Single Technology Appraisal

Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Pharma&**

2. **Company summary of information for patients (SIP)**

3. **Clarification questions and company responses**
   a. Addendum to the clarification

4. **Expert personal perspectives from:**
   a. **Martin Scott-Brown – clinical expert, clinical expert, nominated by nominated by Astellas Pharma Ltd**
   b. **Ceri Steele, patient expert nominated by OG Support**

5. **External Assessment Report prepared by Liverpool Reviews and Implementation Group (LRiG)**

6. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Zolbetuximab with chemotherapy for untreated CLDN18.2-positive HER2-negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Document B

Company evidence submission

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Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ADCC	Antibody-dependent cellular toxicity
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BNF	British National Formulary
CAPOX	Capecitabine and oxaliplatin
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CLDN18.2	Claudin 18.2
CPS	Combined positive score
CR	Complete response
CSR	Clinical study report
DCR	Disease control rate
DoR	Duration of response
DoT	Duration of treatment
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EOX	Epirubicin, oxaliplatin and capecitabine
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
FOLFOX	Folinic acid in combination with fluorouracil and oxaliplatin
GC	Gastric cancer
GEE	Generalised estimating equation
GEJ	Gastro-oesophageal junction
GEJC	Gastro-oesophageal junction cancer
G/GEJC	Gastric/gastro-oesophageal junction cancer
GHS	Global health status
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQL	Health-related quality of life
IHC	Immunohistochemistry
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LY	Life year

Abbreviation	Definition
mFOLFOX6	Modified folinic acid in combination with fluorouracil and oxaliplatin
MIMS	Monthly Index of Medical Specialties
NE	Not estimable
NHS	National Health Service
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PFS2	Progression-free survival following subsequent anti-cancer treatment
PH	Proportional hazard
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
QLQ-C30	Quality of Life Questionnaire Core-30
QLQ-OG25	Quality of Life Oesophago-Gastric
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RxDx	Pharmaceutical Diagnostic
SAE	Serious adverse event
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TTCD	Time to confirmed deterioration
VAS	Visual analogue scale
WTP	Willingness-to-pay

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	First-line treatment of patients with advanced unresectable HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive	First-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive	Aligns with anticipated marketing authorisation
Intervention	Zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy	As per final scope	Not applicable
Comparator(s)	• Chemotherapy only, including: – Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin • For patients whose tumours express PD-L1: – Nivolumab with chemotherapy (PD-L1 CPS ≥ 5) – Pembrolizumab with chemotherapy (with CPS of 10 or more and for gastro-oesophageal junction adenocarcinoma only) – Pembrolizumab with chemotherapy (with CPS 1 or more and for gastric or GEJ adenocarcinoma – subject to NICE evaluation)	• Chemotherapy only, including: – Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin • For patients whose tumours express PD-L1 – Nivolumab with	Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a very small overlap ([redacted] between patients with GC/GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10).[1] Therefore, because the overlap in the CPS ≥ 10 patient population is very small and pembrolizumab

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		chemotherapy (PD-L1 CPS ≥ 5)	with chemotherapy is not recommended in patients with CPS ≥ 1 (NICE [ID4030][2]), pembrolizumab with chemotherapy has not been included as a comparator
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per final scope	Not applicable
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. • The use of zolbetuximab is conditional on the presence of CLDN18.2. The economic modelling should include the costs associated with diagnostic testing for CLDN18.2 in	As per final scope	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	people with gastric or gastro-oesophageal junction adenocarcinoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#companion-diagnostics)		
Key: CLDN18.2, claudin 18.2; CPS, combined positive score; GC, gastric cancer; GEJ, gastro-oesophageal junction; GEJC, gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.			

B.1.2. Description of the technology being evaluated

The draft Summary of Product Characteristics (SmPC) is presented in Appendix C.

Table 2 provides a summary of the technology being appraised.

Table 2: Technology being evaluated

UK approved name and brand name	Zolbetuximab (suggested brand name: VYLOY™)
Mechanism of action	Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human IgG1) monoclonal antibody directed against the tight junction molecule CLDN18.2. Non-clinical data suggest zolbetuximab binds selectively to cell lines transfected with CLDN18.2 or those that endogenously express CLDN18.2. Zolbetuximab depletes CLDN18.2-positive cells via ADCC and CDC.
Marketing authorisation/CE mark status	MHRA national (150-day) route with an expected marketing authorisation date of [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy is anticipated to be indicated for the 'first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive'.
Method of administration and dosage	Treatment with zolbetuximab should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Zolbetuximab is for IV use. The recommended dose is administered by IV infusion over a minimum of 2 hours. Zolbetuximab must not be administered as an IV push or bolus injection. If zolbetuximab and fluoropyrimidine- and platinum-containing chemotherapy are administered on the same day, zolbetuximab must be administered first. Zolbetuximab should be administered via IV infusion with the following dosing: • Single loading dose: 800 mg/m^2 IV on Cycle 1 Day 1 • Maintenance dose: – 600 mg/m^2 IV every 3 weeks, or – 400 mg/m^2 every 2 weeks – Duration of therapy is until disease progression or unacceptable toxicity

	Zolbetuximab should be administered in combination with fluoropyrimidine- and platinum-containing chemotherapy.
Additional tests or investigations	CLDN18.2 positivity (defined as ≥ 75% of tumour cells demonstrating moderate-to-strong membranous CLDN18 IHC staining) should be determined by a validated test. The VENTANA CLDN18 (43-14A) RxDx Assay is an under development Companion Diagnostic (CDx) IHC test for CLDN18.2. This CDx specific to zolbetuximab is expected to be approved once the medicine is licensed. See Appendix M.1.1 for further details.
List price and average cost of a course of treatment	Proposed list price: £410/100mg vial. Zolbetuximab treatment consists of an initial loading dose of 800 mg/m^2 in the initial cycle followed by maintenance doses of 600 mg/m^2 in subsequent 21-day cycles or maintenance doses of 400 mg/m^2 in subsequent 14-day cycles. The modelled acquisition cost of Zolbetuximab per 21-day treatment cycle using list price and a mean body surface area of 1.70 m^2 (based on the pooled average of SPOTLIGHT and GLOW) is: £5,106 (loading dose) and £3,830 (maintenance dose 21-day cycle)
Patient access scheme (if applicable)	NHS England have confirmed that the simple discount Patient Access Scheme (PAS) proposal for zolbetuximab (Vyloy) may be considered by NICE as part of the appraisal.

Key: ADCC, antibody-dependent cellular toxicity; CDC, complement-dependent cytotoxicity; CDx, companion diagnostic; CLDN18.2, claudin 18.2; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; IHC, immunohistochemistry; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, Patient Access Scheme; PASLU, Patient Access Schemes Liaison Unit; RxDx, Pharmaceutical Diagnostic.
Source: Zolbetuximab SmPC.[3]

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

B.1.3.1. Disease overview

Gastric/gastro-oesophageal junction cancer (G/GEJC) comprises cancer that occurs in the lining of the stomach and the gastro-oesophageal junction (GEJ; between the stomach and the oesophagus), respectively.[4, 5] Adenocarcinoma is the most common type of G/GEJC and affects approximately 95% of patients with the disease.[6] There are several known risk factors associated with G/GEJC including increased age (≥ 70 years)[7, 8], obesity[8, 9], smoking[7, 10, 11], diet[7, 8, 10, 12, 13] and being male.[12] As gastric cancer (GC) and gastro-oesophageal junction cancer (GEJC) are similar, both histologically and in terms of treatment response, patients with GC and GEJC are commonly the combined target population in clinical trials.[14-16] Therefore, data from GC are applied to the G/GEJC population in this submission when data from GEJC are not available.

In the UK, GC accounts for approximately 2% of all new cancer cases and 3% of all cancer deaths.[17] GC is more common in men than women, with an average of 3,405 new cases diagnosed in men and 1,810 new cases in women each year in England between 2016 and 2018.[18] Around half of all new cases of GC are diagnosed in people aged 75 years and over.[19] The 5-year age-standardised survival rate for patients newly diagnosed patients with GC is 21.6%, reducing to 13.9% in patients aged ≥ 75 years.[20] Survival is strongly related to stage at diagnosis, with 1-year age-standardised survival falling from 88.5% at Stage I to 21.4% at Stage IV.[20] There are currently no UK-specific 5-year survival statistics for Stage IV GC, as most people do not survive for 5 years after diagnosis. In a study including 511 patients with advanced oesophagogastric adenocarcinoma treated at the Royal Marsden between 2009 and 2015 (58% were human epidermal growth factor receptor 2 [HER2]-negative), 2% of patients remained alive at the end of follow-up (105 months).[21]

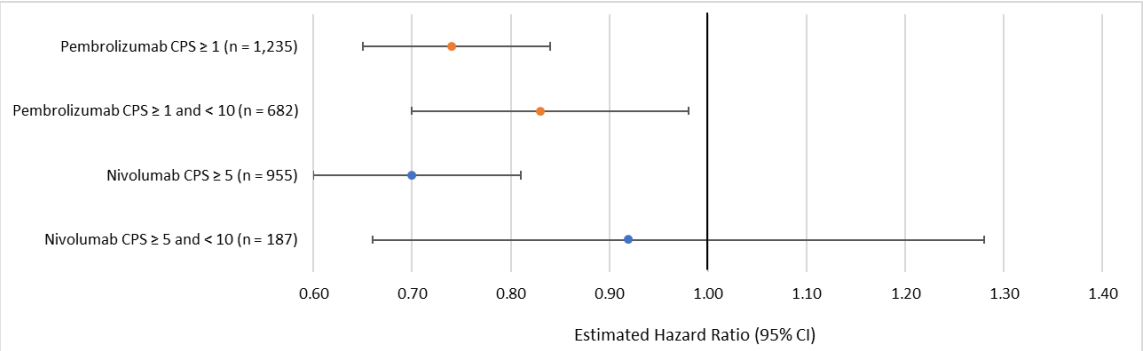
The management of G/GEJC is evolving towards biomarker identification with targeted treatment options.[4, 22] Predictive biomarkers of relevance to current UK clinical practice include HER2 and, more recently, programmed death-ligand 1 (PD-

L1). PD-L1 prevalence in G/GEJC has been reported in multiple studies, as assessed by PD-L1 combined positive score (CPS). In the CheckMate 649 study, PD-L1 CPS ≥ 5 was 60% (955/1,581) among patients with HER2-negative disease.[23] Other studies have reported PD-L1 CPS ≥ 5 ranging between 13% and 31%.[24-26] However, some studies suggest that CPS positivity rates in the real world may be smaller than those observed in clinical trials.[27, 28] For patients with HER2-negative tumours, the checkpoint inhibitors (CPIs) pembrolizumab and nivolumab are currently reimbursed in the UK depending on tumour PD-L1 expression based on CPS (see Section B.1.3.3).[29, 30]

Limited expression of PD-L1 means many patients are ineligible for treatment with CPIs. In the specific population eligible for zolbetuximab (i.e., HER2-negative and Claudin 18.2 [CLDN18.2]-positive), the overlap between CLDN18.2-positivity and PD-L1 CPS ≥ 5 was 17.4%, whilst with PD-L1 CPS ≥ 10 was [redacted]%. This is consistent with the Pellino et al study, a single centre Italian study which found that approximately 18% (21/117) of patients who were CLDN18.2-positive also had PD-L1 CPS ≥ 5.[28]

Furthermore, trial data show that the efficacy of CPIs is dependent on PD-L1 CPS, and patients with lower CPS scores generally have less benefit (Figure 1).[4, 22, 31-33] Outcomes for both patients with HER2-negative disease ineligible for CPIs (PD-L1 CPS < 5 or with contraindications) and patients with intermediate expression (PD-L1 CPS ≥ 5 and <10) remain poor, with current chemotherapies associated with high rates of disease progression and poor overall survival (OS).[34-36]

Figure 1: Forest plot of treatment effect of CPI + chemotherapy on OS by PD-L1 CPS status



Key: CI, confidence interval; CPI, checkpoint inhibitor; CPS, combined positive score; OS, overall survival; PD-L1, programmed death-ligand 1; SmPC, Summary of Product Characteristics.
Notes: Data included are from subgroup analyses based on PD-L1 CPS status for pembrolizumab or nivolumab in combination with chemotherapy.
Source: Pembrolizumab SmPC[32]; nivolumab SmPC.[33]

CLDN18.2 is a tight junction protein selectively expressed in the gastric mucosa that may be retained during malignant transformation, representing a novel biomarker and promising treatment target in G/GEJC.[37, 38] Molecular characterisation of CLDN18.2 expression in G/GEJC has demonstrated CLDN18.2 positivity (defined as moderate-to-strong membrane expression in ≥ 75% of tumour cells) estimates in 24.0–51.4% of patients.[24, 28, 39, 40] The estimate most relevant to this submission is from the SPOTLIGHT and GLOW trials (CLDN18.2 positivity in 42.3% of patients), as this provides data from the largest sample size from two multicentre studies that include UK patients.[41] Therapeutic targeting of CLDN18.2 with zolbetuximab in addition to standard chemotherapy leads to improved survival in patients with HER2-negative, locally advanced unresectable or metastatic G/GEJC that is positive for CLDN18.2 (see Section B.2.6).[24, 42]

CLDN18.2 expression has not been shown to be a prognostic factor to date in the natural history of G/GEJC or response to chemotherapy; this conclusion is based on four studies.[28, 39, 43, 44] Dottermusch et al and Arnold et al are retrospective studies of German patients with G/GEJC, including 430 and 414 patients, respectively. Both studies found no association between CLDN18.2 expression and OS.[43, 44] Pellino et al and Kubota et al are retrospective studies looking at the correlation between CLDN18.2 expression with other biomarkers that may be associated with

prognosis.[28, 39] No significant correlation between CLDN18.2 positivity (based on the VENTANA CLDN18 43-14A assay and the 75% cut-off for defining positive expression at ≥75% of tumour cells) and the expression of biomarkers such as MMRd, PD-L1 and HER2 was observed. Furthermore, the OS curves stratified by CLDN18.2 were very similar, supporting the conclusion that CLDN18.2 expression is not a prognostic factor or effect modifier for chemotherapy.

The VENTANA CLDN18 (43-14A) Pharmaceutical Diagnostic (RxDx) Assay, a semi-quantitative immunohistochemistry (IHC) assay, has been developed as a companion diagnostic to aid in identifying patients with G/GEJC who may be eligible for treatment with zolbetuximab (see Appendix M.1.1 for further details). The analytical performance of this investigational assay has demonstrated repeatability and consistency, including between pathologists and between laboratories, as well high levels of specificity and sensitivity.[45] When approved, the VENTANA CLDN18 (43-14A) RxDX Assay will be the only analytically and clinically validated test for zolbetuximab patient selection. However, data from the RING study confirms that a range of other antibodies and platforms can also be used to achieve the required quality of IHC staining for evaluation of CLDN18.2 status in G/GEJC samples.[46] IHC testing methodology is well established within molecular pathology laboratories, enabling easy implementation of new biomarkers in to routine clinical testing. Furthermore, CLDN18 staining patterns and scoring is well documented, and a clear cut-off for CLDN18.2 positivity has been validated, which is important when compared to interpretation of other IHC biomarkers in GC.[42, 47]

In contrast, there are a number of issues with testing PD-L1 expression in G/GEJ adenocarcinoma using CPS, especially with interpretation at lower cut-offs. Recent studies demonstrate that there can be variability in PD-L1 CPS results among pathologist readers.[48-50] Additionally, although studies are limited, some studies show differences in results when using the 22C3 assay and 28-8 assay to measure PD-L1 CPS in GC, particularly for low CPS.[51-55] Furthermore, there is uncertainty in the concordance rate of PD-L1 expression between primary tumours and metastases in G/GEJC, and also between surgical specimen and smaller biopsy samples.[56-58] Whether the uncertainty in CPS levels, particularly at lower cut-offs,

relates to the smaller clinical benefit of CPIs in patients with lower CPS (Figure 1)[32, 33], has not been investigated to the company's knowledge.

B.1.3.2. Burden of disease

Symptoms of G/GEJC depend on the extent and stage of disease. Patients with early-stage G/GEJC usually have mild or non-specific symptoms; therefore, patients are typically diagnosed at advanced or late stage disease, and present with more severe symptoms such as abdominal pain, weight loss, anorexia, vomiting, gastric obstruction and bleeding.[59-61]

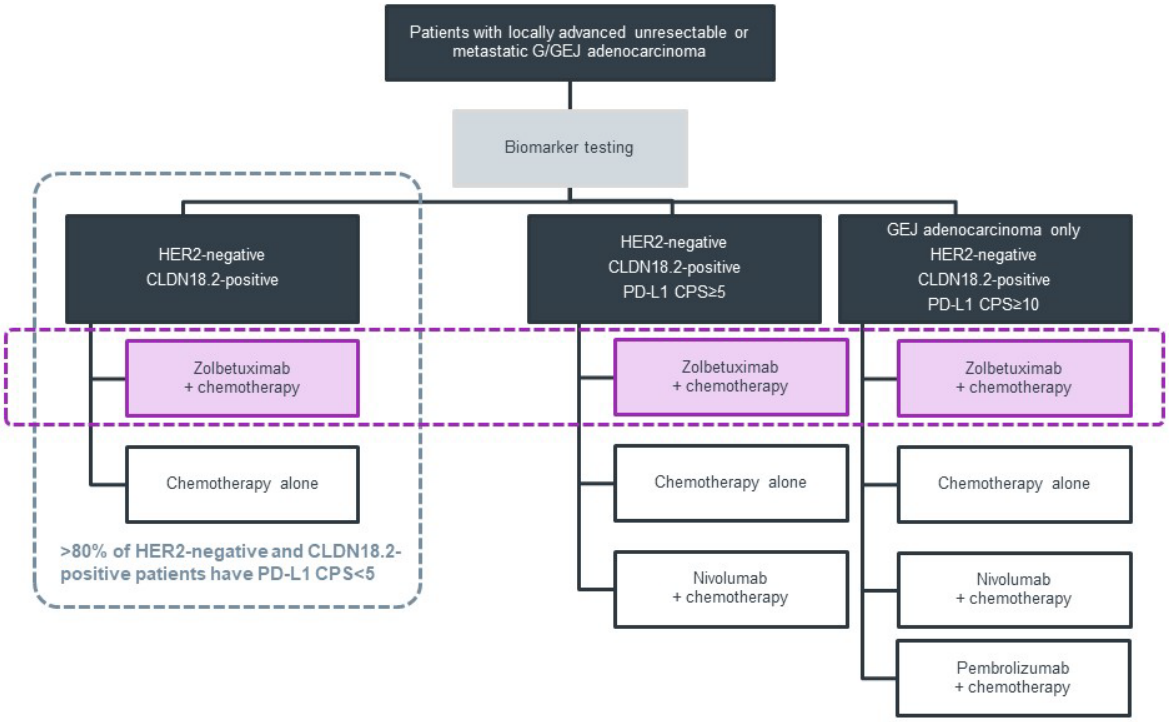
Given the range of symptoms, each with their associated burden, G/GEJC can substantially impact patient health-related quality of life (HRQL) including physical, emotional and social functioning, which worsen with disease progression. Patients with G/GEJC experience worsening HRQL as the disease progresses, with patients reporting worse physical, emotional and social functioning in the advanced stages of disease.[62] In addition, HRQL is worse for patients with G/GEJC compared with patients with other cancers.[63, 64] In a study comparing HRQL across different gastrointestinal cancers (n = 335), patients with GC had significantly worse general wellbeing (p = 0.001), functional difficulties (p = 0.001) and symptoms (p = 0.001) than patients with colorectal cancer.[63] Another study reported that in a comparison of eight different cancer types (n = 350), patients with G/GEJC had the worst mean score for physical functioning, the third worst score for emotional functioning, the sixth worst cognitive functioning score, the fifth worst global health status, and the fourth worst role and social functioning score.[64]

Caregivers of patients with G/GEJC also experience substantial burden, as caring for a patient with G/GEJC is associated with depression and negative impacts on HRQL.[65, 66] In addition, worry about the patient's death or deterioration, frustration about the adverse effects of treatment, difficulty in managing the patient's pain, and feelings of guilt and anxiety all increase the caregiver's psychological burden.[65] Caregivers can also suffer financial difficulties due to time spent on illness-related activities and subsequent productivity loss.[67]

B.1.3.3. Current pathway of care

Figure **2**shows the current clinical pathway of care for locally advanced or metastatic HER2-negative G/GEJC patients in England and the proposed placement for zolbetuximab within the treatment pathway.

Figure 2**: Current pathway of care for locally advanced or metastatic HER2-negative G/GEJC adenocarcinoma and proposed positioning of zolbetuximab**



Key: CLDN18.2, claudin 18.2; CPS, combined positive score; GEJ, gastro-oesophageal junction; G/GEJ, gastric/gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.
Notes: Pembrolizumab + chemotherapy currently being assessed for PD-L1 CPS ≥ 1, draft guidance states that pembrolizumab + chemotherapy is not recommended in patients with PD-L1 CPS ≥ 1.[2]
Source: NICE [NG83] 2018[68]; NICE [TA737] 2021[30]; NICE [TA857] 2023[29]; NICE [ID4030] 2024[2]; Shitara et al. 2023.[41]

The NICE clinical guideline 83 (NG83) recommends palliative combination chemotherapy as first-line treatment for patients who have a performance status of 0 to 2 and no significant comorbidities.[68] Chemotherapy combinations include:

- Doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
- Triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin + epirubicin

Clinical expert input provided during the recent NICE appraisals of pembrolizumab and nivolumab indicated that dual therapy is preferred with most people receiving capecitabine and oxaliplatin (CAPOX; also known as XELOX).[30, 69] Quantitative market research (n = 48 medical and clinical oncologists) undertaken by Astellas demonstrated predominant use of CAPOX for the treatment of first-line, HER2-negative metastatic G/GEJC along with significant use of other regimens including folinic acid in combination with fluorouracil and oxaliplatin (FOLFOX), and cisplatin in combination with either capecitabine or fluorouracil.[70]

More recently, the CPIs pembrolizumab and nivolumab have been reimbursed for use in patients with HER2-negative disease. However, as these recommendations, licenses and indeed efficacy depend on tumour PD-L1 expression based on CPS (as assessed by the antibody used in their respective clinical trials[71]), not all patients are eligible or will benefit (see Section B.1.3.1):

- Nivolumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated, HER2-negative, advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 5, if the company provides it according to the commercial arrangement[29]
- Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated, locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative GEJ adenocarcinoma in adults whose tumours express PD-L1

with a CPS ≥ 10, if the company provides it according to the commercial arrangement[30]

B.1.3.3.1. Positioning of zolbetuximab within the treatment pathway

Zolbetuximab is anticipated to be indicated for 'first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative G/GEJ adenocarcinoma whose tumours are CLDN18.2 positive'.[3]

Astellas has conducted a targeted literature review, which demonstrated that PD-L1 CPS is not a prognostic factor in G/GEJC.[16] In brief, eight studies reported on the association of PD-L1 status with outcomes in populations that are predominantly inoperable or metastatic GC/GEJC and in which treatment was not assigned as part of the study protocol. Five studies showed no association between PD-L1 and survival. Of the three remaining studies, in one study patients received third-line immunotherapy, which was associated with longer survival in patients with PD-L1 CPS ≥ 5; one study evaluated PD-L1 expression as circulating expression by an RT-PCR assay (rather than IHC of tumour samples as in clinical practice); one study reported ambiguous results. Furthermore, the subgroup analyses of the five identified CPI trials by CPS expression showed overlapping confidence intervals in the median progression-free survival (PFS) and OS in the chemotherapy arms, and similar response rates.

Post hoc subgroup analyses of the pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated that PD-L1 CPS is not a treatment-effect modifier for zolbetuximab (see Section B.2.7).[72] Therefore, zolbetuximab offers an effective treatment option for patients with HER2-negative, CLDN18.2-positive G/GEJC regardless of PD-L1 CPS status. This is supported by the 2024 Pan-Asian adapted European Society for Medical Oncology (ESMO) Clinical Practice Guidelines that recommend the addition of zolbetuximab to chemotherapy for patients with CLDN18.2-positive HER2-negative tumours in the first-line metastatic disease setting.[73] These guidelines state that although it is difficult to select either zolbetuximab + chemotherapy or a CPI + chemotherapy due to the absence of direct comparisons, zolbetuximab might be the preferred choice for patients with PD-L1-

negative or low expression (i.e. CPS < 5 and CLDN18.2-positive tumours). Additionally, these guidelines note that when treating patients whose disease has overlapping characteristics (such as CPS ≥ 5 and CLDN18.2 positivity), choosing between these two regimens becomes less clear-cut, and either approach could be a reasonable treatment option.[73]

Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a small overlap (17.4%) between patients eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and CPIs (PD-L1 CPS ≥ 5).[41] Therefore, the majority of patients who are eligible for zolbetuximab are limited to chemotherapy as their sole alternative treatment option, which is the main comparator in this submission. For patients eligible for CPIs, nivolumab with platinum- and fluoropyrimidine-based chemotherapy is the relevant comparator for patients with HER2-negative G/GEJC with PD-L1 CPS ≥ 5.[29]

Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW), in the patients who could be tested, demonstrated a very small overlap ([redacted] between patients with GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10).[1] Therefore, because the overlap in the CPS ≥ 10 patient population is very small and pembrolizumab with chemotherapy is not recommended in patients with CPS ≥ 1 (NICE [ID4030][2]), pembrolizumab with chemotherapy has not been included as a comparator.

B.1.3.4. Unmet need

Survival rates are poor for patients with HER2-negative G/GEJC, particularly those with advanced disease, with 1-year age-standardised survival falling from 88.5% at Stage I to 21.4% at Stage IV and (See Section B.1.3.1)[20], and due to non-specific presenting symptoms, patients are usually diagnosed at a late stage.[59-61]

There is a lack of effective first-line targeted treatment options for patients with HER2-negative locally advanced unresectable or metastatic G/GEJC that can improve poor survival rates.[34, 36] While the CPIs pembrolizumab and nivolumab have been reimbursed for use in patients with HER2-negative G/GEJC, these

recommendations depend on tumour PD-L1 CPS. Trial data show that the efficacy of these CPIs is dependent on CPS, and patients with lower CPS scores generally have less benefit (see Figure 1); as such, not all patients are eligible or will benefit (see Section B.1.3.1).[29, 30] Additionally, patients with disease such as liver metastases or autoimmune conditions are often unsuitable for treatment with CPIs.[32, 33]

For patients with HER2-negative tumours who are ineligible for CPIs (PD-L1 CPS < 5), chemotherapy is the current standard of care but is associated with high rates of disease progression and poor OS, highlighting the unmet need in these patients.[34-36]

There is an urgent unmet need for novel and effective first-line therapies against targets that are selectively expressed in G/GEJC, such as CLDN18.2, in order to provide additional treatment options for patients with HER2-negative, locally advanced unresectable or metastatic G/GEJC, regardless of PD-L1 CPS status.

B.1.4. Equality considerations

No equality issues are foreseen.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the systematic literature review (SLR) process and methods used to identify and select the clinical evidence relevant to the technology being evaluated. Of the 90 studies identified by the SLR, only four studies (across 12 publications) were considered relevant to the decision problem specified in the final scope (Table 1); these included three studies providing efficacy and safety evidence for zolbetuximab + chemotherapy, and one for nivolumab + chemotherapy.

B.2.2. List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for zolbetuximab is presented in Table 3.

The pivotal trials for zolbetuximab in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable/metastatic G/GEJ adenocarcinoma are the two Phase III trials SPOTLIGHT and GLOW.[24, 42] Supportive evidence is provided by the earlier FAST trial, a Phase II trial designed to assess the efficacy and tolerability of zolbetuximab in patients with advanced G/GEJ or oesophageal adenocarcinoma with moderate-to-strong CLDN18.2 expression in ≥ 40% tumour cells.[74]

Table 3: Clinical effectiveness evidence

Study	**SPOTLIGHT**	**GLOW**	**FAST**
Study design	Phase III, double-blind RCT	Phase III, double-blind RCT	Phase II, randomised, open-label trial
Population	Adults with CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	Adults with CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	Adults with CLDN18.2-positive (≥ 40% of tumour cells with 2+ or 3+ staining intensity), HER2/neu-negative patients with HER2/neu-positive status, but not eligible for trastuzumab therapy by discretion of the investigator, advanced G/GEJ and oesophageal

Study	SPOTLIGHT	GLOW	FAST
			adenocarcinoma Relevant to this appraisal is the subgroup with CLDN18.2 expression in ≥ 70% of tumour cells
Intervention(s)	Zolbetuximab + mFOLFOX6 (n = 283)	Zolbetuximab + CAPOX (n = 254)	Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 77)
Comparator(s)	mFOLFOX6 (n = 282)	CAPOX (n = 253)	EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 84)
Indicate if study supports application for marketing authorisation	Yes	Yes	No
Indicate if study used in the economic model	Yes	Yes	No
Rationale if study not used in the model	N/A	N/A	The relevant subgroup from FAST was included in a scenario of the indirect treatment comparison. As results were similar to the base-case analysis without the FAST subgroup, the scenario analysis was not taken forward to the economic model.
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival** • Response rate • Adverse events • HRQL	• **Overall survival** • **Progression-free survival** • Response rate • Adverse events • HRQL	• **Overall survival** • **Progression-free survival** • Response rate • Adverse events
All other reported outcomes	• Time to confirmed deterioration • Pharmacokinetics • Immunogenicity	• Time to confirmed deterioration • Pharmacokinetics • Immunogenicity	• Time to progression

Study	SPOTLIGHT	GLOW	FAST
Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin and capecitabine; G/GEJ, gastric/gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; HRQL, health-related quality of life; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N/A, not applicable; RCT, randomised controlled trial. **Notes:** Bolded outcomes are those used in the economic modelling. **Source:** Shitara et al. 2023[24]; SPOTLIGHT clinical study report[75]; Shah et al. 2023[42]; GLOW clinical study report[76]; Sahin et al. 2021.[74]			

Full details of the pivotal trials (SPOTLIGHT and GLOW) are provided in Sections B.2.3 to B.2.6 of this submission. Relevant outcomes of the supportive trial (FAST) are provided in Section B.2.6; details of the methods, population and safety data are provided in Appendix M.4.

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

B.2.3.1. SPOTLIGHT

B.2.3.1.1. Study design

SPOTLIGHT was a Phase III, multicentre, double-blind, randomised controlled trial (RCT) designed to evaluate the efficacy and safety of zolbetuximab + folinic acid in combination with fluorouracil and oxaliplatin (mFOLFOX6) versus placebo + mFOLFOX6 as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma.[24, 75] This study was conducted at 232 sites in 20 countries, with 9 sites in the UK.[77] The final database lock for the SPOTLIGHT trial took place on [redacted]. Data analysis is currently ongoing and is expected to be submitted with responses to clarification questions.

To determine the effects of zolbetuximab + mFOLFOX6 compared with placebo + mFOLFOX6, 565 patients were randomised in a 1:1 ratio to two treatment arms[75]:

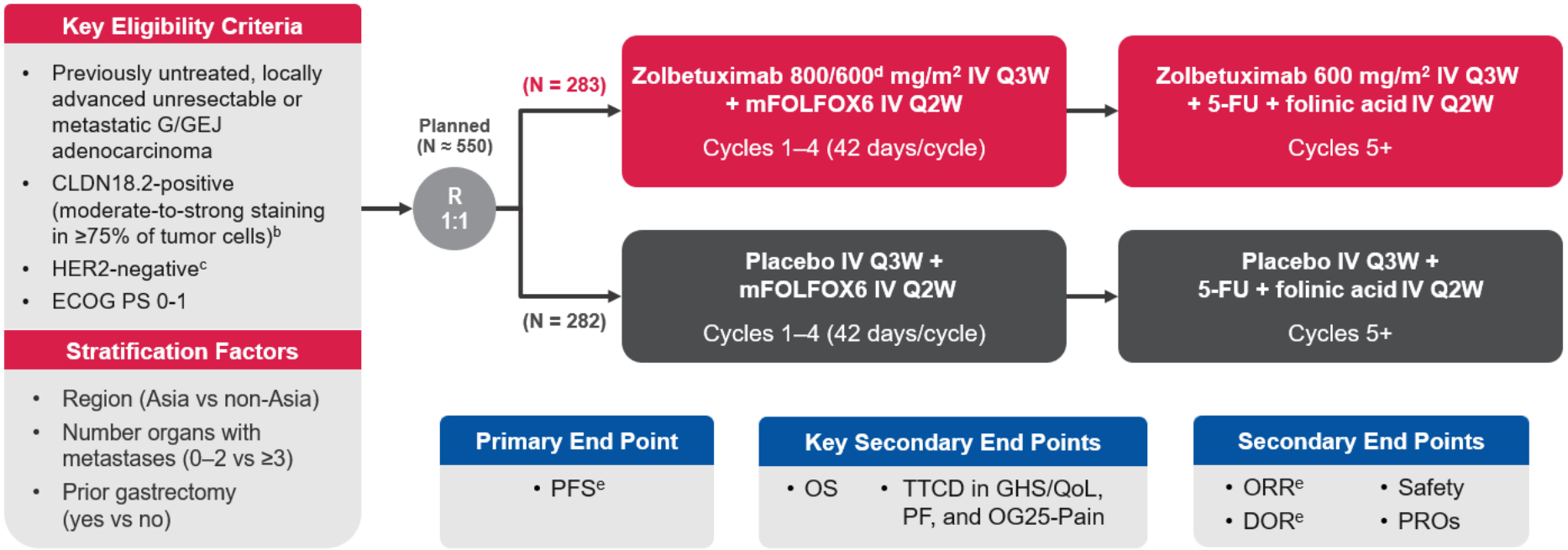
- Arm A – zolbetuximab + mFOLFOX6
- Arm B – placebo + mFOLFOX6

The study consisted of six periods: screening, treatment, safety follow-up, post-treatment follow-up for PFS, long-term follow-up for PFS following subsequent anti-cancer treatment (PFS2), and OS. The SPOTLIGHT trial design is presented in Figure 3 and a summary of the trial methodology is presented in Appendix M.1.

For inclusion in SPOTLIGHT, patients were ≥ 18 years of age with CLDN18.2-positive (defined as ≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining, determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay), HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma.[24, 75, 78] Patients who met the trial criteria also had radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and adequate organ function.[24, 75, 78]

The primary efficacy endpoint of SPOTLIGHT was PFS per RECIST 1.1, as determined by an independent review committee (IRC).[24, 75, 78] Key secondary endpoints included OS and time to confirmed deterioration (TTCD). Other secondary endpoints included objective response rate (ORR), duration of response (DoR) and HRQL. Details of all endpoints are provided in Figure 3 and Appendix M.3.1.

Figure 3: Study design of SPOTLIGHT



Key: 5-FU, fluorouracil; CLDN18.2, claudin 18.2; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G/GEJ, gastric/gastro-oesophageal junction; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRC, independent review committee; IV, intravenous; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; QoL, quality of life; R, randomised; RECIST, Response Evaluation Criteria In Solid Tumours; TTCD, time to confirmed deterioration.
Notes: [a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m^2 at Cycle 1 Day 1 followed by 600 mg/m^2 on Cycle 1 Day 22 and Days 1 and 22 of subsequent cycles; [e] As per RECIST v1.1 by IRC.
Source: Shitara et al. 2023.[47]

B.2.3.1.2. Patient characteristics

The baseline characteristics for patients in SPOTLIGHT are presented in Table 4. The median age of patients was 61.0 years, 62.1% were male, 76% of patients presented with GC, 24% of patients presented with GEJC, and the majority of patients (99.8%) had an ECOG performance status of either 0 or 1.[24, 75] Demographic and baseline characteristics were generally similar between the two study groups, except for disease histology.

Table 4: SPOTLIGHT: patient demographics and baseline disease characteristics

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Median age (IQR), years	62.0 (51.0, 69.0)	60.0 (50.0, 69.0)
Sex, n (%)		
Male	176 (62.2)	175 (62.1)
Female	107 (37.8)	107 (37.9)
Region, n (%)		
Asia	88 (31.0)	89 (32.0)
Non-Asia	195 (69.0)	193 (68.0)
Ethnicity, n (%)		
Hispanic or Latino	36 (13.8)	37 (14.8)
Not Hispanic or Latino	225 (86.2)	213 (85.2)
Missing	22 (8.0)	32 (11.0)
Organs with metastases, n (%)		
0–1	219 (77.0)	219 (78.0)
≥ 3	64 (23.0)	63 (22.0)
Location of metastases, n (%)*		
Lymph node	101 (36.0)	109 (39.0)
Peritoneum	94 (33.0)	76 (27.0)
Liver	62 (22.0)	75 (27.0)
Lung	36 (13.0)	33 (12.0)
Bone	28 (10.0)	23 (8.0)
Abdominal cavity	19 (7.0)	17 (6.0)
Ovary	16 (6.0)	19 (7.0)
Previous gastrectomy, n (%)		
Yes	84 (30.0)	82 (29.0)
No	199 (70.0)	200 (71.0)

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Primary site, n (%)		
GC	219 (77.4)	210 (74.5)
GEJC	64 (22.6)	72 (25.5)
Lauren classification, n (%)		
Diffuse	82 (29.1)	117 (42.1)
Intestinal	70 (24.8)	66 (23.7)
Mixed	31 (11.0)	13 (4.7)
Unknown	49 (17.4)	40 (14.4)
Other	50 (17.7)	42 (15.1)
Missing	1 (< 1.0)	4 (1.0)
ECOG performance status score, n (%)		
0	125 (44.8)	115 (41.4)
1	153 (54.8)	163 (58.6)
2†	1 (0.4)	0 (0.0)
Missing‡	4 (1.0)	4 (1.0)
Measurable disease, n (%)		
Yes	211 (75)	211 (75)
No	72 (25)	71 (25)

Key: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented. † Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG performance status score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment. ‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG performance status score of 0 or 1 and were thus eligible for enrolment.
Source: Shitara et al. 2023[24]; SPOTLIGHT clinical study report.[75]

B.2.3.2. GLOW

B.2.3.2.1. Study design

GLOW is a Phase III, multicentre, double-blind RCT designed to evaluate the efficacy and safety of zolbetuximab + CAPOX versus placebo + CAPOX as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma.[42, 76] This study was conducted

at 176 sites in 18 countries, with 4 sites in the UK.[79] The final database lock for the GLOW trial took place on [redacted], and data analysis is currently ongoing.

To determine the effects of zolbetuximab + CAPOX compared with placebo + CAPOX, 507 patients were randomised in a 1:1 ratio to two treatment arms[76]:

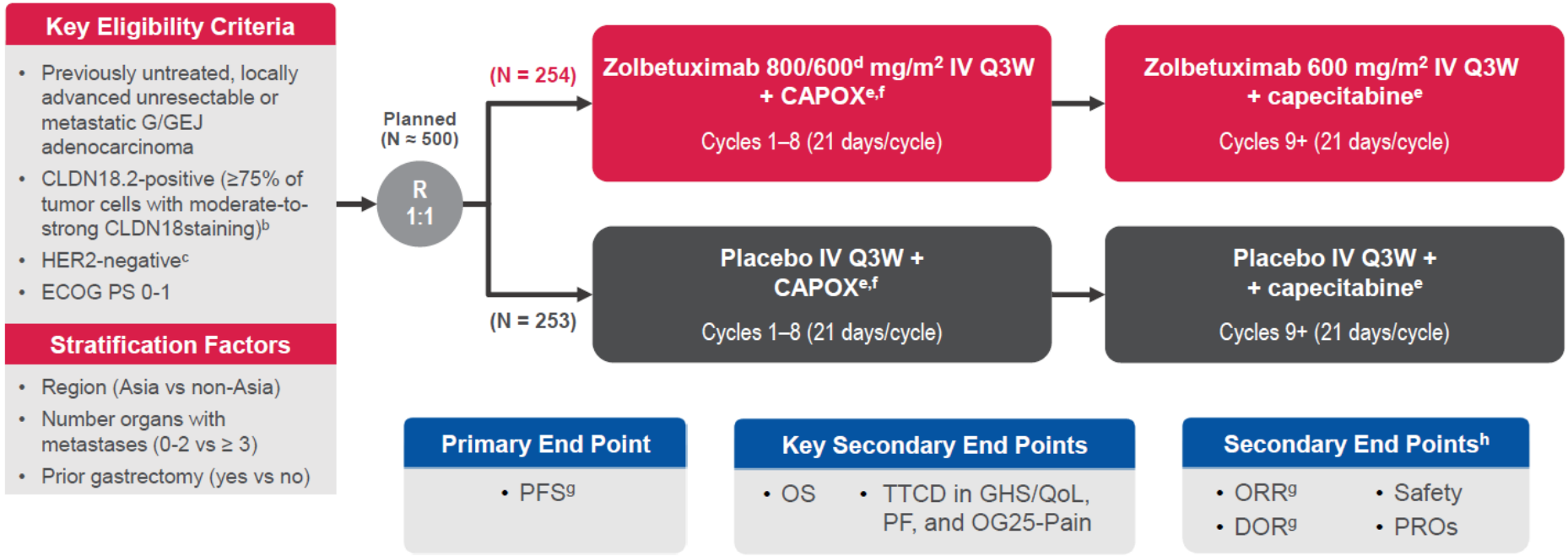
- Arm A – zolbetuximab + CAPOX
- Arm B – placebo + CAPOX

The study consisted of six periods: screening, treatment, safety follow-up, post-treatment follow-up for PFS and long-term follow-up for PFS2 and OS. The GLOW trial design is presented in Figure 4, and a summary of the trial methodology is presented in Appendix M.1.

For inclusion in GLOW, patients were ≥ 18 years of age with CLDN18.2-positive (defined as ≥ 75% of tumour cells with moderate-to-strong membranous CLDN18 staining, determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay), HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GEJC, with radiologically evaluable disease according to RECIST version 1.1, an ECOG performance status score of 0 or 1, and adequate organ function.[42, 76]

The primary efficacy endpoint of GLOW is PFS per RECIST 1.1 by IRC.[42, 76] Key secondary endpoints include OS and TTCD; other secondary endpoints include ORR, DoR and HRQL. Details of all endpoints are provided in Figure 4 and Appendix M.3.2.

Figure 4: Study design for GLOW



Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18 isoform 2; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; QoL, quality of life; R, randomised; TTCD, time to confirmed deterioration.
Notes: [a]Study was conducted at 166 sites in 18 countries across Asia, Europe, North America, and South America. [b]By central IHC using the VENTANA CLDN18.2 (43-14A) RxDx. [c]By central or local HER2 testing (IHC 0–1, or IHC2/FISH-). [d]800 mg/m^2 on Day 1 of subsequent cycles. [e]1,000 mg/m^2 capecitabine orally BID on Days 1–14 of each cycle. [f]130 mg/m^2 oxaliplatin IV on Day 1 of each cycle. [g]RECIST V 1.1 per IRC assessment.
Source: Xu et al. 2023.[80]

B.2.3.2.2. Patient characteristics

The baseline characteristics for patients in GLOW are presented in Table 5. The median age of patients was 60.0 years, 62.1% were male, 84.4% of patients presented with GC, 15.6% of patients presented with GEJC, and all patients (100.0%) had an ECOG performance status of either 0 or 1.[42, 75] Demographic and baseline characteristics were generally well-balanced between groups.

Table 5: GLOW: patient demographics and baseline disease characteristics

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
Median age (range), years	61.0 (22, 82)	59.0 (21, 83)
Sex, n (%)*		
Male	159 (62.6)	156 (61.7)
Female	95 (37.4)	97 (38.3)
Region, n (%)		
Asia	157 (61.8)	158 (62.5)
Non-Asia	97 (38.2)	95 (37.5)
Ethnicity, n (%)		
Hispanic or Latino	10 (4.0)	7 (2.8)
Not Hispanic or Latino	242 (96.0)	241 (97.2)
Missing	2	5
Organs with metastases, n (%)		
0–2	189 (74.4)	188 (74.3)
≥ 3	65 (25.6)	65 (25.7)
Prior gastrectomy, n (%)		
Yes	75 (29.5)	75 (29.6)
No	179 (70.5)	178 (70.4)
Primary site, n (%)		
GC	219 (86.2)	209 (82.6)
GEJC	35 (13.8)	44 (17.4)
Lauren classification, n (%)		
Diffuse	87 (34.4)	100 (39.5)
Intestinal	36 (14.2)	41 (16.2)
Mixed	20 (7.9)	21 (8.3)
Unknown†	76 (30.0)	64 (25.3)
Other	34 (13.4)	27 (10.7)
Missing	1	0

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
ECOG performance status score, n (%)		
0	108 (42.7)	108 (43.2)
1	145 (57.3)	142 (56.8)
Missing‡	1	3
Measurable disease, n (%)**		
Yes	195 (76.8)	205 (81.0)
No	59 (23.2)	48 (19.0)

Key: CAPOX, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; n, number of patients.
Notes: *Sex was reported by study site staff through an interactive response technology system with options 'male' or 'female'. † Patients with Lauren classification 'unknown' had adenocarcinoma without Lauren classification. ‡ Baseline measurements were reported at Cycle 1, Day 1. Patients reported as 'Missing' did not receive any treatment, thus no baseline was defined per the statistical analysis plan. However, at screening, these patients had an ECOG performance status score of 0 or 1 and were thus eligible for enrolment. ** Based on central assessment.
Source: Shah et al. 2023[42]; GLOW clinical study report.[76]

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

B.2.4.1. SPOTLIGHT

B.2.4.1.1. Trial populations

The following predefined analysis populations were used to analyse the SPOTLIGHT trial data[75]:

- **Full analysis set:** consists of all patients who were randomised to one of the treatment arms. Patients were analysed according to the treatment arm to which they were randomised. The full analysis set has been used for describing baseline characteristics and all efficacy analyses
- **Safety analysis set:** consists of all patients who received at least one dose of any study drug (zolbetuximab or placebo/mFOLFOX6). Patients were analysed according to the treatment arm they actually received. The safety analysis set was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables

- **Pharmacokinetic analysis set:** consists of a subset of the safety analysis set for which at least one zolbetuximab concentration measurement was available. The pharmacokinetic analysis set was used for the description of pharmacokinetic data

B.2.4.1.2. Statistical analysis

The hypothesis and associated statistical analysis methods in SPOTLIGHT are summarised in Appendix M.2.

One final analysis was planned for PFS, whereas an interim analysis and final analysis were planned for OS.[75] The OS interim and final analyses were to be performed only if the primary PFS analysis was significant. The OS interim analysis occurred at the same time as final PFS analysis after the pre-specified number of PFS events (300 events). The final OS analysis was performed on [redacted] after the pre-specified number of OS events were observed.

The hypothesis testing on the primary analysis was performed at an overall one-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in the zolbetuximab + mFOLFOX6 arm compared with the placebo + mFOLFOX6 arm (versus the alternative hypothesis that PFS is prolonged in the zolbetuximab + mFOLFOX6 arm compared with the placebo + mFOLFOX6 arm).[75]

B.2.4.1.3. Patient disposition

Overall, 565 patients were randomised in SPOTLIGHT, including 283 in the zolbetuximab + mFOLFOX6 arm and 282 in the placebo + mFOLFOX6 arm.[24] At least one dose of treatment was administered to 279 (99%) patients in the zolbetuximab + mFOLFOX6 arm and 278 (99%) in the placebo + mFOLFOX6 arm. At the latest data cut-off (29 June 2023), [redacted] ([redacted]%) patients in the zolbetuximab + mFOLFOX6 arm discontinued zolbetuximab and [redacted] ([redacted]%) patients in the placebo + mFOLFOX6 arm discontinued placebo.[77] The most frequent reasons for discontinuation in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms were disease progression ([redacted]% vs [redacted]%, respectively) followed by adverse events (AEs; [redacted]% vs [redacted]%) and withdrawal by patient ([redacted]% vs [redacted]%). Further information on patient disposition is presented in Appendix D.2.

B.2.4.2. GLOW

B.2.4.2.1. Trial populations

The following predefined analysis populations were used to analyse the SPOTLIGHT trial data[76]:

- **Final analysis set**: consists of all patients who were randomised to one of the two treatment arms. Patients were analysed according to the treatment arm to which they were randomised. The final analysis set was used for summaries of demographic and baseline characteristics and all efficacy analyses
- **Safety analysis set**: consists of all patients who received at least one dose of any study drug (zolbetuximab or placebo/CAPOX). Patients were analysed according to the actual treatment they received. The safety analysis set was used for summaries of demographic and baseline characteristics and all safety and tolerability-related variables
- **Pharmacokinetic analysis set**: consists of a subset of the safety analysis set for which at least one zolbetuximab concentration measurement was available. The pharmacokinetic analysis set was used for the description of pharmacokinetic data

B.2.4.2.2. Statistical analysis

The hypothesis and associated statistical analysis methods in GLOW are summarised in Appendix M.3.2.

One final analysis was planned for PFS, whereas an interim analysis and final analysis were planned for OS.[76] The OS interim analysis occurred at the same time as the final PFS analysis (after the pre-specified number of PFS events, i.e. 300), and the final OS analysis was to be performed after the pre-specified number of OS events were observed if the interim OS was not statistically significant. The OS interim and final analyses were to be performed only if the primary PFS analysis was significant.

The hypothesis testing on the primary analysis was performed at an overall one-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in the zolbetuximab + CAPOX arm compared with the placebo + CAPOX arm (versus

the alternative hypothesis that PFS is prolonged in the zolbetuximab + CAPOX arm compared with the placebo + CAPOX arm).[76]

B.2.4.2.3. Patient disposition

Overall, 507 patients were randomised in GLOW, including 254 patients in the zolbetuximab + CAPOX arm and 253 patients in the placebo + CAPOX arm.[42] At least one dose of treatment was administered to 253 (99.6%) patients in the zolbetuximab + CAPOX arm and 250 (98.8%) patients in the placebo + CAPOX arm. At the latest data cut-off (29 June 2023), [redacted] ([redacted]%) patients in the zolbetuximab + CAPOX arm had discontinued zolbetuximab and [redacted] ([redacted]%) patients in the placebo + CAPOX arm had discontinued placebo.[79] The most frequent reasons for discontinuation in the zolbetuximab + CAPOX and placebo + CAPOX arms were disease progression ([redacted]% vs [redacted]%, respectively) followed by AEs ([redacted]% vs [redacted]%) and withdrawal by patient ([redacted]% vs [redacted]%). Further information on patient disposition is presented in Appendix D.2.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

SPOTLIGHT and GLOW were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies. A complete quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented in Appendix D.3. The overall risk of bias for both studies is considered to be low.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. SPOTLIGHT

In this section, efficacy results are presented for SPOTLIGHT with a data cut of 29 June 2023, unless otherwise specified.[77] This was not a pre-specified data cut; therefore, not all data were updated during this analysis. All other efficacy results are from the pre-specified interim analysis with a data cut of 09 September 2022.[24, 47] The final database lock for the SPOTLIGHT trial took place on [redacted], and data analysis is currently ongoing. These data will be provided during

clarification questions, but results are anticipated to be very similar to the 29 June 2023 data cut given that the timings of the two data cuts are close together.

