented in the CS for the comparison of chemotherapy versus trastuzumab+fluorouracil+cisplatin
Outcomes	The outcome measures to be considered include: • OS • PFS • RR • AEs • HRQoL	As per scope	Direct evidence for the comparison of nivolumab+chemotherapy versus chemotherapy is presented in the CS for all of the outcomes listed in the final scope[16] issued by NICE The two primary outcomes in the CheckMate 649 trial are (BICR) PFS and OS in patients with PD-L1 CPS≥5. However, [redacted] Indirect evidence for OS and PFS is provided in the CS for all of the comparators in the company NMAs

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
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 PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	As NICE reference case	The company has provided cost effectiveness results in the form of ICERs per QALY gained for the comparisons of nivolumab+chemotherapy versus chemotherapy The time horizon considered is 50 years Costs are calculated from the perspective of the NHS and PSS The PAS price for nivolumab and list prices for the comparator drugs are used in the company analyses

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	ERG comment
Other considerations	If evidence allows subgroups by PD-L1 status will be considered Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	Pre-defined subgroups provided, including PD-L1 status	Clinical effectiveness results are available in the CS for patients in the CheckMate 649 trial with PD-L1 CPS≥1 or PD-L1 CPS≥5 subgroups Scenario analyses are presented in the cost effectiveness section of the CS for patients in the PD-L1 CPS≥1 or PD-L1 CPS≥5 subgroups In response to the ERG's clarification requests (Question B1 and B2), the company did not provide K-M data or scenario analyses for OS, PFS and time to treatment discontinuation for patients in the CheckMate 649 trial PD-L1 CPS<1 andPD-L1 CPS<5 subgroups but did provide HRs for OS, PFS and ORR for these subgroups. All other requested CPS subgroup data requested as part of the clarification process were provided by the company

AE=adverse event; CPS=combined positive score; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; PAS=Patient Access Scheme; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PSS=Personal and Social Services; QALY=quality adjusted life year; RR=response rate; XELOX=capecitabine+oxaliplatin
Source: Final scope issued by NICE[16] and CS, Table 1

2.6.1 Source of direct clinical effectiveness data

The primary source of the clinical effectiveness evidence presented by the company is the CheckMate 649[17] trial. This is an ongoing, open-label, international, multi-centre, phase III, randomised controlled trial (RCT) that compares the clinical effectiveness of nivolumab+chemotherapy (n=789) with chemotherapy (n=792). The chemotherapy treatments administered in this trial are either FOLFOX or XELOX. Clinical efficacy results are not reported separately for the different chemotherapy treatment combinations. The results of the company's pre-specified subgroup analyses indicate that there is no difference in efficacy between the chemotherapy regimens, and clinical advice to the ERG is that no differences in efficacy would be expected in NHS clinical practice. The results of the CheckMate 649 trial presented in the CS are based on a minimum follow-up of 12.1 months. The company estimates that the trial will end on 6th October 2022.

In a third arm of the CheckMate 649 trial, patients received nivolumab+ipilimumab; however, treatment with nivolumab+ipilimumab is not relevant to the appraisal discussed in this ERG report.

2.6.2 Population

In line with the final scope[16] issued by NICE, the company has presented clinical effectiveness evidence for patients with untreated, locally advanced or metastatic, oesophago-gastric adenocarcinoma. The ERG notes that the baseline median age of patients in the CheckMate 649 trial was [redacted] years and most patients ([redacted] were aged under 65 years. At baseline, all patients in the trial had an ECOG PS of 0 or 1. Clinical advice to the ERG is that the average age of patients treated in the NHS is 70 to 75 years at diagnosis. Furthermore, in line with NICE guideline NG83,[11] patients with an ECOG PS of 2 are routinely offered treatment with platinum doublet chemotherapy. This means that the results of the CheckMate 649 trial may not be generalisable to all patients treated in the NHS.

Patients with HER2-positive gastric and gastro-oesophageal junction adenocarcinoma are a subgroup of the population specified in the final scope[16] issued by NICE. The company highlighted that patients who were known to have HER2-positive disease were excluded from the CheckMate 649 trial. Whilst the HER2 status of patients' tumours was not known for a considerable proportion ([redacted]) of patients, it is likely that <15%[5] of the overall patient population would have had HER2-positive disease. In the absence of an identified subgroup of patients in the CheckMate 649 trial with HER2-positive disease, the ERG considers that no conclusions can be drawn about the clinical effectiveness of nivolumab+chemotherapy in patients with HER2-positive gastric or gastro-oesophageal disease.

2.6.3 Intervention

The intervention in the CheckMate 649 trial is nivolumab+chemotherapy; patients received treatment with nivolumab+FOLFOX or nivolumab+XELOX. The company has provided the following information about nivolumab+chemotherapy (CS, Table 2 and CS, page 23):

(i) nivolumab+chemotherapy does not currently have a marketing authorisation in the UK for use in the patient population discussed in this appraisal. On [redacted], the company submitted a conditional marketing authorisation application to the European Medicines Agency (EMA) for [redacted] The company expects the decision from the EMA Committee for Medicinal Products for Human Use (CHMP) during [redacted]

(ii) the company expects the recommended treatment regimen to be nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy. The dosing of nivolumab is dependent on the chemotherapy cycle length. When combined with a 3-weekly chemotherapy cycle, the dose of nivolumab is 360mg, and when combined with a 2-weekly chemotherapy cycle, the dose of nivolumab is 240mg of nivolumab. Treatment continues until disease progression or unacceptable toxicity, with a maximum treatment duration of 2 years.

Clinical advice to the ERG is that patients in the NHS typically receive six cycles of XELOX and eight to ten cycles of FOLFOX.

Clinical advice to the ERG is that fewer than 10% of NHS patients with gastro-oesophago adenocarcinoma are treated with FOLFOX.

Clinical advice to the ERG is that treatment with XELOX is standard of care in most NHS treatment centres because capecitabine is administered orally. In the CheckMate 649 trial, capecitabine is given at a dose of 1000mg/m^2 twice daily (BID) on days 1 to 14 of a 21-day cycle and oxaliplatin is given at a dose of 130mg/m^2 IV on day 1. Clinical advice to the ERG is that in the NHS, the doses of capecitabine and oxaliplatin are tailored to patients' PS and their ability to tolerate treatment, with the aim of maximising the number of treatment cycles. In the NHS, capecitabine may be administered at a dose of between 375mg/m^2 (mainly frail patients) and 625mg/m^2 BID over 21 days and oxaliplatin is administered at a dose of 80mg/m^2 to 130mg/m^2 on day 1.

2.6.4 Comparators

Oesophago-gastric adenocarcinoma (not HER2-positive)

A discussion of the FOLFOX and XELOX regimens and their relevance to treatments in the NHS has been provided in Section 2.6.1 and Section 2.6.3 of this ERG report. Clinical advice to the ERG is that, for FOLFOX and XELOX, the company's assumption of equal efficacy (OS and PFS) is reasonable and is supported by results from CheckMate 649 subgroup analyses (CS, Section B.2.7).

The company conducted NMAs to compare the clinical effectiveness of chemotherapy (FOLFOX) versus fluorouracil+cisplatin and versus capecitabine+cisplatin. The company did not present any NMA results for the comparison of nivolumab+chemotherapy versus fluorouracil+cisplatin or versus capecitabine+cisplatin in the CS.

The results of the NMAs were not used to inform the company's base case cost effectiveness analyses. The ERG notes that the trials in the networks only included patients with gastric or gastro-oesophageal junction adenocarcinoma; the clinical outcomes for patients with oesophageal adenocarcinoma are therefore unknown. Clinical advice to the ERG is that fluorouracil+cisplatin and capecitabine+cisplatin treatment combinations are rarely used to treat patients in the NHS.

Clinical advice to the company and the ERG is that epirubicin is rarely used in the NHS to treat patients with untreated, locally advanced or metastatic, oesophago-gastric adenocarcinoma. Due to the limited evidence base (CS, p59) the company was unable to conduct any NMAs to allow a comparison of nivolumab+chemotherapy with triplet chemotherapy combinations that include epirubicin. The company has provided a narrative summary of the clinical effectiveness evidence available for epirubicin-containing triplet chemotherapy combinations (CS, Appendix D1, Table 8).

HER2-positive gastric or gastro-oesophageal junction adenocarcinoma

The comparator(s) listed in the final scope[16] issued by NICE for patients with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma is trastuzumab with cisplatin plus capecitabine or fluorouracil. The company has conducted NMAs to allow a comparison of chemotherapy (FOLFOX) with trastuzumab+capecitabine+cisplatin. However, in the NMAs, two out of the three included studies[18,19] include patients with gastric or gastro-oesophageal junction adenocarcinoma of unknown HER2 status, therefore comparisons made within the NMAs may not be wholly applicable to patients with HER2-positive disease (see Section 3.6.4 and Section 3.6.5 of this ERG report).

2.6.5 Outcomes

The outcomes listed in the final scope[16] issued by NICE are overall survival (OS), progression free-survival (PFS), response rates (RR), adverse events (AEs) and health-related quality of life (HRQoL). Clinical advice to the ERG is that these are the most relevant outcomes for the patient population considered in this appraisal. The ERG highlights that direct evidence (from the CheckMate 649 trial) for nivolumab+chemotherapy versus chemotherapy is available for all of the outcomes listed in the final scope[16] issued by NICE.

The two primary outcomes in the CheckMate 649 trial are (BICR) PFS and OS in patients with PD-L1 combined positive score (CPS) ≥5. However, [redacted].

The company NMAs provide OS and PFS results for the comparisons of chemotherapy (FOLFOX) versus:

- fluorouracil+cisplatin
- capecitabine+cisplatin
- trastuzumab+capecitabine+cisplatin

2.6.6 Economic analysis

The company has carried out base case cost effectiveness analyses for the comparisons of (i) nivolumab+FOLFOX versus FOLFOX and (ii) nivolumab+XELOX versus XELOX, irrespective of patient tumour PD-L1 level of expression. The company has also provided scenario analyses for the comparisons of nivolumab+chemotherapy versus FOLFOX and versus XELOX for the subgroups of patients with a tumour PD-L1 CPS ≥5 and PD-L1 CPS≥1. In response to clarification questions B1 and B2, the company declined to provide Kaplan-Meier (K-M) data and scenario analyses for the subgroups of patients with PD-L1 CPS<1 ([redacted]) and PD-L1 CPS<5 ([redacted]) subgroups on the basis that these subgroups were small and insufficiently powered to detect differences in outcomes. However, the company did provide OS, PFS and objective response rate (ORR) hazard ratios (HR) for each of these PD-L1 CPS subgroups.

Company cost effectiveness results are expressed in terms of incremental cost per quality adjusted life years (QALYs) gained. These results were generated using the Patient Access Price (PAS) price for nivolumab. None of the other drugs used in the company analyses are available to the NHS at discounted PAS prices. Outcomes were assessed over a lifetime horizon (up to 50 years) and costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.6.7 Subgroups

In the final scope[16] issued by NICE, it is stated that if the evidence allows, subgroups based on tumour PD-L1 expression level should be considered. Clinical effectiveness results are available in the CS for patients in the CheckMate 649 trial with PD-L1 CPS≥1 or CPS≥5 (see Section 3.3 of this ERG report). Further, in response to clarification question B1, the company presented OS, PFS and ORR HRs for the following subgroups: PD-L1 CPS<1 ([redacted]), PD-L1 CPS≥1 (n=1019), PD-L1 CPS<5 ([redacted]) and PD-L1 CPS≥5 (n=769).

Clinical advice to the ERG is that in the NHS, oesophago-gastric adenocarcinomas are not tested for PD-L1 expression.

2.6.8 Other considerations

The company considers that treatment with nivolumab+chemotherapy meets the NICE End of Life criteria.[20] The ERG agrees that the available data suggest that life expectancy for the population described in the final scope[16] issued by NICE is <24 months. However, when estimating median OS, the ERG highlights that results from the CheckMate 649 trial show that a gain of ≥3 months was **only** evident for the PD-L1 CPS≥5 subgroup; an OS gain of ≥3 months is not demonstrated for the whole population. The ERG identified weaknesses in the company's approach to generating OS estimates that mean any predicted survival gain is highly uncertain.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's systematic review methods

Full details of the methods used by the company to identify and select relevant evidence to demonstrate the clinical effectiveness of nivolumab+chemotherapy for untreated advanced oesophago-gastric adenocarcinoma are presented in the CS (Appendix D). The ERG did not find any relevant studies in addition to those identified by the company. An assessment of the extent that the review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 2. The ERG has identified some minor issues (described in Table 2) but considers that these do not affect the quality and completeness of the evidence used to inform this appraisal.

Table 2 ERG appraisal of the company's systematic review methods

Review process	ERG response	ERG comments
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D1, Table 2 and Section 6.5
Were appropriate sources searched?	Yes	See CS, Appendix D1, Section 6.3
Was the timespan of the searches appropriate?	Yes	Databases were searched from inception to September 2020. Conference proceedings published from January 2016 to October 2020 were hand searched
Were appropriate search terms used?	Yes	No ERG comment
Were the eligibility criteria appropriate to the decision problem?	Yes	No ERG comment
Was study selection applied by two or more reviewers independently?	Yes	No ERG comment
Was data extracted by two or more reviewers independently?	Yes	One reviewer extracted data and the data were then checked by a second (independent) reviewer. The ERG considers that this is standard practice
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company used the quality assessment checklist for clinical trials devised by the CRD at the University of York[21]
Was the quality assessment conducted by two or more reviewers independently?	No	One reviewer conducted quality assessment
Were attempts to synthesise evidence appropriate?	Yes	See Section 3.2.5 and Section 3.6.3 for a discussion of the company's methods and the ERG's critique of the syntheses of direct and indirect evidence

CRD=Centre for Reviews and Dissemination; CS=company submission; ERG=Evidence Review Group Source: LR*i*G in-house checklist

3.2 ERG summary and critique of clinical effectiveness evidence

3.2.1 Included trials

The company identified two studies that provided evidence of the clinical effectiveness of nivolumab+chemotherapy for untreated, locally advanced or metastatic oesophago-gastric adenocarcinoma:

(iii) the CheckMate 649 trial

(iv) the ATTRACTION-4 trial[22]

The company considered (CS, p25) that the ATTRACTION-4 trial population had limited relevance to patients with untreated, locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma seen in NHS practice because the trial population was exclusively Asian and nearly two-thirds of patients (64.1%) received chemotherapy treatment with SOX (tegafur, gimeracil, oteracil [S-1] and oxaliplatin), a regimen that is not used in NHS practice. However, the company presented evidence (CS, p25) from the ATTRACTION-4 trial for completeness.

Clinical advice to the ERG agrees with the company's conclusion that evidence from the ATTRACTION-4 trial should not be considered a primary source of clinical effectiveness evidence for this appraisal. Clinical advice to the ERG is that there are screening programmes in East Asia that lead to early diagnosis of gastric cancer and that this means that patients with untreated, locally advanced or metastatic oesophago-gastric adenocarcinoma in Asia are typically younger and fitter than patients seen in NHS practice. Most patients with untreated advanced oesophago-gastric adenocarcinoma in Asia receive more subsequent lines of therapy, are suitable for more aggressive therapies and have longer OS times than patients seen in NHS practice.[5]

For information, the key characteristics of part 1 and part 2 of the ATTRACTION-4 trial are summarised in Appendix 9.1 and Table 44 of this ERG report. The baseline characteristics of patients participating in part 1 (phase II) and part 2 (phase III) of the ATTRACTION-4 trial are summarised in Table 45 and Table 46, respectively (Appendix 9.1).

3.2.2 Characteristics of the CheckMate 649 trial

The CheckMate 649 trial (NCT02872116) is an ongoing, open-label, international, multi-centre, phase III, RCT of nivolumab+chemotherapy versus chemotherapy for patients with untreated, locally advanced or metastatic oesophago-gastric adenocarcinoma. Patients receive either the FOLFOX or XELOX chemotherapy regimen. The CheckMate 649 trial is being conducted in 175 centres across 29 countries.

The company has presented evidence from the 10th July 2020 database lock. At the time of the database lock, data were available from 1581 patients including 38 patients recruited from five UK centres.

As discussed in Section 2.6.3 of this ERG report, clinical advice to the ERG is that treatment with capecitabine+oxaliplatin (XELOX) is standard of care in most NHS treatment centres. Clinical advice to the ERG is that the FOLFOX regimen is used to treat fewer than 10% of patients in the NHS.

The key characteristics of the CheckMate 649 trial are summarised in Table 3.

Table 3 Key characteristics of the CheckMate 649 trial

Trial parameter	CheckMate 649 trial
Design	Ongoing, open-label, international, multi-centre, phase III, RCT 175 centres across 29 countries (Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Taiwan, Turkey, United Kingdom, and United States) Includes 38 patients recruited from 5 UK centres Estimated completion date: 6th October 2022
Patient population	Adults (≥18 years), with untreated, inoperable metastatic or locally advanced gastric or gastro-oesophageal junction or distal oesophageal cancer that is histologically confirmed as predominant adenocarcinoma ECOG PS 0 or 1 and measurable disease per RECIST v1.1 No prior systemic therapy (including HER2 inhibitors) unless neoadjuvant or adjuvant chemo/radio or chemoradiotherapy completed ≥6 months before randomisation or palliative radiotherapy completed ≥2 weeks before randomisation Patients with known HER2 positive status and patients with untreated CNS metastases were excluded
Intervention	Nivolumab+FOLFOX: 2-weekly chemotherapy cycle; nivolumab 240mg IV (30 minutes) on day 1, plus oxaliplatin 85mg/m,^{2} folinic acid 400mg/m^2 and fluorouracil 400mg/m^2 IV on day 1 and fluorouracil 1200mg/m^2 24 hours IV continuous infusion on days 1 and 2 or Nivolumab+XELOX: 3-weekly chemotherapy cycle; nivolumab 360mg IV (30 minutes) on day 1, plus oxaliplatin 130mg/m^2 IV and capecitabine 1000mg/m^2 orally BID on days 1 to 14
Comparator	FOLFOX: 2-weekly chemotherapy cycle; oxaliplatin 85mg/m^2, folinic acid 400mg/m^2 and fluorouracil 400mg/m^2 IV on day 1 and fluorouracil 1200mg/m^2 24 hours IV continuous infusion on days 1 and 2 or XELOX: 3-weekly chemotherapy cycle; oxaliplatin 130mg/m^2 IV and capecitabine 1000mg/m^2 orally BID on days 1 to 14
Primary outcome	PFS by BICR for patients with PD-L1 CPS≥5 OS for patients with PD-L1 CPS≥5
Secondary outcomes	OS PFS Response rate Adverse events Health-related quality of life
Report period for database lock	17th April 2017 (first patient randomised) to 10th July 2020 (database lock) Clinical cut-off date for the database lock: 27th May 2020 (last patient last visit) Minimum follow-up: 12.1 months

BID=twice daily; BICR=blinded independent central review; CNS=central nervous system; CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HER2=human epidermal growth factor receptor 2; IV=intravenous; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PS=performance status; RCT=randomised controlled trial; RECIST v1.1=response evaluation criteria in solid tumours (version 1.1); XELOX=capecitabine+oxaliplatin
Source: Adapted from CS, Table 4 and Table 5

3.2.3 Characteristics of patients in the CheckMate 649 trial

The baseline characteristics of patients participating in the CheckMate 649 trial are provided in Table 4. The ERG agrees with the company (CS, p38) that the characteristics of patients participating in the CheckMate 649 trial are well-balanced across the treatment arms.

The median baseline age of patients in the CheckMate 649 trial was [redacted] years and nearly [redacted] of patients ([redacted]) were aged under 65 years. Over [redacted] of patients were white ([redacted]), male ([redacted]) and were initially diagnosed with gastric cancer ([redacted]). When tumour PD-L1 expression levels were measured using CPS, approximately [redacted] of patients ([redacted]) had PD-L1 CPS≥1 (CSR, Table 5.2.2.1-2); when PD-L1 expression levels were measured using tumour proportion score (TPS), most patients ([redacted]) had PD-L1 TPS<1% (CSR, Table 5.2.2.1-1).

The ERG notes that in the CheckMate 649 trial, nearly [redacted] of patients ([redacted]) were Asian and nearly [redacted] ([redacted]) of patients were recruited from Asia (see Section 3.2 for discussion).

Clinical advice to the ERG is that the CheckMate 649 trial population is younger and fitter (ECOG PS 0 to 1) than patients with untreated, locally advanced or metastatic, oesophago-gastric adenocarcinoma seen in NHS practice (often ECOG PS 2). This may limit the generalisability of results from the CheckMate 649 trial to NHS clinical practice.

Table 4 CheckMate 649 trial baseline patient characteristics (ITT population)

Baseline characteristic	Nivolumab+chemotherapy (n=789)	Chemotherapy (n=792)	Total (N=1581)
Age, years			
Mean	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Age group, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]	[redacted]
75 to <85 years	[redacted]	[redacted]	[redacted]
85 years and over	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Initial diagnosis, n (%)			
Gastroesophageal junction cancer	[redacted]	[redacted]	[redacted]
Gastric cancer	[redacted]	[redacted]	[redacted]
Oesophageal adenocarcinoma	[redacted]	[redacted]	[redacted]
PD-L1 CPS expression status, n (%)[a]			
Quantifiable at baseline	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥10	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥5	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥1	[redacted]	[redacted]	[redacted]
PD-L1 CPS<1	[redacted]	[redacted]	[redacted]
Indeterminate	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
Missing at baseline	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]

BICR=blinded independent central review; CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; ITT=intention-to-treat; RECIST v1.1=response evaluation criteria in solid tumours (version 1.1); SD=standard deviation; TPS=tumour proportion score

[a] Calculated as a percentage of all randomised patients

Source: Adapted from CS, Table 9 and CSR,[17] Table 5.2.2-1, Table 5.2.2.1-1 and Table 5.2.2.1-2

3.2.4 Quality assessment of the CheckMate 649 trial

The company conducted a quality assessment of the CheckMate 649 trial using the quality assessment checklist for clinical trials devised by the Centre for Reviews and Dissemination (CRD) at the University of York[21] (see CS, Table 7). The company (CS, p36) considered that there were no quality issues. The ERG considers that the CheckMate 649 trial is a good quality trial (see Table 5 for details).

Table 5 CheckMate 649 trial quality assessment summary

Study questions	Company assessment	ERG assessment	ERG comment
Was randomisation carried out appropriately?	Yes	Yes	
Was the concealment of treatment allocation adequate?	N/A	Yes	Randomisation by IRT concealed allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	Partly	Blinded outcome assessors completed planned analysis, blinded independent radiologists reviewed all tumour assessments and the study team were blind to patients' tumour PD-L1 expression levels The ERG notes that the different dosing schedules and the adverse event profile of nivolumab makes blinding of patients impossible
Were there any unexpected imbalances in drop-outs between groups?	No	No	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	

ERG=Evidence Review Group; IRT=interactive response technology; ITT=intention-to-treat; N/A=not applicable; PD-L1=programmed cell death-ligand 1
Source: Adapted from CS, Table 7

3.2.5 Statistical approach adopted for the analysis of the CheckMate 649 trial data

Information about the statistical approach that the company used when analysing CheckMate 649 trial data has been extracted from the primary Clinical Study Report (CSR)[17] (which is based on the 10th July 2020 database lock), the trial protocol (version 8.0, dated 15 November 2018),[23] the trial statistical analysis plan (TSAP, version 4.0, dated 4 August 2020),[24] and the CS. A summary of the ERG checks of the pre-planned statistical approach used by the company to analyse data from the CheckMate 649 trial is provided in Table 6.

The ERG considers that the pre-planned statistical approach used by the company was pre-specified and is appropriate.

Table 6 ERG assessment of statistical approaches used in the CheckMate 649 trial

Item	ERG assessment	Statistical approach	ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Clinical effectiveness results are presented in the CS (Section B.2.6.1) for all randomised patients (regardless of PD-L1 expression level), for all randomised patients with PD-L1 CPS≥5 (the primary analysis population) and for all randomised patients with PD-L1 CPS≥1.	The ERG is satisfied that the analysis populations of the CheckMate 649 trial are clearly defined and pre-specified (Protocol, Section 8.2).
Was an appropriate sample size calculation pre-specified?	Yes	Sample size and design considerations of the CheckMate 649 trial are outlined in the CS (Section B.2.4.2) and are pre-specified (Protocol, Section 8.1). Amendments to the trial design (see next row) had implications for the sample size and, therefore, the original sample size calculation was revised (Protocol, Section 8.1).	The ERG is satisfied that the sample size calculation and the revisions of the sample size calculations, related to the trial design amendments, are appropriate.
Were all protocol amendments made prior to analysis?	Yes	A summary of changes from the original protocol (version 1.0) are provided in the document history of version 8.0 (the latest version, 15 November 2018) of the CheckMate 649 trial protocol. Major amendments were made to the trial design to stop recruitment to the original nivolumab+ipilimumab arm, to add a nivolumab+chemotherapy arm, and to change the definition of the primary analysis population. Amendments were also made to outcome definitions and analysis populations and revisions were made to the sample size calculation related to trial design amendments.	The ERG is satisfied that all protocol amendments were appropriate and were made prior to the latest database lock date (10 July 2020).
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary outcomes of the CheckMate 649 trial are PFS by BICR in patients with tumour PD-L1 CPS≥5 and OS in patients with tumour PD-L1 CPS≥5 (CS, Table 5). Secondary and exploratory outcomes include OS, PFS by BICR and ORR by BICR in all randomised patients and across tumour PD-L1 CPS cut-offs (e.g., PD-L1 CPS≥1 or CPS≥10), DoR, PFS and ORR by investigator assessment. A complete list of primary, secondary and exploratory endpoints is pre-specified (Protocol, Table 8.3-1, Section 8.3.1 to 8.3.3).	The ERG is satisfied that efficacy outcomes were clearly defined, pre-specified, analysed appropriately, and that relevant primary and secondary efficacy outcomes are presented in the CS (Section B.2.6.1).
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were change from baseline in HRQoL, collected using the EQ-5D-3L generic health status measure and the gastric cancer-specific FACT-Ga health status measure, reported for the 'outcome research' population (i.e., all randomised patients who had an assessment at baseline and at least one follow-up assessment; Protocol, Section 8.2).	The ERG is satisfied that the PRO outcome definitions and analysis approaches were pre-specified (Protocol; Section 5.7) and are appropriate.

Item	ERG assessment	Statistical approach	ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were assessed and graded using the NCI CTCAE version 4.0 classification system within the 'all treated' population (Protocol, Section 5.3.2, Section 8.2). AEs are presented as numbers and percentages of patients experiencing events. No formal statistical analyses of AEs were conducted. All-causality AEs, AEs leading to study drug discontinuation, specific TRAES in ≥15% of patients in either treatment arm (any Grade and Grade 3-4 events), TRAEs with potential immunologic aetiology and SAEs are presented in the CS (Table 21 and Table 22).	The ERG is satisfied that the analysis approach for AEs was pre-specified (Protocol, Section 8.4.3) and is appropriate. The ERG also notes that additional summary tables of AEs, TRAEs and SAEs are provided in the CSR (Section 8, pp123-154).
Were modelling assumptions (e.g. proportional hazards) assessed?	Yes	In response to clarification question A2, the company assessed the PH assumption for OS and PFS by BICR for all randomised patients (regardless of tumour PD-L1 expression level), for all randomised patients with tumour PD-L1 CPS≥5 and for all randomised patients with tumour PD-L1 CPS≥1 by plotting the log cumulative hazard versus log(time), by plotting Schoenfeld residuals versus time and by using the Grambsch-Therneau test of PH.[25] Based on these assessments, the company considers that over the observed period the assumption of PH was not violated for OS or PFS by BICR for any subgroup considered.	The ERG is satisfied that the assessments of PH were appropriate, and the ERG agrees that there is no evidence that the assumption of PH is violated over the observed period.
Was a suitable approach employed for handling missing data?	Yes	Missing data were handled with censoring rules for time-to-event outcomes (Protocol, Section 8.3.1 to 8.3.3) and complete-case analysis was conducted for PROs (Protocol, Section 5.7). An algorithm outlining imputation procedures for partially missing dates is described in Appendix 2 of the TSAP.	The ERG is satisfied that all pre-specified methods for handling missing data are appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses by region, tumour location, histology (presence of signet ring), Lauren classification, peritoneal metastases, liver metastases, MSI status, tumour PD-L1 expression level (TPS<1% or ≥1%) and HER2 status are presented for OS and PFS in patients with tumour PD-L1 CPS≥5 and also in all randomised patients for OS (CS; Section B 2.7). No sensitivity analyses were presented in the CS.	The ERG is satisfied that all of the subgroup analyses of the primary outcomes defined (CS; Table 5, p29) and presented (CS; Section B 2.7) were pre-specified. (TSAP; Section 7.5.2.3; Section 7.5.2.6).

AE=adverse event; BICR=blinded independent central review; CPS=combined positive score; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; DoR=duration of response; ERG=Evidence Review Group; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; MSI=microsatellite instability; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PH=proportional hazards; PRO=patient reported outcome; SAE=serious adverse event; TRAE=treatment related adverse event; TPS=tumour proportion score; TSAP=trial statistical analysis plan

Source: Extracted from the CS, the primary CSR, the most recent version of the trial protocol and TSAP, company's response to the clarification letter, and includes ERG comment

3.3 Efficacy results from the CheckMate 649 trial

At the time of database lock (10th July 2020), [redacted] patients had been randomised to the nivolumab+chemotherapy arm (median follow-up [redacted] months) and [redacted] patients had been randomised to the chemotherapy arm (median follow-up [redacted] months). Data are available from both treatment arms for a minimum follow-up period of 12.1 months.

At the time of analysis, [redacted] and [redacted] of patients receiving nivolumab+chemotherapy and chemotherapy respectively were still receiving the study treatment. The most common reason ([redacted] of randomised participants) for discontinuing study treatment was disease progression (CS, Table 8).

3.3.1 Overall survival

A summary of CheckMate 649 trial OS results is presented in Table 7.

Table 7 Summary of CheckMate 649 trial OS results

	Nivolumab+chemotherapy	Chemotherapy
All randomised patients		
N	789	792
Events: n (%)	[redacted]	[redacted]
Median OS (95% CI),[a] months	13.83 (12.55 to 14.55)	11.56 (10.87 to 12.48)
HR (CI)[b]	0.80 (99.3% CI: 0.68 to 0.94)	
p-value[c]	0.0002	
All randomised patients with PD-L1 CPS≥5 (co-primary outcome)		
N	473	482
Events: n (%)	[redacted]	[redacted]
Median OS (95% CI),[a] months	14.39 (13.11 to 16.23)	11.10 (10.02 to 12.09)
HR (CI)[b]	0.71 (98.4% CI: 0.59 to 0.86)	
p-value[c]	<0.0001	
All randomised patients with PD-L1 CPS≥1		
N	641	655
Events: n (%)	[redacted]	[redacted]
Median OS (95% CI),[a] months	13.96 (12.55 to 14.98)	11.33 (10.64 to 12.25)
HR (CI)[b]	0.77 (99.3% CI: 0.64 to 0.92)	
p-value[c]	<0.0001	

CI=confidence interval; CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; OS=overall survival; PD-L1=programmed cell death-ligand 1; XELOX=capecitabine+oxaliplatin

[a] Calculated from Kaplan-Meier estimates

[b] Stratified Cox proportional hazards model. HR<1 indicates an advantage to nivolumab+chemotherapy over chemotherapy. Confidence intervals calculated according to hierarchical testing procedure

[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia vs USA vs rest of the word), ECOG (0 vs 1), Tumour Cell PD-L1 (≥ 1% vs <1% [including indeterminate]) and chemotherapy (XELOX vs FOLFOX)

Source: Extracted and adapted from CS, Table 11; CSR, Table 7.1-2

In all randomised patients, median OS was statistically significantly longer in the nivolumab+chemotherapy arm compared to the chemotherapy arm (HR=0.80, 99.3% confidence interval [CI]: 0.68 to 0.94, p=0.0002). Median OS was also statistically significantly longer in the nivolumab+chemotherapy arm compared to the chemotherapy arm in all randomised patients with PD-L1 CPS≥5 (HR=0.71, 98.4% CI: 0.59 to 0.86, p<0.0001) and in all randomised patients with PD-L1 CPS≥1 (HR=0.77, 99.3% CI: 0.64 to 0.92, p<0.0001).

For randomised patients with PD-L1 CPS≥5 subgroup (CS, Figure 11) and in all randomised patients (CS, Figure 12, Figure 13, Figure 14) subgroup analyses of OS demonstrate an advantage for patients treated with nivolumab+chemotherapy compared to chemotherapy for most subgroups. Notably, OS results are very similar for the two different chemotherapy regimens; XELOX (unstratified HR [redacted]) and FOLFOX (unstratified HR [redacted]).

The ERG considers that the imprecision of comparative results, reflected by wide 95% CIs (due to small sample sizes and low event counts) and also the imbalanced group sizes should be considered when drawing conclusions about some subgroup results.

3.3.2 Progression-free survival

A summary of blinded independent central review (BICR)-assessed PFS results is presented in Table 8.

Table 8 Summary of CheckMate 649 trial BICR-assessed PFS results

	Nivolumab+chemotherapy	Chemotherapy
All randomised patients		
N	789	792
Events: n (%)	[redacted]	[redacted]
Median PFS (95% CI),[a] months	7.66 (7.10 to 8.54)	6.93 (6.60 to 7.13)
HR (CI)[b]	0.77 (95% CI: 0.68 to 0.87)	
p-value[c]	Not tested	
All randomised patients with PD-L1 CPS≥5 (co-primary outcome)		
N	473	482
Events: n (%)	[redacted]	[redacted]
Median PFS (95% CI),[a] months	7.69 (7.03 to 9.17)	6.05 (5.55 to 6.90)
HR (CI)[b]	0.68 (98% CI: 0.56 to 0.81)	
p-value[c]	<0.0001	
All randomised patients with PD-L1 CPS≥1		
N	641	655
Events: n (%)	[redacted]	[redacted]
Median PFS (95% CI,)[a] months	7.49 (7.03 to 8.41)	6.90 (6.08 to 7.03)
HR (CI)[b]	0.74 (95% CI: 0.65 to 0.85)	
p-value[c]	Not tested	

BICR=blinded independent central review; CI=confidence interval; CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; XELOX=capecitabine+oxaliplatin
[a] Calculated from Kaplan-Meier estimates
[b] Stratified Cox proportional hazards model. HR<1 indicates an advantage to nivolumab+chemotherapy over chemotherapy. Confidence intervals calculated according to hierarchical testing procedure
[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia vs USA vs rest of the word), ECOG (0 vs 1), Tumour Cell PD-L1 (≥ 1% vs <1% [including indeterminate]) and chemotherapy (XELOX vs FOLFOX)
Source: Extracted and adapted from CS, Table 11; CSR, Table 7.1-2

In all randomised patients, BICR-assessed PFS was longer in the nivolumab+chemotherapy arm compared to the chemotherapy arm (median BICR-assessed PFS 7.66 months compared to 6.93 months, HR=0.77, 95% CI: 0.68 to 0.87, not tested for statistical significance according to pre-specified hierarchical testing procedure). BICR-assessed PFS was longer in the nivolumab+chemotherapy arm compared to the chemotherapy arm in all randomised patients in the PD-L1 CPS≥5 subgroup (HR=0.68, 98% CI: 0.56 to 0.81, p<0.0001) and in all randomised patients in the PD-L1 CPS≥1 subgroup (HR=0.74, 95% CI: 0.65 to 0.85, not tested for statistical significance according to pre-specified hierarchical testing procedure).

Results by investigator assessment were consistent with BICR-assessed results (CSR, Section 7.2.2, Section 7.3.2 and 7.4.2; response to question A3 of the clarification letter).

Results from all randomised patients with PD-L1 CPS≥5 for BICR-assessed PFS (CS, Section B.2.7; CSR, Figure 7.2.2.1-1) demonstrate an advantage for nivolumab+chemotherapy compared to chemotherapy for most subgroup analyses. Notably, BICR-assessed PFS results are very similar for two different chemotherapy regimens; XELOX (unstratified HR=[redacted]) and FOLFOX (unstratified HR=[redacted]).

The ERG considers that the imprecision of comparative results, reflected by wide 95% CIs (due to small sample sizes and low event counts) and also the imbalanced group sizes should be considered when drawing conclusions about some subgroup results.

3.3.3 Overall response rate and duration of response

A summary of BICR-assessed ORR results is presented in Table 9.

Table 9 Summary of CheckMate 649 trial BICR-assessed ORR (CR+PR) results

	Nivolumab+chemotherapy	Chemotherapy
All randomised patients		
N responders, n/N (%)	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]
Difference of ORR (95% CI)[b]	[redacted]	
All randomised patients with PD-L1 CPS≥5		
N responders, n/N (%)	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]
Difference of ORR (95% CI)[b]	[redacted]	
All randomised patients with PD-L1 CPS≥1		
N responders, n/N (%)	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]
Difference of ORR (95% CI)[b]	[redacted]	

BICR=blinded independent central review; CI=confidence interval; CPS=combined positive score; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ORR=objective response rate; PD-L1=programmed cell death-ligand 1; PR=partial response; XELOX=capecitabine+oxaliplatin
[a] Confirmed CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method
[b] Difference in response rate is adjusted for the stratification factors based on DerSimonian and Laird methodology
Source: Extracted and adapted from CS, Table 11

In all randomised patients, ORR was [redacted] in the nivolumab+chemotherapy arm compared to the chemotherapy arm ([redacted] compared to [redacted]). ORR was also [redacted] in the nivolumab+chemotherapy arm compared to the chemotherapy arm in all randomised patients in the PD-L1 CPS≥5 subgroup and in all randomised patients in the PD-L1 CPS≥1 subgroup. Furthermore, ORR was [redacted] in all patient populations with measurable disease (CS, Table 11). The duration of response in

responders with measurable disease was [redacted] in the nivolumab+chemotherapy arm than in the chemotherapy arm in all patient populations (CS, Table 11).

