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]

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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]

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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).

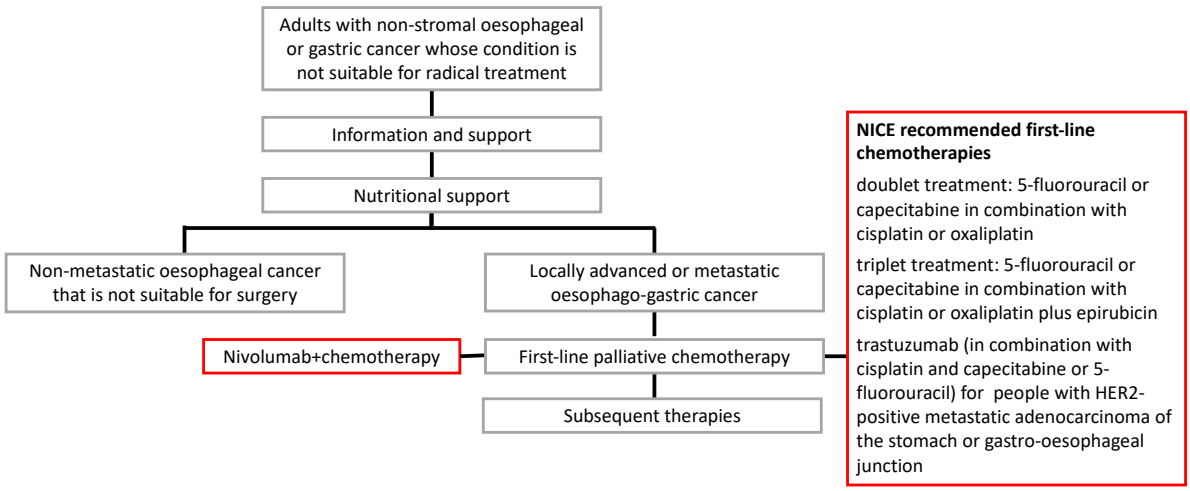


Figure 1 Treatment pathway for patients with advanced oesophago-gastric cancer

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.

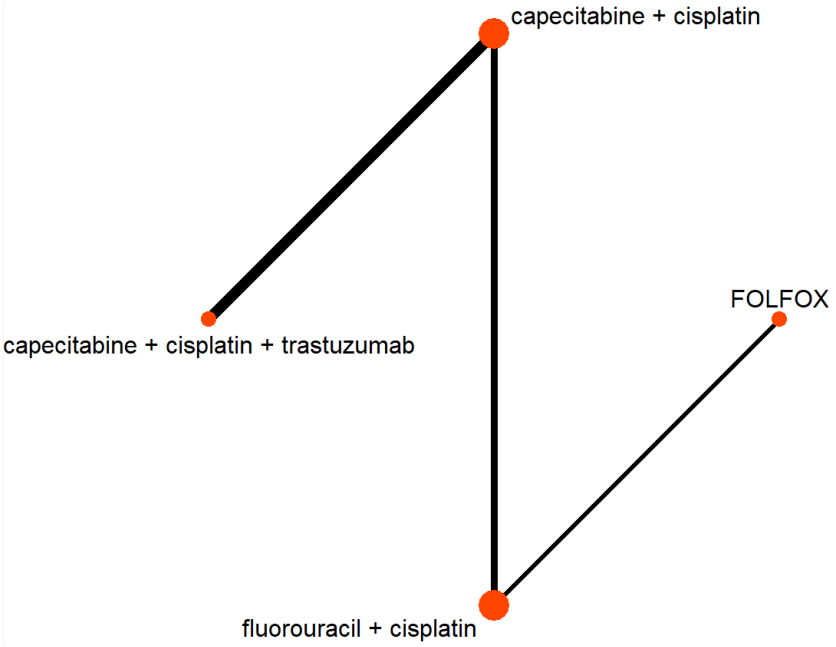


Figure 2 Network diagram for OS and PFS NMAs following clarification response

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.