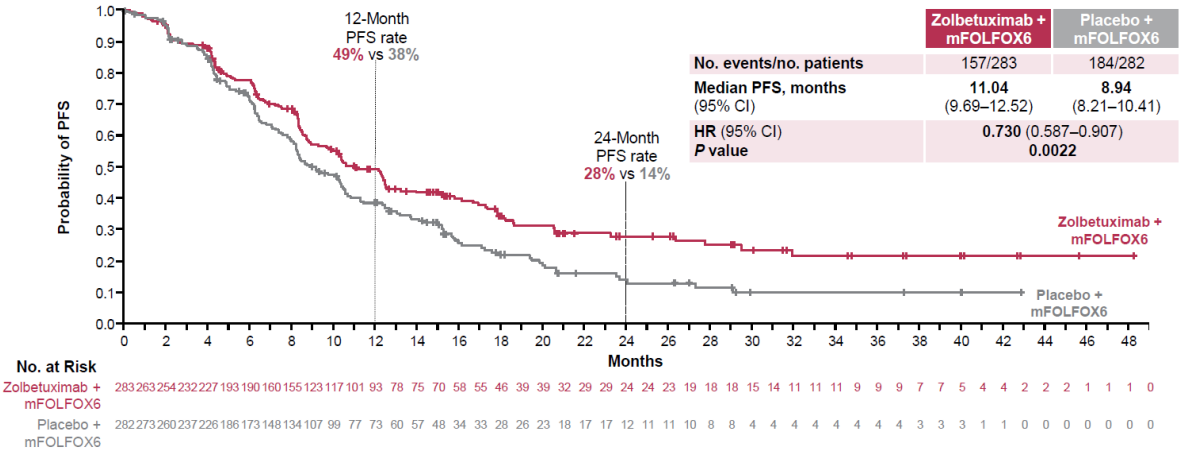
B.2.6.1.1. Primary efficacy endpoint: progression-free survival

Zolbetuximab + mFOLFOX6 was associated with a statistically significant and clinically meaningful PFS benefit with a 27% reduction in the risk of disease progression or death compared with placebo + mFOLFOX6 (hazard ratio [HR] 0.730 [95% confidence interval [CI]: 0.587, 0.907]; one-sided p = 0.0022).[77, 81]

Median follow-up for PFS was 17.87 months (95% CI: [redacted]) in the zolbetuximab + mFOLFOX6 arm and 15.18 months (95% CI: [redacted]) in the placebo + mFOLFOX6 arm.[77, 81] Median PFS was 11.04 months (95% CI: 9.69, 12.52) in the zolbetuximab + mFOLFOX6 arm compared with 8.94 months (95% CI: 8.21, 10.41) in the placebo + mFOLFOX6 arm (Figure 5).

In the zolbetuximab + mFOLFOX6 arm, PFS rates were 49.28% (95% CI: [redacted]) and 27.79% (95% CI: [redacted]) at 12 months and 24 months, respectively. In the placebo + mFOLFOX6 arm, these were 38.47% (95% CI: [redacted]) and 13.99% (95% CI: [redacted]), respectively.[77, 81]

Figure 5: SPOTLIGHT: Kaplan–Meier plot of PFS assessed by IRC (FAS)



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.
Notes: Data cut-off: 29 June 2023. Median follow-up = 17.87 months (zolbetuximab + mFOLFOX6) vs 15.18 months (placebo + mFOLFOX6). [a] As per RECIST 1.1
Source: Ajani et al. 2023.[81]

B.2.6.1.2. Secondary efficacy endpoints

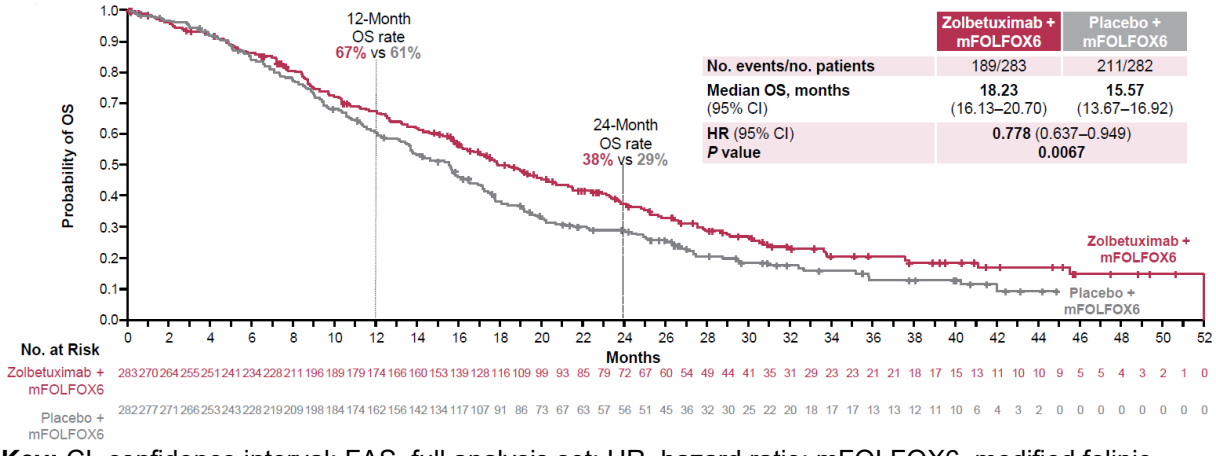
B.2.6.1.2.1. Overall survival

In the interim analysis of OS, zolbetuximab + mFOLFOX6 showed a statistically significant and clinically meaningful OS benefit with a reduction of 22% in the risk of death compared with placebo + mFOLFOX6 (HR 0.778 [95% CI: 0.637, 0.949]; p = 0.0067).[77, 81]

A total of 189 (66.8%) patients in the zolbetuximab + mFOLFOX6 arm and 211 (74.8%) patients in the placebo + mFOLFOX6 arm had died.[77, 81] Median follow-up time for OS was 31.11 months (95% CI: [redacted]) in the zolbetuximab + mFOLFOX6 arm and 29.57 months (95% CI: [redacted]) in the placebo + mFOLFOX6 arm. Median OS was 18.23 months (95% CI: 16.13, 20.70) in the zolbetuximab + mFOLFOX6 arm compared with 15.57 months (95% CI: 13.67, 16.92) in the placebo + mFOLFOX6 arm (Figure 6).

The probability of being alive at 30 months and 36 months was [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted], respectively, in the zolbetuximab + mFOLFOX6 arm compared with [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) in the placebo + mFOLFOX6 arm.[77]

Figure 6: SPOTLIGHT: Kaplan–Meier plot of OS (FAS)



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; OS, overall survival.
Notes: Data cut-off: 29 June 2023. Median follow-up = 31.11 months (zolbetuximab + mFOLFOX6) versus 29.57 months (placebo + mFOLFOX6).
Source: Ajani et al. 2023.[81]

B.2.6.1.2.2. Objective response rate

In the zolbetuximab + mFOLFOX6 arm, the ORR per IRC was [redacted] (95% CI: [redacted]) and the disease control rate (DCR) was [redacted] (95% CI: [redacted]), compared with [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) in the placebo + mFOLFOX6 arm (Table 6).[77] In the zolbetuximab + mFOLFOX6 arm, [redacted] patients had a complete response (CR) and [redacted] patients had a partial response (PR). In the placebo + mFOLFOX6 arm, [redacted] patients had a CR and [redacted] patients had a PR.

Table 6: SPOTLIGHT: summary of ORR assessed by IRC – unconfirmed responses (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Best overall response, n (%)†	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/non-progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
No disease	[redacted]	[redacted]
Not available‡	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]
95% CI for ORR (%)§	[redacted]	[redacted]
Stratified one-sided p-value¶	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR (%)§	[redacted]	[redacted]
Stratified one-sided p-value¶	[redacted]	

Key: CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 29 June 2023. † The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm. ‡ No post-baseline imaging assessment. § Using exact method based on binomial distribution (Clopper–Pearson). ¶ Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. †† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease.
Source: Astellas, data on file 2023.[77]

B.2.6.1.2.3. Duration of response

Median DoR as assessed by the IRC was [redacted] months (95% CI: [redacted]) in the zolbetuximab + mFOLFOX6 arm and [redacted] months (95% CI: [redacted]) in the placebo + mFOLFOX6 arm ([redacted]; Figure 7).[77]

Figure 7: SPOTLIGHT: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)

Key: CI, confidence interval; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients.
Notes: Data cut-off: 29 June 2023. Arm A: zolbetuximab + mFOLFOX6; Arm B: placebo + mFOLFOX6. P-value is generated from stratified one-sided log-rank test for the comparison of Arm A and Arm B. HR with 95% CI is based on stratified Cox proportional hazard model, with treatment as the only explanatory variable and stratified by region, number of metastatic sites, and prior gastrectomy. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in hazard rate in favour of treatment arm.
Source: Astellas, data on file 2023.[77]

B.2.6.1.3. Health-related quality of life

The secondary HRQL endpoints collected via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), the Quality of Life Oesophago-Gastric (QLQ-OG25), and the EQ-5D-5L questionnaire were analysed with summary of change from baseline over time

through to the end of mFOLFOX6 treatment. However, no formal statistical testing was performed on these descriptive summary measures.[82]

At the 29 June 2023 data cut-off, only utilities data were updated to inform the economic model (see Section B.3.4.1). Therefore, the data presented below are based on the primary analysis data cut (cut-off date of 09 September 2022).[82, 83] The compliance rate for patient-reported outcomes completion was ≥ 71.0% for any treatment visits where there were more than 50 patients remaining on the study.[75] The compliance rates were similar between the treatment arms during the treatment and follow-up periods of the study. Baseline total scores and subscale scores were comparable between treatment arms.

Overall, HRQL was comparable for patients in the zolbetuximab + mFOLFOX6 arm and patients in the placebo + mFOLFOX6 arm, demonstrating that treatment with zolbetuximab + mFOLFOX6 has no adverse impact on patients' HRQL compared with mFOLFOX6.[82, 83]

B.2.6.1.3.1. EORTC QLQ-C30

Patients entered the study with moderate HRQL scores (baseline global health status [GHS]/quality of life [QoL]: [redacted]) that were maintained during the study.[82] There were no clinically meaningful changes in EORTC QLQ-C30 GHS observed for either treatment arm, and although some initial deterioration was observed for patients on zolbetuximab + mFOLFOX6, this levelled off from Cycle 5 onwards.

EORTC QLQ-C30 physical functioning deteriorated on average approximately [redacted] points (scale range 0–100) for patients receiving zolbetuximab + mFOLFOX6 through the first 10 cycles, whereas physical functioning for patients receiving placebo + mFOLFOX6 remained relatively stable.[82]

There was an initial increase in nausea and vomiting in the first six cycles of treatment for patients who received zolbetuximab + mFOLFOX6 compared with those in placebo + mFOLFOX6 arm, which returned to baseline levels at Cycle 6.[82] No significant differences were observed for either treatment arm for the remaining

EORTC QLQ-C30 functioning and symptom domains. A summary of all results for all key domains is presented in Appendix M.3.1.1.1.

B.2.6.1.3.2. EORTC QLQ-OG25

Patients entered the study with low symptom burden (pain and discomfort) scores that were maintained during the study.[82] Improvements were observed in the EORTC QLQ-OG25-Pain score for patients in both treatment groups, but this did not reach a clinically meaningful change (< 10 points). No significant differences were observed for either treatment arm for the remaining EORTC QLQ-OG25 domains (see Appendix M.3.1.1.2).

B.2.6.1.3.3. EQ-5D-5L

Baseline EQ-5D™ questionnaire index score and EQ-VAS (visual analogue scale) scores were comparable between treatment arms.[75] No significant differences were observed for either treatment arm for the EQ-5D questionnaire index score and EQ-VAS during the treatment and follow-up periods (see Appendix M.3.1.1.3).

B.2.6.1.3.4. Time to confirmed deterioration

TTCD was defined as the time from randomisation to first clinically meaningful deterioration that is confirmed at the next scheduled visit using physical functioning, OG25-Pain, and GHS/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25.[75] The number of patients experiencing deterioration in HRQL (TTCD) was similar in the zolbetuximab + mFOLFOX6 arm and placebo + mFOLFOX6 arm for physical functioning ([redacted] vs [redacted], respectively), OG25-Pain ([redacted] vs [redacted]), and GHS/QoL ([redacted] vs [redacted]) using the literature-based threshold and excluding death.[77]

Based on a total of [redacted] deterioration events in physical functioning score, median TTCD was 10.71 months (95% CI: 6.01, non-estimable [NE]) for participants who received zolbetuximab + mFOLFOX6 and 12.32 months (95% CI: 9.26, NE) for participants who received placebo + mFOLFOX6 (HR [redacted] [95% CI: [redacted]]).[82, 83]

Based on a total of [redacted] deterioration events in the OG25-Pain score, median TTCD was not yet reached for participants who received zolbetuximab + mFOLFOX6 or placebo + mFOLFOX6 (HR [redacted] [95% CI: [redacted]]).[82]

Based on a total of [redacted] deterioration events in GHS/QoL score, median TTCD for GHS/QoL was 15.44 months (95% CI: 6.90, 22.83) for participants who received zolbetuximab + mFOLFOX6 and 11.83 months (95% CI: 8.74, 15.08) for participants who received placebo + mFOLFOX6 (HR [redacted] [95% CI: [redacted]) Further information is presented in Appendix M.3.1.2.[82, 83]

B.2.6.2. GLOW

In this section, efficacy results are presented for GLOW with a data cut-off of 29 June 2023, unless otherwise specified.[79, 84] The final database lock for the GLOW trial took place on [redacted], and data analysis is currently ongoing.

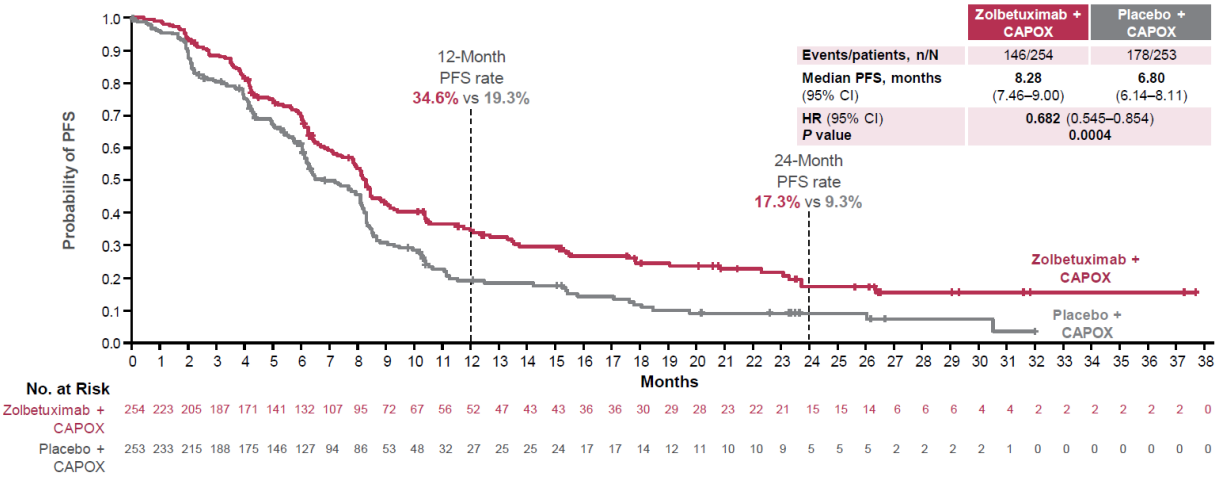
B.2.6.2.1. Primary efficacy endpoint: progression-free survival

Zolbetuximab + CAPOX demonstrated a statistically significant benefit as first-line treatment in CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJC, with a 31.8% reduction in risk of progression or death versus placebo + CAPOX (HR 0.682 [95% CI: 0.545, 0.854], one-sided p = 0.0004).[79, 84]

Median follow-up for PFS was 17.81 months (95% CI: [redacted]) in the zolbetuximab + CAPOX arm and 15.05 months (95% CI: [redacted]) in the placebo + CAPOX arm.[79, 84] Median PFS was 8.28 months (95% CI: 7.46, 9.00) in the zolbetuximab + CAPOX arm versus 6.80 months (95% CI: 6.14, 8.11) in the placebo + CAPOX arm (Figure 8).

In the zolbetuximab + CAPOX arm, PFS rates were 34.56% (95% CI: [redacted]) and 17.32% (95% CI: [redacted]) at 12 months and 24 months, respectively, compared with 19.25% (95% CI: [redacted]) and 9.31% (95% CI: [redacted]) in the placebo + CAPOX arm.[79, 84]

Figure 8: GLOW: Kaplan–Meier plot of PFS assessed by IRC (FAS)



Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.
Notes: Data cut-off: 29 June 2023. Median follow-up = 17.81 months (zolbetuximab + CAPOX) vs 15.05 months (placebo + CAPOX). [a] As per RECIST 1.1.
Source: Lordick et al. 2023.[84]

B.2.6.2.2. Secondary efficacy endpoints

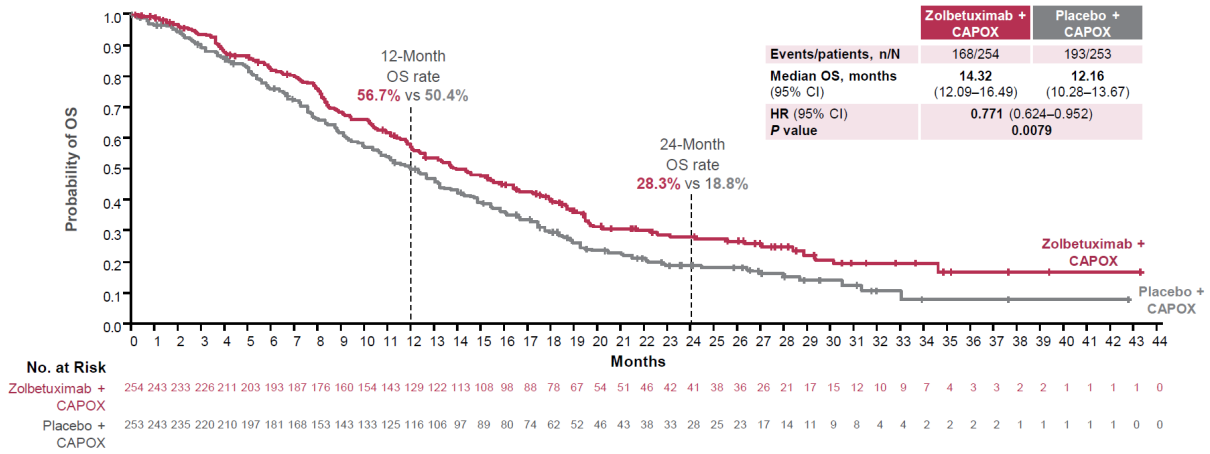
B.2.6.2.2.1. Overall survival

The interim analysis of OS showed a statistically significant benefit of zolbetuximab + CAPOX with a 22.9% reduction in the risk of death compared with placebo + CAPOX (HR 0.771 [95% CI: 0.624, 0.952]; one-sided p = 0.0079).[79, 84]

A total of 168 (66.1%) patients in the zolbetuximab + CAPOX arm and 193 (76.3%) patients in the placebo + CAPOX arm had died.[79, 84] Median follow-up time for OS was 26.09 months (95% CI: [redacted]) in the zolbetuximab + CAPOX arm and 26.18 months (95% CI: [redacted]) in the placebo + CAPOX arm. Median OS was 14.32 months (95% CI: 12.09, 16.49) in the zolbetuximab + CAPOX arm and 12.16 months (95% CI: 10.28, 13.67) in the placebo + CAPOX arm (Figure 9).

The probability of being alive at 30 months and 36 months was [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively, in the zolbetuximab + CAPOX arm; for the placebo + CAPOX arm, the respective probabilities were [redacted](95% CI: [redacted]) and [redacted] (95% CI: [redacted]).[79]

Figure 9: GLOW: Kaplan–Meier plot of OS (FAS)



Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; N, number of patients; OS, overall survival.
Notes: Data cut-off: 29 June 2023. Median follow-up = 26.09 months (zolbetuximab + CAPOX) versus 26.18 months (placebo + CAPOX).
Source: Lordick et al. 2023.[84]

B.2.6.2.2.2. Objective response rate

In the zolbetuximab + CAPOX arm, the ORR per IRC was [redacted] (95% CI: [redacted]) and the DCR was [redacted] (95% CI: [redacted]), compared with [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) in the placebo + CAPOX arm, respectively (Table 7).[79] In the zolbetuximab + CAPOX arm, [redacted] patients had a CR and [redacted] patients had a PR. In the placebo + CAPOX arm, [redacted] patients had a CR and [redacted] patients had a PR.

Table 7: GLOW: summary of ORR assessed by IRC – (FAS)

	Zolbetuximab + CAPOX (n = 254)	**Placebo + CAPOX (n = 253)**
Best overall response, n (%)†	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/non-progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
No disease	[redacted]	[redacted]
Not available‡	[redacted]	[redacted]

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
ORR, n (%)	[redacted]	[redacted]
95% CI for ORR§	[redacted]	[redacted]
p-value*	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR§	[redacted]	[redacted]
p-value*	[redacted]	

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 29 June 2023. † The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm. ‡ No post-baseline imaging assessment. § Using exact method based on binomial distribution (Clopper–Pearson). Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of metastatic sites and prior gastrectomy. * Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy. †† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).
Source: Astellas, data on file 2023.[79]

B.2.6.2.2.3. Duration of response

Median DoR as assessed by the IRC was [redacted] months (95% CI: [redacted]) in the zolbetuximab + CAPOX arm and [redacted] months (95% CI: [redacted]) in the placebo + CAPOX arm ([redacted]; Figure 10).[79]

Figure 10: GLOW: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 29 June 2023. Arm A: zolbetuximab + CAPOX; Arm B: placebo + CAPOX. DoR was defined as the time from the date of the first response (CR/PR) until the date of progressive disease as assessed by IRC per RECIST v1.1 or date of death from any cause, whichever was earliest. p-value is generated from stratified one-sided log-rank test for the comparison of Arm A and Arm B. HR and 95% CI is based on stratified Cox proportional hazard model, with treatment as the only explanatory variable and stratified by region, number of metastatic sites, and prior gastrectomy. Assuming proportional hazards, an HR < 1 indicates a reduction in hazard rate in favour of treatment arm.
Source: Astellas, data on file 2023.[79]

B.2.6.2.3. Health-related quality of life

The secondary HRQL endpoints collected via the EORTC QLQ-C30 and QLQ-OG25 and EQ-5D-5L questionnaire were analysed with a summary of change from baseline over time through to the end of CAPOX treatment, but no formal statistical testing was performed on these descriptive summary measures.[85]

At the 29 June 2023 data cut-off, only utilities data were updated to inform the economic model (see Section B.3.4.1).[84] Therefore, the data presented below are based on the primary analysis data cut (cut-off date of 07 October 2022).[83, 85] The compliance rate for patient-reported outcome completion was ≥ 85.3% for any

treatment visits where there were more than 50 patients remaining on the study and ≥ 64.6% for the end of treatment visit. Compliance rates were similar between the treatment arms during the treatment and follow-up phases of the study, although no formal statistical testing was performed on these descriptive summary measures. Baseline total scores and subscale scores were comparable between treatment arms.

Overall, HRQL was comparable for patients in the zolbetuximab + CAPOX arm and patients in the placebo + CAPOX arm, demonstrating that treatment with zolbetuximab + CAPOX has no adverse impact on patients' HRQL compared with CAPOX.[76, 83]

B.2.6.2.3.1. EORTC QLQ-C30

Patients entered the study with moderate HRQL scores (baseline GHS/QoL: [redacted]), which were maintained during the study.[85] There were no clinically meaningful changes in EORTC QLQ-C30 GHS observed for either treatment arm, despite small differences observed between the treatment arms at Cycle 17 Day 1 (LS mean was [redacted] in the zolbetuximab + CAPOX arm and [redacted] in the placebo + CAPOX arm; difference for zolbetuximab + CAPOX versus placebo + CAPOX was [redacted] (95% CI: [redacted], [redacted]); [redacted]).

EORTC QLQ-C30 physical functioning scores deteriorated in both treatment arms, but the changes were not clinically meaningful (as defined by a 10-point change). Patients receiving zolbetuximab + CAPOX experienced a deterioration of approximately [redacted] points (scale range 0–100) in physical functioning throughout the study.

Although nausea and vomiting worsened during the first few cycles of zolbetuximab treatment, levels of nausea and vomiting returned to baseline levels after the first 6–8 zolbetuximab treatments (i.e., 18–24 weeks) without clinically meaningful deterioration.[76, 83] For the EORTC QLQ-C30 insomnia domain, patients receiving zolbetuximab + CAPOX had improved scores versus baseline at Cycle 17 Day 1 (LS mean was [redacted] in the zolbetuximab arm and [redacted] in placebo arm; LS mean difference for zolbetuximab arm vs placebo arm was [redacted], 95% CI [redacted], [redacted]];

[redacted]), and placebo-treated patients experienced worsening of symptoms.[85] No significant differences were observed for either treatment arm for the remaining EORTC QLQ-C30 functioning and symptom domains. A summary of all results for all key domains is presented in Appendix M.3.2.1.1.

B.2.6.2.3.2. EORTC QLQ-OG25

Patients entered the study with low symptom burden (pain and discomfort) scores that were maintained during the study.[85] Improvements were observed in the EORTC QLQ-OG25-Pain score for patients in both treatment groups, but this did not reach clinically meaningful change (< 10 points). Significant differences were found at Cycle 17 Day 1 for: trouble with coughing (LS mean was [redacted] in the zolbetuximab arm and [redacted] in the placebo arm; difference zolbetuximab vs placebo: [redacted]; p = [redacted]) and trouble talking (LS mean was [redacted] in the zolbetuximab arm and [redacted] in the placebo arm; difference zolbetuximab vs placebo: [redacted]; p = [redacted]).[85] Significant difference were found over the 17 Cycles for trouble with taste (LS mean was [redacted] in the zolbetuximab arm and [redacted] in the placebo arm; difference zolbetuximab vs placebo: [redacted]; p = [redacted]) and belching (LS mean was [redacted] in the zolbetuximab arm and [redacted] in the placebo arm; difference zolbetuximab vs placebo: [redacted]; p = [redacted]). No significant differences were observed for either treatment arm for the remaining EORTC QLQ-OG25 domains (see Appendix M.3.2.1.2).

B.2.6.2.3.3. EQ-5D-5L

Baseline EQ-5D questionnaire index scores and EQ-VAS scores were comparable between treatment arms.[85] No significant differences were observed for either treatment arm for the EQ-5D questionnaire index score and EQ-VAS during the treatment and follow-up periods (see Appendix M.3.2.1.3).

B.2.6.2.3.4. Time to confirmed deterioration

TTCD was defined as the time from randomisation to first clinically meaningful deterioration that is confirmed at the next scheduled visit using physical functioning, OG25-Pain and GHS/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25.[85] The numbers of patients experiencing deterioration in HRQL (TTCD) was similar in the zolbetuximab + CAPOX and placebo + CAPOX arms for physical

functioning ([redacted] vs [redacted], respectively), OG25-Pain ([redacted] vs [redacted]), and GHS/QoL ([redacted] vs [redacted]) using the primary threshold and excluding death.

Based on a total of [redacted] deterioration events in physical functioning score, median TTCD was 8.31 months (95% CI: 5.88, 19.81) for participants who received zolbetuximab + CAPOX and 7.92 months (95% CI: 6.47, 11.10) for participants who received placebo + CAPOX (HR [redacted] [95% CI: [redacted]]).[83, 85]

Based on a total of [redacted] deterioration events in OG25-Pain score, median TTCD for OG25-Pain was not yet reached for participants who received zolbetuximab + CAPOX and was [redacted] months (95% CI: [redacted]) for participants who received placebo + CAPOX (HR [redacted] [95% CI: [redacted]]).[85]

Based on a total of [redacted] deterioration events in GHS/QoL score, the median TTCD for GHS/QoL was 9.69 months (95% CI: 7.39, NE) for participants who received zolbetuximab + CAPOX and 7.49 months (95% CI: 6.11, 9.86) for participants who received placebo + CAPOX (HR [redacted] [95% CI: [redacted]]).[83, 85] Further information is presented in Appendix M.3.2.2.

B.2.6.3. FAST

FAST was a Phase II trial designed to assess the efficacy and tolerability of zolbetuximab in patients with advanced G/GEJ or oesophageal adenocarcinoma with moderate-to-strong CLDN18.2 expression in ≥ 40% tumour cells.[74, 86]

For inclusion in FAST, patients were ≥ 18 years of age with histologically confirmed, locally advanced, inoperable, recurrent, or metastatic G/GEJ and oesophageal adenocarcinoma positive for CLDN18.2 expression (defined as ≥ 40% of tumour cells with 2+ or 3+ staining intensity on CLAUDETECT™18.2 IHC assay).[74, 86] Further details of the methodology are provided in Appendix M.4.1

Data are presented here for patients with moderate-to-strong CLDN18.2 expression in ≥ 70% of tumour cells treated with zolbetuximab + epirubicin, oxaliplatin and capecitabine (EOX; n = 57) and EOX (n = 59)[74, 86], as these patients align more closely with patients included in the pivotal SPOTLIGHT and GLOW trials (CLDN18.2 expression in ≥ 75% of tumour cells). The CLDN18.2 test used in the

FAST trial differs to the test used in SPOTLIGHT and GLOW trials, and the threshold for defining CLDN18.2-positive (in the subgroup analysis) was 70% rather than 75%. However, Ventana Medical Systems has compared the CLDN18.2 test used in the FAST trial (CLAUDETECT) and the test used in the SPOTLIGHT and GLOW trials (and which will be used in clinical practice), reporting that the 70% cut-off threshold with CLAUDETECT is equivalent to the 75% threshold with the Ventana Medical Systems test.[87]

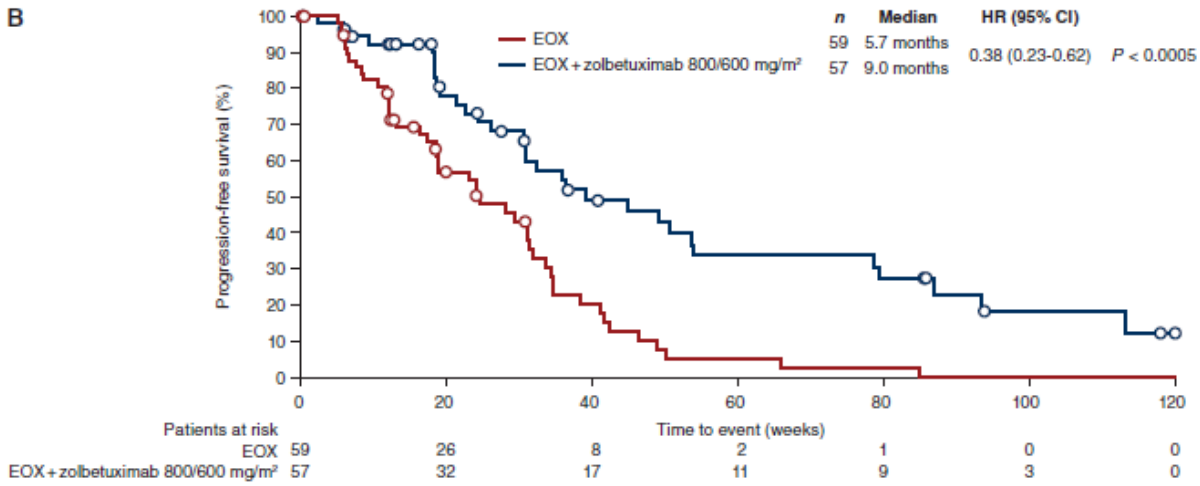
Efficacy outcomes for the overall population and patients with 40–69% of tumour cells positive for CLDN18.2 are presented in Appendix M.4.2. The cut-off date for the final analysis was 31 January 2019, with a median follow-up of 54.7 months (range: 2.3–68.2).[74, 86]

B.2.6.3.1. Progression-free survival

Zolbetuximab + EOX was associated with a statistically significant and clinically meaningful PFS benefit with a 62% reduction in the risk of disease progression or death compared with EOX alone (HR 0.38 [95% CI: 0.23, 0.62]; $p < 0.0005$) in patients with moderate-to-strong CLDN18.2 expression in ≥ 70% of tumour cells.[74, 86]

Figure 11 presents the Kaplan–Meier curve of PFS for patients with ≥ 70% of tumour cells positive for CLDN18.2.[74] Median PFS was 9.0 months (95% CI: 7.1, 12.4) in the zolbetuximab + EOX arm and 5.7 months (95% CI: 4.3, 7.2) in the EOX arm. No differences were observed based on pre-specified subgroup analyses (See Appendix M.4.2.1).

Figure 11: Kaplan–Meier curve of PFS in FAST (patients with ≥ 70% of tumour cells positive for CLDN18.2)



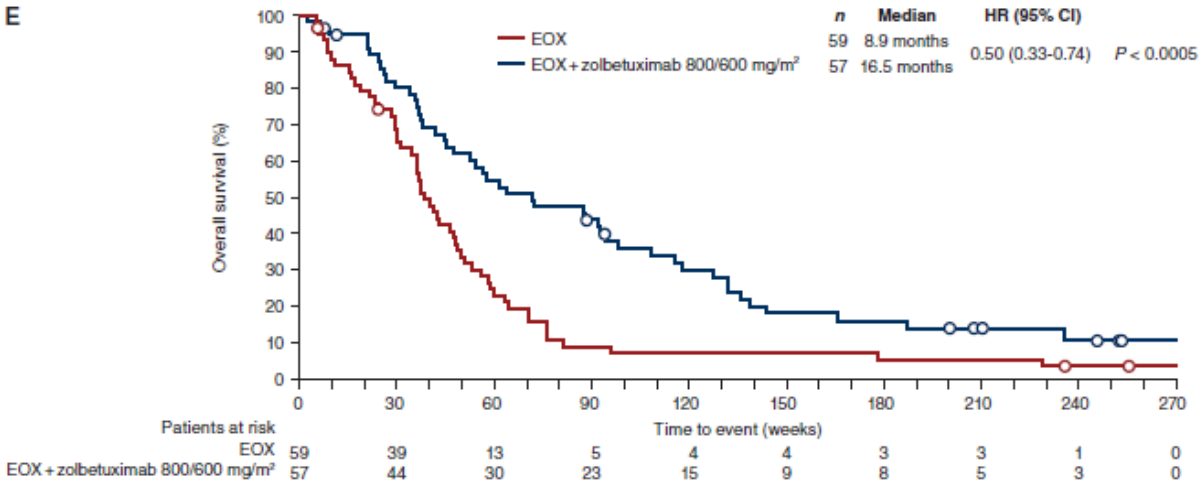
Key: CI, confidence interval; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin and capecitabine; HR, hazard ratio; PFS, progression-free survival.
Source: Sahin et al. 2021.[74]

B.2.6.3.2. Overall survival

Zolbetuximab + EOX showed a statistically significant and clinically meaningful OS benefit with a reduction of 50% in the risk of death compared with EOX alone (HR 0.50 [95% CI: 0.33, 0.74]; p < 0.0005) in patients with moderate-to-strong CLDN18.2 expression in ≥ 70% of tumour cells.[74, 86]

Figure 12 presents the Kaplan–Meier curve of OS for patients with ≥ 70% of tumour cells positive for CLDN18.2.[74] Median OS was 16.5 months (95% CI: 10.4, 21.7) in the zolbetuximab + EOX arm and 8.9 months (95% CI: 7.1, 11.0) in the EOX arm. No differences were observed based on pre-specified subgroup analyses (see Appendix M.4.2.2).

Figure 12: Kaplan–Meier curve of OS in FAST (patients with ≥ 70% of tumour cells positive for CLDN18.2)



Key: CI, confidence interval; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin and capecitabine; HR, hazard ratio; OS, overall survival.
Source: Sahin et al. 2021.[74]

B.2.7. Subgroup analysis

B.2.7.1. SPOTLIGHT

At the latest data cut-off (29 June 2023), the treatment effect of zolbetuximab + mFOLFOX6 versus placebo + mFOLFOX6 in SPOTLIGHT on PFS was consistently favourable across the majority of the pre-specified subgroups including age, sex, geographical region, number of metastatic sites, prior gastrectomy, tumour type, country, and race at baseline.[77, 81] Similar results were observed for OS, as the treatment effect of zolbetuximab + mFOLFOX6 versus placebo + mFOLFOX6 was consistently favourable across the majority of the pre-specified subgroups including age (except > 75 years), sex, geographical region, number of organs with metastatic sites, gastric tumour location, prior gastrectomy, tumour type and disease location (except GEJ distal location), country, race, and tobacco history at baseline. Further details on subgroup analyses are presented in Appendix E.1.

Of particular interest, in a post hoc subgroup analysis by PD-L1 CPS status (≥ 5 vs < 5, ≥ 1 versus < 1 and Unknown), the treatment effect of zolbetuximab + mFOLFOX6

versus placebo + mFOLFOX6 was consistently favourable across most subgroups for both PFS and OS, demonstrating that CPS is not a treatment-effect modifier for zolbetuximab.[72] CPS data is not available for all randomised subjects due to various restrictions on testing that resulted in a more limited subset of patient data that may not be reflective of entire study population. This analysis is based on ad-hoc analyses. The analysis has not been designed to address the relationship between zolbetuximab activity and PD-L1 expression.

B.2.7.2. GLOW

At the latest data cut-off (29 June 2023), the treatment effect of zolbetuximab + CAPOX versus placebo + CAPOX in GLOW on PFS was consistently favourable across the majority of the pre-specified subgroups including age, sex, geographical region, number of organs with metastatic sites, prior gastrectomy, tumour type, country, and race at baseline.[79, 84] Similar results were observed for OS, as the treatment effect of zolbetuximab + CAPOX versus placebo + CAPOX was consistently favourable across most of the pre-specified subgroups including age, sex, geographic region, number of organs with metastatic sites, gastric tumour location, prior gastrectomy, tumour type and disease location, country, race, and tobacco history at baseline. Further details on subgroup analyses are presented in Appendix E.2.

Of particular interest, in a post hoc subgroup analysis by PD-L1 CPS status (≥ 5 vs < 5, ≥ 1 versus < 1, and unknown), the treatment effect of zolbetuximab + CAPOX versus placebo + CAPOX was consistently favourable across all subgroups for both PFS and OS, demonstrating that CPS is not a treatment-effect modifier for zolbetuximab.[72]

B.2.8. Meta-analysis

Formal meta-analyses have not been conducted. A qualitative overview of key outcomes from both trials is provided in Table 8.

Table 8: Overview of key outcomes from SPOTLIGHT, GLOW and FAST

Outcomes	SPOTLIGHT[a]		GLOW[a]		FAST[b]	
	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)	Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 57)	EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 59)
ORR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
CR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Median PFS	11.04 months	8.94 months	8.28 months	6.80 months	9.0 months	5.7 months
HR (95% CI)	0.730 (0.587, 0.907)		0.682 (0.545, 0.854)		0.38 (0.23, 0.62)	
p-value	0.0022		0.0004		p < 0.0005	
Median OS	18.23 months	15.57 months	14.32 months	12.16 months	16.5 months	8.9 months
HR (95% CI)	0.778 (0.637, 0.949)		0.771 (0.624, 0.952)		0.50 (0.33, 0.74)	
p-value	0.0067		0.0079		0.0005	

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CLDN18.2, claudin 18.2; CR, complete response; EOX, epirubicin, oxaliplatin and capecitabine; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
Notes: [a] Data cut-off: 29 June 2023. [b] Data cut off: 31 January 2019.
Source: Ajani et al, 2023[81]; Astellas, data on file 2023[77]; Lordick et al, 2023[84]; Astellas, data on file 2023[79]; Sahin et al. 2021.[74]

B.2.9. Indirect and mixed treatment comparisons

As detailed in Appendix D.1, four trials (reported across 12 publications) were identified through an SLR that could be considered for inclusion in an indirect treatment comparison (ITC) of interest to this appraisal; these trials investigated zolbetuximab and nivolumab. Alongside the three zolbetuximab studies (SPOTLIGHT, GLOW and FAST), this evidence base included one trial comparing nivolumab + chemotherapy to chemotherapy in patients with PD-L1 CPS ≥ 5 (CheckMate 649 PD-L1 CPS ≥ 5 subgroup).

A comparative summary of the methods, key patient characteristics and outcomes from the seven studies is summarised in Table 9, Table 10 and Table 11, respectively. As can be seen from these data, there is observed heterogeneity across studies with regard to trial design and patient population. Key differences include the following:

- The FAST trial did not include any Asian sites
- Chemotherapy regimens varied across the trials – however, CAPOX and FOLFOX are thought to be equivalent
- The median survival estimate for the chemotherapy arm was higher in SPOTLIGHT (15.5 month) compared with the other studies (8.9–11.1 months)
- A variation in the median follow-up was observed across trials, ranging from 15.1 months in GLOW to 36 months in CheckMate 649.
- CLDN18.2 expression status was not reported in non-zolbetuximab trials. However, this is not expected to be a limitation, as CLDN18.2 status has been shown not to affect outcomes with chemotherapy and is not expected to affect outcomes with CPIs[16, 74]

Table 9: Comparative summary of studies considered for indirect treatment comparison

	SPOTLIGHT	GLOW	FAST	CheckMate 649
Study design	Phase III, double-blind RCT	Phase III, double-blind RCT	Phase II, randomised, open-label	Phase III, randomised, open-label
Population	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	CLDN18.2-positive (≥ 40% of tumour cells with 2+ or 3+ staining intensity), advanced G/GEJ and oesophageal adenocarcinoma	Previously untreated, unresectable advanced or metastatic HER2-negative, G/GEJ, or oesophageal adenocarcinoma, regardless of PD-L1 expression
Intervention	Zolbetuximab + mFOLFOX6 (n = 283)	Zolbetuximab + CAPOX (n = 254)	Zolbetuximab + EOX (n = 77)	Nivolumab + CAPOX/FOLFOX (n = 789)
Comparator	mFOLFOX6 (n = 282)	CAPOX (n = 253)	EOX (n = 84)	CAPOX/FOLFOX (n = 792)
Primary endpoint	PFS	PFS	PFS	PFS and OS
Median follow-up duration	26.6–31.1 months*	26.1–26.2 months	54.7 months	36 months

Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCT, randomised controlled trial.
Note: * Median follow-up for OS differed between treatment arms; therefore a range has been included.
Source: Ajani et al. 2023[81]; Astellas, data on file 2023[77]; Lordick et al. 2023[84]; Astellas, data on file 2023[79]; Sahin et al. 2021[74]; Janjigian et al. 2023.[88]

Table 10: Patient characteristics at baseline for studies considered for indirect treatment comparison

	SPOTLIGHT		GLOW		FAST		CheckMate 649	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)	Nivolumab + CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)
Age (years), median	62.0	60.0	61.0	59.0	59.0	57.0	62.0	61.0
Male gender, %	62.2	62.1	62.6	61.7	61.0	66.7	68.0	71.0
Race, %								
White	53.6	53.0	37.0	36.0	NR	NR	77.0	78.0
Asian	36.8	38.3	62.0	62.0	NR	NR	23.0	22.0
ECOG, %								
0	44.8	41.4	42.7	43.2	29.9	29.8	41.0	42.0
1	54.8	58.6	57.3	56.8	70.0	70.0	59.0	57.0
2	< 1.0	0.0	0.0	0.0	0.0	0.0	< 1.0	< 1.0
Tumour location, %								
Oesophagus	0.0	0.0	0.0	0.0	2.6	4.8	13.0	14.0
GEJ	22.6	25.5	13.8	17.4	16.9	14.3	17.0	16.0
GC	77.4	74.5	86.2	82.6	80.5	81.0	70.0	70.0
HER2 status, %								
Positive	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0
Negative	100.0	100.0	100.0	100.0	0.0	0.0	NR	NR
Unknown	0.0	0.0	0.0	0.0	100.0	100.0	~40.0	~40.0

	SPOTLIGHT		GLOW		FAST		CheckMate 649	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)	Nivolumab + CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)
CPS score, %								
≥ 5	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	60.0	61.0

Key: CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Source: Ajani et al. 2023[81]; Astellas, data on file 2023[77]; Lordick et al. 2023[84]; Astellas, data on file 2023[79]; Sahin et al. 2021[74]; Janjigian et al. 2023;[88] Astellas, data on file 2023;[72] Janjigian et al. 2023.[89]

Table 11: Summary of outcomes used for clinical studies considered for indirect treatment comparison

	SPOTLIGHT	GLOW	FAST	CheckMate 649
Median OS	• Zolbetuximab + mFOLFOX6: 18.23 months • mFOLFOX6: 15.57 months	• Zolbetuximab + CAPOX: 14.32 months • CAPOX: 12.16 months	• Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 16.5 months • EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 8.9 months	• Nivolumab + CAPOX/FOLFOX PD-L1 CPS ≥ 5: 14.4 months • CAPOX/FOLFOX PD-L1 CPS ≥ 5: 11.1 months • Nivolumab + CAPOX/FOLFOX ITT: 13.8 months • CAPOX/FOLFOX ITT: 11.6 months
Median PFS	• Zolbetuximab + mFOLFOX6: 11.04 months • mFOLFOX6: 8.94 months	• Zolbetuximab + CAPOX: 8.28 months • CAPOX: 6.80 months	• Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 9.0 months • EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 5.7 months	• Nivolumab + CAPOX/FOLFOX PD-L1 CPS ≥ 5: 8.3 months • CAPOX/FOLFOX PD-L1 CPS ≥ 5: 6.1 months • Nivolumab + CAPOX/FOLFOX ITT: 7.7 months • CAPOX/FOLFOX ITT: 6.9 months

Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ITT, intention-to-treat; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Source: Ajani et al. 2023[81]; Astellas, data on file 2023[77]; Lordick et al. 2023[84]; Astellas, data on file 2023[79]; Sahin et al. 2021[74]; Janjigian et al. 2023.[88]

B.2.9.1. Proportional hazards assumption

The synthesis of time-to-event outcomes regarding treatment effects is typically based on a comparison of HRs derived from the Cox proportional hazard (PH) model. When utilising the Cox regression model, it is crucial to consider the assumption of PH, which refers to the condition where HRs remain independent of time, resulting in a constant HR over time. However, if there are explanatory

variables in the model in which coefficients change over time, or if there are time-dependent explanatory variables, the assumption of PH is violated.[90]

Proportionality of hazards was assessed for OS and PFS for all trials and endpoints with an available Kaplan–Meier curve. Log-cumulative hazard plots were used to evaluate the validity of the PH assumption. These plots help determine if the log-cumulative hazard function between different treatment groups is parallel, indicating that the assumption holds. Furthermore, a plot of Schoenfeld residuals against survival times was also created. In this plot, if the PH assumption is satisfied, the residuals should follow a horizontal line, indicating that the HR does not vary over time. Additionally, a formal Schoenfeld statistical test was used to test this assumption. The null hypothesis assumes that the PH assumption is valid, while the alternative hypothesis suggests that it does not hold. Hence, a p-value < 0.05 indicates evidence against the null hypothesis at the 5% level and suggests a violation of the PH assumption.[90]

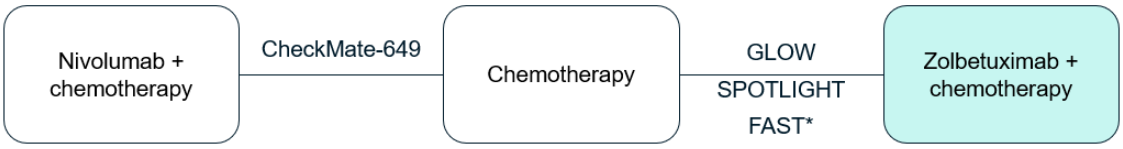
Exploratory analyses for the PH assumption checks are presented in full in Appendix D.1.4.1. The results offer some evidence that the PH assumption does not hold for all studies, therefore supporting the use of non-PH methods. This is supported by the recent NICE committee evaluation of a similar evidence base for pembrolizumab [ID4030, Paragraph 3.4].[2]

B.2.9.2. Non-proportional hazards network meta-analysis – methods

All four studies compared two treatments, which allowed the selected studies to form a network through common comparator arms. However, as each study used a different chemotherapy control arm, there was no common comparator across trials – so a connected network of evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed. This assumption of similar outcomes was supported in the recent NICE committee evaluation of pembrolizumab [ID4030] and of nivolumab (TA857).[2] [29]

Figure 13 presents the overall network of evidence, which contains all four studies in the evidence base, regardless of data availability.

Figure 13: Overall network diagram



Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; EOX, epirubicin + oxaliplatin + capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin.
Note: The chemotherapy node in the network represents CAPOX or FOLFOX. *FAST CLDN18.2 ≥ 70% subgroup was explored in sensitivity analyses as EOX is used infrequently in the UK and a different test method was used for CLDN18.2.

Full details of the methods adopted for network meta-analysis (NMA) are provided in Appendix D.1.4. First- and second-order fractional polynomial NMA models were explored initially. However, the first-order models provided a poor fit to all trials in the evidence base (for both OS and PFS), and there were convergence issues with the second-order models, meaning relative effects could not be reliably estimated. Notably, the less flexible first-order models could not accurately model the long-term plateau in survival observed in the trials – not only of the new agents (i.e. zolbetuximab and nivolumab), but also the chemotherapy arms, leading to validity concerns. Given that the second-order models did not provide reliable results, these analyses used spline NMA as an alternative, flexible modelling approach.

NMAs using spline methods were preferred for all outcomes, as this type of survival model has been recognised by NICE to adequately capture complex shapes, facilitating more realistic estimations of hazard and survivor functions.[91]

Spline NMAs using one, two and three knots were explored for the primary analysis scenario. The best-fitting model for each endpoint and scenario was selected based on the deviance information criterion statistic. For both OS and PFS endpoints, this included:

- The intention-to-treat (ITT; all-comers) population for the SPOTLIGHT and GLOW trials
- The CPS ≥ 5 subgroup for the nivolumab trial CheckMate 649

Results from the primary scenario are presented in Section B.2.9.3 and have been used in the base case economic analysis (See Section B.3.9).

A sensitivity analysis was conducted including the FAST trial CLDN18.2 ≥ 70% subgroup. The FAST trial was not included in the base-case because it used a different CLDN18.2 test used compared with SPOTLIGHT and GLOW, and the infrequent use of the chemotherapy backbone EOX in the UK. Nevertheless, the FAST trial CLDN18.2 ≥ 70% subgroup provides relevant evidence about the efficacy of zolbetuximab + chemotherapy versus chemotherapy. These analyses are presented in Appendix D.1.4. and briefly summarised in the next section.