Results by investigator assessment were consistent with BICR-assessed results (CSR, Section 7.2.3, Section 7.3.3 and 7.4.3; response to question A3 of the clarification letter).

3.4 Patient reported outcomes from the CheckMate 649 trial

HRQoL data for patients with untreated, locally advanced or metastatic, oesophago-gastric adenocarcinoma were provided in the CS (Section B.2.6.1.4). They were collected from all randomised patients during the CheckMate 649 trial using the EuroQol 5-dimensions 3-level[26] (EQ-5D-3L) questionnaire, the EQ-5D Visual Analogue Scale (VAS) and the Functional Assessment of Cancer Therapy-Gastric[27] (FACT-Ga) tools. HRQoL was assessed at baseline (prior to drug administration on day 1 of the first chemotherapy cycle), every 6 weeks during the treatment phase and every 3 months thereafter until the end of follow-up. Data were available from [redacted] of patients at baseline and [redacted] of patients at 'most' time points during the treatment period (CSR, p164) but the company did not report numbers of patients providing evaluable data at each time point.

3.4.1 Summary of EQ-5D data

The mean baseline EQ-5D-3L utility index (UI) scores were similar in the nivolumab+chemotherapy ([redacted]) and chemotherapy ([redacted]) arms. The company used the previously defined[28] minimum important difference (MID) in EQ-5D-3L UI score of a mean change from baseline of ≥0.08 points (CS, p45) to assess whether UI scores differed from baseline. The company reported (CS, p45) that:

- compared to baseline, patients in the nivolumab+chemotherapy arm had improvement in mean UI scores at all assessments during the treatment phase through to week 103 with the mean change from baseline exceeding MID at weeks 91, 97 and 103
- patients in the chemotherapy arm had improvement in mean UI scores at most assessments during the treatment phase with the mean change from baseline exceeding MID at week 97
- mean UI scores decreased from baseline (worsened) following treatment discontinuation with the mean change near to or exceeding MID for patients in both the nivolumab+chemotherapy and chemotherapy arms at most assessments.

Mean baseline EQ-5D visual analogue scores (VAS) for all randomised patients were similar for the nivolumab+chemotherapy and chemotherapy arms ([redacted]). The company considered (CS, p46) a MID for EQ-5D VAS as a mean change ≥7 points from the EQ-5D VAS baseline score. The company reported (CS, p46) that:

- the mean EQ-5D VAS scores for all randomised patients increased over time in both arms
- mean change from baseline for patients in the nivolumab+chemotherapy arm met or exceeded MID (≥7 points) at all evaluable assessments (time points with data from ≥10 patients) after week 85
- mean change from baseline did not meet or exceed the MID for the chemotherapy arm at any assessment.

3.4.2 Summary of FACT-Ga data

Mean baseline FACT-Ga total scores for all randomised patients were similar for the nivolumab+chemotherapy ([redacted]) and chemotherapy ([redacted]) arms. The company did not provide a MID for FACT-Ga total scores. The company reported (CS, p46) that there was an increase from baseline (improvement) in mean FACT-Ga scores in both treatment arms at all evaluable assessments during the treatment phase, through to week 103 for the nivolumab+chemotherapy arm and through to week 109 for the chemotherapy arm. The company did not report the numbers of patients providing evaluable data at each time point.

Mean baseline scores for the gastric cancer subscale (GaCS) for all randomised patients were similar for the nivolumab+chemotherapy ([redacted]) and chemotherapy ([redacted]) arms. The company used (CS, p46) the previously defined[27] MID in GaCS score of a mean change from baseline of ≥8.2 points. The company reported that:

- mean GaCS score increased from baseline for both treatment arms
- mean change from baseline for patients in the nivolumab+chemotherapy arm met or exceeded MID (≥8.2 points) at all evaluable assessments during the treatment phase after week 31
- mean change from baseline did not meet or exceed the MID for the chemotherapy arm.

3.5 Safety and tolerability results from the CheckMate 649 trial

Safety and tolerability data from the 10th July 2020 database lock of the CheckMate 649 trial were presented in the CS (Section B.2.11). The AEs in the trial were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 classification system.

Exposure to study treatment

The CheckMate 649 trial treatment exposure data were summarised in the CS (Tables 19 and 20). The median duration of treatment exposure was longer in the nivolumab+chemotherapy arm [redacted] than in the chemotherapy arm ([redacted].

3.5.1 Summary of safety and tolerability data from the CheckMate 649 trial

The company provided a summary of all AEs experienced by ≥15% of patients in the CheckMate 649 trial (Table 10). The company highlights (CS, p81) that similar rates of AEs of any grade due to any cause were reported in the nivolumab+chemotherapy and chemotherapy arms of the trial ([redacted] and [redacted] respectively) and that more patients in the nivolumab+chemotherapy arm ([redacted]) than in the chemotherapy arm ([redacted]) experienced Grade 3 or Grade 4 AEs due to any cause.

The ERG notes that rates of Grade 3 or Grade 4 treatment-related AEs (TRAEs), Grade 3 or Grade 4 treatment-related serious AEs (SAE) and Grade 3 or Grade 4 TRAEs that resulted in treatment discontinuation were all greater in the nivolumab+chemotherapy arm than in the chemotherapy arm ([redacted]versus [redacted] [redacted] versus [redacted] and [redacted] versus [redacted], respectively).

Table 10 Summary of adverse events in the CheckMate 649 trial

	Nivolumab+chemotherapy (N=360)		Chemotherapy (N=422)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
AEs (any cause)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs	[redacted]	[redacted]	[redacted]	[redacted]
SAEs (any cause)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related SAEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation (any cause)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; SAEs=serious adverse event
Source: Adapted from CS, Table 21

Treatment-related adverse events (Grade 3 and Grade 4)

The frequencies of Grade 3 and Grade 4 TRAEs (≥15% of patients in either treatment group) are presented in Table 11. In the nivolumab+chemotherapy arm, the most frequently reported Grade 3 or Grade 4 TRAEs were neutropenia ([redacted]), decreased neutrophil count ([redacted]) and anaemia ([redacted]). In the chemotherapy arm, the most frequently reported Grade 3 or Grade 4 TRAEs were neutropenia ([redacted]), decreased neutrophil count ([redacted]), and diarrhoea and vomiting ([redacted]).

Table 11 Grade 3 or Grade 4 treatment-related adverse events (≥15% of patients in any treatment group)

TRAE	Nivolumab+chemotherapy (N=360)	Chemotherapy (N=422)
	Grade 3-4 (%)	Grade 3-4 (%)
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]

TRAEs=treatment-related adverse events
Source: Adapted from CS, Table 21

Serious adverse events

The company discussed the all-cause SAE data in the CS (CS, p83). Malignant neoplasm progression ([redacted]), vomiting ([redacted]) and anaemia ([redacted]) were the most frequently reported SAEs in the nivolumab+chemotherapy arm. The most common SAEs in the chemotherapy arm were malignant neoplasm progression ([redacted]), vomiting ([redacted]) and dysphagia ([redacted]).

In the nivolumab+chemotherapy arm, diarrhoea ([redacted]), pneumonitis ([redacted]) and febrile neutropenia ([redacted]) were the most commonly reported treatment-related SAEs. Vomiting ([redacted]), diarrhoea ([redacted]) and decreased appetite ([redacted]) were the most common treatment-related SAEs reported in the chemotherapy arm.

Adverse events leading to treatment discontinuation or death

The company explains (CS, p84) that AEs leading to treatment discontinuation were events that caused one or more of the drugs in a particular treatment regimen to be discontinued, even though the patient remained on treatment or in follow-up.

The most common TRAEs of any grade that caused patients to discontinue treatment in the nivolumab+chemotherapy arm and the chemotherapy were peripheral neuropathy ([redacted] and [redacted], respectively) and peripheral sensory neuropathy ([redacted] and [redacted], respectively).

[redacted] patients in the nivolumab+chemotherapy arm and [redacted] patients in the chemotherapy arm died due to treatment-related toxicity. In the nivolumab+chemotherapy arm, trial investigators reported these deaths as being due to nivolumab ([redacted]), nivolumab+chemotherapy [redacted]) and chemotherapy ([redacted]). [redacted] in the nivolumab+chemotherapy arm described as 'other' were considered by the investigators to have been related to nivolumab.

Select and immune-mediated adverse events and other events of special interest

The company definitions of 'select' AEs, immune-mediated AEs (IMAE) and other events of special interest (OESI) are provided in the CSR (p15). In summary:

- select AEs are the AEs identified by the company as potentially related to the use of nivolumab. The select AEs are endocrinopathies, diarrhoea or colitis, hepatitis, pneumonitis, interstitial nephritis and rash
- the IMAEs are diarrhoea or colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrinopathies
- the OESIs include (but are not limited to), myositis/rhabdomyolysis, myocarditis, demyelination, Guillain-Barre syndrome, pancreatitis, uveitis, encephalitis, myasthenic syndrome, and graft versus host disease.

The company highlighted (CS, p77) that in the CheckMate 649 trial:

- select AEs, IMAEs and OESIs were more frequently reported in the nivolumab+chemotherapy arm than in the chemotherapy arm
- most select AEs and IMAEs were Grade 1 or Grade 2 in severity, although some Grade 3 and Grade 4 IMAEs were reported (hepatitis, nephritis and renal dysfunction, and diarrhoea/ colitis)
- the rates of other events of special interest were low in both trial arms.

3.5.2 ERG conclusions: safety and tolerability

The company states (CS, p77 and p85) that, consistent with the known safety profiles of nivolumab and chemotherapy, treatment with nivolumab+chemotherapy has a manageable toxicity profile, with no new safety concerns identified. Clinical advice to the ERG is that no unexpected safety concerns associated with the use of nivolumab+chemotherapy arose during the CheckMate 649 trial.

3.6 ERG critique of the indirect evidence

3.6.1 Studies included in the NMAs

The company conducted a systematic literature review (see Section 3.1 of this report for further details). The company search process identified four relevant RCTs[14,18,19,29] of comparator treatments for untreated advanced or metastatic oesophago-gastric adenocarcinoma reporting relative outcome data (i.e., HRs and 95% CIs or K-M data) for OS and PFS that could be included in the company NMAs.

The company noted that:

> *"…as nivolumab has a different mechanism of action, survival profile and distribution of events to other arms in the network, a point estimate HR may not be fully capable to describe the time to event in this arm."* (CS, Section B.2.10.4.3, p69).

The company therefore decided not to include CheckMate 649 trial data in the NMAs (response to clarification question A7). Clinical advice to the ERG is that capecitabine+cisplatin and fluorouracil+cisplatin are rarely used in patients with untreated advanced or metastatic oesophago-gastric adenocarcinoma in the NHS.

In response to clarification question A6, the company confirmed that the Chen et al paper[29] reported a re-analysis of a subset (n=126) of Chinese patients recruited to the ML17032 study; the primary publication of the ML17032 study is by Kang et al.[19] The company stated that both sets of data were included in the NMAs presented in the CS due to uncertainty around the overlap of patients in the two publications.[19,29] NMA methods assume that all data points (i.e., patients) included are independent;[30] this means that any overlap of patients within an NMA is inappropriate. Therefore, the ERG presented company NMA results which excluded data from the Chen et al paper;[29] these company NMA results were from a sensitivity analysis that was made available to the ERG during the clarification process.

The NMAs, provided in response to clarification question A6 and in Appendix L to the CS, include only three RCTs.[14,18,19] A network diagram of the three RCTs is provided in Figure 2 and a summary of the study and participant baseline characteristics of the three RCTs is provided in Table 12.

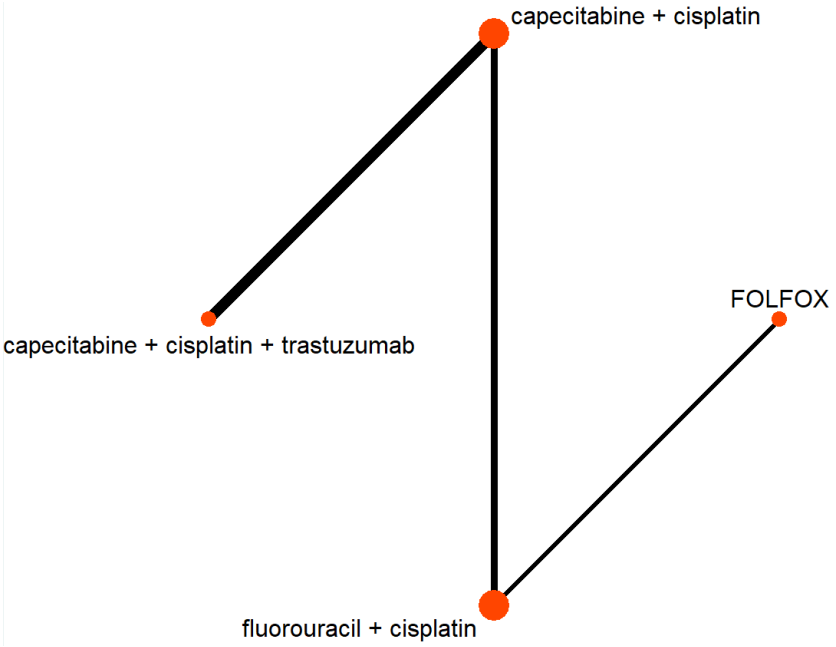


Figure 2 Network diagram for OS and PFS NMAs following clarification response

The size of the node (i.e., the circle) indicates the number of studies that include the treatment and the thickness of the lines corresponds to the numbers of participants contributing to the comparison

The company performed an assessment of heterogeneity of the included trials[14,18,19] (CS, Section B2.10.3). Median age and the distribution of sex (i.e., majority male) are generally consistent across the included trials, and consistent with median age and sex of patients in the CheckMate 649 trial. Most patients (77.8% to 100% by treatment arm) had gastric cancer (i.e., primary tumour site in the stomach), and 17.9% to 22.2% by treatment arm had their primary tumour site in the gastro-oesophageal junction. No patients in the trials of comparators were diagnosed with oesophageal adenocarcinoma and therefore the results of the NMAs are not directly applicable to patients with this type of cancer.

The proportions of patients of Asian, White and of other ethnicities varied across the included studies but were in line with the ethnicity of patients in the CheckMate 649 trial. This is an important potential source of heterogeneity due to expected differences in prognosis for Asian patients compared to White patients.[31]

In contrast to the CheckMate 649 trial which recruited only participants with ECOG PS of 0 or 1, a small proportion (8% to 10.2% by treatment arm) of patients included in the trial reported by Al-Batran et al[18] and the trial reported by Bang et al[14] had an ECOG PS of 2 at baseline and, as noted by the company, these participants are likely to experience significantly poorer outcomes than patients with higher ECOG PS.

Table 12 Study and participant baseline characteristics of trials included in NMAs

Trial		**Al-Batran et al[18]**		**Kang et al[19]**		**Bang et al[14]**	
Treatment		**FOLFOX**	**Fluorouracil+ cisplatin**	**Capecitabine+ cisplatin**	**Fluorouracil+ cisplatin**	**Capecitabine (or fluorouracil)+cisplatin + trastuzumab[b]**	**Capecitabine (or fluorouracil) +cisplatin[b]**
N		112	108	160	156	298 (capecitabine: 256)	296 (capecitabine: 255)
Doses		Fluorouracil 2,600mg/m^2 Q2W + oxaliplatin 85mg/m^2	Fluorouracil 2,000mg/m^2 Q1W + cisplatin 50mg/m^2 Q2W	Capecitabine 1,000mg/m^2 BID + cisplatin 80mg/m^2	Fluorouracil 800mg/m^2/day by continuous infusion days 1 to 5 Q3W + cisplatin 80mg/m^2	Capecitabine 1000mg/m^2 BID or fluorouracil 800mg/m^2 + cisplatin 80mg/m^2 + trastuzumab 8mg/kg	Capecitabine 1000mg/m^2 BID or fluorouracil 800mg/m^2 + cisplatin 80mg/m^2
Study Design		Randomised, phase III, multi-centre		Randomised, phase III, open-label, multi-centre, international		Randomised, phase III, open-label, multi-centre, international	
Median age (range)		64 (33 to 86)	64 (27 to 85)	56 (26 to 74)	56 (22 to 73)	59.4 (10.8)[a]	58.5 (11.2)[a]
Male sex (%)		57.1	75	64	69	77	75
ECOG score (%)	0	NA	NA	NR	NR	NA	NA
	1	NA	NA	NR	NR	NA	NA
	0-1	92.0	89.8	NR	NR	90	91
	2	8.0	10.2	NR	NR	10	9
Primary tumour site (%)	Gastric cancer	82.1	77.8	100	100	80	83
	Gastro-oesophageal junction	17.9	22.2	0	0	20	17
	Oesophagus	0	0	0	0	0	0
	White	NR	NR	19	19	39	36

Ethnicity (%)	Asian	NR	NR	66	67	51	54
	Hispanic	NR	NR	11	10	NR	NR
	Black	NR	NR	NR	NR	<1	1
	Other / Not reported	NR	NR	4	4	9	9

[a] Mean and standard deviation of age reported.
[b] Patients randomised to capecitabine or fluorouracil plus cisplatin, with or without trastuzumab; 511 patients received capecitabine and 73 received fluorouracil
BID=twice per day; ECOG=Eastern Cooperative Oncology Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; NR=not reported; Q2W=every 2 weeks; Q3W=every 3 weeks
Source: Extracted and adapted from the CS, Table 15; Al-Batran et al,[18] Kang et al[19] and Bang et al[14] trial publications

Furthermore, ECOG PS at baseline was not reported by Kang et al[19] and patient ethnicity was not reported by Al-Batran et al.[18] The ERG also notes that none of the three included studies[14,18,19] of comparators reported any information about tumour level of PD-L1 expression. Therefore, the extent of heterogeneity relating to these prognostic factors that may have been introduced into the NMAs is unknown.

Outcome data (PFS and OS) for the three trials[14,18,19] of comparators included in the NMAs are presented in Table 13.

Table 13 OS and PFS outcome data included in the NMAs

Trial	Al-Batran et al[18]		Kang et al[19]		Bang et al[14]	
Treatment	**FOLFOX**	**Fluorouracil +cisplatin**	**Capecitabine +cisplatin**	**Fluorouracil +cisplatin**	**Capecitabine +cisplatin+ trastuzumab**	**Capecitabine +cisplatin**
N	112	108	PP: 139	PP: 137	256	255
Median follow-up (months)	14 months for surviving patients		21.5[a]	21.4[a]	18.6[b]	17.1[b]
PFS						
Analysis approach	ITT population, unadjusted results		Per protocol population, stratified by region and adjusted for pre-specified prognostic factors		ITT population (who received randomised treatment), stratified results	
Assessment method	Not stated		Investigator assessed (primary analysis) and BICR[c]		Not stated	
Median PFS (95% CI), months	5.8 (4.5 to 6.6)	3.9 (3.1 to 4.8)	5.6 (4.9 to 7.3)	5.0 (4.2 to 6.3)	6.7[b] (6 to 8)	5.5[b] (5 to 6)
HR (95% CI)	Not stated[c]		Investigator assessed: 0.81 (0.63 to 1.04) BICR: 0.90 (0.69 to 1.18)		All patients: 0.71 (0.59 to 0.85)[b]	
OS						
Analysis approach	ITT population, unadjusted results		Per protocol population, stratified by region and adjusted for pre-specified prognostic factors		ITT population (who received randomised treatment), stratified results	
Median OS (95% CI), months	10.7 (8.5 to 13.9)	8.8 (7.7 to 12.0)	10.5 (9.3 to 11.2)	9.3 (7.4 to 10.6)	13.8[b] (12 to 16)	11.1[b] (10 to 13)
HR (95% CI)	Not stated[c]		0.85 (0.64 to 1.13)		All patients: 0.74 (0.60 to 0.91)[b] Capecitabine subgroup: 0.75 (0.60 to 0.95)	

[a] Median follow-up for all randomised patients rather than for per-protocol population (Kang et al[19])
[b] Median follow-up, median OS and median PFS and HRs reported for all randomised patients, including 73 who received fluorouracil rather than capecitabine. Subgroup analysis for 511 patients receiving capecitabine in their chemotherapy regimen reported for OS; unclear which OS results have been used in the NMA
[c] The ERG assumes that investigator assessed results (i.e. the primary analysis of PFS in Kang et al[19]) have been used in the NMA, although this is not stated in response to question A8 of the clarification letter
[c] HRs and 95% CIs calculated for inclusion in the NMAs from digitised Kaplan-Meier estimates
BICR=blinded independent central review; CI=confidence interval; FE=fixed effects; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; ITT=intention to treat; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PP=per protocol
Source: Extracted from the Al-Batran et al,[18] Kang et al[19] and Bang et al[14] trial publications; response to question A8 of the clarification letter

The ERG notes that the analysis populations (intention-to-treat [ITT] or per protocol) and approaches to analysis of OS and PFS (i.e., stratified or unstratified, and adjusted or unadjusted results) used in the three trials[14,18,19] differ. It was also not clear, except for in the Kang et al study, [19] whether reported PFS data were BICR- or investigator-assessed.

Furthermore, the trial reported by Bang et al[14] included two different chemotherapy regimens (capecitabine+cisplatin and fluorouracil+cisplatin). Only the comparison of capecitabine+cisplatin versus capecitabine+cisplatin+trastuzamab was included in the network (Figure 2), but PFS outcome data from the trial reported by Bang et al[14] have been generated using data from all randomised patients, including 73 who received fluorouracil rather than capecitabine. OS subgroup analysis results for 511 patients receiving capecitabine as part of their chemotherapy regimen were reported by Bang et al;[14] however, it is not clear whether subgroup results or results for all patients were used in the NMA.

The ERG considers that, as far as possible, results included in NMAs should be consistent in terms of population, analysis approach and outcome definition to minimise heterogeneity and to facilitate interpretation of NMA results. However, in the company's NMAs, where multiple OS or PFS results were reported, these results were generally quite similar. Therefore, the ERG is not concerned that the observed variability of OS and PFS data across trials had an important impact on NMA conclusions.

The ERG highlights that, by choosing to exclude CheckMate 649 trial clinical effectiveness data from the NMAs, the company was not able to present any results for the comparison of nivolumab+chemotherapy versus fluorouracil+cisplatin, versus capecitabine+cisplatin or versus trastuzumab+capecitabine+cisplatin in the CS.

3.6.2 Quality assessment of the trials included in the NMAs

Quality assessment of the trials of comparators was not provided in the CS. Therefore, the ERG conducted a quality assessment of the three trials[14,18,19] using a seven question checklist based on the recommendations of the University of York CRD,[21] according to the minimum criteria set out in the NICE Guide to the Methods of Technology Appraisal.[32] The results of the ERG's quality assessments are presented in Table 14.

Table 14 Quality assessment of the trials of comparators included in the NMAs

Quality assessment item	ERG assessment		
	Al-Batran et al[18]	Kang et al[19]	Bang et al[14]
Was randomisation carried out appropriately?	Unclear	Yes	Yes
Was the concealment of treatment allocation adequate?	Unclear	Unclear	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Unclear	Partially	No
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Source: ERG judgements based on information reported in the Al-Batran et al,[18] Kang et al[19] and Bang et al[14] trial publications

The trial reported by Bang et al[14] was generally of good quality with adequate methods of randomisation and allocation concealment, balanced patient characteristics and prognostic factors at baseline, appropriate use of an ITT analysis and reporting of all measured outcomes. However, the trial was of an open-label design and it was not stated whether PFS was assessed by BICR to minimise performance or detection biases.

The trials reported by Al-Batran et al[18] and Kang et al[19] reported all measured outcomes, and patient characteristics were mostly balanced at baseline. However, as noted in Section 3.6.1 of this ERG report, important prognostic factors were not reported in these studies (ECOG PS by Kang et al[19] and ethnicity by Al-Batran et al[18]), nor were methods of randomisation and/or allocation concealment clearly reported in these two studies. It was also unclear whether any blinding was used in the trial reported by Al-Batran et al,[18] but blinded, independent review of PFS was conducted in the trial reported by Kang et al.[19]

3.6.3 Methodological approach to the NMAs

A summary and the ERG critique of the company approach to the NMAs is provided in Table 15.

Table 15 ERG summary and critique of statistical approaches used for the NMAs

Item	ERG assessment	Approach	ERG comments
Was the network of comparators appropriate for OS and PFS?	Yes (following clarification)	The company search process identified four relevant RCTs[14,18,19,29] of comparator treatments for untreated advanced or metastatic oesophago-gastric adenocarcinoma reporting relative outcome data (i.e., HRs and 95% CIs or K-M data) for OS and PFS. The company included only studies forming a complete network including XELOX or FOLFOX. To construct the network, the company assumed that XELOX and FOLFOX had equal efficacy, in line with the results of the CheckMate 649 trial. Following clarification, the resulting networks of OS and PFS included three RCTs[14,18,19] and included the following comparators (Figure 2): • FOLFOX (assumed to be of equal efficacy to XELOX) • capecitabine+cisplatin • fluorouracil+cisplatin • trastuzumab+capecitabine+cisplatin. The trial reported by Bang et al[14] included two different chemotherapy regimens; capecitabine+cisplatin (511 patients) and fluorouracil+cisplatin (73 patients) but only data relating to the comparison of capecitabine+cisplatin versus capecitabine+cisplatin+trastuzumab were included in the network.	The ERG considers that the assumption of equal efficacy of XELOX and FOLFOX for the NMAs of OS and PFS is reasonable and is supported by results from CheckMate 649 subgroup analyses (CS, Section B.2.7). The ERG agrees with the company that dosing regimens for treatments included in more than one trial (CS, Table 16) were comparable and constructing a network is appropriate. The company clarified that: • Chen et al[29] reports on a subset of the patients within the trial reported by Kang et al[19] (response to clarification question A6). Including both trials counts patients twice in the NMAs, therefore, the ERG has presented NMA results which exclude the data reported by Chen et al[29] in this section • the CheckMate 649 trial data were not included in the NMAs (response to clarification question A7), as nivolumab has a different mechanism of action, survival profile and distribution of events to other treatments in the network. In the company model, HRs of XELOX/FOLFOX versus comparators estimated from the NMAs have been applied to model chemotherapy arm survival estimates to generate comparator survival estimates. The ERG highlights that, by choosing to exclude clinical

			effectiveness data from the CheckMate 649 trial, the company did not present any NMA results for the comparison of nivolumab+chemotherapy versus fluorouracil+cisplatin, versus capecitabine+cisplatin or versus trastuzumab+capecitabine+cisplatin in the CS.
Were NMA methods for OS and PFS appropriate?	Yes	The NMA methods are described in the CS (Section B.2.10.4). The company used methods in line with NICE DSU TSD 2[30] and TSD 3[33] and NMA analyses were conducted using a Bayesian approach using the BUGSnet R package.[34] The company performed NMAs using both FE and RE models, and presented results (i.e., HRs and 95% CrIs) for each approach. Model fit was assessed according to the DIC statistic and examination of residuals. The company considered that RE models may be more appropriate given differences between the included studies and populations but notes that assessment of heterogeneity is difficult in small networks and that FE models provided the best model fit (CS, Section 2.10.4.4, Figure 21, Figure 22).	The ERG considers that the NMA methods and approach for selecting the best fitting model were appropriate. The ERG notes that model fit in terms of DIC was very similar for FE and RE models for OS and PFS (CS, Figure 21 and Figure 22). The ERG agrees that assessments of heterogeneity are limited when networks are small but, nonetheless, given the differences between studies, which could be important sources of heterogeneity in the NMAs (see Section 3.6.1 of this ERG report), the ERG considers that the results of RE NMA models for OS and PFS are more reliable than results from FE NMA models.
Was inconsistency appropriately assessed in the NMAs?	Not assessed	Due to the small size of the network, with no closed loops, the company could not undertake any formal assessments of inconsistency in the NMAs.	The ERG notes that the consistency of indirect estimates of OS and PFS between the comparators is unknown.
Was PH assumption appropriately assessed within the NMAs of OS and PFS?	No	The company states that use of other methods such as fractional polynomials is not necessary as the PH assumption is not violated (CS, p67). In response to clarification question A9, the company provided an assessment of whether the PH assumption held for the Al-Batran et al[18] OS and PFS data (from digitised K-M data). Results from the assessment showed no evidence of PH violation for PFS but evidence of PH violation for OS. The company also stated that from visual inspection of the K-M plots reported by Bang et al[14] and	The ERG considers that sufficient evidence has not been provided to support the company statement that the PH assumption is not violated in the OS and PFS NMAs. Evidence provided demonstrates that the PH assumption may have been violated for one trial for OS[18], and the validity of the PH assumption for the two other trials[14,19] is unknown. The impact of the uncertainty around the validity of the PH assumption on the NMA results is also unknown.

		Kang et al,[19] there was little evidence of PH violation, but no formal assessments of PH violation were made by the company.	

CrI=credible interval; DIC=deviance information criterion; DSU=decision support unit; FE=fixed-effects; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PH=proportional hazards; RE=random-effects; TSD=technical support document; XELOX=capecitabine+oxaliplatin

Source: Extracted from the CS; Section B.2.10.3, Section B. 2.10.4 and Section B.2.10.5, the company's response to the clarification letter, and ERG comment

3.6.4 Results from the NMAs

Results from the company NMAs for OS and PFS are provided in Table 16.

Table 16 Results from the company NMAs (excluding data from the Chen et al paper) for OS and PFS

Treatment	Outcome	Model	Comparators: HR (95% CrI)[a]			
			FOLFOX[b]	Capecitabine+cisplatin	Fluorouracil+cisplatin	Capecitabine+ cisplatin+trastuzumab
FOLFOX[b]	OS	FE	Reference	0.99 (0.63 to 1.55)	1.16 (0.82 to 1.65)	0.73 (0.44 to 1.20)
		RE		0.98 (0.50 to 1.92)	1.16 (0.71 to 1.91)	0.73 (0.33 to 1.60)
	PFS	FE		1.00 (0.66 to 1.52)	1.23 (0.88 to 1.72)	0.71 (0.45 to 1.12)
		RE		1.00 (0.49 to 2.04)	1.23 (0.73 to 2.08)	0.71 (0.31 to 1.66)
Capecitabine+ cisplatin	OS	FE	1.01 (0.64 to 1.59)	Reference	1.18 (0.88 to 1.56)	**0.74 (0.60 to 0.91)**
		RE	1.02 (0.52 to 1.98)		1.18 (0.74 to 1.86)	0.74 (0.49 to 1.12)
	PFS	FE	1.00 (0.66 to 1.52)		1.23 (0.96 to 1.59)	**0.71 (0.59 to 0.86)**
		RE	1.00 (0.49 to 2.04)		1.23 (0.76 to 2.00)	0.71 (0.45 to 1.13)
Fluorouracil+ cisplatin	OS	FE	0.86 (0.61 to 1.23)	0.85 (0.64 to 1.13)	Reference	**0.63 (0.44 to 0.90)**
		RE	0.87 (0.52 to 1.42)	0.85 (0.54 to 1.34)		0.63 (0.34 to 1.17)
	PFS	FE	0.81 (0.58 to 1.13)	0.81 (0.63 to 1.04)		**0.58 (0.42 to 0.79)**
		RE	0.81 (0.48 to 1.37)	0.81 (0.50 to 1.32)		0.58 (0.30 to 1.12)
Capecitabine+ cisplatin+ trastuzumab	OS	FE	1.37 (0.83 to 2.25)	**1.35 (1.10 to 1.67)**	**1.59 (1.12 to 2.26)**	Reference
		RE	1.38 (0.62 to 3.01)	1.35 (0.89 to 2.05)	1.59 (0.86 to 2.94)	
	PFS	FE	1.41 (0.89 to 2.22)	**1.41 (1.16 to 1.70)**	**1.74 (1.27 to 2.38)**	
		RE	1.41 (0.60 to 3.27)	1.41 (0.89 to 2.22)	1.74 (0.89 to 3.37)	

[a] HR>1 indicates an advantage for the treatment over the comparator; results in bold are statistically significant
[b] FOLFOX is assumed to be of equal efficacy to XELOX
CrI=credible interval; FE=fixed-effects; FOLFOX=fluorouracil+folinic acid+oxaliplatin; FE=fixed effects; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; RE=random-effects; XELOX=capecitabine+oxaliplatin
Source: Extracted and adapted from response to clarification question A6 and Appendix L to the CS

The ERG agrees with the company that OS and PFS results for fixed-effects and random-effects NMAs were mostly similar, and that results of the sensitivity analyses excluding data reported by Chen et al[29] from the NMAs (presented in Table 16) are consistent with the results presented in the CS which include data reported by Chen et al[29] (CS, Table 17 and Table 18).

No statistically significant differences were shown between chemotherapy (FOLFOX) and any of the other comparators for OS or PFS. Statistically significant advantages in terms of both OS and PFS were shown for capecitabine+cisplatin+trastuzumab over capecitabine+cisplatin and fluorouracil+cisplatin in fixed-effects NMAs. However, it should be noted that capecitabine+cisplatin+trastuzumab is only a relevant comparator for patients with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma and the ERG highlights that two of the three studies[18,19] included in the NMAs represent a population of people with gastric or gastro-oesophageal junction adenocarcinoma of unknown HER2 status.

3.6.5 Company indirect comparisons: ERG conclusions

The company did not present any NMA results for the comparison of nivolumab+chemotherapy versus any of the comparators listed in the final scope[16] issued by NICE.

The results of the company NMAs showed no statistically significant differences between chemotherapy (FOLFOX) and any of the other comparators for OS or PFS.

The ERG considers that the observed variability in populations, analysis approaches and outcome definitions across the trials included in the NMAs did not have an important impact on NMA results. However, the ERG is uncertain about the size and direction of the impact of prognostic factors such as HER2 status and tumour level of PD-L1 expression as these factors are not accounted for in the NMAs. There is also additional uncertainty around the validity of the PH assumption (discussed in Table 15) used in the OS and PFS NMAs. The impact of these uncertainties on the NMA results and conclusions that can be drawn from them is unknown.

The ERG considers that comparisons between chemotherapy (FOLFOX) and capecitabine+cisplatin and fluorouracil+cisplatin are of limited relevance to decision-makers as these regimens are rarely used in patients with untreated advanced or metastatic oesophago-gastric adenocarcinoma in the NHS.

3.7 Clinical summary and key issues identified by the ERG

Population

The population considered by the company is in line with the final scope[16] issued by NICE, except that no direct or indirect clinical effectiveness evidence has been provided for patients treated with nivolumab+chemotherapy with known HER2-positive disease.

Comprehensive clinical effectiveness results have been provided for the whole population and the following subgroups: PD-L1 CPS≥1 and PD-L1 CPS≥5. However, only limited clinical effectiveness data for the PD-L1 CPS<1 and CPS<5 subgroups were provided by the company.

Direct clinical effectiveness evidence

The company's main source of direct clinical effectiveness evidence is the CheckMate 649 trial (treatment with nivolumab+chemotherapy [XELOX or FOLFOX] versus chemotherapy [XELOX or FOLFOX] for patients with previously untreated advanced or metastatic oesophago-gastric adenocarcinoma). The ERG considers that the CheckMate 649 trial is a good quality trial and that the eligibility criteria appear generalisable to patients with untreated, locally advanced or metastatic oesophago-gastric adenocarcinoma treated in the NHS. However, at baseline, patients in the trial were younger and fitter than patients with oesophago-gastric adenocarcinoma who are likely to be treated in the NHS.

Clinical advice to the ERG is that the most relevant comparator to nivolumab+chemotherapy for patients with oesophago-gastric adenocarcinoma is capecitabine+oxaliplatin (XELOX). In the NHS, approximately 80% of patients are treated with XELOX and less than 10% are treated with FOLFOX.

CheckMate 649 trial results presented in the CS are based on 10th July 2020 database lock (overall minimum follow-up of 12.1 months). In the whole population (the focus of this appraisal), treatment with nivolumab+chemotherapy was shown to be statistically significantly superior to chemotherapy in terms of median OS and was also shown to lead to a clinically meaningful improvement in BICR assessed PFS (statistical significance was not tested).

Clinical advice to the ERG is that the AEs associated with nivolumab+chemotherapy are likely to be manageable in NHS clinical practice and are similar to the AEs associated with the relevant comparator treatments.

Indirect clinical effectiveness evidence

The company's NMAs generated results for OS and PFS for the comparisons of chemotherapy (FOLFOX) versus fluorouracil+cisplatin, versus capecitabine+cisplatin, and versus trastuzumab+capecitabine+cisplatin. Data from the CheckMate 649 trial were not included in the company's NMAs.

The ERG considers that:

- the comparators in the NMAs are of limited relevance as they are not commonly used in the NHS
- the company's NMA methods were appropriate; however, the ERG has concerns about the validity of some of the company's survival PH assumptions
- the NMAs are unable to account for some prognostic factors, particularly HER2 status and PD-L1 expression level.

Clinical advice to the company and the ERG is that epirubicin is rarely used in the NHS to treat this patient population. Due to the limited evidence base, the company was only able to provide a narrative summary of clinical effectiveness evidence for epirubicin-containing triplet chemotherapy combinations.