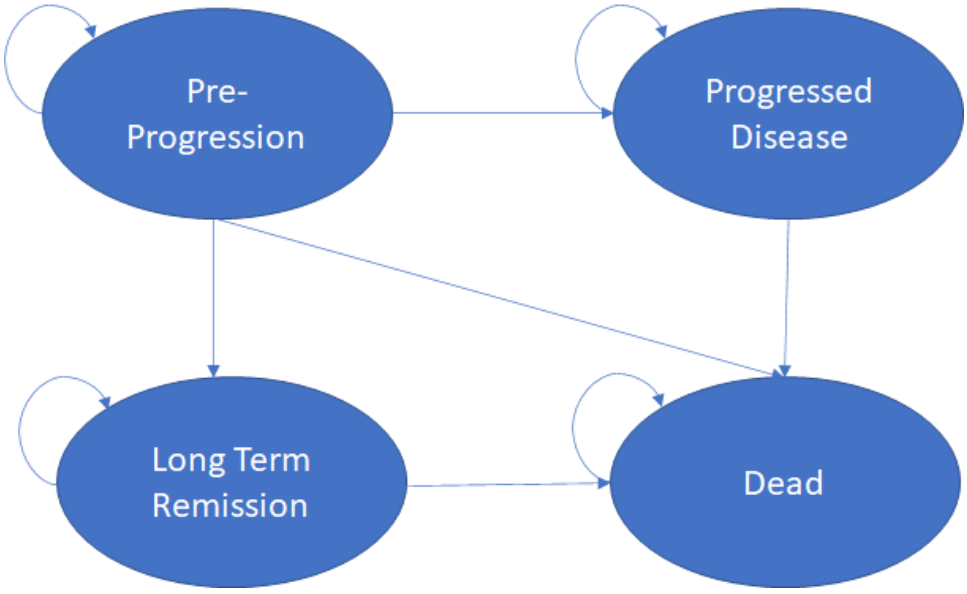


Figure 3 Structure of the company model

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.

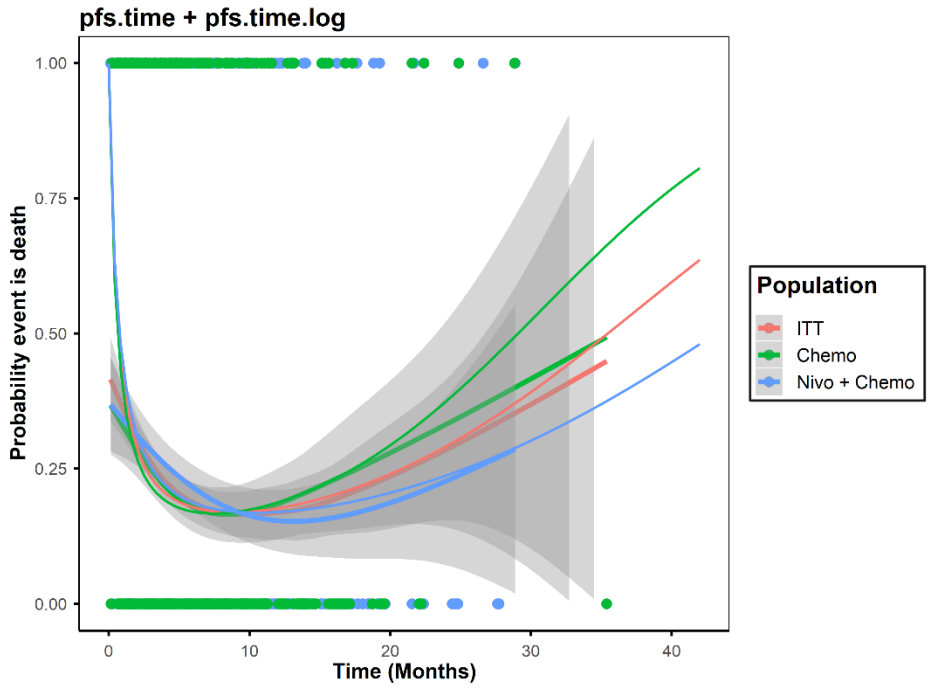


Figure 4 Probability of death on incidence of PFS based on data from the CheckMate 649 trial

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

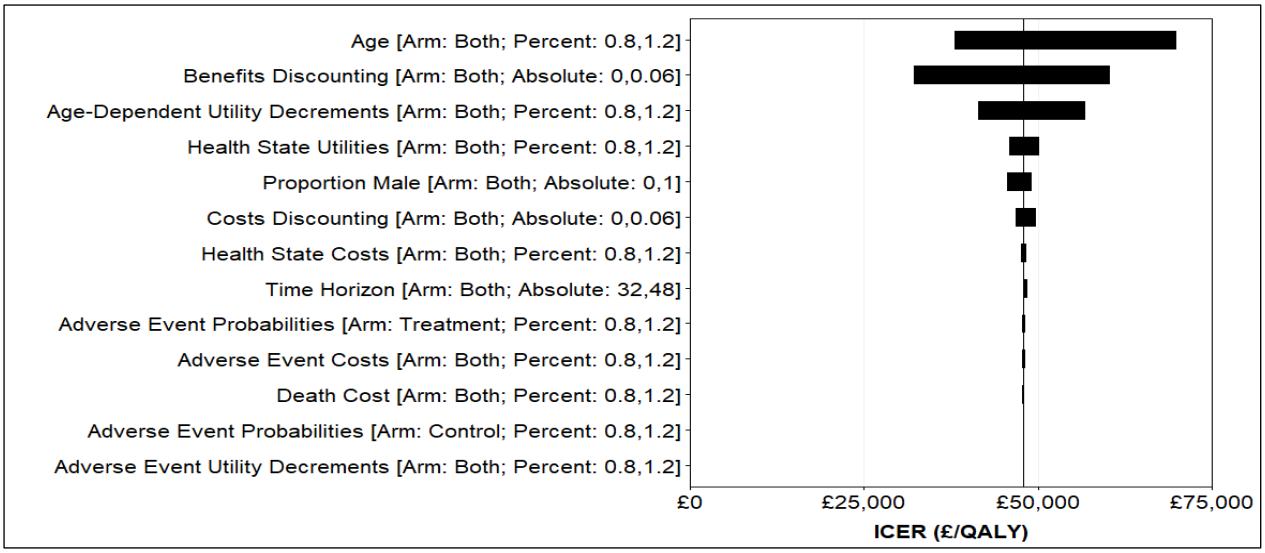
Table 30 Probabilistic pairwise cost effectiveness results of nivolumab+XELOX versus XELOX (PAS price for nivolumab, list prices for other drugs)