B.2.9.3. Non-proportional hazards network meta-analysis – results

B.2.9.3.1. Progression-free survival

Figure 14 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the primary analysis of PFS (3-knot model). The results indicate that the NMA model provides a good fit to the observed data for all trials.

Figure 14: Study-specific survival – primary analysis of PFS (3-knot model)

Key: CPS, combined positive score; Nivo, nivolumab; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

Figure 15 and Table 12 show the estimated HR over time (up to 5 years) for each treatment versus chemotherapy from the primary PFS analysis (3-knot model). The results suggest that zolbetuximab + chemotherapy lowers the rate of progression compared with chemotherapy; this difference is statistically significant from approximately 3 months onwards. The HR is reasonably constant over time, with a slight reduction (i.e., better efficacy over time). The HR for nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 versus chemotherapy increases over time, suggesting lower efficacy over time. In addition, results indicate that zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 have similar HRs versus chemotherapy, suggesting that zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 have similar effects on progression. For comparison, results from a constant proportional hazards analysis are also included. These are consistent with the conclusion of similar efficacy between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5.

Further details on the incorporation into the cost effectiveness model of PFS for each treatment over time are presented in Section B.3.3 and empirical HRs overlaid with estimated HRs over time for each treatment versus chemotherapy are presented in Appendix Section D.1.4.1.2.

Figure 15: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (3-knot model)

Key: HR, hazard ratio; Nivo, nivolumab; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

Table 12: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (3-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]
Constant HR*		[redacted]	[redacted]

Key: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival.
Notes: * Constant HRs are taken from the global NMA presented in Appendix D.1.5.

B.2.9.3.2. Overall survival

Figure 16 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the primary analysis of OS (3-knot model). The results indicate that the 3-knot spline NMA model provides a good fit to the observed data.

Figure 16: Study-specific survival – primary analysis of OS (3-knot model)

Key: CPS, combined positive score; OS, overall survival.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

Figure 17 and Table 13 show the estimated HR over time (up to 5 years) from the primary analysis of OS (3-knot model). Results suggest zolbetuximab + chemotherapy lowers mortality rate compared with chemotherapy; results are statistically significant from approximately 6 months onwards. The HR is reasonably constant over time for both zolbetuximab + chemotherapy vs chemotherapy and nivolumab + chemotherapy vs chemotherapy in patients with PD-L1 CPS ≥ 5. In addition, the results indicate that zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 have similar HRs versus chemotherapy over time, suggesting that zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 have similar effects on mortality. For comparison, results from a constant proportional hazards analysis are

also included. These are consistent with the conclusion of similar efficacy between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5. They also suggest that results from the time-varying NMA may slightly over-estimate the effectiveness of nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 and under-estimate that of zolbetuximab + chemotherapy. The OS time-varying HR for CheckMate 649 estimated from the digitized Kaplan–Meier data were lower than the reported HR due to limits in the digitization of the Kaplan–Meier curve (HR nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 versus chemotherapy of [redacted] to [redacted] from digitized Kaplan–Meier data and 0.70 from publication).

Further details on the incorporation into the cost effectiveness model of OS for each treatment over time are presented Section B.3.3 and empirical HRs overlaid with estimated HRs over time for each treatment versus chemotherapy are presented in Appendix Section D.1.4.1.2.

Figure 17: HRs over time for each treatment versus chemotherapy – primary analysis of OS (3-knot model)

Key: HR, hazard ratio; Nivo, nivolumab; OS, overall survival; Zolbe, zolbetuximab.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

Table 13: HRs over time for each treatment versus chemotherapy – primary analysis of OS (3-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]
Constant HR*		[redacted]	[redacted]

Key: CrI, credible interval; HR, hazard ratio; OS, overall survival.
Notes: * Constant HRs are taken from the global NMA presented in Appendix D.1.5.

B.2.9.3.3. Sensitivity analysis including the FAST trial CLDN18.2 ≥ 70% subgroup

For PFS, the spline NMA model using the 3-knot model (used for the base-case PFS analysis) had a poor fit to the FAST trial CLDN18.2 ≥ 70% subgroup (see Appendix D.1.4.1.2. The estimated PFS HRs of zolbetuximab + chemotherapy vs chemotherapy including the FAST trial CLDN18.2 ≥ 70% subgroup were slightly lower compared to the base-case analysis without, mean estimates ranging from [redacted] to [redacted] (vs [redacted] to [redacted] in the base-case analysis without the FAST trial CLDN18.2 ≥ 70% subgroup).

The OS results followed a similar pattern as the PFS results, in that the spline NMA model had a poor fit to the FAST trial CLDN18.2 ≥ 70% subgroup (see Appendix D.1.4.1.3). The estimated OS HRs of zolbetuximab + chemotherapy vs chemotherapy including the FAST trial CLDN18.2 ≥ 70% subgroup were slightly lower compared to the base-case analysis without, mean estimates ranging from [redacted] to [redacted] (vs [redacted] to [redacted] in the base-case analysis without the FAST trial CLDN18.2 ≥ 70% subgroup).

B.2.9.4. Uncertainties in the indirect and mixed treatment comparisons

This spline-based NMA found that zolbetuximab + chemotherapy has similar efficacy to nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 for PFS and OS outcomes. The base-case analysis, including SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup found similar HRs over time and overlapping credible intervals. The scenario analysis, including the FAST trial CLDN18.2 ≥ 70% subgroup, had a similar finding with more favourable results for zolbetuximab + chemotherapy compared to the base-case analysis. The results are consistent with the proportional hazards NMA, which found also similar HRs and overlapping confidence intervals between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 vs chemotherapy.

Non-PH methods were used as there was evidence that the PH assumption was uncertain in one or more of the randomised controlled trials in the network, for the relative treatment effects of OS and PFS. These methods are recommended when there is evidence against proportionality in at least one trial in the evidence base.[92]

The fractional polynomial NMA approach was previously considered and applied to the network of evidence. However, the first-order models provided a poor fit to some trials in the evidence base, and there were convergence issues with the second-order models, meaning relative effects could not be reliably estimated. Therefore, restricted cubic spline NMAs were conducted. These models provided a reasonably good visual fit to the observed trial data.

Restricted cubic spline NMA methods are not currently as comprehensively defined in the literature as standard NMA methods. Spline NMA methods that incorporate random effects are still in development; therefore, these analyses were conducted under a fixed-effects framework. As such, the uncertainty in relative treatment effect estimates may be underestimated (minimal impact is expected on the HR point estimates). On the other hand, although there are differences in study populations (which may suggest some heterogeneity in the network), a random-effects analysis may not have been able to reliably estimate the between-trial standard deviation

given the small number of trials per treatment comparison in the network. In that case, a fixed-effects framework would have been preferred regardless. Nevertheless, it was not possible to test this assumption given the lack of developed random-effects methodology, which is a limitation of the analysis.

Analyses were conducted based on recommendations from Royston and Lambert, specifically the number and placement of the internal knots.[93] As mentioned, the good visual fit to the evidence base indicated that the selected approach was appropriate.

To allow a connected network of evidence to be formed, the assumption of equivalent chemotherapy regimens was required. This assumption simplified this analysis and avoided the need to include additional studies in the network, which would likely introduce heterogeneity in the network and lead to inconsistencies and uncertainty in results. In addition, there was no evidence of a significant difference in efficacy between chemotherapy regimens in the global NMA (See Appendix D.1.5); in the HRs in SPOTLIGHT and GLOW; or in the subgroup analyses in CheckMate 649.

As mentioned above, the spline NMA models used in this analysis provided a reasonably good fit to the observed data. However, the spline NMA model fitted less well to the observed OS and PFS data in FAST CLDN18.2 ≥ 70% subgroup compared with other zolbetuximab trials (SPOTLIGHT and GLOW). This is likely due to the small sample size of FAST CLDN18.2 ≥ 70% subgroup and the relative treatment effect for zolbetuximab + chemotherapy versus chemotherapy primarily being driven by the larger SPOTLIGHT and GLOW trials. Another contributing factor for the differences in efficacy may be the different chemotherapy backbone in FAST (EOX) compared to SPOTLIGHT, GLOW and CheckMate 649 trials (CAPOX or FOLFOX).

In summary, despite limitations in the comparability of the populations, sample size, data availability, maturity, and heterogeneity, every attempt has been made to provide a robust NMA for the comparison of zolbetuximab + chemotherapy with the comparators relevant to the decision problem (Table 1). The analyses suggest that

zolbetuximab + chemotherapy provides significant improvements in OS and PFS compared with chemotherapy alone and similar to nivolumab + chemotherapy (PD-L1 CPS ≥ 5 subgroup).

B.2.10. Adverse reactions

B.2.10.1. SPOTLIGHT

In this section, safety data are presented for SPOTLIGHT with a data cut of 29 June 2023.[77, 81] The final database lock for the SPOTLIGHT trial took place on [redacted], and data analysis is currently ongoing. These data will be provided during clarification questions, but as the timings of the two data cuts are close together, safety data are anticipated to be very similar.

B.2.10.1.1. Treatment exposure

In the zolbetuximab + mFOLFOX6 arm, the mean duration of treatment with zolbetuximab was [redacted] days.[77] The majority of patients had a cumulative zolbetuximab exposure of > 6 weeks ([redacted]) and > 12 weeks ([redacted]), and exposure to mFOLFOX6 was similar between both treatment arms. Further details on the extent of exposure are presented in Appendix M.3.1.3.

B.2.10.1.2. Treatment-emergent adverse events

The majority (99.6%) of patients experienced at least one treatment-emergent adverse event (TEAE) in both treatment arms.[77, 81] A table presenting any-grade TEAEs occurring in ≥ 10% of patients in either treatment arm is provided in Appendix M.3.1.3.

In the zolbetuximab + mFOLFOX6 arm, the most frequent TEAEs (≥ 20% of patients) were nausea (82.4%), vomiting (67.4%), decreased appetite (48.7%), diarrhoea (40.9%), peripheral sensory neuropathy (38.4%), anaemia (38.0%), neutropenia (36.6%), constipation (35.8%), neutrophil count decreased (34.4%), fatigue (29.7%), asthenia (26.5%), abdominal pain (25.1%), stomatitis (21.5%), pyrexia (20.8%), weight decreased (20.4%), oedema peripheral (18.6%), hypokalaemia (18.3%), white blood cell count decreased (18.3%), aspartate aminotransferase increased

(17.9%), upper abdominal pain (16.8%), hypoalbuminemia (16.5%), paraesthesia (15.8%), and dysgeusia (15.8%).[77, 81] In the placebo + mFOLFOX6 arm, the most frequent TEAEs were nausea (61.5%), diarrhoea (45.0%), peripheral sensory neuropathy (42.8%), constipation (40.6%), anaemia (38.5%), vomiting (36.3%), decreased appetite (34.9%), neutropenia (33.8%), fatigue (33.8%), neutrophil count decreased (32.7%), abdominal pain (31.3%), asthenia (23.0%), stomatitis (21.6%), weight decreased (19.8%), pyrexia (18.0%), alanine aminotransferase increased (18.0%), platelet count decreased (17.6%), paraesthesia (16.9%), aspartate aminotransferase increased (16.9%), and hypokalaemia (15.1%).

The incidence of the most common TEAEs was similar in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms, with the exception of nausea (82.4% vs 61.5%), vomiting (67.4% vs 36.3%), and decreased appetite (48.7% vs 34.9%).[77, 81]

B.2.10.1.3. Grade ≥ 3 treatment-emergent adverse events

Grade ≥ 3 TEAEs were reported in 243 (87.1%) patients in the zolbetuximab + mFOLFOX6 arm and 219 (78.8%) patients in the placebo + mFOLFOX6 arm.[77, 81] The most frequent Grade ≥ 3 TEAEs (≥ 10% of patients) in the zolbetuximab + mFOLFOX6 arm were neutropenia (28.3%), neutrophil count decreased (24.7%), nausea (16.1%) and vomiting (16.1%).[81] The most frequent Grade ≥ 3 TEAEs in the placebo + mFOLFOX6 arm were neutrophil count decreased (24.8%) and neutropenia (23.4%).

B.2.10.1.4. Study intervention-related treatment-emergent adverse events

Zolbetuximab- or placebo-related TEAEs were more frequent in the zolbetuximab + mFOLFOX6 arm than in the placebo + mFOLFOX6 arm (256 [redacted] vs 216 [redacted]).[77] A table presenting study intervention-related TEAEs in ≥ 10% of patients occurring in either treatment arm is provided in Appendix M.3.1.3.

In the zolbetuximab + mFOLFOX6 arm, the most frequent zolbetuximab-related TEAEs (≥ 20% of patients) were nausea ([redacted]), vomiting ([redacted]) and decreased

appetite ([redacted]).[77] In the placebo + mFOLFOX6 arm, the most frequent placebo-related TEAEs were nausea ([redacted]) and fatigue ([redacted]).

B.2.10.1.5. Grade ≥ 3 study intervention-related treatment-emergent adverse events

In the zolbetuximab + mFOLFOX6 arm, [redacted] patients experienced a zolbetuximab-related Grade ≥ 3 TEAE; in the placebo + mFOLFOX6 arm, [redacted] patients experienced a placebo-related Grade ≥ 3 TEAE.[77] The most commonly reported Grade ≥ 3 TEAEs (≥ 10% of patients) that were considered by the investigator to be related to zolbetuximab included neutropenia ([redacted]), vomiting ([redacted]), nausea ([redacted]) and neutrophil count decreased ([redacted]). The most commonly reported Grade ≥ 3 TEAEs that were considered by the investigator to be related to placebo included neutrophil count decreased ([redacted]) and neutropenia ([redacted]).

B.2.10.1.6. Serious adverse events

The number and proportion of patients experiencing a serious adverse event (SAE) was comparable between the zolbetuximab + mFOLFOX6 arm and the placebo + mFOLFOX6 arm (47.0% vs 46.4%, respectively).[77, 81] Overall, [redacted]% of patients in the zolbetuximab + mFOLFOX6 arm and [redacted]% of patients in the placebo + mFOLFOX6 arm had SAEs that the investigator considered to be related to zolbetuximab or placebo.

In the zolbetuximab + mFOLFOX6 arm, the most commonly reported SAEs (≥ 5% of patients) were vomiting ([redacted]) and nausea ([redacted]).[77] Vomiting was the only zolbetuximab-related SAE that occurred in ≥ 5% of patients. In the placebo + mFOLFOX6 arm, the most frequent SAE was vomiting ([redacted]). No placebo-related SAEs occurred in ≥ 5% of patients.

B.2.10.1.7. Discontinuation and/or dose modifications due to treatment-emergent adverse events

TEAEs leading to permanent discontinuation of zolbetuximab or placebo were reported in [redacted] patients in the zolbetuximab + mFOLFOX6 arm and [redacted]

[redacted] patients in the placebo + mFOLFOX6 arm.[77] The most frequently reported TEAEs leading to permanent discontinuation of zolbetuximab were nausea and vomiting ([redacted] each), and most of these events were considered by the investigator to be related to zolbetuximab ([redacted] and [redacted], respectively). In the placebo + mFOLFOX6 arm, [redacted] TEAEs led to permanent discontinuation in [redacted] of patients.

TEAEs leading to dose interruption of zolbetuximab or placebo were reported in [redacted] patients in the zolbetuximab + mFOLFOX6 arm and [redacted] patients in the placebo + mFOLFOX6 arm.[77] The most frequently reported TEAEs leading to dose interruption of zolbetuximab were nausea ([redacted]), vomiting ([redacted]), neutropenia ([redacted]), neutrophil count decreased ([redacted]), abdominal pain ([redacted]), abdominal pain upper ([redacted]) and hypertension ([redacted]). The most frequently reported TEAEs leading to dose interruption of placebo were neutropenia ([redacted]) and neutrophil count decreased ([redacted]).

The TEAEs that led to dose interruption and had ≥ 5% difference in the zolbetuximab + mFOLFOX6 arm compared with the placebo + mFOLFOX6 arm were nausea ([redacted] vs [redacted], respectively), vomiting ([redacted]vs [redacted]), abdominal pain ([redacted] vs [redacted]), abdominal pain upper ([redacted] vs [redacted]) and hypertension ([redacted] vs [redacted]).[77]

B.2.10.1.8. Deaths

The number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms ([redacted] vs [redacted], respectively).[77] The primary cause of death was due to disease progression, occurring in [redacted] patients in the zolbetuximab + mFOLFOX6 arm and [redacted] patients in the placebo + mFOLFOX6 arm. TEAEs that led to death and were considered by the investigator as possibly related to zolbetuximab + mFOLFOX6 or placebo + mFOLFOX6 occurred in [redacted] ([redacted]) of patients in both treatment arms.

B.2.10.2. GLOW

In this section, safety data are presented for GLOW from a data cut of 29 June 2023.[79, 84]

B.2.10.2.1. Treatment exposure

In the zolbetuximab + CAPOX arm, the mean duration of treatment with zolbetuximab was [redacted] days.[79] The majority of patients had cumulative zolbetuximab exposure of > 6 weeks ([redacted]) and > 12 weeks ([redacted]). The mean duration of treatment with the components of CAPOX was similar between both treatment arms. Further details on the extent of exposure are presented in Appendix M.3.2.3.

B.2.10.2.2. Treatment-emergent adverse events

The majority of patients (> 98%) experienced at least one TEAE in both treatment arms.[79, 84] A table presenting any-grade TEAEs occurring in ≥ 10% of patients in either treatment arm is provided in Appendix M.3.2.3.

In the zolbetuximab + CAPOX arm, the most frequent TEAEs (≥ 20% of patients) were nausea (68.9%), vomiting (66.1%), decreased appetite (41.3%), anaemia (36.6%), diarrhoea (32.3%), neutrophil count decreased (28.0%), aspartate aminotransferase increased (24.8%), platelet count decreased (24.0%), hypoalbuminemia (22.4%), peripheral sensory neuropathy (22.4%), and white blood cell count decreased (20.1%).[79, 84]

In the placebo + CAPOX arm, the most frequent TEAEs were nausea (50.2%), anaemia (36.9%), diarrhoea (34.9%), decreased appetite (34.5%), vomiting (31.3%), aspartate aminotransferase increased (30.1%), platelet count decreased (24.9%), neutrophil count decreased (23.7%), peripheral sensory neuropathy (22.5%), constipation (21.3%), alanine aminotransferase increased (21.3%), and abdominal pain (22.1%).[79, 84]

The incidence of common TEAEs was similar in the zolbetuximab + CAPOX and placebo + CAPOX arms, with the exception (difference of ≥ 5%) of nausea (68.9% vs 50.2%, respectively), vomiting (66.1% vs 31.3%), decreased appetite (41.3% vs 34.5%), abdominal pain (16.1% vs 22.1%), hypoalbuminemia (22.4% vs 14.1%), constipation (15.7% vs 21.3%), neutropenia (19.7% vs 14.1%), weight decreased (19.7% vs 10.0%), and peripheral oedema ([redacted] vs [redacted]).[79, 84]

B.2.10.2.3. Grade ≥ 3 treatment-emergent adverse events

Grade ≥ 3 TEAEs were reported in 186 (73.2%) patients in the zolbetuximab + CAPOX arm and 175 (70.3%) patients in the placebo + CAPOX arm.[79, 84] The most frequent Grade ≥ 3 TEAEs (≥ 10% of patients) in the zolbetuximab + CAPOX arm were vomiting (12.2%), anaemia (11.4%) and neutrophil count decreased (10.3%). The most frequent Grade ≥ 3 TEAE in the placebo + CAPOX arm was anaemia (11.2%).

B.2.10.2.4. Study intervention-related treatment-emergent adverse events

Zolbetuximab or placebo-related TEAEs were more frequent in the zolbetuximab + CAPOX arm versus the placebo + CAPOX arm ([redacted] vs [redacted], respectively).[79] A table presenting a summary of study intervention-related TEAEs in ≥ 10% of patients occurring in either treatment arm is provided in Appendix M.3.2.3.

In the zolbetuximab + CAPOX arm, the most frequent zolbetuximab-related TEAEs (≥ 20% of patients) were nausea ([redacted]), vomiting ([redacted]) and decreased appetite ([redacted]).[79] In the placebo + CAPOX arm, the most frequent placebo-related TEAEs were nausea ([redacted]) and decreased appetite ([redacted]).

B.2.10.2.5. Grade ≥ 3 study intervention-related treatment-emergent adverse events

In the zolbetuximab + CAPOX arm, [redacted] patients experienced a zolbetuximab-related Grade ≥ 3 TEAE and [redacted] patients in the placebo + CAPOX arm experienced a placebo-related Grade ≥ 3 TEAE.[79] The most commonly reported (≥ 10% of patients) Grade ≥ 3 TEAE that was considered by the investigator to be related to zolbetuximab was vomiting ([redacted]). [redacted] Grade ≥ 3 TEAEs were reported in ≥ 10% of patients in the placebo + CAPOX arm.

B.2.10.2.6. Serious adverse events

The number and proportion of patients experiencing a SAE was comparable between the zolbetuximab + CAPOX arm and the placebo + CAPOX arm (48.0% vs 50.6%, respectively).[79, 84] Overall, [redacted]% of patients in the zolbetuximab + CAPOX

arm and [redacted]% of patients in the placebo + CAPOX arm had SAEs that the investigator considered to be related to zolbetuximab or placebo.[79]

In the zolbetuximab + CAPOX arm, the most commonly reported SAE (≥ 5% of patients) was vomiting ([redacted]).[79] [redacted] zolbetuximab-related SAEs occurred in ≥ 5% of patients. In the placebo + CAPOX arm, the most frequent SAE was malignant neoplasm progression ([redacted]). [redacted] placebo-related SAEs occurred in ≥ 5% of patients.

B.2.10.2.7. Discontinuation and/or dose modifications due to treatment-emergent adverse events

TEAEs leading to permanent discontinuation of zolbetuximab or placebo were reported in [redacted] and [redacted] patients in the zolbetuximab + CAPOX arm and placebo + CAPOX arm, respectively.[79] In the zolbetuximab + CAPOX arm, vomiting ([redacted]) was the only TEAE leading to permanent discontinuation of zolbetuximab in ≥ 2% of patients, and all events were considered by the investigator to be related to zolbetuximab. In the placebo + CAPOX arm, [redacted] events led to permanent discontinuation of placebo in ≥ 2% of patients.

TEAEs leading to dose interruption of zolbetuximab or placebo were reported in [redacted] patients in the zolbetuximab + CAPOX arm and [redacted] patients in the placebo + CAPOX arm.[79] The most frequently reported TEAEs (≥ 5% of patients) leading to dose interruption of zolbetuximab were vomiting ([redacted]), nausea ([redacted]) and neutropenia ([redacted]). The most frequently reported TEAE leading to dose interruption of placebo was platelet count decreased ([redacted]).

The TEAEs that led to dose interruption and had ≥ 5% difference in the zolbetuximab + CAPOX arm compared with the placebo + CAPOX arm were vomiting ([redacted] vs [redacted], respectively) and nausea ([redacted] vs [redacted]).[79]

B.2.10.2.8. Deaths

The number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + CAPOX and placebo + CAPOX arms ([redacted] vs [redacted], respectively).[79] The primary cause of death was due to

disease progression, occurring in [redacted] patients in the zolbetuximab + CAPOX arm and [redacted] patients in the placebo + CAPOX arm. In total, [redacted] patients in the zolbetuximab + CAPOX arm and [redacted] patients in the placebo + CAPOX arm had TEAEs leading to death that the investigator considered to be related to zolbetuximab or placebo.

B.2.10.3. FAST

A summary of safety data from the FAST trial is provided in Appendix M.4.2.[74, 86] These data were broadly consistent with those observed during SPOTLIGHT and GLOW.

B.2.10.4. Safety profile summary

At the latest data cut-off (29 June 2023), the safety results of SPOTLIGHT and GLOW demonstrated that the safety profile of zolbetuximab in combination with chemotherapy offers a manageable and predictable AE profile specific to the individual products, and that this safety profile was consistent across patients enrolled to the trials.[77, 79] The safety profile of zolbetuximab in combination with chemotherapy was considered acceptable according to trial parameters, with no critical or new safety signals observed. These data were consistent with those observed during the Phase II FAST trial (Appendix M.4.2.2.3)[74, 86]; all studies demonstrate a similar safety profile.

B.2.11. Ongoing studies

The final database lock for the SPOTLIGHT trial took place on [redacted], and data analysis is currently ongoing. The final database lock for the GLOW trial took place on [redacted], and data analysis is currently ongoing.

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings of the clinical evidence base

Zolbetuximab is a first-in-class monoclonal antibody targeting CLDN18.2 for the ‘first-line treatment of adult patients with locally advanced unresectable or metastatic

HER2-negative G/GEJ adenocarcinoma whose tumours are CLDN18.2 positive'.[3] Zolbetuximab offers an effective treatment option for patients with CLDN18.2-positive disease regardless of PD-L1 CPS status (see Section B.1.3.1).[16, 72] Evidence for zolbetuximab as a treatment for HER2-negative G/GEJC comes from a clinical trial programme that includes over 1,000 patients from two key Phase III trials, SPOTLIGHT and GLOW, which provide head-to-head evidence versus chemotherapy – the type of therapy currently received by the majority of patients expected to be eligible for zolbetuximab, and for whom the unmet need is greatest.

Relative efficacy outcomes were consistent across SPOTLIGHT and GLOW and demonstrated that the addition of zolbetuximab to first-line chemotherapy provided a statistically significant survival benefit, with a 22.0–22.9% reduction in the risk of death and a 27.0–31.8% reduction in risk of progression or death versus chemotherapy in patients with HER2-negative, CLDN18.2-positive, locally advanced unresectable or metastatic G/GEJC (see Section B.2.6).[77, 79, 81, 84] Results of the non-PH NMAs further support these results, indicating that the addition of zolbetuximab to chemotherapy provides a [redacted]% reduction in the risk of death and [redacted]% reduction in the risk of progression, compared with chemotherapy alone. Results were statistically significant from approximately 6 months onwards for OS and from approximately 3 months onwards for PFS (See Section B.2.9.3).

Safety data from SPOTLIGHT and GLOW demonstrated that zolbetuximab in combination with chemotherapy offers a manageable and predictable AE profile consistent with that reported in previous clinical studies of zolbetuximab (see Section B.2.10).[77, 79] Safety outcomes were generally consistent between SPOTLIGHT and GLOW, and no new safety signals were observed. These data were consistent with those observed during the Phase II FAST trial (Appendix 4.2).[74, 86]

Importantly, HRQL data collected in the SPOTLIGHT and GLOW trials show no clinically meaningful drop in patient QoL during treatment with zolbetuximab + chemotherapy. In addition, HRQL was generally similar between the zolbetuximab + chemotherapy arm and chemotherapy arm in both trials, demonstrating that treatment with zolbetuximab has no adverse impact on patients' HRQL compared

with chemotherapy.[75, 76] Patients are therefore able to benefit from the improved responses and chances of survival without compromising their QoL.

When comparing zolbetuximab + chemotherapy with nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5, the results of the both the PH and non-PH NMAs indicate that zolbetuximab + chemotherapy has similar effects on mortality and progression to nivolumab + chemotherapy.

B.2.12.2. Strengths and limitations of the clinical evidence base

SPOTLIGHT and GLOW are well-designed, Phase III, multicentre, double-blind RCTs providing head-to-head evidence of zolbetuximab + chemotherapy versus placebo + chemotherapy – the main comparator in this submission. SPOTLIGHT and GLOW were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies, with steps taken to minimise the risk of bias. The overall risk of bias for both studies is considered to be low.

SPOTLIGHT enrolled 565 patients from 232 sites across 20 countries, including 11 sites in the UK that enrolled [redacted] patients.[24, 75] GLOW enrolled 507 patients from 176 sites across 18 countries, including four sites in the UK that enrolled [redacted] patients.[42, 76] The median age of patients in SPOTLIGHT and GLOW was 61 and 60 years, respectively, which is similar to the median age observed for patients in UK clinical practice (55–59 years).[19] In addition, the outcomes used in the trial are consistent with those that would be captured as part of standard practice in the National Health Service (NHS) England.

Despite some small differences in the trial populations of SPOTLIGHT and GLOW, relative outcomes (HR) were very similar in both zolbetuximab trials for PFS (SPOTLIGHT: HR 0.73 versus GLOW: HR 0.68) and OS (SPOTLIGHT: HR 0.78 versus GLOW: HR 0.77), suggesting that the differences in trial populations are not treatment-effect modifiers.[77, 79] Furthermore, the relative effectiveness of zolbetuximab compared with chemotherapy is the same irrespective of the chemotherapy regimen used, supporting the strategy of synthesising the trial results.

A limitation of the SPOTLIGHT and GLOW studies is that they do not provide head-to-head data with comparator treatments outside of chemotherapy. This is reflective of the treatment landscape at the time of trial design, when no CPIs were available in clinical practice. In the absence of head-to-head trial data, both a PH and non-PH NMA were conducted to compare zolbetuximab + chemotherapy with nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

In line with the 'NICE Guide to the methods of technology appraisal 2013'[94], an SLR was conducted to identify cost-effectiveness studies for the treatment of G/GEJ cancer. In brief, electronic database searches (MEDLINE®, Embase®, the Cochrane library and EconLit®) were conducted in September 2018, and subsequently updated in August 2022 and October 2023. Publications describing full economic evaluations of interventions aimed at managing previously untreated advanced or metastatic G/GEJ/oesophageal adenocarcinoma cancer were included. Full details of the process and methods to identify and select the relevant cost-effectiveness evidence, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams, are provided in Appendix G.

Of the 28 studies that were included in the review, only seven are potentially relevant; six are UK-based and one Italian. The remaining studies, which are unlikely to be relevant to a UK context, are based in China, Japan, the Republic of Korea, Hong Kong and Iran (albeit one study based in China that evaluated the cost-effectiveness of zolbetuximab with chemotherapy based on SPOTLIGHT). One UK study was later excluded as it was an abstract, limiting its value.[95] Of the five UK-based studies, two represent Scottish Medicines Consortium (SMC)[96, 97] submissions for drugs that were appraised by NICE (which are also included in the review). As more detail is typically provided for NICE appraisals, the SMC submissions are not reported here, resulting in three relevant UK cost-effectiveness studies that are included in Table 14.[29, 98, 99] The Italian cost-effectiveness analysis[100] was an observational study comparing costs and life years (LYs) for treatment with trastuzumab and chemotherapy compared with chemotherapy alone amongst patients with metastatic GC and a median follow-up of 7.4 months. It is unlikely to provide additional value beyond that of the UK-based studies and so is not discussed further.

Table 14: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA208[98]	2010	Markov economic model to assess the cost-effectiveness of trastuzumab + chemotherapy to treat people with HER2-positive metastatic gastric cancer. The model had three distinct health states: PFS, disease progression and death.	NR	Trastuzumab + cisplatin and capecitabine compared with epirubicin + cisplatin and capecitabine, and compared with epirubicin + oxaliplatin and capecitabine, produced a mean gain of 4.8 months of life for both comparisons. QALYs for each treatment not stated though trastuzumab + cisplatin produced an additional 0.25 QALYs over epirubicin + cisplatin and capecitabine.	All costs are in GBP (£). Included costs for: HER2 testing, drug acquisition, drug administration, monitoring during PFS, treating AEs, care costs in PFS after chemotherapy treatment was stopped, and supportive care costs after progression of disease.	Trastuzumab + cisplatin and capecitabine versus epirubicin + cisplatin and capecitabine produced an ICER of £51,927 per QALY gained. The probability that trastuzumab + cisplatin and capecitabine was cost-effective at £30,000 was 0%.
NICE TA857[29]	2022	Semi-Markov economic model to assess the cost-effectiveness of nivolumab with platinum- and fluoropyrimidine-based chemotherapy as an option for untreated HER2-negative, advanced or metastatic G/GEJC or oesophageal	Mean (SE): 60.3 (12)	Information redacted	All costs are in GBP (£). Included costs: intervention and comparator acquisition costs, administration costs, monitoring/healthcare resource use costs, AEs, one-off terminal care, HER2 testing.	The resulting ICER estimates for nivolumab + chemotherapy were £47,840 per QALY (nivolumab + FOLFOX versus FOLFOX) to £45,172 per QALY gained (nivolumab + XELOX versus XELOX).

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		adenocarcinoma in adults whose tumours express PD-L1 with a CPS of 5 or more. The model had four health states: pre-progression, long-term remission, progressed and dead. A partitioned survival model was also developed.				
Javanbakht et al.[99]	2020	A partitioned survival model followed by state transition Markov model was developed to estimate the cost-effectiveness of the use of pressurised intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin versus palliative chemotherapy for the treatment of advanced gastric cancer in the UK. Two health states include progression free and death. The intervention	NR	Upfront therapy: 1.02 QALYs per patient Second-line therapy: 0.45 QALYs per patient	All costs are in GBP (£). Included costs: drug/procedure acquisition costs, outpatient administration costs, follow-up/monitoring costs, costs associated with AEs, and costs of terminal care.	Upfront therapy: £31,868 Second-line therapy: dominant

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		was assessed at two different levels of care, including upfront therapy and second-line therapy.				

Key: AE, adverse event; CPS, combined positive score; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJC, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; NR, not reported; PFS, progression-free survival; QALY, quality-adjusted life year; SE, standard error; XELOX, oxaliplatin and capecitabine (also known as CAPOX).

B.3.2. Economic analysis

The economic case presented in this submission is based on a conventional cost–utility analysis, assessing the use of zolbetuximab + chemotherapy versus chemotherapy alone for the treatment of previously untreated locally advanced unresectable or metastatic G/GEJC. As discussed in Section B.1.3, Astellas recognises that the greatest unmet need is for patients unsuitable for nivolumab, irrespective of whether patients have a PD-L1 CPS score < 5 or because they are unable to tolerate this regimen. As such, our primary analysis is versus chemotherapy for patients unsuitable for nivolumab. We also undertake a secondary analysis to assess the cost-effectiveness of zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5.

Unless otherwise specified, the data cut informing the economic analysis is the 29 June 2023 data cut. The final database lock for the SPOTLIGHT trial took place on [redacted], and data analysis is currently ongoing. These data will be provided during clarification questions, but results are anticipated to be very similar to the 29 June 2023 data cut given that the timings of the two data cuts are close together. The final database lock for the GLOW trial took place on [redacted], and data analysis is currently ongoing.

B.3.2.1. Patient population

The population included in this model was adult patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJC adenocarcinoma who have not previously been treated for advanced/metastatic disease with chemotherapy. CLDN18.2-positive is defined as patients' tumours expressing CLDN18.2 in ≥ 75% of tumour cells, demonstrating moderate-to-strong membranous staining as determined by central IHC testing. HER2-negative is determined by local or central testing on a G/GEJC tumour specimen.

The population for the primary analyses is patients eligible for chemotherapy, with the characteristics of the patient population at treatment initiation aligned with the ITT population of the SPOTLIGHT and GLOW trials. In the secondary analysis, the model also examines the cost-effectiveness of zolbetuximab with chemotherapy

compared with nivolumab with chemotherapy in patients whose tumours express PD-L1 with a CPS of 5 or more.[29] However, the CPI-eligible population is small, based on overlap from the studies. Of those patients randomised to SPOTLIGHT and GLOW, data on CPS are available for [redacted] and [redacted] patients, respectively. In those patients who could be tested, the proportion with PD-L1 CPS ≥ 5 is [redacted] and [redacted] in SPOTLIGHT and GLOW, respectively[72]. These results are slightly different than those in the public domain, given that [redacted] additional patients were included for the biomarker report. [72] For comparison, the proportion of patients with PD-L1 CPS ≥ 5 according to the SPOTLIGHT and GLOW publications is 17.4% (104/599) and [redacted] according to the biomarker report.

In this secondary analysis, we still use the ITT populations of SPOTLIGHT and GLOW to estimate the efficacy of zolbetuximab + chemotherapy rather than restricting the zolbetuximab trial data by PD-L1 CPS score. This is for three key reasons. Firstly, the literature indicates that PD-L1 expression is not a prognostic factor or treatment-effect modifier for chemotherapy, and as such is only predictive of greater efficacy for nivolumab versus chemotherapy.[16] Secondly, Astellas is not aware of any biological mechanism by which PD-L1 expression can affect the efficacy of zolbetuximab. Thirdly, PD-L1 CPS was not a pre-specified subgroup analysis, and approximately one third of the patients enrolled in the trials could not be tested for PD-L1 CPS[72], thereby increasing the risk of imbalance in baseline characteristics and uncertainty in the results. Zolbetuximab showed consistent benefit across PD-L1 CPS subgroups based on post hoc subgroup analyses. The efficacy of zolbetuximab + chemotherapy should therefore not be influenced by PD-L1 CPS score; breaking randomisation and using a CPS-based subpopulation for zolbetuximab will only lead to an increase in uncertainty regarding its efficacy in this population.

Table 15 shows the baseline characteristics of the patient population in the model. These are based on the baseline characteristics of patients in the SPOTLIGHT and GLOW trials since these include information on all characteristics needed to inform the model as well as being generalisable to the UK clinical practice population.

Table 15: Baseline characteristics of patients included in the model (SPOTLIGHT [75] and GLOW[75])

Patient characteristics	Value	Measurement of uncertainty and distribution (SD)	Reference/source
Starting age (years)	58.50	12.49	SPOTLIGHT[75] and GLOW[75]
Proportion female (%)	37.9%	N/A	SPOTLIGHT[75] and GLOW[75]
Average patient weight (kg)	63.08	14.38	SPOTLIGHT[75] and GLOW[75]
Body surface area (m^2)	1.70	0.22	SPOTLIGHT[75] and GLOW[75]
Key: N/A, not applicable; SD, standard deviation.			

B.3.2.2. Model structure

The cost-effectiveness analysis model used a three-state partitioned survival modelling approach. The model structure is presented in Figure 18, and an illustrative example of the partitioned survival modelling approach is presented in Figure 19. The model comprises three mutually exclusive health states. A description of each health state and the calculation for the proportion of patients in each state in each cycle is given below:

- Pre-progression: patients enter the model in the pre-progression state, and have locally advanced unresectable or metastatic cancer, as per the expected marketing authorisation for zolbetuximab. The state membership is defined by the proportion of patients who are progression free at any given time point based on the PFS curve. Within this health state, patients receive first-line treatment based on modelled duration of treatment curves, which include stopping rules where applicable
- Post-progression: these patients have experienced disease progression. Their state membership is defined as the proportion of patients who are alive at any given time point minus the proportion of patients who have not progressed at the same time point (the percentage of OS and the percentage of PFS, respectively)

- Death: this is set as an absorbing state. The proportion of patients in this health state is defined as 1 minus the proportion of patients alive (1 and the percentage of OS) at a given time point

Figure 18: Model structure

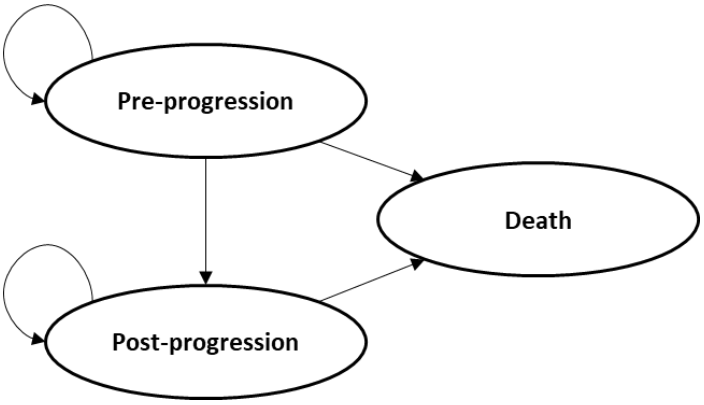
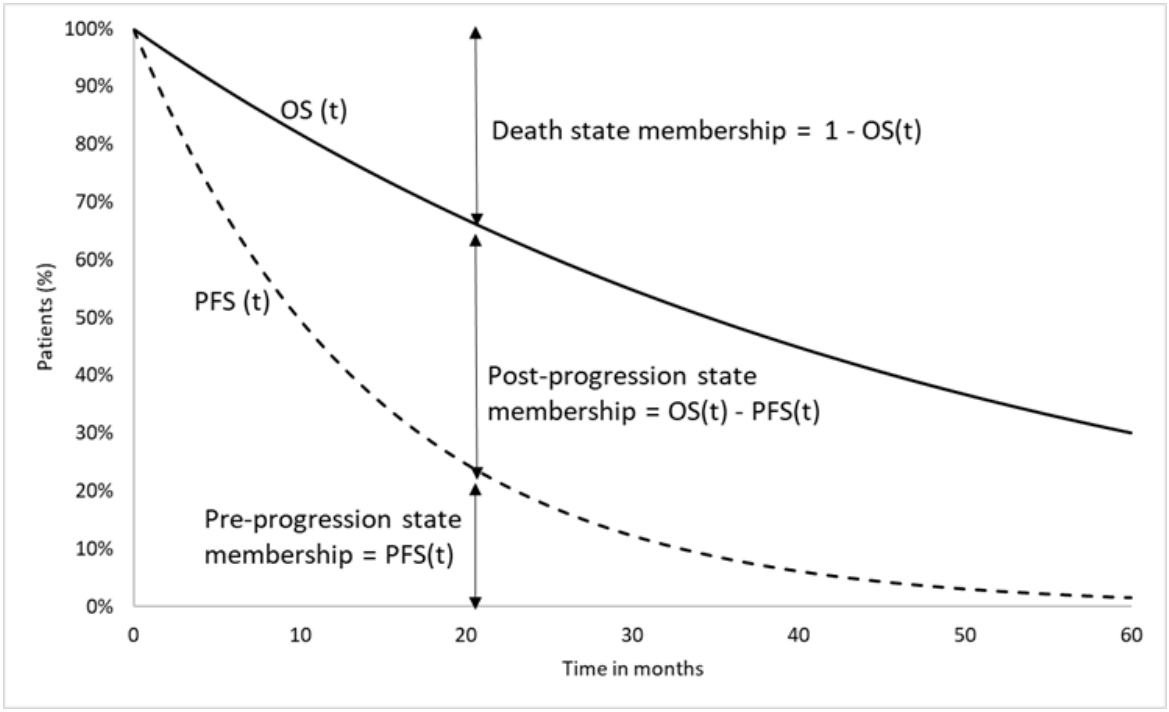


Figure 19: Schematic representation of partitioned survival approach



Key: PFS, progression-free survival; OS, overall survival.

The three-state partitioned survival model structure was selected based on the following considerations:

- PFS is the main endpoint used to assess efficacy outcomes within most oncology studies, and has been used as the primary endpoint in clinical studies in the gastric setting[23, 101-103]
- This includes the SPOTLIGHT and GLOW trials, with OS as a key secondary outcome
- The health states explored in the model allow the direct application of clinical trial data to the economic evaluation
- Given the aggressive nature of the disease and the poor survival of patients, data from the trials capture the majority of PFS and OS events and thus are amenable to a partitioned survival structure
- The partitioned survival modelling approach is a typical method to model therapies for advanced oncology indications

Patients enter the model in the pre-progression health state and are at risk of transitioning to the post-progression or death health states in any model cycle. Patients receive pre-progression treatments as directed by their respective dosing schedules. Patients may experience Grade 3+ AEs associated with pre-progression treatments. Once patients have progressed, they remain in the post-progression state until death, which is an absorbing health state. During the post-progression state, a proportion of patients may receive post-progression treatments. The survival benefit of post-progression treatments was not explicitly modelled and was assumed to be reflected in the long-term OS of pre-progression treatments.

Patients accrue costs, LYs and quality-adjusted life years (QALYs) over the modelled time horizon of 40 years, representing a lifetime horizon. The model includes costs associated with pre-progression treatment, post-progression treatment, AEs, pre-progression disease management (on and off treatment), post-progression disease management, testing, and terminal care. Pre-progression and post-progression health state utilities were adjusted for ageing to capture the HRQL of patients over their lifetime. Health state occupancy was evaluated using a 1-week cycle length to accommodate differences in treatment regimens, with outcomes discounted at 3.5% per annum, consistent with the NICE reference case.[94] The full features of the economic analysis are presented in Table 16.

Table 16: Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	TA191[104]	TA208[98]	TA857[29]	Chosen values	Justification
Patient population	Metastatic or locally advanced inoperable GC	HER2-positive advanced GC	Untreated locally advanced or metastatic gastric or GEJ or oesophageal adenocarcinoma	Adult patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic GC/GEJ adenocarcinoma who have not been previously treated for advanced/metastatic disease with chemotherapy	As per NICE scope
Time horizon	< 1 year	Lifetime (8 years)	Lifetime (up to 50 years)	Lifetime (up to 40 years)	Lifetime horizon for the defined population (NICE reference case) due to the aggressive nature of the indication. This ensures that all events have occurred, and all patients are accounted for
Model structure	Cost minimisation	Three-health-state transition model	Began as a four-health-state semi-Markov model but was later revised to a three-health-state transition model	Three-health-state transition model	Allows the direct application of clinical trial data to the economic evaluation; data from the trials capture the majority of PFS and OS events; enables indirect comparisons, as are required for this submission; typical method to model therapies for

Factor	Previous evaluations			Current evaluation	
	TA191[104]	TA208[98]	TA857[29]	Chosen values	Justification
					advanced oncology indications such as GC
Treatment waning effect	Not applicable	None described outside of preferred extrapolation methods	None – explored within scenario analyses	Included for comparisons against nivolumab after 5 years. Also explored in scenario analysis	Reflects 2-year treatment stopping rules for nivolumab (combined with limited trial follow-up). Zolbetuximab does not have a time-based stopping rule
Source of utilities	No quality-of-life data available	ToGA clinical trial pre-progression. TA179[105] post-progression	CheckMate 649[23] provided EQ-5D-3L data that were used to derive utility inputs for use in nivolumab and comparator arms	Pooled utility values collected from individual SPOTLIGHT and GLOW trials (ESMO data cut) using the EQ-5D-5L questionnaire, mapping to EQ-5D-3L using the 'EEPRU dataset' following the current NICE guideline[106-108]	SPOTLIGHT and GLOW utility data collected using EQ-5D-5L (mapped to EQ-5D-3L). In line with the NICE reference case, trial utilities collected as part of SPOTLIGHT and GLOW have been applied in the base case analysis
Source of costs	NHS reference costs, BNF[109] and published literature	NICE TA179[105], NHS reference costs, BNF[109], PSSRU, expert opinion and published literature	eMIT where possible. Otherwise, as per TA208[98] (either from the newer version of sources or inflated using PSSRU indices)	Intervention and comparator acquisition costs sourced, where possible, from eMIT (actual price paid by hospitals), otherwise BNF. Administration costs sourced from NHS reference costs. Monitoring/healthcare resource use costs sourced from PSSRU or NHS reference costs. One-off terminal care from TA208. Pre-progression (on and off	TA208 and TA857 are relevant given some population overlap; therefore, applying the same values/sources facilitates cross-comparison

Factor	Previous evaluations			Current evaluation	
	TA191[104]	TA208[98]	TA857[29]	Chosen values	Justification
				treatment) and post-progression treatment costs from TA857. AEs from NHS reference costs or published literature, and CLDN18.2 test cost based on an analogue test	

Key: AE, adverse event; BNF, British National Formulary; CLDN18.2, claudin 18.2; EEPRU, Policy Research Unit in Economic Methods of Evaluation of Health and Social Care Interventions; eMIT, drugs and pharmaceutical electronic market information tool; ESMO, European Society for Medical Oncology; GC, gastric cancer; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; MIMS, Monthly Index of Medical Specialties NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Resource Unit.

B.3.2.3. Intervention technology and comparators

The model compares zolbetuximab + fluoropyrimidine- and platinum-based combination chemotherapy ('chemotherapy' for short) with chemotherapy alone. Our base case assumes that all patients receive CAPOX as the chemotherapy backbone for zolbetuximab, and for the chemotherapy regimen as a comparator – given that (1) CAPOX is the less costly than FOLFOX, and (2) clinical feedback and the conclusion of TA857 indicate that most patients receive CAPOX. Scenario analyses explore the impact of some patients using FOLFOX as the chemotherapy backbone and chemotherapy comparator, as a small proportion of patients may use FOLFOX in clinical practice.

The detailed dosing schedules are outlined in Table 17. The dosing schedules for zolbetuximab-containing regimens and chemotherapy regimens were obtained from the clinical study reports (CSRs) for SPOTLIGHT[75] and GLOW.[75] Dosing schedules of nivolumab-containing regimens were obtained from the SmPC for nivolumab.[33]

Table 17: Dosing schedule of treatments

Regimen	Dosing schedule	Reference
Zolbetuximab + CAPOX	• Zolbetuximab: a loading dose of 800 mg/m^2 IV infusion on Day 1 of the first treatment cycle, followed by subsequent doses of 600 mg/m^2 every 3 weeks starting from Day 22 • Oxaliplatin: 130 mg/m^2 IV on Day 1 of each treatment cycle every 3 weeks (up to 24 weeks) • Capecitabine: 1,000 mg/m^2 orally twice daily on Days 1–14 of each treatment cycle every 3 weeks for up to eight treatments (21-day cycle). Capecitabine can be continued beyond eight treatments at clinician's discretion	GLOW CSR[75]
Zolbetuximab + FOLFOX	• Zolbetuximab: a loading dose of 800 mg/m^2 IV infusion on Day 1 of the first treatment cycle, followed by subsequent doses of 600 mg/m^2 every 3 weeks starting from Day 22. The use of zolbetuximab dosing every 2 weeks is explored as a scenario, given that it may be included as part of the final SmPC • Oxaliplatin: 85 mg/m^2 IV every 2 weeks for four cycles (3 treatments each cycle) for a maximum of 12 doses • Folinic acid: 400 mg/m^2 IV every 2 weeks for four cycles (three treatments each cycle). Folinic acid can be	SPOTLIGHT CSR[75]

Regimen	Dosing schedule	Reference
	continued beyond four cycles based on clinician decision • 5-FU bolus: 400 mg/m^2 IV bolus every 2 weeks • 5-FU infusion: 2,400 mg/m^2 IV infusion over 46–48 hours, every 2 weeks for four cycles (three treatments each cycle). 5-FU can be continued beyond 4 weeks based on clinician/investigator decision	
CAPOX	• Oxaliplatin: 130 mg/m^2 IV on Day 1 of each treatment cycle every 3 weeks (up to 24 weeks) • Capecitabine: 1,000 mg/m^2 orally twice daily on Days 1–14 of each treatment cycle every 3 weeks	GLOW CSR[75]
FOLFOX	• Oxaliplatin: 85 mg/m^2 IV on Day 1 of each treatment cycle every 2 weeks (up to 24 weeks) • Folinic acid: 400 mg/m^2 IV every 2 weeks • 5-FU bolus: 400 mg/m^2 IV bolus every 2 weeks • 5-FU infusion: 2,400 mg/m^2 IV infusion over 46–48 hours every 2 weeks	SPOTLIGHT CSR[75]
Nivolumab + CAPOX	• Nivolumab: 360 mg on Day 1 of each treatment cycle every 3 weeks (up to 2 years) • Oxaliplatin: 130 mg/m^2 IV on Day 1 of each treatment cycle every 3 weeks • Capecitabine: 1,000 mg/m^2 orally twice daily on Days 1 to 14 of each treatment cycle every 3 weeks	Opdivo SmPC[33]

Key: 5-FU, fluorouracil; CAPOX, capecitabine and oxaliplatin; CSR, clinical study report; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; IV, intravenous; SmPC, Summary of Product Characteristics.
Note: The above dosing schedules are applicable to blended treatment arms (zolbetuximab + CAPOX/FOLFOX and CAPOX/FOLFOX).