No clinical effectiveness evidence

There is no direct or indirect evidence presented in the CS to demonstrate the clinical effectiveness of:

- nivolumab+chemotherapy versus any comparator listed in the final scope issued by NICE other than FOLFOX or XELOX
- chemotherapy versus trastuzumab+fluorouracil+cisplatin.

4 COST EFFECTIVENESS EVIDENCE

The CS provides cost effectiveness evidence to support the use of nivolumab+chemotherapy as a treatment option for patients with untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. The two key components of the economic evidence presented in the CS are (i) a systematic review to identify relevant economic evidence and (ii) a report of the company's de novo economic evaluation. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 ERG critique of the company systematic review methods

The company searched for cost effectiveness studies that could be used to inform modelling decisions. The date span of the searches was from inception of relevant databases to the date on which the searches were conducted: first search was carried out in March 2018 and two subsequent searches were conducted in August 2019 and September 2020.

The search did not identify any previous cost effectiveness studies of nivolumab+chemotherapy in patients with untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma; however, 11 publications[35-45] evaluating the cost effectiveness of different treatments in that population were identified. The company also searched the literature to identify utility/HRQoL studies and studies containing cost and resource use data (CS, Appendix G1 and G2). The company has provided a summary of studies reporting utility values (Appendix G1, Table 14) and a summary of the studies reporting resource use or cost data (Appendix G1, Table 10). An assessment of the extent to which the company's literature review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 17.

Table 17 ERG appraisal of company review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Partly; HTA website not searched
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Yes

ERG=Evidence Review Group; HTA=health technology assessment; NA=not applicable
Source: LR*i*G in-house checklist

4.2 ERG conclusions regarding company systematic review methods

Searches carried out by the ERG did not identify any additional relevant studies. The ERG is concerned that the company search strategy did not include searching individual HTA websites, but included the search in the Cochrane HTA database. Otherwise, the ERG considers that the methods used by the company to identify evidence to inform modelling decisions were appropriate and is satisfied that there are no relevant economic studies of nivolumab+chemotherapy available.

4.3 ERG summary and critique of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 18 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on the company's economic evaluation
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Partly. Focus is on NHS costs
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Not applicable to the base case cost effectiveness results
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Partly. See Table 34
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Partly. See Table 34

ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[46] and ERG comment

Table 19 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	CheckMate 649 trial complete follow-up data were only available for 12.1 months.
Were all the important and relevant costs and consequences for each alternative identified?	Partly	The inclusion of a long-term health state in the company model is problematic because: - there is no robust clinical evidence to support the existence of long-term remission - the proportion of patients that would achieve long-term remission is unclear and - the onset and duration of long-term remission is speculative
Were costs and consequences measured accurately in appropriate physical units?		
Were the cost and consequences valued credibly?		
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; NMA=network meta-analysis; XELOX=capecitabine+oxaliplatin
Source: Drummond and Jefferson 1996[47] and ERG comment

4.3.2 Population

The modelled population comprises adult patients with previously untreated advanced or metastatic, HER2-negative, gastric or gastroesophageal junction or oesophageal adenocarcinoma. Baseline characteristics of the population (mean age=[redacted] years; proportion of males=[redacted]) were obtained from the CheckMate 649 trial data.

4.3.3 Model structure

The company has developed a de novo cost utility model in Microsoft Excel. The model is a cohort-based semi-Markov model comprising four mutually exclusive health states: pre-progression, progressed disease, long-term remission and dead (see Figure 3). The company states (CS, Section B.3.2.2) that the model structure reflects the nature of gastric cancer and available evidence.

The company's four health state semi-Markov model differs from the three health state (i.e., progression-free, progressed and death) partitioned survival model structure that has frequently been used in NICE oncology technology appraisals.[20,48] The company considered that their design is better than a three-state partitioned survival model at capturing the long-term remission that may occur in a small proportion of patients with locally advanced or metastatic gastric cancer (CS, Section B.3.2.2.1). The company considered that capturing this benefit was important as the CheckMate 649 trial 3-year OS rates suggest that treatment with nivolumab+chemotherapy increases the proportion of patients who achieve long-term remission ([redacted]) when compared with chemotherapy ([redacted]), and hence the introduction of the (additional) 'long-term remission' health state.

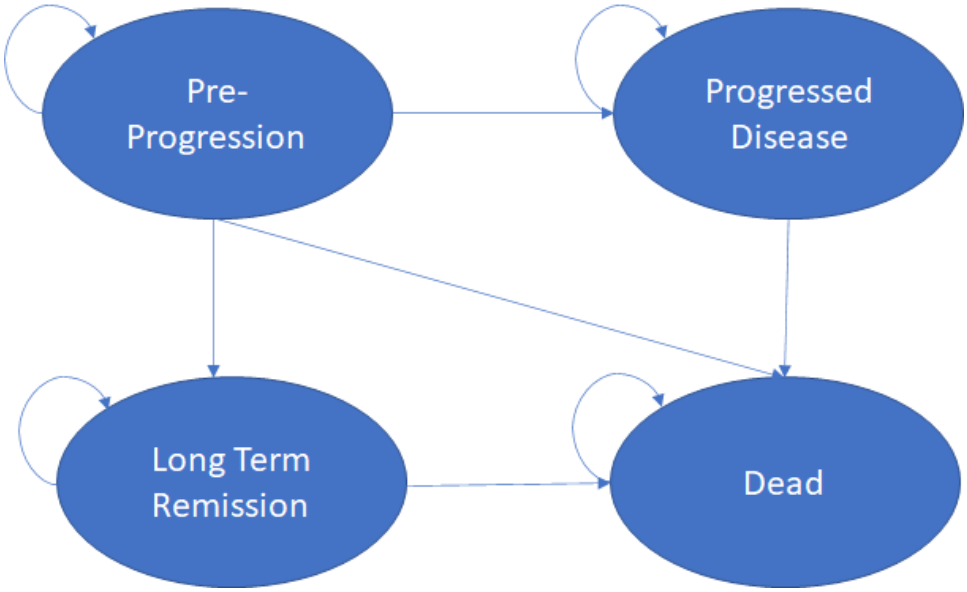


Figure 3 Structure of the company model

Source: CS, Figure 29

Patients enter the model in the pre-progression health state where they remain, transit to the progressed disease health state or die at the end of each model cycle until month 30. Thereafter, patients who remain in the pre-progression health state all move to the long-term remission health state, where their mortality risk is equivalent to that of the general population. The only permitted transition out of the progressed disease health state is death. Dead is an absorbing health state from which no transition is permitted.

4.3.4 Interventions and comparators

The modelled intervention is nivolumab+chemotherapy. The chemotherapy component of the intervention is FOLFOX or XELOX. Not all of the comparators specified in the final scope issued by NICE[16] were considered in the company economic evaluation. The company's justification for choice of comparators (CS, Section B.3.2.3) is summarised in Table 20.

Table 20 Modelled treatments by model population

Population	Intervention/Comparator		Company justification
	Final scope[16]	CS	
Unspecified HER2 status	**Intervention** • Nivolumab+ chemotherapy **Comparators** • Doublet treatment: fluorouracil or capecitabine+ cisplatin or oxaliplatin • Triplet treatment: fluorouracil or capecitabine+ cisplatin or oxaliplatin+ epirubicin	**Intervention** • Nivolumab+FOLFOX **Comparator** • FOLFOX **Intervention** • Nivolumab+XELOX **Comparator** • XELOX	**Clinical advice to the company** • FOLFOX and XELOX are current first-line treatment options in the NHS • A patient who would have received XELOX would receive nivolumab+XELOX and not nivolumab+FOLFOX • Equivalent assumption applies to FOLFOX and nivolumab+FOLFOX **Clinical evidence** • There is direct evidence for the comparison of nivolumab+FOLFOX or nivolumab+XELOX versus FOLFOX or XELOX (CheckMate 069 trial) • There is no published comparative effectiveness evidence for epirubicin-based triplet therapies that could be used to form an ITC
HER2-positive population	**Intervention** • Nivolumab+ chemotherapy **Comparator** • Trastuzumab+ cisplatin+ capecitabine or fluorouracil	Not considered	**Clinical evidence** • There is no effectiveness evidence to support the use of nivolumab+chemotherapy in the HER2-positive population

CS=company submission; FOLFOX=fluorouracil+folinic acid+oxaliplatin; HER2=human epidermal growth factor receptor 2; ITC=indirect treatment comparison; XELOX=capecitabine+oxaliplatin
Source: CS, Section B.3.2.3

4.3.5 Perspective, time horizon and discounting

The company stated that, in line with the NICE Reference Case,[46] the perspective of the model was the NHS and PSS. The company model cycle length is 2 weeks, the structure of the model allows a time horizon of up to 50 years to be considered, and costs and outcomes are discounted at 3.5% per annum.

4.3.6 Treatment effectiveness and extrapolation

The modelled measures of treatment effectiveness (i.e., health state transition probabilities) are: BICR PFS (referred to as PFS from hereon); likelihood of death on progression; and post-progression survival (PPS). Additionally, time-on-treatment (ToT) is used to estimate the proportion of patients receiving first-line treatment during each model cycle.

Clinicians consider that FOLFOX and XELOX represent standard of care in the NHS. The CheckMate 649 trial comparator arm was only powered to show a difference between nivolumab+chemotherapy versus chemotherapy, not versus FOLFOX and versus XELOX separately. The company considered that as efficacy was not expected to vary by fluoropyrimidine therapy, it was appropriate to model the efficacy of chemotherapy, using all the data from the comparator arm, rather than to estimate the efficacy of FOLFOX and XELOX separately.

Effectiveness estimates for the modelled treatment arms were obtained from the CheckMate 649 trial arm (10 July 2020 database lock). Average length of follow-up of patients in the nivolumab+chemotherapy and chemotherapy arms of the CheckMate 649 trial was [redacted] months and [redacted] months respectively. As this period is shorter than the model time frame, parametric models were used to inform the state transitions, including within the unobserved period, up to a lifetime horizon. For these models, it was necessary to generate parameter estimates. Parametric functions (exponential, Weibull, log-logistic, lognormal, Gompertz and generalised gamma) were fitted to the PPS and PFS data from the CheckMate 649 trial. The company also explored the use of semi-parametric models (parametric distributions appended to trial K-M data at 6.44 months). Choices of the most appropriate method to model PPS and PFS were based on the goodness-of-fit of the distributions (assessed using Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), plausibility of mean survival estimates and input from clinical experts. The distributions used in the company base case analyses are shown in Table 21. Full details of the company's approach to choosing the most appropriate approach to model OS, PPS and PFS are presented in Appendix M to the CS.

Table 21 Company base case approaches used to model survival

Outcome	Extrapolation method	
	Nivolumab+chemotherapy	Chemotherapy
PFS	Semi-parametric: log-logistic function appended to K-M data at 6.44 months	
PPS	Fully parametric: log-logistic function used for whole model time-horizon	

K-M=Kaplan-Meier; PFS=progression-free survival; PPS=post-progression survival
Source: CS, Table 29

Modelling pre-progression health state and long-term remission health state occupancy

The proportions of patients who remain in the pre-progression health state at each time point (cycle) up to month 30 were estimated directly from the distribution used to model PFS. All patients in the pre-progression health state at month 30 transitioned to the long-term remission health state.

PFS is a composite outcome capturing mortality and disease progression risks (the two permitted reasons for transitioning out of the pre-progression health state). The company considered that the likelihood of death at progression was time-dependent, followed a similar pattern in both arms, and could be modelled using a logistic model including covariates for time and the natural logarithm of time. A visual representation and the coefficients of the fitted models used in the company base case analyses are shown in Figure 4 and Table 22 respectively.

The estimation of progression risk was calculated by subtracting mortality risk from the composite PFS risk.

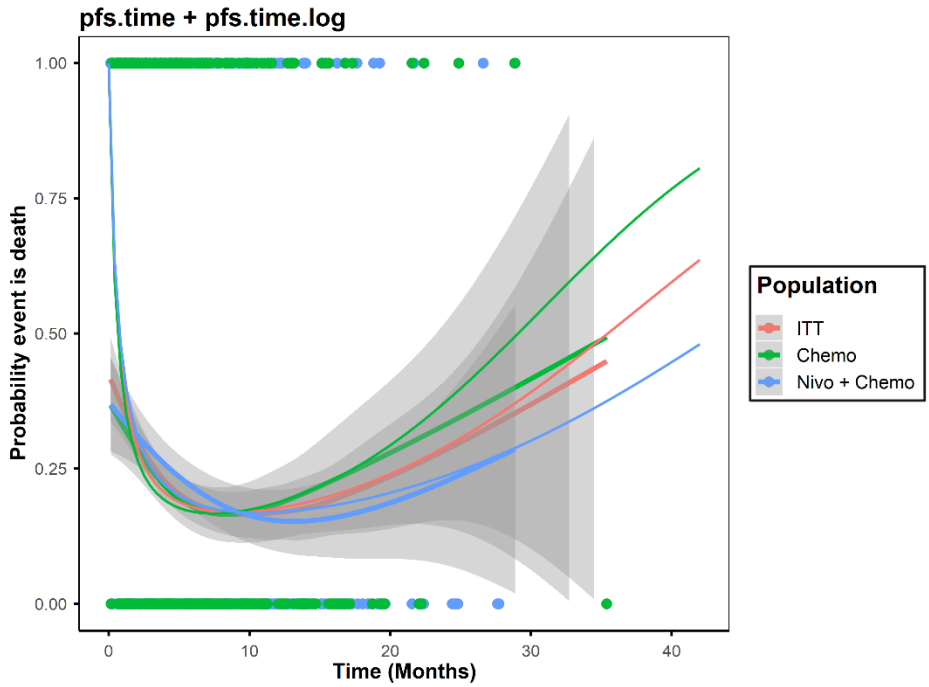


Figure 4 Probability of death on incidence of PFS based on data from the CheckMate 649 trial

Heavier lines denote smoothed observed values; thin lines depict fitted models; grey areas present confidence intervals
Source: CS, Figure 37

Table 22 Coefficients of the model fitted to the likelihood of death at progression data from the CheckMate 649 trial data

Independent variable	Nivolumab+chemotherapy	Chemotherapy
Intercept	-0.30927	-0.56083
Coefficient 1 (time)	0.08991	0.13964
Coefficient 2 (natural log of time)	-0.94883	-1.03879

Source: CS, Table 30

Modelling progressed disease

The proportions of patients in the progressed disease health state during each cycle were obtained directly from the parametric distributions fitted to post-progression survival (PPS) data from the CheckMate 649 trial.

Modelling of time-on-treatment

CheckMate 649 trial time on treatment (ToT) data were mature and were used directly in the company model. Treatment with nivolumab+chemotherapy (i.e., all drugs in the combination treatment) beyond 24 months was not permitted in the model in line with the stopping rule (for nivolumab) that was in place during CheckMate 649 trial.

Modelling general mortality

Age- and gender-specific mortality rates were taken from published UK life tables,[49] using projections for 2017-19. The company applied general mortality rates to all health states (apart from the dead health state) in addition to the disease mortality risks (i.e., likelihood of death at progression rates and PPS rates). Disease mortality rates were not applied in the long-term remission health state, so only the general mortality rates are applied in this health state.

4.3.7 Adverse events

Grade 3+ AEs occurring in ≥15% of patients (CS, Table 21) in the nivolumab+chemotherapy and/or chemotherapy arms of the CheckMate 649 trial were included in the company model. The company assumed that, for all treatments, AEs were applied as a one-off cost in the first model cycle only.

4.3.8 Health-related quality of life

Patients in the CheckMate 649 trial were scheduled to complete the EQ-5D-3L questionnaire every 6 weeks during the treatment phase and every 12 weeks during the follow-up phase. Patient responses were converted to EQ-5D-3L scores using UK EQ-5D-3L tariff.[50] The mean EQ-5D-3L scores were stratified by treatment status and time-to-death:

- on-treatment score ([redacted]) applied during the pre-progression health state
- off-treatment score ([redacted]) applied during the progressed disease health state
- time-to-death disutility ([redacted]) applied to all patients who survived for at least 6 months during the 6 months before death. For patients who died within the first 6 months, disutility was determined by integrating a polynomial formula over the elapsed model time. This integral would equal that given by the quoted average disutility when model time was equal to 6 months.

Age-related disutilities reported by Janssen[51] were also applied for patients in the long-term remission health state. AE disutilities were applied to patients, in the first modelled cycle only, based on the incidence of events reported in the CheckMate 649 trial as shown in Table 23.

Table 23 Adverse event disutility used in the company base case analysis

Adverse event	Utility		Incidence	
	Value	Source	Nivolumab+ chemotherapy	Chemotherapy
Anaemia	-0.115	Swinburn (2010)[52]	0.060	0.027
Diarrhoea	-0.047	Doyle (2008)[53]	0.045	0.031
Fatigue	-0.119	Lloyd (2006)[54]	0.038	0.022
Nausea	-0.103	Equal to vomiting	0.026	0.025
Neutropenia	-0.090	Nafees (2008)[55]	0.151	0.121
Vomiting	-0.103	Swinburn (2010)[52]	0.022	0.031
Thrombocytopenia	-0.110	Tolley (2013)[56]	0.024	0.017

Source: CS, Table 21 and Table 38

4.3.9 Resource use and costs

The cost categories included in the company model were:

- first-line treatment acquisition and administration costs
- subsequent treatment acquisition and administration costs
- health state resource use costs
- AE treatment costs.

First-line treatment acquisition and administration costs

Nivolumab is available to the NHS at a confidential PAS discounted price; this price has been included in the company model. The unit cost of nivolumab was obtained from the British National Formulary (BNF),[57] whilst other unit costs were obtained from the Drugs and Pharmaceutical electronic Market Information Tool (eMIT[58]) database.

Treatment administration costs were not applied to oral medications, but drugs that were administered intravenously were associated with administration costs (per cycle) of £385.28 for the initial dose and £362.35 for subsequent doses. Details of the intervention and comparator drug acquisition costs are presented in Table 24.

Table 24 Drug acquisition costs used in the company model

Regimen (cycle duration)	Drug acquisition					Administration	
	Drug (route)	Dosage	Qty/dose (dose/ cycle)	Cost per dose	Cost per cycle	Cost per dose	Cost per cycle
NIV+ XELOX (3 weeks)	Nivolumab (IV infusion)	360mg on Day 1 of cycle	360mg (1 dose)	£3,950.00	£3,950.00	£385.28	£385.28
	Oxaliplatin (IV infusion)	130mg/m^2 on Day 1 of cycle	222.8mg (1 dose)	£23.19	£23.19	£385.28	£385.28
	Capecitabine (oral)	1,000mg/m^2 Twice daily	1,760mg (28 doses)	£0.783	£21.79	£0.00	£0.00
NIVO+ FOLFOX (2 weeks)	Nivolumab (IV infusion)	240mg on Day 1 of cycle	240mg (1 dose)	£2,633.00	£2,633.00	£385.28	£385.28
	Oxaliplatin (IV infusion)	85mg/m^2 on Day 1 of cycle	149.6mg (1 dose)	£15.16	£15.16	£385.28	£385.28
	Fluorouracil: first dose (IV infusion)	400mg/m^2 on Day 1 of cycle	704mg (1 dose)	£116.71	£116.71	£385.28	£385.28
	Fluorouracil: subsequent dose (IV infusion)	1,200mg/m^2 on two days	2,112mg (2 doses)	£350.20	£700.24	£362.35	£362.35
	Folinic acid (IV infusion)	400mg/m^2 on Day 1 of cycle	704mg (1 dose)	£46.08	£46.08	£0.00*	£0.00*
XELOX (3 weeks)	Oxaliplatin (IV infusion)	130mg/m^2 on Day 1 of cycle	222.8mg (1 dose)	£23.19	£44.98	£385.28	£385.28
	Capecitabine (oral)	1,000mg/m^2 Twice daily	1,760mg (28 doses)	£0.78		£0.00	
FOLFOX (2 weeks)	Oxaliplatin (IV infusion)	85mg/m^2 on Day 1 of cycle	149.6mg (1 dose)	£15.16	£878.19	£385.28	£1,840.63 **
	Fluorouracil: first dose (IV infusion)	400mg/m^2 on Day 1 of cycle	704mg (1 dose)	£116.71		£385.28	
	Fluorouracil: subsequent dose (IV infusion)	1,200mg/m^2 on two days	2,112mg (2 doses)	£350.20		£362.35	
	Folinic acid (IV infusion)	400mg/m^2 on Day 1 of cycle	704mg (1 dose)	£46.08		£0.00*	

Dosing based on 1.76 m^2 body surface area as per CheckMate 649 trial
*=administration with other infusion treatment assumed; **=Includes one-off cost of infusion pump installation of £707.72 obtained from a previous NICE technology appraisal (TA208[13])
FOLFOX=fluorouracil+folinic acid+oxaliplatin; IV=intravenous infusion; m=metre; mg=milligram; qty=quantity;; XELOX=capecitabine+oxaliplatin
Source: CS, Table 41, Table 42, Table 43 and Table 46 and company model

Subsequent treatment drug acquisition and treatment costs

All patients in the model receive single agent taxane after their first-line treatment. This cost is applied to patients in the progressed disease health state but not to those in the long-term remission health state. The type of subsequent treatment is equally split between docetaxel and paclitaxel. The dosing regimen of these therapies is based on a regimen used in a previous NICE technology appraisal (TA378)[59] and unit costs were obtained from the eMIT database.[58] Company model subsequent treatment (acquisition and administration) costs per cycle are provided in Table 25.

Table 25 Per cycle subsequent treatment and administration costs

Treatment	Drug acquisition			Administration cost	Total cost
	Dosage	Unit size	Cost per dose		
Docetaxel	75mg/m^2 Once per 3 weeks	160mg/ 8mL	£20.96	£362.35	£241.57
Paclitaxel	80mg/m^2 Three times per 4 weeks	150mg/ 25mL	£18.88	£362.35	£543.53

mg=milligram; mL=millilitre
Source: CS, Table 50

Resource use by health state

In the company model, resource use depended on health state and, in the pre-progression health state, varied depending on first-line treatment status (i.e., on- or off-treatment). A summary of level of resource use and the resource costs used in the company model is provided in Table 26.

The resource use estimates applied in the pre-progression health state were those used in the NICE TA208[13] company submission. Estimates for the progressed disease health state were those reported in the NICE clinical guideline for advanced breast cancer (NICE CG81),[60] which were also the values used in the NICE TA208[13] company submission. Full details of the health state cost calculations are provided in the CS (Section B.3.5.3).

Table 26 Model resource use and costs

Item	Unit cost	Source	Freq.	Source
Pre- progression (on-first line treatment)				
Oncology consultation	£128.00	Ref cost (2015/16): 370 consultant led[61]	1.0 per 3 weeks	Expert opinion used in TA208[13]
Total				[redacted]
Pre- progression (off-first line treatment)				
Oncology consultation	£128.00	Ref cost (2015/16): 370 consultant led[61]	1.0 per 6 weeks	Expert opinion used in TA208[13]
Cardiac monitoring	£227.16	33% MUGA scan, costs inflated from TA208 (2010)[13]	1.0 per 3 months	Expert opinion used in TA208[13]
Total				[redacted]
Progressed disease				
Nurse home visit	£12.60	PSSRU[62]	1.0 per week	NICE CG81[60]
Nurse specialist	£50.00	PSSRU[62]	1.0 per week	NICE CG81[60]
GP	£39.00	PSSRU[62]	1.0 per 2 weeks	NICE CG81[60]
Therapist	£48.00	PSSRU[62]	1.0 per 2 weeks	NICE CG81[60]
Total				[redacted]*

*=includes the costs of subsequent therapies; CG=clinical guideline; Freq=frequency; GP=general practitioner; MUGA=multigated acquisition; PSSRU=Personal Social Services Research Unit; Ref cost=National Health Service Reference Costs; TA=technology appraisal
Source: Extracted from CS, Table 47, Table 48, and Table 49

Adverse event costs

According to the company, unit costs were obtained from the 2015/2016 NHS Schedule of Reference Costs,[59] NICE TA378[61] and published studies on the cost implications of AEs associated with melanoma treatments[63,64] (see CS, Table 52). These unit costs were applied to the AE rates that were used in the model (see CS, Table 21). The company estimated that the one-off costs (applied to the first cycle) of treating AEs associated with nivolumab+chemotherapy and chemotherapy were [redacted] and [redacted], respectively. The model did not include costs associated with treating the AEs associated with subsequent treatments.

Other costs

The company applied a one-off end of life/terminal care cost of £5,387 to patients who died at the end of each cycle to account for the cost of palliative/terminal care. This is the approach taken in the NICE TA208[13] company submission.

5 COST EFFECTIVENESS RESULTS

The company has provided cost effectiveness results separately for the two types of chemotherapy (FOLFOX and XELOX). As stated in Section 4.3.9, a confidential PAS discount is available for nivolumab and was used to generate the results presented in the CS.

5.1 Base case incremental cost effectiveness analysis results

The company pairwise base case ICERs per QALY gained are shown in Table 27 and Table 28. The PAS discount was applied to the list price of nivolumab, and list prices were used for other treatments.

Table 27 Base case pairwise cost effectiveness results for nivolumab+FOLFOX versus FOLFOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total cost	Total LYs	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYs	QALYs	
Nivolumab +FOLFOX	[redacted]	[redacted]	[redacted]				
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,840**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 55

Table 28 Base case pairwise cost effectiveness results for nivolumab+XELOX versus XELOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total cost	Total LYs	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYs	QALYs	
Nivolumab +XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,172**

LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin
Source: CS, Table 56

5.2 Probabilistic sensitivity analysis

The company carried out probabilistic sensitivity analyses (PSA). Results (means from 1,000 iterations), using a PAS discount for nivolumab, are reproduced in Table 29 and Table 30. The company's probabilistic and deterministic results are similar.

The company estimated that the probability of nivolumab+FOLFOX being a cost effective treatment option versus FOLFOX at a willingness-to-pay threshold of £50,000 per QALY gained was [redacted].

Using the discounted price of nivolumab in the original CS, the company estimated that the probability of nivolumab+XELOX being a cost effective treatment option versus XELOX at a willingness-to-pay threshold of £50,000 per QALY gained was [redacted].

Table 29 Probabilistic pairwise cost effectiveness results of nivolumab+FOLFOX versus FOLFOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total cost	Total LYs	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYs	QALYs	
Nivolumab +FOLFOX	[redacted]	[redacted]	[redacted]				
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,041**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 57

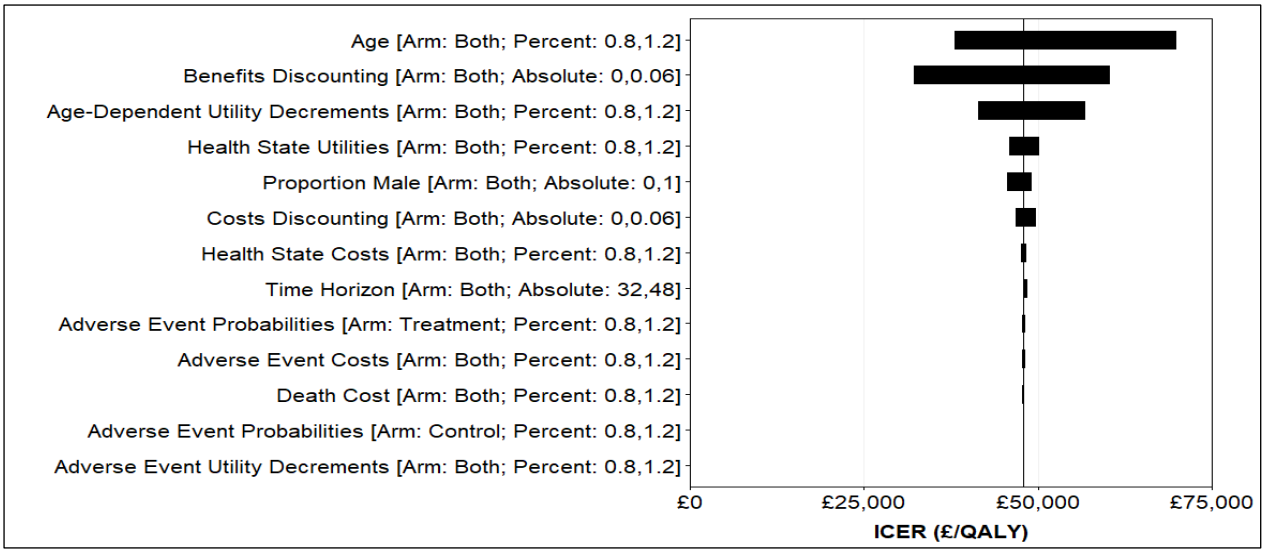
Table 30 Probabilistic pairwise cost effectiveness results of nivolumab+XELOX versus XELOX (PAS price for nivolumab, list prices for other drugs)

Treatment	Total cost	Total LYs	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Nivolumab +XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,305**

LYs=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin
Source: CS, Table 58

5.3 Deterministic sensitivity analyses

Using the PAS discounted price of nivolumab, results from the company's deterministic one-way sensitivity analyses (OWSAs) for the comparison of treatment with nivolumab+FOLFOX versus FOLFOX. The three analyses that had the biggest effect on cost effectiveness results were the baseline age of patients, using a higher discount rate for costs and outcomes, and using a higher age-dependent utility decrement (Figure 5).



FOLFOX=fluorouracil+folinic acid+oxaliplatin; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme
Source: CS, Figure 49

Figure 5 Deterministic sensitivity analysis for nivolumab+FOLFOX versus FOLFOX (PAS price for nivolumab, list prices for other drugs)

Using the PAS discounted price of nivolumab, results from the company's deterministic OWSAs for the comparison of treatment with nivolumab+XELOX versus XELOX. The three analyses that had the biggest effect on cost effectiveness results were increasing the baseline age of patients, using a higher discount rate for costs and outcomes and using a higher age-dependent utility decrement (Figure 6).

QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio; XELOX=capecitabine+oxaliplatin
Source: CS, Figure 50

Figure 6 Deterministic sensitivity analysis for nivolumab+XELOX versus XELOX (PAS price for nivolumab, list prices for other drugs)

5.4 Scenario analyses

Using the PAS discounted price of nivolumab, the company explored seven alternative scenarios (CS, Table 59 to Table 66):

S1. Removal of the long-term remission health state from both the intervention and comparator model arms

S2. Removal of treatment modifier applied to the drug acquisition cost and administration cost of nivolumab+FOLFOX and nivolumab+XELOX

S3. Removal of time-to-death disutility

S4. Level of PD-L1 expression (see Table 32 and Table 33)

S5. Removal of the treatment stopping rule

S6. Use of cisplatin plus 5-fluorouracil and cisplatin plus capecitabine as alternative comparators

S7. Removal of long-term remission health state from the comparator arm only

The ICER per QALY gained was lower than £50,000 for most of these scenarios (see Table 31). A notable exception was the removal of the long-term remission health state for both model arms, which led to ICERs per QALY gained that were just below £100,000.

Table 31 Scenario analysis results (PAS price for nivolumab, list prices for other drugs)

Scenario	ICERs per QALY gained	
	Nivolumab+FOLFOX versus FOLFOX	Nivolumab+XELOX versus XELOX
S1	£99,456	£94,075
S2	£56,018	£51,067
S3	£47,962	£45,287
S4[a]	£43,370	£40,438
S4[b]	£38,157	£34,973
S5	£50,368	£46,943
S6	£29,871*	£56,470**
S7	£27,517	£25,947

[a]=PD-L1 CPS≥1; [b]=PD-L1 CPS≥5; *=comparator is cisplatin+5-fluorouracil; **=comparator is cisplatin+capecitabine; CPS=combined positive score; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PD-L1=programmed cell death-ligand 1; PAS=Patient Access Scheme; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin
Source: CS, Table 59 to Table 66

Table 32 Scenario analysis results in PD-L1 CPS≥1 subgroup (PAS price for nivolumab, list prices for other drugs)

Treatment	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,370**
Nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,438**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years; XELOX=capecitabine+oxaliplatin
Source: CS, Table 62

Table 33 Scenario analysis results in PD-L1 CPS≥5 subgroup (PAS price for nivolumab, list prices for other drugs)

Treatment	Total			Incremental			ICER (£/QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,157**
Nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,973**

FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years; XELOX=capecitabine+oxaliplatin
Source: CS, Table 63

5.5 Model validation and face validity

The company stated that an independent economist reviewed the model and clinical experts validated the model structure and assumptions.

The company noted that, other than the ATTRACTION-4 trial, which is not representative of UK clinical practice and the population treated in the NHS, there are no studies that can be used to validate survival projections of CheckMate 649 nivolumab+chemotherapy data. However, data from a single-centre UK retrospective study[65] suggest that median OS for patients treated with chemotherapy at that centre is similar to median OS for patients in the chemotherapy arm of the CheckMate 649 trial (11.48 and 12.88 months respectively) as described in the CS (Section B.3.9.2).

6 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Model validation

The ERG validated the company model by:

- checking that parameter values in the CS matched those in the company model
- testing the effect of using extreme values of key model parameters on cost effectiveness results
- tracing algorithms from results back to model parameters
- checking PSA parameter values were reasonable and re-running the PSA.

The company model was constructed in MS Excel and uses a combination of formulas in sheets and Visual Basic for Applications (VBA) code to generate results. This type of model makes algorithm checking complex and also makes anything but simple alterations to model parameter values problematic. However, the model algorithm that implements the PPS extrapolation seems to apply a post-progression mortality hazard trajectory that is fixed to the model time horizon and does not take into account the fact that, at any given timepoint, individual patients will experience different mortality hazards depending on the timepoint that they experienced disease progression. As the mortality hazard in the PPS health state declines over time, this leads to overestimates of OS for the modelled nivolumab+chemotherapy arm and the modelled chemotherapy arm. However, as the effect of nivolumab+chemotherapy on PPS is superior to the effect of chemotherapy on PPS, this increases OS for patients receiving nivolumab+chemotherapy proportionally more than for patients receiving chemotherapy. Thus, this error leads to ICER per QALY gained estimates for the comparison of nivolumab+chemotherapy versus chemotherapy that are overly optimistic. Due to the complexity of the model algorithms, correcting the algorithms was beyond the remit of the ERG.

6.2 Overview of ERG company model critique

The company model was constructed as a Markov model with transition probabilities that are time dependent and estimated from either (i) CheckMate 649 trial data for PFS and PPS (directly from the trial K-M data and from the extrapolation of the trial K-M data) or (ii) from life tables[49] (for long-term remission to death inputs). The company states that this approach was necessary to capture the benefits that patients experience when they enter long-term remission. The ERG considers that the company's modelling approach is unnecessarily complicated; a basic partitioned survival model with a simple adjustment to the OS hazard at a specific time point to explore the impact of long-term remission on OS (if such an impact exists) would have been sufficient.

The economic issues identified by the ERG are as follows:

- company OS estimates are not in line with company model estimates over the first 12 months of the model time horizon
- there is no evidence to support the company's assumption that, at 30 months, all patients remaining in the PFS health state enter the long-term remission heath state (and are effectively cured)
- model utility values are high compared to age-related norms and to values used in previous NICE TAs in this disease area
- a treatment modifier is inappropriately only applied to the drug and administration costs associated with nivolumab
- baseline age of patients is too low
- the company's focus is on the effect of treatment on the whole population rather than on the effect of treatment on subgroups differentiated by level of tumour PD-L1 expression

Summary details of all the issues identified by the ERG are provided in Table 34.

Table 34 Summary of ERG company model critique

Aspect considered	ERG comment	Section of ERG report
Population	The model populations match the trial populations (i.e., excluding patients with HER2-positive disease). However, the ERG notes that patients in the CheckMate 649 trial are younger and fitter than patients treated in the NHS	6.7
Comparators	The company has produced cost effectiveness results for all comparators except any chemotherapy regimens containing epirubicin or any containing trastuzumab (this means that there are no comparative cost effectiveness results that are relevant for the population with HER2-positive disease who are eligible for treatment with trastuzumab) The ERG considers that the only comparators of relevance to this appraisal are XELOX and FOLFOX	6.9
Model structure	The company model is unnecessarily complicated and, as routinely used in NICE TA submissions for Stage 4 cancer, a simple partitioned survival model would have been sufficient	6.1 and 6.4
Modelling OS*	CheckMate 649 trial results presented in the CS are based on a database lock on 10th July 2020, providing an overall minimum follow-up of 12.1 months. Company model OS estimates for patients receiving nivolumab+chemotherapy and chemotherapy are higher than actual survival results from the CheckMate 649 trial at 12 months There is no evidence to support the company assumptions that: • patients with gastric cancer enter long-term remission • patients in the long-term remission health state experience the same mortality risk as the general population	6.3 and 6.4
Modelling PFS*	The approach to modelling PFS is satisfactory after the removal of the company's assumption that all patients alive and in the PFS heath state at 30 months enter long-term remission	6.4
Utility values*	Utility values are high compared to age-related norms and to values used in previous NICE TAs[13,59] in this disease area	6.5

Resource use costs*	Clinical advice to the ERG is that the levels of resource use in the model are reasonable. However, some of the resource use costs used in the model are out of date (NHS Reference Costs 2015/16)[61] and are related to breast cancer The ERG considers that it is inappropriate to apply a treatment modifier to the costs of only one of the treatments considered in the company base case analysis	6.6
Discounting*	Discounting starts from the end of the first cycle rather than at the beginning of the second year. Discounting from the first cycle normally leads to results from pair-wise cost effectiveness analyses that favour the treatment that incurs the higher cost during the first year	6.2
PSA	The PSA was undertaken accurately	6.2
AEs	AEs have a minimal impact on cost and QALYs and are not a driver of cost effectiveness	NA

* Aspect has been considered in ERG alternative cost effectiveness analyses
AE=adverse event; ERG=Evidence Review Group; HER2=human epidermal growth factor receptor 2; NA=not applicable; NICE=National Institute for Health and Care Excellence; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; TA=Technology Appraisal
Source: LR*i*G in-house checklist

6.3 Overall survival estimates over 12 months

CheckMate 649 trial data show that, at 12 months, 55% of patients in the nivolumab+chemotherapy arm and 48% of patients in the chemotherapy arm were alive (CS, Figure 7A). The company base case analysis generates estimates that show that at 12 months, [redacted] of patients in the nivolumab+chemotherapy arm and [redacted] of patients in the chemotherapy arm are still alive.