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.

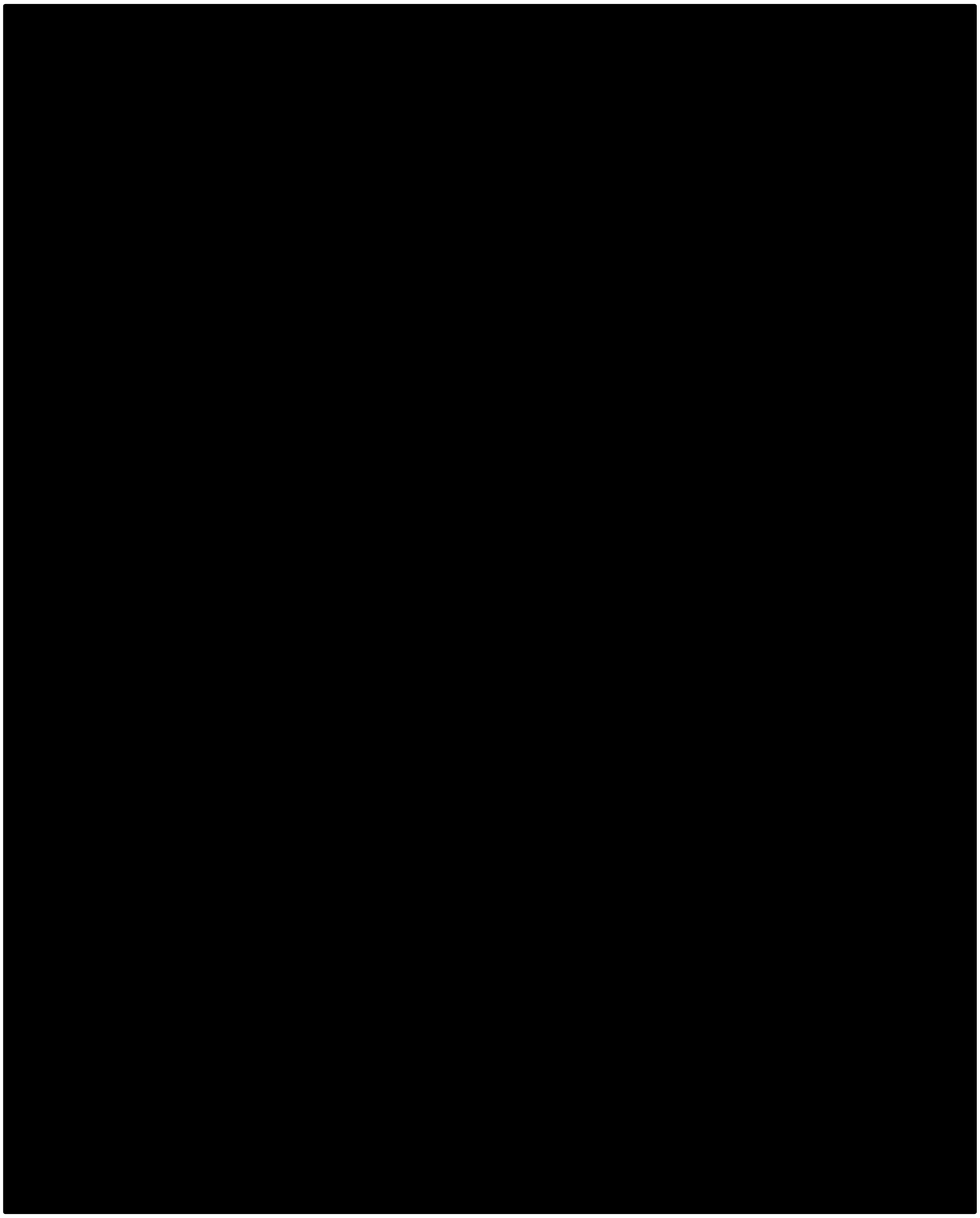
6.7 Age of patients starting treatment with advanced gastric cancer

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))