B.3.3. Clinical parameters and variables

B.3.3.1. Chemotherapy

B.3.3.1.1. Progression-free survival and Overall survival

For this appraisal, primary evidence on outcomes for patients receiving chemotherapy is available from three trials: SPOTLIGHT, GLOW and CheckMate 649. CheckMate 649 compares nivolumab + chemotherapy to chemotherapy (+ placebo), of which the PD-L1 CPS ≥ 5 subgroup is relevant here since nivolumab is licensed and recommended in these patients.

For the base case analysis, chemotherapy outcomes were obtained by pooling evidence from these three trials. This approach is consistent with both the cost-effectiveness principle of using all relevant evidence and the evidence used in the ITC of Section B.2.9. Particular advantages of this approach are that it increases the sample size (leading to more robust estimates of survival model parameters), and it allows for incorporation of trial evidence from CheckMate 649 that has longer follow-up than the zolbetuximab trials, resulting in more robust extrapolations. Maximum OS follow-up across SPOTLIGHT and GLOW is approximately 3 years, compared to 5 years for CheckMate 649. NICE TA857 (nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, GEJ or oesophageal adenocarcinoma) concluded that CheckMate 649 was generalisable to NHS clinical practice.

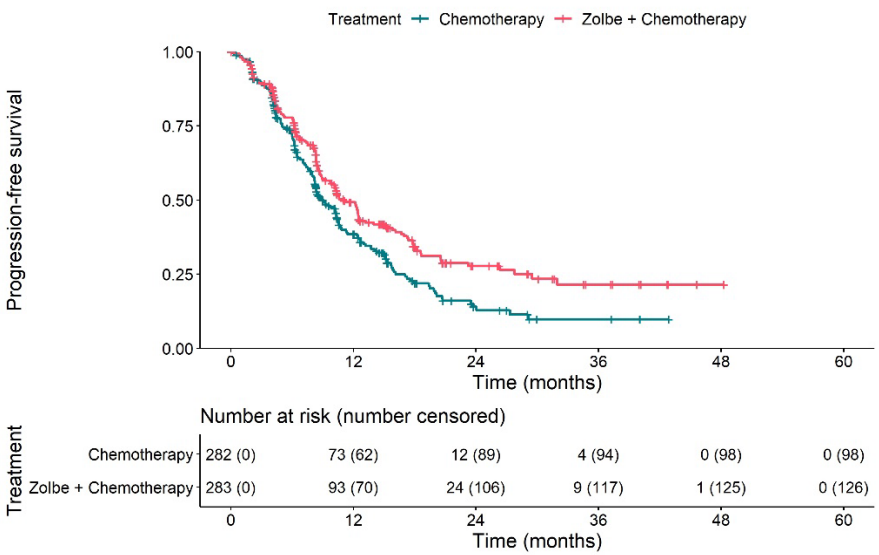
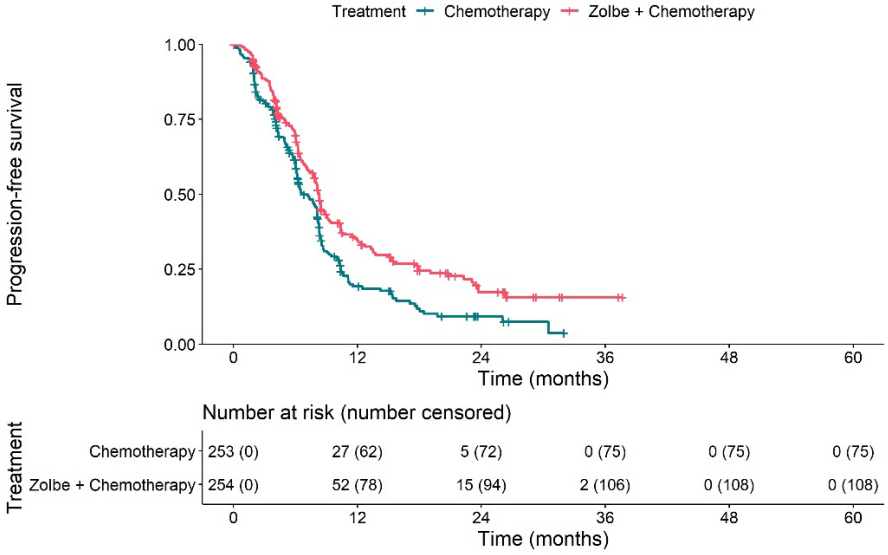
The survival extrapolation approach was informed by good practice guidance for selecting survival models to inform economic evaluations of cancer immunotherapies.[110]. Although specifically designed for cancer immunotherapies, the algorithm is generalisable to other cancer drugs, given that it provides a systematic evidence-based approach to select the survival methods to explore. As such, external data was reviewed to understand the likely shape of the survival curves (reported in Section B.3.3.1.1.1) The proportional hazards assumption was assessed (reported in the Appendix D.1.4.1.1) and the shape of the hazard function examined (reported in Appendix P). The expert beliefs referred to in NICE TA857 were also considered.

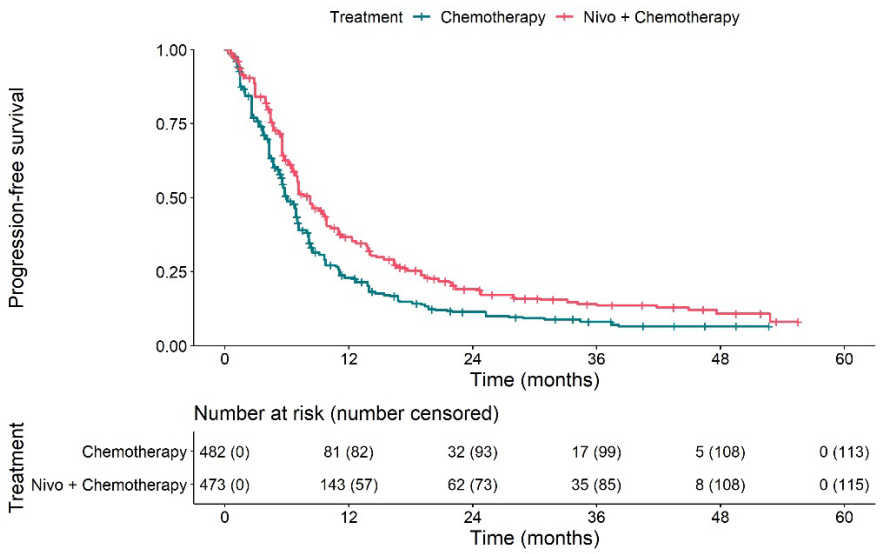
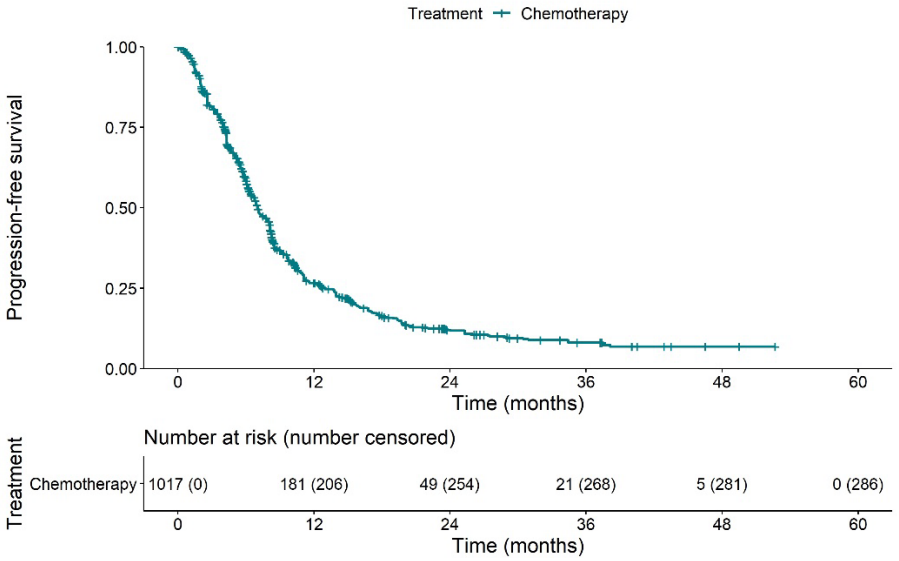
Basing the chemotherapy outcomes on the three trials (SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup) makes three assumptions, all supported by evidence. Firstly, it assumes that CAPOX and FOLFOX are broadly equivalent for PFS and OS outcomes. This assumption was made in NICE TA857 and reflects the trial design of CheckMate 649, which was investigator choice between CAPOX and FOLFOX. This assumption of similar outcomes was also checked with clinical experts, who agreed that CAPOX and FOLFOX are broadly equivalent, as well as being supported in a recent pembrolizumab appraisal [ID4030]. Secondly, CLDN18.2 is not an effect modifier of outcomes for chemotherapy or CPIs. As discussed in

B.1.3.1, four studies found similar survival outcomes irrespective of CLDN18.2 expression. [28, 39, 43, 44] Furthermore, the company is not aware of a biological mechanism by which high expression of CLDN18.2 would affect efficacy of chemotherapy or of CPIs. Thirdly, PD-L1 CPS is not an effect modifier of outcomes for chemotherapy or zolbetuximab, which is supported by the available evidence. [16, 74] Finally, it is noted that whilst the CheckMate 649 trial included patients with oesophageal cancer, their number is small at 12% (118/955) and real-world evidence suggests that their outcomes are similar to those for patients with G/GEJC (see Section B.3.3.1.1.1).

The Kaplan–Meier plots of the three trials included in the primary analyses for PFS and OS are presented in Table 18 and Table 19, respectively, along with the pooled chemotherapy outcomes. These visually demonstrate similarity of outcomes, further reinforcing the suitability of pooling all the relevant evidence.

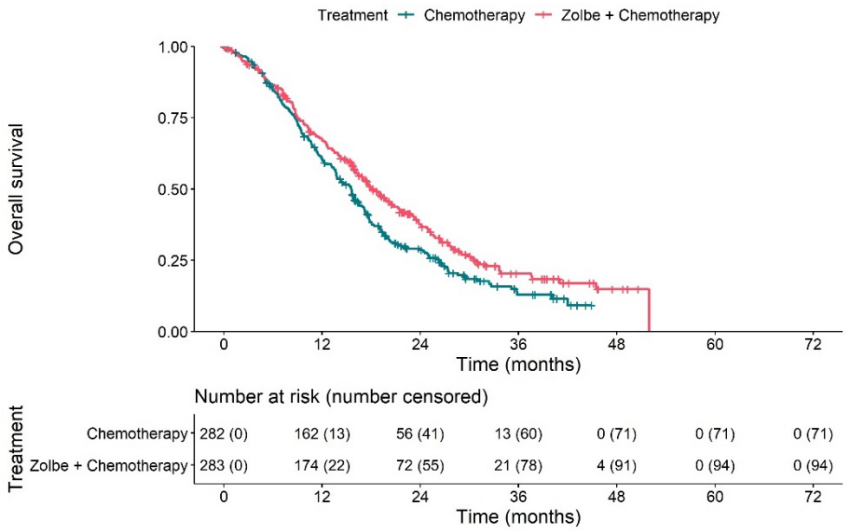
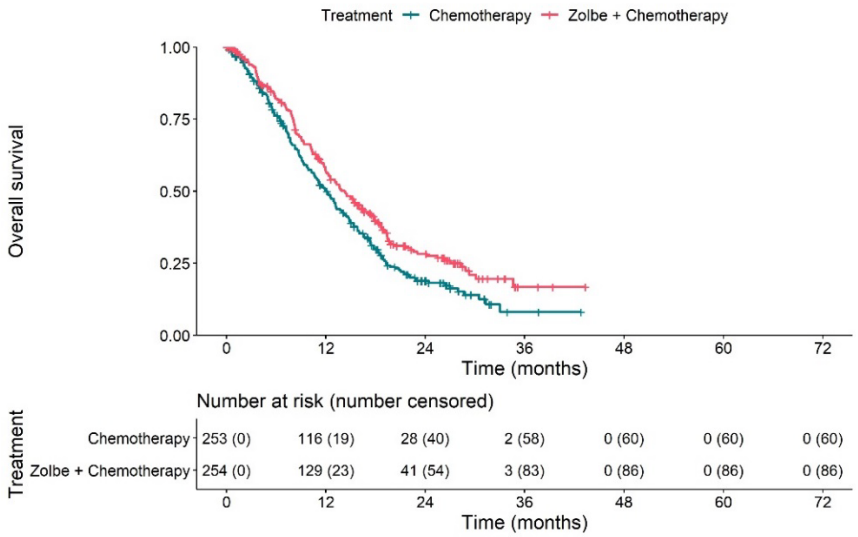
Table 18: Observed PFS for relevant trials included in primary NMAs

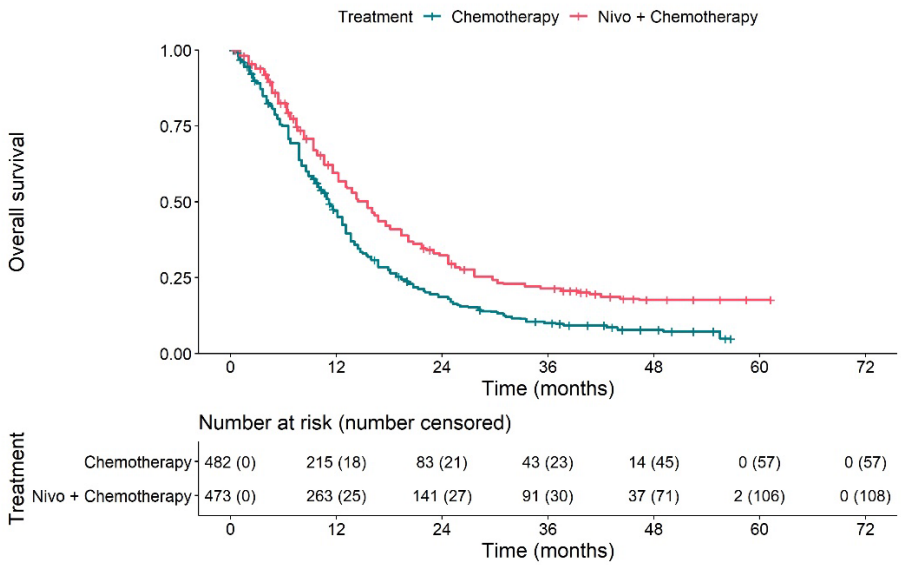
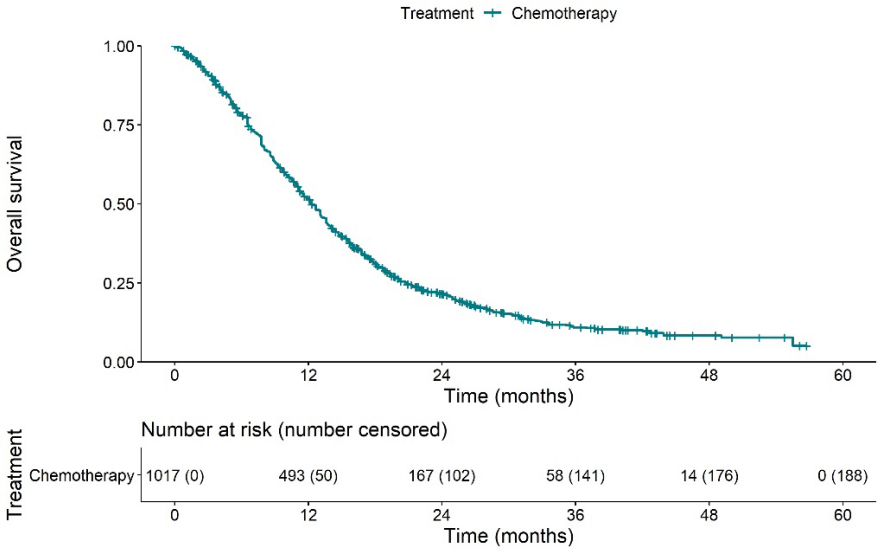
SPOTLIGHT	GLOW
	

CheckMate 649 (PD-L1 ≥ 5)	Pooled chemotherapy arms
	

Key: CPS, combined positive score; nivo, nivolumab; NMA, network meta-analysis; PD-L1, programmed death-ligand 1; PFS, progression-free survival; zolbe, zolbetuximab.

Table 19: Observed OS for relevant trials included in the primary NMA

SPOTLIGHT	GLOW
	

CheckMate 649 (PD-L1 CPS ≥ 5)	Pooled chemotherapy arms
	

Key: CPS, combined positive score; nivo, nivolumab; NMA, network meta-analysis; OS, overall survival; PD-L1, programmed death-ligand 1; zolbe, zolbetuximab.

B.3.3.1.1.1. Supportive evidence on survival outcomes of chemotherapy from real-world studies

For both PFS and OS outcomes, the pooled chemotherapy plots demonstrate evidence of a small proportion of patients remaining alive and progression free; this is particularly notable for the PFS outcomes. Additional real-world evidence on chemotherapy outcomes is available from a number of publications, including the Royal Marsden HER2-negative cohort in the UK[21], the BECOME study in France[111], the Flatiron cohort[15] in the US, the Cavanagh study in Scotland[112], and the Ontario Cancer Registry oesophageal cancer or GC cohort [113] in Canada. The Chau et al. meta-analysis study[114] presents pooled data from four RCTs in patients with locally advanced or metastatic cancer of the oesophagus, GEJ or gastric adenocarcinoma and provides additional evidence of survival.

Both the real-world evidence and the RCT evidence suggest that a small proportion of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma remain alive to and beyond 5 years. Specifically, 3% of patients of the Royal Marsden HER2-negative cohort are alive at 5 years, and 11% of patients in the French BECOME study are alive at 5 years. From visual inspection of the Kaplan–Meier curves, a small proportion of patients in both the Ontario Cancer Registry and the US Flatiron cohort were alive at 5 years; similarly, a small proportion were still alive in the Scottish Cavanagh cohort at 3 years. Furthermore, a small proportion of patients in the Chau meta-analysis are alive up to 9 years.

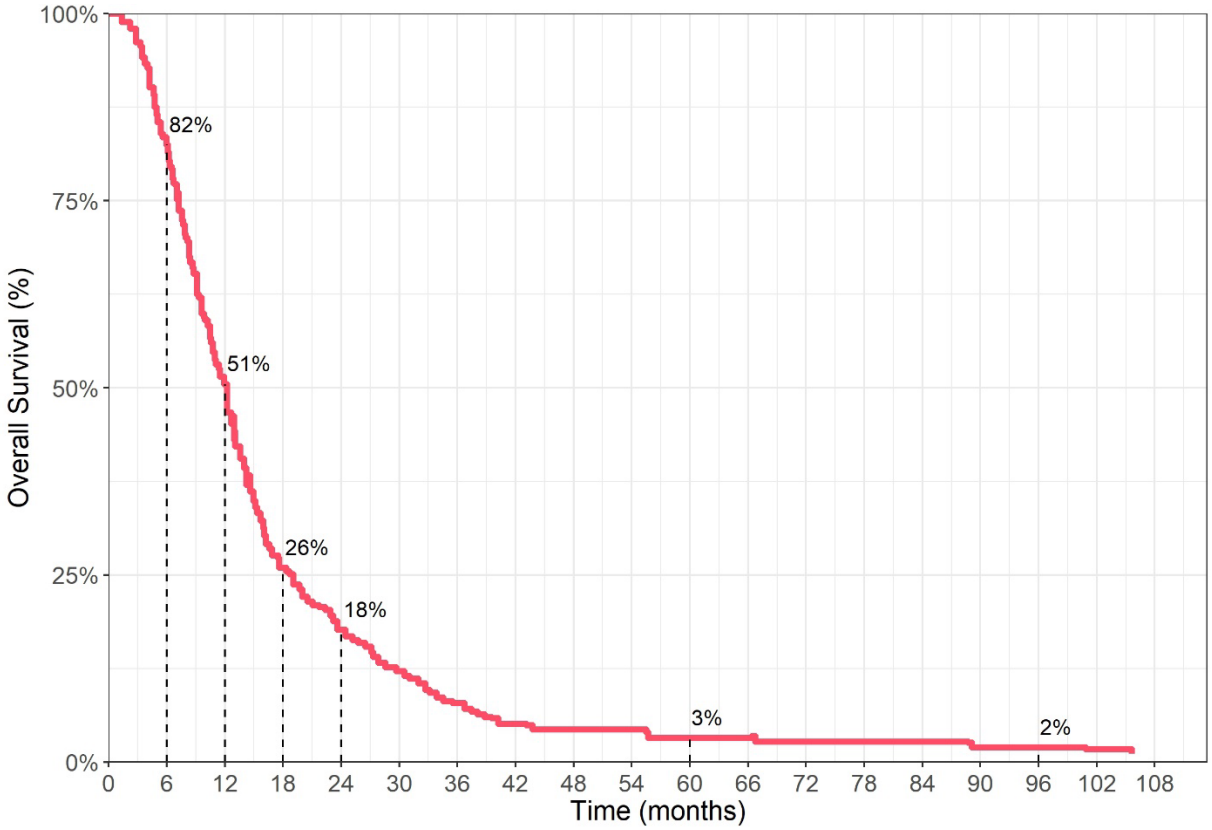
The expectation of a small survival plateau with chemotherapy is further supported by the discussion of clinical experts during the NICE appraisal of nivolumab (TA857)[69], which indicated that “about 4% of people could be expected to achieve long-term remission with chemotherapy”. Also, data from CheckMate 649 suggest that 5% of patients receiving chemotherapy alone are still alive at 5 years.[23] Collectively, the evidence suggests a complex survival curve, with a small proportion of long-term survivors.

The aforementioned studies are presented in more detail in the rest of this section.

B.3.3.1.1.1.1. Royal Marsden study

The Royal Marsden study[21] was used to inform the choice of extrapolation curves for chemotherapy in the nivolumab TA857 NICE appraisal. The Royal Marsden study included 511 patients with advanced oesophagogastric adenocarcinoma treated at the Royal Marsden between 2009 and 2015, of which 58% were HER2-negative (for 28% of patients HER2 status was not reported). Median age was 66 years (range 24-90), and 75% of patients were male. Median OS for the whole cohort was 11.5 months, with a range of treatments used in first-, second- and third-line settings. Figure 20 presents the survival of patients from the HER2-negative subset of the Royal Marsden cohort, with the corresponding Kaplan–Meier summary table presented in Table 20. OS was 51% and 18% at 1 and 2 years, with approximately 2% of patients still alive at 96 months (8 years).

Figure 20: Survival of patients with HER2-negative cancer (Royal Marsden cohort)[21]



Key: HER2, human epidermal growth factor receptor.
Notes: This figure is based on the digitisation of Figure 3A of the Davidson publication.[21]

Table 20: OS Kaplan–Meier summary for patients with HER2-negative cancer (Royal Marsden cohort)

		Davidson et al. (2018)[21]
Number at risk		511
Median survival (95% CI), months		11.48 (10.46, 12.47)
OS (%)	Month 6	82
	Month 12	51
	Month 18	26
	Month 24	18
	Month 60	3
	Month 96	2

Key: CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival
Notes: OS estimations are based on the digitisation of Figure 3A of the Davidson publication.

B.3.3.1.1.1.2. BECOME study

The BECOME study[111] was conducted to explore the disease burden, epidemiology, treatment patterns and healthcare resource utilisation in France for patients with locally advanced unresectable or metastatic G/GEJ, using a linked population of the FRench EsoGAstric Tumours (FREGAT) and SNDS (French National Healthcare Data System) databases between 01 January 2015 and 30 December 2019. Four study populations were identified among the FREGAT-SNDS linked G/GEJ adenocarcinoma population as part of the BECOME study, including 264 patients with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma who were not participating in clinical trials. Mean age was 63.7 years (median was 64.2; interquartile range: 55.9 to 72.5 years), and 77% of patients were male.

Of these patients, 128 were on first-line chemotherapy. The majority of patients (54.7%) received FOLFOX. Table 21 presents a summary of OS since treatment initiation for patients with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. Median OS since diagnosis for first-line patients with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma (n = 128) was 15 months, with 10% (95% CI: 5%, 17%) of patients

still alive at 60 months. Similarly, median OS since treatment initiation was 13 months, with 11% (95% CI: 5%, 18%) still alive at 60 months.

Table 21: OS Kaplan–Meier summary for patients with HER2-negative locally advanced unresectable or metastatic G/GEJ adenocarcinoma since initiation of treatment (BECOME study cohort)[111]

		BECOME study cohort[111] N = 128
Median survival since treatment initiation, months		13
OS (%) [95% CI]	Month 6	81 [73, 87]
	Month 12	55, [46, 63]
	Month 18	34 [26, 42]
	Month 24	23 [16, 31]
	Month 30	17 [11, 25]
	Month 36	14 [8, 21]
	Month 42	12 [7, 19]
	Month 48	11 [5, 18]
	Month 54	11 [5, 18]
	Month 60	11 [5, 18]
Key: CI, confidence interval; G/GEJ, gastric/gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; OS, overall survival.		

B.3.3.1.1.1.3. Ontario Cancer Registry (Merchant cohort)

The Ontario Cancer Registry identified 9,848 patients diagnosed with incurable oesophageal cancer or GC from 2007 to 2016, of which most patients had GC.[113] The cohort excluded patients who received curative-intent surgery or radiotherapy. Of these patients with GC, 27% received palliative chemotherapy. The most commonly received first-line treatment was fluoropyrimidine- and platinum-containing chemotherapy (70% patients), with the most frequent regimen being triplet epirubicin and cisplatin chemotherapy (in 64% of patients). The median OS of patients from initiation of first-line palliative chemotherapy was 9.5 months, with a non-negligible proportion of patients alive at 5 years.

B.3.3.1.1.1.4. Scotland's Cavanagh cohort

The Cavanagh cohort consisted of 127 patients from Scotland who were diagnosed with advanced gastroesophageal adenocarcinoma (including oesophageal, GEJ or gastric) during 2016–2017. [112] Median age was 68 (range: 36–95 years), and 73% of patients were male. Palliative chemotherapy was received by 52 patients (41%), with the most common regimens being EOX (54%) and CAPOX (27%). Forty-four (85%) patients had an ECOG score 0–1, six (12%) had an ECOG score 2–4, and two (4%) had unknown values. The median OS for first-line therapy was 8.9 months. The OS Kaplan–Meier curves are presented in the respective publication, with visual inspection suggesting a small survival plateau at 36 months.[112]

B.3.3.1.1.1.5. US Flatiron cohort

The Flatiron study[15] included 2,083 patients diagnosed with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma between 01 January 2011 and 30 November 2018, identified through the Flatiron health database in the US. Patients with confirmed HER2-positive tumours were excluded. Median age was 66 years (range: 25–85 years), and 67% of patients were male. Of these patients, 75.5% (n = 1,753) received first-line therapy, with a range of treatments used in the first-line setting. Median OS from the start of first-line treatment was 9.7 months (95% CI: 9%, 10.2%), with 15.5% of patients alive at 2 years (standard deviation 1.3), with a small subset remaining alive at 5 years as indicated by the visual inspection of the Kaplan-Meier presented in the publication. [15]

B.3.3.1.1.1.6. Chau cohort

Though not real-world evidence, another valuable source of evidence is the Chau cohort.[114] This cohort consisted of 2,110 patients from four RCTs in UK and Australia who were diagnosed with locally advanced or metastatic cancer of the oesophagus, GEJ or stomach between 1992 and 2005. Of these patients, 1,775 (84%) had adenocarcinoma with oesophageal (n = 485), OGJ (n = 457) or gastric (n = 833) origins. Median age was 63 years (range: 22–84 years), and 80% of patients were male. All patients had an ECOG performance status of between 0 and 2, with the majority having a performance status of between 0 and 1 (83%). Three of the four

trials included the epirubicin, cisplatin, and infused fluorouracil chemotherapy regimen, making it the most common across the study. The median OS for first-line therapy was 8.7 months in GC, with a small proportion of patients alive at 9 years.

The evidence from the real-world evidence presented above (Royal Marsden, BECOME, the Ontario Cancer Registry and the Flatiron cohort) along with the pooled long-term RCT evidence from the Chau cohort corroborate the suggestion of a small proportion of patients remaining alive for a long time, as observed for the pooled chemotherapy outcomes.

B.3.3.1.2. Survival modelling

Given the evidence presented in B.3.3.1.1.1 suggests a complex survival curve, with a small proportion of long-term survivors, standard parametric survival models may not be sufficiently flexible to adequately model the observed data and provide plausible extrapolations. As such, for the base case, more flexible-spline-based models were considered. This is in-line with the approach adopted in the recent Pembrolizumab appraisal (ID4030) of modelling OS and PFS with splines, an approach which was endorsed by the Evidence Assessment Group (EAG).[2] Use of standard parametric models was considered in scenario analyses. For these spline-based models, up to three internal knots were considered along with three different model specifications:

- '**Hazard'**, corresponding to an extension of the Weibull model
- '**Normal'**, corresponding to an extension of the lognormal model
- '**Odds'**, corresponding to an extension of the log-logistic model

Hence, a total of nine models were considered for each outcome (OS and PFS). All nine models are presented in Appendix P for both OS and PFS. The number of knots had a larger impact on survival estimates than the choice of scale, although visually models provided similar good fit to the observed data. Within-sample goodness of fit is provided in Table 22 and Table 24 for OS and PFS, respectively. However, it is noted that within-sample fit is of limited value in predicting the plausibility of long-term estimate.[110, 115] Landmark estimates from the nine models are displayed in

Table 23 and Table 25 for OS and PFS, respectively, and demonstrate that the different models resulted in some differences for long-term estimates.

The 3-knot models (5-year survival 5.5% for all three scales) had the best fit based on Akaike information criterion (AIC), with near-identical estimates and AIC values. The best-fitting model based on Bayesian information criterion (BIC) was the 1-knot odds model (5-year survival 4.3%); this is the fourth best-fitting based on AIC. In addition, 5-year estimates from all of the 1-knot and 2-knot models were all less than 5%, which is likely to be an under-estimate of true survival given the outcomes observed in CheckMate 649. As goodness of fit was similar for the three-knot models, whereby they all predicted the same 5-year survival (5.5%), the odds were chosen to represent the anticipated long-term survival in a small proportion of survivors. The 3-knot odds resulted in slightly higher long-term estimates (e.g. 10-year survival of 1.9%, compared to 1.4% and 1.5% for the hazard and normal models). The odds model is an extension of the log-logistic model, which can model ‘n-shaped’ hazards; this aligns with the empirical hazard plots provided in Appendix P, further supporting this choice of model. The observed and modelled OS for this chosen model are presented in Figure 21.

Figure 21: Observed and modelled overall survival for chosen spline model: pooled chemotherapy arms

Table 22: Goodness of fit, pooled chemotherapy overall survival

Model	AIC	BIC
1-knot hazard spline	8,758	8,772
1-knot odds spline	8,735	8,749
1-knot normal spline	8,747	8,761
2-knot hazard spline	8,735	8,755
2-knot odds spline	8,736	8,755
2-knot normal spline	8,740	8,760
3-knot hazard spline	8,733	8,758
3-knot odds spline	8,734	8,758
3-knot normal spline	8,734	8,759

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Notes: Chosen spline model for overall survival is highlighted in blue.

Table 23: Observed and landmark survival estimates, pooled chemotherapy overall survival

Time (Year)	0	1	2	3	4	5
Numbers at risk	1,017	493	167	58	14	-
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Chosen spline model for overall survival is highlighted in blue.

The choice of PFS model was based on the relationship between observed PFS and OS, as the real-world studies did not report PFS. The observed pooled chemotherapy data suggest that approximately 74% of patients who were alive at 3 years were also progression free; assuming this ratio holds at 5 years, this suggests that the 5-year PFS should be approximately 4%. Compared to this, estimates from the 3-knot spline models appear to be too large (4.9% for all three models), while those from 1-knot spline models appear to be too small (range: 1.4% to 2.6%). Hence, a 2-knot spline model was chosen, with the odds model used for consistency with the analysis of OS. The observed and modelled PFS for this chosen model is presented in Figure 22.

Figure 22: Observed and modelled progression-free survival for chosen spline model: pooled chemotherapy arms

Table 24: Goodness of fit, pooled chemotherapy progression-free survival

Model	AIC	BIC
1-knot hazard spline	7,026	7,040
1-knot odds spline	7,009	7,024
1-knot normal spline	7,032	7,047
2-knot hazard spline	7,001	7,021
2-knot odds spline	7,005	7,025
2-knot normal spline	7,007	7,026
3-knot hazard spline	6,994	7,019
3-knot odds spline	6,993	7,017
3-knot normal spline	6,995	7,019

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion
Notes: Chosen spline model for progression-free survival is highlighted in blue.

Table 25: Observed and landmark survival estimates, pooled chemotherapy progression-free survival

Time (Years)	0	1	2	3	4	5
Numbers at risk	1,017	181	49	21	5	-
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot – normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Chosen spline model for progression-free survival is highlighted in blue.

B.3.3.1.3. Duration of treatment

Evidence on duration of treatment (DoT) over time was available from both SPOTLIGHT and GLOW, but not from the CheckMate 649 PD-L1 CPS ≥ 5 subgroup. Hence, it was not possible to use pooled DoT from all three trials. Patients typically receive chemotherapy until they discontinue due to either toxicity or disease progression. As the rates of TEAEs leading to discontinuation were relatively low ([redacted]% and [redacted]% in SPOTLIGHT and GLOW, respectively), and both zolbetuximab + chemotherapy and chemotherapy do not have time-dependent stopping rules, there will be an association between DoT and PFS. Consideration of the PFS Kaplan–Meier curves for the chemotherapy arms of the three included trials shows close agreement between GLOW PFS and the pooled PFS for the start of follow-up, when the majority of patients are at risk (see Section B.3.3.1.1). Therefore, GLOW DoT was used to represent the pooled DoT. Modelled DoT was capped to ensure modelled PFS was not exceeded.

Standard parametric models were fit to the observed GLOW DoT. Visual fit is provided in Figure 23, and within-sample goodness of fit is shown in Table 26. The models provide similar estimates up to approximately 60 weeks, after which

estimates for the log-logistic and lognormal are higher than for the other models, providing poor fit. As the Weibull had the lowest AIC and BIC along with plausible extrapolations, this was used to model DoT for pooled chemotherapy.

Figure 23: Fit of parametric models to GLOW duration of treatment

Key: CI, confidence interval.

Table 26: Goodness of fit for parametric models fit to GLOW duration of treatment

Model	AIC	BIC
Exponential	2,086	2,090
Weibull	2,078	2,085
Log-Logistic	2,100	2,107
Lognormal	2,137	2,144
Gompertz	2,086	2,093
Gamma	2,078	2,086
Generalised gamma	2,080	2,091

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion
Notes: Chosen model for duration of treatment is highlighted in blue.

B.3.3.2. Zolbetuximab + chemotherapy

B.3.3.2.1. Overall survival and progression-free survival

The approach to modelling OS and PFS for zolbetuximab + chemotherapy was consistent with that for chemotherapy alone in that it made the best use of all the available evidence. For zolbetuximab, this meant using the outcomes from the ITC, which provided estimates of relative treatment effectiveness over time. Details of the methods and results of the ITC are provided in Section B.2.9. The resulting time-varying treatment effects for zolbetuximab were applied to the baseline chemotherapy outcomes (derived as described in Section B.3.3.1.1) to provide estimates of OS and PFS over time. The resulting estimates of OS and PFS for both zolbetuximab + chemotherapy and chemotherapy alone up to 10 years (520 weeks) are displayed in Figure 24 and Figure 25, respectively. A summary of landmarked OS estimates for zolbetuximab + chemotherapy versus chemotherapy is presented in Table 27.

Figure 24: Modelled overall survival for zolbetuximab and chemotherapy capped by general population mortality

Table 27: Landmark overall survival estimates for zolbetuximab and chemotherapy capped by general population mortality

Months		Zolbetuximab and chemotherapy	Chemotherapy
OS (%)	Month 6	83	78
	Month 12	59	51
	Month 18	41	31
	Month 24	30	21
	Month 36	19	12
	Month 60	11	6
Key: OS, overall survival			

Figure 25: Modelled progression-free survival for zolbetuximab and chemotherapy capped by overall survival

B.3.3.2.2. Duration of treatment

As noted in Section B.3.3.1, OS and PFS for chemotherapy were obtained by pooling evidence from the chemotherapy arm of three trials (SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup), with OS and PFS for zolbetuximab + chemotherapy obtained by applying time-varying relative treatment effects to the chemotherapy outcomes. Consistent with this approach, DoT for zolbetuximab +

chemotherapy was obtained by applying time-varying relative treatment effects to the chemotherapy DoT. As it was not possible to obtain relative treatment effects for DoT, relative treatment effects for PFS were instead used. This was motivated by the known association between PFS and DoT, as discussed in Section B.3.3.1.3.

B.3.3.3. Nivolumab + chemotherapy

B.3.3.3.1. Overall survival and progression-free survival

As there were no trials that directly compared nivolumab + chemotherapy (PD-L1 CPS ≥ 5) with zolbetuximab + chemotherapy, the relative effectiveness was estimated from the spline-based ITC, for which methods and results are described in Section B.2.9. This provided time-varying relative treatment effects for both OS and PFS. These demonstrate that the estimates of treatment effectiveness were very similar between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5, for both OS and PFS. This assumption of similar outcomes was supported by clinical advisors, while recent clinical guidelines have emphasised that both zolbetuximab + chemotherapy and checkpoint inhibitors should be considered in patients with PD-L1 CPS ≥ 5.[116] Because of this, a simplifying assumption was used whereby the OS and PFS for nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5were set equal to that for zolbetuximab + chemotherapy. This aligns with the NICE committee's preferred approach in the recent pembrolizumab appraisal (ID4030) whereby a cost-minimisation approach (comparing nivolumab + chemotherapy to pembrolizumab + chemotherapy) was adopted, with the evidence indicating no difference in efficacy. [2]

B.3.3.3.2. Duration of treatment

As with OS and PFS, it was assumed that DoT for nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 would be the same as for zolbetuximab + chemotherapy. Hence, the same approach was used to obtain DoT estimates over time as described in Section B.3.3.2.2. In addition, a 2-year stopping rule for nivolumab was implemented.

B.3.4. Measurement and valuation of health effects

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

SPOTLIGHT and GLOW included assessment of HRQL during the study, which can be used to derive utilities for modelling analysis. In both trials, assessments of EQ-5D status were carried out at screening, every 3 weeks, at study treatment discontinuation and at 30- and 90-day post-zolbetuximab and post-placebo treatment from all randomised subjects as one of the secondary endpoints. The schedule of EQ-5D-5L data collection was independent from the progression status; that is, regardless of whether patients experienced disease progression in the trial follow-up period, their EQ-5D-5L data collection followed the pre-specified schedule. The current analysis presented here used data from SPOTLIGHT and GLOW trial (data cut-off of 29 June 2023)[77, 79]. In the SPOTLIGHT trial, the numbers of patients who provided EQ-5D-5L data at pre-progression and post-progression status were 531 and 175, respectively; in the GLOW trial, the numbers of patients were 464 and 169, respectively. Pooling data from the two trials, the numbers of patients were 995 and 344, respectively. No imputation was performed for missing evaluations, and thus a patient who did not have an evaluation on a scheduled visit were excluded from the analysis for that visit.

B.3.4.1.1. Disutility related to ageing

Given the lifetime horizon, age- and gender-matched general population utility values were used to adjust health state utility values over time, using patient demographics from the SPOTLIGHT and GLOW trials. A multiplicative approach was taken to multiply the health state utility values by an adjustment index derived from a UK-specific population utility value set.[117]

B.3.4.2. Mapping

EQ-5D data were mapped from EQ-5D-5L to EQ-5D-3L as described in Section B.3.4.5.

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify utility data from the published literature associated with patients with G/GEJC. Appendix H describes the full details of the SLR process and methods used to identify and select the literature relevant to the technology being evaluated.

Of the 17 studies identified and extracted by the SLR, useful studies are those that reported EQ-5D utility data, either by progression status or time to death. While the majority of these studies used an EQ-5D instrument, it was either unclear whether the health states were valued using UK societal preferences or if the study was representative of the UK population. The SLR also identified five health technology assessment (HTA) submissions in patients with advanced G/GEJC, of which two represent SMC[96, 97] submissions for drugs appraised by NICE (with the NICE appraisal also included in the SLR). Given that greater detail is typically provided for NICE appraisals, the SMC submissions are not reported here, resulting in a total of three relevant UK studies.[29, 98, 104] These studies are reported in Table 28.

Table 28: Summary list of published health-related quality-of-life studies

NICE appraisal	Year	Patient population	Notes on utility data
TA191	2010	Metastatic or locally advanced inoperable GC	• As the base case was a cost-minimisation analysis, only a PFS utility value was considered as part of a QALY threshold analysis • The estimate was reported to have been derived from a BO18255 trial using the EQ-5D utility instrument, and assumes the value of 0.73
TA208	2010	HER2-positive advanced GC	• Utility value for the PFS health state was calculated using results from the EQ-5D data collected at baseline, and then every 3 weeks until progression in the ToGA trial • The manufacturer estimated a baseline utility value of 0.7292, which increased daily by 0.000142 during PFS • For the progressive disease health state, an estimate from the literature was used because EQ-5D data were not collected after disease progression in the ToGA trial. The utility value of 0.577 for progressive disease was taken from 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE TA179)
TA857	2022	Untreated locally advanced or metastatic gastric or GEJ or oesophageal adenocarcinoma	• The health utility of patients is dependent upon their disease state. Consequently, during each cycle, patients are assigned the health utility value equivalent to their current disease state based on the results from the CheckMate 649 trial • Actual values are confidential in the document
Key: GC, gastric cancer; GEJ, gastro-oesophageal junction; PFS, progression-free survival; QALY, quality-adjusted life year.			

B.3.4.4. Adverse reactions

Safety data from the GLOW[79], SPOTLIGHT[77] and CheckMate 649[23] trials were used within the economic model to explore the impact of AEs on patient utility. Treatment-related Grade 3+ AEs with an incidence of ≥ 5% in any arm of the GLOW, SPOTLIGHT and CheckMate-649 trials were included.

To incorporate the impact of AEs on patient utility, the proportion of patients who experienced a given AE was taken from the SPOTLIGHT, GLOW, and CheckMate 649 trials and an associated loss in utility ('utility decrement' or 'disutility') was sourced from published sources. Patients incurred a one-time QALY loss associated with AEs by taking the product of the disutility, the percent of trial participants that experienced each AE, and the AE duration. Disutility values for AEs were independent of treatment and applied to all treatment options. Disutility inputs were derived from two published NICE HTAs (TA857[29] and TA306[118]) and published literature.[119] Table 29 presents the disutility values and AE duration reported in the published literature and NICE HTAs used to estimate the QALY decrement due to each AE.

Table 29: Disutility values associated with AEs

Grade 3+ AEs	Utility impact	Source	Duration (weeks)	Source
Nausea	-0.103	NICE TA857[29]	1.00	Shah et al. (2022) [119]
Diarrhoea	-0.050	Shah et al. (2022) [119]	1.00	
Vomiting	-0.103	NICE TA857[29]	1.00	
Anaemia	-0.120	Shah et al. (2022)[119]	2.13	
Decreased appetite	0.000		0.00	
Platelet count decreased	-0.050		1.70	
Neutrophil count decreased	-0.050		2.41	
Neutropenia	-0.090		1.89	
Lipase increased	0.000		2.86	

Key: AE, adverse event.

Table 30 provides a summary of intervention-related Grade 3+ AE incidence rates used in the model, and the total QALY decrement for each treatment. The intervention-related Grade 3+ AE incidence rates for the individual SPOTLIGHT and GLOW trials are provided in Section B.2.10. The loss in utility due to AEs was accounted for within the economic model as a lump sum upon treatment initiation for each treatment arm.

Table 30: Intervention-related Grade 3+ AEs with incidence ≥ 5%

Adverse event	Used in model base case		
	Zolbetuximab + chemotherapy	**Chemotherapy**	**Nivolumab + chemotherapy**
Nausea	10.7%	2.3%	2.6%
Diarrhoea	2.8%	3.4%	4.5%
Vomiting	12.6%	2.4%	2.2%
Anaemia	7.1%	7.0%	6.0%
Decreased appetite	4.9%	2.0%	1.8%
Platelet count decreased	3.6%	3.8%	2.6%
Neutrophil count decreased	10.7%	11.6%	10.6%
Neutropenia	10.5%	7.2%	15.1%
Lipase increased	0.0%	0.0%	5.8%
Reference	SPOTLIGHT and GLOW	SPOTLIGHT and GLOW	Janjigian et al. (2021)
Total QALY decrement	-0.0015	-0.0010	-0.0012

Key: AE, adverse event; QALY, quality-adjusted life year.
Notes: The adverse event incidence for Zolbetuximab + chemotherapy is derived from the weighted average of the individual SPOTLIGHT and GLOW trials, based on the primary analysis data cut of 09 September 2022 for SPOTLIGHT and 7 October 2022 for GLOW.

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

EQ-5D-5L was used to measure patients' HRQL in the SPOTLIGHT and GLOW trials. EQ-5D values were estimated using the pooled data of SPOTLIGHT and GLOW for the health states considered in the model base case:

- EQ-5D measures for the pre-progression health state: any EQ-5D assessments corresponding to patients in the PFS state were used. This includes all data collected from randomisation date up to the earlier of the date of progressive disease, death, or being censored following the rule for analysis of PFS
- EQ-5D measures for the post-progression health state: any EQ-5D assessments corresponding to alive patients not in the pre-progression health state were included. For patients who were censored for PFS, EQ-5D assessments occurring after the censor date were excluded from the analysis

The analysis considered health state utilities to be independent of treatments, and data were therefore pooled among all treatment arms. The impact of treatment-related AEs on utilities was considered separately as discussed earlier.

All available EQ-5D-5L measures from the 29 June 2023 data cut of the SPOTLIGHT[77] and GLOW[79] trials were included in the utility analysis. A generalised estimating equation (GEE) model was developed to estimate utility scores with a robust variance estimator to account for correlation within patients' repeated assessments. For the GEE model, utilities from all included patients were used. The dependent variable was EQ-5D-5L utilities, and the independent variable was the health state (pre- versus post-progression), with pre-progression as the reference group. A robust variance estimator was used to account for correlation within patients' repeated assessments.

The EQ-5D-5L utility scores were mapped to EQ-5D-3L scores using the mapping function developed by the NICE Decision Support Unit, with the Policy Research Unit in Economic Evaluation of Health and Social Care Interventions (EEPRU) dataset.[107, 108]

A mixed-effects model was also developed, the use of which was explored as part of scenario analysis. For the mixed-effects model, utilities from all included patients were used. The dependent variable was EQ-5D-5L utility, and the independent variable was the health state (pre- versus post-progression), again with pre-progression as the reference group. Both random intercepts and slopes were considered in the analysis. The patient effects were included as random effects to

account for unobserved, patient-specific characteristics and multiple observations per patient. The population-averaged estimates are the average of individual patient results.

Both the GEE and mixed-effects model are appropriate for analysing HRQL data, and they provide similar results to each other, especially for the pre-progression utility value ([redacted] versus [redacted]). While results are slightly more different for the post-progression utility value ([redacted] versus [redacted]), this is based on fewer observations (1,149 versus 11,030 for pre-progression) and is therefore inherently more uncertain. As shown in Table 28, there are few studies reporting utilities of patients with advanced or metastatic G/GEJC. The utility data used in TA857 on nivolumab is redacted, whilst the data used in the ongoing appraisal of pembrolizumab[2] was redacted. Evidence from the literature suggests[redacted] utilities than those estimated from the SPOTLIGHT and GLOW trials; at 0.797 and 0.577 for pre- and post-progression, respectively.[120] Therefore, these are used in a scenario.

Evidence on the number of observations per trial and health state is provided in Table 31. As the GEE model estimates cohort-level (marginal) utility values directly, it was preferred over the mixed-effects model, for which cohort-level utility values are derived from patient-level estimates. The estimated pre- and post-progression health state utilities from GLOW, SPOTLIGHT, and the pooled analysis are presented in Table 32.

Table 31: Number of patients and observations with non-missing EQ-5D data

Data source	All subjects			
	Pre-progression		Post-progression	
	Number of patients	Number of observations	Number of patients	Number of observations
SPOTLIGHT	531	6,509	175	648
GLOW	464	4,521	169	501
Pooled	995	11,030	344	1149
Note: The analysis presented here uses the SPOTLIGHT and GLOW data cut off from 29 June 2023.				

Table 32: Utility inputs using GEE model[77, 79]

Health state	Mean	Standard error	Reference
Pre-progression	[redacted]	[redacted]	Pooled SPOTLIGHT and GLOW as used in the base case
Post-progression	[redacted]	[redacted]	
Pre-progression	[redacted]	[redacted]	GLOW
Post-progression	[redacted]	[redacted]	
Pre-progression	[redacted]	[redacted]	SPOTLIGHT
Post-progression	[redacted]	[redacted]	

Key: GEE, generalised estimating equation.
Note: The analysis presented here uses the SPOTLIGHT and GLOW data cut off from 29 June 2023.

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

In line with the 'NICE guidelines to the methods of technology appraisal 2013', studies[94] describing costs and healthcare resource use for patients with gastric/GEJ cancer were identified systematically. This search was undertaken as part of the SLR conducted for cost-effectiveness studies, described within Appendix I. Across the original SLR's August 2022 update, and October 2023 update, a total of 29 studies were considered for extraction. Of these, none were conducted in the UK and were therefore not considered of relevance to inform the model.