Comparative OS data are available from a retrospective review of 511 patients (from the Royal Marsden hospital) with locally advanced (unresectable), de novo metastatic or relapsed metastatic after radical treatment, oesophago-gastric adenocarcinoma who were treated during a 6-year period. All patients received a chemotherapy regimen in the first-line setting. A comparison of survival data at 6, 12 and 24 months between the CheckMate 649 trial, the company model and digitised published K-M data from the Royal Marsden Hospital[65] is shown in Table 35.

Table 35 Comparative overall survival data from three sources

	Nivolumab+chemotherapy		Chemotherapy		
	CheckMate 649 trial	**Company model**	**CheckMate 649 trial**	**Company model**	**Royal Marsden Hospital[65]**
6 months	80%	[redacted]	76%	[redacted]	74%
12 months	55%	[redacted]	48%	[redacted]	44%
24 months	27%	[redacted]	19%	[redacted]	16%

Source: CS, Table 10, company model and Davidson et al[65]

Whilst the disparities in OS between the three sources have largely closed by 24 months (although the model projections are still optimistic compared to CheckMate 649 trial and Royal Marsden Hospital[65] data), the marked differences in OS between model estimates, CheckMate 649 trial and Royal Marsden Hospital[65] data over the first 12 months suggest that model results are not robust.

The company model PFS estimates closely match the CheckMate 649 trial PFS data over 6, 12 and 24 months (CS, Table 31). As OS is indirectly modelled through PFS, the cause of the company model producing overly optimistic OS for the first 12 months of the model time horizon could be due to the chosen PPS distributions, the error in the algorithms associated with PPS (described in Section 6.1) or the model death on progression formula. The ERG was unable to identify the cause of the overestimation. Construction of the model as a partitioned survival model would have allowed the company's model OS results to have been adjusted by the ERG.

Failure of the company model to adequately project OS over the first 12 months of the model time horizon, i.e., for the period when robust trial data are available, casts doubt not only on the model results generated over the first 12 months, but also on the robustness of model results beyond 2 years when limited or no trial evidence is available to validate model projections for nivolumab+chemotherapy.

6.4 Evidence does not support patients who have not progressed by 30 months being cured

The company has assumed that all patients who have not progressed by 30 months, regardless of treatment received, enter a long-term remission health state where the only risk is death and the modelled risk of death in this health state is equal to age-specific background mortality. Essentially, this means that patients who have not progressed by 30 months are cured (although PFS health state costs and utility values are applied whilst in the long-term remission state). Progression and mortality rates over time for the population receiving nivolumab+chemotherapy are shown in Figure 7 (the shape of the mortality rates for patients receiving nivolumab+chemotherapy are similar to the shape for patients receiving chemotherapy).

ACM=all-cause mortality; CX=chemotherapy; NIV=nivolumab; PFS=progression-free survival
Source: Company model

Figure 7 Progression and mortality rates over time for nivolumab+chemotherapy from the company model compared with all-cause mortality

In the company base case, at 30 months, [redacted] of patients receiving nivolumab+chemotherapy and [redacted] of patients receiving chemotherapy are estimated to be progression free and so enter the long-term remission health state. Of patients still alive at 5 years, [redacted] of patients receiving nivolumab+chemotherapy and [redacted] of patients receiving chemotherapy are in the long-term remission heath state. As mortality in the PPS health state declines over time, this means that by 5 years, overall mortality in the model is almost identical to background mortality. Clinical advice to the ERG is that, in current practice, only a small percentage of patients may achieve long-term remission (perhaps 1%), and that at least some residual excess mortality is likely to remain for many years, if not for life, even for this small group of patients.

To support their claims of long-term remission, the company has provided evidence from several sources[65-70] of OS data for patients with advanced, unresectable or metastatic gastric cancer who have received at least one line of treatment. The company claims that the data presented in these studies[65-70] show that (i) mortality plateaus between 3 and 5 years, (ii) there are few mortality events between years 5 and 10, and (iii) these data confirm that long-term

remission is clinically plausible for this population (company response to clarification question B3). The company used data from the CheckMate 649 trial as evidence to support a decline in mortality to meet background mortality for patients in the PFS health state at 30 months. These claims are discussed in Section 6.4.1.

6.4.1 Long-term remission data sources

COUGAR-02[70] survival data show that at 18 months, only 5/168 patients were still at risk (alive, uncensored). Therefore, data from the COUGAR-02 trial[70] cannot provide any information about the survival of patients beyond 18 months. However, the study does include information to support the view that most patients do not survive for 2 years. Further, three papers[65-67] all include information about patients who did[65] or may have[66,67] received subsequent treatments and so the survival data reported in these papers cannot robustly support the assumption of long-term remission after one treatment.

The papers[65-67] all report data for at least 5 years and these data show that the mortality hazard is the same in Year 1 and in Year 2[65,66] or increases.[67] Data from the CheckMate 649 trial show that the annual mortality hazard in the nivolumab+chemotherapy arm increases from 0.45 in Year 1 to [redacted] in Year 2 and in the chemotherapy arm increases from 0.52 in Year 1 to [redacted] in Year 2 (estimated by the ERG using data from CS, Table 10). None of these three studies[65-67] include data that support the assumption that patients enter long-term remission.

In all papers[65-70] highlighted by the company, over 80% of patients are reported to be dead by 2 years; this means that the size of the population providing data to estimate mortality at 2 years is small. Further, after 2 years, the numbers of patients at risk decline rapidly. For example, the real-world study reported by Shankaran et al[67] considered a population of 2,326 patients, however, the numbers of patients at risk at the end of Year 2 and Year 3 were 192 (8.2%) and 75 (3.2%) respectively, and by Year 5 there were only 14 patients still at risk (alive, uncensored). Further, whilst the company stated that in the Royal Marsden Hospital[65] review, some patients were still alive beyond 100 months (company response to clarification question B3), the published K-M data from the Royal Marsden Hospital suggest that all patients are expected to have died by the end of Year 9. The published data[65] suggest that the mortality hazard for this population remains substantially above the background mortality hazard.

Additionally, in studies[65-67] that report survival data at 5 years, survival at this point is between 3% and 4%, whereas the company model suggests that [redacted] of patients receiving chemotherapy will still be alive at 5 years. When the long-term remission health state is removed from the company model, 5-year survival for patients receiving chemotherapy is 4%, which is in line with the data presented in the published studies.[65-67]

6.4.2 Mortality rates in the PFS health state in the CheckMate 649 trial

The company states that CheckMate 649 trial data support the assumption that mortality declines over time towards background mortality (company response to clarification question B3). The company modelled the mortality hazard over time using data from the nivolumab+chemotherapy arm of the CheckMate 649 trial (

Figure 8) and the company suggests that these data show that "…the OS hazard was predicted by several estimators to reduce to approximately match the general population in the full ITT population" (company response to clarification question B3). The company did not provide any description of the process taken to choose the three distributions displayed in

Figure 8. In the ERG's experience, the distributions presented by the company are not commonly used in models developed to estimate the cost effectiveness of drugs to treat metastatic cancer.

In

Figure 8, wide credible intervals at all time points after 12 months suggest that it is impossible to select any distribution to robustly model the mortality hazard after 2 years. It would also be very difficult to argue that the two distributions (see

Figure 8) chosen by the company show a declining hazard from month 24 'approximately match' the mortality hazard data. One of the distributions (the kernel smoothed) generates mortality hazard predictions that are outside the credible interval and actually fall below background mortality and another distribution (the Bspline) generates predictions that are towards the lower end of the credible interval. The ERG considers that the most plausible of the three distributions presented by the company is the R-P spline, which sits in the middle of the credible interval and shows the mortality hazard plateauing well above background mortality after 2 years.

Figure 8 Mortality hazard from first treatment; CheckMate 649, nivolumab+chemotherapy, intention-to-treat

Source: Company response to clarification question B3 (Figure 6)

Due to the small size of the population still at risk in the PFS health state at 18 months in the CheckMate 649 trial (nivolumab+chemotherapy: n=83; chemotherapy: n=38), trial-based estimates of mortality in the PFS health state after 18 months are highly uncertain. As shown in

Figure 8, plots of mortality hazard over time conditional on PFS produced by the company in response to clarification question B3 show high levels of uncertainty around mortality hazard rate estimates. However, the ERG considers that all of the evidence provided by the company

shows that mortality hazards are likely to plateau above background mortality, rather than fall to background mortality as modelled by the company.

6.4.3 Impact of removing long-term remission health state

The ERG considers that the company has not provided any evidence to demonstrate that patients achieve long-term remission (i.e., reach a point where their mortality hazard matches background mortality hazard). The company stated in response to clarification question B3 that "…evidence to support specific outcomes for patients in long-term remission is sparse". The ERG considers that robust evidence to support long-term remission is not available. Therefore, the long-term remission health state should not have been included in the company base case and should only have been used to inform an unevidenced 'what if?' scenario

CX=chemotherapy
Source: Company model and ERG digitised data from Davidson et al[65]

Figure 9 Company model overall survival estimates for patients receiving chemotherapy and Royal Marsden retrospective review OS data

6.5 Utility values used in the PFS and PPS health states are too high

The company model is populated with utility values derived from data collected as part of the CheckMate 649 trial (PFS health state: [redacted], progressed disease health state: [redacted], time to death disutility [applied 6 months before death]: 0.406[51]). The ERG considers the PFS and progressed disease health state utility values appear to be too high given the symptom burden associated with advanced gastric cancer. The reference utility value used in the PFS health state for patients more than 6 months from death is only [redacted] lower than the general population age dependent utility at 60 years of age in the company model ([redacted]), which

suggests the symptom burden associated with having gastric cancer is very low. Further, the utility values used in the company model are higher than utility values used in other NICE TAs for advanced or metastatic cancer and values reported in published literature on utility in this disease area (Table 36) The utility values used in NICE TA208[13] and NICE TA378[59] are very similar to each other. The utilities used in NICE TA208[13] are drawn from the same population as this submission (i.e., patients receiving first-line treatment for advanced gastric cancer); however, NICE TA378[59] relates to patients who have received two or more prior treatments. The ERG has carried out a scenario analysis using the NICE TA208[13] utility values.

Table 36 Company model and alternative sources of utility values considered by the ERG

Data source	Population	Health state utility values
CheckMate 649 trial	Untreated advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma	PFS: [redacted] PD: [redacted] Time to death disutility (applied 6 months before death): 0.406[51]
NICE TA208[13] Trastuzumab	Previously untreated inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction	PFS: 0.7292 PD: 0.577 Difference: 0.1522
NICE TA378[59] Ramucirumab	Metastatic or non-resectable locally advanced gastric cancer after 1 previous therapy	PFS: 0.737 PD: 0.587 Difference: 0.15
NICE TA669[71] Trifluridine–tipiracil	Metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in adults after 2 or more therapies	PFS: 0.764 PD: 0.652 Difference: 0.112
Curran et al[72] Multi-country	Patients had histologically confirmed metastatic adenocarcinoma of the stomach or esophagogastric junction, with measurable or evaluable metastatic disease, or locally recurrent disease	Post-baseline 5-FU: 0.76 (SD: 0.23) Post-baseline cisplatin+5-FU: 0.66 (SD: 0.27)
Kontodimopoulos et al[73] Greece	Patients had previously attended 2–4 chemotherapy sessions (≥20 days previously), and had undergone surgery (n = 48)	Baseline: pre-treated patients attending hospital for chemotherapy (considered as currently receiving chemotherapy) EQ-5D=0.550 (SD: 0.307) SF-6D=0.606 (SD: 0.094) SF-15D=0.685 (SD: 0.166)

EQ-5D=EuroQol-5 dimensions; 5-FU=5-fluorouracil; NICE=National Institute for Health and Care Excellence; PD=progressed disease; PFS=progression-free survival; SD=standard deviation; SF=Short Form; TA=technology appraisal
Source: ERG summary

6.6 Treatment modifier

The company has applied a treatment modifier to the drug acquisition and administration costs of nivolumab (reduction of 11.7%) to adjust for costs not incurred due to missed doses. Whilst application of a treatment modifier is acceptable, it is reported in the CS that adjustments are only made to account for missed doses of nivolumab (CS, Table 41 and Table 42). In the absence of evidence from the CheckMate 649 trial on the number of missed chemotherapy doses (in the nivolumab+chemotherapy arm and in the chemotherapy arm), the ERG considers that the base case analysis should not include adjustments to the cost of acquiring and administering nivolumab.

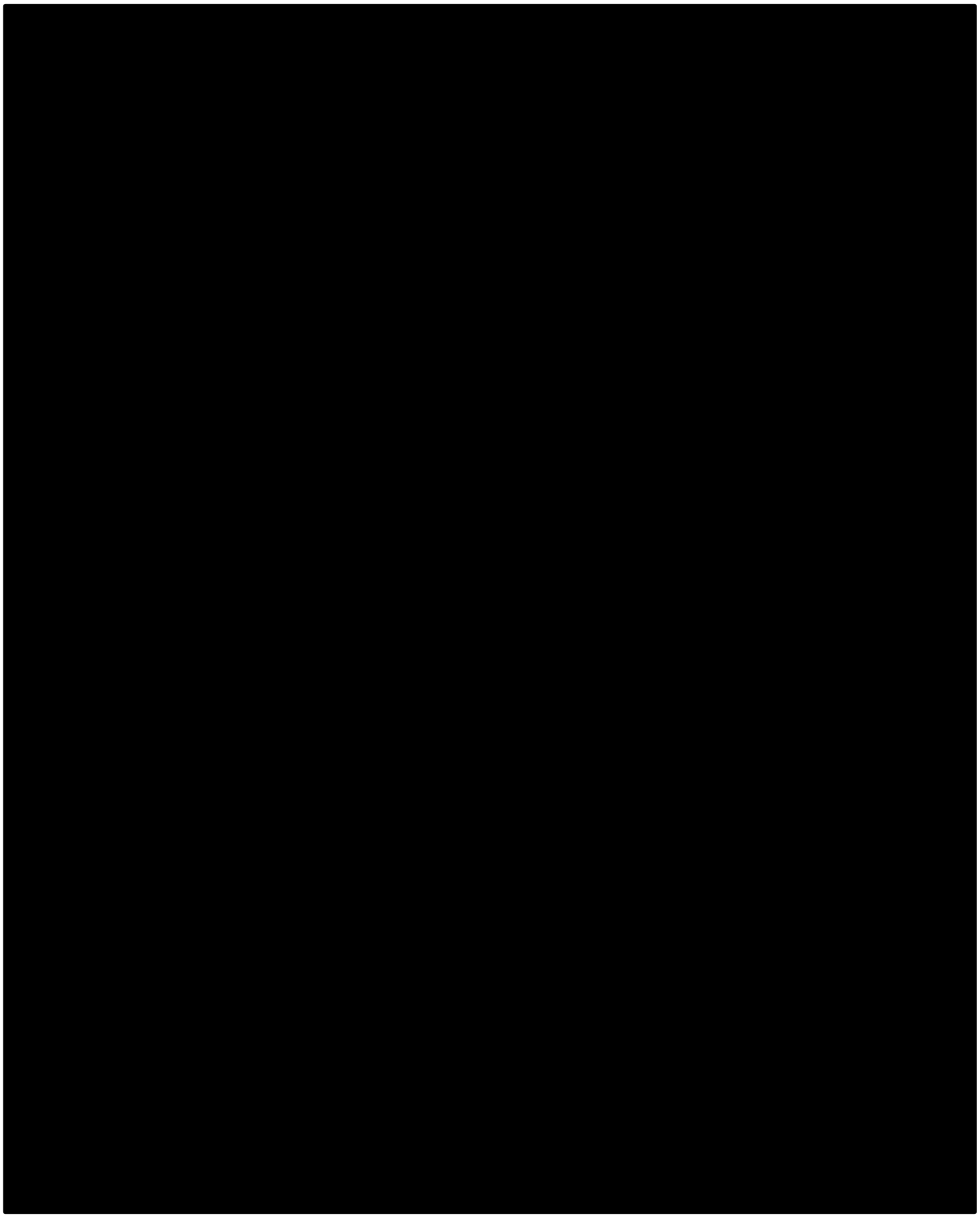
6.7 Age of patients starting treatment with advanced gastric cancer

At baseline, the mean age of patients participating in the CheckMate 649 trial is [redacted] years (company response to clarification question B4) and this age was used as the population baseline age in the company model. However, clinical advice to the ERG is that in the UK,

patients presenting with advanced gastric cancer who are treated with chemotherapy may be considerably older than [redacted] years of age. The median age of patients who provided data for the Royal Marsden Hospital[65] review was 66 years (range: 24-90). At clarification, the ERG asked the company to provide further evidence to support the model assumption that it was appropriate to use a mean baseline age of [redacted] years. In response, the company produced cost effectiveness results based on Cancer Research UK (CRUK)[74] data that suggest that the mean age of patients having at least one line of treatment for advanced gastric cancer is 64.15 years. The ERG is confident that this age is more reflective of the average age of patients treated in the NHS than the age used in the company base case analysis.

6.8 Analysis by PD-L1 subgroups

The co-primary outcomes in the CheckMate 649 trial are OS and BICR-assessed PFS in patients with PD-L1 CPS≥5. It is stated in the final scope[16] issued by NICE that, if evidence allows, subgroups by PD-L1 level of expression should be considered. The company has presented cost effectiveness results for PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups. However, the ERG considers that results for the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups should have been provided and asked for cost effectiveness results for these subgroups at clarification (question B1 and question B2). The company did not provide these results, stating that the CheckMate 649 trial was not powered to show a difference in PFS or OS for the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups. With [redacted] patients in the PD-L1 CPS<1 subgroup and [redacted] patients in the PD-L1 CPS<5 subgroup, the ERG considers that whilst the CheckMate 649 trial may not have been powered to detect a difference in PFS and OS, the subgroup sample sizes are sufficient (particularly the PD-L1 CPS<5 subgroup) to produce results that are informative to decision makers. In response to the clarification letter the company provided OS, PFS and ORR HRs for the four PD-L1 CPS subgroups (reproduced in Figure 4). The HRs for OS and PFS for the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups are much closer to one than the OS HRs for the PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups (i.e., less clinically effective); these results suggest that using the current model nivolumab+chemotherapy may be less cost effective for patients in the PD-L1 CPS<1 and PD-L1 CPS<5 subgroups compared with patients in the PD-L1 CPS ≥1 and PD-L1 CPS≥5 subgroups.



Source: Company response to clarification question B1 (Figure 4)

Figure 10 PD-L1 CPS subgroup hazard ratios

6.9 Comparators

The ERG considers that XELOX and FOLFOX are the most relevant comparators for nivolumab+XELOX and nivolumab+FOLFOX respectively. Whilst the company has produced cost effectiveness results for fluorouracil+cisplatin and capecitabine+cisplatin, the ERG does not consider these to be informative for decision making as clinical advice to the ERG is that these treatments are rarely used in the NHS and has not produced revised ICERs per QALY gained for these comparators. No cost effectiveness results have been generated for any of the triplet chemotherapy regimens listed in the final scope[16] issued by NICE.

6.10 Impact on the ICER per QALY gained of additional ERG analyses

The ERG has not implemented any changes to the model relating to population, comparators, model structure, PSA and AEs (see Table 34 for further details).

The ERG has made five revisions to the company model to generate an ERG preferred base case:

- R1: discounting starting from the beginning of Year 2
- R2: long-term remission health state removed from the company model
- R3: alternative utility values used in the PFS and progressed disease health states
- R4: removal of treatment modifier used to adjust costs of treatment with nivolumab
- R5: model baseline population age increased to 64.15 years.

These revisions have been applied to three different populations (the whole population, PD-L1 CPS≥1, PD-L1 CPS≥5) with two different comparators (XELOX and FOLFOX). Details of how the ERG revised the company model are presented in Appendix 9.2 of this ERG report.

The results of the ERG analyses (Table 37 to Table 41) show that correcting discounting (R1) and reducing utility values (R3) had a minor impact on the cost effectiveness results, but increasing the baseline age of patients (R5) added between £4,000 and £6,000 to the ICER per QALY gained for the comparison of nivolumab+chemotherapy versus XELOX or FOLFOX and removing the treatment modifier (R4) increased the ICER per QALY gained for the comparison of nivolumab+chemotherapy versus XELOX or FOLFOX by between £4,000 and £9,000. However, the revision that had the biggest impact on the cost effectiveness results was removal of the long-term remission health state (R2) from the model. Removing this health state added between £33,000 and £52,000 to the ICER per QALY gained for the comparison of nivolumab+XELOX or nivolumab+FOLFOX versus XELOX or FOLFOX respectively.

Applying all the ERG revisions to the company model increased the ICERs per QALY gained by:

- £71,540 to £116,712 for nivolumab+XELOX versus XELOX (whole population)
- £80,030 to £127,870 for nivolumab+FOLFOX versus FOLFOX (whole population)
- £68,209 to £108,647 for nivolumab+XELOX versus XELOX (PD-L1 CPS≥1)
- £76,862 to £120,232 for nivolumab+FOLFOX versus FOLFOX (PD-L1 CPS≥1)
- £49,832 to £84,805 for nivolumab+XELOX versus XELOX (PD-L1 CPS≥5)
- £56,917 to £95,074 for nivolumab+FOLFOX versus FOLFOX (PD-L1 CPS≥5).

Table 37 ERG revisions to company model and preferred ICER per QALY gained, whole population: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£45,172***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,503	-£669
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,075	£48,903
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,995	£823
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,067	£5,895
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,293	£5,121
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£116,712***	***£71,540***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table 38 ERG revisions to company model and preferred ICER per QALY gained, whole population: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£47,840***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,197	-£643
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£99,456	£51,616
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,711	£871
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,018	£8,178
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,263	£5,423
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£127,870***	***£80,030***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

Table 39 ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS≥1: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£40,438***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,854	-£584
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£88,305	£47,867
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,195	£757
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,662	£5,224
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,016	£4,578
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£108,647***	***£68,209***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table 40 ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS≥1: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£43,370***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,803	-£567
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,497	£51,127
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,183	£813
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,615	£7,245
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,279	£4,909
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£120,232***	***£76,862***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

Table 41 ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS≥5: nivolumab+XELOX vs XELOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+XELOX			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£34,973***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,504	-£469
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,246	£33,273
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,791	£818
R4) Removal of treatment modifier for nivolumab+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,370	£4,397
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,776	£3,803
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£84,805***	***£49,832***

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; XELOX=capecitabine+oxaliplatin

Table 42 ERG revisions to company model and preferred ICER per QALY gained, PD-L1 CPS≥5: nivolumab+FOLFOX vs FOLFOX (PAS price for nivolumab, list prices for other drugs)

Scenario/ERG amendment	Nivolumab+FOLFOX			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£38,157***	
R1) Discounting commences from the start of the second year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,694	-£463
R2) Long-term remission removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,210	£36,053
R3) Alternative utility values in PFS and progressed states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,049	£892
R4) Removal of treatment modifier for nivolumab+FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,255	£6,098
R5) Increasing start age of model to 64.15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,307	£4,150
B. ERG preferred scenario (R1-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£95,074***	***£56,917***

ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year

6.11 Conclusions of the cost effectiveness section

The ERG considers that the modelling approach undertaken by the company produces OS estimates over the first 12 months of the model time horizon that are not in line with the CheckMate 649 trial estimates. These estimates cast doubt on the robustness of all OS estimates and all of the cost effectiveness results presented by the company.

Even if the company's modelling approach was robust, for the base case ICERs per QALY gained that are generated by the model to be under £50,000, the assumption must hold that patients enter a long-term remission health state if they have not progressed after 30 months, at which point they no longer have any excess mortality associated with having advanced oesophago-gastric cancer (i.e., these patients are cured). The ERG considers there is no substantive clinical effectiveness evidence presented by the company to support entry into such a long-term remission health state at any point, even if a patient has not progressed. A long-term remission health state should not have been included in the company base case and removal of this health state increases the ICERs per QALY gained substantially above £50,000, even when the population is limited to patients in the PD-L1 CPS≥5 subgroup. For all populations considered, all the ERG's preferred ICERs per QALY gained generated for the comparison of nivolumab+XELOX or nivolumab+FOLFOX versus XELOX or FOLFOX, respectively, exceed £84,000.

The ERG considers that discounting was not correctly applied in the company model, utility values used in the company base case were too high, the age of patients at baseline was too low and a treatment modifier should have been applied to all drug and administration costs, not just to the costs associated with nivolumab. Further, results should have been presented by tumour level of PD-L1 expression for those below PD-L1 CPS thresholds i.e., not only for those above thresholds. However, the available evidence from the CheckMate 649 trial shows that, for the comparison of nivolumab+XELOX or nivolumab+FOLFOX versus XELOX or FOLFOX, respectively, the OS hazard ratios for patients in the PD-L1 CPS<1 and<5 subgroups are higher than the OS hazard ratios for patients in the PD-L1 CPS≥1 and ≥5 subgroups. These results suggest that nivolumab+chemotherapy may be less cost effective for patients in the PD-L1 CPS<1 and <5 subgroups compared with patients in the PD-L1 CPS≥1 and ≥5 subgroups.

7 NICE END OF LIFE CRITERIA

The company considers that the NICE End of Life criteria apply to the current appraisal of nivolumab+XELOX and nivolumab+FOLFOX versus XELOX and FOLFOX, respectively. The company's and the ERG's assessments of whether NICE End of Life criteria apply to the current appraisal are provided in Table 43.

Table 43 Company and ERG assessments of whether NICE End of Life criteria are met

Criterion	Company evidence	ERG comment
The treatment is indicated for patients with a short life expectancy, normally <24 months	• 1-year net survival in the UK is 21.4% at Stage 4[10] • Median OS for patients in the chemotherapy arm of the CheckMate 649 trial was 11.56 months and 1-year survival was 47.9% • Royal Marsden Hospital[65] retrospective review: median OS 11.5 months	The ERG agrees that available data suggest that life expectancy for the population described in the final scope[16] issued by NICE is <24 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**CheckMate 649 median OS results (whole population)** Nivolumab+chemotherapy: 13.83 (95% CI: 12.55 to 14.55) months Chemotherapy: 11.56 (95% CI: 10.87 to 12.48) months for current treatment (i.e., chemotherapy alone) **Mean survival** For the comparison of nivolumab+chemotherapy versus chemotherapy, the company base case model predicts a mean survival gain of 9.2 months	**CheckMate 649 trial median OS results** (CS, Table 11) A gain of ≥3 months was **only** evident for the PD-L1 CPS≥5 subgroup Nivolumab+chemotherapy: 14.39 (95% CI: 13.11 to 16.23) months Chemotherapy: 11.10 (95% CI: 10.0 to 12.09) months **Mean survival** The weakness identified by the ERG in the company approach to generating OS estimates means any predicted survival gain is highly uncertain. However, the ERG base case analysis predicts incremental life years exceeding 3 months

CI=confidence interval; CPS=combined positive score; HR=hazard ratio; OS=overall survival; PD-L1=programmed cell death-ligand 1
Source: CS, Table 24

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9 APPENDIX

9.1 Appendix 1: The ATTRACTION-4 trial

The ATTRACTION-4 trial (NCT02746796) was a two-part (phase II/III) trial. Part 1 of the ATTRACTION-4 trial was an open-label, international, multi-centre, phase II, randomised trial of nivolumab+SOX (tegafur, gimeracil, oteracil [S-1] and oxaliplatin) versus nivolumab+XELOX for patients with HER2-negative untreated advanced or recurrent gastric or gastro-oesophageal junction cancer. Part 2 of the trial was a double-blind, international, multi-centre, phase III, RCT of nivolumab+chemotherapy versus chemotherapy for patients with HER2-negative untreated advanced or recurrent gastric or gastro-oesophageal junction cancer. Part I (phase II) of the ATTRACTION-4 trial was conducted in 13 centres across two countries (Japan, and South Korea) and part II (phase III) was conducted in 130 centres across three countries (Japan, South Korea, Taiwan). In both part 1 and part 2 patients received SOX or XELOX as chemotherapy.

9.1.1 Differences in trial characteristics between the CheckMate 649 and ATTRACTION-4 trials

The ERG notes that the CheckMate 649 trial included a proportion of patients from Asia (22.5%), but that nearly two-thirds of patients (60.8%) were from the rest of the world, including Europe. The ERG notes that the ATTRACTION-4 trial population was recruited exclusively in Asian countries (Japan, South Korea, Taiwan). The CheckMate 649 trial population is largely representative of patients with untreated advanced gastric or gastro-oesophageal junction cancer in NHS practice while the ATTRACTION-4 trial population were not.

The ERG considers that XELOX and FOLFOX chemotherapy regimens used in the CheckMate 649 trial are SoC in the NHS, however, nearly two-thirds patients (64.1%) in the ATTRACTION-4 trial received SOX which is not used in NHS practice. The ERG also notes that the chemotherapy regimen that patients received in the CheckMate 649 trial and in part 2 of the ATTRACTION-4 trial was the treating clinicians' choice. However, the chemotherapy regimen that patients received in part 1 of the ATTRACTION-4 trial was allocated by randomisation.

Key characteristics of the ATTRACTION-4 trial are presented in Table 44 and baseline characteristics are presented in Table 45 (phase II) and Table 46 (phase III).

Table 44 Key characteristics of the ATTRACTION-4 trial

Trial parameter	ATTRACTION-4 trial Part I (Phase II)	ATTRACTION-4 trial Part II (Phase III)
Design	Open-label, international, multi-centre, phase II, randomised trial 13 centres across 2 countries (Japan, and South Korea)	Double-blind, international, multi-centre, phase III, RCT 130 centres across 3 countries (Japan, South Korea, Taiwan)
Patient population	Adults (≥20 years), with previously untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer that has been histologically confirmed to be adenocarcinoma. ECOG performance status 0 or 1 and measurable disease per RECIST v1.1. No prior chemotherapy (unless neoadjuvant or adjuvant completed >180 days before randomisation) Patients with known HER2 positive status or indeterminate gastric cancer were excluded	
Intervention	Nivolumab+SOX 3-weekly chemotherapy cycle; nivolumab 360mg every 3 weeks (2 doses counted as one cycle), plus oxaliplatin 130mg/m^2 IV every 3 weeks and S-1 80mg/m^2 on days 1 to 14 (40mg/m^2, twice daily), 7 days off or Nivolumab+XELOX 3-weekly chemotherapy cycle; nivolumab 360mg every 3 weeks (2 doses counted as one cycle), oxaliplatin 130mg/m^2 IV every 3 weeks and capecitabine 2000mg/m^2 orally BID on days 1 to 14, 7 days off	
Comparator	No comparator	Placebo+SOX Placebo IV (30 minutes) every 3 weeks, plus SOX using dosage as above or Placebo+XELOX Placebo IV (30 minutes) every 3 weeks, plus XELOX using dosage as above
Chemotherapy	SOX or XELOX were randomly allocated 1:1	Treating clinicians' choice of SOX or XELOX
Primary outcome	AEs graded according to CTCAE	PFS OS
Secondary outcomes	ORR OS PFS DOR BOR DCR TTR Change in tumour burden	ORR DOR DCR TTR BOR Change in tumour burden AEs

AE=adverse event; BID=twice daily; BICR=blinded independent central review; BOR=best overall response; CNS=central nervous system; CTCAE=Cancer Institute Common Terminology Criteria for Adverse Events; DCR=disease control rate; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; OS=overall survival; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RECIST v1.1=response evaluation criteria in solid tumours (version 1.1); SOX=S-1 (tegafur, gimeracil, oteracil)+oxaliplatin; TTR=time to response; XELOX=capecitabine+oxaliplatin
Source: Adapted from CS, Table 13, Boku 2019[22] and NCT02746796

Table 45 ATTRACTION-4 phase II trial baseline patient characteristics (ITT population)

Baseline characteristic	Nivolumab+SOX (n=21)	Nivolumab+XELOX (n=19)	Total (N=40)
Age, years			
Median (range)	61 (37 to 77)	65 (39 to 80)	62.5 (37-80)
Sex, n (%)			
Male	12 (57.1)	15 (78.9)	27 (67.5)
Country, n (%)			
Japan	10 (47.6)	10 (52.6)	20 (50.0)
South Korea	11 (52.4)	9 (47.4)	20 (50.0)
PD-L1 TPS expression status, n (%)			
PD-L1 TPS≥1%	4 (21.1)	2 (11.1)	6 (15.0)
PD-L1 TPS<1%	15 (78.9)	16 (88.9)	31 (75.5)
ECOG PS, n (%)			
0	10 (47.6)	10 (52.6)	20 (50,0)
1	11 (52.4)	9 (47.4)	20 (50.0)
Disease status classification, n (%)			
Recurrent	15 (71.4)	9 (47.4)	24 (60.0)
Advanced	6 (28.6)	10 (52.6)	16 (40.0)

ECOG=Eastern Cooperative Oncology Group; NIVO+SOX=nivolumab+S-1 (tegafur, gimeracil, oteracil)+oxaliplatin; NIVO+XELOX=nivolumab+capecitabine+oxaliplatin; PD-L1=programmed cell death-ligand 1; PS=performance status; TPS=tumour proportion score
Source: Adapted from Boku 2019[22] and the company's response to clarification question A11

Table 46 ATTRACTION-4 phase III trial baseline patient characteristics (ITT population)

Baseline characteristic	Nivolumab+chemotherapy (n=362)	Placebo+chemotherapy (n=362)
Age, years		
Median (range)	63.5 (25 to 86)	65.0 (27 to 89)
Sex, n (%)		
Male	253 (69.9%)	270 (74.6%)
Country, n (%)		
Japan	198 (54.7%)	197 (54.4%)
Taiwan	16 (4.4%)	22 (6.1%)
South Korea	148 (40.9%)	143 (39.5%)
PD-L1 TPS expression status, n (%)		
PD-L1 TPS≥1%	58 (16.0%)	56 (15.5%)
PD-L1 TPS<1%	304 (84.0%)	306 (84.5%)
ECOG PS, n (%)		
0	195 (53.9%)	194 (53.6%)
1	167 (46.1%)	168 (46.4%)
Chemotherapy regimen, n (%)		
SOX	232 (64.1)	232 (64.1)
XELOX	130 (35.9)	130 (35.9)

ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed cell death-ligand 1; PS=performance status; SOX=S-1 (tegafur, gimeracil, oteracil)+oxaliplatin; TPS=tumour proportion score; XELOX=capecitabine+oxaliplatin
Source: Adapted from the company's response to clarification question A11

9.2 Appendix 2: Microsoft Excel revisions made by the ERG to the company's model

Instructions for modifying the company model

Note: It may be necessary to force a full calculation in the model to update array formulas after making amendments: CTRL+ALT+F9. Changes that are made with ERG switches should also be verified to ensure they have occurred in the correct sheets (ensuring the value in the "Used" column of the "Data Library" sheet has also updated to the desired values.

1. Paste the following table into D69:E71 in the sheet "Model Control" name the switches with the modification names

Revision #	Cell	Name	Description	Instructions
R1	D69 ="R1"	E69 "Revision1"	Corrects discounting error.	Cell E69 = 1 if revision active, 0 if not.
R3	D70="R3"	E70 "Revision3"	Uses alternative utility values.	Cell E70 = 1 if revision active, 0 if not
R5	D71="R5"	E71 "Revision5"	Changes model start age to 64.15.	Cell E71 = 1 if revision active, 0 if not.

2. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number	Sheet(s)	Cells	Modified formulae
R1	"Treatment Trace" and "Control trace"	I11:J11	=IF(Revision1=0,1,1)
R1	"Treatment Trace" and "Control trace"	I12	=IF(Revision1=0,1/((1+dblDscntCosts)^$H12),1) Copy formula to range I13:I37
R1	"Treatment Trace" and "Control trace"	J12	=IF(Revision1=0,1/((1+dblDscntBenefits)^$H12),1) Copy formula to range J13:J37
R1	"Treatment Trace" and "Control trace"	I38	=IF(Revision1=0,1/((1+dblDscntCosts)^$H38),1/((1+dblDscntCosts)^$H12)) Copy formula to range I39:I1342
R1	"Treatment Trace" and "Control trace"	J38	=IF(Revision1=0,1/((1+dblDscntBenefits)^$H38),1/((1+dblDscntBenefits)^$H12)) Copy formula to range J39:J1342
R2	"Model Control"	O22 (long term remission dropdown)	Select "Off"
R3	"Data Library"	F252	=IF(Revision3=0,OFFSET(dblUtilityStatePfsMean,0,(3*(intUtilityInd-1))+19),0.737)
R3	"Data Library"	F253	=IF(Revision3=0,OFFSET(dblUtilityStatePdMean,0,(3*(intUtilityInd-1))+19),0.587)
R4	"Model Control"	O26 (treatment dropdown)	For NIV+FOLFOX select "NIVOLUMAB+FOLFOX" For NIV+XELOX select "NIVOLUMAB+XELOX"
R5	"Data Library"	F33	=IF(Revision5=1,64.15,OFFSET(dblBaseAgeMean,0,(3*(intBaseInd-1))+19))

As per the company's National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

'*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 Tuesday 4 May 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.17 Section 1.6 The ERG notes: However, when estimating median OS, the ERG highlights that results from the CheckMate 649 trial show that a gain of ≥3 months was only evident for the PD-L1 CPS≥5 subgroup; an OS gain of ≥3 months is not demonstrated for the whole population However, it should be acknowledged that this is based on median survival only	However, when estimating median OS, the ERG highlights that results from the CheckMate 649 trial show that a gain of ≥3 months was only evident for the PD-L1 CPS≥5 subgroup; a median OS gain of ≥3 months is not demonstrated for the whole population	The proposed amendment adds clarity, as mean OS gain is demonstrated for the overall population.	Thank you. The text in the ERG report has been changed as suggested
p.17 Section 1.6 and p.118 Section 7 The ERG note that the mean OS gain estimation is highly uncertain; however, the ERG base case analysis notes that incremental LYs for the overal population were [redacted].	The text should be updated to read: The weakness identified by the ERG in the company approach to generating OS estimates means any predicted survival gain is highly uncertain. However, the ERG base case analysis predicts incremental LYs exceeding 3 months.	It is of note that the ERG-preferred ICERs are obtained in scenarios where end of life criteria would be met.	Thank you. The text in the ERG report has been changed as suggested

Issue 2 Patient age

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.12 Section 1.4 The ERG note: In the CheckMate 649 trial: patients are younger than patients seen in NHS clinical practice (CheckMate 646 trial: mean age=[redacted] years; clinical advice to the ERG is that average age of patients treated in the NHS is 70-75 years) However, this does not align with Cancer Research data presented at clarification stage.	This statement should be updated to reflect that this opinion does not align with UK registry evidence demonstrating that baseline age lies significantly below 70-75 years.	The stated clinician opinion does not align with UK registry data for UK presented at clarification stage. This is an independent source that demonstrates that average age of gastric cancer patients receiving chemotherapy lies below <70 years.	This is not a factual error. This is a statement of clinical advice to the ERG. However, we have added the following text: The Cancer Research UK dataset shows that, during 2013-2015, approximately 42% of patients diagnosed with stomach cancer treated with chemotherapy were aged ≥70 years and 57.5% were aged ≤69 years

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.12 Section 1.4 Issue 2 Lack of generalisability of CheckMate 649 trial data Typo: Checkmate 646	Needs to be amended to Checkmate649	Typing error	Thank you. The report has been corrected as suggested
p.12 Section 1.4 Issue 2 Lack of generalisability of CheckMate 649 trial data ERG used mean age [redacted]	Whole population mean age in the CSR is [redacted]	CSR mean age for whole population is [redacted] Table 5.2.2-1	[redacted] years is the age used in the model and discussed in the company's clarification letter. No change required
p.15 Section 1.5 Issue 7 Low model baseline population age ERG used mean age [redacted]	Whole population mean age in the CSR is [redacted]	CSR mean age for whole population is [redacted] Table 5.2.2-1	[redacted] years is the age used in the model and discussed in the company's clarification letter. No change required
p. 43 Section 3.2.3 1.1.1 Characteristics of patients in the CheckMate 649 trial ([redacted]) had PD-L1 CPS≥1 (CSR, Table 5.2.2.1-2)	82.1% is incorrect – should be amended to [redacted] for the whole population.	Table 5.2.2.1-2 in the CSR. [redacted] is only for the nivo+chemo arm, whereas [redacted] is for the whole population	Thank you. The report has been corrected as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.56 Table 10 Summary of adverse events in the CheckMate 649 trial There is a typographical error in the table for chemotherapy, any grade, treatment related AEs [redacted]	Should be amended to [redacted]	CSR Table 8.1-1	Thank you. The report has been corrected as suggested
p.56 Table 11 Grade 3 or 4 TRAEs There is a typographical error in the table for nivo+chemo, peripheral sensory neuropathy [redacted]	Should be amended to [redacted]	CSR Table 8.1-1	The number quoted in the ERG report was taken directly from Table 21 of the CS. However, as per the company's request, the ERG report has been amended
p.57 Adverse events leading to treatment discontinuation and death There are typographical errors in the values for peripheral neuropathy: ([redacted] and [redacted], respectively)	Should be amended to [redacted] and [redacted] respectively.	CSR Page 133, Section 8.4	The numbers quoted in the ERG report are relevant to treatment-related adverse events and were taken from the text on p85 of the CS. The alternative numbers suggested by the company are relevant to all-cause adverse events. No change required.

Issue 4 Cost-Effectiveness section errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.32 Section 2.6 Table 1 Summary of decision problem – Economic analysis ERG state "the time horizon considered is 50 years"	Amend text to "The time horizon considered is lifetime up to a technical limitation of 50 years"	Table 28, Document B of company submission states that a time horizon of "lifetime (up to 50 years)" is chosen per the NICE reference case which "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" (Table 1, Document B of CS)	This is not a factual error. No change required

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 76 Section 4.2 ERG conclusions regarding company systematic review methods The ERG state: "*The ERG is concerned that the company search strategy did not include searching HTA websites, but otherwise considers that the methods used by the company to identify evidence to inform modelling decisions were appropriate and is satisfied that there are no relevant economic studies of nivolumab+chemotherapy available."*	The ERG is concerned that the company search strategy did not include searching individual HTA websites but included the search in the Cochrane HTA database. Otherwise, the ERG considers that the methods used by the company to identify evidence to inform modelling decisions were appropriate and is satisfied that there are no relevant economic studies of nivolumab+chemotherapy available.	Although individual HTA websites were not searched, the Cochrane HTA database was as stated in the SLR report	Thank you. The report has been corrected as suggested
p.78 Section 4.3.2 ERG used mean age [redacted]	Whole population mean age in the CSR is [redacted]	CSR mean age for whole population is [redacted] Table 5.2.2-1	[redacted] years is the age used in the model and discussed in the company's clarification letter. No change required

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 81 Section 4.3.6 Treatment effectiveness and extrapolation The ERG state: *"As this period is shorter than the model time horizon, it was necessary to generate parameter estimates."*	Amended text: As this period is shorter than the model time frame, parametric models were used to inform the state transitions, including within the unobserved period, up to a lifetime time horizon. For these models, it was necessary to generate parameter estimates	ERG text did not make clear the reasoning for needing to generate estimates of parameters	Thank you. The report has been corrected as suggested
p. 84 Section 4.3.8 Health-related quality of life The ERG state: "*time-to-death disutility ([redacted]) applied to all patients 6 months before death.*"	Amended text: Time-to-death disutility ([redacted]), applied to all patients who survived for at least 6 months during the 6 months before death. For patients who died within the first 6 months, disutility was determined by integrating a polynomial formula over the elapsed model time. This integral would equal that given by the quoted average disutility when model time was equal to 6 months.	ERG text is incorrect for patients who are modelled as dying within the first 6 months.	Thank you. The report has been corrected as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 88 Section 4.3.9 Resource use and costs: Adverse event costs The ERG state: *"The company estimated that the one-off costs (applied to the first cycle) of treating AEs associated with nivolumab+chemotherapy and chemotherapy were £[redacted] and £[redacted], respectively."*	The company estimated that the one-off costs (applied to the first cycle) of treating AEs associated with nivolumab+chemotherapy and chemotherapy were [redacted] and [redacted], respectively.	The calculated AE cost values provided by the ERG are not those based on the model or document B. Using the information in table 21 in document B (AE rates) and table 52 in document B (AE costs), we have provided the correct values generated by the model.	Thank you. The report has been corrected as suggested
p. 98 Section 6.3 Overall survival estimates over 12 months, Table 35 Company model values at 12 months are [redacted]% for nivolumab + chemotherapy, [redacted]% for chemotherapy	Company model values at 12 months are [redacted]% for nivolumab + chemotherapy and [redacted]% for chemotherapy	Within the company model, at 12 months, [redacted]% of patients are alive in nivolumab + chemotherapy, and [redacted]% of patients are alive in chemotherapy arm.	Thank you. The report has been corrected as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.101 Section 6.4.1 The ERG state: Further, whilst the company claims that in the Royal Marsden Hospital review, some patients were still alive beyond 100 months (company response to clarification question B3), the published K–M data from the Royal Marsden Hospital suggest that all patients had died by the end of Year 9.	Amended text: Further, whilst the company stated that in the Royal Marsden Hospital review, some patients were still alive beyond 100 months (company response to clarification question B3), the published K–M data from the Royal Marsden Hospital suggest that all patients are expected to have died by the end of Year 9.	Replace “claim”, the observation is not in dispute as the Royal Marsden study shows the K-M curve extending beyond 100 months (Figure 3A). Include “expected to have died” as the KM estimator does not show survival outcomes for patients not followed up to 9 years; only an estimate of the expected survival rate given the observations under an assumption of non-informative censoring, which may be violated by changes in treatment practice determined by enrolment period.	Thank you. The report has been corrected as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p. 104 Section 6.5 Utility values used as economic model input are misattributed. The ERG state: *"The utility value used in the PFS health state is only 0.016 lower than the general population age dependent utility"* Within the outputs of the economic model, the effective marginal health state utility value (HSUV) is a combination of the reference HSUV per PFS and PD state and the influence of patients within 6 months of death. They are not directly comparable to the constant HSUVs quoted in Table 36.	*"The utility value used in the PFS health state is only 0.016 lower than the general population age dependent utility"* should read "*The reference utility value used in the PFS health state for patients more than 6 months from death is only 0.016 lower than the general population age dependent utility"* The PFS and PD HSUVs for CheckMate 649 in Table 36 should be clearly marked as incomparable to the constant HSUVs for the other rows, e.g. "reference PFS utility" and "reference PD utility"	The ERG is drawing a comparison between HSUVs that are representative of all time in state (for other data sources) versus reference HSUVs that are modified by proximity to death for CheckMate 649. The comparison is not correct without consideration of the time-varying impact of proximity to death on the effective HSUV in the economic model states	Thank you. The report has been corrected as suggested

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
p.129 Section 9.2 Appendix 2: Microsoft Excel revisions made by the ERG to the company's model, Rows 4 and 5, 'modified formulae' column	Row 4: =IF(Revision1=0,1/((1+dblDscntCosts)^$H38),1/((1+dblDscntCosts)^($H38-1))) Copy formula to range I39:I1342 Row 5: =IF(Revision1=0,1/((1+dblDscntBenefits)^$H38),1/((1+dblDscntBenefits)^($H38-1))) Copy formula to range J39:J1342	Discounting not applied correctly: at row 38, 1.035 years have passed, therefore discounting should be applied based on 0.035 years as opposed to 0.038 years (H12 value)	Making the change identified by the company increases the ICER by less than £10 per QALY gained. Further, it is unclear that a value of 0.035 should have been used instead of 0.038. No change required

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

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: **Thursday 10 June 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	**Bristol-Myers Squibb Ltd**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	[redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Executive Summary

Updated Patient Access Scheme

Ahead of addressing the key issues presented in the Technical Engagement response, there is one further update to the data to be presented: an updated PAS. For clarity, all results and argumentation presented in this response apply this updated PAS. The impact of this update is described briefly below and in appendices.

The agreed PAS for nivolumab has been updated from [redacted]% to [redacted]% impacting on vial costs as follows:

- Nivolumab costs without PAS[1]
    - £2,633.00 per 240 mg (24 mL) vial;
    - £1,097.00 per 100 mg (10 mL) vial;
    - £439.00 per 40 mg (4 mL) vial.
- Nivolumab costs with PAS
    - [redacted] per 240 mg (24 mL) vial;
    - [redacted] per 100 mg (10 mL) vial;
    - [redacted] per 40 mg (4 mL) vial.

This updated PAS has been applied within this response. For reference, previous base case analyses including this PAS are provided in Table 1 alongside the company's preferred base case post-technical engagement.

Table 1. Cost-effectiveness results for model versions

Model version:	Model version 1.0	Model version 2.0	Model version 2.1	Model version 3.0
	Original company submission	**Updated company submission based on clarification questions**	**Updated PAS***	**Post technical engagement base case**
Key model changes	No changes, using former PAS	Updated discounting application within the model. Increased baseline age to 64.15 years. Using former PAS	Updated PAS, and other changes as applied in version 2.0	Updated death on progression parameters, and treatment modifiers. Other changes as applied in v2.1
DBL used:	**July 2020**	**July 2020**	**July 2020**	**July 2020**
NIVO + FOLFOX vs FOLFOX	£47,840	£52,549	£48,804	£51,808
NIVO + XELOX vs XELOX	£45,172	£49,550	£45,692	£48,832
*Analysis results presented in 'Key issues for engagement' below are based on modifications to this model version (referred to as model v2.1) Further detail of the changes to the model made at this technical engagement stage are detailed in the "Summary of changes to the company's cost-effectiveness estimate(s)"				

Updated outcomes from CheckMate 649

Following submission, limited outcomes from an updated database lock from CheckMate 649 ([redacted]) have become available. Full analysis of this data has not yet become available. However, the available data is [redacted] with the previously database lock, providing extended follow-up and addressing uncertainty around maintenance of outcomes.

For the CHEMO arm, median OS was [redacted] based on extended follow-up, while median OS [redacted] for the NIVO+CHEMO arm. However, the Kaplan-Meier data provided in Figure 1 to Figure 4 demonstrate that overall outcomes are [redacted] compared with the previous database lock.

Table 2. CheckMate 649 key efficacy results ([redacted] DBL)

Endpoint	All randomised patients		All randomised patients with PD-L1 CPS ≥5	
	NIVO+CHEMO (N=789)	CHEMO (N=792)	NIVO+CHEMO (N=473)	CHEMO (N=482)
OS				
Median OS [95% CI][a], months	[redacted]	[redacted]	[redacted]	[redacted]
HR (CI)[b]	[redacted]		[redacted]	
PFS per BICR				
Median PFS [95% CI][a], months	[redacted]	[redacted]	[redacted]	[redacted]
HR (CI)[b]	[redacted]		[redacted]	

[a]based on Kaplan Meier estimates; [b]Stratified Cox proportional hazards model.
BICR: blinded independent central review; CHEMO: chemotherapy; CI: confidence interval; CPS: combined positive score; NIVO: nivolumab; OS: overall survival; PD-L1: programmed death ligand-1; PFS: progression-free survival..

[redacted]

Figure 1. CheckMate 649 overall survival in all randomised patients ([redacted] DBL)

[redacted]

Figure 2. CheckMate 649 overall survival in patients with PD-L1 CPS ≥5 ([redacted] DBL)

[redacted]

Figure 3. CheckMate 649 progression-free survival in all randomised patients ([redacted] DBL)

[redacted]

Figure 4. CheckMate 649 progression-free survival in patients with PD-L1 CPS ≥5 ([redacted] DBL)

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
Issue 1 – limited population and comparators included in the decision problem	No	**CheckMate 649 was designed to assess the clinical effectiveness of nivolumab combination therapy in a population appropriate to UK clinical practice, versus UK-relevant comparators and reporting outcomes important to patients** **Population:** Per the CheckMate 649 protocol, patients with known HER2-positive status were excluded. Hence, the efficacy data presented in CheckMate 649 does not adequately reflect outcomes in patients with HER2-positive status. It should be noted that although HER2 positive status at baseline was reason for exclusion from CheckMate 649, some patients who were enrolled at baseline with unknown HER2 status but were tested during the study. In the 10th July 2020 DBL, there were [redacted] subjects with HER2 positive status. However, after the DBL, the site confirmed that [redacted] of the [redacted] subjects with confirmed HER2 positive status was actually negative and that the data was entered incorrectly. This patient's data will be updated in the next DBL and the report will reflect a total of [redacted] HER2 positive subjects included in the final ITT analysis. CheckMate 649 may be considered representative of outcomes in a HER2 positive population. Although a recent UK retrospective study demonstrated that OS was significantly improved for HER2-positive patients versus HER2-negative patients (15.0 months versus 11.9 months),[2] this may be related to increased use of trastuzumab-based therapies, as opposed to differences in prognosis based on HER2 status. Further, PD-L1 expression is observed independent of HER2 status.[3] Although the expression of PD-L1 may occur slightly more frequently in HER2-negative patients than HER2-positive cohorts,[3,4] this may be related to PD-L1 assessment techniques: one study determined slightly higher PD-L1 positivity

		(defined as staining in ≥1% of tumour or immune cells) for HER2 negative patients using tumour proportion score, combined positive score and interface pattern but found numerically higher PD-L1 expression in HER2 positive patients based on staining of tumour associated immune cells. In summary, there is no data to suggest differential effect of nivolumab in HER2-positive cohort. Available evidence supports equivalent effect between HER2-positive and HER2-negative patients. Despite benefit in HER2 positive patients, it is noted that HER2 testing is standard of care for gastric cancer patients in the UK and it is assumed that patients who test positive for HER2 would preferentially receive a trastuzumab-based therapy instead of nivolumab plus chemotherapy. This assumption is aligned with NICE guidance TA208.[5] **Comparators**: Direct evidence for comparative efficacy of NIVO+CHEMO vs CHEMO may be drawn from the CheckMate 649 study, so that no meta-analysis was required. Indirect treatment comparisons deriving comparative efficacy using CheckMate 649 were presented in Company submission Document B Section B.2.10. Of the 136 unique studies that reported either OS or PFS in the SLR, 42 studies reported at least one treatment of interest for this NMA. Studies were restricted to those reporting relative outcomes in the form of HR, or Kaplan-Meier data that could be used to estimate comparative outcomes including at least two potential comparators that could be used to form a network. Studies reporting only absolute outcomes were not considered. Only studies forming part of a complete network including XELOX or FOLFOX were included in the NMA, with XELOX and FOLFOX assumed to have equivalent efficacy in line with assumptions for cost-effectiveness analysis and CheckMate 649 trial design. Clinical advice indicates that epirubicin is no longer used in the UK for 1L treatment of gastro-oesophageal cancers,[6] hence it was not used in this analysis. Additional discussion of the NMA is provided in response to Issue 3. **Outcome:** The two primary endpoints were evaluating benefit in a narrower population of patients than addressed in this submission, i.e., patients with PD-L1 CPS ≥5. However, CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%). Further, key secondary endpoints included assessment of PFS and OS in all randomised patients, so that this can be considered an appropriate approach. OS and PFS

		outcomes remained improved in the nivolumab combination therapy arm across the overall population and the PD-L1 ≥ 1 subgroup. [redacted] [redacted] Reflecting the study design and available data, the submission contains subgroup analyses for the PD-L1 subgroups; however, the population of interest is the overall population.
Issue 2 - Lack of generalisability of CheckMate 649 data	**No**	**Although CheckMate 649 was limited by study design and patient accrual, the enrolled patients can be considered representative of a UK population** **Age:** CheckMate 649 broadly reflected the baseline characteristics for patients starting chemotherapy for advanced gastric in clinical practice. As noted in the submission, median baseline age (62 years in the NIVO+CHEMO arm and 61 years in the CHEMO arm) was similar but slightly younger that for the Royal Marsden retrospective review[7] (median age: 66 years) and the COUGAR-2[8] clinical study (median age: 65 years in the docetaxel arm and 66 years in the active symptom control arm). Patients in the UK REAL-2 clinical study had similar baseline age (median age: 65 years in arm 1, 64 years in arm 2, 61 years in arm 3 and 62 years in arm 4).[9] Of note, data collected by the NHS, produced by the Cancer Research UK – Public Health England Partnership and provided by the National Cancer Registration and Analysis Service (CRUK dataset) show that 75 years is over the median age at diagnosis for patients with stomach cancer treated with chemotherapy, and that the majority are below 70 years.[10] Of the 5,840 patients who received chemotherapy for gastric cancer in this dataset, 3,357 were aged ≤69 years and 2,483 were aged ≥70 years. It is not possible to identify median age due to the broad categories of age reported; but the median age is below 70 years. Aligned with the UK data sources outlined above, NHS patients would need to be fit and eligible for treatment with chemotherapy in order to receive treatment with nivolumab combination therapy. The evidence clearly demonstrates that the focus should be on baseline characteristics of patients who are treated with chemotherapy and not the full population diagnosed with gastric cancer, as they would be significantly older than the diagnosed population. More patients eligible for treatment in UK clinical practice are in the age range closer to the CheckMate 649 trial population.

		Further, to inform technical engagement, UK clinical experts suggested that the CheckMate 649 population and CRUK dataset both seemed appropriate in terms of age, with an average patient lying between these two estimates. Hence, when considering the model and patients eligible for nivolumab; the analysis is reflective of the Checkmate 649 median baseline age and this is validated by relevant UK data sources. **ECOG status:** Compared with other UK studies,[2,8] slightly fewer patients with ECOG status of 1 were enrolled and no patients with ECOG status of 2 were enrolled. Clinical trials commonly specify performance scores as an inclusion criterion, typically based on either ECOG or Karnofsky scale. This leads to limited evidence of net clinical benefit for patients with certain performance scores, typically those with worse scores. This absence of evidence contributes to a reluctance to provide certain treatments to patients of reduced performance score. However, this is limited evidence to suggest different outcomes between patients with different performance score. A 2017 SLR and meta-analysis of RCTs assessed clinical benefit by performance score subgroups.[11] This identified 110 RCTs, with 66 (60%) reporting performance score subgroups for efficacy and none reporting subgroups for toxicity. For these 66 RCTs, pooled HRs for good performance score and reduced performance score subgroups were 0.65 (95% CI 0.61 to 0.70) and 0.67 (95% CI 0.62 to 0.72), respectively, with no difference between the two groups (p=0.68). Sensitivity analyses based on drug or cancer type and type of endpoints (OS or PFS) demonstrated similar results.[11]
Issue 3 – Company network meta-analyses do not include treatment with nivolumab+chemotherapy	**No**	**An indirect comparison for nivolumab+chemotherapy versus chemotherapies of interest was not supported by the available data. Further, this comparison was not necessary to draw the conclusion that there was no statistically significant difference in PFS or OS between FOLFOX and any other comparator.** The ERG presented several criticisms of the NMA, which are summarised as: 1. Inconsistency was not assessed in the NMA

		a. This was an acknowledged limitation due to the small size of the network, but the network represents the best available evidence for indirect comparison 2. Proportional Hazards assumption was not appropriately assessed within the NMAs. a. The ERG implies that there is evidence that the PH assumption may have been violated for one trial of OS and indicates the paper of Al-Batran et al[12] as a source. The company has assumed that the ERG is referring to Figure 5 (Figure 2c in the original publication). The company notes that these two treatments are very well matched in outcomes and that evidence of survival crossing alone is not evidence to reject the proportional hazards assumption, as such crossings can occur by chance, particularly where there are few patients at risk and there is little separation between the curves. Due to the similar composition of and mechanism of action of the treatments investigated in Al-Batran et al[12], there is no a-priori reason to suspect non-proportional hazards and there is insufficient evidence provided within this paper to suggest that proportionality of hazards has been violated.

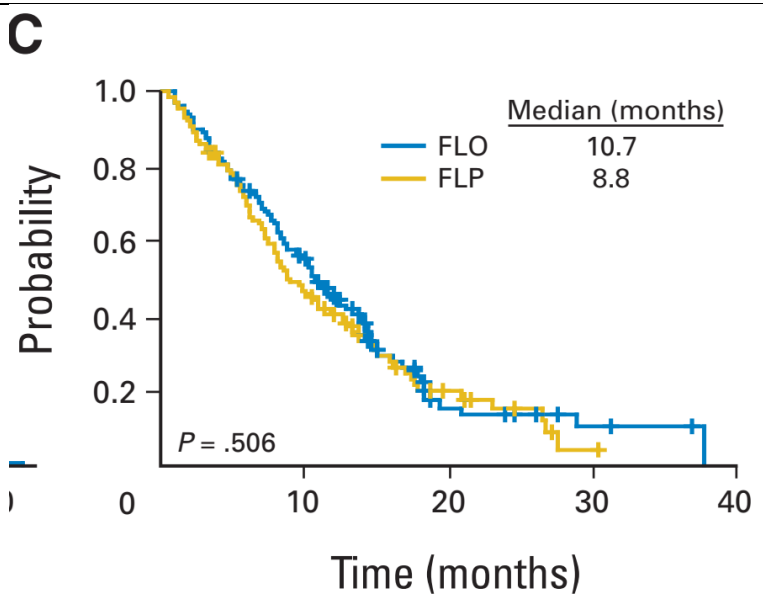

Figure 5. Al-Batran 2008[12] Figure 2C - comparison of overall survival for fluorouracil plus oxaliplatin versus fluorouracil plus cisplatin

3. Given the difference in mechanism of action between the nivolumab+chemotherapy and chemotherapy alone arm of CheckMate 649, non-proportional hazards were expected a-priori and the initial power analysis of the study was conducted upon such a basis. Given the expected and measured time-varying hazard ratio, the Cox modelled hazard ratio, as an expression of treatment effect, is dependent upon the extent of follow-up and so this result is not transitive across a network with heterogenous follow-up. As such, the treatment effect measured in CheckMate 649 was not included in the network due to the violation of the transitivity assumption and the results were not contaminated by this inappropriate data. The results derived were sufficient to support the conclusion of the NMA.

		In summary, the company believes that the NMA has been undertaken appropriately, with the best available evidence, and does acknowledge where the ERG considers there to be residual uncertainty. The company supports the conclusion that the "comparisons between chemotherapy (FOLFOX) and capecitabine+cisplatin and fluouracil+cisplatin are of limited relevance to decision makers" and so does not consider this residual uncertainty to be impactful upon the decision problem.
Issue 4 - Long-term remission health state: evidence does not support patients who have not progressed by 30 months only having background mortality	**Yes**	**There is significant evidence to support long-term remission in a proportion of patients. This evidence suggests that patients enter long-term remission between two years and three years and experience significantly reduced hazards following this point. A scenario analysis incorporating a ratio that increased the hazard of death (in comparison to the general population) led to a small increase in the ICER.** **Plausibility of long-term remission in this population** The evidence supporting plausibility of long-term remission in this patient cohort has been presented in the initial company submission and in the subsequent response to clarification questions: • Published evidence: Multiple real-world studies have observed a small proportion of patients demonstrate improved outcomes versus the overall cohort, achieving long-term remission, as detailed in Section B.2.14.1.1 of Document B.[10,12-14] This includes a UK retrospective study by the Royal Marsden Hospital,[2] which reflected NHS patients comparable to CheckMate 649, where an initial high hazard is observed followed by low hazard from approximately 36 months. At 60 months (five years), OS was 4%, with very few events occurring between 60 months and 96 months. Another UK study, COUGAR-2,[8] indicated that a small proportion of patients had prolonged survival; although follow-up is limited to 18 months, OS was 6% in the docetaxel arm and 2% in patients assigned to active symptom control. Similarly, a retrospective database study in the US showed that Kaplan-Meier data plateaued from three years and 3% remained alive at five years.[13] This benefit has been shown to be maintained long-term: Chau et al.,[14] reviewed the data from four RCTs conducted in the UK and Australia and demonstrated a five-year survival rate of 4% in patients with gastric primary lesion sites and 3% in patients with GEJ primary lesion sites. Maximum follow-up was beyond 110 months for these patients, and OS remained at 4% and 3% respectively. • Clinical expert opinion: Clinical experts contacted to support the company submission considered long-term remission to be plausible in patients who had not progressed after an extended period. Clinical advisors contacted to inform technical engagement agreed that this would be plausible, with this more likely to occur after treatment with an immunotherapy. The advisers were uncertain as to the timing or the impact of this remission on long-term outcomes. • Evidence from CheckMate 649: As noted in the company submission, evidence from CheckMate 649 was presented to support the plausibility of long-term remission in the gastric

		cancer population. Additional evidence from the updated database lock is presented to support long-term remission. Based on the [redacted] database lock, the observed PFS in CheckMate 649 showed a similar profile on both arms, visible in Figure 8, reflecting a decreasing marginal hazard, with PFS approaching an asymptote representing a fraction of patients at dramatically reduced hazard of progression or death relative to the majority of the ITT population. Consideration of the similarity of the hazard profiles over patient-follow-up suggests that the higher risk population is being exhausted at a similar rate on both arms, and so PFS benefit for nivolumab+chemotherapy is being driven by a larger LTR fraction. **Timepoint where patients are considered to have achieved long term remission** As noted in the response to clarification questions, this assumption is primarily supported by CheckMate 649, as this study has large patient numbers and patient-level data is available so that it is possible to assess the precise hazard profile and identify the hazard turning point. However, supporting evidence is available from the published literature. Several studies outlined below demonstrate survival plateaus that start at approximately 36 months, including the Royal Marsden study and a large US database study.[2,13] Within CheckMate 649, the marginal hazard of progression or death among patients who had not yet progressed decreased steadily through time and approached a plateau during trial follow-up. To the [redacted] DBL, of the [redacted] patients ([redacted] nivolumab+chemotherapy; [redacted] chemotherapy) who had [redacted] and were followed-up [redacted], [redacted]. Within the economic model, the long-term response fraction is identified by the assumption that all patients who have not progressed by a nominated time point will, from that point onwards be subject to no hazard of progression. This approach supposes the coexistence of an unidentified LTR fraction and its complement, those without long-term response (non-LTR), with the members of the non-LTR fraction being removed from the PFS state at a greater rate than those with LTR. The time at which the assumption that all patients who have not progressed are in the LTR fraction is therefore required to be one where the presence of non-LTR patients in the PFS state is negligible. However, due to the increasing proportion of patients remaining at risk being within the LTR fraction the PFS event hazard is expected to decrease rapidly prior to effective exhaustion of the non-LTR fraction, even if this sub-population should be experiencing stable or increasing hazards. This expected profile is visible in the trial data, as can be seen in **Figure 6, with the event hazard in both arms decreasing towards the general population mortality hazard. As can be seen, the marginal hazard of the nivolumab+chemotherapy arm is expected to have reached lifetable mortality within current follow-up, whilst the chemotherapy arm lags slightly. Based upon the final hazards of the smoothers extrapolated constantly, the chemotherapy arm expects an additional 4.17 years of

		progression-free survival, whilst the nivolumab+chemotherapy arm expects an additional 18.15 years of progression-free survival, which would be expected to be significantly curtailed by all cause mortality. Though it is unknown exactly when the non-LTR fraction will have formed a negligible portion of the remaining cohort pre-progression, these observations of PFS from CheckMate 649 indicate that it likely near 30 months. Due to the consistently higher hazard of progression or death in the chemotherapy arm, establishing the LTR at earlier time points is expected to favour chemotherapy, as the event rate is expected to be higher in this arm until the LTR is established. **Mortality in patients achieving long term remission** Within the company's economic model, patients who have not progressed at 30 months are considered to be in long term remission. These patients have a mortality hazard which aligns with general population all cause mortality (derived from lifetables). CheckMate 649 patients in both treatment arms demonstrated a similar profile, with the same reduction in long-term hazard observed. Among patients not progressed at 12, 18 and 24 months, hazard of death decreased on both arms (**Figure 7); very few patients who had not progressed by month 24 died under current follow-up. Due to both selection pressure and therapeutic effect, the marginal hazard would be expected to continue to decline towards background mortality at further landmarks. As can be seen, the OS hazard was predicted by several estimators to reduce to approximately match the general population in the full ITT population (**Figure 6 and **Figure 7), indicating that patient numbers and follow-up in this region were sufficient to indicate a plateauing of survival from this point. [redacted]***Figure 6. Bspline smoothed hazard of progression per BICR or death censoring for subsequent treatment – CheckMate 649, [redacted]*** *Hazards extrapolated as constant from time of last observation in survival predictions* [redacted]***Figure 7. OS conditional upon PFS to 12, 18 and 24 months; CheckMate 649, [redacted]*** The model predictions using the LTR fraction established at 30 months remained well calibrated to the updated CheckMate 649 database lock of [redacted], with [redacted] events having been observed beyond the 30 month point for establishment of the LTR fraction. Of the [redacted] events that were so far observed beyond month 24 within the trial ([redacted] patients with follow-up), [redacted] were deaths without progression. Of the [redacted] events observed beyond month 30 ([redacted] patients with follow-up), there were [redacted] progressions and [redacted] death, [redacted].

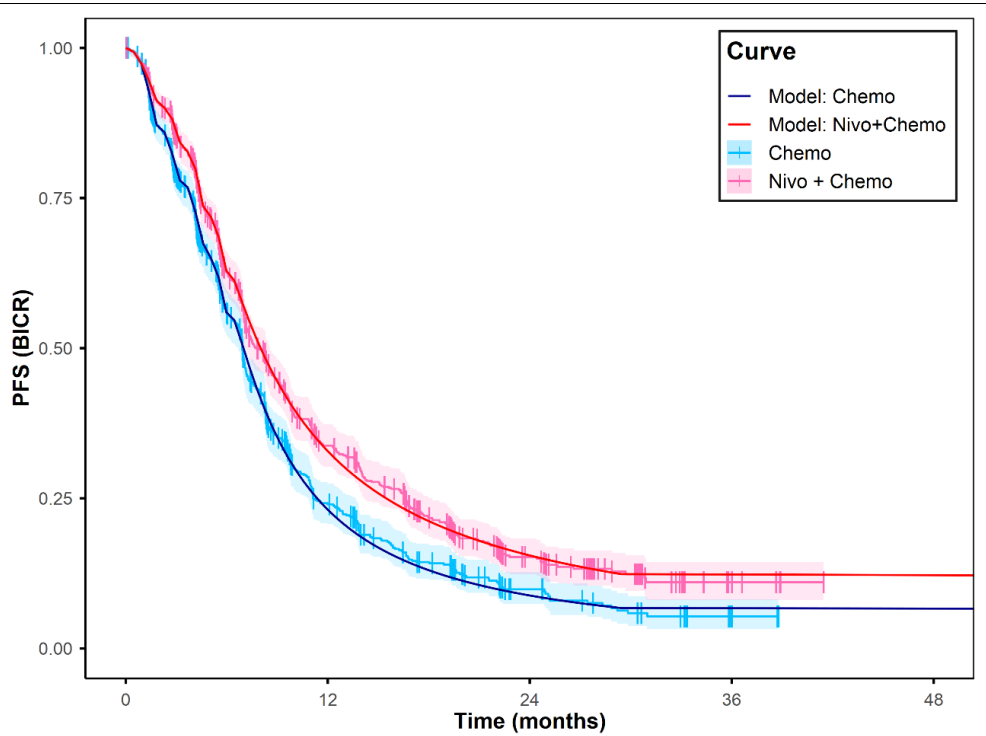

Figure 8. Model predicted PFS versus observed PFS per BICR from CheckMate 649 (Feb 2021 DBL)

In addition, OS estimates from the economic model incorporating the LTR fraction remain well calibrated to these new data, with the conditional OS after month 30 being aligned with the Kaplan-Meier estimator, as evidenced by Figure 9.

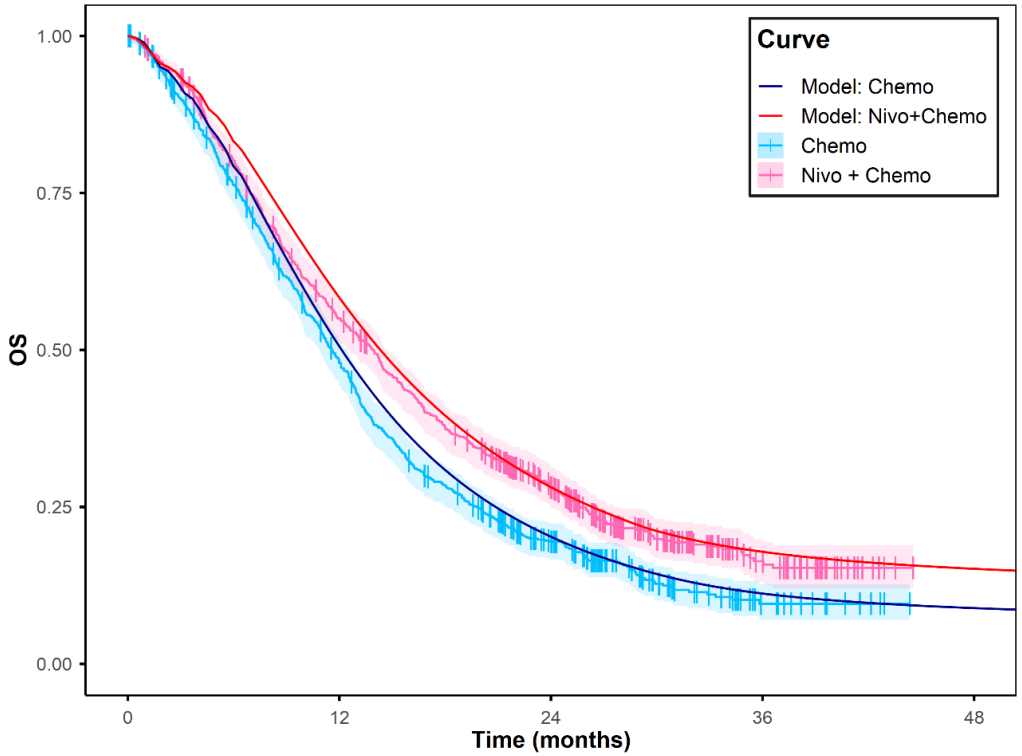

Figure 9. Model predicted OS versus observed OS from CheckMate 649 (Feb 2021 DBL)

However, the company acknowledges that there may be uncertainty of the mortality of this patient population within long-term remission, due to the length of trial follow up within the July 2020 database lock. Therefore, the company explored a scenario within the economic model to allow for a standardised mortality ratio to be applied to the long-term remission health state. A standardised mortality ratio describes whether a population is more or less likely to die than the general population, where a ratio exceeding 1 means that there is a higher risk than the general population. Incorporation of a standardised mortality ratio adjusts the hazard of death derived from lifetables over all patients in all states, inclusive of long-term remission, in either or both treatment arms. In the modelled scenario, this has been applied whereby patients who are in remission have a standardised

mortality ratio of 1.5 (i.e. patients in the remission health state have 1.5 times the risk of death than that of the general population).