B.3.5.1. Intervention and comparators' costs and resource use

The drug acquisition cost per administration was calculated as a function of dosage, unit drug cost, relative dose intensity (RDI), and wastage, with dosing schedules and stopping rules presented in Section B.3.2.3. As per the trial design for GLOW (Section B.2.3.2), oxaliplatin was administered for up to a maximum of 24 weeks. Nivolumab was administered for a maximum of 24 months, as per the SmPC for nivolumab.[33] The unit cost for zolbetuximab was provided by Astellas, and the unit costs for other drugs were retrieved from the Monthly Index of Medical Specialties (MIMS), the British National Formulary (BNF) or the drugs and pharmaceutical electronic market information tool (eMIT).[121] The costs of the model interventions and comparators, including drug procurement and administration, are applied each

cycle based on acquisition costs detailed in Table 33. RDIs for pre-progression treatments were obtained from relevant clinical trials (Table 34) or assumed to be 100% where information was not available, in the case of nivolumab.

The base case assumes that all patients receive CAPOX as the chemotherapy comparator and backbone. This is because CAPOX has lower acquisition and administration costs, it is the regimen most used in the UK (accordingly it was used for NICE TA857 on nivolumab)[69], and CAPOX and FOLFOX are thought to be equivalent (as supported in recent pembrolizumab appraisal ID4030)[2]. A scenario is also presented where 80% of patients receive CAPOX and 20% of patients receive FOLFOX, based on clinical advice and the EAG report from the nivolumab appraisal (TA857).[29]

Table 33: Drug acquisition unit cost

Drug	mg per unit	Unit cost* (2023 GBP)	Discount	Reference	Use in model
Zolbetuximab	100	410	[redacted]	Astellas	Model base case: CAPOX is chemotherapy backbone for zolbetuximab arm and chemotherapy comparator
Capecitabine	150	0.11	N/A	eMIT (2023)[122]	
Oxaliplatin	100	24.44	N/A	eMIT (2023)[122]	
Nivolumab	240	2,633.00	N/A	BNF (2023)[109]	Comparator in model for those eligible for Nivolumab
Docetaxel	160	15.67	N/A	eMIT (2023)[122]	Used in model base case as post-progression treatments
Paclitaxel	100	8.49	N/A	eMIT (2023)[122]	
Fluorouracil (bolus)	500	6.08	N/A	BNF (2023)[109]	Used in scenario analyses
Fluorouracil (infuser)	1,000	3.93	N/A	eMIT (2023)[122]	

Key: BNF, British National Formulary; CAPOX, capecitabine and oxaliplatin; eMIT, electronic market information tool; N/A, not applicable.
Notes: * The lowest cost per mg unit was chosen if multiple strengths were available.

Table 34: Relative dose intensity

Treatment	Regimen	Drug	Relative dose intensity	Reference	Use in model
Zolbetuximab + chemotherapy	Zolbetuximab + chemotherapy	Zolbetuximab (loading)	[redacted]	SPOTLIGHT & GLOW	Model base case as a combined zolbetuximab + chemotherapy arm using the weighted average from SPOTLIGHT and GLOW for zolbetuximab. Chemotherapy components using the RDI from GLOW (CAPOX)
		Zolbetuximab (maintenance)	[redacted]		
		Oxaliplatin	[redacted]		
		Capecitabine	[redacted]		
Chemotherapy	CAPOX	Oxaliplatin	[redacted]	GLOW	Model base case as a combined chemotherapy arm using GLOW (CAPOX) RDI
		Capecitabine	[redacted]		
Nivolumab + chemotherapy	Nivolumab + CAPOX	Nivolumab	100%	RDI was unavailable so an RDI of 100% was assumed	Comparison made to nivolumab as part of secondary analyses for those eligible to Nivolumab
		Oxaliplatin	100%		
		Capecitabine	100%		
Zolbetuximab + FOLFOX	Zolbetuximab + FOLFOX	Zolbetuximab (loading)	[redacted]	SPOTLIGHT	Explored in scenario analysis as part of trial-specific costing
		Zolbetuximab (maintenance)	[redacted]		
		Oxaliplatin	[redacted]		
		Leucovorin	[redacted]		
		Fluorouracil (bolus)	[redacted]		
		Fluorouracil (infuser)	[redacted]		
FOLFOX	FOLFOX	Oxaliplatin	[redacted]	SPOTLIGHT	Explored in scenario analysis as part of trial-specific costing
		Leucovorin	[redacted]		
		Fluorouracil (bolus)	[redacted]		

Treatment	Regimen	Drug	Relative dose intensity	Reference	Use in model
		Fluorouracil (infuser)	[redacted]		
Key: CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; RDI, relative dose intensity. **Notes:** [1]RDI's presented here are from the interim data cut 1					

Unit administration costs were derived from the National Cost Collection based on the route of administration (Table 35), inflated to 2023 cost year.[123] First attendance administration costs were applied on the first treatment day of each cycle, and subsequent administration days in the same treatment cycle incurred the subsequent elements administration cost. In the base case, it was assumed that all intravenous (IV) administrations would occur in an outpatient setting and that dispensing of oral chemotherapy in combination with IV chemotherapy would not incur any costs.

Table 35: Drug administration unit cost

Route of administration	Service	Procedure code	Unit cost (2023 GBP)	Reference
Oral	N/A	N/A	0	Assumption
Complex chemotherapy (prolonged IV); first attendance	Outpatient	CHEM SB14Z	452.70	National Cost Collection 2021–2022, inflated to 2023
Chemotherapy (IV; per cycle); subsequent elements	Outpatient	CHEM SB15Z	335.34	
Key: IV, intravenous; N/A, not applicable.				

B.3.5.1.1. Patient access scheme

A patient access scheme (PAS) is applicable, comprising a discount of [redacted] from the zolbetuximab list price. Costs with and without the PAS are provided in Table 36. In order to best replicate the true economic impact of a positive recommendation for zolbetuximab as an add-on to chemotherapy, the economic evaluation presented in this submission applies the PAS in the base case analysis.

Table 36: Acquisition cost of zolbetuximab at list price and following application of PAS

	Zolbetuximab 100 mg vial
No PAS	£410
PAS	[redacted]
Key: PAS, patient access scheme.	

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. Pre-progression treatment costs

Pre-progression treatment costs were calculated based on the drug acquisition cost per administration, drug administration cost per administration, number of administrations per week, and proportion of patients remaining on treatment at each week according to DoT curves. A summary of the intervention and comparator dosing and acquisition costs (with PAS applied) is presented in Table 37.

Table 37: Intervention and comparator dosing and acquisition cost without discounting at list price and following application of PAS

Treatment	Treatment components	Treatment cycle	Acquisition cost per administration (with PAS discount)	Total pre-progression drug costs per arm (with PAS)	Use in model
Zolbetuximab + chemotherapy	Zolbetuximab loading	Q3W	[redacted]	[redacted]	Model base case as zolbetuximab + chemotherapy arm, with CAPOX costing applied
	Zolbetuximab maintenance	Q3W	[redacted]		
	Oxaliplatin (high dose)	Q3W	[redacted]		
	Capecitabine	BID Days 1–14 Q3W	[redacted]		
Chemotherapy	Oxaliplatin (high dose)	Q3W	[redacted]	[redacted]	Model base case as chemotherapy arm, with CAPOX costing applied
	Capecitabine	BID Days 1–14 Q3W	[redacted]		
Nivolumab + chemotherapy	Nivolumab	Q3W	£3,949.50	£51,597.29	Comparison made with nivolumab as part of secondary analyses for those eligible to Nivolumab
	Oxaliplatin (high dose)	Q3W	£54.08		
	Capecitabine	BID Days 1–14 Q3W	£33.88		

Key: BID, twice daily; CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; PAS, patient access scheme; Q3W, every 3 weeks. The total pre-progression drug costs per arm are discounted to present values.

In the base case, patients were assumed to remain on treatment until the earlier of discontinuation of treatment (estimated by DoT curves), progression or death (estimated by PFS curves), or maximum treatment duration as specified by the dosing schedule or product label (where applicable; see Table 17). In the scenarios where only SPOTLIGHT and GLOW are used to inform the survival outcomes, and given the assumption that the chemotherapy regimen used in clinical practice is mostly CAPOX, SPOTLIGHT's DoT is adjusted. The motivation for this is that if CAPOX had been used in SPOTLIGHT, the same effectiveness outcomes (OS, PFS) would have been observed, but DoT would be different, reflecting potential differences in adherence due to the different route and duration of administration. Therefore, to make this adjustment, it was assumed that there would be a relationship between DoT and PFS. This relationship was taken from GLOW, with separate relationships for the chemotherapy regimen depending on whether it was part of a combination with zolbetuximab. Evidence on PFS was taken from the log-logistic survival model, as the best-fitting model. This ratio was then applied to the modelled PFS of both FOLFOX and zolbetuximab + FOLFOX from the SPOTLIGHT trial to estimate the DoT had CAPOX been used. This relationship (between DoT and PFS) was based on the ratio of the two areas under the curve. Note that a different adjustment was made if using chemotherapy evidence from all of SPOTLIGHT, GLOW and CheckMate 649, as described in Section B.3.3.1.3.

For regimens including nivolumab, the treatment costs were estimated based on CAPOX, as this was cheaper than any of the other chemotherapy regimens included in the respective trials.

B.3.5.2.2. Post-progression treatment costs

A proportion of patients in the post-progression state were assumed to receive post-progression anti-cancer treatments and incur a lump sum post-progression treatment cost at the point of progression. Based on NICE TA857, it was assumed that post-progression therapy would consist of taxane monotherapy, equally split between docetaxel and paclitaxel irrespective of the first-line treatment.[69]

The total post-progression treatment cost per patient was calculated as the product of the proportion of progressed patients receiving post-progression treatments, distribution of post-progression treatments, weekly cost of each treatment, and mean duration of each treatment. The dosing schedule and cost of each post-progression treatment are presented in Table 38. The lump sum cost of post-progression treatment by pre-progression treatment is presented in Table 39.

Table 38: Dosing schedule and cost of each post-progression treatment

Post-progression treatment	Dosing schedule	Relative dose intensity	Drug acquisition and administration costs per week (2023 GBP)	Mean treatment duration (weeks)	Lump sum treatment cost (2023 GBP)	Reference for treatment duration
Docetaxel	75 mg/m^2 Q3W	100%	155.07	9.21	2,060.41	NICE TA378
Paclitaxel	80 mg/m^2	100%	289.52	24.68	10,308.45	NICE TA378

Key: eMIT, drugs and pharmaceutical electronic market information tool; NHS, National Health Service; Q3W, every 3 weeks.
Notes: Dosing regimen source: TA378[124], as used in NICE TA857 (assuming body surface area of 1.70 m^2); unit size and cost source: eMIT[122]; administration cost source: NHS reference costs[123] (intravenous infusion); within progressed disease, assumed an equal split between docetaxel and paclitaxel; the mean treatment duration was estimated based on the reported median duration of treatment.

Table 39: Post-progression treatment costs by pre-progression treatment

Pre-progression treatment	Percentage of patients receiving post-progression treatment	Lump sum cost (2023 GBP)	Reference for proportion of patients receiving post-progression treatment	Use in model
Zolbetuximab + chemotherapy	47%	2,913.71	Pooled SPOTLIGHT and GLOW	Model base case as a combined zolbetuximab arm and CAPOX as the chemotherapy backbone
Chemotherapy	54%	3,329.19	Pooled SPOTLIGHT and GLOW	
Nivolumab + chemotherapy	37%	2,301.18	Janjigian et al. 2021	

Key: CAPOX, capecitabine and oxaliplatin.

B.3.5.3. Adverse reaction unit costs and resource use

To assess the costs associated with AEs, the information was sourced from NHS reference costs 2021–2022 and inflated to 2023. As NHS Cost Inflation Indices are only available to 2022, it was assumed that the inflation between 2021 and 2022 also applied between 2022 and 2023 (Table 40).[123] The unit costs and disutilities associated with each of the individual AEs were assumed to be the same across the different treatment arms; therefore, the difference in costs and disutilities associated with AEs in the model is driven by the AE incidence rates (Section B.3.4.4). The lump sum cost due to AEs for each treatment arm is shown in Table 41.

Table 40: Adverse event unit cost

Adverse event	Unit cost (2023 GBP)	Reference
Nausea	£536	National Cost Collection 2021–2022 inflated to 2023
Diarrhoea	£551	
Vomiting	£551	
Anaemia	£3,150	
Decreased appetite	£608	
Platelet count decreased	£840	
Neutrophil count decreased	£469	
Neutropenia	£810	
Lipase increased	£3,622	

Table 41: Total AE cost for each treatment arm

Treatment arm	Total AE cost (2023 GBP)	Use in model
Zolbetuximab + chemotherapy	£560	Model base case as a combined zolbetuximab arm and CAPOX as the chemotherapy backbone
Chemotherapy	£421	
Nivolumab + chemotherapy	£652	
Key: AE, adverse event; CAPOX, capecitabine and oxaliplatin.		

B.3.5.4. Disease management cost

The disease management cost associated with each health state included costs of visits to healthcare professionals, medical procedures, and hospitalisations. Unit costs of resource use are summarised in Table 42. The frequencies of resource use

were obtained from the NICE TA857 submission, and are summarised for the pre-progression (on and off treatment) (Table 43 and Table 44) and post-progression (Table 45) separately. Costs were inflated to 2023 using the approach described previously.[69]

Table 42: Unit cost of resource use

Procedures and Monitoring Services	Unit cost (2023 GBP)	Reference
Oncologist consultation	£227	National Cost Collection 2021–2022
Nurse, home visit	£20	PSSRU (2021)
Clinical nurse specialist	£56	
General practitioner	£166	
Therapist	£56	
Cardiac monitoring	£347	National Cost Collection 2021–2022
Key: PSSRU, Personal Social Services Research Unit.		

Table 43: Pre-progression annual resource use (on treatment)

Procedures and Monitoring Services	Annual frequency	Reference
Oncologist consultation	17.38	NICE TA857 (original source TA208)

Table 44: Pre-progression annual resource use (off treatment)

Procedures and Monitoring Services	Annual frequency	Reference
Oncologist consultation	8.69	NICE TA857 (original source TA208)
Cardiac monitoring	4.00	

Table 45: Post-progression annual resource use

Procedures and Monitoring Services	Annual frequency	Reference
Nurse, home visit	52.14	NICE TA857 (original source NICE CG81)
Clinical nurse specialist	52.14	
General practitioner	26.07	
Therapist	26.07	

B.3.5.5. Testing costs

Patients receiving zolbetuximab-containing regimens were assumed to incur CLDN18.2 testing costs at model entry. HER2 and PD-L1 testing costs were not included as they were assumed to be standard of care for all patients. The proportion of screened patients with CLDN18.2-positive expression ≥ 75%, with moderate-to-strong staining, was 42.3% in both the SPOTLIGHT and GLOW trials; therefore, an average of 2.4 tests were required to identify one patient with CLDN18.2-positive expression.

The VENTANA CLDN18 (43-14A) RxDx Assay was used in SPOTLIGHT and GLOW. As the list price of this is not available, instead the cost of the Agilent PD-L1 IHC 22C3 pharmDx test was used as an analogue to estimate the cost to identify CLDN18.2-positive patients. The Agilent PD-L1 IHC 22C3 pharmDx test is an immunohistochemistry test similar to the Roche VENTANA CLDN18 (43-14A) RxDx Assay; both are used in GC and have similar testing components and methodology. The VENTANA CLDN18 (43-14A) Companion Diagnostic Assay is however expected to be easier to interpret than the Agilent PD-L1 IHC 22C3 pharmDx test. The Agilent PD-L1 IHC 22C3 pharmDx test costs £74.48 per test, based on a box of 60 tests at a list price of £4,469 (2023 costs).[125] Therefore, the estimated 2023 cost to detect one patient with CLDN18.2-positive expression was £176.08.

For the comparison with nivolumab, the exclusion of PD-L1 testing costs is a conservative assumption given that the introduction of zolbetuximab may lead to fewer patients being tested for PD-L1.

B.3.5.6. Terminal care costs

In the current model, all patients were assumed to incur one-time terminal care costs before death.[126] The terminal care cost per death was estimated as £5,131 based on the ramucirumab submission to NICE for the treatment of GC (TA378, as used in TA857). The cost was intended to reflect the intensive palliative and hospice-related care that is necessary at the end of life.

B.3.6. Severity

Patients with unresectable advanced G/GEJC experience both a worse HRQL and shorter life expectancy than the general population. As noted in Section B.1.3.2, the impact of G/GEJC on HRQL is typically worse than that of other cancers. The expected general population QALYs for the modelled population were calculated in the model using the Office for National Statistics (ONS) Life Tables[127] and McNamara et al. general population utilities.[117] Patient characteristics used in the analysis were consistent with those informing the base case economic analysis. The QALY shortfall calculator developed by Schneider et al. 2022 was used to validate absolute and proportional QALY shortfall estimates using HRQL norms from the NICE reference case.[128] Patient characteristics used in the analysis were consistent with those informing the base-case economic analysis.

A summary of the QALY shortfall analysis is presented in Table 46. A starting mean age of 58.5 years and a proportion of females at 38% were used, based on the pooled baseline characteristics of SPOTLIGHT and GLOW. General population patients have an expected 24.98 undiscounted LYs remaining, corresponding to 19.23 undiscounted QALYs, and 12.28 discounted QALYs. Patients with G/GEJC who are treated with chemotherapy accrue an average of [redacted] discounted QALYs, corresponding to an absolute shortfall of [redacted] QALYs and a proportionate shortfall of [redacted]%, as presented in Table 47. Hence, in line with the TSD23 guidance on severity shortfall calculations[129], the severity modifier of 1.2 is most appropriate. A summary of health state benefits and utility values for QALY shortfall analysis is provided in Table 48.

This severity modifier is inconsistent with that used for nivolumab in TA857, where the end-of-life modifier was applicable. In TA857, the end-of-life modifier was 1.7, resulting in an effective threshold of £50,000/QALY. Had this appraisal been conducted prior to the recent change in NICE methods, the comparison between zolbetuximab + chemotherapy and chemotherapy would have met these same criteria for the end-of-life modifier. Average undiscounted LYs for patients with G/GEJC who are treated with chemotherapy is estimated to be [redacted] years, below the previous criteria of 24 months. Similarly, the mean undiscounted extension to life

associated with zolbetuximab + chemotherapy is [redacted] months, above the previous criteria of three months. Therefore, use of a £36,000 threshold instead of a £50,000 threshold risks sub-optimal and potentially incorrect decision-making due to the inconsistency across appraisals.

Table 46: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion of females	38%	See Sections B.2.2 and B.3.2.1
Starting age (mean)	58.5	See Sections B.2.2 and B.3.2.1
Key: QALY, quality-adjusted life year.		

Table 47: Summary of QALY shortfall analysis (discounted values)

Treatment	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall (absolute / proportional)
Zolbetuximab + chemotherapy	12.28	N/A	N/A
Chemotherapy		[redacted]	[redacted]
Key: N/A, not applicable; QALY, quality-adjusted life year.			

Table 48: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Discounted life years
Progression-free (chemotherapy)	[redacted]	1.09
Post-progression (chemotherapy)	[redacted]	0.45
Progression-free (zolbetuximab + chemotherapy)	[redacted]	1.82
Post-progression (zolbetuximab + chemotherapy)	[redacted]	0.29

B.3.7. Uncertainty

Uncertainty in the available evidence base has been thoroughly explored where possible through evaluation of the associated parameter uncertainty and testing of the various structural assumptions made within the economic model. The key areas of uncertainty in the economic analysis are considered to be the following:

- Data on OS and PFS from SPOTLIGHT and GLOW are not complete, which leads to uncertainty in the true long-term outcomes for both chemotherapy and zolbetuximab + chemotherapy. For the chemotherapy arm, this is mitigated by the use of pooled data from all the relevant trials (SPOTLIGHT, GLOW and CheckMate 649) in the base case and by following the Palmer et al algorithm to select survival extrapolations to explore in a systematic and evidence-base manner. In particular, data from CheckMate-649 has follow-up for up to 60 months and demonstrates a subset of patients with long-term survival. This finding is corroborated by long-term survival outcomes from real-world studies which similarly demonstrate the existence of a small subset of patients with long-term survival (Section B.3.3.1.1.1). As such, the survival extrapolations used in the base-case capture the emergence of a small survival plateau with chemotherapy.
- Zolbetuximab's efficacy is modelled based on the relative efficacy estimated in the spline-based NMA, which retains randomisation of the SPOTLIGHT and GLOW trials, appropriately synthesises the two trials, and is consistent with the spline-based extrapolation used for chemotherapy outcomes. The relative efficacy of the NMA base-case analysis was used to inform the model, based on the SPOTLIGHT and GLOW trials, whilst the NMA scenario analysis including FAST providing additional supportive evidence of the efficacy of zolbetuximab + chemotherapy.
- Both zolbetuximab and nivolumab are biologics with potentially complex mechanisms of action. This is evidenced by the delayed separation of survival curves, followed by a potential long-term plateau. Flexible spline-based models have been used for both the baseline chemotherapy outcomes and the time-varying relative treatment effects. These are more suitable than standard

parametric models and proportional hazards models for capturing – and hence extrapolating – any complex hazard functions

- There is no direct evidence comparing zolbetuximab with nivolumab. The relative efficacy of these comparators was informed by an NMA (see Section B.2.9) that was conducted following best practice when only aggregate data are available for comparator trials. This approach is, however, inherently more uncertain than a direct comparison
- As no UK-specific clinical data were available for any of the comparators, all efficacy data in the model are taken from global trials. However, these trials are broadly aligned with UK practice. In TA857, the NICE Committee concluded that CheckMate 649 was generalisable to NHS clinical practice providing precedent for utilising this trial in our submission

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A table of variables and inputs used in the base-case analysis along with uncertainty and distributions is provided in Appendix O.

B.3.8.2. Assumptions

The key model assumptions for the base case analysis are presented in Table 49.

Table 49: Key model assumptions for the base case analysis

Parameter	Assumptions	Justification/reason
Perspective and discounting	NHS and PSS payer perspective with costs and QALYs discounted by 3.5% annually.	In line with the NICE reference case.
Utilities by health states	Utilities of health states were assumed to be dependent only on health states, age and gender, but independent of the specific treatments.	See Section B.3.4.
Patient demographics	Patient characteristics based on SPOTLIGHT and GLOW.	The patient demographics from the SPOTLIGHT and GLOW trials were assumed

Parameter	Assumptions	Justification/reason
		generalisable to the UK patient population.
Time horizon	40 years.	Lifetime, in line with the NICE reference case (See Section B.3.2).
Model structure	Three-state partitioned survival model.	Appropriate for an oncology model (See Section B.3.2).
Chemotherapy regimen	All patients assumed to receive CAPOX as chemotherapy backbone and comparator	CAPOX is the least costly regimen; most patients receive CAPOX in NHS clinical practice
Medical costs	Patients were assumed to incur different disease management cost in the pre-progression (on treatment), pre-progression (off treatment) and progressed health states independent of treatment, based on TA857 (which, in turn, based them on TA208). All patients treated with zolbetuximab-containing regimens were assumed to incur testing costs for CLDN18.2, with this cost representing the testing costs to identify one CLDN18.2-positive patient given the prevalence of CLDN18.2 positivity and the cost of testing one patient. All patients incurred a one-time terminal care cost before death.	In line with the NICE reference case and, where applicable the TA857 (See Section B.3.5).
Post-progression treatment costs	A lump sum cost based on taxane treatment, but representing a basket of post-progression treatments, was assumed to represent the costs of post-progression in clinical practice. Post-progression treatment outcomes were not explicitly modelled. It was assumed that the OS data reflected the survival benefit of subsequent therapies.	Consistent with the approach taken in TA857 as validated with clinicians.
AE costs	AE management costs and associated disutilities for Grade 3+ AEs were considered in the model as a one-time cost and one-time impact on QALYs.	Captures the most clinically relevant adverse events, while accounting for potential differences in trial duration (See Section B.3.5.3).
Chemotherapy effectiveness	The effectiveness of chemotherapy is similar irrespective of chemotherapy regimen.	Consistent with the assumption employed in TA857 (See Section B.3.3.1).

Parameter	Assumptions	Justification/reason
	The relative effectiveness of zolbetuximab and nivolumab is not affected by the chemotherapy regimen that they are used with or compared against.	
Use of SPOTLIGHT, GLOW and CheckMate 649 trials	The three trials have been used in the model for data on survival outcomes, QoL, treatment duration and adverse events, as far as evidence allows. The CheckMate-649 PD-L1 CPS ≥ 5 subgroup is used given that this is the subpopulation where nivolumab is recommended.	All three trials are generalisable to clinical practice; TA857 concluded that CheckMate 649 was generalisable to NHS clinical practice.
Suitability of evidence for indirect treatment comparisons	It is appropriate to form a network from GLOW, SPOTLIGHT and CheckMate 649 PD-L1 CPS ≥ 5 subgroup. Zolbetuximab effectiveness based on the ITC estimates.	Key assumption required for the ITC of Section B.2.9. Validated by clinical experts.
Treatment duration	Oxaliplatin is given for a maximum of 24 weeks, nivolumab is given for a maximum of two years. All treatments are capped at progression.	Reflective of trial design and clinical practice.
Treatment waning	There is treatment waning of OS and PFS for nivolumab but not for zolbetuximab.	As nivolumab has treatment stopping rules, patients receiving these are likely to experience treatment waning as per TA857. There is no such stopping rule for zolbetuximab.
Key: AE, adverse event; CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; ITC, indirect treatment comparison; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year.		

B.3.9. Base case results

B.3.9.1. Base case incremental cost-effectiveness analysis results of zolbetuximab + chemotherapy versus chemotherapy

The full incremental cost-effectiveness results when using list prices and with PAS applied for zolbetuximab are presented in Table 50. The full incremental cost-effectiveness results when applying the severity modifier discussed in Section B.3.6

(with both the list price and with application of PAS) are presented in Table 51. The disaggregated results for both analyses are presented in Appendix J.

In the base case analysis vs chemotherapy, patients treated with zolbetuximab + chemotherapy accrued [redacted] QALYs compared with [redacted] for those receiving chemotherapy alone. This represents an incremental life year gain of [redacted] years and an incremental QALY gain of 0.46 QALYs. When applying the severity modifier in the base case analysis vs chemotherapy, this represents an incremental QALY gain of 0.56. Astellas considers this to be a substantial and clinically meaningful improvement in both LYs gained and QALYs gained, considering the substantial unmet need within this population. The incremental cost-effectiveness ratio (ICER) comparing zolbetuximab + chemotherapy with chemotherapy at list price is [redacted] per QALY and [redacted] with PAS applied for zolbetuximab. The ICER when applying the severity modifier at list price is [redacted] per QALY and [redacted] per QALY with PAS applied for zolbetuximab. This demonstrates that zolbetuximab + chemotherapy is cost-effective compared with chemotherapy when considering the appropriate severity modifier and the £30,000 per QALY threshold (or equivalently, using a modified WTP threshold of £36,000 per QALY when the severity modifier is not applied to the incremental QALYs).

Table 50: Base case results (deterministic) of zolbetuximab + chemotherapy versus chemotherapy alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £36,000
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]	[redacted]
With PAS applied								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.								

Table 51: Base case results with the severity modifier applied (deterministic) of zolbetuximab + chemotherapy versus chemotherapy alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.56	[redacted]	[redacted]
With PAS applied								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.56	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.3.9.2. Base case results of the secondary analysis

As part of secondary analysis, the model also examines the cost-effectiveness of zolbetuximab + chemotherapy compared with nivolumab + chemotherapy in patients whose tumours express PD-L1 with a CPS of 5 or more.[29] As detailed in B.2.9.3, and validated by clinicians, nivolumab is considered broadly equivalent to zolbetuximab. As such, a comparison of costs is presented below in Table 52 zolbetuximab at list price and Table 53 incorporating PAS for zolbetuximab. For both analyses, use of zolbetuximab + chemotherapy leads to reduced overall costs to the NHS. This is primarily due to the lower pre-progression treatment costs.

Table 52: Base case results of list price zolbetuximab + chemotherapy versus list price of nivolumab + chemotherapy

Costs category, discounted (£)	Zolbetuximab + chemotherapy	Nivolumab + chemotherapy
Pre-progression treatment costs	[redacted]	£51,597
Post-progression treatment costs	£2,689	£2,124
Adverse event costs	£560	£652
Pre-progression disease management costs	£6,512	£6,512
Post-progression disease management costs	£2,832	£2,832
Testing costs	£176	£0
Terminal care costs	£4,684	£4,684
Total costs	[redacted]	**£68,401**

Table 53: Base case results of zolbetuximab + chemotherapy with PAS applied zolbetuximab + chemotherapy versus list price of nivolumab + chemotherapy

Costs category, discounted (£)	Zolbetuximab + chemotherapy	Nivolumab + chemotherapy
Pre-progression treatment costs	[redacted]	£51,597
Post-progression treatment costs	£2,689	£2,124
Adverse event costs	£560	£652
Pre-progression disease management costs	£6,512	£6,512
Post-progression disease management costs	£2,832	£2,832
Testing costs	£176	£0
Terminal care costs	£4,684	£4,684
Total costs	[redacted]	**£68,401**

B.3.10. Exploring uncertainty

To assess the impact of parameters on the model outcomes, deterministic sensitivity analyses were used to vary the data inputs by a set amount. Uncertainty around the input data was assessed using probabilistic analyses, while alternative assumptions were examined in scenario analyses.

B.3.10.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously by sampling their values from uncertainty distributions for 1,000 iterations. A total of 1,000 simulations of the model were required in order to enable the model results to converge to a sufficient degree of accuracy.

Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on parameter variability, a standard error of 10% of the mean was assumed.

The ICER scatterplots for the base case analysis at list price and with confidential discount, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 26 and Figure 27, respectively. The cost-effectiveness acceptability curve at list price and with confidential discount are presented in Figure 28 and Figure 29, respectively. These figures do not incorporate the severity modifier of 1.2. Instead a modified WTP threshold of £36,000 is used to reflect the severity modifier.

Figure 26: ICER scatterplot: zolbetuximab + chemotherapy versus chemotherapy at list price

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 27: ICER scatterplot: zolbetuximab + chemotherapy versus chemotherapy at PAS

Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 28: Cost-effectiveness acceptability curve: zolbetuximab + chemotherapy versus chemotherapy at list price

Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 29: Cost-effectiveness acceptability curve: zolbetuximab + chemotherapy versus chemotherapy at PAS

Key: PAS, patient access scheme; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Based on this analysis, the probability that zolbetuximab + chemotherapy is cost-effective versus chemotherapy (incorporating PAS discount) is estimated to be [redacted]% at a modified WTP threshold of £36,000 per QALY.

The probabilistic base case results at list price and with PAS applied for zolbetuximab are presented in Table 54, with results incorporating the severity modifier for zolbetuximab presented in Table 55.

Table 54: Probabilistic base case results of zolbetuximab + chemotherapy versus chemotherapy alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.49	[redacted]	[redacted]
With PAS applied								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.49	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 55: Probabilistic base case results of zolbetuximab + chemotherapy versus chemotherapy alone with the severity modifier applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]	[redacted]
With PAS applied								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.3.10.2. Deterministic sensitivity analysis

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

- Baseline characteristics (i.e. percent female, starting age)
- Proportion of patients receiving CAPOX for chemotherapy and zolbetuximab
- Health state utility: pre-progression and post-progression
- Discounting of costs and benefits
- Discounting: benefits
- Disease management costs
- Treatment costs: pre-progression and post-progression
- Administration costs
- AE costs and AE-related disutility
- Pre- and post-progression RDI

Results of the deterministic sensitivity analysis are presented in Figure 30 and Figure 31 for zolbetuximab + chemotherapy vs chemotherapy, at list price and PAS, respectively, representing the impact of specific parameters on ICER estimates. These figures do not incorporate the severity modifier of 1.2. Instead a modified WTP threshold of £36,000 is used to reflect the severity modifier. The tornado diagrams below show the parameters the ICER is most sensitive to; while there is movement in the ICER estimate, this is modest and relatively stable. The factors with the greatest impact on the ICER were post-progression disease management costs, and – to a smaller extent – pre-progression disease management costs and utility pre- and post-progression. The widest ICER range was in the analysis varying post-progression disease management costs with chemotherapy, at between [redacted] per QALY (at PAS prices). The ICER is also relatively stable when different pre- and post- utility sources are used, as evidenced by the scenario analyses presented in Section B.3.10.3.

Figure 30: Deterministic sensitivity analysis for zolbetuximab + chemotherapy versus chemotherapy – impact on ICER at list price

Key: AE, adverse event; CAPOX, capecitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALY, quality-adjusted life year; RDI, relative dose intensity.

Figure 31: Deterministic sensitivity analysis for zolbetuximab + chemotherapy versus chemotherapy – impact on ICER at PAS

Key: AE, adverse event; CAPOX, capecitabine and oxaliplatin; ICER, incremental cost-effectiveness ratio; IV, intravenous; PAS, patient access scheme; QALY, quality-adjusted life year; RDI, relative dose intensity.

B.3.10.3. Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. A summary of the scenarios explored with justification is presented in Table 56.

Table 56: A summary of scenarios explored as part of sensitivity analysis

#	Base case	Scenario	Justification
1.	Chemotherapy OS and PFS based on pooled chemotherapy arms of SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup trials, extrapolated with splines Zolbetuximab + chemotherapy OS and PFS based on relative efficacy estimates from spline-based NMA applied to chemotherapy reference	Chemotherapy OS & PFS based on the pooled chemotherapy arms of the SPOTLIGHT and GLOW trials; parametric function - Log-logistic (best fitting); zolbetuximab + chemotherapy outcomes based on spline NMA as per base-case	Assess the impact of using alternative extrapolating models and using only the zolbetuximab trials; log-logistic chosen as the best-fitting that also models a small subset of long-term survivors for OS and PFS
2.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy Pooled spline chemotherapy trials for estimation of OS and PFS for chemotherapy	Zolbetuximab + chemotherapy and chemotherapy OS & PFS based on the pooled SPOTLIGHT and GLOW trials; Best fitting survival curves for extrapolation for both arms.	This assumes that the two pooled trials represent the outcomes in clinical practice in their relative proportions, and the statistically best fitting survival curves represent the most appropriate extrapolations.
3.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy	Zolbetuximab + chemotherapy outcomes based on proportional hazards NMA	As time-varying hazard ratios were near-constant, use of a constant hazard ratio
4.	Chemotherapy OS and PFS based on pooled chemotherapy arms of SPOTLIGHT, GLOW and CheckMate 649 649 PD-L1 CPS ≥ 5 subgroup trials, extrapolated with splines	Chemotherapy OS and PFS based on the pooled chemotherapy trials; Best fitting survival curves for extrapolation	This assumes that the two pooled trials represent the outcomes with chemotherapy in clinical practice in their relative proportions, and the statistically best fitting survival curves represent the most appropriate extrapolations.
5.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy Pooled spline chemotherapy trials for estimation of OS and PFS for chemotherapy	Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted average of chemotherapy with 80% CAPOX, 20% FOLFOX	The outcomes are the weighted average of the individual trials at 80% GLOW and 20% SPOTLIGHT (representing the approach that 80% of patients have CAPOX as per GLOW and 20% have FOLFOX as per

#	Base case	Scenario	Justification
	CAPOX costing		SPOTLIGHT), with parametric extrapolation and trial specific costing
6.	Discounting of cost and health outcomes at 3.5%	No discounting	As per NICE methods guide
7.	Cost of managing treatment-related Grade 3+ AEs with an incidence of ≥ 5%	No AE cost	As per NICE methods guide
8.	Vial sharing: remaining amount in vials used for one patient are assumed to be used for another patient	Vials are not shared between patients	To explore potential efficiencies by sharing vials where possible
9.	100% of patients receive CAPOX	80% receive CAPOX and 20% receive FOLFOX	The ERG report for the nivolumab appraisal (TA857) stated that at least 80% of patients received CAPOX based on clinical opinion.
10.	100% of patients receive CAPOX	80% receive CAPOX and 20% receive FOLFOX with Q2W zolbetuximab dosing	The ERG report for the nivolumab appraisal (TA857) stated that at least 80% of patients received CAPOX based on clinical opinion. Q2W is used to reflect that when zolbetuximab is used with a FOLFOX backbone, Q2W dosing is used for zolbetuximab.
11.	GEE utility model (See Section B.3.4.5)	Mixed-effects utility model (See Section B.3.4.5) Pre-progression=[redacted] Post-progression=[redacted]	There is uncertainty over the best statistical model to apply to longitudinal utility data
12.	Age at treatment start – 58.5 years	64.15 years	This was explored in the TA857[69], due to concerns that the patients' age in the trial was younger than in NHS clinical practice

#	Base case	Scenario	Justification
13.	Including CLDN18.2 testing costs for zolbetuximab	Removing CLDN18.2 testing costs for zolbetuximab	As per NICE methods guide
14.	GEE utility model (See Section B.3.4.5)	Utility source – Literature (ToGa trial) Pre-progression = 0.797 Post-progression = 0.577	Alternative values for pre- and post-progression that have been used in existing analyses[120]
Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.			

The results of the scenario analyses are presented in Table 57, Table 58, Figure 32 and Figure 33. These results do not incorporate the severity modifier of 1.2. Instead a modified WTP threshold of £36,000 is used to reflect the severity modifier.

Table 57: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. base case
Base case	[redacted]	-
1. Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) – Log-logistic	[redacted]	9.8%
2. Zolbetuximab + Chemotherapy & Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) – Best fitting	[redacted]	3.2%
3. Zolbetuximab + Chemotherapy (Hazard ratio)	[redacted]	0.2%
4. Chemotherapy OS & PFS Parametric Function (Pooled chemotherapy trials) – Best fitting (Log-logistic)	[redacted]	2.4%
5. Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted average of chemotherapy with 80% CAPOX, 20% FOLFOX	[redacted]	-7.5%
6. No discounting	[redacted]	-16.3%
7. No AE cost	[redacted]	-0.3%
8. No vial sharing	[redacted]	3.9%
9. 80% receiving CAPOX; 20% FOLFOX	[redacted]	1.0%
10. 80% receiving CAPOX; 20% FOLFOX - Q2W Zolbetuximab dosing with FOLFOX	[redacted]	1.1%
11. Utility - Mixed effects model	[redacted]	2.1%
12. Age at treatment start (64.15 years)	[redacted]	-0.3%
13. No CLDN18.2 testing costs	[redacted]	-0.3%
14. Utility source – ToGA trial	[redacted]	-3.8%

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

Table 58: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy with PAS applied

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. base case
Base case	[redacted]	-
1. Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) - Log-logistic	[redacted]	11.1%
2. Zolbetuximab + Chemotherapy & Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) - Best fitting	[redacted]	13.3%
3. Zolbetuximab + Chemotherapy (Hazard ratio)	[redacted]	2.5%
4. Chemotherapy OS & PFS Parametric Function (Pooled chemotherapy trials) – Best fitting (Log-logistic)	[redacted]	2.8%
5. Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted average of chemotherapy with 80% CAPOX, 20% FOLFOX	[redacted]	1.3%
6. No discounting	[redacted]	-14.9%
7. No AE cost	[redacted]	-0.9%
8. No vial sharing	[redacted]	3.3%
9. 80% receiving CAPOX; 20% FOLFOX	[redacted]	0.4%
10. 80% receiving CAPOX; 20% FOLFOX - Q2W Zolbetuximab dosing with FOLFOX	[redacted]	0.2%
11. Utility – Mixed effects model	[redacted]	2.1%
12. Age at treatment start (64.15 years)	[redacted]	-0.3%
13. No CLDN18.2 testing costs	[redacted]	-1.1%
14. Utility source – ToGA trial	[redacted]	-3.8%

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

Figure 32: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

Figure 33: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy with PAS applied

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

The results were generally robust to the alternative scenarios. The most sensitive scenarios relate to the use of discounting and the chosen approach for the extrapolation of OS and PFS for both zolbetuximab + chemotherapy and chemotherapy alone. When extrapolating chemotherapy outcomes it is important that the chosen models are able to capture the anticipated long-term subset of survivors to provide plausible estimates. To retain randomisation of the SPOTLIGHT and GLOW trials and appropriately synthesise the efficacy evidence, it is also important to use relative treatment effects for zolbetuximab + chemotherapy. Multiple scenarios were tested with the results remaining under the modified £36,000 WTP threshold for most of the scenarios when the PAS discount for zolbetuximab was applied. This gives confidence that the results from the economic model are stable under reasonable assumptions.

B.3.11. Subgroup analysis

There are no relevant subgroups; hence, subgroup analyses were not performed.

B.3.12. Benefits not captured in the QALY calculation

The benefits of zolbetuximab + chemotherapy on improved OS and PFS have been captured in the QALY calculation.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

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

B.3.13.2. Validation of survival extrapolations for chemotherapy

In addition to the validation of extrapolation data against observed survival rates from SPOTLIGHT and GLOW (see Appendix N), validation was conducted against real-world evidence and one meta-analysis, which was previously discussed in Section B.3.3.1.1.

The focus of this comparison is on the OS rates at 5 years, given that this is a time point reported by most of the studies while being beyond the follow-up of period of the chemotherapy reference arm informing the model (Table 59). To summarise, the predicted OS rate at Year 5 for chemotherapy was similar to the reported OS rates from the real-world and historical evidence with sufficient follow-up. Specifically, the predicted OS rate is 6% at 5 years, while in the real-world and historical cohorts the predicted OS ranges from 4% to 11%. OS rates are higher in the more recent studies. One potential explanation might be that Marsden, Merchant and Chau cohorts are from an earlier time period, whereas the Flatiron and BECOME studies are more contemporary and may better represent current clinical practice. There are also differences in patient characteristics across these studies, particularly in terms of prognostic factors such as performance score, which may impact long-term survival. Overall, the predicted OS for the chemotherapy arms seem to validate well with real-world evidence.

Table 59: External validation of OS data from GLOW, SPOTLIGHT, Marsden Cohort, Flatiron, Merchant, Chau and Cavanagh cohort

Study		**Time (months)**		
		36	**48**	**60**
Pooled SPOTLIGHT[77] & GLOW[79] & CheckMate 649 PD-L1 CPS ≥ 5 subgroup chemotherapy	Observed OS (%)	11%	8%	NR
	Predicted OS (%)	12%	8%	6%
Marsden Cohort[21]	Observed OS (%)	9%	4%	2%
BECOME cohort	Observed OS (%)	14%	11%	11%
Flatiron cohort[15]	GC observed OS (%)	12%	8%	4%
	GEJC observed OS (%)	14%	10%	6%
Merchant cohort[113]	Observed OS (%)	7%	5%	5%

Study		Time (months)		
		36	48	60
Chau cohort[114]	Observed OS (%)	7%	5%	4%
Cavanagh cohort[112]	Observed OS (%)	7%	NR	NR
Key: GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; NR, not reported; OS, overall survival				

B.3.14. Interpretation and conclusions of economic evidence

This is the first economic evaluation focused on assessing the cost-effectiveness of zolbetuximab in combination with chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive in the UK. The economic evaluation reflects patients assessed in SPOTLIGHT and GLOW and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

The discounted incremental costs of zolbetuximab + chemotherapy were estimated to be [redacted] versus chemotherapy under base case assumptions (and incorporating the confidential discount for zolbetuximab), with a resulting ICER of [redacted] per QALY (using a QALY severity modifier of 1.2), which is considered to be cost-effective at the WTP threshold of £30,000 per QALY. In the deterministic and probabilistic sensitivity analyses, zolbetuximab + chemotherapy was cost-effective in most of the scenarios when using a severity modifier of 1.2. Extensive scenario analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis.

As part of secondary analysis, a cost comparison was made between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients whose tumours express PD-L1 with a CPS of 5 or more[29]. At both list and PAS price for zolbetuximab, zolbetuximab + chemotherapy resulted in reduced overall costs to the NHS.

Section B.1.3.4 highlighted the lack of effective first-line targeted treatment options for patients with HER2-negative locally advanced unresectable or metastatic G/GEJC, reflected by the poor survival rates. [34, 36] While it is recognised that nivolumab + chemotherapy has been recommended for use in patients with HER2-negative G/GEJC with CPS ≥ 5 disease, not all patients are eligible or will benefit from this, and effectiveness is highly dependent on CPS (see Section B.1.3.1).[29, 30] Additionally, clinicians have highlighted that patients with liver metastases or autoimmune conditions are ineligible for treatment with CPIs.[32, 33]. Validation meetings conducted with clinicians have further emphasised the importance of wider treatment choice for both clinicians and patients as well as the potential for zolbetuximab to make a significant impact on health-related benefits and address a current unmet need.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zolbetuximab with chemotherapy for untreated CLDN18.2-positive HER2-negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Summary of Information for Patients (SIP)

March 2024

File name	Version	Contains confidential information	Date
ID5123_Zolbetuximab_Summary of Information for Patients_ 18032024_ FINAL	1.0	No	18/03/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the HTAi PCIG. Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Zolbetuximab (suggested brand name: VYLOY™)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The main patient population is people with cancer originating in the stomach (also known as gastric cancer) or where the food pipe meets the stomach (gastroesophageal junction cancer; GEJC) that has grown into the tissues around the stomach, or nearby organs, and cannot be removed by surgery (locally advanced unresectable cancer) or has spread to other parts of the body (metastatic cancer). The patient's cancer also needs to be human epidermal growth factor receptor 2 (HER2)-negative and claudin 18.2 (CLDN18.2)-positive: • HER2 is a protein expressed on the surface of cells. To be HER2-negative means the cancer cells do not have abnormal (overexpressed) levels of the HER2 protein • CLDN18.2 is a protein expressed on the surface of gastric cancer cells. To be CLDN18.2-positive means it has been found to be overexpressed in the cancer cells

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The application for marketing authorisation with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) is currently ongoing. The current anticipated date of approval can be found in Table 2 of Document B.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Collaborations with patient groups in 2023 – Q1 2024:

- Less Survivable Cancers Taskforce – corporate sponsorship £20,000
- GUTS UK – £240 for a presentation to Astellas staff
- GUTS UK has helped to identify a surviving patient to help review Astellas patient-facing materials. No payment will be made to GUTS UK for this and reimbursement of time will be paid directly to the patient
- GUTS UK also helped to identify the above patient and a caregiver to work with Astellas on a series of patient and caregiver disease awareness videos. This will be taking place in March/April of 2024. Payment is due to be made to GUTS UK on the patient's and caregiver's behalf. This will be £75 per hour for circa 9 hours each (a total sum of circa £1,350.00)

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Gastric cancer occurs in the lining of the stomach, and GEJ cancer develops at the junction between your food pipe (oesophagus) and your stomach.[1, 2]

Gastric cancer is more common in men than women, with an average of 3,405 new cases diagnosed in men and 1,810 new cases in women each year in England between 2016 and 2018.[3] Around half of all new cases of gastric cancer are diagnosed in people aged 75 years and over.[4]

Survival is strongly linked to how advanced the disease is at diagnosis, which is scored based on tumour size and how far the cancer has spread.[5] For patients diagnosed with early-stage disease (Stage I), it is estimated that 88.5% of patients are alive after 1 year; this reduces to just 21.4% in patients diagnosed with advanced disease (Stage IV).[6]

Since most patients in the early stages (i.e. Stage I, II) of disease have no symptoms, most patients present in later stages (i.e. Stage III , IV), when they are experiencing more severe symptoms, such as abdominal pain, weight loss, anorexia, vomiting, gastric obstruction and bleeding.[7-9] Given the wide range of symptoms, each with their own burden, patients experience a substantially reduced quality of life that decreases further as the disease progresses.[10]

Gastric and GEJ cancer also has a negative impact on the quality of life of caregivers. Caregivers are more likely to be depressed and their mental wellbeing affected due to: worrying about the patient's death or deterioration; feelings of guilt and frustration about the adverse effects of treatment; and anxiety and difficulty in managing the patient's pain. Caregivers can also suffer financial difficulties due to time spent on illness-related activities and subsequent productivity loss (i.e. the time taken out of work resulting in a loss of income).[11]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients with suspected gastric and GEJ cancer undergo a variety of tests to first confirm the diagnosis and then find out the stage of cancer, including whether the cancer has spread.[12]

A GP or specialist will refer patients for an endoscopy where a small camera is fed down into the stomach. A small sample of cells (called a biopsy) may be collected during this procedure and sent to a laboratory to check for cancer.[12, 13] Patient biopsies undergo laboratory diagnostic tests to assess the stage of disease and expression levels of specific biomarkers (e.g. HER2, CLDN18.2), which helps inform treatment decisions.[1, 14] For example, zolbetuximab is being evaluated for patients with HER2-negative and CLDN18.2-positive disease (defined as ≥ 75% of tumour cells demonstrating moderate-to-strong membranous CLDN18 immunohistochemistry staining). For further details on diagnostic testing, please refer to Document B, Appendix M.1.1.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

NICE guidelines (NG83) recommend palliative combination chemotherapy as first-line treatment for patients who have an Eastern Cooperative Oncology Group performance (ECOG) status of 0 to 2 (i.e. patients who have no symptoms or who are symptomatic, capable of all self-care but unable to carry out any work activities) and no significant other health conditions.[15] Chemotherapy combinations include:

- Doublet chemotherapy: 5-fluorouracil (known as 5-FU) or capecitabine in combination with cisplatin or oxaliplatin
- Triplet chemotherapy: 5-FU or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin

Feedback from UK clinicians indicated that doublet treatment is preferred, with most patients receiving capecitabine and oxaliplatin (CAPOX; also known as XELOX).[16, 17]

More recently, treatments known as checkpoint inhibitors (pembrolizumab and nivolumab) were recommended by NICE for some patients with advanced and metastatic HER2-negative gastric and GEJ cancer. To be eligible for treatment with a checkpoint inhibitor, a patient's tumour needs to express the programmed death-ligand 1 (PD-L1) protein at a certain level. The level of PD-L1 expression is based on what is known as combined positive score (CPS), a scoring method to evaluate the number of PD-L1 cells compared with all tumour cells. The NICE recommendations for pembrolizumab and nivolumab are as follows:

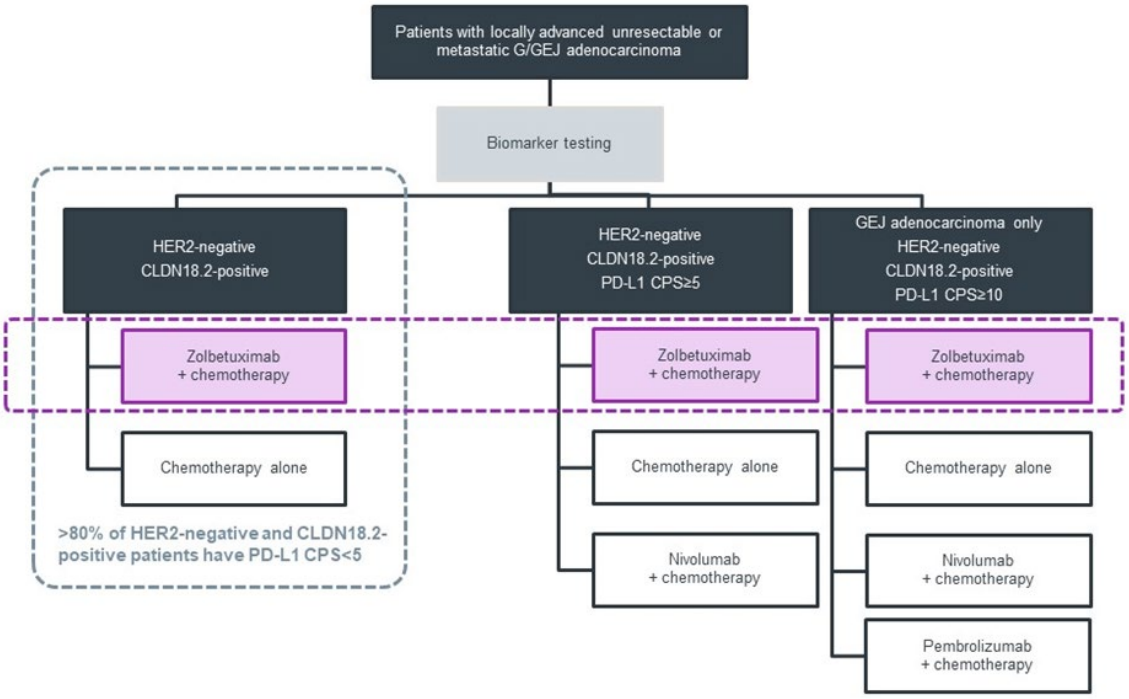
- *"Nivolumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated, HER2-negative, advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 5, if the company provides it according to the commercial arrangement"*[18]

- *"Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated, locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative GEJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10, if the company provides it according to the commercial arrangement"*[17]

If licenced, it is anticipated that zolbetuximab will offer a new targeted treatment option for adult patients with locally advanced unresectable or metastatic gastric or GEJ cancers who are HER2-negative and CLDN18.2-positive, irrespective of PD-L1 CPS.

Figure 1 shows the current clinical pathway of care for patients in England with locally advanced or metastatic HER2-negative gastric and GEJ cancer including the proposed positioning of zolbetuximab.

Figure 1: Treatment options for adult patients with locally advanced unresectable or metastatic HER2-negative gastric and GEJ cancer, including if zolbetuximab plus chemotherapy is available



Key: CLDN18.2, claudin 18.2; CPS, combined positive score; G/GEJ, gastric/gastro-oesophageal junction cancer; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1.
Notes: Pembrolizumab + chemotherapy currently being assessed for PD-L1 CPS≥1 but outcome not known at the time of this submission.
Source: NICE [NG83] 2018[15]; NICE [TA737] 2021[17]; NICE [TA857] 2023[18]; NICE [ID4030] 2023[19]; Shitara et al. 2023.[20]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or

experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with advanced gastric and GEJ cancer face many challenges, including severe symptoms that can substantially impact patient health-related quality of life, and the mental and emotional impacts associated with the diagnosis of a fatal illness.

Section 2a outlines the general symptoms of advanced cancers, which include abdominal pain, weight loss, anorexia, vomiting, gastric obstruction and bleeding.[7-9] Given the wide range of symptoms, each with their own burden, patients experience a substantially reduced quality of life including physical, emotional and social functioning, that decreases further as the disease progresses.[10]

Another burden faced by patients is the adverse effects of treatment. Patients differ in their susceptibility and tolerance of different treatment types and associated adverse events. Common side effects of chemotherapy include increased risk of infection, bruising and bleeding, anaemia, feeling sick, diarrhoea, hair loss and loss of appetite.[21-25]

As described in Section 2a, gastric and GEJ cancer also has a substantial impact on caregivers. Caregivers are more likely to be depressed and report negative impacts on their mental wellbeing due to experiencing feelings of worry, guilt, frustration and anxiety about various aspects of the patient's condition.[26] Furthermore, caregivers report financial difficulties due to being unable to work following increased caregiving responsibilities.[11]

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Zolbetuximab is a monoclonal antibody (mAb) – a targeted drug therapy that recognises and finds specific proteins on the surface of cancer cells – that targets the CLDN18.2 protein. It is estimated that 24.0–51.4% of patients with gastric and GEJ cancer express high levels of the CLDN18.2 protein in their cancer cells.[27-30]

How do monoclonal antibodies work?

Antibodies are found naturally in our blood and help us to fight infection. mAb therapies mimic natural antibodies but are made in a laboratory. Monoclonal means all one type. So each mAb therapy is a lot of copies of one type of antibody. Each mAb recognises one specific protein on the surface of a cancer cell and works by either killing the cancer cell, or by stopping the cancer from growing.

How does zolbetuximab work?

Zolbetuximab is a mAb that sticks to CLDN18.2 on the cancer cell surface of gastric and GEJ cancer cells.[31, 32] Pre-clinical studies (i.e. studies before human clinical trials) showed that binding to CLDN18.2 activates two distinct immune system pathways that work to kill the cancer cell – antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). If approved, zolbetuximab will be the first mAb that targets CLDN18.2.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Zolbetuximab should be administered in combination with chemotherapy.[31, 32] Section 3a describes zolbetuximab and Section 2c describes doublet chemotherapy.

Zolbetuximab in combination with chemotherapy has been shown to improve survival and duration of clinical benefit compared to chemotherapy alone.[31, 32]

Safety data from two Phase III trials (SPOTLIGHT[33] and GLOW[34]) and one Phase II trial (FAST[35]) have demonstrated a manageable safety profile for zolbetuximab plus chemotherapy. For further information on safety and side effects, see Section 3g.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Treatment with zolbetuximab should be started and supervised by a clinician experienced with administering anti-cancer therapies. Zolbetuximab is administered as an intravenous (IV) infusion over a minimum of 2 hours.[31, 32] An IV infusion is a way of delivering medicine directly into the bloodstream over a long period of time. The dose of zolbetuximab is calculated based on body surface area as follows:

- Single loading dose: 800 mg/m^2 IV on day 1 of treatment regime (first cycle of chemotherapy)
- Maintenance dose: 600 mg/m^2 IV every 3 weeks or 400 mg/m^2 IV every 2 weeks until disease progression or unacceptable toxicity

As described in Section 3a, zolbetuximab should be administered in combination with chemotherapy. Zolbetuximab will usually be administered on the same day as chemotherapy, to reduce the number of times the patient needs to visit the hospital, but must be administered before chemotherapy.

The doublet chemotherapy CAPOX (capecitabine plus oxaliplatin) is preferred by UK clinicians.[7, 69] Other doublet and triplet chemotherapies include combinations of 5-fluorouracil or capecitabine with cisplatin or oxaliplatin ± epirubicin.[15] Of these different chemotherapies, only capecitabine is given in a tablet.[23] Some chemotherapy drugs are given as IV infusion, namely cisplatin over 6-8 hours, oxaliplatin over 2-6 hours and epirubicin over 3-5 minutes.[22, 24, 25] 5-fluorouracil is usually given over 5 days as a continuous infusion through a small portable pump which can be taken home.[21]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Evidence for zolbetuximab comes from a clinical trial programme that includes over 1,000 patients from two key Phase III trials, named SPOTLIGHT and GLOW, which provide

head-to-head evidence versus chemotherapy.

SPOTLIGHT

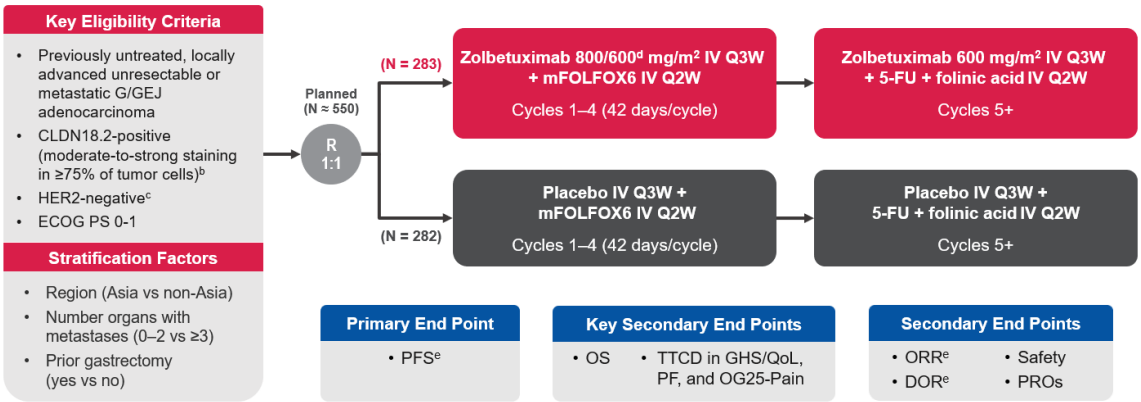
SPOTLIGHT was a Phase III trial designed to evaluate the efficacy and safety of zolbetuximab plus folinic acid in combination with fluorouracil and oxaliplatin (mFOLFOX6) versus placebo plus mFOLFOX6 as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ cancer.[29] This study was conducted at 232 sites in 20 countries, with 11 sites in the UK.[33] To be included in the trial, patients had to meet the following criteria:[29]

- ≥ 18 years of age
- CLDN18.2-positive (defined as ≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining, determined by central immunohistochemistry assay), HER2-negative, previously untreated, locally advanced unresectable or metastatic gastric or GEJ cancer
- Radiologically evaluable disease (measurable or non-measurable)
- Have an ECOG status score of 0 or 1 (i.e. patients who have no symptoms or are symptomatic but able to walk/not confined to bedrest)
- Adequate organ function

The SPOTLIGHT trial design is presented in Figure 2. A total of 565 patients were randomised in a 1:1 ratio to one of the following treatment arms:

- Zolbetuximab plus mFOLFOX6
- Placebo plus mFOLFOX6

Figure 2: SPOTLIGHT trial design



Key: 5-FU, fluorouracil; CLDN18.2, claudin 18.2; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G/GEJ, gastric/gastro-oesophageal junction; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRC, independent review committee; IV, intravenous; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; QoL, quality of life; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; TTCD, time to confirmed deterioration.
Source: Shitara et al. 2023.[31] Further details in Document B, Section B.2.3.1.1.

Further information/publications for SPOTLIGHT:
Clinicaltrials.gov (NCT03504397) – https://clinicaltrials.gov/study/NCT03504397
Publication (Shitara et al. 2023[29]) – https://pubmed.ncbi.nlm.nih.gov/37068504/

GLOW

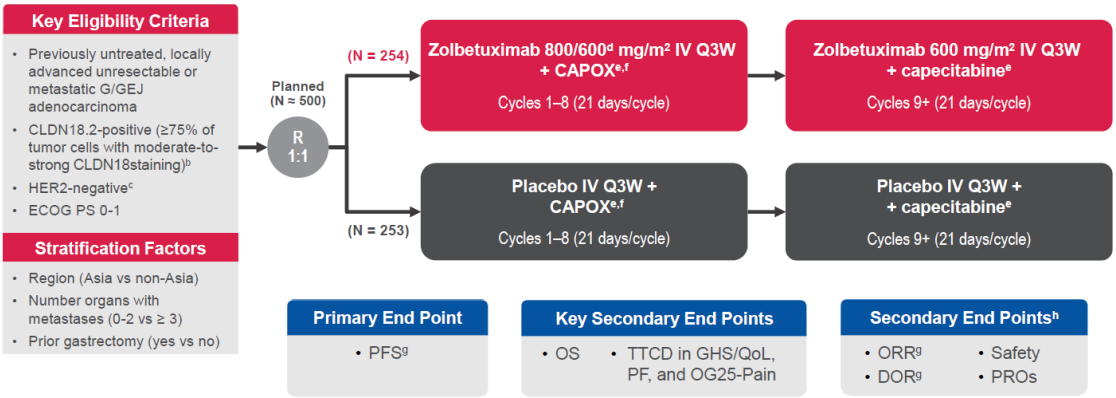
GLOW is a Phase III trial designed to evaluate the efficacy and safety of zolbetuximab plus CAPOX versus placebo plus CAPOX as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ cancer.[32] This study is ongoing and is being conducted at 176 sites in 18 countries, with four sites in the UK.[34]

To be included in the GLOW trial, patients had to meet the same criteria as described above for SPOTLIGHT.[32]

The GLOW trial design is presented in Figure 3. To determine the effects of zolbetuximab plus CAPOX compared with placebo plus CAPOX, 507 patients were randomised in a 1:1 ratio to two treatment arms[32]:

- Zolbetuximab plus CAPOX
- Placebo plus CAPOX

Figure 3: GLOW trial design



Key: BID, twice daily; CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18 isoform 2; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescent in situ hybridisation; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; LA, locally advanced; mG/GEJ, metastatic gastric/gastroesophageal junction; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; QoL, quality of life; R, randomised; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1; TTCD, time to confirmed deterioration.
Source: Shah et al. 2023.[32] Further details in Document B, Section B.2.3.2.1.

Further information/publications for GLOW:
Clinicaltrials.gov (NCT03653507) – https://clinicaltrials.gov/study/NCT03653507
Publication (Shah et al. 2023[32]) – https://www.nature.com/articles/s41591-023-02465-7

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

All data presented in this section for the SPOTLIGHT and GLOW trials are from the June 2023 data-cut (that is, collected up to June 2023). Efficacy outcomes for the SPOTLIGHT and GLOW trials were similar, demonstrating that the addition of zolbetuximab to chemotherapy provided a statistically significant survival benefit, with a 22.0–22.9% reduction in the risk of death and a 27.0–31.8% reduction in the risk of progression or death versus chemotherapy in patients with HER2-negative, CLDN18.2-positive, locally advanced unresectable or metastatic gastric or GEJ cancer.[33, 34] Statistical significant means that the results are unlikely to be due to chance. The results for each of the trials are provided below.

SPOTLIGHT

Primary endpoint: progression-free survival

The primary endpoint of the trial was progression-free survival, meaning the length of time between starting the treatment and the appearance of any signs that the cancer has started to grow again.[36]

Zolbetuximab plus mFOLFOX6 was associated with a statistically significant and clinically meaningful PFS benefit with a 27% reduction in the risk of disease progression or death compared with placebo plus mFOLFOX6.[33] Clinically meaningful means that the impact of zolbetuximab is large enough to be important to patients and health professionals.

By June 2023, median progression-free survival was 11.04 months in the zolbetuximab plus mFOLFOX6 arm compared with 8.94 months in the placebo plus mFOLFOX6 arm. The percentage of patients who had not progressed by 12 months was 49.3% with zolbetuximab plus mFOLFOX6, compared with 38.5% of patients receiving placebo plus mFOLFOX6.[33]

Secondary endpoint: overall survival

A secondary endpoint for SPOTLIGHT was overall survival, meaning how long the patients lived after starting treatment.[36]

Zolbetuximab plus mFOLFOX6 showed a statistically significant and clinically meaningful overall survival benefit with a reduction of 22% in the risk of death compared with placebo plus mFOLFOX6.[33]

By June 2023, 189 (66.8%) patients in the zolbetuximab plus mFOLFOX6 arm and 211 (74.8%) patients in the placebo plus mFOLFOX6 arm had died.[33] Median overall survival was 18.2 months in the zolbetuximab plus mFOLFOX6 arm compared with 15.6 months in the placebo plus mFOLFOX6 arm.

For further details on other trial endpoints assessed in the SPOTLIGHT trial, please see Document B Section B.2.6.1.

GLOW

Primary endpoint: progression-free survival

Zolbetuximab plus CAPOX demonstrated a statistically significant benefit as first-line treatment in CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ cancer, with a 31.8% reduction in risk of progression or death versus placebo plus CAPOX.[34]

By June 2023, median progression-free survival was 8.28 months (95% CI: 7.46, 9.00) in the zolbetuximab plus CAPOX arm versus 6.80 months (95% CI: 6.14, 8.11) in the placebo plus CAPOX arm. [34] The percentage of patients who had not progressed by 12 months was 34.6% with zolbetuximab plus CAPOX, compared with 19.3% of patients receiving placebo plus CAPOX.

Secondary endpoint: overall survival

Zolbetuximab plus CAPOX demonstrated a statistically significant benefit, with a 22.9% reduction in the risk of death compared with placebo plus CAPOX.[34]

By June 2023, 168 (66.1%) patients in the zolbetuximab plus CAPOX arm and 193 (76.3%) patients in the placebo plus CAPOX arm had died.[34] Median overall survival was 14.3 months in the zolbetuximab plus CAPOX arm and 12.2 months in the placebo plus CAPOX arm.

For further details on other trial endpoints assessed in the GLOW trial, please see Document B Section B.2.6.2.

Indirect treatment comparison

A minority of patients who could be treated with zolbetuximab (if it is recommended) can also have checkpoint inhibitors (nivolumab and pembrolizumab). There are no randomised controlled trials comparing zolbetuximab to these treatments. An indirect comparison is a method to compare the efficacy of treatments that were not tested against each other in randomised controlled trial. We conducted an indirect comparison comparing zolbetuximab to nivolumab in patients who can have both treatments. We found that zolbetuximab had similar outcomes to nivolumab.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Given the range of symptoms, each with their associated burden, gastric or GEJ cancer can substantially impact patient quality of life, which worsens as the disease progresses.[10, 37, 38]

Changes in quality of life were measured in the SPOTLIGHT and GLOW trials by validated routinely used questionnaires including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), the Quality of Life Oesophago-Gastric (QLQ-OG25), and the EQ-5D-5L questionnaire.

Results from the SPOTLIGHT and GLOW trials demonstrated that patients maintained their quality of life during treatment with zolbetuximab plus chemotherapy, demonstrating that treatment with zolbetuximab has no negative impact on patients' quality of life compared with chemotherapy. Patients are therefore able to benefit from the improved responses and chances of survival without compromising their quality of life.[39] See Document B, Sections B.2.6.1.3 and B.2.6.2.3 for more details.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

As of June 2023, safety data from SPOTLIGHT and GLOW demonstrated that zolbetuximab in combination with chemotherapy offers a manageable and predictable

adverse event profile. Safety results of the SPOTLIGHT and GLOW trials were largely similar.

SPOTLIGHT

Nearly all patients (99.6%) experienced at least one adverse event following treatment. In the zolbetuximab plus mFOLFOX6 arm, the most frequently reported adverse events were feeling sick (nausea) (82.4%), vomiting (67.4%), decreased appetite (48.7%) and diarrhoea (40.9%).[33] In the placebo plus mFOLFOX6 arm, the most frequent adverse events were nausea (61.5%), diarrhoea (45.0%), peripheral sensory neuropathy (42.8%) and constipation (40.6%).[33]

Adverse events that were considered to be related to treatment were more frequently reported in the zolbetuximab plus mFOLFOX6 arm compared with the placebo plus mFOLFOX6 arm. The number and proportion of patients experiencing a serious adverse event was similar for patients in the zolbetuximab plus mFOLFOX6 arm and the placebo plus mFOLFOX6 arm (47.0% vs 46.6%, respectively).[33] Please refer to Document B, Section B.2.10.1, for further details.

GLOW

Nearly all patients (> 98%) experienced at least one adverse event following treatment. In the zolbetuximab plus CAPOX arm, the most frequent adverse events were feeling sick (nausea) (68.9%), vomiting (66.1%) and a decreased appetite (41.3%).[34] In the placebo plus CAPOX arm, the most frequent adverse events were nausea (50.2%), anaemia (36.9%), diarrhoea (34.9%) and a decreased appetite (34.5%).[34]

Adverse events that were considered to be related to treatment were more frequently reported in the zolbetuximab plus CAPOX arm compared with the placebo plus CAPOX arm. The number and proportion of patients experiencing a serious adverse event was comparable between the zolbetuximab plus CAPOX arm and the placebo plus CAPOX arm (48.0% vs 50.6%, respectively).[34] Please refer to Document B, Section B.2.10.2, for further details.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

Zolbetuximab is being assessed as a treatment option for patients with untreated gastric and GEJ cancer whose tumours are HER2-negative and CLDN18.2-positive.

Zolbetuximab is a first in kind targeted mAb that works by binding to CLDN18.2, a protein known to be highly expressed in patients with gastric and GEJ cancer.

Zolbetuximab extends life expectancy by 22.0–22.9% and time to disease progression by 27.0–31.8% versus chemotherapy alone. This was shown in two Phase III trials, SPOTLIGHT and GLOW, which included over 1,000 patients.[33, 34] These trials also showed that zolbetuximab in combination with chemotherapy has manageable side effects. Patients in these trials reported similar quality of life irrespective of whether they had received zolbetuximab.[33, 34]

Prior to zolbetuximab, patients whose tumours are HER2-negative and CLDN18.2-positive could be treated with chemotherapy alone or, for the minority of patients whose tumours also express the PD-L1 biomarker, a checkpoint inhibitor (nivolumab or pembrolizumab) in combination with chemotherapy.

With chemotherapy alone, patients have high rates of disease progression and poor life expectancy (median life expectancy: 9.2–12.0 months).[40-42]

Patients may have a checkpoint inhibitor depending on the how much their tumours express the PD-L1 biomarker, as patients with lower levels are likely to benefit less (See Document B Section B.1.3.1).[43, 44]

Additionally, some patients may not be able to receive a checkpoint inhibitor because of their other health conditions. For example, patients with liver metastases or certain autoimmune conditions should not have a checkpoint inhibitor. In an indirect comparison, zolbetuximab was found to have similar outcomes to the checkpoint inhibitor nivolumab.

In summary, patients with advanced or metastatic gastric and GEJ cancer have few treatment options, are at high risk of progression and generally have poor life expectancy. If recommended, zolbetuximab offers an innovative, effective, and safe treatment option for patients whose tumours are HER2-negative and CLDN-positive.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The key disadvantages to patients and their caregivers may include:

- Patients treated with zolbetuximab plus chemotherapy are at increased risk of nausea and vomiting.[33, 34] However, the use of anti-sickness medication, slowing the rate of

zolbetuximab infusion and dose interruption may help to reduce the risk of nausea and vomiting[45] Nausea and vomiting are expected to be managed well as clinicians get more experience with zolbetuximab.

- Patients treated with zolbetuximab require a longer infusion time compared to patients receiving chemotherapy alone, because zolbetuximab takes a minimum of 2 hours, in addition to the time of chemotherapy[31, 32]
- Patients treated with zolbetuximab have a longer time on treatment compared to chemotherapy alone, because zolbetuximab is given until disease progression and time to progression is longer[31, 32]
- Zolbetuximab has no clinically meaningful impact on patient quality of life[39]

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model approach

To assess the value for money of zolbetuximab, a cost-effectiveness model was developed. The model compares using zolbetuximab plus chemotherapy versus chemotherapy alone, and versus nivolumab plus chemotherapy in patients for whom nivolumab is a therapeutical option. This model uses a simplified representation of gastric or GEJ cancer; it models a patient's progression through a set of distinct health states, which have a certain amount of costs and quality of life.

The following health states were used in this cost-effectiveness model:

- Progression-free: a patient's disease is stable or responding to treatment and not actively progressing. Costs in this health state are because of the treatment received, its administration, management of disease and adverse events. Quality of life is higher compared with patients with progressed disease and is also affected by adverse events
- Progressed disease: a patient's disease is assumed to have progressed. Costs in this health state are because of the treatment received, its administration and management of disease. Quality of life is lower compared with patients with progression-free disease
- Death: This state includes one-off end-of-life costs

The model uses data from clinical trials on life expectancy before progression (i.e., 'progression-free survival') to estimate how long patients spend in the progression-free state, and on their life expectancy (i.e., 'overall survival') to estimate how fast patients progress to death.

The time spent in each health state is then adjusted for the quality of life of a patient in that health state, to calculate the total number of quality-adjusted life years (QALYs) gained by a patient as a result of the treatment received. QALYs combine life expectancy by the quality of life that is lived in; 1 QALY represents 1 year of life lived in full health.

This is then compared with the total costs associated with that treatment. This allows for an assessment of whether the costs due to using zolbetuximab plus chemotherapy are justifiable given the gains in life expectancy and quality of life.

Clinical benefits included in the model:

The model predicted that treatment with zolbetuximab plus chemotherapy would lead to greater benefit (i.e. more QALYs) gained than treatment with chemotherapy alone (please note that the exact results are confidential). This benefit was driven by improvements in both progression-free survival and overall survival for zolbetuximab plus chemotherapy over chemotherapy alone.

As described earlier (see 3e) Efficacy), the indirect treatment comparison found that zolbetuximab plus chemotherapy is likely to have equal efficacy to nivolumab plus chemotherapy in patients for whom nivolumab is an option. Therefore, the model assumes that nivolumab plus chemotherapy leads to the same benefits as zolbetuximab plus chemotherapy.

Costs included in the model:

Zolbetuximab is subject to a confidential price agreement with the NHS, so full cost information cannot be presented. However, treatment with zolbetuximab plus chemotherapy had with higher costs than treatment with chemotherapy alone. This was mostly driven by higher treatment costs of zolbetuximab, and as patients live for longer, more disease management costs are accrued. Zolbetuximab plus chemotherapy had lower costs than nivolumab plus chemotherapy when using nivolumab's publicly available list price. As nivolumab is subject to a confidential price agreement with the NHS, the

costs of nivolumab and zolbetuximab, including their confidential discounts, are not known at this stage.

Model results:

Overall, the model found that treatment with zolbetuximab plus chemotherapy improved patient outcomes (QALYs) and increased healthcare costs compared with chemotherapy. These findings remained if different methods are used to calculate the benefits of zolbetuximab. Additionally, zolbetuximab plus chemotherapy had lower costs compared to nivolumab plus chemotherapy.

Uncertainty:

The best available evidence was used to calculate the value for money of zolbetuximab and tried different methods so that we can be confident of the results. Some assumptions were needed for the calculations, which were tested and checked as much as possible. The main ones are:

- To inform the model, the zolbetuximab clinical trials, which are all international trials, were assumed reflect the outcomes of UK patients. This is a valid assumption because these trials included UK patients, the chemotherapy treatments in the trials are used in the UK, and the way the trials were conducted are broadly similar to UK clinical practice.
- To calculate the proportion of patients alive beyond the period that the clinical trials cover, the trends from the clinical trials were projected forward. The projections were calculated with different methods and were checked against findings from studies in the real-world and with UK clinicians.
- To compare zolbetuximab to nivolumab an indirect comparison was conducted because there are no trials comparing the two drugs. Indirect comparisons need some assumptions, which means that they are not as reliable as a trial.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f).

Patients with HER2-negative locally advanced unresectable or metastatic gastric or GEJ cancer have few treatment options.

CLDN18.2 is a novel biomarker and promising treatment target in HER2-negative gastric or GEJ cancer.[46, 47] Between 24.0–51.4% of patients with HER2-negative gastric and GEJ cancer have CLDN18.2 positive disease (defined as moderate-to-strong membrane

expression in ≥ 75% of tumour cells).[27-30]

Zolbetuximab is a first of its kind targeted mAb against CLDN18.2 that extends life expectancy and time to disease progression offering an effective treatment option for patients with HER2-negative, CLDN18.2-positive disease regardless of PD-L1 CPS status.[31, 32]

No major QALY benefits beyond those captured in the economic model are anticipated.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No equality issues were identified.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open-access materials or provide copies that patients can access.

NICE guidance:

NICE guidance on oesophago-gastric cancer – https://www.nice.org.uk/guidance/ng83

NICE guidance on nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, GEJ or oesophageal adenocarcinoma - https://www.nice.org.uk/guidance/ta857

NICE guidance on pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and GEJ cancer – https://www.nice.org.uk/guidance/ta737

Further information/publications on SPOTLIGHT:

Clinicaltrials.gov (NCT03504397) – https://classic.clinicaltrials.gov/ct2/show/NCT03504397

Publication (Shitara et al. 2023[29]) – https://pubmed.ncbi.nlm.nih.gov/37068504/

Further information/publications on GLOW :

Clinicaltrials.gov (NCT03653507) –https://www.clinicaltrials.gov/study/NCT03653507

Publication (Shah et al. 2023[32]) – https://www.nature.com/articles/s41591-023-02465-7

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Adenocarcinoma: Cancer that forms in the glandular tissue, which lines certain internal organs and makes and releases substances in the body, such as mucus, digestive juices, and other fluids.[48]

Adverse event/side effect: An unexpected medical event that arises during treatment with a drug or other therapy. Adverse events can be classified as mild, moderate or severe.[49]

Anaemia: Anaemia is a condition in which the number of red blood cells or the haemoglobin concentration within them is lower than normal.[50]

Asymptomatic: Having no signs or symptoms of disease.[48]

Clinically meaningful: A term used to demonstrate that a treatment results in real, noticeable, or self-reported change in patients' lives.[51]

Clinical trial: A study performed to investigate the safety and/or efficacy of a new treatment.[49]

Combined positive score: The number of PD-L1 positive cells in relation to total tumour cells.[52]

Comorbidity: The condition of having two or more diseases at the same time.[48]

Early-stage cancer: A term used to describe cancer that is early in its growth and may not have spread to other parts of the body. What is called early-stage may differ between cancer types.[48]

Efficacy: A measure of a medicine's desired effect under ideal conditions (e.g. a clinical trial).[49]

Eligibility criteria: In clinical trials, requirements that must be met for a patient to be included in a trial. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.[48]

First-line therapy (also called induction therapy, primary therapy, and primary treatment): The first treatment given for a disease which is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it does not cure the disease or it causes severe side effects, other treatment may be added or used instead.[48]

GEJ cancer: Cancer that develops where the oesophagus connects to the stomach.[48]

Gastric cancer: Cancer that forms in the lining of the stomach.[48]

Immunohistochemistry: A laboratory method that uses antibodies to look for markers (antigens) in a tissue sample.[53]

Indication: The condition a medicine is used to treat; this can include the treatment, prevention and diagnosis of a disease.[49]

Indirect treatment comparison: A comparison of two different competitor treatments using data from different studies. For example, if two competitor treatments have never been compared against each other directly, but have been compared in separate studies to a common comparator, then an indirect treatment comparison can be completed to estimate the difference in the two competitor treatments.[54]

IV infusion: Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein, into the bloodstream.[48]

Marketing authorisation: The approval to market a medicine in one, several or all European Union Member States.[49]

Median: The median is the middle value.

Metastatic: The spread of cancer from the primary site (i.e. where the cancer started) to other places in the body.[48]

Overall survival: How long a patient lives after treatment.[36]

PD-1 inhibitor: A type of immunotherapy (i.e. nivolumab and pembrolizumab) that blocks PD-1 checkpoint proteins, thereby turning the immune system on so that immune cells can attack cancer cells.[55]

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.[48]

Peripheral sensory neuropathy: A condition that occurs when the nerves located outside of the brain and spinal cord (peripheral nerves) are damaged and often causes weakness, numbness and pain, usually in the hands and feet.[56]

Progression-free survival: The time measured between treatment aimed at shrinking or controlling cancer, and signs that it has started to grow again.[36]

Quality-adjusted life year: A measurement that shows how many additional months or years of life of a reasonable quality a patient may gain due to treatment

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[57]

Statistically significant: A statistically significant result means that it is unlikely the results can be explained by chance or random factors. A statistically significant result has a very low chance of occurring if there were no true effect from treatment.[58]

Unresectable: Unable to be removed by surgery.[59]

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Zolbetuximab with chemotherapy for untreated CLDN18.2-positive HER2-negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID5123 EAG Clarification Letter 03052024_CIC_redacted	1.0	No	3 May 2024

Notes for company

Highlighting in the template

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

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

Section A: Clarification on effectiveness data

Literature searches

A 1. Please confirm which 'relevant websites' were searched to identify additional clinical effectiveness evidence (Appendix D, p. 24)

Please see the Table 19 in the Appendix used for searching for relevant websites, conference proceedings and clinical trial registries.

A 2. Please provide the search terms and access dates for all additional websites, trials registers and conference proceedings searched in Appendices D, G, H and I.

Please see Table 19 to Table 22 in the Appendix.

A 3. Please provide the missing data in Appendix D, Table 1, line #8.

The missing information in line #8 “or (capecitabine or Xeloda or CAPOX or CapeOx or CAPE-OX or XELOX).mp.”

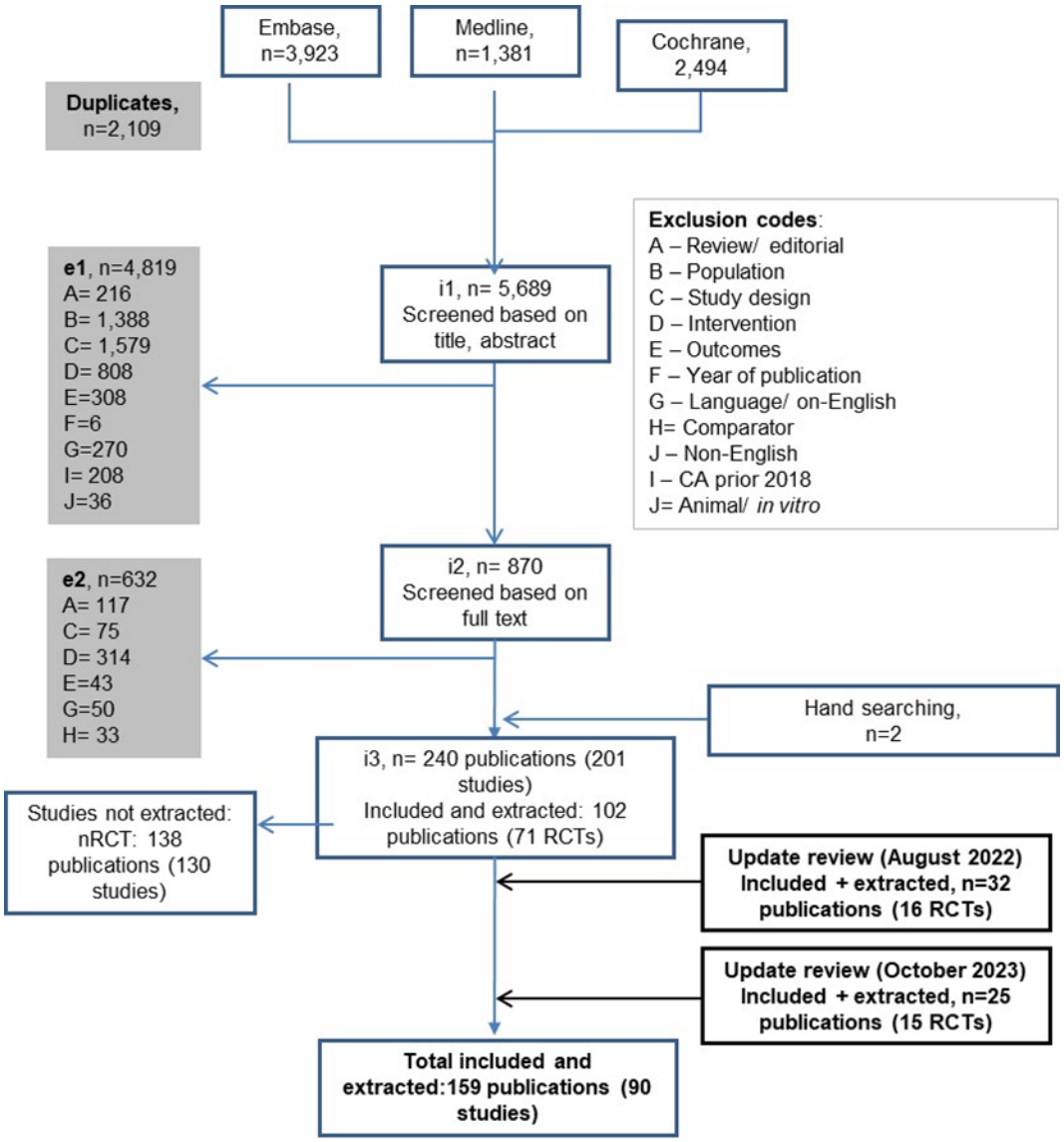
A 4. Please confirm that the heading for Appendix D, Table 8 should read '<1946 to October 27th, 2023>', not '<1946 to October 27th, 2022>'.

Yes, this is a typo and it should be read as 2023 as mentioned in the accessed date.

A 5. Please confirm that the MEDLINE and Embase results in the top boxes of the PRISMA flow diagram (Appendix D, Figure 1) have been mis-labelled.

Yes, this is correct. Please see below the updated PRISMA with corrected labels.

Figure 1: Updated PRISMA flow diagram



Decision problem

A 6. **Priority question: The NICE final scope highlighted the subgroup of patients with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥5. However, the company submission (CS) provided data for the indirect treatment comparison between the overall population of SPOTLIGHT and GLOW trials and the subgroup of patients with PD-L1 CPS ≥5 from the CheckMate-649 trial. Given that the indirect treatment comparison was based**

on the data from the overall population of SPOTLIGHT and GLOW trials rather than the subgroup of patients with PD-L1 CPS ≥5 from these two trials, the CS did not properly address the NICE final scope relating to this subgroup with PD-L1 CPS ≥5. Please comment on this issue and, if possible, provide all relevant data for the aforementioned subgroup.

The NICE final scope was addressed appropriately, given that the submission includes evidence comparing zolbetuximab with nivolumab in patients with PD-L1 CPS ≥ 5. For the reasons outlined below, the network meta-analysis (NMA) used ITT data of the SPOTLIGHT and GLOW trials. As discussed in more detail in response to question B3 a), for simplicity the cost-effectiveness analysis assumes equivalent clinical outcomes for overall survival (OS) and progression-free survival (PFS) for zolbetuximab and nivolumab (both + chemotherapy) versus chemotherapy, as presented in the Addendum.

Using the PD-L1 CPS ≥ 5 subgroup data for zolbetuximab to inform the NMA and cost-effectiveness analysis is not appropriate. Firstly, as this is a post-hoc subgroup, patients included in SPOTLIGHT and GLOW were not stratified by PD-L1 CPS status. Therefore, there is a risk of imbalance in patient characteristics that may affect outcomes. For example, in the SPOTLIGHT PD-L1 CPS ≥ 5 subgroup, the proportion of patients aged > 65 years was [redacted] in the zolbetuximab + mFOLFOX6 arm compared to the placebo + mFOLFOX6 arm ([redacted]).[1] In addition, it was not possible to test all patients taking part in the trials, therefore PD-L1 CPS status is not known for [redacted] patients in SPOTLIGHT and [redacted] in GLOW.

In the post-hoc subgroup analysis, hazard ratios (HRs) were analysed for PFS and OS by PD-L1 CPS subgroups at the PD-L1 CPS 5 cut-off (≥ 5 vs < 5) initially using the interim data-cut and subsequently at the PD-L1 CPS 5 and 1 cut-offs (≥ 5 vs < 5 vs unknown, and ≥ 1 vs < 1 and unknown) using the second data-cut.[1] Overall, there was a consistent trend similar to that of the overall population for both PD-L1 CPS cut-offs, supporting the conclusion that PD-L1 CPS does not affect PFS and OS with zolbetuximab.

Furthermore, Astellas is not aware of a biological mechanism by which PD-L1 CPS could affect zolbetuximab's mechanism of action and the SmPC is not expected to refer to PD-L1 CPS.[2] Zolbetuximab is a monoclonal antibody directed against the tight junction molecule claudin 18.2 (CLDN18.2). In contrast, checkpoint inhibitors (CPIs) such as nivolumab and pembrolizumab are monoclonal antibodies that bind to the programmed death-1 (PD-1) receptor and block its interaction with PD-L1 and PD-L2. The licenses of the CPIs and indeed efficacy depend on tumour PD-L1 expression based on CPS.[3, 4]

The CPS is defined as the number of PD-L1-positive tumour cells (partial or complete membrane staining), lymphocytes, and macrophages (membrane staining or intracellular staining, or both) divided by the total number of viable tumour cells multiplied by 100. As described in the company submission, Astellas conducted a targeted literature review, which demonstrated that PD-L1 CPS does not affect outcomes with chemotherapy.[5] In brief, eight studies reported on the association of PD-L1 status with outcomes in populations that are predominantly inoperable or metastatic GC/GEJC and in which treatment was not assigned as part of the study protocol. Five studies showed no association between PD-L1 and survival. Of the three remaining studies, in one study patients received third-line immunotherapy, which was associated with longer survival in patients with PD-L1 CPS ≥ 5; one study evaluated PD-L1 expression as circulating expression by an RT-PCR assay (rather than IHC of tumour samples as in clinical practice); one study reported ambiguous results. Furthermore, the subgroup analyses of the five identified CPI trials by CPS expression showed overlapping confidence intervals in the median PFS and OS in the chemotherapy arms, and similar response rates.

In summary, the ITT populations in SPOTLIGHT and GLOW data are generalisable to the patients with PD-L1 CPS in terms of outcomes with zolbetuximab and chemotherapy. Hence use of the ITT data appropriately addresses the NICE final scope. Using the post-hoc subgroup with PD-L1 CPS ≥ 5 increases uncertainty and the risk of bias, and therefore is not appropriate.

A 7. **Priority question: The company's decision problem omits pembrolizumab with chemotherapy as a comparator on the basis of the lack of overlap between patients with gastric cancer/gastro-esophageal junction cancer) (GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10). Could the company verify that the decision problem is to be amended to exclude the overlap subgroup i.e. GC / GEJC patients with both CLDN18.2 positivity in ≥ 75% of tumour cells) and with CPS ≥ 10. If not, then please include an analysis of effectiveness and cost effectiveness for this subgroup with pembrolizumab with chemotherapy as comparator.**

Astellas are seeking a positive recommendation in the entire licensed indication. As described in the company submission, biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a very small overlap ([redacted] between patients with GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with PD-L1 CPS ≥ 10) and overlap in GEJC patients will be even smaller.[6] Therefore, pembrolizumab with chemotherapy (with PD-L1 CPS ≥ 10) has not been included as a comparator. Furthermore, and as discussed in response to question B3 b), patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated to zolbetuximab. Given the ongoing appraisal for pembrolizumab, which the ID4030 draft guidance confirmed will supersede TA737[7], Astellas have now provided clinical and cost-effectiveness evidence versus pembrolizumab in patients with PD-L1 CPS ≥ 1 (see Addendum B.1.3 and B.2.6.3).

A 8. Please provide clarification on the difference between the population defined in the NICE final scope and the population in the CS. The population defined in the NICE final scope is "first-line treatment of patients with advanced unresectable HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive." The population in the CS is "first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive."

Please elaborate on the impact of this difference on the standard of care in this population.

This is a minor difference in terminology, which has no impact on the standard of care in this population. In the NICE scope, the term "advanced unresectable" refers to patients with locally advanced unresectable adenocarcinoma as well as patients with metastatic adenocarcinoma. Furthermore, the patient population in the submission aligns with the expected marketing authorisation.

Systematic review

A 9. Page 26 of Document B Appendices (Appendix D; Table 10) presents the eligibility criteria of the systematic review. However, the eligibility criteria did not properly address the NICE final scope because the eligible interventions included other checkpoint inhibitors that are not relevant to the NICE final scope. Please revise the eligibility criteria of the systematic review in order to properly address the NICE final scope.

The SLRs were conducted to meet the needs of health technology assessment agencies internationally, therefore include interventions that are not available in the UK. The wider inclusion criteria do not compromise the validity or the usefulness of the SLRs to inform the NICE appraisal of zolbetuximab, as all comparators relevant to the UK were included.

A 10. Please revise the PRISMA flow diagram accordingly after revising the eligibility criteria of the systematic review.

Please see response to previous question.

A 11. Please confirm whether quality appraisals were conducted by two independent reviewers and if so how any disagreements were resolved? If not, please describe the approach taken.

Quality assessments were performed for all the final studies included in the SLR by two reviewers independently to assess the likelihood of bias. Any disagreements were resolved by discussion and/or additional referees.

Clinical effectiveness evidence

A 12. **Priority question: Please provide further justification for the pooling of the three chemotherapy arms with different regimens (FOLFOX and CAPOX), as in Tables 18 and 19 the chemotherapy outcomes in the SPOTLIGHT (FOLFOX), GLOW (CAPOX) and CheckMate 649 (investigator choice of FOLFOX and CAPOX), trials seem different based on the Kaplan-Meier curves for OS and PFS. Please also provide a full explanation of the method used to pool the trials.**

As described in the company submission, there are particular advantages of pooling chemotherapy evidence from the SPOTLIGHT, GLOW and CheckMate 649 trials. For example, this approach increases the sample size (leading to more robust estimates of survival model parameters), and it allows for incorporation of trial evidence from CheckMate 649 that has longer follow-up than the zolbetuximab trials, resulting in more robust extrapolations. Maximum OS follow-up across SPOTLIGHT and GLOW is approximately [redacted] years, compared to 5 years for CheckMate 649. In addition, NICE TA857 (nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, GEJ or oesophageal adenocarcinoma) concluded that CheckMate 649 was generalisable to NHS clinical practice.[8]

Although there are numerical differences in the survival outcomes between GLOW and SPOTLIGHT, survival outcomes between CheckMate 649 and GLOW are similar (see Figure 2 and Figure 3). Additionally, all trials follow a similar shape in the Kaplan–Meier curves for chemotherapy. Slight differences are to be expected due to chance and variability in the trial populations. These small differences do not necessarily preclude pooling or the generalisability of the pooled chemotherapy outcomes. Furthermore, there is no evidence that the different chemotherapy regimens affect survival outcomes, and indeed this was also assumed in NICE TA857[8] as well as in the ongoing pembrolizumab appraisal ID4030.[7]

Figure 2: Progression-free survival for SPOTLIGHT, GLOW and CheckMate 649

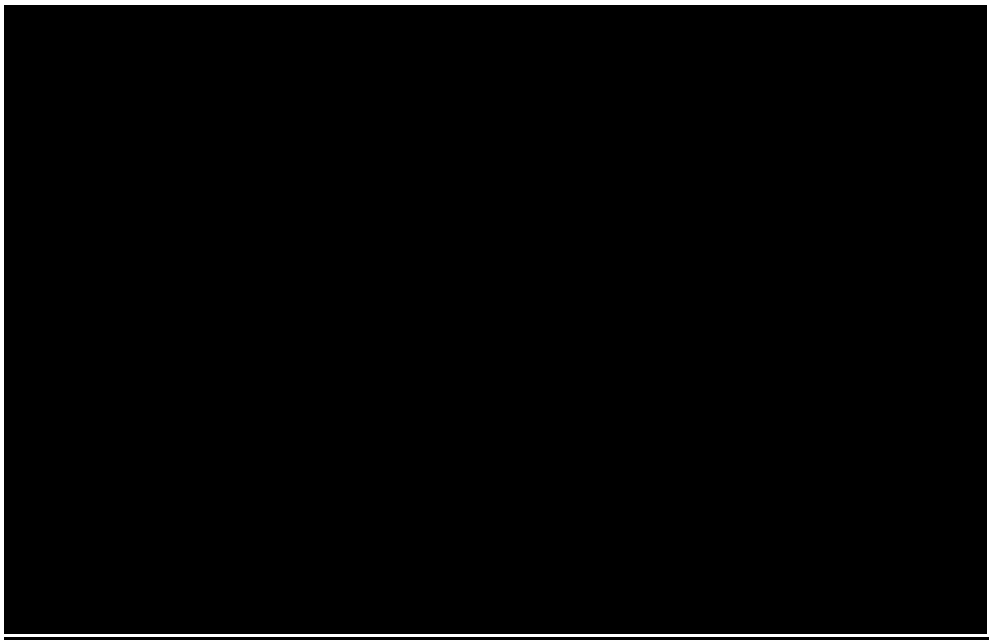
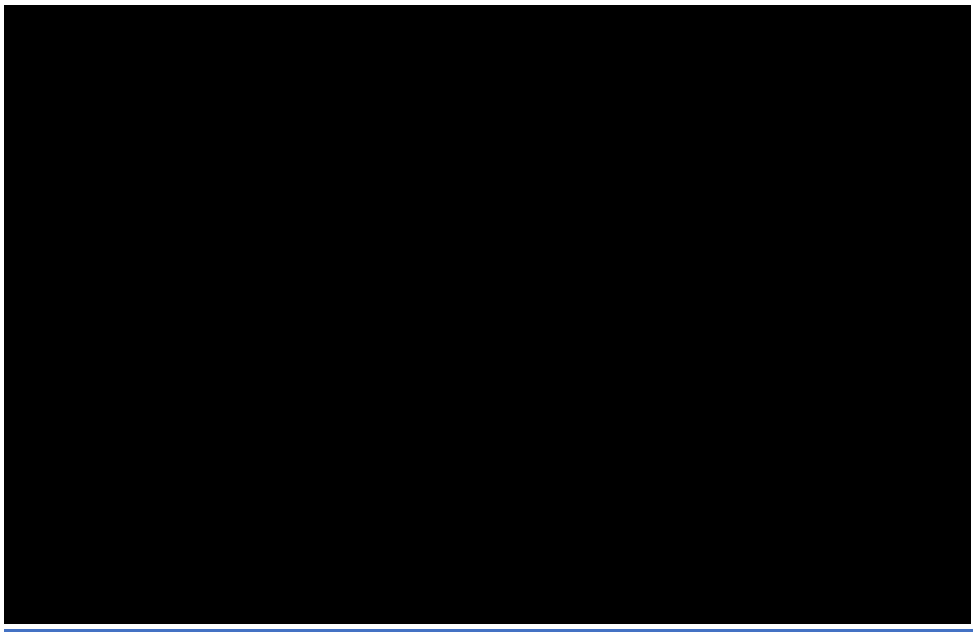


Figure 3: Overall survival for SPOTLIGHT, GLOW and CheckMate 649



The survival curves from CheckMate 649 trial were digitised and the individual level data recreated using the Guyot et algorithm.[9] Data were pooled by combining the patient-level data from GLOW, SPOTLIGHT, and the recreated data from CheckMate 649 into a single dataset. No adjustment for differences in patient

characteristics was made given the numerical differences in survival outcomes are expected to be due to chance.

A 13. Page 26 of the CS states that the final database lock for the SPOTLIGHT trial took place on [redacted]. Please provide further results based on the final database lock time on [redacted] for this trial if available, as the data cut-off point for the analysis for the SPOTLIGHT trial presented in the CS was 29 June 2023, which was not the pre-specified data cut-off point for the SPOTLIGHT trial.

All relevant clinical effectiveness results from the 8 September 2023 data cut-off for SPOTLIGHT are provided in Section B.1.1 of the Addendum.[10]

A 14. Page 31 of the CS states that the final database lock for the GLOW trial took place on [redacted]. Please provide further results based on the final database lock time on [redacted] for this trial if available, as the data cut-off point for the analysis for the GLOW trial presented in the CS was 29 June 2023, which was not the pre-specified data cut-off point for the GLOW trial.

All relevant clinical effectiveness results from the final data cut, dated [redacted] data cut-off for GLOW are provided in Section B.1.2 of the Addendum.[11] To clarify, the final data cut of GLOW took place on [redacted], while the database lock took place on [redacted]

A 15. Please provide detailed information on statistical methods for key efficacy analyses of SPOTLIGHT, GLOW and FAST trials.