Table 3. NIVO+FOLFOX vs FOLFOX – the impact of adding standardised mortality ratio in long term remission

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: with standardised mortality ratio of 1.5							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,581	2.359	1.472	[redacted]	[redacted]	[redacted]	£54,067
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 4. NIVO+XELOX vs XELOX – the impact of adding standardised mortality ratio in long term remission

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: with standardised mortality ratio of 1.5							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,408	2.359	1.472	[redacted]	[redacted]	[redacted]	£50,620

		ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied
Issue 5 – Company model generates overall survival estimates that are not in line with the first 12 months of the model time horizon	**Yes**	**The company base case has been updated with survival curves which improve the OS estimates generated by the model within the first 12 months of the model time horizon.** As suggested by the ERG, the company has re-evaluated the survival estimates produced by the model. The company has amended death on progression values to reflect outcomes using the BICR definition of survival (as per the input survival curves). The model OS outputs within the updated CEM are compared with trial data in Table 5. The estimates generated by the updated CEM, based on updated death on progression inputs, are consistently within 3% of the trial data. It should be noted that the trial data represent a population with a variety of baseline ages, whose matched general population mortality is more widely distributed than the patient at the age simulated in the economic model, which results in a lower initial hazard of mortality and a lower long-term hazard of mortality from other causes, which contributes to improved initial survival, but also curtailment of long-term benefit as those younger patients within an LTR fraction would be expected to have increased life expectancy. These features are visible in Figure 9, when comparing to the Feb 2021 DBL. ***Table 5. Estimates of overall survival – July 2020 DBL***

	Timepoint	Trial data (% alive)	Former survival modelling within the CEM		Updated survival modelling within the CEM	
			% Alive	Difference to trial	% Alive	Difference to trial
PFS (treatment arm)	0.5 years	[redacted]	[redacted]	[redacted]	62.73%	0.08%
	1 year	33.41%	32.75%	-0.66%	32.75%	-0.66%
	1.5 years	[redacted]	[redacted]	[redacted]	21.10%	0.72%
PFS (control arm)	0.5 years	[redacted]	[redacted]	[redacted]	55.84%	0.14%
	1 year	23.23%	23.04%	-0.19%	23.04%	-0.19%
	1.5 years	[redacted]	[redacted]	[redacted]	12.97%	0.05%
OS (treatment arm)	0.5 years	[redacted]	[redacted]	[redacted]	83.17%	3.03%
	1 year	54.96%	60.40%	5.44%	58.21%	3.25%
	1.5 years	[redacted]	[redacted]	[redacted]	39.42%	2.41%
OS (control arm)	0.5 years	[redacted]	[redacted]	[redacted]	79.18%	2.92%
	1 year	47.94%	52.84%	4.90%	50.46%	2.52%
	1.5 years	[redacted]	[redacted]	[redacted]	30.77%	3.11%

Table 6. NIVO+FOLFOX vs FOLFOX – the impact of changing death on progression values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: updated death on progression values							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,671	2.589	1.556	[redacted]	[redacted]	[redacted]	£50,225
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 7. NIVO+XELOX vs XELOX – the impact of changing death on progression values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: updated death on progression values							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,497	2.589	1.556	[redacted]	[redacted]	[redacted]	£46,945
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Issue 6 - High utility values in the progression free survival and progressed disease health states	**No**	**The company considers the utility values used in the economic model for progression free and progressed disease to be appropriate, as the reference health state utility values are modified using a time-to-death disutility. However, this has limited impacted on the ICER.** Although the reference utility values for the health states (PFS health state: [redacted], progressed disease health state: [redacted]) are close to the age-dependent utility values (value of [redacted] for 60 year old), the utility values are not comparable, since an additional time-to-death disutility modifier is applied to the reference utility values for health states. While it is not possible to quantify the impact of this modify on specific health state utilities, the overall impact is considerable. The time-to-death disutility ([redacted]), is applied to all patients who survived for at least 6 months during the 6 months before death. For patients who died within the first 6 months, disutility was determined by integrating a polynomial formula over the elapsed model time. This integral would equal that given by the quoted average disutility when model time was equal to 6 months. All utility values within the model (time-to-death disutility value, and health state utility values) were derived from the clinical trial data. Conversely, the health state utilities described by the ERG (from TA208, published in 2010[5]) are sourced from the wider literature, and do not incorporate a time-to-death disutility. Further, given the publication date for TA208 (2010), it is unclear how relevant these utilities are to current clinical practice. This is of particular relevance given that outcomes from TA208 (assessing trastuzumab in the first-line setting) are broadly equivalent to outcomes from TA378 (assessing ramucirumab in the second-line setting). This means that the health state utility values used within the ERG model, compared with the reference health state utility values used within the company's economic model, are not comparable. It is not feasible to separate deaths from each health state, therefore the absolute impact of this disutility on deaths from each health state (and consequently the utility of each health state) cannot be determined. However, within the submission base case analysis, inclusion of the time-to-death disutility within the company's CEM results in a reduction of [redacted] QALY for the nivolumab arm, and [redacted] for the chemotherapy arm (undiscounted). For ERG analysis, which used alternative health state utility values but included the Checkmate 649 time to death disutility, the impact of removing this disutility on health economic outcomes are shown in Table 8 and Table 9. This has a minimal impact on QALY accrual, aligned with that observed from switching to alternate values, per the ERG base case.

Table 8. NIVO+FOLFOX vs FOLFOX – the impact of removing time to death disutilities from ERG analysis

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1 with ERG utility values							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.448	[redacted]	[redacted]	[redacted]	£49,785
Scenario: ERG utility values without time to death disutility							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.509	[redacted]	[redacted]	[redacted]	£49,909
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 9. NIVO+XELOX vs XELOX – the impact of removing time to death disutilities from ERG analysis

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1 with ERG utility values							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.448	[redacted]	[redacted]	[redacted]	£46,611
Scenario: ERG utility values without time to death disutility							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.509	[redacted]	[redacted]	[redacted]	£46,727
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Issue 7 – Low model baseline population age	**No**	**CheckMate 649 can be considered relevant to UK clinical practice, but alternative scenarios for baseline age are presented** As noted in the response to Issue 2, CheckMate 649 broadly reflected the baseline characteristics for patients starting chemotherapy for advanced gastric in clinical practice. However, in order to provide an informed technical engagement response, UK clinical experts were contacted to assess typical baseline characteristics for a patient in UK clinical practice. These experts suggested that the CheckMate 649 population and CRUK dataset both seemed appropriate in terms of age, with an average patient lying between these two estimates. A scenario is provided using a mean OS of 60.15 years; however, it should be noted that the base case of 64 years may be conservative. **Alternative age scenario:** A scenario analysis was undertaken using a baseline age of 60.15 years. The results of this analysis are shown in Table 10 and Table 11. When patient age is increased to 64.15 years (base case), fewer patients are able to achieve long-term remission due to the impact of all-cause mortality in months 0-30. This has minimal impact on incremental QALYs, which increases slightly from the base case analysis to this scenario analysis. ***Table 10. NIVO+FOLFOX vs FOLFOX – the impact of changing baseline age***

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1: baseline age 64.15 years (CRUK data)							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: [redacted] years (based on clinical trial data)							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,676	2.802	1.649	[redacted]	[redacted]	[redacted]	£43,833
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 11. NIVO+XELOX vs XELOX – the impact of changing baseline age

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1: baseline age 64.15 years (CRUK data)							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: [redacted] years (based on clinical trial data)							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,503	2.802	1.649	[redacted]	[redacted]	[redacted]	£41,038

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Issue 8 – Limited cost-effectiveness results for PD-L1 subgroups.	**No**	**The licensed indication will not be restricted to the PD-L1 CPS <1 or <5 population. Additionally, the subgroup of patients with baseline PD-L1 CPS <1 and <5 is smaller and hence may be non-informative** The licensed indication is not yet finalised; all relevant data to support that indication has been provided to NICE for assessment. Clinical and cost-effectiveness data has been provided for the overall population and for the PD-L1 CPS subgroups of interest (PD-L1 CPS ≥1 and CPS ≥5), [redacted]. However, the licensed indication will certainly not be restricted to the [redacted]. In all randomised patients with PD-L1 CPS quantifiable at baseline, [redacted] and [redacted]) had a baseline PD-L1 CPS ≥1 in the NIVO+CHEMO and CHEMO arms, respectively. Hence, there are only [redacted] patients in the NIVO+CHEMO arm and [redacted] patients in the CHEMO arm with baseline PD-L1 CPS <1. This subgroup is insufficiently powered to detect differences in outcomes and the small patient numbers would not provide informative data. Similarly, [redacted] and [redacted] had a baseline PD-L1 CPS ≥5 in the NIVO+CHEMO and CHEMO arms, respectively. Although there are more patients with baseline PD-L1 CPS <5 than with

		CPS <1 ([redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm), this subgroup remains insufficiently powered to detect differences in outcomes. For this reason, cost-effectiveness data for the PD-L1 CPS score <1 or <5 subgroups are not provided.
Issue 9 - Inappropriate treatment modifier	**Yes**	**The company base case has been updated to incorporate a treatment modifier in both arms, with minimal impact on cost-effectiveness conclusions.** The approach taken within the company submission applied a treatment modifier to account for missed nivolumab doses in the NIVO+CHEMO arm only; as nivolumab dosing could not be modified, only interrupted, this treatment modifier was derived based on expected doses received versus those actually received. However, there are significant limitations to estimating the treatment modifier for the chemotherapy components, as this would need to incorporate both missed doses and dose modifications. It was determined that any treatment modification would apply similarly to the chemotherapy components of both arms and would have relatively low cost impact, so it was assumed to be negligible. However, the ERG's preference was to apply a treatment modifier to both arms or to neither arm. Based on the data available to the ERG, they removed this treatment modifier from the treatment arm (i.e. neither arm had a treatment modifier in place). Incorporating the treatment modifier provides a more accurate estimation of accrued costs in UK clinical practice; removing this treatment modifier provides an overestimate of cost accrual, particularly impacting the nivolumab arm due to the higher acquisition costs. Hence, a rough estimation of the treatment modifier was derived for the chemotherapy components for both arms using relative dose intensity; to align with this approach, the nivolumab component was also updated. This updated treatment modifier was then applied to the cost-effectiveness analyses, as suggested by the ERG. Each component had a different modifier (Table 12), and values were applied to both acquisition and administration costs. The outcomes of cost-effectiveness analysis with the updated treatment modifier values are displayed in Table 13 and Table 14. As can be seen, this does not impact greatly on cost-effectiveness, but provides a more accurate estimate of accrued costs.

Table 12. Treatment modifier values

Treatment:	Component	Treatment modifier value
FOLFOX	5-FLUOROURACIL	[redacted]
	LEUCOVORIN	[redacted]
	OXALIPLATIN	[redacted]
	5-FLUOROURACIL CONTINUOUS	[redacted]
XELOX	OXALIPLATIN	[redacted]
	CAPECITABINE	[redacted]
NIVO+FOLFOX	NIVOLUMAB	[redacted]
	5-FLUOROURACIL	[redacted]
	LEUCOVORIN	[redacted]
	OXALIPLATIN	[redacted]
	5-FLUOROURACIL CONTINUOUS	[redacted]
NIVO+XELOX	NIVOLUMAB	[redacted]
	OXALIPLATIN	[redacted]
	CAPECITABINE	[redacted]

Table 13. NIVO+FOLFOX vs FOLFOX – the impact of updating treatment modifier values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: Updated treatment modifier values							

		<table><tr><td>Nivolumab + FOLFOX</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>FOLFOX</td><td>£32,662</td><td>2.566</td><td>1.554</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£50,304</td></tr><tr><td colspan="8">ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied</td></tr></table> ***Table 14. NIVO+XELOX vs XELOX – the impact of updating treatment modifier values*** <table><tr><th>Technology</th><th>Total costs (£)</th><th>Total life years</th><th>Total QALYs</th><th>Inc. costs (£)</th><th>Inc. life years</th><th>Inc. QALYs</th><th>ICER (£/QALY)</th></tr><tr><td colspan="8">Base case for model v2.1</td></tr><tr><td>Nivolumab + XELOX</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>XELOX</td><td>£20,465</td><td>2.566</td><td>1.554</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£45,692</td></tr><tr><td colspan="8">Scenario: Updated treatment modifier values</td></tr><tr><td>Nivolumab + XELOX</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>XELOX</td><td>£19,953</td><td>2.566</td><td>1.554</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£47,482</td></tr><tr><td colspan="8">ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied</td></tr></table>
Issue 10 - NICE End of life (EoL) criteria	**Yes**	**Nivolumab plus chemotherapy meets end of life criteria, providing substantial survival benefit over standard of care** As noted in Table 43 of the ERG report, the ERG agrees that available data suggest that life expectancy for the population of interest is <24 months. However, the ERG raises uncertainty around the degree of benefit for NIVO+CHEMO versus standard of care. Based on the original database lock from CheckMate 649, NIVO+CHEMO was associated with a median OS of 13.83 months compared with 11.56 months for current treatment (i.e., chemotherapy alone), indicating substantial survival benefit based on median OS data alone (2.27 months). This

		median OS benefit increases to 3.29 months in the PD-L1 CPS ≥5 population. However, the OS data from the trial are not yet complete and end of life criteria typically accounts for mean OS. In the updated company base case (outlined at the end of this document), the predicted mean OS benefit for NIVO+CHEMO is 1.174 years. Further, the ERG preferred scenario reflects incremental life years of 0.717 for NIVO+CHEMO versus CHEMO, substantially exceeding the three-month benefit criteria. Additionally, using the updated database lock from CheckMate 649, NIVO+CHEMO was associated with a median OS of [redacted] months compared with [redacted] months for chemotherapy alone, indicating median OS benefit of [redacted] months. This median OS benefit increases to [redacted] months in the PD-L1 CPS ≥5 population. Based on this evidence, NIVO+CHEMO meets both end of life criteria for the indication of previously untreated patients with gastric cancer.

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
None			

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
I**ssue 4:** long term remission mortality	Patients not progressing after 30 months experience mortality determined by lifetables only (i.e. general population all cause mortality)	Patients not progressing after 30 months experience mortality based on lifetables, and a standardized mortality ratio of 1.5, i.e. greater hazard of mortality than general population all cause mortality.	**No update to the base case. Scenario analysis only.** **ICER (cost per QALY):** **NIVO+FOLFOX:** No change to base case **NIVO+XELOX:** No change to base case
Issue 5: overall survival	Death on progression parameters using per investigator values	Death on progression parameters updated to per independent review committee values	**ICER (cost per QALY):** **NIVO+FOLFOX: £50,225** **NIVO+XELOX: £46,945**
Issue 9: treatment modifier	Treatment modifier to account for dose intensity, missed doses, applied to nivolumab arm only	Treatment modifier to account for dose intensity, missed doses, applied to both arms	**ICER (cost per QALY):** **NIVO+FOLFOX: £50,304** **NIVO+XELOX: £47,842**

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	**Incremental QALYs:** NIVO+FOLFOX vs FOLFOX: [redacted] NIVO+FOLFOX vs XELOX: [redacted]	**Incremental costs:** NIVO+FOLFOX vs FOLFOX: [redacted] NIVO+FOLFOX vs XELOX: [redacted]	**ICER (cost per QALY):** NIVO+FOLFOX vs FOLFOX: £51,808 NIVO+FOLFOX vs XELOX: £48,832

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Appendix: Cost-effectiveness results after technical engagement

Table of Contents

Tables and Figures

B.1 Summary of cost-effectiveness results

Note: all ICERs presented below apply the updated PAS for nivolumab of [redacted].

Table 1 presents the summary of cost-effectiveness outcomes. Each row represents the cumulative impact of the additional assumptions and it runs from the NICE submission company base case down to the updated company base case.

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	
		FOLFOX	XELOX
NICE submission pre-technical engagement base case			
-	NICE submission pre-technical engagement [redacted] DBL with initial PAS	£47,840	£45,172
-	NICE submission pre-technical engagement [redacted] DBL with updated PAS, updated discounting, and increased baseline age – model v2.1	£48,804	£45,692
Issue 5: OS estimates not in line with first 12 months of model time horizon			
1	Changing death on progression values	£50,225	£46,945
Issue 9: inappropriate treatment modifier			
2	Updated treatment modifier	£50,304	£47,482
Company base case post-technical engagement – thereafter "base case"			
-	**Company base case**	**£51,808**	**£48,832**

DBL: database lock; FOLFOX: 5-FU, folinic acid and oxaliplatin; OS: overall survival; PD: progressed disease: PFS: progression free survival; XELOX:capecitabine and oxaliplatin .

B.1.1 Base-case results

B.1.1.1 Base-case incremental cost-effectiveness analysis results

Total discounted costs associated with NIVO+CHEMO (with PAS), accrued over the modelled time horizon, were predicted to be [redacted] for NIVO+FOLFOX and [redacted] for NIVO+XELOX. By comparison, total discounted costs associated with comparators were notably lower. Incremental discounted costs for NIVO+FOLFOX were predicted to be [redacted] (versus FOLFOX), and for NIVO+XELOX were predicted to be [redacted] (versus XELOX), under base case assumptions. The resulting ICER estimates for NIVO+CHEMO were £51,808 per QALY (NIVO+FOLFOX versus FOLFOX) to £48,832 per QALY (NIVO+XELOX versus XELOX).

The results of the base-case analysis are summarised in Table 2 and Table 3.

Table 2. NIVO+FOLFOX base-case results

	NIVO+FOLFOX	FOLFOX
Patient level survival (undiscounted)		
Median ToT (years)*	[redacted]	0.422
Mean ToT (years)*	[redacted]	0.580
Median PFS (years)	[redacted]	0.613
Mean PFS (years)	[redacted]	1.993
Median OS (years)	[redacted]	1.035
Mean OS (years)	[redacted]	2.591
Patient-level progression		
Time in pre-progression (years)	[redacted]	0.780
Time in long term remission (years)	[redacted]	1.211
Time in post-progression (years)	[redacted]	0.598
Costs (with PAS)		
HS costs	[redacted]	£11,105
Treatment costs	[redacted]	£16,417
AE costs for initial therapy	[redacted]	£429
Discontinuation costs	[redacted]	£43
Death costs	[redacted]	£5,129
Total costs	[redacted]	£32,694
Health benefits		
HS QALYs	[redacted]	1.618
Age-dependent utility	[redacted]	0.000
Adverse event utility	[redacted]	-0.001
Time-to-death utility	[redacted]	-0.061
Total QALYs	[redacted]	1.556
Total LYs (undiscounted)	[redacted]	2.589
Incremental results		
Incremental total costs	-	[redacted]
Incremental QALYs	-	[redacted]
Incremental LYs (undiscounted)	-	[redacted]
Cost/QALY	-	**£51,808**

AE: adverse event; HS: health state; LY: life year; OS: overall survival; PFS: progression free survival; QALY: quality-adjusted life year; ToT: Time on Treatment.

Table 3. NIVO+XELOX base-case results

	NIVO+XELOX	XELOX
Patient level survival (undiscounted)		
Median ToT (years)*	[redacted]	0.422
Mean ToT (years)*	[redacted]	0.580
Median PFS (years)	[redacted]	0.613
Mean PFS (years)	[redacted]	1.993
Median OS (years)	[redacted]	1.035
Mean OS (years)	[redacted]	2.591
Patient-level progression		
Time in pre-progression (years)	[redacted]	0.780
Time in long term remission (years)	[redacted]	1.211
Time in post-progression (years)	[redacted]	0.598
Costs (with PAS)		
HS costs	[redacted]	£11,105
Treatment costs	[redacted]	£3,708
AE costs for initial therapy	[redacted]	£429
Discontinuation costs	[redacted]	£43
Death costs	[redacted]	£5,129
Total costs	[redacted]	£19,985
Health benefits		
HS QALYs	[redacted]	1.618
Age-dependent utility	[redacted]	0.000
Adverse event utility	[redacted]	-0.001
Time-to-death utility	[redacted]	-0.061
Total QALYs	[redacted]	1.556
Total LYs (undiscounted)	[redacted]	2.589
Incremental results		
Incremental total costs	-	[redacted]
Incremental QALYs	-	[redacted]
Incremental LYs (undiscounted)	-	[redacted]
Cost/QALY	-	**£48,832**

AE: adverse event; HS: health state; LY: life year; OS: overall survival; PFS: progression free survival QALY: quality-adjusted life year; ToT: Time on Treatment.

B.1.2 Sensitivity analyses

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses 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.

B.1.2.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (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, probabilities and proportions: beta). These analyses were 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 were sampled independently, with the exception of semi-parametric survival estimates, where parameters associated with individual survival function were sampled using a common random number.

Several inputs were 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.

In order to enable the model results to converge to a sufficient degree of accuracy, 1,000 simulations of the model were required.

B.1.2.1.1 PSA results

The ICER scatterplots for the base case analysis, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 1 and Figure 2, while the cost-effectiveness acceptability curves (CEAC) are presented in Figure 3 and Figure 4.

Figure 1. ICER scatterplot: Nivolumab + FOLFOX versus FOLFOX

Figure 2. ICER scatterplot: Nivolumab + XELOX versus XELOX

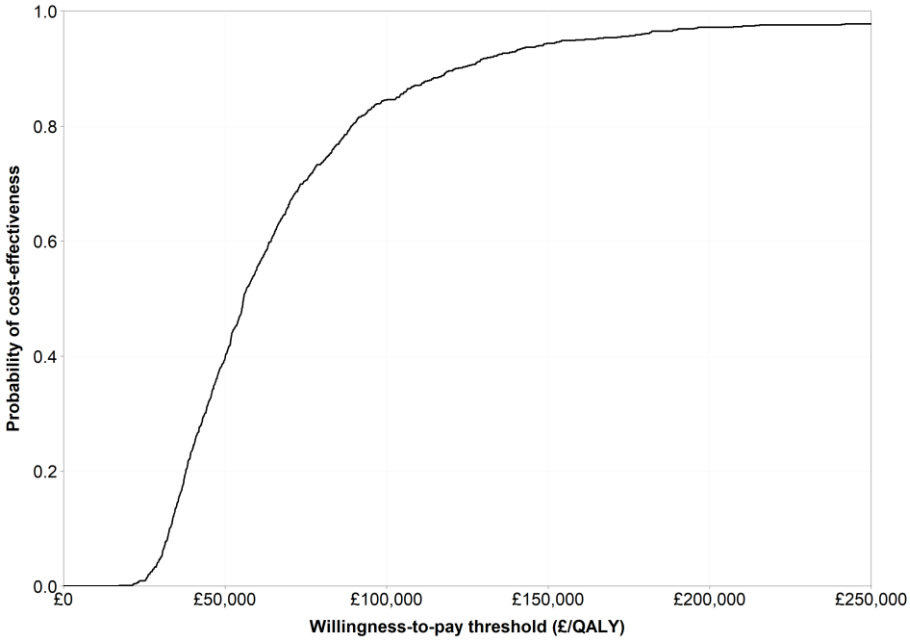

Figure 3. Cost-effectiveness acceptability curve: Nivolumab + FOLFOX versus FOLFOX

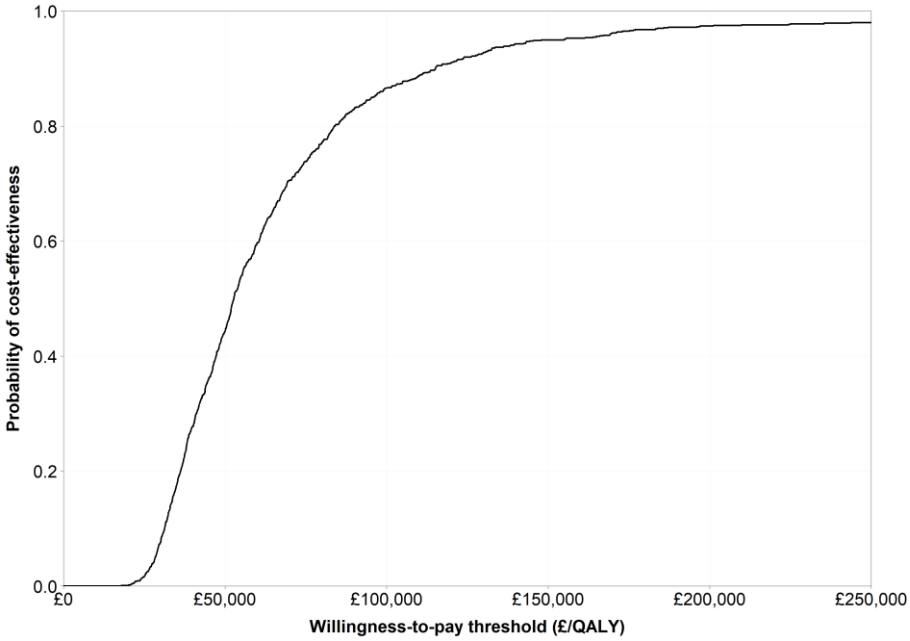

Figure 4. Cost-effectiveness acceptability curve: Nivolumab + XELOX versus XELOX

Based on this analysis, the probability that nivolumab + FOLFOX is cost-effective versus FOLFOX is estimated to be [redacted]% at a willingness-to-pay threshold of £50,000 per QALY, and the same probability for nivolumab + XELOX versus XELOX is estimated to be [redacted]%. The base case results are presented in Table 4 and Table 5.

Table 4. Base case results (probabilistic): Nivolumab + FOLFOX versus FOLFOX

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£53,444**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 5. Base case results (probabilistic): Nivolumab + XELOX versus XELOX

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,389**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

B.1.2.2 Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, regarding the following assumption and parameters:

- Time horizon (32 and 48 years)
- Discounting: costs (0% and 6%)
- Discounting: benefits (0% and 6%)
- Baseline characteristics: age (± 20%, impacting on all-cause mortality)
- Baseline characteristics: sex (0% and 100% male, impacting on all-cause mortality)
- Life table mortality rates (± 20%)
- Health state costs: pre-progression and post-progression (± 20%)
- Health state costs: death (± 20%)
- Adverse event costs (± 20%)
- Health state utility: pre-progression and post-progression (± 20%)
- Adverse event disutility (± 20%)

Note; where (± 20%) is specified, the mean value is multiplied by 0.8 or 1.2 so to assess the impact of a 20% change in a value.

Results of the deterministic sensitivity analysis are presented in Figure 5 and Figure 6. These figures demonstrate the impact of specific parameters on ICER estimates. In both cases, the factors with the greatest impact on the ICER were baseline age of patients, discounting, and age-dependent utilities.

In the majority of scenarios, the ICER for NIVO+CHEMO versus FOLFOX stayed near the £50,000 per QALY willingness-to-pay threshold; scenarios where the ICER exceeded the £50,000 threshold included the value increasing the benefits discounting, as well as increasing the baseline age of patients and the age-dependent utility decrements.

In the majority of scenarios, the ICER for NIVO+CHEMO versus XELOX stayed near the £50,000 per QALY willingness-to-pay threshold; scenarios where the ICER exceeded this threshold included increasing the benefits discounting, baseline age of patients and the age-dependent utility decrements.

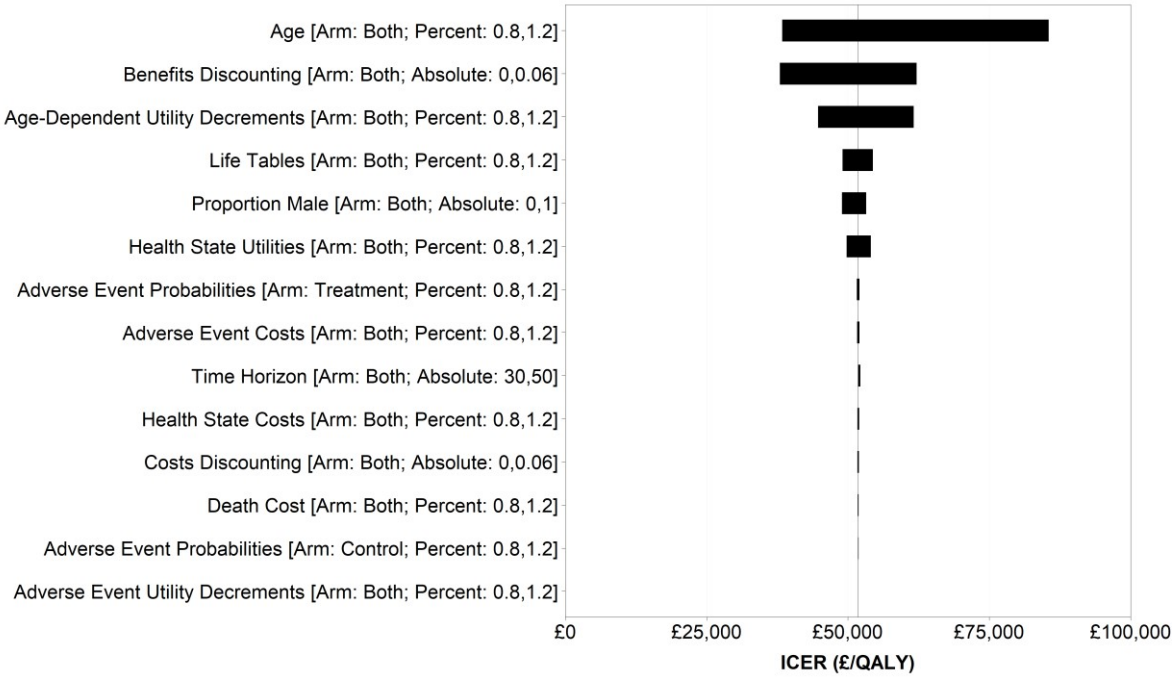

Figure 5. Deterministic sensitivity analysis for nivolumab + FOLFOX versus FOLFOX: impact on ICER

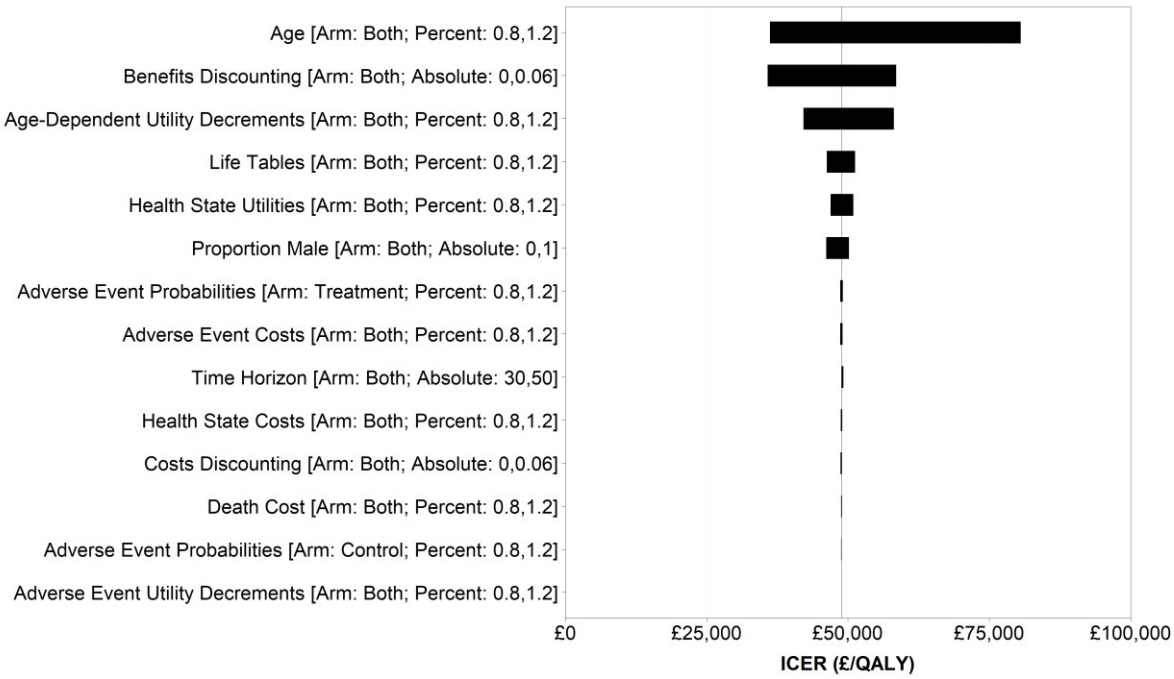

Figure 6. Deterministic sensitivity analysis for nivolumab + XELOX versus XELOX: impact on ICER

B.1.2.3 Scenario analysis

B.1.2.3.1 Efficacy by PD-L1 CPS subgroup

CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%). However, the two primary endpoints evaluated the benefit of NIVO+CHEMO in patients with PD-L1 combined positive score (CPS) ≥5. This allowed for the evaluation of the benefit of NIVO+CHEMO in three subgroups determined by CPS score: CPS ≥ 1 (Table 6) and CPS ≥ 5 (Table 7). The results demonstrated a reduction in ICERs for both comparisons that increased with a higher CPS score threshold.

Table 6. Scenario analysis: results in CPS ≥1 subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,593**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,389**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

Table 7. Scenario analysis: results in CPS ≥5 subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,659**
Comparison B							
NIVO+CHEMO	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,973**

*Applied to both NIVO+FOLFOX and NIVO+XELOX

FOLFOX = Fluorouracil, oxaliplatin, folinic acid; ICER, incremental cost-effectiveness ratio; Inc.: incremental; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; XELOX = Capecitabine, oxaliplatin

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

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 **Thursday 15 May 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 [redacted], all information submitted under [redacted] 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 untreated advanced gastric or gastro-oesophageal junction cancer and current treatment options	
About you	
1. Your name	**Wasat Mansoor**
2. Name of organisation	**Christie Hospital NHS Foundation Trust**
3. Job title or position	**Professor, Consultant Medical 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 untreated advanced gastric or gastro-oesophageal junction cancer? **x**☐ a specialist in the clinical evidence base for untreated advanced gastric or gastro-oesophageal junction cancer or technology? ☐ 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	☐ yes, I agree with it ☐ no, I disagree with it **x**☐ 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.)

nominating organisation's submission)	
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 untreated advanced gastric 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 improve survival. Within this condition improvement in survival is the main unmet need. The median survival for Her-2 negative patients (approx. 85% of all patients) remains less than 12 months and treatments options are limited relative to options for other cancers
9. What do you consider a clinically significant treatment	An improvement in median overall survival of 3 or more months with improvement or no deterioration in QOL compared to the control arm.

response? (For example, a reduction in tumour size by x cm, 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 untreated advanced gastric or gastro-oesophageal junction cancer?	Yes, effective treatment options are still limited and remain an important unmet need. We continue to have to use myelosuppressive chemotherapy options which offer modest response rates and modest survival benefits. Where we have had the opportunity to use biomarker driven treatment options (eg traztusumab), the outcomes have been more impressive
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	For Her-2 negative non resectable or stage IV cancer patients, most institutions are using doublet chemotherapy which included oxaliplatin and capecitabine. This recommendation has now also been published by Augis and supported by trials (eg GO-2 , Symour M et al, JAMA).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, ESMO, NICE
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is well defined. The major variation is in the use of doublet or triplet chemotherapy (as described in section 11), however, most institutions are now starting to use doublet chemotherapy options. At second line, most centres treat with a taxane therapy and beyond this, best supportive care is accepted as the SOC.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	My recommendation would be to use this technology for patients where they have been shown to have CPS>=5 (as per the primary end point of the Checkmate 649 trial). To do this, the diagnostic pathway would need to be changed to accommodate this test. Ideally, the test would need to be done as a reflex test rather than at request (because these patients relapse rapidly so ideally, need to be started on the correct regimen from the beginning of treatment). We must learn from our experience of HER-2 testing which was not generally done by reflex testing, so, Traztusumab often started after patients had typically had many cycles of chemotherapy.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as an out-patient service. No alteration in the timing of CT scans. More scans will be required for the extra cycles given to the patients who are doing well.
• How does healthcare resource use differ between the technology and current care?	The diagnostic pathway will alter with the requirement of CPS scoring (assuming this is approved). Patients have more median cycles of treatment with the technology compared to current SOC therapy. To that end, more out-patient visits will be required and more re-staging CT scans will be required.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology will be used in Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The facility and the pathology expertise to do the CPS testing

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, it is expected to provide a clinically meaningful improvement in survival with an associated stabilisation in QOL
• Do you expect the technology to increase length of life more than current care?	Yes – especially for those patients demonstrating a CPS>=5
• Do you expect the technology to increase health-related quality of life more than current care?	I expect the HR-QOL to be maintained / stabilised for a longer period of time than the current care can achieve
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be especially effective for those patients with a CPS>=5 and in contrast, the technology would work proportionally less well as the CPS reduces
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	Nivolumab is a well-tolerated immune therapy which is now well established in oncology care. It is not expected that it would make it more or less difficult to give to patients or for patients to tolerate. It is important to note, however, that nivolumab has a different side effect profile to the chemotherapy it will be given with. Healthcare professionals and

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.)	patients will have to be aware of this. Although this will not require any specific testing, if clinical situations arise which raise suspicion of immunotherapy toxicity, investigations and treatment maybe required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, radiological progression, clinical progression or intolerance to the therapy would stop treatment. As discussed, the CPS testing would also be pre-treatment stop/start signal
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?	The treatment pathway will alter with respect to how long patients remain on 1st line therapy and in the 'remission' state due to the superior efficacy of this technology. Patients will, therefore, maintain a better HR QOL level for longer than with current treatments.
18. Do you consider the technology to be innovative in its potential to make a significant and	Yes

substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, the median survival for patients with CPS>=5 have improved survival beyond 12 months. This constitutes a watershed moment for this cancer
• Does the use of the technology address any particular unmet need of the patient population?	Yes, in the context of the statement above, it offers patients a survival outcome which is superior to a terminal prognosis
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?	As per the checkmate 649 trial, there were no safety concerns for chemotherapy + nivolumab regimen compared to chemotherapy alone. No new safety signals were identified in the trial or are expected in real world practice.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, in the trial, the XELOX regimen used capecitabine at a dose of 1000mg/m^2 from days 1 to 14. Currently, most people use capecitabine in this regimen according to the REAL 2 EOX regimen which is capecitabine 1000mg/m^2 over 21 days. The total capecitabine dose is approximately the same in both regimens. The 2 versions of this regimen are interchangeable.