The statistical analysis plans for the SPOTLIGHT, GLOW and FAST trials have now been included in the reference pack.[12-14]

A 16. The VENTANA CLDN18 (43-14A) RxDx Assay is currently an under development Companion Diagnostic (CDx) IHC test for CLDN18.2. As per CS, this CDx specific to zolbetuximab is expected to be approved once the medicine is licensed. Please provide any available information on how much time would require approving the CDx, if zolbetuximab would be approved.

The VENTANA CLDN18 (43-14A) RxDx Assay is being developed as a companion diagnostic device (CDx) to zolbetuximab. The analytical and clinical utility of the

device for the identification of CLDN18.2 positive G/GEJ cancer patients who may benefit from zolbetuximab has been shown in two phase 3 clinical trials (GLOW and SPOTLIGHT); the device will require a CE mark prior to use as a CDx to zolbetuximab.

A submission to obtain a CE mark for the VENTANA CLDN18 (43-14A) RxDx Assay was submitted by Ventana/Roche Diagnostics to the EU notified body under the 2017/746 IVDR regulation on [redacted] and is currently under assessment. The device has already been approved as a CDx to zolbetuximab in Japan therefore no obstacles are foreseen to obtaining approval in EU and UK.

As soon as the EU CE mark is obtained (currently expected [redacted], Ventana/Roche Diagnostics will submit an application for the CDx in the UK, cross referring to the EU IVDR CE mark. The pathway in the UK is expected to take a couple of weeks following receipt of approval of the EU CE mark.

Until approval of the CDx for zolbetuximab treatment in the UK, laboratories can use an alternative validated test to evaluate CLDN18.2 expression in G/GEJ cancer patients. Such alternative tests include the Ventana CLDN18 (43-14A) IVD assay that has received its CE-IVD mark in the EU under IVDD and is intended for the immunohistochemical detection of CLDN18; a number of laboratories have experience in the use of this device from their participation in a recently published global ring study. In the same study, this device has been shown to be reproducible in the evaluation of CLDN18.2 expression in gastric cancer across a cohort of 27 laboratories.[15]

A 17. Page 55 of the CS states that formal meta-analyses have not been conducted. Please provide the rationale for not performing formal meta-analysis.

The zolbetuximab trials were not meta-analysed in a separate analysis, however the trials were meta-analysed in the network meta-analysis, as reported in Section B.2.10 of the original submission and Section B.1.3 of the Addendum.

A 18. For Table 12 (Page 66 of the CS), please provide clarification on the PD-L1 CPS status for patients receiving zolbetuximab plus chemotherapy.

Table 1 presents an overview of the PD-L1 CPS status of all randomised patients in the SPOTLIGHT and GLOW trials.

Table 1: PD-L1 CPS status of the SPOTLIGHT and GLOW trials for all randomised patients

PD-L1 CPS subgroup, n (%)	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = [redacted])	Zolbetuximab + CAPOX (n = [redacted])	Placebo + CAPOX (n = [redacted])
Patients with known CPS[1]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with unknown CPS[1]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients (%) by PD-L1 CPS group in patients with known CPS				
PD-L1 CPS <1	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥1	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS <5	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥5	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS <10	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥10	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; n, number of patients; PD-L1, programmed death-ligand 1.
Notes: [1] PD-L1 CPS results outside the 24-month cut-slide stability window and patients' samples that were not tested were labeled as "unknown". PD-L1 CPS results were accepted for analysis if the CPS results were within the established cut-slide stability window of 24 months and the patient was randomized.
Source: Astellas data on file. 2024.[1,6]

A 19. For Table 13 (Page 69 of the CS), please provide clarification on the PD-L1 CPS status for patients receiving zolbetuximab plus chemotherapy.

Please see response to previous question.

Indirect treatment comparison (ITC)

A 20. **Priority question: Please provide the base case network meta-analysis (NMA) results for the subgroup of patients with PD-L1 CPS ≥5 from the**

included trials (SPOTLIGHT, GLOW and CheckMate-649), see also question A6 above.

Please see response to question A6 above.

A 21. **Priority question: Please provide a Table that summarizes patient characteristics at baseline for the subgroup of patients with PD-L1 CPS ≥5 from the included trials (SPOTLIGHT, GLOW and CheckMate-649) for the base case network meta-analysis. It is important to make sure that the assumption of exchangeability for the purpose of the network meta-analysis is acceptable (as highlighted in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 2).**

As described in the response to question A6, using the PD-L1 CPS ≥ 5 subgroup data SPOTLIGHT and GLOW to inform the NMA and cost-effectiveness analysis is not appropriate, as the ITT populations in SPOTLIGHT and GLOW data are generalisable irrespective of PD-L1 CPS. Table 2 presents a summary of the patient characteristics at baseline for the ITT population in SPOTLIGHT and GLOW, and for patients with PD-L1 CPS ≥ 5 in CheckMate-649.

Table 2: Patient characteristics at baseline for studies considered for indirect treatment comparison

	SPOTLIGHT (ITT)		GLOW (ITT)		CheckMate 649 (PD-L1 CPS ≥ 5)	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Nivolumab + CAPOX/ FOLFOX (n = 473)	CAPOX/ FOLFOX (n = 482)
Age (years), median	62.0	60.0	61.0	59.0	63.0	62.0
Male gender, %	62.2	62.1	62.6	61.7	70.0	72.0
Race, %						
White	53.6	53.0	37.0	36.0	75.0	76.0
Asian	36.8	38.3	62.0	62.0	25.0	24.0
ECOG, %						
0	44.8	41.4	42.7	43.2	41.0	42.0
1	54.8	58.6	57.3	56.8	59.0	58.0
2	< 1.0	0.0	0.0	0.0	< 1.0	< 1.0
Tumour location, %						
Oesophagus	0.0	0.0	0.0	0.0	12.0	13.0
GEJ	22.6	25.5	13.8	17.4	18.0	18.0
GC	77.4	74.5	86.2	82.6	70.0	69.0
HER2 status, %						
Positive	0.0	0.0	0.0	0	0.0	0.0
Negative	100.0	100.0	100.0	100.0	NR	NR
Unknown	0.0	0.0	0.0	0.0	NR	NR
CPS score, % [1]						
≥ 5	[redacted]	[redacted]	[redacted]	[redacted]	100.0	100.0

Key: CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.

	SPOTLIGHT (ITT)		GLOW (ITT)		CheckMate 649 (PD-L1 CPS ≥ 5)	
	Zolbetuximab + mFOLFOX6 (n = 283)	**mFOLFOX6 (n = 282)**	**Zolbetuximab + CAPOX (n = 254)**	**CAPOX (n = 253)**	**Nivolumab + CAPOX/ FOLFOX (n = 473)**	**CAPOX/ FOLFOX (n = 482)**
Notes: [1] The proportion of patients with PD-L1 CPS ≥ 5 refers to those for whom the PD-L1 CPS result was known. **Source**: Ajani et al. 2023[16]; Astellas, data on file 2023[17]; Lordick et al. 2023[18]; Astellas, data on file 2023[19]; Astellas, data on file 2023[1]; Janjigian et al. 2021.[20]						

A 22. The patient baseline characteristics in the SPOTLIGHT trial as detailed in Table 4 confirm over 68% of participants are from 'Non-Asia' with over 85% of participants having an ethnicity described as 'Not Hispanic or Latino'. Please provide data detailing the patient characteristics from Europe and from the United Kingdom specifically and with relevant breakdown by ethnicity within those populations

Table 3 presents the baseline characteristics of European and UK patients in SPOTLIGHT. Table 4 presents the baseline characteristics of UK patients in SPOTLIGHT.

Table 3: Baseline characteristics of European and UK patients in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 (n = [redacted])	**Placebo + mFOLFOX6 (n = [redacted])**
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		

	Zolbetuximab + mFOLFOX6 (n = [redacted])	**Placebo + mFOLFOX6 (n = [redacted])**
Abdominal Cavity	[redacted]	[redacted]
Adrenal Gland	[redacted]	[redacted]
Bone	[redacted]	[redacted]
Chest	[redacted]	[redacted]
Colon	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Heart	[redacted]	[redacted]
Kidney	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Mediastinum	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ovary	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Rectum	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Spleen	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG performance status score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2[†]	[redacted]	[redacted]
Missing[‡]	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 (n = [redacted])	Placebo + mFOLFOX6 (n = [redacted])
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented. † Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG performance status score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment. ‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG performance status score of 0 or 1 and were thus eligible for enrolment.
Source: Astellas Data on File, 2024.[21]

Table 4: Baseline characteristics of UK patients in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 (n = 16)	Placebo + mFOLFOX6 (n = 18)
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Bone	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Other	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 (n = 16)	Placebo + mFOLFOX6 (n = 18)
Ovary	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG performance status score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2†	[redacted]	[redacted]
Missing‡	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented. † Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG performance status score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment. ‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG performance status score of 0 or 1 and were thus eligible for enrolment.
Source: Astellas Data on File, 2024.[21]

A 23. The patient baseline characteristics in the GLOW trial as detailed in Table 5 confirm over 60% of participants are from Asia with over 96% of participants having an ethnicity described as ‘Not Hispanic or Latino’. Please provide data detailing the patient characteristics from Europe and from the United Kingdom specifically and with relevant breakdown by ethnicity within those populations.

Table 5 presents the baseline characteristics of European and UK patients in GLOW.

Table 6 presents the baseline characteristics of UK patients in GLOW.

Table 5: Baseline characteristics of European and UK patients in GLOW

	Zolbetuximab + CAPOX (n = [redacted])	**Placebo + CAPOX (n = [redacted])**
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Adrenal Gland	[redacted]	[redacted]
Bone	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Mediastinum	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ovary	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Pelvis	[redacted]	[redacted]
Pericardium	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Spleen	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		

	Zolbetuximab + CAPOX (n = [redacted])	Placebo + CAPOX (n = [redacted])
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.
Source: Astellas Data on File, 2024.[21]

Table 6: Baseline characteristics of UK patients in GLOW

	Zolbetuximab + CAPOX (n = 4)	Placebo + CAPOX (n = 6)
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Bone	[redacted]	[redacted]

	Zolbetuximab + CAPOX (n = 4)	Placebo + CAPOX (n = 6)
Oesophagus	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status score, n (%)		
0	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Key: ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.
Source: Astellas Data on File, 2024.[21]

A 24. Please detail how generalisable these data are to the relevant clinical population in the United Kingdom

There is limited recent evidence on the characteristics of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma who receive first line treatment in the NHS. Patients included in SPOTLIGHT and GLOW have similar characteristics to those included in CheckMate 649, which was deemed generalisable to NHS clinical practice.[8] Furthermore, patients included in SPOTLIGHT and GLOW have similar characteristics to those included KEYNOTE-

859, which was used in ID4030.[7] To address the concerns raised in NICE TA857 that patients in the CheckMate 649 trial were younger than those in NHS clinical practice[8], scenario 12 of the company submission increased the age at treatment start from 58.5 years to 64.15 years; this had a negligible impact on cost-effectiveness results (ICER increased by 0.8%).

Adverse events

A 25. Please provide all adverse event data for the comparison of the treatment arm versus the control arm of the SPOTLIGHT, GLOW and FAST trials in a Table.

Table 7 provides an overview of adverse events in the SPOTLIGHT, GLOW and FAST trials.

Table 7: Summary of AEs across the SPOTLIGHT, GLOW and FAST trials

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any grade TEAEs occurring in ≥ 10% of patients in either treatment arm						
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	74 (96.1)	84 (100)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	53 (68.8)	50 (59.5)
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	35 (45.5)	30 (35.7)
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	34 (44.2)	29 (34.5)
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	12 (15.6)	9 (10.7)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	76 (90.5)	70 (90.9)
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	63 (81.8)	64 (76.2)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	52 (67.5)	46 (54.8)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	14 (18.2)	31 (36.9)
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	14 (18.2)	10 (11.9)
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	14 (18.2)	10 (11.9)
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	54 (70.1)	56 (66.7)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	24 (31.2)	17 (20.2)

Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	19 (24.7)	19 (22.6)
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	9 (11.7)	17 (20.2)
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	10 (13.0)	6 (7.1)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	41 (53.2)	47 (56.0)
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	25 (32.5)	26 (31.0)
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	7 (9.1)	11 (13.1)
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	6 (7.8)	9 (10.7)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	24 (31.2)	23 (27.4)
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	15 (19.5)	19 (22.6)
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	9 (11.7)	17 (20.2)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	35 (45.5)	42 (50.0)

Peripheral sensory neuropathy						
Paraesthesia					10 (13.0)	9 (10.7)
Dysgeusia						
Dizziness						
Headache					12 (15.6)	18 (21.4)
Psychiatric disorders						
Insomnia						
Respiratory, thoracic and mediastinal disorders					20 (23.8)	19 (24.7)
Cough						
Dyspnoea						
Vascular disorders					12 (14.3)	12 (15.6)
Hypertension						
Grade ≥ 3 TEAEs in > 10% of patients in either treatment arm						
Any Grade ≥ 3 TEAE					54 (70.1)	54 (64.3)
Blood and lymphatic system disorders						
Neutropenia					25 (32.5)	18 (21.4)
Gastrointestinal disorders						
Nausea					5 (6.5)	4 (4.8)
Vomiting					8 (10.4)	3 (3.6)
Investigations						
Neutrophil count decreased						

Any grade study intervention-related TEAEs in ≥ 10% of patients in either treatment arm						
Any intervention-related TEAE*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥ 3 study intervention-related TEAEs in ≥ 10% of patients in either treatment arm						

Any Grade ≥ 3 intervention-related TEAEs*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs in ≥ 5% of patients in either treatment arm						
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	19 (24.7)	27 (32.1)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (2.4)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasm malignant	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.9)	7 (8.3)

Key: CAPOX, capecitabine and oxaliplatin; EOX, epirubicin, oxaliplatin and capecitabine; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; n, number of patients; SAE, serious adverse event; TEAE, treatment-emergent adverse event
Notes: *, for SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm.
Source: SPOTLIGHT final data cut, 2024[10]; GLOW final data cut, 2024[11]; FAST clinical study report[22]; Sahin et al. 2021.[23]

A 26. Please provide detailed information on reasons for treatment discontinuation for SPOTLIGHT, GLOW and FAST trials.

Table 8 present a summary of discontinuation and dose interruption of study drug across the SPOTLIGHT, GLOW, AND FAST trials.

Table 8: Summary of discontinuation and dose interruption of study drug across the SPOTLIGHT, GLOW, AND FAST trials

System Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Discontinuation due to TEAEs in ≥ 5% of patients in either treatment arm						
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption due to TEAEs in ≥ 5% of patients in either treatment arm						
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; EOX, epirubicin, oxaliplatin and capecitabine; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; n, number of patients; TEAE, treatment-emergent adverse event

Source: SPOTLIGHT final data cut, 2024[10], GLOW final data cut, 2024[11], FAST clinical study report.[22]

Section B: Clarification on cost-effectiveness data

B 1. Please update the economic model and analyses with the latest evidence of both SPOTLIGHT and GLOW trials.

The model has now been updated with the latest evidence from the SPOTLIGHT[10] and GLOW[11] trials as well as the latest clinical effectiveness evidence from CheckMate 649.[24] SPOTLIGHT evidence is from 8 September 2023, GLOW evidence is from [redacted], and CheckMate 649 evidence is from 29 May 2023. Details on the evidence used and updated cost-effectiveness results are provided in the Addendum. Of note, the base case cost-effectiveness estimates for zolbetuximab + chemotherapy compared to chemotherapy improves from [redacted] in the original submission to [redacted] (with the confidential discount applied).

Population

B 2. HER2 testing is needed to identify the population for this appraisal and PD-L1 testing is needed to identify the subgroup of patients eligible for nivolumab. Please provide evidence and/or expert opinion on that this is already done as standard in clinical practice.

HER2 testing is part of standard of care in clinical practice. It is recommended in the NICE clinical guideline 83 on the assessment and management of oesophago-gastric cancer in adults: "*1.3.8 Offer HER2 testing to people with metastatic oesophago-gastric adenocarcinoma (see the NICE technology appraisal guidance on trastuzumab for HER2-positive metastatic gastric cancer). [2018]*".[25] Similarly, in the NICE appraisal of nivolumab (TA857), clinical input was that HER2 testing was part of clinical practice.[8]

PD-L1 testing is part of standard of care, given that it is needed for informing treatment decisions with nivolumab (licensed and recommended only in patients with PD-L1 CPS ≥ 5)[8] and pembrolizumab (licensed in patients with PD-L1 CPS ≥ 1; at the time of clarification responses, recommended only in patients with PD-L1 CPS ≥ 10 and GEJC).[3, 26] In the ongoing appraisal of pembrolizumab for patients with PD-

L1 CPS ≥ 1, the EAG did not disagree that NHS clinical practice includes PD-L1 testing alongside HER2 testing, hence these testing costs were not included in the cost-effectiveness analysis.[27]

Intervention & comparators

B 3. Priority question: The comparators are not in line with the NICE scope. No cost effectiveness analyses are performed versus comparators other than chemotherapy, while in the decision problem the company states to include both chemotherapy and nivolumab + chemotherapy as comparators to zolbetuximab + chemotherapy. In the CS, it seems like a cost-effectiveness analysis for zolbetuximab + chemotherapy compared to nivolumab + chemotherapy was conducted, for example in section B.3.2. where it is stated that "We also undertake a secondary analysis to assess the cost-effectiveness of zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5", however, the EAG was not able to find the results of this analysis in the CS.

a) **For patients whose tumours express PD-L1 with CPS of 5 or more: the company provide a cost comparison only. However, the company did undertake an anchored indirect comparison with nivolumab as a comparator. Please provide the methods and results of a cost effectiveness analysis versus nivolumab + chemotherapy using results from this comparison and provide fully incremental analysis.**

The company believes the current approach is the most appropriate due to the reasons outlined below.

The clinical decision as to whether to treat with a checkpoint inhibitor (CPI) such as nivolumab or pembrolizumab, as summarised in section B.1.3.4 of document B, involves a consideration of the patient's PD-L1 CPS (with higher PD-L1 CPS judged predictive of a deeper response from the CPI) [8, 26] and any health conditions which might make a CPI less suitable such as some autoimmune conditions.[3, 4]

Clinical experts indicated that because higher PD-L1 CPS are associated with a stronger response to CPIs, other things equal, the higher the patient's PD-L1 CPS, the more likely they are to receive a CPI. As such, a patient with a PD-L1 CPS ≥10 is likely to receive a CPI unless they have a contraindication to these therapies.

As a result, the average PD-L1 CPS in the patient population considered for both zolbetuximab and nivolumab in clinical practice is likely to be lower than the average PD-L1 CPS in the PD-L1 CPS ≥ 5 subgroup in CheckMate 649, in which 80% of patients (768/955) had PD-L1 CPS ≥ 10.[4] Given that the efficacy of nivolumab + chemotherapy versus chemotherapy alone depends on PD-L1 CPS level, nivolumab's efficacy in the patient population considered for both nivolumab and zolbetuximab is also likely to be lower (i.e., nivolumab has a higher HR) than the efficacy observed in the CheckMate 649 PD-L1 CPS ≥ 5 subgroup. Arguably, if the patient population in clinical practice has on average a lower PD-L1 CPS, efficacy is more likely to trend towards the 0.92 (95% CI 0.66-1.28) OS HR of the CheckMate 649 PD-L1 CPS 5-9 subgroup than the 0.65 (95% CI 0.55-0.78) in the PD-L1 CPS ≥ 10 subgroup.[4]

The implication being that an NMA that compares zolbetuximab to nivolumab based on CheckMate 649 CPS ≥ 5 subgroup data is likely to overestimate the efficacy of nivolumab in the patient population likely to be considered for both treatments.

Nonetheless, the NMA was conducted and provided to support the committee's decision making. This showed that, if the distribution of PD-L1 CPS in the CheckMate 649 PD-L1 CPS ≥ 5 subgroup is representative of the distribution of PD-L1 CPS in patients considered for both zolbetuximab and nivolumab, zolbetuximab has similar efficacy to nivolumab, as the hazard ratios are numerically similar and the credible intervals overlap, in both the spline-based NMA and the proportional hazards NMA (CS B.2.9.2).

However, as discussed above, PD-L1 CPS of patients considered for both zolbetuximab and nivolumab is likely to be lower than in the CheckMate 649 PD-L1 CPS ≥ 5 subgroup. Therefore, it is not appropriate to use the numerical results of the

NMA to inform the cost-effectiveness analysis, as these numerical differences are unlikely to be representative of differences in efficacy in clinical practice.

As such, the company believes modelling the likely biased point estimates of relative treatment effect between nivolumab + chemotherapy vs. zolbetuximab + chemotherapy would be a case of spurious over-precision.

Therefore, in the cost-effectiveness analysis, it was assumed that survival outcomes were the same between the two treatment options. Whilst survival outcomes are assumed to be the same, treatment-specific adverse events are included. As the result is a minimal QALY difference, the results were reported in terms of differences in costs. The addendum now presents full cost-effectiveness results (see Addendum *B.2.6.2.*).

A proportional hazards NMA was conducted using the same methods as reported in Appendix D and CS B.2.9. A non-proportional NMA in the PD-L1 CPS 5-9 was unfeasible because the Kaplan-Meier curves for this subgroup of CheckMate 649 are not publicly available. In the comparison nivolumab + chemotherapy vs chemotherapy alone in the CPS 5-9 subgroup, the HR for OS was [redacted] (95% credible interval [CrI] [redacted]); in the comparison zolbetuximab + chemotherapy vs chemotherapy alone the HR for OS was [redacted] (95% CrI [redacted]) – therefore numerically superior but the credible intervals overlap (see Addendum Section B.1.3.3). This analysis could not be conducted for PFS because the HR for PFS for nivolumab + chemotherapy vs chemotherapy in the CPS 5-9 subgroup is not publicly available as far as the company is aware. This result further strengthens the approach of assuming that zolbetuximab and nivolumab are equivalent for OS and PFS in the patients considered for both treatments.

Finally, it should be noted that **the company is seeking a positive recommendation in the expected licensed indication – i.e., patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive – irrespective of PD-L1 CPS.**

b) **For patients whose tumours express PD-L1 with CPS of 10 or more and for gastro-oesophageal junction adenocarcinoma only: the company considered the overlapping proportion of patients eligible for both treatments too small. However, it is questionable whether proportions are also small in clinical practice and therefore the EAG would like to see this explored. Please provide the methods and results of a cost effectiveness analysis versus pembrolizumab + chemotherapy in this population and provide a fully incremental analysis.**

As outlined in B3 a) above and as discussed in section B.1.1 of document B, a comparison with pembrolizumab in patients with PD-L1 CPS ≥10 group and gastro-oesophageal junction adenocarcinoma was not conducted, because: 1) the overlap with the patient population eligible for zolbetuximab is very small and 2) unless contraindicated to a CPI, patients with PD-L1 CPS scores this high are likely to receive a CPI rather than zolbetuximab.

In order to support efficient decision making given the ongoing NICE appraisal on pembrolizumab in PD-L1 CPS ≥1, cost-effectiveness estimates versus pembrolizumab in the PD-L1 CPS ≥1 population are provided as per response to question c) below.

c) **For patients with CPS 1 or more and for gastric or GEJ adenocarcinoma: the reason for not performing a comparison with pembrolizumab + chemotherapy was that it was not recommended by NICE(ID4030). The EAG notes that this guidance was not yet final, so it would prefer if a cost effectiveness analysis could be provided against pembrolizumab + chemotherapy.**

To enable efficient decision making in the event pembrolizumab is recommended, Astellas has conducted a cost-effectiveness analysis comparing zolbetuximab + chemotherapy to pembrolizumab + chemotherapy in patients with PD-L1 CPS ≥ 1. In this cost-effectiveness analysis, Astellas assumed that pembrolizumab +

chemotherapy in patients with PD-L1 CPS ≥ 1 had equivalent OS and PFS as zolbetuximab + chemotherapy. This assumption is based on the results of an NMA, which is reported in Addendum section B.1.3.3.

As discussed in response to sub question a) above, the point estimates of the NMA are likely an overestimate of pembrolizumab's efficacy in patients with PD-L1 CPS ≥ 1 relative to zolbetuximab in the patients who are considered for both treatments in clinical practice. This is because the PD-L1 CPS ≥ 1 data used for pembrolizumab + chemotherapy includes patients with high PD-L1 CPS (≥ 10) who: 1) will typically receive a greater treatment benefit from pembrolizumab than patients with lower PD-L1 CPS scores[8, 26] and 2) these patients with the highest PD-L1 CPS scores will typically not be considered for zolbetuximab + chemotherapy unless they are unsuitable for treatment with a CPI.

Specifically, in the KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup, 551/1235 (45%) of patients had PD-L1 CPS ≥ 10. The HR for OS in the PD-L1 CPS ≥ 1 subgroup was 0.74 (95% confidence interval (CI) 0.65; 0.84). In the PD-L1 CPS 1-9 group it was 0.83 (95% CI 0.70; 0.98). It was 0.65 (0.53; 0.79 in the PD-L1 CPS ≥ 10 subgroup.[28]

In clinical practice, the proportion of patients with PD-L1 CPS ≥ 10 who are considered for either zolbetuximab + chemotherapy or pembrolizumab + chemotherapy is likely to be small and well below 45%. Therefore, the efficacy of pembrolizumab + chemotherapy in patients who are also considered for zolbetuximab + chemotherapy in clinical practice is likely to be lower than the efficacy observed in the KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup (i.e., higher HRs).

Despite this limitation, both the spline-based NMA and the proportional hazards NMA found that the HRs of zolbetuximab + chemotherapy and pembrolizumab + chemotherapy in the PD-L1 CPS ≥ 1 (which assumes a PD-L1 CPS distribution as per KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup) versus chemotherapy were numerically similar and with overlapping credible intervals. Furthermore, a proportional hazards NMA was conducted comparing zolbetuximab + chemotherapy vs chemotherapy and pembrolizumab + chemotherapy vs chemotherapy in the patients with PD-L1 CPS 1-9. Zolbetuximab + chemotherapy vs

chemotherapy had numerically lower hazard ratios than pembrolizumab + chemotherapy vs chemotherapy in the patients with PD-L1 CPS 1-9 and overlapping credible intervals (see Addendum Table 26).

As such, assuming the same survival outcomes for the cost-effectiveness analysis is a pragmatic and appropriate approach to inform the committee's decision making.

B 4. Priority question: Please provide the proportions to which CAPOX / FOLFOX are used in clinical practice with supporting evidence and / or expert opinion. Please provide a scenario analysis in which the pooling of treatment effectiveness (OS, PFS, DoT) and costs are weighted according to these proportions.

As noted in the company submission, clinical advice received by the EAG for TA857 is that approximately 80% of patients would receive CAPOX with the remaining 20% receiving FOLFOX.[8] This assumption was already tested in Scenario 5 of the company submission, which uses GLOW for CAPOX outcomes and SPOTLIGHT for FOLFOX outcomes. Note that this weighting applies to the chemotherapy arm for OS, PFS and DoT, for zolbetuximab this weighting only applies to DoT. For OS and PFS, SPOTLIGHT and GLOW are weighted based on their sample sizes. Due to time constraints, it was not possible to implement in the model the option of weighting the OS and PFS zolbetuximab arm of the SPOTLIGHT and GLOW trials according to user-defined proportions.

B 5. Please clarify whether, in the zolbetuximab arm of the model, when treatment with zolbetuximab is stopped before 24 weeks, treatment with chemotherapy is also stopped, and the same in the nivolumab arm of the model. Please provide supporting evidence and justification.

For all treatments that are provided in addition to chemotherapy (zolbetuximab, nivolumab, pembrolizumab), separate durations of treatment are modelled for both components (e.g., separately for zolbetuximab and for chemotherapy, and similarly for nivolumab + chemotherapy and pembrolizumab + chemotherapy).

B 6. Please describe what subsequent treatments are typically provided to patients in this population in UK clinical practice, providing supportive evidence and / or

expert opinion. Please elaborate on subsequent treatment use (what treatments, what proportion of patients per treatment arm, duration) as observed in the SPOTLIGHT and GLOW trials.

Clinical advice to Astellas from four UK clinical experts (three in England and one in Scotland) at an advisory board in 2022 was that second-line treatments include FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) in England, and docetaxel and irinotecan in Scotland. Third-line treatment includes any chemotherapy not used in the second-line as well as trifluridine/tipiracil and nivolumab.[29]

This feedback is broadly consistent with the distribution of subsequent therapies used in the company's base-case of ID4030, which was based on clinical expert opinion. For second-line, this was FOLFIRI (60%), paclitaxel (30%) and irinotecan (10%); and for third-line, this is FOLFIRI (6%), paclitaxel (12%), and trifluridine/tipiracil (12%).[27] For the cost-effectiveness model, the company of ID4030 applied a lump sum cost upon progression. At list prices, this was £16,779 for the pembrolizumab + chemotherapy arm and £35,203 for the chemotherapy arm. If these lump sum costs are used in the cost-effectiveness model (changing cells G74:G75 on sheet 'Post-Prog Trt Cost'), zolbetuximab + chemotherapy's ICER reduces to [redacted] and [redacted], respectively (using the confidential discount for zolbetuximab). This suggests that the simplifying assumption of assuming that patients receive docetaxel or paclitaxel on progression is conservative against zolbetuximab + chemotherapy.

An overview of the most commonly received subsequent anticancer therapies in SPOTLIGHT and GLOW is provided in Table 9. Data on duration of subsequent treatments is not available.

Table 9: Subsequent anticancer therapies

	SPOTLIGHT		**GLOW**	
	Zolbetuximab + mFOLFOX6 (n = 279)	**Placebo + mFOLFOX6 (n = 278)**	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
Any subsequent therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy n	[redacted]	[redacted]	[redacted]	[redacted]

	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	**Placebo + mFOLFOX6 (n = 278)**	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
(%)				
Most common systemic therapies				
Taxanes				
Paclitaxel n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel nanoparticle albumin-bound n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Targeted therapies				
Ramucirumab n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Combination therapies				
Paclitaxel + ramucirumab n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy-based regimens				
Calcium folinate + fluorouracil + irinotecan hydrochloride n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil + folinic acid + oxaliplatin n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fluorouracil n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Gimeracil + oteracil potassium + tegafur n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Oxaliplatin n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapies				
Nivolumab n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.

Treatment effectiveness

B 7. Priority question: In the CS on page 64 it is stated that "Results from the primary scenario are presented in Section B.2.9.3 and have been used in the base case economic analysis (See Section B.3.9)".

a) **Please clarify how exactly the spline NMA results were used in the base-case economic analysis.**

b) **As stated in the CS, the base-case economic analysis only considers the cost-effectiveness of zolbetuximab versus chemotherapy. Please justify why the NMA data was used in the base case, instead of using the pooled estimates from the SPOTLIGHT and GLOW trials as in scenario analysis 2?**

The spline-based NMA was used to derive estimates of the time-varying relative effect of zolbetuximab + chemotherapy. These relative effects were then applied to the baseline (absolute) modelled survival outcomes for chemotherapy, to obtain the absolute survival outcomes for zolbetuximab + chemotherapy.

The company considers that CheckMate 649 PD-L1 CPS ≥ 5 subgroup provides relevant evidence, not only on nivolumab's outcomes but also on chemotherapy outcomes. Hence the chemotherapy arm was pooled with the SPOTLIGHT and GLOW chemotherapy arms to increase sample size, follow-up, and generalisability to the clinical practice population.

Additionally, the survival extrapolation was informed by real-world evidence, which showed that there is a small proportion of patients on chemotherapy who have longer term survival. This is reflected in the long-term CheckMate 649 chemotherapy outcomes, further emphasising the importance of including this relevant evidence.

To maintain randomisation and appropriately synthesise the relative efficacy of zolbetuximab + chemotherapy, zolbetuximab + chemotherapy's outcomes were based on the spline-based NMA.

Scenario 2 of the company submission uses evidence from SPOTLIGHT and GLOW alone to inform OS, PFS and DoT. The two trials were pooled together and analysed as if they were one single trial. Therefore the relative weight of each trial to the results is in proportion to the relative number of patients at the start of the trial (47.2% GLOW and 52.8% SPOTLIGHT). Scenario 2 was provided in recognition that SPOTLIGHT and GLOW may be considered the only relevant evidence to inform NICE decision-making and real-world evidence is not relevant to inform extrapolation choice; therefore only this data is used and extrapolations are based on statistical best fit.

The results of fitting parametric survival models to the latest SPOTLIGHT and GLOW data are provided in the Addendum (Sections B.2.1.3 and B.2.2.3). For PFS there is a notably poor fit of all models to the tails of the observed Kaplan-Meier curves, with no model capturing the small plateau observed in the trials.

In contrast, the base-case extrapolations capture the small survival plateau and are consistent with real-world evidence. Therefore, Scenario 2 is presented as supportive evidence only, with the more informative primary analyses based on evidence from SPOTLIGHT, GLOW and CheckMate 649.

B 8. Priority question: It is unclear whether the guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses was followed. Please provide, for OS, PFS and duration of treatment (DoT) separately for zolbetuximab + chemotherapy, nivolumab + chemotherapy and chemotherapy alone:

a) Tables with the numbers of patients at risk, per 3 months.

See Addendum Sections B.2.1 and B.2.2.

b) To examine the proportional hazard assumption:

i. Plot the scaled Schoenfeld residuals versus time (all survival curves)

ii. Plot the log cumulative hazard versus log time

For the base case analysis, as survival models were only fit to the chemotherapy group, it was not necessary to test the proportional hazards assumption. For scenarios that use parametric models fit to the pooled SPOTLIGHT and GLOW trials, these diagnostic plots are provided in the Addendum Sections B.2.1.3 and B.2.2.3.

c) To examine the heuristics of the hazard function over time:

i. Plot the smoothed hazards over time

See Addendum Sections B.2.1, B.2.2, and B.2.3.

d) To examine diagnostics of parametric survival models (using the observed data):

ii. Plot the cumulative hazard versus time

iii. Plot the log smoothed hazard versus time

iv. Plot the standard normal quartiles versus log time

v. Plot the log survival odds versus log time

Due to time constraints in responding to the clarification questions, not all of these plots could be generated. Where available, these plots are provided in the Addendum Sections B.2.1, B.2.2, and B.2.3.

e) Please show the results of fitting treatment-dependent survival models or justify why this approach was deemed inappropriate.

This is discussed in the response to B9.

f) To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant external data and/or expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.

The base case approach to extrapolation includes relevant external data in the form of chemotherapy outcomes from CheckMate 649. Additional relevant external data is presented and discussed in Section B.3.3.1.1.1. *Supportive evidence on survival outcomes of chemotherapy from real-world studies* of the company submission. Some of these studies were subsequently used for comparison with the base-case extrapolations in Section B.3.13.2."*Validation of survival extrapolations for chemotherapy*" in the company submission. The external evidence suggests that there is a small proportion of patients with long-term survival, which is reflected in the base-case extrapolations.

g) Please justify the selection of the approaches to estimate and extrapolate OS, PFS, and DoT, taking into account the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.

This is discussed in the response to B9.

h) As suggested in NICE DSU TSD 14, please provide "substantial justification" in case different types of parametric models are used for different treatment arms.

This is discussed in the response to B9.

B 9. Priority question: As per NICE DSU TSD 14, exponential, Weibull, Gompertz, log-logistic, log normal and Generalised Gamma parametric models should first be considered when performing survival analysis modelling. Please assess the suitability of said distributions by providing the following information:

a) Please show each parametric survival model on the Kaplan Meier curves for OS, PFS and DoT including the extrapolations over a 15+ year time horizon.

See Addendum Sections B.2.1, B.2.2, and B.2.3. Note that, to aid interpretation, extrapolations are sometimes shown for shorter time horizons (particularly when they are near-identical after a certain time point). In the base-case, the survival

extrapolations for zolbetuximab + chemotherapy and nivolumab + chemotherapy (for patients with PD-L1 CPS ≥ 5) are based on the spline-based NMA applied to the spline extrapolation of the chemotherapy arm rather than being based on parametric extrapolations. For completeness, parametric extrapolations and statistical goodness of fit are also provided for the analysis using pooled SPOTLIGHT and GLOW data for both zolbetuximab + chemotherapy and chemotherapy.

b) Please fill in the following table with the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) for each of the distributions.

Fitted function		Zolbetuximab + chemotherapy		Statistical rank	Nivolumab + chemotherapy		Statistical rank	Chemotherapy alone		Statistical rank
		AIC	BIC		AIC	BIC		AIC	BIC	
OS	Log-logistic									
	Generalized gamma									
	Log-normal									
	Gamma									
	Weibull									
	Gompertz									
	Exponential									
PFS	Log-logistic									
	Generalized gamma									
	Log-normal									
	Gamma									
	Weibull									
	Gompertz									
	Exponential									

DoT	Log-logistic									
	Generalized gamma									
	Log-normal									
	Gamma									
	Weibull									
	Gompertz									
	Exponential									

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, Duration of Treatment; OS, Overall survival; PFS, Progression-free survival.

See Addendum Sections B.2.1, B.2.2, and B.2.3. These sections include statistical goodness of fit values for spline models as well as parametric models, to aid in comparisons.

c) To assess the clinical plausibility of the distributions, please fill in the following table for the distributions:

	Distribution 1	Distribution 2	Distribution 3	Distribution …	Trial data	Experts' opinion
OS median						
OS 3 years						
OS 5 years						
OS 10 years						
PFS median						
PFS 3 years						
PFS 5 years						
DoT 3 years						
DoT 5 years						

Given the time constraints, and due to the large number of survival models considered (including spline-based models), along with combinations of these across OS, PFS, and DoT, it was not feasible to fill in the table for all possible models. The requested information is reported in Table 10 for the five combinations of models that are considered to provide the most informative evidence. This is provided for the chemotherapy arm, as for the zolbetuximab + chemotherapy arm there is no natural trial data to which to compare the majority of extrapolations (which are derived by applying relative treatment effects to the chemotherapy survival outcomes, which for OS and PFS are derived from pooled SPOTLIGHT, GLOW and CheckMate 649 data). The results suggest close agreement between the modelled and observed outcomes. They also demonstrate that there is little variation in the spline-based estimates of OS and PFS between the best-fitting and second-best fitting models, which is a benefit of the spline-based approach to modelling.

Table 10: Modelled and observed outcomes: chemotherapy

	Base case	Chemotherapy - Next best fitting spline extrapolation OS: 3-knot odds & PFS: 3-knot normal)	Chemotherapy- Parametric function (pooled chemotherapy) OS & PFS: Log-logistic (Best-fitting)	Trial data (pooled chemotherapy trials: SPOTLIGHT, GLOW, CheckMate-649)	Chemotherapy- Parametric function (pooled SPOTLIGHT / GLOW) OS & PFS: Log-logistic	Chemotherapy- Parametric function (pooled SPOTLIGHT / GLOW): PFS – Log-logistic & OS – Gamma (Best-fitting)	Trial data (pooled SPOTLIGHT / GLOW)
OS median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Max follow-up of 50 months
OS 10 years	[redacted]	[redacted]	[redacted]	Max follow-up of 68 months	[redacted]	[redacted]	Max follow-up of 50 months
PFS median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Max follow-up of 46 months
DoT 3 years	[redacted]	[redacted]	[redacted]	Not available	[redacted]	[redacted]	Not available
DoT 5 years	[redacted]	[redacted]	[redacted]	Not available	[redacted]	[redacted]	Not available

Additional information to support the chosen approach to survival modelling is provided in the Addendum. Due to time constraints in responding to clarification questions, not all of the requested information could be obtained.

As detailed in the response to B7, it is most appropriate to use evidence from SPOTLIGHT, GLOW and CheckMate 649 to inform survival modelling for chemotherapy. With this approach, to preserve randomisation, it is most appropriate to model outcomes for zolbetuximab + chemotherapy as relative effects, with these estimates coming from the time-varying spline-based NMA to account for a potential violation of the proportional hazards assumption. As per sections B.2.1 and B.2.2 of the Addendum, both spline-based modelling and the log-logistic survival model provide a good fit to the observed pooled chemotherapy data, and the extrapolations aligned with the real world-evidence. Similarly, the results of the time-varying spline-based NMA provide a good fit to the observed survival data. Use of a spline-based model for both the absolute and relative clinical outcomes also has the advantage of consistency in statistical methods.

For the exploratory scenarios that use effectiveness evidence from SPOTLIGHT and GLOW alone, visual inspection of the diagnostic plots (Schoenfeld residuals and log-log cumulative hazards) suggest that the assumption of proportional hazards is violated for the observed data. It is important to also consider the plausibility of assuming proportional hazards in the long-term. Guidance from the Canadian Agency for Drugs and Technologies in Health (CADTH) is that "*The assumption of proportional hazards is unlikely to hold long term in most cases*".[30] Extrapolating a fixed treatment effect beyond the range of the observed data can lead to biased estimates of survival.[31] In addition, NICE TSD 14 states that:

> "*Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm, or to allow for time-varying hazard ratios.*"[32]

For all of these reasons, neither proportional hazards models nor accelerated failure time models were considered, with time-varying hazard ratios used in the base case, and separately fit parametric models used in scenarios.

As the scenarios using effectiveness evidence from SPOTLIGHT and GLOW alone are exploratory, they use the best-fitting models for each treatment. For OS this leads to different survival models (log-logistic for zolbetuximab + chemotherapy, gamma for chemotherapy). Plots of observed vs modelled survival (provided in the Addendum) illustrate that if the same parametric model were used for both treatments the visual fit would be very poor when using either gamma for zolbetuximab + chemotherapy or log-logistic for chemotherapy.

B 10. Priority question: A three internal knots spline model is used to estimate and extrapolate zolbetuximab + chemotherapy, nivolumab + chemotherapy and chemotherapy alone.

As detailed in response to B7, for the base case approach of using SPOTLIGHT, GLOW and CheckMate 649 to model chemotherapy outcomes, relative treatment effects should be used to model zolbetuximab + chemotherapy (and nivolumab + chemotherapy, as it is assumed that its relative effectiveness is equivalent to zolbetuximab + chemotherapy). Hence the response to this question focuses on the modelling of chemotherapy. Duration of treatment curves were only extrapolated with standard parametric models (and not with spline-based models), given that over [redacted]% of patients had discontinued treatment at the presented datacuts, and the best-fitting standard parametric models had reasonable fit to the observed data.

For each specific sub-question responses are provided, as well as over-arching responses at the end.

a) **Please provide further evidence (using the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14) and expert opinion that standard parametric survival models are not appropriate to estimate and extrapolate zolbetuximab + chemotherapy, nivolumab + chemotherapy and chemotherapy alone.**

For the use of standard parametric models, please see responses to B8 and B9. In summary, for the chemotherapy arm, the log-logistic is the only model to provide an acceptable within-sample fit to OS and to PFS when using pooled SPOTLIGHT, GLOW and CheckMate 649 data, therefore the log-logistic model is suitable for estimation and extrapolation. However, spline-based models perform better than the log-logistic model (as detailed below). Hence, for the base-case spline-based models are used, with the log-logistic model considered in scenario analyses.

b) Please show each spline-based model (including the locations of the knots) on the Kaplan Meier curves for OS, PFS and DoT including the extrapolations over a 15+ year time horizon.

c) Please clarify for the estimated spline-based models how many patients were at risk (per treatment) after the specified knot locations.

b) and c) Neither NICE DSU TSD 14 nor 21 provide guidance on the location of knots. Instead published guidance from international experts in extrapolation and technology appraisal was followed, which is to "*place the knots uniformly along the distribution of uncensored log event times, with boundary knots placed at the minimum and maximum*".[33] Information on the log-times of these placements is provided in the submitted model (sheet 'Raw_splines' columns G and T). For PFS, internal knots are at [redacted], [redacted] and [redacted] weeks, with [redacted], [redacted] and [redacted] patients at risk at these times, respectively. For OS, internal knots are at [redacted], [redacted] and [redacted] weeks, with [redacted], [redacted] and [redacted] patients at risk at these times, respectively.

d) Please justify, also based on the responses to the previous question, the use of the three internal knots spline model, i.e. why specifically 3 knots and why at these specific locations?

The best-fitting spline models, which had 3 knots for both OS and PFS, also provided extrapolations consistent with real-world evidence, so these were used. See responses to sub-questions above and below for further details.

e) When extrapolating based on spline-based models, this is based completely on the linearity assumption (on a transformed scale of the survival function), which may result in implausible projections. Please

justify that the linearity assumption is plausible for extrapolating (technically beyond the last placed knot).

Whilst spline-based models require an assumption of linearity (on a given scale) after the last knot, this is arguably a less restrictive assumption than most standard parametric models which make an assumption of linearity (on a given scale) for the entire time period.[34]

f) To examine the validity of the extrapolation beyond the data, please provide supporting evidence that the extrapolations are consistent with relevant expert opinion. Please provide a full description of the methods and results of the expert consultation conducted.

Long-term external evidence from CheckMate 649 has been formally incorporated in the extrapolations, which are compared to long-term outcomes from real world studies (see company submission Document B Section B.3.3.1.1.1). The expectation of a small proportion of long-term survivors with chemotherapy is consistent with the feedback of clinical experts to the NICE committee for TA857.[8] Additionally, survival estimates are capped in the cost-effectiveness model by general population mortality.

Experts were consulted for their feedback on the survival extrapolations for the pooled chemotherapy arm (2 clinicians and 1 health economist).[35] The clinicians considered the observed survival to be broadly aligned to clinical practice but estimates of long-term survivorship with chemotherapy to be optimistic compared to clinical practice, potentially due to differences in patients' characteristics between clinical practice and trials, and clinical management across countries (e.g., trials tend to recruit younger and fitter patients than the clinical practice population; Asian countries tend to use more subsequent therapies).

This evidence was considered alongside the conclusions from TA857, which concluded CheckMate 649 generalisable to UK clinical practice, the expert opinion at the committee meeting where the expectation was of 4% long-term survivorship with chemotherapy, and the real-world evidence on long-term survivorship. Collectively, the evidence suggests a complex survival curve, with a small proportion of long-term

survivors, although there is uncertainty about the magnitude of survivorship in UK clinical practice.

g) To assess the clinical plausibility of the spline-based models, please fill in the following table for the most plausible spline-based models:

	Spline-based model 1	Spline-based model 2	Spline-based model 3	Spline based model ...	Trial data	Experts' opinion
OS median						
OS 3 years						
OS 5 years						
OS 10 years						
PFS median						
PFS 3 years						
PFS 5 years						
DoT 3 years						
DoT 5 years						

Please see the response to B9.

h) Spline-based models are known for their risk of overfitting to short-term data, while predictive accuracy in the extrapolation period is decreased. Please elaborate on the measures taken to ensure predictive accuracy is maintained, e.g. cross-validation.

Several studies have been performed that assess the extrapolation performance of spline-based models; these have not identified any issues with over-fitting, and conversely have shown that the additional flexibility of spline-based models may be required.[36-40] Use of spline-based models along with supportive external evidence follows best practice modelling of complex hazard functions, including NICE DSU TSD 21.[33, 41] To ensure predictive accuracy, the predicted hazard rates were compared to the empirical hazard rates and the survival extrapolations were compared to external real-world data.

i) **Please justify the use of the spline-based models given the responses to the preceding (sub-)questions.**

Additional details to support the approach to modelling chemotherapy OS and PFS is provided in the Addendum, Sections B.2.1 and B.2.2 (extrapolations are visualised for up to 10 years as beyond this time estimates are very similar and use of 10 years allows for easier comparisons against the observed outcomes). This includes both parametric survival models and spline-based models. This additional evidence suggests that spline-based models provide superior within-sample goodness of fit, whilst also producing extrapolations aligned with the real-world evidence. Of the standard parametric survival models, only the log-logistic model captures the observed turning point in the hazard function as well as having good within-sample fit. Hence it is appropriate to model OS and PFS using either spline-based models or the log-logistic model. For consistency with the company submission, spline-based models are retained in the base case, with use of the log-logistic model explored in a scenario.

To summarise, spline-based models provide a better within-sample fit than standard parametric survival models, whilst also resulting in plausible extrapolations with no indication of over-fitting. Use of a spline-based model to extrapolate chemotherapy OS and PFS is also consistent with the use of spline-based models to estimate the time-varying relative effectiveness of zolbetuximab + chemotherapy. Use of the best fitting parametric survival model (log-logistic model) was assessed in a scenario analysis, with very similar cost-effectiveness results (see Addendum, scenario 4; the ICER decreased by 3.6%).

B 11. Priority question: In the CS base-case no treatment effect waning was assumed, i.e. the PFS and OS hazard rates were assumed to be different for zolbetuximab and the chemotherapy for the whole duration of the time horizon.

a) **Please justify the assumption of no treatment effect waning, i.e. that there is a lifetime difference in PFS and OS hazard rates based on the initial treatment.**

b) **Please provide an updated economic model and scenario analyses while assuming treatment effect waning (at different time points).**

Treatment waning was not included for zolbetuximab + chemotherapy as there is no time-based stopping rule for zolbetuximab and no evidence to suppose that the observed treatment benefit would reduce over time. This is reflected in the observed data, with near-constant empirical hazard ratios observed for zolbetuximab + chemotherapy in comparison to chemotherapy (results provided in Addendum B.1.3).

Scenario analyses have now been conducted to explore the impact of assuming waning of the treatment effect of zolbetuximab + chemotherapy similar to the approach taken for TA857. However, TA857 assessed nivolumab, which has a stopping rule at two years, whereas zolbetuximab does not have a time-based stopping rule.

The scenarios with treatment effect waning are implemented by assuming that the risk of death of patients treated with zolbetuximab + chemotherapy after a given time point is the same as if patients had been treated with chemotherapy alone (i.e., the hazard rates of the chemotherapy arm are used to inform the hazard rates of the zolbetuximab + chemotherapy arm). Three time points were explored at which zolbetuximab + chemotherapy is assumed to no longer affect survival, specifically at 5, 6, and 7 years given the precedent of TA857 and ID4030 where time points between 5 and 7 years were used.

At these time-points the modelled proportion of patients alive for zolbetuximab + chemotherapy was [redacted]%, [redacted]% and [redacted]%, respectively. Results are provided in the Addendum, and demonstrate a moderate impact on the ICER, with values ranging from £[redacted] to £[redacted] (using the confidential discount for zolbetuximab).