In addition to the comments on generalisability of CheckMate 469 identified as key issues by the Evidence Review Group in its Executive Summary, the ERG also noted clinical advice suggesting that XELOX doses in CheckMate 469 are different to doses used in the NHS. Please share your thoughts on this.	Doublet vs triplet chemotherapy: this has been covered previously. In UK practice most people are using doublet chemotherapy by dropping epirubicin.
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Median OS, HR QOL, Response Rates
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but	No

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. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA191, TA208 and NG83?	No
23. How do data on real-world experience compare with the trial data?	As evidenced by audits done of our practice where we have used trial data as a comparator, the data is very comparable
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

24b. Consider whether these issues are different from issues with current care and why.	NA

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 – limited population and comparators included in the decision problem ***Population*** *The ERG notes that clinical evidence may have been provided for a narrower population than defined in the scope issued by NICE.* • *No evidence for people with HER2-positive disease as CheckMate 649 excluded people with known HER2-positive disease* • *Primary outcomes from CheckMate 649 were collected for people with PD-L1 CPS≥5* ***Comparators*** *Clinical effectiveness and cost effectiveness estimates are presented only for nivolumab +*	• *No evidence for people with HER2-positive disease as CheckMate 649 excluded people with known HER2-positive disease – this is correct. Patients with HER2 positive disease would be given targeted chemotherapy (traztusumab)* • *Primary outcomes from CheckMate 649 were collected for people with PD-L1 CPS≥5 – Yes, primary endpoint was mOS for patients with CPS>=5* •

chemotherapy (FOLFOX [fluorouracil + folinic acid + oxaliplatin] or XELOX [capecitabine + oxaliplatin]) vs chemotherapy (FOLFOX or XELOX) (based on CheckMate 649. *No clinical evidence is presented in the company submission for the comparison of nivolumab + chemotherapy versus:* • *The doublet chemotherapy regimens fluorouracil + cisplatin or oxaliplatin, and capecitabine + cisplatin (n.b. a comparison of fluorouracil + cisplatin, and capecitabine + cisplatin with chemotherapy was included in a network meta-analysis [NMA; see ERG issue 3], but no comparisons vs. nivolumab+chemotherapy were made).* • *Trastuzumab with cisplatin plus capecitabine or fluorouracil in the HER2-positive population (n.b. a comparison of trastuzumab + fluorouracil + cisplatin with chemotherapy was carried out in a NMA [see ERG issue 3]), but no comparisons vs. nivolumab+chemotherapy were made).* • *Only a narrative summary of the clinical evidence was available for epirubin-containing triplet chemotherapy combinations.* *Cost-effectiveness results presented by the company in addition to the base case:* • *scenario analyses comparing nivolumab + chemotherapy with cisplatin + fluorouracil and with cisplatin + capecitabine.*	

Any comments on the population and comparators addressed in the company submission are welcome. This may include your thoughts on whether clinical effectiveness of nivolumab + chemotherapy has been demonstrated in the whole population who may have it in clinical practice, whether the data from the clinical trial is generalisable to the whole population and whether data has been provided comparing nivolumab + chemotherapy therapy with all treatments currently used in clinical practice.	
Issue 2 - Lack of generalisability of CheckMate 649 data *The ERG consider that people in CheckMate 646 are younger and fitter than people who would be treated in clinical practice.* What is your clinical opinion on the generalisability of the CheckMate 649 trial results to NHS practice?	I agree, the trial patients have a median age of 61- 62 compared to the average of a uk patient which is higher. However, fitness for therapy is decided by performance status rather than age. In the absence of morbidity scoring (eg Carlson score etc) in the trial or in general practice, the correlation between age and fitness for therapy in both trial and real world was largely made by assessing performance status. In the trial and in general practice, chemotherapy is given to those patients with performance status 0/1. Based on the above, the generalisability of the trial to NHS practice is reasonable and representative.
Issue 3 – Company network meta-analyses do not include treatment with nivolumab+chemotherapy *The ERG considers that results from the company NMAs are of limited use to decision-makers:* • *out of the three included trials, one trial only recruited patients with HER2-positive disease and level of HER2-positive disease of patients participating in the other two trials is unknown*	

• *there is uncertainty around the size and direction of impact of missing data on prognostic factors* • *there is uncertainty around the validity of some of the overall survival (OS) and progression free survival (PFS) proportional hazards assumptions for trials included in the network* *No clinical effectiveness results were presented for the comparison with nivolumab+chemotherapy. The company considered that including nivolumab+chemotherapy in the network was not appropriate as nivolumab has a different mechanism of action, survival profile and distribution of events to other treatments in the network. It presented results for FOLFOX (XELOX is assumed to be of equal efficacy as FOLFOX) vs:* • *fluorouracil +cisplatin* • *capecitabine+cisplatin, and* • *trastuzumab+capecitabine+cisplatin* *Hazard ratios estimated from the NMAs were then applied to the FOLFOX arm in CheckMate 649.* *The NMAs results are not used in the company's base case or ERG's preferred analysis.* Any comments on the company's NMAs are welcome.	
Issue 4 - Long-term remission health state: evidence does not support patients who have not	In the metastatic state, it is reasonable to consider that people who are disease free at 30 months have the same chance of dying as people without the condition

progressed by 30 months only having background mortality *The company modelling assumes that patients who have not progressed by 30 months enter a long-term remission health state in which mortality is equal to background mortality. ERG says this effectively means that people who have entered the long-term health state are cured.* *The ERG considers that this assumption is not supported by the evidence presented by the company and removes this assumption from its preferred base case. This has a large impact on the estimated cost effectiveness results and increases the incremental cost effectiveness ratio.* Any comments on the company's long-term remission assumption are welcome.	(effectively cured). The caveat to this is that people can relapse beyond this time rarely.
Issue 5 – Company model generates overall survival estimates that are not in line with the first 12 months of the model time horizon *At 12 months, the modelled proportions of patients alive in the nivolumab+chemotherapy and chemotherapy arms are higher than the proportions of CheckMate 649 trial patients alive at this time point.* *As the company model does not reflect CheckMate 649 trial survival estimates over this short time frame, confidence in model long-term survival projections is*	It is not clear why the company estimation of 12 month survival is high. For the chemotherapy arm, the Royal Marsden RWE data suggests 44% which would be more in line with my thinking. The 649 data reports 48% which can be accounted for by selection bias.

limited. As model OS projections are not reliable, model cost effectiveness results cannot be reliable. Any comments on OS estimates are welcome.	
Issue 6 - High utility values in the progression free survival and progressed disease health states *The company used utility values derived from CheckMate 649 trial data. These values appear high compared to population norms, values used in previous NICE technology appraisal (TA) submissions, and published studies in advanced gastric cancer.* *ERG used lower utility values (TA280) in its preferred base-case.* Any comments on utility values are welcome.	
Issue 7 – Low model baseline population age *The company's model baseline population mean age is [redacted] years (mean baseline age of CheckMate 649 trial population). This age is lower than the average age suggested by the ERG's clinical advisor and lower than the average age reported in some UK sources.* *The ERG prefers to use baseline population mean age of 64.15 based on Cancer Research UK data as provided in company's scenario analysis.* Any comments on the model's baseline population mean age are welcome.	Would agree with the ERG viewpoint. Low age in trial reflects younger patients in SE Asia

Issue 8 – Limited cost-effectiveness results for PD-L1 subgroups *It is stated in the final scope issued by NICE that results from subgroup analyses by level of tumour PD-L1 expression would be considered if evidence allowed.* *Whilst the company provided cost-effectiveness results for the PD-L1 CPS≥1 and PD-L1 CPS≥5 subgroups, no cost-effectiveness results results or Kaplan Meier data were provided for PD-L1 CPS<1 and PD-L1 CPS<5 subgroups.* *The ERG considers the sample sizes for the CPS<1 and CPS<5 populations in the CheckMate 649 trial are sufficient for the company to undertake cost effectiveness analyses.* Any comments on the cost-effectiveness of the PD-L1 CPS subgroups are welcome. This may include your thoughts on differences in clinical effectiveness across the PD-L1 subgroups or the use of PD-L1 testing in gastric or gastro-oesophageal junction cancer.	As per the ERG view, because the primary end point for this study was mOS for CPS>=5 patients, I think this is the relevant population that needs to be considered as this is where the biggest efficacy gains are
Issue 9 - Inappropriate treatment modifier *The company applied treatment modifiers to the nivolumab costs to account for missed doses in CheckMate 649. The ERG considers that it is inappropriate to apply a treatment modifier to the costs of only one of the treatments considered in the company base case analyses.*	It is not necessarily so that when nivolumab doses are missed that chemo doses will also be missed. Nivolumab toxicity is a separate entity to chemotherapy toxicity

In the absence of evidence from CheckMate 649 trial the number of missed chemotherapy doses (in both arms), the ERG removed the nivolumab treatment modifier from its preferred base-case. Any comments on the use of a treatment modifier in the model are welcome.	
Issue 10 - NICE End of life (EoL) criteria *The ERG considers that the available data suggest that life expectancy for the population described in the final scope issued by NICE is <24 months. However, when estimating median OS, the ERG highlights that results from the CheckMate 649 trial show that a gain of ≥3 months was only evident for the PD-L1 CPS≥5 subgroup; a median OS gain of ≥3 months is not demonstrated for the whole population.* *The ERG identified weaknesses in the company's approach to generating OS estimates (see issue 5 for more information) that mean that any predicted survival gain is highly uncertain. However, the ERG base case analysis predicts incremental life years exceeding 3 months.* Any comments on long-term survival estimates are welcome.	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- nivolumab improves mOS significanty bith statistically and clinically in a meaningful way
- the group that benefits the most is the group with CPS>=5. As this was the primary end point of the trial, novoumab should be used for this population
- CPS scoring will need to become a reflex test in the diagnostic pathway where some pathologist may need training
- The Checkmate 649 trial can be considered representative of the UK population
- The addition of nivolumab to chemotherapy does not significantly worsen toxicity or tolerability
-
-
-
-

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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Response from the Association of Cancer Physicians

I write in response to the Single Technology Appraisal of Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465].

Platinum-fluoropyrimidine combination chemotherapy has formed the basis of first-line systemic therapy for advanced gastro-oesophageal adenocarcinoma. HER2 is the only routinely targeted biomarker through the addition of trastuzumab to first-line chemotherapy. Approximately 15% of patients are HER2-positive [1]. Consequently, management, and by extension patient outcomes, for the majority of patients who have HER2-negative disease has remained unchanged at approximately 11 months for many years [2].

Triplet combinations containing anthracyclines are currently recommended by NICE NG83 for patients who are medically fit, require substantial tumour downsizing and have access to frequent toxicity assessment. However, the addition of anthracyclines to platinum-fluoropyrimidine combinations is contentious [3] and the use of triplet combinations is now uncommon. Results from a recently presented study have also shown that XELOX (capecitabine and oxaliplatin) resulted in a non-inferior progression-free survival (PFS) when compared to EOX (epirubicin, oxaliplatin and capecitabine), in addition to lower rates of toxicity and dose reductions [4]. The REAL-2 study also showed non-inferiority of cisplatin and oxaliplatin and of intravenous 5-fluorouracil and oral capecitabine [2]. This has led to flexibility in the selection of individual platinum-fluoropyrimidine components and doublet chemotherapy regimens (XELOX/CAPOX, FOLFOX and cisplatin and capecitabine) are standard regimens used in the United Kingdom as first-line treatment in this tumour type.

Although known HER2-positive patients were excluded from CheckMate 649, approximately 40% of patients recruited had HER2-unknown status [5]. Given that only 15% of patients with advanced oesophago-gastric adenocarcinoma are deemed HER2-positive [1], this would only account for a minority of patients recruited into CheckMate 649. This relatively small proportion of patients would unlikely affect the overall outcome of CheckMate 649, which should therefore be considered in the context of first-line therapy for HER2-negative disease only. HER2 testing in patients with newly diagnosed advanced oesophago-gastric adenocarcinoma is already routine in the UK as it is recommended in the NICE NG83 guideline.

Older and/or frail patients are underrepresented in cancer trials. Forty percent (40%) of patients in CheckMate 649 were aged ≥65 (age range in all randomised patients 53 – 69) [5], in

comparison to 42% of patients with gastric cancer treated with chemotherapy in the UK are aged ≥70 years. The randomised phase III study GO2 evaluated the optimum dose of oxaliplatin and capecitabine in 514 frail, elderly patients recruited in the United Kingdom, with a median age of 76 and deemed unsuitable for full dose triplet chemotherapy [6]. Thirty-one (31%) of patients with a performance status of ≥2 were included in the study. GO2 demonstrated that the lowest dose level (60% dose), versus 80% and standard dose, was non-inferior for PFS (lowest dose versus standard HR 1.10, 95% CI 0.90–1.33), with patients experiencing less toxicity and better overall treatment utility (considered a composite of clinical benefit, tolerability, quality of life, and patient value). Therefore, elderly patients should not be precluded from receiving chemotherapy and appropriate dose modifications should be considered on an individual basis. Subgroup analyses of all patients randomised in CheckMate 649 showed a HR of 0.82 for patients aged <65 and 0.75 for patients aged ≥65, suggesting benefit in older patients [5]. No new safety signals were identified with chemotherapy + nivolumab and the majority treatment-related adverse events with potential immunological cause In CheckMate 649 were of grade 1 or 2 severity [7]. These should be manageable within an NHS clinical setting as immunotherapies are established therapies in other tumour types such as melanoma and lung cancer. Therefore, the decision to use chemotherapy + nivolumab in elderly patients should not be solely guided by age, but based on overall patient fitness and co-morbidities.

The dual primary endpoints of CheckMate 649 were OS and PFS in PD-L1 Combined Positive Score (CPS) of ≥5 patients [5]. Both OS and PFS were significantly longer with chemotherapy + nivolumab compared to chemotherapy alone (HR 0.71 and HR 0.68 respectively). The statistical analysis plan was based on a hierarchical testing approach where the OS survival of PD-L1 CPS ≥1 and all randomised patients could be tested provided statistically significant results were seen in PD-L1 ≥5 patients. Indeed the margin of survival benefit seen in the PD-L1 CPS ≥1 (HR 0.77) and all randomised (HR 0.80) populations were smaller compared to PD-L1 CPS ≥5 and these results may have been influenced by the relatively high proportion of patients with CPS ≥5 in the overall population (approximately 60%). The exploratory subgroup analyses of PD-L1 CPS <1 and <5 suggest less efficacy in these subpopulations (HR 0.92 and 0.94 respectively). However, the overall response rates seen with chemotherapy + nivolumab were higher in all subgroups, including PD-L1 CPS <1 and <5, which may translate into an improvement in survival benefit with longer follow-up given the potential for delayed treatment effect associated with immunotherapy. PD-L1 expression in oesophago-gastric adenocarcinoma also displays spatial and temporal heterogeneity [8]. A single biopsy may therefore not be representative of potential benefit from immunotherapy.

Based on the results of CheckMate 649, chemotherapy + nivolumab represents a new standard-of-care first-line treatment of advanced oesophago-gastric adenocarcinoma. Given the uncertainties in the survival benefit obtained in patients in PD-L1 CPS <1 and <5 subgroups, PD-L1 status should not be used to define patient selection for chemotherapy + nivolumab in the absence of further data.

References

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4. Guo W, Zhu X, Huang M et al. Phase III trial comparing XELOX regimen (oxaliplatin plus capecitabine) versus EOX regimen (epirubicin, oxaliplatin and capecitabine) as first-line treatment for advanced gastric cancer: EXELOX trial. J Clin Oncol 2021; 39(15):4014.
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Technical engagement response form

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

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: **Thursday 10 June 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]. 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], [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**

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
Issue 1 – limited population and comparators included in the decision problem	No	The ERG report comments on uncertainty regarding the prognostic value of HER2 and PD-L1 in the company report. HER2 and PD-L1 have not been demonstrated to be prognostic in oesophagogastric adenocarcinoma (OGA). The ERG comments that no trials used in the company report recruited oesophageal adenocarcinoma. Most oesophageal adenocarcinoma exist in a continuum the gastroesophageal junction (and are thus classified as GOJ adenocarcinoma). Biologically an oesophageal adenocarcinoma is identical to a GOJ cancer so there are no concerns that the results are not generalizable to this population. The ERG comments that the results of the CheckMate 649 study are not compared to cisplatin-based regimens. We can assume based on REAL-2 that cisplatin-based regimens would have similar outcomes to oxaliplatin based regimens. Comparison with trastuzumab containing regimens for HER2 positive patients would not be reasonable as HER2 positive patients will not be treated with chemo + nivolumab. While the company is seeking approval for all PD-L1 status patients, evidence is only sufficient for PD-L1 CPS ≥ 5 patients.

Issue 2 - Lack of generalisability of CheckMate 649 data	No	The ERG raises a concern that patients treated in CM649 are younger than the average age of diagnosis of OGA in the NHS. All trials in OGA tend to recruit a median age of 62-65, and thus this argument would suggest that no trial would ever be generalisation to the non-trial population. While it is true that many patients diagnosed with OGA are older, not all the patients will receive treatment, reducing the median age of treated patients. There is no evidence in CM649 that treatment was less effective in older patients (HR similar in >65 and <65y). Treatment is reserved for fit patients regardless of age, and it is performance status rather than age which is a driver of immunotherapy efficacy.
Issue 3 – Company network meta-analyses do not include treatment with nivolumab+chemotherapy	**No**	Patients with HER2 positive cancers will not be treated with chemotherapy + nivolumab, nor would patients who are PD-L1 <5. However, neither of these biomarkers are prognostic. It would be reasonable to assume that the efficacy of cisplatin/5FU and cisplatin/capecitabine would be equivalent to oxaliplatin/5FU and oxaliplatin/capecitabine based on the REAL2 trial. In older patients (>65y) a German study shows improved survival for oxaliplatin based regimens. Meta-analysis and clinical trials also show cisplatin is associated with increased toxicity and mortality. Finally, on oncology day units in the UK, cisplatin regimens are not preferred as cisplatin requires an all-day infusion when including fluids and mannitol, and due to the shortage of chemotherapy trained nurses in the UK this leads to increased waiting times for patients. Many chemotherapy units have 3-4 week waits for chemotherapy currently. Thus, it would be a theoretical exercise to compare nivolumab + chemotherapy to these regimens, but not useful in practice as this is not an NHS standard. Trastuzumab regimens should not be included in the comparison.
Issue 4 - Long-term remission health state: evidence does not support patients who	No	It is very reasonable to project that there will be long term survivors treated with chemotherapy plus nivolumab. This has been the case in all cancers

have not progressed by 30 months only having background mortality		treated with immunotherapy (for example in lung cancer now 25% long term survival with this approach). Specifically in OGA, if we examine the long term survival for nivolumab monotherapy in ATTRACTION-2 patients who respond to treatment have a median OS of ~2 years (PMID 31863227). When it is considered that patients in ATTRACTION-2 were chemorefractory with an anticipated survival of <6 months and treated with single agent nivolumab, it is very likely that treatment with chemotherapy plus nivolumab at an earlier stage will lead to even better results. The long term results from CheckMate 032 could also be considered if these are available.
Issue 5 – Company model generates overall survival estimates that are not in line with the first 12 months of the model time horizon	No	Agree with ERG comment – survival should reflect CM649 results.
Issue 6 - High utility values in the progression free survival and progressed disease health states	No	It does not seem unreasonable to have utilities in line with other first line studies (for example trastuzumab TA). However, one might consider that the deeper and more prolonged tumour responses seen with chemotherapy plus nivolumab could impact on symptoms from OGA more than chemotherapy plus trastuzumab leading to an overall reduced burden of symptoms from disease. Added to this, nivolumab is given with oxaliplatin based chemotherapy which is associated with fewer toxicities and improved quality of life compared to cisplatin.
Issue 7 – Low model baseline population age	No	As per issue 2 above. All trials in OGA tend to recruit a median age of 62-65, and thus this argument would suggest that no trial would ever be generalisation to the non-trial population. While it is true that many patients diagnosed with OGA are older, not all the patients will receive treatment, reducing the median age of treated patients. There is no evidence in CM649 that treatment was less effective in older patients (HR similar in >65

		and <65y). Treatment is reserved for fit patients regardless of age, and it is performance. Modelling using age as a single variable does not take other factors into account and may thus be inaccurate.
Issue 8 – Limited cost-effectiveness results for PD-L1 subgroups.	No	Agree with the ERG. The results of CM649 support treatment in CPS ≥ 5 patients and this is the group suggested to model. Treatment in patients with CPS < 5 is not supported by HR in the trial.
Issue 9 - Inappropriate treatment modifier	No	The modifier suggested is that 11% of nivolumab doses are missed. Evidence from CM649 would be helpful in this regard but it should be noted that in this respect clinical trials would be more stringent with dosing than oncologists in practice. Clinically, it would be reasonable to assume that 10%-15% of doses might be missed for various reasons (neutropenia or other toxicity), family events or holidays. Patients are often given treatment breaks for these reasons.
Issue 10 - NICE End of life (EoL) criteria	No	Agree with ERG and company. Increase in life expectance > 3 months can be expected in PD-L1 CPS ≥ 5 population. There is uncertainty around the mean estimates, but this should be > 3 months if not reaching the company prediction of 9 months. As above, agree with company that long-term survival is likely for some patients based on a) nivolumab monotherapy data in other trials and b) efficacy of chemotherapy plus immunotherapy in other diseases.

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: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

NICE National Institute for Health and Care Excellence

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
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**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]

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: **Thursday 10 June 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	**Bristol-Myers Squibb Ltd**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	[redacted]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Executive Summary

Updated Patient Access Scheme

Ahead of addressing the key issues presented in the Technical Engagement response, there is one further update to the data to be presented: an updated PAS. For clarity, all results and argumentation presented in this response apply this updated PAS. The impact of this update is described briefly below and in appendices.

The agreed PAS for nivolumab has been updated from [redacted]% to [redacted]% impacting on vial costs as follows:

- Nivolumab costs without PAS[1]
    - £2,633.00 per 240 mg (24 mL) vial;
    - £1,097.00 per 100 mg (10 mL) vial;
    - £439.00 per 40 mg (4 mL) vial.
- Nivolumab costs with PAS
    - [redacted] per 240 mg (24 mL) vial;
    - [redacted] per 100 mg (10 mL) vial;
    - [redacted] per 40 mg (4 mL) vial.

This updated PAS has been applied within this response. For reference, previous base case analyses including this PAS are provided in Table 1 alongside the company's preferred base case post-technical engagement.

Table 1. Cost-effectiveness results for model versions

Model version:	Model version 1.0	Model version 2.0	Model version 2.1	Model version 3.0
	Original company submission	**Updated company submission based on clarification questions**	**Updated PAS***	**Post technical engagement base case**
Key model changes	No changes, using former PAS	Updated discounting application within the model. Increased baseline age to 64.15 years. Using former PAS	Updated PAS, and other changes as applied in version 2.0	Updated death on progression parameters, and treatment modifiers. Other changes as applied in v2.1
DBL used:	**July 2020**	**July 2020**	**July 2020**	**July 2020**
NIVO + FOLFOX vs FOLFOX	£47,840	£52,549	£48,804	£51,808
NIVO + XELOX vs XELOX	£45,172	£49,550	£45,692	£48,832
*Analysis results presented in 'Key issues for engagement' below are based on modifications to this model version (referred to as model v2.1) Further detail of the changes to the model made at this technical engagement stage are detailed in the "Summary of changes to the company's cost-effectiveness estimate(s)"				

Updated outcomes from CheckMate 649

Following submission, limited outcomes from an updated database lock from CheckMate 649 ([redacted]) have become available. Full analysis of this data has not yet become available. However, the available data is [redacted] with the previously database lock, providing extended follow-up and addressing uncertainty around maintenance of outcomes.

For the CHEMO arm, median OS was [redacted] based on extended follow-up, while median OS [redacted] for the NIVO+CHEMO arm. However, the Kaplan-Meier data provided in

Figure 1 to Figure 4 demonstrate that overall outcomes are [redacted] compared with the previous database lock.

Table 2. CheckMate 649 key efficacy results (Feb 2021 DBL)

Endpoint	All randomised patients		All randomised patients with PD-L1 CPS ≥5	
	NIVO+CHEMO (N=789)	CHEMO (N=792)	NIVO+CHEMO (N=473)	CHEMO (N=482)
OS				
Median OS [95% CI][a], months	[redacted]	[redacted]	[redacted]	[redacted]
HR (CI)[b]	[redacted]		[redacted]	
PFS per BICR				
Median PFS [95% CI][a], months	[redacted]	[redacted]	[redacted]	[redacted]
HR (CI)[b]	[redacted]		[redacted]	

[a]based on Kaplan Meier estimates; [b]Stratified Cox proportional hazards model.
BICR: blinded independent central review; CHEMO: chemotherapy; CI: confidence interval; CPS: combined positive score; NIVO: nivolumab; OS: overall survival; PD-L1: programmed death ligand-1; PFS: progression-free survival..

[redacted]

Figure 1. CheckMate 649 overall survival in all randomised patients ([redacted] DBL)

Figure 2. CheckMate 649 overall survival in patients with PD-L1 CPS ≥5 ([redacted] DBL)

Figure 3. CheckMate 649 progression-free survival in all randomised patients (***** DBL)***

Figure 4. CheckMate 649 progression-free survival in patients with PD-L1 CPS ≥5 (***** DBL)***

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
Issue 1 – limited population and comparators included in the decision problem	No	**CheckMate 649 was designed to assess the clinical effectiveness of nivolumab combination therapy in a population appropriate to UK clinical practice, versus UK-relevant comparators and reporting outcomes important to patients** **Population:** Per the CheckMate 649 protocol, patients with known HER2-positive status were excluded. Hence, the efficacy data presented in CheckMate 649 does not adequately reflect outcomes in patients with HER2-positive status. It should be noted that although HER2 positive status at baseline was reason for exclusion from CheckMate 649, some patients who were enrolled at baseline with unknown HER2 status but were tested during the study. In the 10th July 2020 DBL, there were [redacted] subjects with HER2 positive status. However, after the DBL, the site confirmed that [redacted] of the [redacted] subjects with confirmed HER2 positive status was actually negative and that the data was entered incorrectly. This patient's data will be updated in the next DBL and the report will reflect a total of [redacted] HER2 positive subjects included in the final ITT analysis. CheckMate 649 may be considered representative of outcomes in a HER2 positive population. Although a recent UK retrospective study demonstrated that OS was significantly improved for HER2-positive patients versus HER2-negative patients (15.0 months versus 11.9 months),[2] this may be related to increased use of trastuzumab-based therapies, as opposed to differences in prognosis based on HER2 status. Further, PD-L1 expression is observed independent of HER2 status.[3] Although the expression of PD-L1 may occur slightly more frequently in HER2-negative patients than HER2-positive cohorts,[3,4] this may be related to PD-L1 assessment techniques: one study determined slightly higher PD-L1 positivity

		(defined as staining in ≥1% of tumour or immune cells) for HER2 negative patients using tumour proportion score, combined positive score and interface pattern but found numerically higher PD-L1 expression in HER2 positive patients based on staining of tumour associated immune cells. In summary, there is no data to suggest differential effect of nivolumab in HER2-positive cohort. Available evidence supports equivalent effect between HER2-positive and HER2-negative patients. Despite benefit in HER2 positive patients, it is noted that HER2 testing is standard of care for gastric cancer patients in the UK and it is assumed that patients who test positive for HER2 would preferentially receive a trastuzumab-based therapy instead of nivolumab plus chemotherapy. This assumption is aligned with NICE guidance TA208.[5] **Comparators**: Direct evidence for comparative efficacy of NIVO+CHEMO vs CHEMO may be drawn from the CheckMate 649 study, so that no meta-analysis was required. Indirect treatment comparisons deriving comparative efficacy using CheckMate 649 were presented in Company submission Document B Section B.2.10. Of the 136 unique studies that reported either OS or PFS in the SLR, 42 studies reported at least one treatment of interest for this NMA. Studies were restricted to those reporting relative outcomes in the form of HR, or Kaplan-Meier data that could be used to estimate comparative outcomes including at least two potential comparators that could be used to form a network. Studies reporting only absolute outcomes were not considered. Only studies forming part of a complete network including XELOX or FOLFOX were included in the NMA, with XELOX and FOLFOX assumed to have equivalent efficacy in line with assumptions for cost-effectiveness analysis and CheckMate 649 trial design. Clinical advice indicates that epirubicin is no longer used in the UK for 1L treatment of gastro-oesophageal cancers,[6] hence it was not used in this analysis. Additional discussion of the NMA is provided in response to Issue 3. **Outcome:** The two primary endpoints were evaluating benefit in a narrower population of patients than addressed in this submission, i.e., patients with PD-L1 CPS ≥5. However, CheckMate 649 enrolled patients regardless of PD-L1 expression, applying expression levels as a stratification factor for randomisation (≥1% versus <1%). Further, key secondary endpoints included assessment of PFS and OS in all randomised patients, so that this can be considered an appropriate approach. OS and PFS outcomes remained improved in the nivolumab combination therapy arm across the overall population and the PD-L1 ≥ 1 subgroup. [redacted]

		[redacted] Reflecting the study design and available data, the submission contains subgroup analyses for the PD-L1 subgroups; however, the population of interest is the overall population.
ERG comment		No comment required. See ERG report, Section 2.6, Section 3.2, Section 3.6, Section 4.3, Section 6.2 and Section 6.9.
Issue 2 - Lack of generalisability of CheckMate 649 data	**No**	**Although CheckMate 649 was limited by study design and patient accrual, the enrolled patients can be considered representative of a UK population** **Age:** CheckMate 649 broadly reflected the baseline characteristics for patients starting chemotherapy for advanced gastric in clinical practice. As noted in the submission, median baseline age (62 years in the NIVO+CHEMO arm and 61 years in the CHEMO arm) was similar but slightly younger that for the Royal Marsden retrospective review[7] (median age: 66 years) and the COUGAR-2[8] clinical study (median age: 65 years in the docetaxel arm and 66 years in the active symptom control arm). Patients in the UK REAL-2 clinical study had similar baseline age (median age: 65 years in arm 1, 64 years in arm 2, 61 years in arm 3 and 62 years in arm 4).[9] Of note, data collected by the NHS, produced by the Cancer Research UK – Public Health England Partnership and provided by the National Cancer Registration and Analysis Service (CRUK dataset) show that 75 years is over the median age at diagnosis for patients with stomach cancer treated with chemotherapy, and that the majority are below 70 years.[10] Of the 5,840 patients who received chemotherapy for gastric cancer in this dataset, 3,357 were aged ≤69 years and 2,483 were aged ≥70 years. It is not possible to identify median age due to the broad categories of age reported; but the median age is below 70 years. Aligned with the UK data sources outlined above, NHS patients would need to be fit and eligible for treatment with chemotherapy in order to receive treatment with nivolumab combination therapy. The evidence clearly demonstrates that the focus should be on baseline characteristics of patients who are treated with chemotherapy and not the full population diagnosed with gastric cancer, as they would be significantly older than the diagnosed population. More patients eligible for treatment in UK clinical practice are in the age range closer to the CheckMate 649 trial population.

		Further, to inform technical engagement, UK clinical experts suggested that the CheckMate 649 population and CRUK dataset both seemed appropriate in terms of age, with an average patient lying between these two estimates. Hence, when considering the model and patients eligible for nivolumab; the analysis is reflective of the Checkmate 649 median baseline age and this is validated by relevant UK data sources. **ECOG status:** Compared with other UK studies,[2,8] slightly fewer patients with ECOG status of 1 were enrolled and no patients with ECOG status of 2 were enrolled. Clinical trials commonly specify performance scores as an inclusion criterion, typically based on either ECOG or Karnofsky scale. This leads to limited evidence of net clinical benefit for patients with certain performance scores, typically those with worse scores. This absence of evidence contributes to a reluctance to provide certain treatments to patients of reduced performance score. However, this is limited evidence to suggest different outcomes between patients with different performance score. A 2017 SLR and meta-analysis of RCTs assessed clinical benefit by performance score subgroups.[11] This identified 110 RCTs, with 66 (60%) reporting performance score subgroups for efficacy and none reporting subgroups for toxicity. For these 66 RCTs, pooled HRs for good performance score and reduced performance score subgroups were 0.65 (95% CI 0.61 to 0.70) and 0.67 (95% CI 0.62 to 0.72), respectively, with no difference between the two groups (p=0.68). Sensitivity analyses based on drug or cancer type and type of endpoints (OS or PFS) demonstrated similar results.[11]
ERG comment		No comment required. See ERG report, Section 2.6, Section 3.2 and Section 6.2.
Issue 3 – Company network meta-analyses do not include treatment with nivolumab+chemotherapy	**No**	**An indirect comparison for nivolumab+chemotherapy versus chemotherapies of interest was not supported by the available data. Further, this comparison was not necessary to draw the conclusion that there was no statistically significant difference in PFS or OS between FOLFOX and any other comparator.** The ERG presented several criticisms of the NMA, which are summarised as: 1. Inconsistency was not assessed in the NMA

		a. This was an acknowledged limitation due to the small size of the network, but the network represents the best available evidence for indirect comparison 2. Proportional Hazards assumption was not appropriately assessed within the NMAs. a. The ERG implies that there is evidence that the PH assumption may have been violated for one trial of OS and indicates the paper of Al-Batran et al[12] as a source. The company has assumed that the ERG is referring to Figure 5 (Figure 2c in the original publication). The company notes that these two treatments are very well matched in outcomes and that evidence of survival crossing alone is not evidence to reject the proportional hazards assumption, as such crossings can occur by chance, particularly where there are few patients at risk and there is little separation between the curves. Due to the similar composition of and mechanism of action of the treatments investigated in Al-Batran et al[12], there is no a-priori reason to suspect non-proportional hazards and there is insufficient evidence provided within this paper to suggest that proportionality of hazards has been violated.

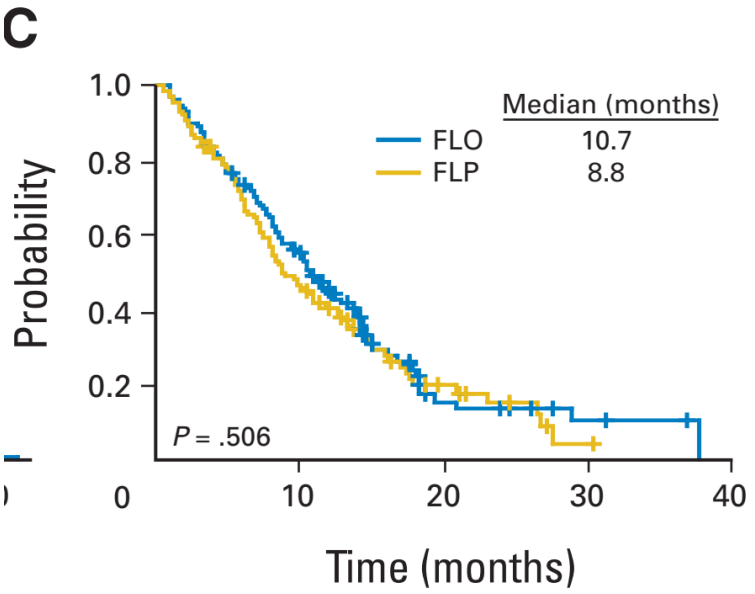

Figure 5. Al-Batran 2008[12] Figure 2C - comparison of overall survival for fluorouracil plus oxaliplatin versus fluorouracil plus cisplatin

3. Given the difference in mechanism of action between the nivolumab+chemotherapy and chemotherapy alone arm of CheckMate 649, non-proportional hazards were expected a-priori and the initial power analysis of the study was conducted upon such a basis. Given the expected and measured time-varying hazard ratio, the Cox modelled hazard ratio, as an expression of treatment effect, is dependent upon the extent of follow-up and so this result is not transitive across a network with heterogenous follow-up. As such, the treatment effect measured in CheckMate 649 was not included in the network due to the violation of the transitivity assumption and the results were not contaminated by this inappropriate data. The results derived were sufficient to support the conclusion of the NMA.

In summary, the company believes that the NMA has been undertaken appropriately, with the best available evidence, and does acknowledge where the ERG considers there to be residual uncertainty.

		The company supports the conclusion that the "comparisons between chemotherapy (FOLFOX) and capecitabine+cisplatin and fluouracil+cisplatin are of limited relevance to decision makers" and so does not consider this residual uncertainty to be impactful upon the decision problem.
ERG comment		**Proportional hazards** Please note there is a typographical error in Table 15 of the ERG report. The ERG considers that the assessments presented by the company (response to clarification question A9) demonstrate no evidence that the PH assumption has been violated for **OS**, but there is evidence that the PH assumption may have been violated for **PFS**. The ERG still concludes that the impact of the uncertainty around the validity of the PH assumption on the NMA results for OS and PFS is unknown. **Inclusion of nivolumab+chemotherapy in the NMAs** The ERG agrees with the company that the NMAs have been undertaken appropriately and that the network of comparators has been constructed appropriately (see Table 15 of the ERG report for the ERG critique of the NMA methods). Nonetheless, although the methodological approach to the NMAs is appropriate, the ERG notes that no comparative clinical effectiveness results are available for the comparison of nivolumab+chemotherapy versus fluorouracil+cisplatin, versus capecitabine+cisplatin, or versus trastuzumab+capecitabine+cisplatin.
Issue 4 - Long-term remission health state: evidence does not support patients who have not progressed by 30 months only having background mortality	**Yes**	**There is significant evidence to support long-term remission in a proportion of patients. This evidence suggests that patients enter long-term remission between two years and three years and experience significantly reduced hazards following this point. A scenario analysis incorporating a ratio that increased the hazard of death (in comparison to the general population) led to a small increase in the ICER.** **Plausibility of long-term remission in this population** The evidence supporting plausibility of long-term remission in this patient cohort has been presented in the initial company submission and in the subsequent response to clarification questions: • Published evidence: Multiple real-world studies have observed a small proportion of patients demonstrate improved outcomes versus the overall cohort, achieving long-term remission, as detailed in Section B.2.14.1.1 of Document B.[10,12-14] This includes a UK retrospective study by the Royal Marsden Hospital,[2] which reflected NHS patients comparable to CheckMate 649, where an initial high hazard is observed followed by low hazard from approximately 36 months. At 60 months (five years), OS was 4%, with very few events occurring between 60 months and

		96 months. Another UK study, COUGAR-2,[8] indicated that a small proportion of patients had prolonged survival; although follow-up is limited to 18 months, OS was 6% in the docetaxel arm and 2% in patients assigned to active symptom control. Similarly, a retrospective database study in the US showed that Kaplan-Meier data plateaued from three years and 3% remained alive at five years.[13] This benefit has been shown to be maintained long-term: Chau et al.,[14] reviewed the data from four RCTs conducted in the UK and Australia and demonstrated a five-year survival rate of 4% in patients with gastric primary lesion sites and 3% in patients with GEJ primary lesion sites. Maximum follow-up was beyond 110 months for these patients, and OS remained at 4% and 3% respectively. • Clinical expert opinion: Clinical experts contacted to support the company submission considered long-term remission to be plausible in patients who had not progressed after an extended period. Clinical advisors contacted to inform technical engagement agreed that this would be plausible, with this more likely to occur after treatment with an immunotherapy. The advisers were uncertain as to the timing or the impact of this remission on long-term outcomes. • Evidence from CheckMate 649: As noted in the company submission, evidence from CheckMate 649 was presented to support the plausibility of long-term remission in the gastric cancer population. Additional evidence from the updated database lock is presented to support long-term remission. Based on the [redacted] database lock, the observed PFS in CheckMate 649 showed a similar profile on both arms, visible in Figure 8, reflecting a decreasing marginal hazard, with PFS approaching an asymptote representing a fraction of patients at dramatically reduced hazard of progression or death relative to the majority of the ITT population. Consideration of the similarity of the hazard profiles over patient-follow-up suggests that the higher risk population is being exhausted at a similar rate on both arms, and so PFS benefit for nivolumab+chemotherapy is being driven by a larger LTR fraction. **Timepoint where patients are considered to have achieved long term remission** As noted in the response to clarification questions, this assumption is primarily supported by CheckMate 649, as this study has large patient numbers and patient-level data is available so that it is possible to assess the precise hazard profile and identify the hazard turning point. However, supporting evidence is available from the published literature. Several studies outlined below demonstrate survival plateaus that start at approximately 36 months, including the Royal Marsden study and a large US database study.[2,13] Within CheckMate 649, the marginal hazard of progression or death among patients who had not yet progressed decreased steadily through time and approached a plateau during trial follow-up. To the [redacted] DBL, of the [redacted] patients ([redacted] nivolumab+chemotherapy; [redacted] chemotherapy) who had [redacted] and were followed-up [redacted], [redacted].

		Within the economic model, the long-term response fraction is identified by the assumption that all patients who have not progressed by a nominated time point will, from that point onwards be subject to no hazard of progression. This approach supposes the coexistence of an unidentified LTR fraction and its complement, those without long-term response (non-LTR), with the members of the non-LTR fraction being removed from the PFS state at a greater rate than those with LTR. The time at which the assumption that all patients who have not progressed are in the LTR fraction is therefore required to be one where the presence of non-LTR patients in the PFS state is negligible. However, due to the increasing proportion of patients remaining at risk being within the LTR fraction the PFS event hazard is expected to decrease rapidly prior to effective exhaustion of the non-LTR fraction, even if this sub-population should be experiencing stable or increasing hazards.

		This expected profile is visible in the trial data, as can be seen in  Figure 6, with the event hazard in both arms decreasing towards the general population mortality hazard. As can be seen, the marginal hazard of the nivolumab+chemotherapy arm is expected to have reached lifetable mortality within current follow-up, whilst the chemotherapy arm lags slightly. Based upon the final hazards of the smoothers extrapolated constantly, the chemotherapy arm expects an

		additional 4.17 years of progression-free survival, whilst the nivolumab+chemotherapy arm expects an additional 18.15 years of progression-free survival, which would be expected to be significantly curtailed by all cause mortality. Though it is unknown exactly when the non-LTR fraction will have formed a negligible portion of the remaining cohort pre-progression, these observations of PFS from CheckMate 649 indicate that it likely near 30 months. Due to the consistently higher hazard of progression or death in the chemotherapy arm, establishing the LTR at earlier time points is expected to favour chemotherapy, as the event rate is expected to be higher in this arm until the LTR is established. **Mortality in patients achieving long term remission** Within the company's economic model, patients who have not progressed at 30 months are considered to be in long term remission. These patients have a mortality hazard which aligns with general population all cause mortality (derived from lifetables). CheckMate 649 patients in both treatment arms demonstrated a similar profile, with the same reduction in long-term hazard observed. Among patients not progressed at 12, 18 and 24 months, hazard of

		death decreased on both arms ( Figure 7); very few patients who had not progressed by month 24 died under current follow-up. Due to both selection pressure and therapeutic effect, the marginal hazard would be expected to continue to decline towards background mortality at further landmarks. As can be seen, the OS hazard was predicted by several estimators to reduce to approximately match the general population in the full ITT

		population ([redacted]

		Figure 6 and  Figure 7), indicating that patient numbers and follow-up in this region were sufficient to indicate a plateauing of survival from this point.

Figure 6. Bspline smoothed hazard of progression per BICR or death censoring for subsequent treatment – CheckMate 649, [redacted]

Hazards extrapolated as constant from time of last observation in survival predictions

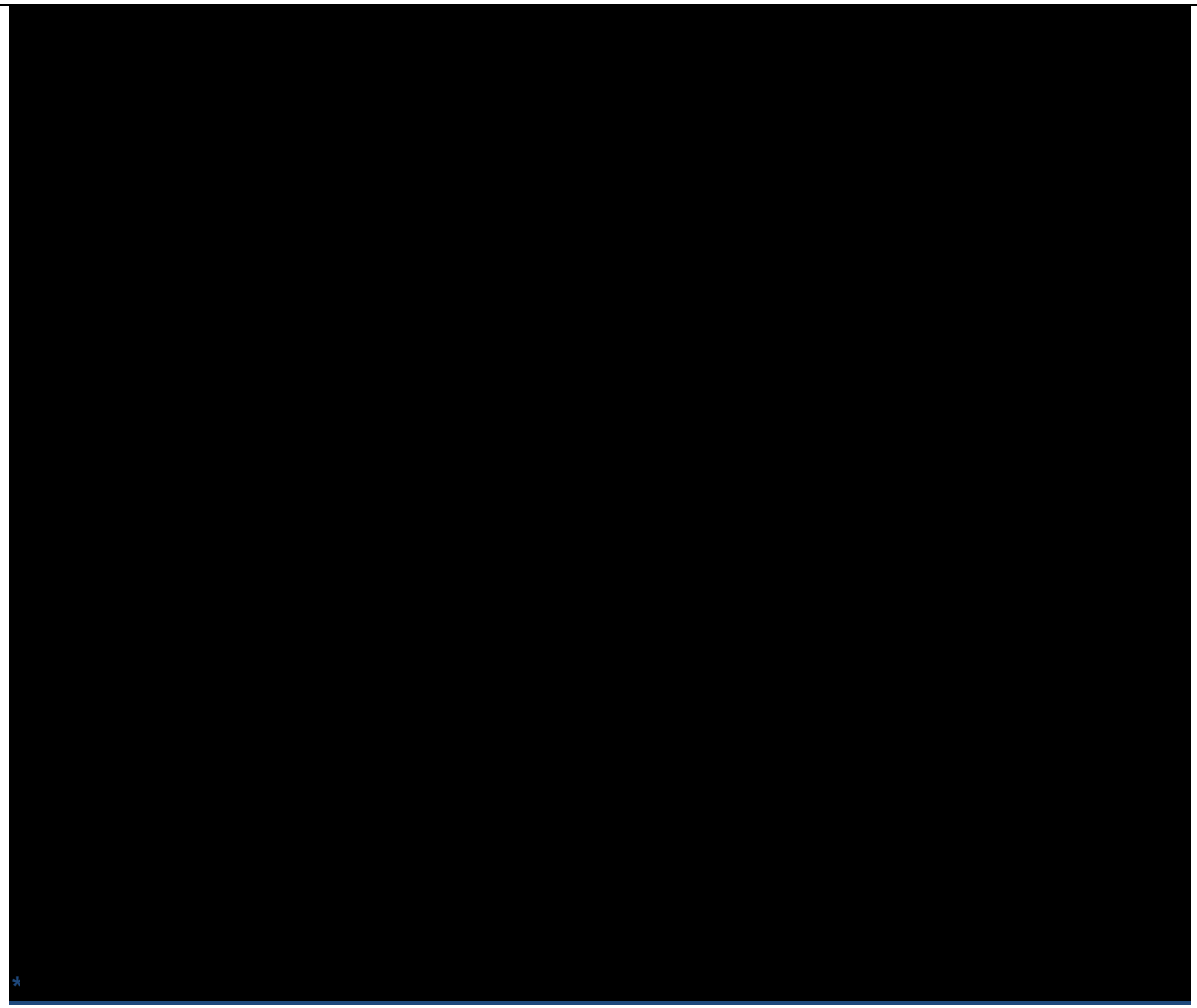

Figure 7. OS conditional upon PFS to 12, 18 and 24 months; CheckMate 649, [redacted]

The model predictions using the LTR fraction established at 30 months remained well calibrated to the updated CheckMate 649 database lock of [redacted], with [redacted] events having been observed beyond the 30 month point for establishment of the LTR fraction. Of the [redacted] events that were so far observed

beyond month 24 within the trial ([redacted] patients with follow-up), [redacted] were deaths without progression. Of the [redacted] events observed beyond month 30 ([redacted] patients with follow-up), there were [redacted] progressions and [redacted] death, [redacted].

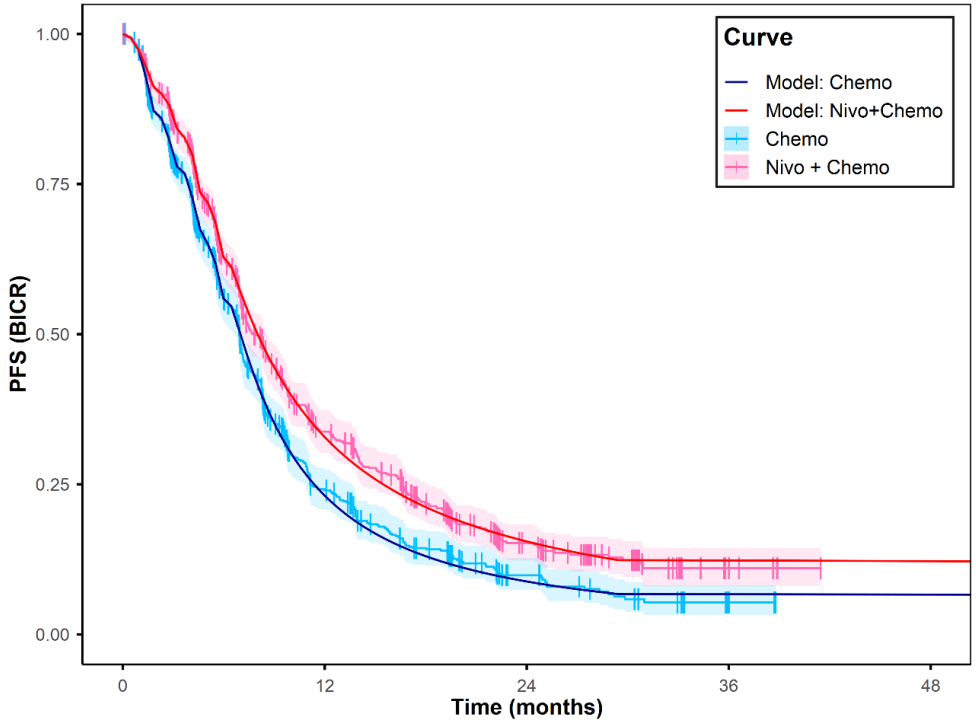

Figure 8. Model predicted PFS versus observed PFS per BICR from CheckMate 649 (Feb 2021 DBL)

In addition, OS estimates from the economic model incorporating the LTR fraction remain well calibrated to these new data, with the conditional OS after month 30 being aligned with the Kaplan-Meier estimator, as evidenced by Figure 9.

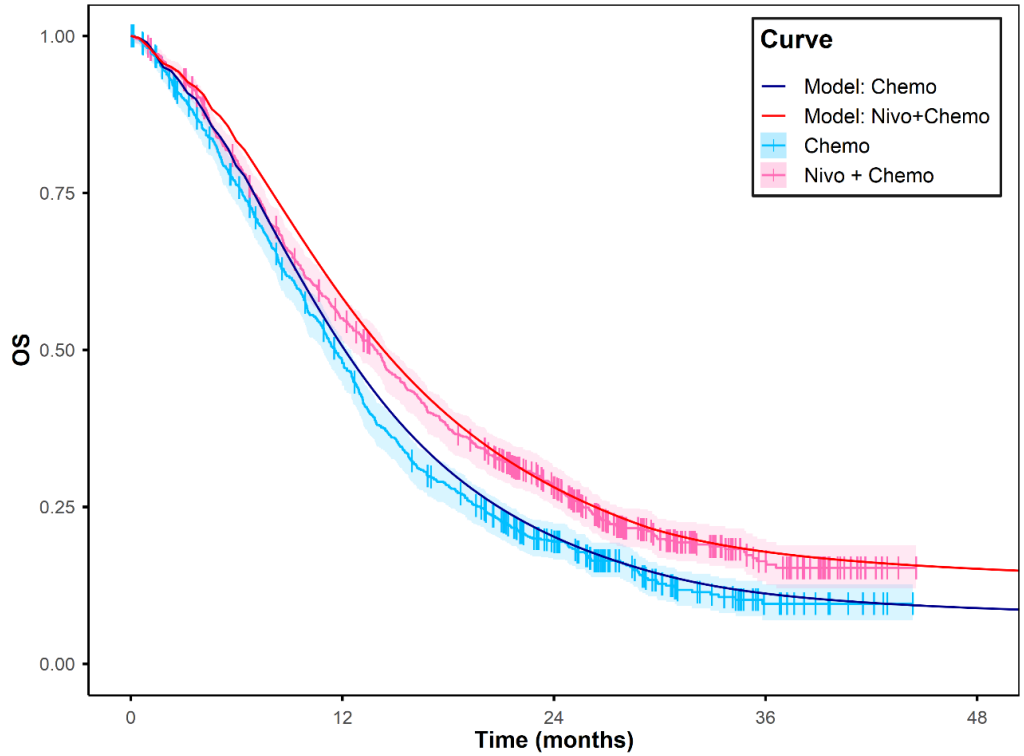

Figure 9. Model predicted OS versus observed OS from CheckMate 649 (Feb 2021 DBL)

However, the company acknowledges that there may be uncertainty of the mortality of this patient population within long-term remission, due to the length of trial follow up within the July 2020 database lock. Therefore, the company explored a scenario within the economic model to allow for a standardised mortality ratio to be applied to the long-term remission health state. A standardised mortality ratio describes whether a population is more or less likely to die than the general population, where a ratio exceeding 1 means that there is a higher risk than the general population.
Incorporation of a standardised mortality ratio adjusts the hazard of death derived from lifetables over all patients in all states, inclusive of long-term remission, in either or both treatment arms. In the modelled scenario, this has been applied whereby patients who are in remission have a standardised mortality

ratio of 1.5 (i.e. patients in the remission health state have 1.5 times the risk of death than that of the general population).

Table 3. NIVO+FOLFOX vs FOLFOX – the impact of adding standardised mortality ratio in long term remission

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: with standardised mortality ratio of 1.5							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,581	2.359	1.472	[redacted]	[redacted]	[redacted]	£54,067
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 4. NIVO+XELOX vs XELOX – the impact of adding standardised mortality ratio in long term remission

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: with standardised mortality ratio of 1.5							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,408	2.359	1.472	[redacted]	[redacted]	[redacted]	£50,620

		ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied
ERG comment		The company has presented updated results from the latest CheckMate649 trial data-cut ([redacted]). However, the company has still not provided any substantive evidence to support (i) patients in the PFS health state at 30 months entering long-term remission and (ii) mortality in the long-term remission health state being equal to background mortality. The company's response to Issue 4 does provide any new insights. The company arguments remain largely the same as those provided in the CS and in the company clarification response. The ERG's critique of the evidence therefore remains the same. The ERG considers that the company's new assumption that mortality rates for patients with long-term remission would be equal to 1.5 times the background rate is arbitrary.
Issue 5 – Company model generates overall survival estimates that are not in line with the first 12 months of the model time horizon	**Yes**	**The company base case has been updated with survival curves which improve the OS estimates generated by the model within the first 12 months of the model time horizon.** As suggested by the ERG, the company has re-evaluated the survival estimates produced by the model. The company has amended death on progression values to reflect outcomes using the BICR definition of survival (as per the input survival curves). The model OS outputs within the updated CEM are compared with trial data in Table 5. The estimates generated by the updated CEM, based on updated death on progression inputs, are consistently within 3% of the trial data. It should be noted that the trial data represent a population with a variety of baseline ages, whose matched general population mortality is more widely distributed than the patient at the age simulated in the economic model, which results in a lower initial hazard of mortality and a lower long-term hazard of mortality from other causes, which contributes to improved initial survival, but also curtailment of long-term benefit as those younger patients within an LTR fraction would be expected to have increased life expectancy. These features are visible in Figure 9, when comparing to the Feb 2021 DBL. ***Table 5. Estimates of overall survival – July 2020 DBL***

	Timepoint	Trial data (% alive)	Former survival modelling within the CEM		Updated survival modelling within the CEM	
			% Alive	Difference to trial	% Alive	Difference to trial
	0.5 years	[redacted]	[redacted]	[redacted]	62.73%	0.08%
	1 year	33.41%	32.75%	-0.66%	32.75%	-0.66%

PFS (treatment arm)	1.5 years	[redacted]	[redacted]	[redacted]	21.10%	0.72%
PFS (control arm)	0.5 years	[redacted]	[redacted]	[redacted]	55.84%	0.14%
	1 year	23.23%	23.04%	-0.19%	23.04%	-0.19%
	1.5 years	[redacted]	[redacted]	[redacted]	12.97%	0.05%
OS (treatment arm)	0.5 years	[redacted]	[redacted]	[redacted]	83.17%	3.03%
	1 year	54.96%	60.40%	5.44%	58.21%	3.25%
	1.5 years	[redacted]	[redacted]	[redacted]	39.42%	2.41%
OS (control arm)	0.5 years	[redacted]	[redacted]	[redacted]	79.18%	2.92%
	1 year	47.94%	52.84%	4.90%	50.46%	2.52%
	1.5 years	[redacted]	[redacted]	[redacted]	30.77%	3.11%

Table 6. NIVO+FOLFOX vs FOLFOX – the impact of changing death on progression values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: updated death on progression values							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,671	2.589	1.556	[redacted]	[redacted]	[redacted]	£50,225
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 7. NIVO+XELOX vs XELOX – the impact of changing death on progression values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)

		Base case model v2.1 Nivolumab + XELOX: [redacted] - - - - XELOX: £20,465 2.566 1.554 [redacted] £45,692 **Scenario: updated death on progression values** Nivolumab + XELOX: [redacted] - - - - XELOX: £20,497 2.589 1.556 [redacted] £46,945 ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied
ERG comment		The company's revised approach to modelling OS has led to estimates at 12 months that are more in line with CheckMate 649 trial data than the approach presented in the CS; however, company model estimates, for both the intervention and comparator model arms, are still optimistic. The continued inability of the company model to accurately estimate OS for both treatment and comparator model arms raises concerns about whether the model can accurately estimate OS over the whole model time horizon. The ERG is unable to provide more accurate estimates of OS for the treatment and comparator model arms.
Issue 6 - High utility values in the progression free survival and progressed disease health states	**No**	**The company considers the utility values used in the economic model for progression free and progressed disease to be appropriate, as the reference health state utility values are modified using a time-to-death disutility. However, this has limited impacted on the ICER.** Although the reference utility values for the health states (PFS health state: [redacted], progressed disease health state: [redacted]) are close to the age-dependent utility values (value of [redacted] for 60 year old), the utility values are not comparable, since an additional time-to-death disutility modifier is applied to the reference utility values for health states. While it is not possible to quantify the impact of this modify on specific health state utilities, the overall impact is considerable. The time-to-death disutility ([redacted]), is applied to all patients who survived for at least 6 months during the 6 months before death. For patients who died within the first 6 months, disutility was determined by integrating a polynomial formula over the elapsed model time. This integral would equal that given by the quoted average disutility when model time was equal to 6 months. All utility values within the model (time-to-death disutility value, and health state utility values) were derived from the clinical trial data.

Conversely, the health state utilities described by the ERG (from TA208, published in 2010[5]) are sourced from the wider literature, and do not incorporate a time-to-death disutility. Further, given the publication date for TA208 (2010), it is unclear how relevant these utilities are to current clinical practice. This is of particular relevance given that outcomes from TA208 (assessing trastuzumab in the first-line setting) are broadly equivalent to outcomes from TA378 (assessing ramucirumab in the second-line setting). This means that the health state utility values used within the ERG model, compared with the reference health state utility values used within the company's economic model, are not comparable.

It is not feasible to separate deaths from each health state, therefore the absolute impact of this disutility on deaths from each health state (and consequently the utility of each health state) cannot be determined. However, within the submission base case analysis, inclusion of the time-to-death disutility within the company's CEM results in a reduction of [redacted] QALY for the nivolumab arm, and [redacted] for the chemotherapy arm (undiscounted).

For ERG analysis, which used alternative health state utility values but included the Checkmate 649 time to death disutility, the impact of removing this disutility on health economic outcomes are shown in Table 8 and
Table 9. This has a minimal impact on QALY accrual, aligned with that observed from switching to alternate values, per the ERG base case.

Table 8. NIVO+FOLFOX vs FOLFOX – the impact of removing time to death disutilities from ERG analysis

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1 with ERG utility values							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.448	[redacted]	[redacted]	[redacted]	£49,785
Scenario: ERG utility values without time to death disutility							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.509	[redacted]	[redacted]	[redacted]	£49,909

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
NB: baseline age 64.15 years applied

Table 9. NIVO+XELOX vs XELOX – the impact of removing time to death disutilities from ERG analysis

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case model v2.1 with ERG utility values							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.448	[redacted]	[redacted]	[redacted]	£46,611
Scenario: ERG utility values without time to death disutility							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.509	[redacted]	[redacted]	[redacted]	£46,727

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
NB: baseline age 64.15 years applied

ERG comment

Using the TA208 utility values without the time to death disutility or the company utility values with time to death utility makes minimal difference to cost effectiveness results. Therefore, the ERG is satisfied that the company approach to including utility values generates results that are suitable for decision making.

Issue 7 – Low model baseline population age

No

CheckMate 649 can be considered relevant to UK clinical practice, but alternative scenarios for baseline age are presented

As noted in the response to Issue 2, CheckMate 649 broadly reflected the baseline characteristics for patients starting chemotherapy for advanced gastric in clinical practice. However, in order to provide an informed technical engagement response, UK clinical experts were contacted to assess typical baseline characteristics for a patient in UK clinical practice. These experts suggested that the CheckMate 649 population and CRUK dataset both seemed appropriate in terms of age, with an average patient lying

between these two estimates. A scenario is provided using a mean OS of 60.15 years; however, it should be noted that the base case of 64 years may be conservative.

Alternative age scenario: A scenario analysis was undertaken using a baseline age of 60.15 years. The results of this analysis are shown in Table 10 and Table 11. When patient age is increased to 64.15 years (base case), fewer patients are able to achieve long-term remission due to the impact of all-cause mortality in months 0-30. This has minimal impact on incremental QALYs, which increases slightly from the base case analysis to this scenario analysis.

Table 10. NIVO+FOLFOX vs FOLFOX – the impact of changing baseline age

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1: baseline age 64.15 years (CRUK data)							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: [redacted] years (based on clinical trial data)							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,676	2.802	1.649	[redacted]	[redacted]	[redacted]	£43,833
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year							

Table 11. NIVO+XELOX vs XELOX – the impact of changing baseline age

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1: baseline age 64.15 years (CRUK data)							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: [redacted] years (based on clinical trial data)							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-

		XELOX | £20,503 | 2.802 | 1.649 | [redacted] | [redacted] | [redacted] | £41,038 ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
ERG comment		The ERG agrees with the company that a baseline age of 64.15 years should be used in their base case analysis.
Issue 8 – Limited cost-effectiveness results for PD-L1 subgroups.	**No**	**The licensed indication will not be restricted to the PD-L1 CPS score <1 or <5 population. Additionally, the subgroup of patients with baseline PD-L1 CPS <1 and <5 is smaller and hence may be non-informative** The licensed indication is not yet finalised; all relevant data to support that indication has been provided to NICE for assessment. Clinical and cost-effectiveness data has been provided for the overall population and for the PD-L1 CPS subgroups of interest (PD-L1 CPS ≥1 and CPS ≥5), [redacted]. However, the licensed indication will certainly not be restricted to the [redacted]. In all randomised patients with PD-L1 CPS quantifiable at baseline, [redacted] and [redacted]) had a baseline PD-L1 CPS ≥1 in the NIVO+CHEMO and CHEMO arms, respectively. Hence, there are only [redacted] patients in the NIVO+CHEMO arm and [redacted] patients in the CHEMO arm with baseline PD-L1 CPS <1. This subgroup is insufficiently powered to detect differences in outcomes and the small patient numbers would not provide informative data. Similarly, [redacted] and [redacted] had a baseline PD-L1 CPS ≥5 in the NIVO+CHEMO and CHEMO arms, respectively. Although there are more patients with baseline PD-L1 CPS <5 than with CPS <1 ([redacted] in the NIVO+CHEMO arm and [redacted] in the CHEMO arm), this subgroup remains insufficiently powered to detect differences in outcomes. For this reason, cost-effectiveness data for the PD-L1 CPS score <1 or <5 subgroups are not provided.
ERG comment		No comment required. See ERG report, Section 6.8 and Section 6.11.
Issue 9 - Inappropriate treatment modifier	**Yes**	**The company base case has been updated to incorporate a treatment modifier in both arms, with minimal impact on cost-effectiveness conclusions.** The approach taken within the company submission applied a treatment modifier to account for missed nivolumab doses in the NIVO+CHEMO arm only; as nivolumab dosing could not be modified, only

interrupted, this treatment modifier was derived based on expected doses received versus those actually received. However, there are significant limitations to estimating the treatment modifier for the chemotherapy components, as this would need to incorporate both missed doses and dose modifications. It was determined that any treatment modification would apply similarly to the chemotherapy components of both arms and would have relatively low cost impact, so it was assumed to be negligible.

However, the ERG's preference was to apply a treatment modifier to both arms or to neither arm. Based on the data available to the ERG, they removed this treatment modifier from the treatment arm (i.e. neither arm had a treatment modifier in place).

Incorporating the treatment modifier provides a more accurate estimation of accrued costs in UK clinical practice; removing this treatment modifier provides an overestimate of cost accrual, particularly impacting the nivolumab arm due to the higher acquisition costs. Hence, a rough estimation of the treatment modifier was derived for the chemotherapy components for both arms using relative dose intensity; to align with this approach, the nivolumab component was also updated. This updated treatment modifier was then applied to the cost-effectiveness analyses, as suggested by the ERG. Each component had a different modifier (Table 12), and values were applied to both acquisition and administration costs. The outcomes of cost-effectiveness analysis with the updated treatment modifier values are displayed in Table 13 and Table 14. As can be seen, this does not impact greatly on cost-effectiveness, but provides a more accurate estimate of accrued costs.

Table 12. Treatment modifier values

Treatment:	Component	Treatment modifier value
FOLFOX	5-FLUOROURACIL	[redacted]
	LEUCOVORIN	[redacted]
	OXALIPLATIN	[redacted]
	5-FLUOROURACIL CONTINUOUS	[redacted]
XELOX	OXALIPLATIN	[redacted]
	CAPECITABINE	[redacted]

NIVO+FOLFOX	NIVOLUMAB	[redacted]
	5-FLUOROURACIL	[redacted]
	LEUCOVORIN	[redacted]
	OXALIPLATIN	[redacted]
	5-FLUOROURACIL CONTINUOUS	[redacted]
NIVO+XELOX	NIVOLUMAB	[redacted]
	OXALIPLATIN	[redacted]
	CAPECITABINE	[redacted]

Table 13. NIVO+FOLFOX vs FOLFOX – the impact of updating treatment modifier values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£34,639	2.566	1.554	[redacted]	[redacted]	[redacted]	£48,804
Scenario: Updated treatment modifier values							
Nivolumab + FOLFOX	[redacted]	[redacted]	[redacted]	-	-	-	-
FOLFOX	£32,662	2.566	1.554	[redacted]	[redacted]	[redacted]	£50,304
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

Table 14. NIVO+XELOX vs XELOX – the impact of updating treatment modifier values

Technology	Total costs (£)	Total life years	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Base case for model v2.1							

Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£20,465	2.566	1.554	[redacted]	[redacted]	[redacted]	£45,692
Scenario: Updated treatment modifier values							
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	£19,953	2.566	1.554	[redacted]	[redacted]	[redacted]	£47,482
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year NB: baseline age 64.15 years applied							

ERG comment		The ERG considers that treatment modifiers should be applied to all treatments. Therefore, the approach described by the company is appropriate.
Issue 10 - NICE End of life (EoL) criteria	**Yes**	Nivolumab plus chemotherapy meets end of life criteria, providing substantial survival benefit over standard of care As noted in Table 43 of the ERG report, the ERG agrees that available data suggest that life expectancy for the population of interest is <24 months. However, the ERG raises uncertainty around the degree of benefit for NIVO+CHEMO versus standard of care. Based on the original database lock from CheckMate 649, NIVO+CHEMO was associated with a median OS of 13.83 months compared with 11.56 months for current treatment (i.e., chemotherapy alone), indicating substantial survival benefit based on median OS data alone (2.27 months). This median OS benefit increases to 3.29 months in the PD-L1 CPS ≥5 population. However, the OS data from the trial are not yet complete and end of life criteria typically accounts for mean OS. In the updated company base case (outlined at the end of this document), the predicted mean OS benefit for NIVO+CHEMO is 1.174 years. Further, the ERG preferred scenario reflects incremental life years of 0.717 for NIVO+CHEMO versus CHEMO, substantially exceeding the three-month benefit criteria. Additionally, using the updated database lock from CheckMate 649, NIVO+CHEMO was associated with a median OS of [redacted] months compared with [redacted] months for chemotherapy alone, indicating median OS benefit of [redacted] months. This median OS benefit increases to [redacted] months in the PD-L1 CPS ≥5 population.

		Based on this evidence, NIVO+CHEMO meets both end of life criteria for the indication of previously untreated patients with gastric cancer.
ERG comment		Median OS results calculated from ********** data are very similar to median OS results presented in the CS. The ERG still considers that the results from the CheckMate 649 trial show that an OS gain of ≥3 months is only evident for the PD-L1 CPS≥5 subgroup; an OS gain of ≥3 months is not demonstrated for the whole population.

Additional issues raised by NICE during the technical engagement process

Issue	ERG comment
Cost of PD-L1 testing	Clinical advice to the ERG is that oesophago-gastric adenocarcinomas are not tested for PD-L1 expression in the NHS. The ERG highlights that estimating the cost of PD-L1 testing is not straightforward as it requires decisions about the type of test, the cut-off point and the underlying proportions of patients treated in the NHS with PD-L1 positive disease. The ERG suggests that NICE takes advice from NHS England re the cost of PD-L1 testing.

ERG UPDATED COST EFFECTIVENESS RESULTS

The company response to technical engagement included an updated model. The new company base case model included the following revisions:

- discounting starting from the beginning of Year 1
- model baseline age (64.15 years)
- treatment effect modifiers applied to all treatments
- death on progression parameters using per investigator values
- company time to death utility values applied.

The ERG considers that all these revisions are reasonable. However, the company base case still includes the assumptions that (i) patients in the PFS health state at 30 months entering long-term remission and (ii) mortality in the long-term remission health state being equal to background mortality. The ERG's preferred base case matches the company's new base case, except that the assumptions around long-term remission have been removed.

Revised cost effectiveness results for the comparison of nivolumab+XELOX versus XELOX and nivolumab+FOLFOX versus FOLFOX for three populations (ITT, PD-L1 CPS≥1, PD-L1 CPS≥5) are presented in Table 15 and Table 16.

Table 15 ERG preferred ICER per QALY gained, nivolumab+XELOX vs XELOX (new PAS price for nivolumab, list prices for other drugs)

Analysis	Nivolumab+XELOX (new PAS)			XELOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
ITT											
A. Company base case	[redacted]	[redacted]	[redacted]	£19,985	1.556	2.146	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from model	[redacted]	[redacted]	[redacted]	£20,936	1.113	1.553	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥1											
A. Company base case	[redacted]	[redacted]	[redacted]	£19,518	1.502	2.074	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from company new base case	[redacted]	[redacted]	[redacted]	£20,388	1.062	1.485	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥5											
A. Company base case	[redacted]	[redacted]	[redacted]	£19,378	1.597	2.200	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from company new base case	[redacted]	[redacted]	[redacted]	£20,513	1.125	1.565	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CPS=combined positive score; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; ITT=intention to treat; PAS=Patient Access Scheme; PD-L1=programmed death-ligand 1;; QALY=quality adjusted life year; ITT=intention to treat; XELOX=capecitabine+oxaliplatin

Table 16 ERG preferred ICER per QALY gained, nivolumab+FOLFOX vs FOLFOX (new PAS price for nivolumab, list prices for other drugs)

Analysis	Nivolumab+FOLFOX (new PAS)			FOLFOX			Incremental			ICER	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
Whole population											
A. Company base case	[redacted]	[redacted]	[redacted]	£32,694	1.556	2.146	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from company new base case	[redacted]	[redacted]	[redacted]	£33,645	1.113	1.553	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥1											
A. Company base case	[redacted]	[redacted]	[redacted]	£31,980	1.502	2.074	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from company new base case	[redacted]	[redacted]	[redacted]	£32,850	1.062	1.485	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥5											
A. Company base case	[redacted]	[redacted]	[redacted]	£31,624	1.597	2.200	[redacted]	[redacted]	[redacted]	[redacted]	
B. ERG preferred scenario Long-term remission removed from company new base case	[redacted]	[redacted]	[redacted]	£32,759	1.125	1.565	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CPS=combined positive score; ERG=Evidence Review Group; FOLFOX=fluorouracil+folinic acid+oxaliplatin; ICER=incremental cost effectiveness ratio; ITT=intention to treat; PAS=Patient Access Scheme; PD-L1=programmed death-ligand 1; QALY=quality adjusted life year

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
Issue 4: long term remission mortality	Patients not progressing after 30 months experience mortality determined by lifetables only (i.e. general population all cause mortality)	Patients not progressing after 30 months experience mortality based on lifetables, and a standardized mortality ratio of 1.5, i.e. greater hazard of mortality than general population all cause mortality.	No update to the base case. Scenario analysis only. ICER (cost per QALY): NIVO+FOLFOX: No change to base case NIVO+XELOX: No change to base case
Issue 5: overall survival	Death on progression parameters using per investigator values	Death on progression parameters updated to per independent review committee values	ICER (cost per QALY): NIVO+FOLFOX: £50,225 NIVO+XELOX: £46,945
Issue 9: treatment modifier	Treatment modifier to account for dose intensity, missed doses, applied to nivolumab arm only	Treatment modifier to account for dose intensity, missed doses, applied to both arms	ICER (cost per QALY): NIVO+FOLFOX: £50,304 NIVO+XELOX: £47,842

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	Incremental QALYs: NIVO+FOLFOX vs FOLFOX: [redacted] NIVO+FOLFOX vs XELOX: [redacted]	Incremental costs: NIVO+FOLFOX vs FOLFOX: [redacted] NIVO+FOLFOX vs XELOX: [redacted]	ICER (cost per QALY): NIVO+FOLFOX vs FOLFOX: £51,808 NIVO+FOLFOX vs XELOX: £48,832

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