B 12. Priority question: Duration of treatment (DoT) for all arms was estimated using PFS data from the GLOW study only.

a) **Please elaborate on the methods used for the determination of the DoT curves.**

b) **Please justify the assumption that GLOW PFS is representative for DoT. Could patients discontinue earlier or later than they experienced disease progression? How is this reflected in the DoT curve?**

c) **Please justify that GLOW PFS is representative for DoT in the chemotherapy arm.**

d) **Please provide Kaplan-Meier curves for zolbetuximab + chemotherapy and chemotherapy where patients are censored at the time of treatment discontinuation. Please use weighted pooling of the two chemotherapy regimens reflective of UK clinical practice.**

e) **Please follow NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses to extrapolate the time to treatment discontinuation Kaplan-Meier curves, if not yet mature.**

f) **Please provide a scenario analysis using these time to treatment discontinuation curves in the economic model.**

Following the clarification meeting with the EAG and NICE, the EAG clarified that this request is for Kaplan-Meier curves for time to treatment discontinuation (i.e., duration of treatment) where patients who progressed are not assumed to have discontinued treatment. The company confirms that the requested analysis consists of the analysis that was originally provided, as the Kaplan-Meier curves for time to treatment discontinuation do not consider progression; i.e., progression is not a discontinuation event nor a censoring event.

The date of treatment discontinuation was defined as per the data collected in the eCRF in the fields “Date discontinued the zolbetuximab treatment period”, “Date completed or discontinued the treatment period for last component of mFOLFOX6” [(for SPOTLIGHT) or CAPOX (for GLOW)].

For the analysis, patients were censored if treatment discontinuation occurred due to death (censoring date = date of death), patients were lost to follow-up (censoring date = date of loss to follow-up), and if patients were alive but had not yet experienced treatment discontinuation at the analysis cut-off date (censoring date = analysis cut-off date).

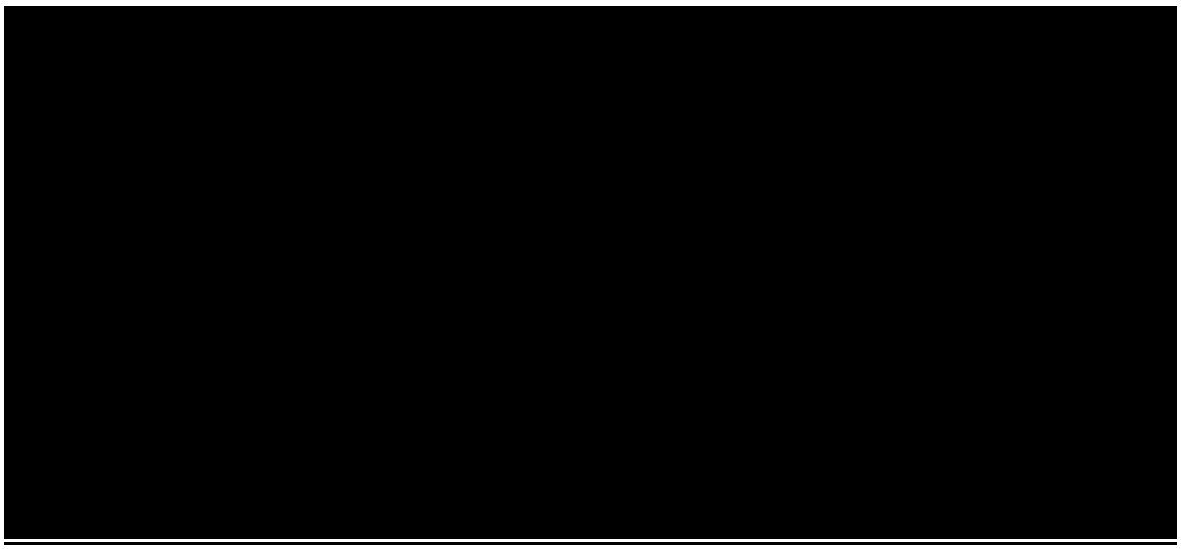
As described in the company submission Section B.3.3.1 and further elaborated on in the response to clarification questions B7, B8, B9 and B10, the base-case survival analysis for chemotherapy uses pooled evidence from SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup for both OS and PFS. Outcomes for zolbetuximab + chemotherapy are obtained by applying time-varying relative treatment effects (from the spline-based NMA) to these chemotherapy outcomes.

For consistency, ideally evidence on duration of treatment would also be obtained from a pooled analysis of SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup (as this was the data used for OS and PFS). However, as described in the company submission, this evidence was not available for CheckMate 649 PD-L1 CPS ≥ 5 subgroup. Hence an alternative approach was required, which would be applicable to DoT for chemotherapy, zolbetuximab + chemotherapy, nivolumab + chemotherapy and pembrolizumab + chemotherapy. Following published best-practice for survival modelling, in particular both TSD 14 and 21, the use of external evidence was considered to help inform the approach to survival modelling. In particular, as noted in the company submission (Section B.3.3.1.3), it is assumed that there is an association between DoT and PFS given that zolbetuximab treatment should be discontinued upon progression. Because of this, PFS evidence (which may be viewed as external to DoT as it is for a different outcome) was considered. The first step was to consider, based on the available PFS evidence, if chemotherapy outcomes from either SPOTLIGHT or GLOW (for which DoT outcomes are available) could be used to approximate the outcomes from the pooled SPOTLIGHT, GLOW and CheckMate 649 data.

The results of this comparison are provided in Figure 4. The graph suggests that the use of FOLFOX (SPOTLIGHT) PFS would be a poor representation of the pooled

PFS, but use of CAPOX (GLOW) PFS would provide a good approximation. This is particularly true for the first 40 weeks of follow-up, after which the number of patients still on treatment will be reduced (and hence any discrepancies less important). Hence because CAPOX (GLOW) PFS can be used to approximate the pooled PFS in the earlier time periods, it was assumed that CAPOX (GLOW) DoT could be used to approximate the pooled DoT. For consistency with this approach, estimates of DoT for zolbetuximab + chemotherapy, nivolumab + chemotherapy and pembrolizumab + chemotherapy are all obtained via relative effects. This is because any discrepancies between the modelled chemotherapy DoT and the pooled DoT would also apply to the other interventions, and so with regards to incremental outcomes the impact is expected to be minor. Due to the lack of relative treatment effects for DoT, it was assumed that relative treatment effects for PFS could be used (i.e., the relative effectiveness for PFS is assumed generalisable to DoT).

Figure 4:Comparison of observed progression free survival values



The Addendum also now includes an additional scenario that explores the use of GLOW for both chemotherapy and for zolbetuximab + chemotherapy. For this scenario, DoT for nivolumab + chemotherapy and pembrolizumab + chemotherapy are also assumed to be the same as that for zolbetuximab + chemotherapy. Cost-effectiveness results for this scenario are very similar to the base case, with a slight decrease in the ICER for zolbetuximab + chemotherapy compared to chemotherapy.

When using DoT evidence from GLOW, good practice guidance was followed. Supportive plots and tables are provided in the Addendum Section B.2.3.2. In particular, diagnostic plots indicated that it would be inappropriate to fit dependent models. For example, the log-log cumulative hazard plots showed convergence and there was a trend in the Schoenfeld residuals. Visual estimates of DoT demonstrated that the models with the best internal fit also provided plausible extrapolations; for example there were no unrealistically long or unrealistically short extrapolations. Hence the best-fitting model was used.

Adverse events

B 13. Duration of AEs was derived from Shah et al. (2022), which reports on a different patient population than the population in this appraisal. Please provide the average duration of AEs from the SPOTLIGHT and/or GLOW trials and a scenario analysis applying these AE durations in the economic model.

It was not possible to conduct this analysis within the timelines of the clarification questions. This is because the trial data on AE durations has not been prepared for analysis, given that it was not needed for regulatory or publication purposes. It is noted that duration of AEs has a negligible impact on the cost-effectiveness results as shown by the deterministic scenario analysis.

Quality of life

B 14. Priority question: In the SPOTLIGHT and GLOW trials, EQ-5D-5L was used to measure patients' health related quality of life. The health state utilities used in the model were derived from the pooled EQ-5D values from both trials.

a) **Treatment independent utility values were used in the economic model. Please provide the utility values for the zolbetuximab + chemotherapy and chemotherapy arms separately using both methods (GLM and GEE) incorporated as scenario analyses in the model.**

b) **Please also provide the utility values for FOLFOX and CAPOX arms separately using both methods (GLM and GEE).**

In the current model, treatment independent health state utilities were used, along with treatment specific AE disutilities. To respond to this question, treatment dependent utility values have now been estimated using both GEE and mixed effects models, using the final data from the SPOTLIGHT trial (data cut-off on 8 September 2023)[10] and final data from the GLOW trial (data cut-off on [redacted]).[11]

The original models have health states as the independent variables to estimate utilities. These new models use health states, treatments, and interactions between health states and treatment to estimate treatment specific utilities. The results from these new models show that neither effects of treatments (on utility) nor the interactions between treatments and health state are significant. Additionally, the direction of the effect is inconsistent across analyses. Please see Table 11 to Table 13 below summarizing all the results. Given the effects of treatments on utility and interactions between treatments and health states are not significant, and the inconsistency in the direction of effect, treatment independent health states utilities should be used in the cost-effectiveness analysis. Furthermore, using treatment-independent utilities avoids double counting the impact of adverse events, which is captured separately in the model. This approach is also consistent with the NICE appraisals TA857[42] and ID4030[27], neither of which models treatment-specific utility values.

Table 11 EQ-5D-5L utilities based on regression analysis (SPOTLIGHT and GLOW)

	Health State Utility (GEE), independent				Health State Utility (GEE), exchangeable				Health State Utility (mixed effects model)				Health State Utility (descriptive)			
	Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Pooled	[redacted]															
Zolbe+chemo	[redacted]															
Chemo	[redacted]															
P-value (treatment)	[redacted]															
P-value (health state*treatment)	[redacted]															

Table 12 EQ-5D-5L utilities based on regression analysis (SPOTLIGHT)

	Health State Utility (GEE), independent				Health State Utility (GEE), exchangeable				Health State Utility (mixed effects model)				Health State Utility (descriptive)			
	Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Pooled	[redacted]															
Zolbe+chemo	[redacted]															
Chemo	[redacted]															
P-value (treatment)	[redacted]															
P-value (health state*treatment)	[redacted]															

Table 13 EQ-5D-5L utilities based on regression analysis (GLOW)

	Health State Utility (GEE), independent				Health State Utility (GEE), exchangeable				Health State Utility (mixed effects model)				Health State Utility (descriptive)			
	Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression		Pre-progression		Post-progression	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Pooled	[redacted]															
Zolbe+chemo	[redacted]															
Chemo	[redacted]															
P-value (treatment)	[redacted]															
P-value (health state*treatment)	[redacted]															

c) **On page 123, when explaining the EQ-5D measures considered for the post progression state, it is stated that: "For patients who were censored for PFS, EQ-5D assessments occurring after the censor date were excluded from the analysis". However, this would mean that patients that have experienced disease progression (i.e., patients in the post progression state in the trial) are excluded. Please elaborate on why these data were excluded and provide an updated model including them.**

The EQ-5D measures collected after the censoring date of PFS among patients without progression or death event were excluded because, after the censoring date, it is unknown whether a patient has progressed or not. If a patient has progressed, their post-progression utilities values collected before their date of death were included in analyses. For this reason, an updated model is not provided.

B 15. Priority question: A generalised estimating equation (GEE) model was developed to estimate the trials' utility scores. Other commonly used methods are the generalized linear model (GLM) and the generalized linear mixed model (GLMM). The company provided a scenario analysis using a pooled mixed effects model, which resulted in slightly lower utility values than the base-case for both pre-progression (GEE: [redacted], mixed-effects: [redacted]) and post-progression (GEE:[redacted], mixed-effects: [redacted]). The company justified the bigger difference in the post-progression ([redacted]) as compared to the pre-progression state ([redacted]) due to the fewer observations during post-progression (11,030 vs 1,149) and claimed that these were "inherently more uncertain". However, these differences could be due to the different models used and reflect some methodological uncertainty.

a) **Please discuss the reasons for choosing the GEE over GLM or GLMM for the base-case.**

b) **Please elaborate on the implications the different methods would have on the final utility values.**

Response to questions a) and b):

As the differences could be due to different assumptions underlying each model, please see detailed results from two types of GEE models explored and the mixed effect model using the final trial data for both SPOTLIGHT and GLOW in response to question B14 b).

The GEE model is a marginal or population-average model that provides the population-averaged estimates of the parameters. Conceptually, the GEE model was equivalent to taking the average of the patients' utility scores as long as these were collected in the same health state. As a result, GEE estimates were almost identical to descriptive analyses results especially when an independent working matrix is used. The response to question B14 b) includes results from two GEE models using different working correlation structure, one with independent working correlation structure and the other one with exchangeable working correlation. The former assumed no correlation among observations from the same subject, while the latter model assumed a constant correlation.

The mixed effects model used in this analysis is the same as GLMM, accounting for correlations. A mixed effects model is a subject specific model, where both population-averaged estimates and subject specific random effects are of interest. The model is a likelihood-based parametric model, and a Gaussian distribution was assumed for the outcome. Both random intercepts and slopes were considered in the analysis. The patient effects were included as random effects to account for unobserved, patient's specific characteristics and multiple observations per patient. The population-averaged estimates are the average of individual subject results.

All these models have underlying assumptions, thus multiple approaches were explored. The ICER results are robust to these different utility sets, as shown in the scenario results (updated results provided in Addendum).

The rationale for choosing the GEE model is two-fold. First, it is more comparable to the descriptive results. The estimates from GEE can be considered as conservative given that the difference between pre-progression utility and post-progression utility was smaller with GEE approach (difference of [redacted]) than the mixed effect model (difference of [redacted]). Secondly, as noted in the company submission (Document B Section B.3.4.5) as a marginal model it directly estimates cohort-level utilities, which aligns with the use of a cohort-level cost-effectiveness model.

c) **The utility of the general population of this age group (male: 0.809, female: 0.791, average for the modelled population: 0.802) is lower than the average of the pre-progressed population, based on the GEE results ([redacted]). Please elaborate on the face-validity of this difference in utilities, especially given the significant low weight of the population considered in the appraisal in comparison with the general population.**

The population start age is 58.5 years. Based on the DSU report on EQ-5D by age and sex for the UK,[43] the utility values for this age group range from 0.8283 to 0.8568 (Table 14). The estimated utility value for PFS, at [redacted] was [redacted] than that of the general population, supporting its validity. Furthermore, the NICE health technology evaluation manual recommends using EQ-5D utilities reported by patients in a relevant study, as was conducted for this submission.[44]

Other submissions in similar indications also used utilities that appeared to be higher than expected given the general population utility, but which were subsequently considered by the NICE committee to be appropriate to inform decision making. In TA857, whilst the progression-free utility value is redacted, the EAG commented that the utility values used by the company were high; the NICE committee agreed that the company's utility values were appropriate for decision making.[8] The utility values used in ID4030 were also redacted. The EAG commented that the values were high compared to the utility of the general population, whilst the committee agreed with the company's approach at the draft guidance.[27]

Table 14 General population expected EQ-5D-3L

Age	Female	Male
58	0.8321	0.8568
59	0.8283	0.8538

B 16. Priority question: Health related quality of life data were collected in the SPOTLIGHT and GLOW trials. However, as per CS, no imputation was performed for missing evaluations. The assumption that data were missing at random is questionable.

a) **Please provide the pattern of missingness of EQ-5D data per arm for both trials.**

Based on data from SPOTLIGHT trial (data cut-off on 8 September 2023) and data from GLOW (data cut-off on [redacted]), at patient level, almost all patients have contributed to at least one EQ-5D level.

Only [redacted]% of patients in SPOTLIGHT and [redacted]% of patients in GLOW did not have any EQ-5D values. For the EQ-5D analysis, patients were further required to provide EQ-5D values after randomization and during the period with known status for progression (i.e. values after PFS censoring date are not considered – refer to question B12c). The number of patients who contributed to EQ-5D analysis were summarized in Table 15.

Table 15 Patient numbers from SPOTLIGHT and GLOW in EQ-5D analysis

	N randomized in trial	N with any EQ-5D measure	Missingness	N contributed to EQ-5D analysis*	Percent not contributing to utility analysis
SPOTLIGHT					
Zolbe+FOLFOX	283	[redacted]	[redacted]	[redacted]	[redacted]
FOLFOX	282	[redacted]	[redacted]	[redacted]	[redacted]
Total	**565**	[redacted]	[redacted]	[redacted]	[redacted]
GLOW					
Zolbe+CAPOX	254	[redacted]	[redacted]	[redacted]	[redacted]
CAPOX	253	[redacted]	[redacted]	[redacted]	[redacted]
Total	**507**	[redacted]	[redacted]	[redacted]	[redacted]

*Number of patients who have EQ-5D measures post-randomization and during the trial period who have contributed to either PFS or post-progression state utilities.

The proportion of patients who completed the EQ-5D questionnaire at each is summarized in Figure 5 for SPOTLIGHT and Figure 6 for GLOW for the patients who were still on treatment and in the PFS state. The average completeness is [redacted]% and [redacted]% in SPOTLIGHT and GLOW respectively. Given the design of the SPOTLIGHT and GLOW trials, after treatment discontinuation, a maximum of three EQ-5D values could be collected. As treatment discontinuation is highly correlated with progression, missing is not summarized for the post-progression period. Since the missingness at visit level was not considered substantial in either trial, imputation was not conducted. Furthermore, based on the publicly available information, imputation was not conducted by the submitting company or requested by the EAG for TA857 or ID4030.[8, 27]

Figure 5 Missing EQ-5D measures by visit (SPOTLIGHT)

Figure 6 Missing EQ-5D measures by visit (GLOW)

b) Based on the previous response, please justify the decision of not performing data imputation for missing evaluations and elaborate on the risk of bias introduced by it.

Missingness of EQ-5D values, as summarized previously, is not substantial in either SPOTLIGHT or GLOW. As any imputation approach will involve some assumptions and

there is no consensus in the literature on the best approach to be used for missing EQ-5D values, no imputation was conducted. Scenarios that assess the impact of alternative utility estimates (from SPOTLIGHT and GLOW using a different statistical model specification as well as from the literature) are already included as scenario analyses (with updated results included in the Addendum) and show that cost-effectiveness results are robust to these alternatives.

c) **Please perform data imputation for the missing EQ-5D data from the trials. Please provide an updated model and scenario analyses with the updated EQ-5D data.**

Please see previous responses. No imputation was done for EQ-5D given the missingness was small in SPOTLIGHT and GLOW.

B 17. After the SLR, three studies were deemed relevant to the UK context. For the studies with known utility values (i.e., TA191 (PFS: 0.73) and TA208 (Baseline:0.729, PFS:0.577)), utilities are lower than the ones used in the CS (Pre-progression: [redacted] and post-progression:[redacted]). Please comment on potential reasons for the different utility values based on the population characteristics.

A direct comparison of the progression-free utility value of 0.729 from TA208 (reported as 0.73 in TA191) is not appropriate as the latter is based on a model with a time-varying increase in utility. A more direct comparison is with the value of 0.797, which is from the same source but without the time-varying change (albeit this value is from the Japanese scoring algorithm which hampers its comparability); this value is much closer to the utility values observed in SPOTLIGHT and GLOW and is already tested in Scenario 14.

The value of 0.577 for progressed disease (from TA208) is sourced from a different study and is for patients who have progressed after second-line treatment, hence it is not directly comparable. Specifically, the utility value of 0.577 for progressive disease was based on the NICE appraisal of sunitinib, for the second line treatment of gastrointestinal stromal tumours (see EAG report p58).[45]

Intuitively, patients who have received more lines of treatment are likely to have worse health-related quality of life (i.e., utility) and health-related quality of life may not generalise across cancers. As previously noted, scenarios that assess the impact of alternative utility estimates (from SPOTLIGHT and GLOW using a different statistical model specification as

well as from the literature) are already included in the scenario analyses (with updated results included in the Addendum) and show that cost-effectiveness results are robust to these alternatives.

B 18. CS Table 28 summarises the disutilities associated with AEs in the economic model.

a) As per CS, disutility values were obtained from NICE TA857, NICE TA306, and Shah et al. (2022). However, NICE TA306 does not appear cited in any table or text. Please clarify which disutilities were derived from TA306.

NICE TA306 was referred to in error. Please disregard this. Table 28 of the company submission Document B has the correct references.

b) Disutilities for diarrhoea (-0.050), anaemia (-0.120), and neutropenia (-0.090), were derived from Shah et al. (2022). However, these were also included in TA857 (-0.0468, -0.115, and -0.897). Please justify this choice, given that Shah et al. (2022) was based on adults with relapsed/refractory B-Cell acute lymphoblastic leukaemia and TA857 for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Astellas believe the disutilities reported in Shah et al. 2022 for diarrhoea, anaemia, and neutropenia used the same underlying sources as those from TA857. Specifically, anaemia was derived from Swinburn et al. 2010, diarrhoea from Doyle et al. 2008 and neutropenia from Nafees et al. 2008. These same studies were cited in the Shah et al. 2022 publication (within which full references may be found). Any differences in values between TA857 and Shah et al. 2022 are likely to be due to rounding issues. Additionally, the company submission for ID4030 also used the same sources for adverse event disutilities as TA857.

c) The disutilities applied in TA857 were derived from multiple health state utility studies from different conditions (e.g., renal cancer, lung cancer, breast cancer). Please reflect on the appropriateness of the disutilities for the case of G/GEJC.

It is correct that the disutilities applied in TA857 were from different disease conditions and the company current submission has the same limitation. The underlying assumption is that the disutility of an adverse event is mainly driven by the event itself, instead of the primary disease, therefore the disutilities are assumed to be generalisable. Given this

rationale, and the minor impact of varying utilities in the ICER (in the deterministic sensitivity analysis), this approach is considered to be appropriate.

Costs and resource use

B 19. Post-progression treatment costs were applied as a lump sum costs at the point of progression. Post-progression therapy was based on taxane monotherapy, equally split between docetaxel and paclitaxel, irrespective of first-line treatment.

a) Please justify the assumption of equally splitting docetaxel and paclitaxel. Please refer to published literature and/or clinical expert opinion to support your arguments.

The assumption of equal splitting between docetaxel and paclitaxel was the same as that used in TA857,[8] and accepted by the NICE committee as appropriate for decision making. In ID4030,[27] the company informed the post-progression therapies based on expert clinical advice, as discussed in response to question B6. The sensitivity of cost-effectiveness results to these alternative costs was tested in sensitivity analyses (see response to below sub-question). The results suggest that, if the post-progression costs are higher and more aligned to what was used in ID4030, the base case approach may underestimate the cost-effectiveness of zolbetuximab + chemotherapy, as the base-case ICER is higher than the ICERs in these scenarios.

b) As the duration of post progression survival is shorter for zolbetuximab than for chemotherapy, subsequent treatment costs should not have a major impact on the ICER. Please include a scenario analysis setting subsequent treatment costs to £0 and discuss the results.

Results from this scenario have been included in the updated economic model and addendum, demonstrating a minimal impact (ICER increases by 2.8%). However, the assumption of £0 for subsequent treatment costs is not realistic since some patients who progress receive subsequent therapies. A plausible alternative is to use a cost of either £16,779, or £35,203 as discussed in response to B6. Using these values in the economic model (by changing cells G74, G75 on sheet 'Post-Prog Trt Cost') results in lower ICERs of [redacted] and [redacted], respectively, using the confidential discount for zolbetuximab.

B 20. Drug acquisition costs per administration were calculated as a function of dosage, unit drug cost, relative dose intensity (RDI), and wastage.

a) Lack of vial sharing between patients was only explored in a scenario analysis. Please explain the rationale for including vial sharing in the base case and refer to available literature or clinical expert opinion to support that this is possible in NHS clinical practice.

b) Please modify the base case to not include vial sharing.

The decision to assume full vial-sharing follows the approach used in TA737 (pembrolizumab) during which clinical experts confirmed that vial sharing is routine in clinical practice and it is encouraged for expensive chemotherapies.[26] This is reflected by the use of national dose banding tables for chemotherapies and other systemic cancer drugs such as nivolumab and pembrolizumab.[46] As such it is not considered appropriate to include wastage (i.e., no vial sharing) in the base case. A scenario that assumed vial sharing was included in the company submission. The results with the updated economic model are provided in the addendum and show a minor impact on estimates of cost-effectiveness (ICER increase of 3.1%)

c) As relative dose intensity (RDI) was not available for the nivolumab arm, a RDI of 100% was assumed by the company. Please elaborate on the face-validity of this assumption. Please provide an updated scenario analysis with the same RDIs for nivolumab and zolbetuximab.

The company was not able to identify an appropriate value for nivolumab RDI, therefore as a simplifying assumption 100% was applied in the cost-effectiveness analysis. In the submitted economic model for each component of zolbetuximab + chemotherapy an RDI of between [redacted]% and [redacted]% was applied based on evidence from SPOTLIGHT and GLOW. In the updated analysis provided in the Addendum these values were updated but remained consistent with the earlier range.

Given the different safety profiles of nivolumab and zolbetuximab, it is unlikely that the RDI generalises from zolbetuximab to nivolumab. To explore the impact of this assumption, a scenario testing the impact of using zolbetuximab RDI for nivolumab was included, which demonstrated a minimal change in the ICER (see Addendum B.2.7.3).

B 21. In the economic model, dosing regimen was based on body surface area (BSA). The base-case average BSA was 1.70m2, which differs from TA857 (BSA= 1.76m2).

a) Please provide data on the average weight and height of the GLOW and SPOTLIGHT trials.

Table 16 provides the average weight, height and body surface area (BSA) of patients in the SPOTLIGHT and GLOW trials.

Table 16 Patient demographic characteristics from SPOTLIGHT and GLOW

	SPOTLIGHT	GLOW
Mean weight, kg (sd)	[redacted]	[redacted]
Mean height, cm (sd)	[redacted]	[redacted]
Mean BSA, m2 (sd)	[redacted]	[redacted]

b) Please provide the average weight and height of UK patients in the GLOW and SPOTLIGHT trials

Table 17 provides the average weight, height and BSA of UK patients in the SPOTLIGHT and GLOW trials.

Table 17: Patient demographic characteristics from SPOTLIGHT and GLOW (UK patients)

	SPOTLIGHT (n = 34)	GLOW (n = 10)
Mean weight, kg (sd)	[redacted]	[redacted]
Mean height, cm (sd)	[redacted]	[redacted]
Mean BSA, m2 (sd)	[redacted]	[redacted]

c) Please clarify whether the BSA used and the BSA of the UK patients in the trials is reflective of the UK patient population.

d) If BSA used is not reflective for the UK patient population, please provide a scenario analysis using a BSA reflective of the UK patient population.

The BSA used in the model, at 1.70m^2 based on the pooled SPOTLIGHT and GLOW data, is likely to be broadly generalisable to the UK population. This is based on the evidence provided in the company's submission for ID4030 that "a large cancer centre in London" reported that BSA (Du Bois Method): mean, 1.73m^2; median, 1.74m^2; IQR, 1.57 – 1.84m^2 (see committee papers p276) and the BSA of KEYNOTE-859 and CheckMate 649, which were used to inform ID4030 and TA857 respectively.[8, 27]

The BSA in the KEYNOTE-859 trial, used to inform ID4030 (pembrolizumab), was also 1.70m^2 and this was accepted by the EAG.[27] The BSA in CheckMate 649, used to inform TA857 (nivolumab), was 1.77m^2. This is in line with the European patients of SPOTLIGHT and GLOW at [redacted]m^2 and [redacted]m^2 respectively, although still above the BSA in the trials overall, the evidence from the London cancer centre, and KEYNOTE-859.

BSA has a minor impact on the ICER. In the scenario using a mean BSA of 1.73m^2, the ICER per QALY increased from £[redacted] (base case) to £[redacted] (increase of 1.2%; see Addendum). If a mean BSA of 1.77m^2 is used (changing cell E23 of 'Settings' sheet), the ICER per QALY increases by 3.0% to £[redacted].

B 22. A one-off terminal care costs of £5,131 was applied to patients who died at the end of each cycle, based on TA208. As stated in the CS, TA857, published in 2021, also based their calculation on TA208. However, TA857 used a value of £5,387 for the one-off terminal care costs. Please clarify why the inflated price for the terminal costs this submission than the one from 2021. Please updated the price for the respective inflation of 2023, if necessary

The one-off terminal care cost of £5,131 was based on the £4,000 cost used in TA208, inflated from 2010 to 2023.

It is unclear how the approach to calculate the inflated terminal care costs in TA857 differs from the approach taken here. In TA857 the company submission states: "*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 company submission*." Separately it is noted that "*Where required, costs were inflated to 2019-2020 costs using PSSRU indices*'. It is not clear from this which PSSRU inflation indices were applied in TA857 and therefore Astellas is unable to replicate this calculation to understand the difference.

Inflating the £5,387 cost used in TA857 from 2021 to 2023 results in £5,684. If this cost is used, the impact on the ICER per QALY is negligible (decreasing from £[redacted] in the base case to £[redacted]).

Terminal care costs in the economic model were inflated using the NHS Cost Inflation Index published in the PSSRU 2022.

B 23. The use of zolbetuximab is conditional on the presence of CLDN18.2; therefore, CLDN18.2 testing was included in the economic model, as patients with gastric or GEJ adenocarcinoma would not have been tested otherwise.

a) Patients treated with zolbetuximab are modelled to incur CLDN18.2 testing costs at model entry. In the model, it is assumed that patients will require an average of 2.4 tests to identify the CLDN18.2 positive expression, because 42.3% of patients in the SPOTLIGHT and GLOW trials were tested positive. Please explain in detail the reasoning for this assumption. Please elaborate on how this is representative of UK clinical practice, referring to published literature or clinical expert opinion if necessary.

The assumption of an average of 2.4 tests was calculated based on the proportion of patients screened for SPOTLIGHT and GLOW that tested positive for CLDN18.2-positive expression (≥ 75%, with moderate-to-strong staining). In the Europe and Middle East region, 671/1524 (44.0%) of patients screened were CLDN18.2-positive.[47] To identify the number of tests required to identify one patient with CLDN18.2 positive expression the following calculation was performed:

100 / 42.3 = 2.4

SPOTLIGHT and GLOW remain the best data sources for this assessment (based on total patient numbers and specifically UK patients). The assumption of 42.3% is also supported by the UK specific data, with [redacted] patients screened in SPOTLIGHT were CLDN18.2-positive, and [redacted] in GLOW. The CLDN18.2 prevalence across both trials is in line with the European and UK specific estimates and consistent with the other inputs into the model.

Evidence on the prevalence of CLDN18-2-positivity is limited. This is likely because zolbetuximab is expected to be the first licensed drug that targets this biomarker. Astellas is aware of five published real-world studies, although none in the UK (three in US, one in Italy and one in Japan), [48-52] that report CLDN18.2 prevalence using IHC and the 43-14A antibody (Roche Ventana; the same as was used in the trials and that Astellas expect to be used in clinical practice). However, there were no studies specific to the UK and the identified studies did not necessarily restrict patients by HER2-status. CLDN18.2 positivity varied between 23.5% (N=561 patients from surgically resected G\GEJ adenocarcinomas

at various stages) in a single US centre [49] to 44.4% (N=304 samples from a tissue biorepository in a single US centre). [53] On average, across these five studies, the proportion of patients who were CLDN18.2-positive was 31.8%. This is similar, albeit slightly smaller, to the proportion of CLDN18.2-positive patients irrespective of HER2 status in the trial. An overview of these evidence sources is provided in Table 18. Using a lower prevalence of 31.8% (achieved by changing cell C35 on sheet 'Raw_MedCost') had a negligible impact on results.

Table 18: Summary of studies assessing CLDN18.2 expression in gastric or gastro-oesophageal junction cancer

Study	Country	Design	Population	Gastric:GEJ	CLDN18.2+, n (%)*
Sewastjanow et al.[53]	US	A retrospective translational study analysed CLDN18.2 status in FFPE tissue samples from MD Anderson Cancer Center (US) FFPE tissue samples from a tissue biorepository, assessed by IHC using antibody clone 43-14A (Roche Ventana)	Patients with histologically confirmed G/GEJ adenocarcinoma, stages not confirmed (n=304)	177:127 (58%:42%)	Total: 135 (44.4%) Gastric: 51% GEJ: 35%
Kubota et al.[51]	Japan	Single institution in Japan All specimens were biopsy specimens collected from the primary tumours CLDN18.2 expression was assessed by IHC using Clone 43-14A (Roche Ventana) on FFPE tissue specimens	Patients with unresectable, locally advanced or metastatic GC/GEJC, who received systemic chemotherapy from October 2015 to December 2019 with archival tissue sample (n=408)	363:45 (89%:11%)	98 (24.0%)
Pellino et al.[52]	Italy	Single centre study (Veneto Institute of	Patients with advanced GC and GEC diagnosed	280:70 (80%:20%)	117 (33%)

		Oncology of Padua, Italy) IHC performed using 43-14A antibody (Roche Ventana) on FFPE tumour samples	from January 2010 to July 2019 (n=350)		
McHugh et al.[48]	US	IHC performed using 43-14A antibody (Roche Ventana) on tissue microarrays US authors but no details provided on location or centres	Gastroesophageal adenocarcinomas, stages not confirmed (n=155)	100% GEJ	61 (39%)
Wong et al.[49]	US	Single centre study (University of Pittsburgh Medical Center, US) IHC performed on tissue microarrays using 43-14A antibody (Roche Ventana)	Surgically resected G\GEJC adenocarcinomas, across all stages (n=561)	286: 275 (51%:49%)	Total: 155 (23.5%) GACs: 55 (19%) E/GEJ: 77 (28%)
Notes: *CLDN18 positivity defined as moderate-to-strong expression in ≥ 75% of tumour cells **Key:** IHC: immunohistochemistry; GEJ: gastro-oesophageal junction					

b) CLDN18.2 testing costs were based on the Agilent PD-L1 IHC 22C3 pharmDx test, as it has similar testing components and methodology. Please vary these costs in an OWSA and discuss the results.

The results are robust to changes in the unit cost of the test. The unit cost used per test used in the base-case is £74.48. If this cost is increased by 50% to £111.72 (by changing cell C39 on sheet 'Raw_MedCost'), the ICER per QALY increases from £[redacted] in the base case to £[redacted] (0.51% increase); and if the cost is reduced by 50% to £49.65, the ICER reduces to £[redacted] (0.34% decrease).

c) Related to question B2: include the testing costs for HER2 and PD-L1 in the cost-effectiveness analyses if not deemed standard of care.

As outlined in the response to question B2, testing for HER2 and PD-L1 is deemed standard of care.

B 24. In page 130 of the CS, it is stated that "In the base case, it was assumed that all intravenous (IV) administrations would occur in an outpatient setting and that dispensing of oral chemotherapy in combination with IV chemotherapy would not incur any costs". Please clarify whether dispensing oral chemotherapy in combination with IV chemotherapy would at least incur the costs of the stated (complex) chemotherapy costs.

According to NHS costing guidance: "*312. Patients receiving both an infusion and oral treatment as part of a single regimen on the same day are considered to have received one delivery and this is coded to an intravenous delivery code*."[54] Therefore, the administration cost of CAPOX is expected to reflect the cost of one IV administration for both elements.

B 25. CS Table 44 reports the annual frequency of some of the post-progression procedures and services that patients require. However, these were derived from NICE CG81 and are related to breast cancer. Please provide specific frequencies for G/GEJC.

The systematic literature review on resource use did not identify any studies reporting post-progression procedures and services in this patient population in the UK (see Appendix I.6.2. of the company submission). Therefore, the same resource data as in the company submission of TA857 was used given this precedent had been accepted by the NICE.[8] This approach was also used in ID4030.[27]

B 26. The disease management costs included in the model were related to the healthcare professional visits, medical procedures, and hospitalisations. The frequencies of resource use were derived from TA857; however, the population of this TA was patients with untreated advanced gastric or gastroesophageal junction cancer, which slightly differs from the population addressed by the company in this submission. Please elaborate on whether the additional patients included (i.e., metastatic) would incur different disease management costs or frequencies of resource us.

The patient population is similar between TA857 and the current appraisal, with the main difference being that TA857 included patients with oesophageal cancer. Specifically, TA857 recommended nivolumab in patients with untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal or oesophageal adenocarcinoma in adults whose tumours express PD-L1 CPS≥5; i.e., metastatic patients are included in TA857's scope.[42]

Based on the NICE guideline 83 ' Oesophago-gastric cancer: assessment and management in adults',[25] patients with locally advanced unresectable or metastatic oesophageal cancer are managed in a similar way as patients with gastric and gastro-oesophageal at the same level of progression. Therefore, the resources associated with disease management used in TA857 are generalisable to the target population of zolbetuximab.

Severity

B 27. Using the data from CS Table 45 in QALY shortfall calculator from Schneider et al. (https://shiny.york.ac.uk/shortfall/) gives slightly different results than reported in the CS, see below.

a) Please justify these differences.

The differences between the results using data from the CS Table 45 and those reported using the Schneider et al tool are likely due to the specific lifetable used to calculate the proportion of general population alive at any time and reference dataset for the general population utility values. The life table used in the model was the 2017-2019 United Kingdom life table, whereas the Schneider et al. tool uses the 2017-2019 England life table. In addition, the utility values used in the company submission reflect the HSE 2017-2018 dataset, whereas the default option for the Schneider et al. tool uses the HSE 2015 dataset. Both shortfall calculators result in a QALY severity weight of 1.2.

b) Due to uncertainty, the appropriate severity weight may not be 1.2 for every situation. Please indicate for each PSA run which severity weight is applicable (1.0, 1.2 or 1.7) and report the percentages.

The NICE Methods Guide recommends that committees will consider the severity of the condition in terms of the associate absolute and proportional QALY shortfall and apply severity modifiers accordingly. However, the NICE Methods Guide does not mention that the proportion of probabilistic results meeting the criteria should be used to inform the severity modifier.

Using the PSA results to calculate the proportion of simulations by severity weight shows that all of the iterations of the PSA run results in a severity weight of 1.2 (i.e., 100%).

Validation

B 28. Priority question: Please provide the minutes of meetings conducted with UK clinicians and health economists as cited for example in the Validation section B.3.13.1.

Formal meeting minutes were not developed. Where clinical opinion provided to the company has been referenced in the evidence submission or response to clarification questions, a summary of the expert feedback received has been provided in the reference pack.[35]

B 29. The results of the internal validity assessments are not described nor are detailed validation exercises (i.e. specific black-box tests) described (in CS section B.3.13).

a) Please provide a detailed description of the internal validity assessment performed as well as the results.

All checks listed in the published TECH-VER checklist were included in the quality control check that was performed. Checks from the TECH-VER checklist as well as checks from other published sources (Drummond, Phillips) and additional checks developed internally are included in the proprietary checklist.

b) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

The completed TECH-VER checklist is included in Appendix.

B 30. Please provide a detailed cross validation with relevant NICE TA857 and ongoing ID4030 and elaborate on the identified differences regarding:

a) Input parameters in clinical effectiveness, health state utility values, resource use and costs.

b) The modelling of a proportion of long term survivors.

c) Estimated (disaggregated) outcomes per comparator/ intervention, i.e. Life years, QALYs and Costs.

In general, the feasibility of comparisons with TA857 and ID4030 is limited due to the volume of redacted evidence. The key approaches were the same, including:

- Use of pivotal trials for evidence on effectiveness and safety – zolbetuximab's SPOTLIGHT and GLOW trials, together with CheckMate 649 (used in TA857), were used to inform effectiveness and safety; KEYNOTE-062 and KEYNOTE-859 (used in ID4030) were also used to inform indirect comparisons in this submission.
- Use of a three-state partitioned survival model, with pre-progression and progressed disease.
- No treatment waning in the base case.
- In ID4030 the estimates of healthcare resource use for both progression-free and progressed disease were based on those used in TA857 – the same approach as is used in this submission.

There were some differences in the modelling of utilities. As well as modelling by health state (progression free and progressed, as in this submission), TA857 included a time to death disutility. Given that the entire modelled cohort ultimately dies, the impact of this disutility is anticipated to be minor (this is also implied by Tables 8 and 9 of the technical engagement for TA857, where removing this disutility had a very small impact on the cost-effectiveness results). In ID4030 utilities were based on time to death alone (based on ≥360 days, 180 to 359 days, 30 to 179 days, and <30 days). As noted, given that all the modelled cohort eventually dies it is unclear if this approach will fully reflect the impact of improved treatment control (delayed time to progression) on health-related quality of life.

The one-off end-of-life cost used in TA857 was very similar to that used in this submission (£5,387 compared to £5,131), whilst the value used in ID4030 was much larger (£13,113). The one-off subsequent treatment costs used in ID4030 were also much larger than the one-off subsequent treatment costs used in both TA857 and this appraisal. The impact on cost-effectiveness results of using these alternative values has been explored in scenarios; see response to questions B.6 and B.22 for more details; in all the scenarios the results were more favourable to zolbetuximab + chemotherapy).

Finally, there were very few unredacted results. In TA857 chemotherapy was associated with 1.53 life years, compared to [redacted] in this submission. In ID4030 the incremental QALY for pembrolizumab + chemotherapy compared to chemotherapy was 0.64 in the patients

with PD-L1 CPS ≥ 1, compared to 0.54 for zolbetuximab + chemotherapy vs chemotherapy in this submission (without weighting with the severity modifier).

B 31. The EAG notes that life-years in the post-progression state are shorter in the zolbetuximab arm than in the comparator. Please explain the mechanism by which this occurs.

Results from the time-varying NMA (reported in the Addendum) suggest that zolbetuximab + chemotherapy improves both OS and PFS compared to chemotherapy alone. The magnitude of this improvement is greater for PFS than for OS at all time points. Hence the overall improvement is greater for pre-progression than for post-progression (that is, patients stay alive longer in the pre-progression health state). As such, the difference in pre-progression survival between zolbetuximab + chemotherapy and chemotherapy arm is larger than the difference in overall survival, and post-progression survival is necessarily smaller.

Technical implementation of the model

B 32. Priority question: Probabilistic sensitivity analysis is included in the model but does not seem to work properly.

a) **When pressing the 'run PSA' button on the PSA_Figures tab, it asks if 'you wish to regenerate utilities based on the difference method'. Please explain the effects of either pressing 'yes' or 'no' on model calculations and outcomes.**

The 'difference method' mentioned refers to the approach to generating post-progression health state utility values based on the modelled pre-progression value and observed difference between pre- and post-progression values in the analysis of EQ-5D measures from the SPOTLIGHT and GLOW trials. This is done to maintain the logic of these utilities, preventing post-progression quality-of-life from exceeding pre-progression quality-of-life. When 'yes' is selected, the pre-progression utility value and the difference between pre-progression and post-progression utility values are both re-sampled using a Beta distribution. If 'no' is selected there is no re-sampling.

b) After the PSA is run, it does not display any probabilistic results (no PSA cloud, CEAC with vertical lines, etc.). Please provide an updated model with properly working PSA.

As discussed during the clarification call, Astellas have not had issues with running the PSA.

B 33. Please provide an updated economic model with a 'model control' tab where all modifiable inputs for scenario analyses are presented.

An option has now been programmed in the updated economic model to only run the EAG-requested scenarios. There is also an option to only run scenario analyses (this runs all the scenario analyses; previously these could only be run at the same time as running deterministic sensitivity analyses). The option is available on Cell F14 of sheet 'DSA_Figures'

Appendix

Table 19: Appendix D: Clinical SLR

Original review			
Conference proceedings			
Name of the conference	**Website**	**Date accessed**	**Search terms**
ISPOR 2018, Baltimore USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia pacific 2018, Japan	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2018, Barcelona, Spain	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, New Orleans, USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Latin America	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Europe	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2019	https://www.igca.info/	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2018	https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222018%22%7D%5D%7D	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal	https://ascopubs.org/toc/jco/37/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal

Cancers Symposium, 2019			junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2020	https://ascopubs.org/toc/jco/38/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2018	https://ascopubs.org/toc/jco/36/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2019	https://ascopubs.org/toc/jco/37/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Annual Meeting International Conference on Malignant Lymphoma (ICML), 2019	https://onlinelibrary.wiley.com/toc/10991069/2019/37/S2	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2018	https://www.annalsofoncology.org/issue/S0923-7534(18)X6800-8	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2019	https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Clinical trial registries			
NIH U.S. National Library of Medicine Clinical Trials database	http://www.clinicaltrials.gov	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
WHO meta-registry “International Clinical Trials Registry	https://trialsearch.who.int/Default.aspx	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review August 2022			
Conference proceedings			
ISPOR 2020, Orlando, FL, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia Pacific 2020, Seoul, South Korea	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

ISPOR Europe 2020, Milan, Italy	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2021, Montreal, Canada	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2021, Copenhagen, Denmark	https://www.ispor.org/heorresources/presentations-database/search	08/09/2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2022, Washington, DC, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR ASIA Pacific 2022, virtual	https://www.ispor.org/heorresources/presentations-database/search	08/09/2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2021	https://www.igca.info/	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2021	https://ascopubs.org/toc/jco/38/4_suppl	08/09/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2022	https://ascopubs.org/toc/jco/40/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2020	https://ascopubs.org/toc/jco/38/15_suppl	08/09/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2021	https://ascopubs.org/toc/jco/39/3_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2022	https://ascopubs.org/toc/jco/40/16_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2021	https://onlinelibrary.wiley.com/toc/10991069/2021/39/S2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer,

			GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2020	https://www.annalsofoncology.org/issue/S0923-7534(20)X0014-7	08/09/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2021	https://www.annalsofoncology.org/issue/S0923-7534(21)X0014-2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Clinical trial registries			
NIH U.S. National Library of Medicine Clinical Trials database	http://www.clinicaltrials.gov	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
WHO meta-registry “International Clinical Trials Registry Other sources"	https://trialsearch.who.int/Default.aspx	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review (October 2023)			
Conference proceedings			
ISPOR Europe 2022	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2023	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2023	https://site2.convention.co.jp/igcc2023/program/	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2023	https://ascopubs.org/toc/jco/41/16_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2023	https://ascopubs.org/toc/jco/41/4_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2023	https://onlinelibrary.wiley.com/toc/10991069/2023/41/S2	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2022	https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	31/10/2023	Gastric cancer, Gastroesophageal junction cancer,

			GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2023	https://www.sciencedirect.com/journal/annals-of-oncology/vol/34/suppl/S2	18/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Trial registries			
US National Institutes of Health (NIH) registry and results database: Clinicaltrials.gov	http://www.clinicaltrials.gov	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
WHO meta-registry "International Clinical Trials Registry	https://trialsearch.who.int/Default.aspx)	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

Table 20: Appendix G: Cost effectiveness studies

Original review			
Conference proceedings			
Name of the conference	**Website**	**Date accessed**	**Search terms**
ISPOR 2018, Baltimore USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia pacific 2018, Japan	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2018, Barcelona, Spain	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, New Orleans, USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Latin America	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Europe	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association	https://www.igca.info/	08/10/2020	Gastric cancer, Gastroesophageal

(IGCC) – Biennial, 2019			junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2018	https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222018%22%7D%5D%7D	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2019	https://ascopubs.org/toc/jco/37/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2020	https://ascopubs.org/toc/jco/38/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2018	https://ascopubs.org/toc/jco/36/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2019	https://ascopubs.org/toc/jco/37/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Annual Meeting International Conference on Malignant Lymphoma (ICML), 2019	https://onlinelibrary.wiley.com/toc/10991069/2019/37/S2	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2018	https://www.annalsofoncology.org/issue/S0923-7534(18)X6800-8	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2019	https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA Submissions			
NICE	https://www.nice.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer,

			GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other relevant sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review August 2022			
Conference proceedings			
ISPOR 2020, Orlando, FL, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia Pacific 2020, Seoul, South Korea	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2020, Milan, Italy	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2021, Montreal, Canada	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2021, Copenhagen, Denmark	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

ISPOR 2022, Washington, DC, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR ASIA Pacific 2022, virtual	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial	https://www.igca.info/	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2021	https://ascopubs.org/toc/jco/38/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2022	https://ascopubs.org/toc/jco/40/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2020	https://ascopubs.org/toc/jco/38/15_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2021	https://ascopubs.org/toc/jco/39/3_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2022	https://ascopubs.org/toc/jco/40/16_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2021	https://onlinelibrary.wiley.com/toc/10991069/2021/39/S2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2020	https://www.annalsofoncology.org/issue/S0923-7534(20)X0014-7	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2021	https://www.annalsofoncology.org/issue/S0923-7534(21)X0014-2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer,

			GEJC, Stomach cancer
SMC:	https://www.scottishmedicines.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH:	https://www.cadth.ca/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D	www.euroqol.org	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA:	http://www.inahta.org	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review (October 2023)			
Conference proceedings			
ISPOR Europe 2022	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2023	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2023	https://site2.convention.co.jp/igcc2023/program/	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2023	https://ascopubs.org/toc/jco/41/16_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer

ASCO-Gastrointestinal Cancers Symposium, 2023	https://ascopubs.org/toc/jco/41/4_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2023	https://onlinelibrary.wiley.com/toc/10991069/2023/41/S2	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2022	https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2023	https://www.sciencedirect.com/journal/annals-of-oncology/vol/34/suppl/S2	18/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant Sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer,

			GEJC, Stomach cancer

Table 21: Appendix H: HSUV studies

Original review			
Conference proceedings			
Name of the conference	**Website**	**Date accessed**	**Search terms**
ISPOR 2018, Baltimore USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia pacific 2018, Japan	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2018, Barcelona, Spain	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, New Orleans, USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Latin America	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Europe	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2019	https://www.igca.info/	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2018	https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222018%22%7D%5D%7D	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

ASCO-Gastrointestinal Cancers Symposium, 2019	https://ascopubs.org/toc/jco/37/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2020	https://ascopubs.org/toc/jco/38/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2018	https://ascopubs.org/toc/jco/36/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2019	https://ascopubs.org/toc/jco/37/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Annual Meeting International Conference on Malignant Lymphoma (ICML), 2019	https://onlinelibrary.wiley.com/toc/10991069/2019/37/S2	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2018	https://www.annalsofoncology.org/issue/S0923-7534(18)X6800-8	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2019	https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA Submissions			
NICE	https://www.nice.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other relevant sources (Cost & Resource use, Economic evaluation, Health state utility)			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer,

			GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review August 2022			
Conference proceedings			
ISPOR 2020, Orlando, FL, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia Pacific 2020, Seoul, South Korea	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2020, Milan, Italy	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2021, Montreal, Canada	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2021, Copenhagen, Denmark	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2022, Washington, DC, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR ASIA Pacific 2022, virtual	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial	https://www.igca.info/	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

Gastrointestinal Cancers Symposium, 2021	https://ascopubs.org/toc/jco/38/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2022	https://ascopubs.org/toc/jco/40/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2020	https://ascopubs.org/toc/jco/38/15_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2021	https://ascopubs.org/toc/jco/39/3_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2022	https://ascopubs.org/toc/jco/40/16_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2021	https://onlinelibrary.wiley.com/toc/10991069/2021/39/S2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2020	https://www.annalsofoncology.org/issue/S0923-7534(20)X0014-7	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2021	https://www.annalsofoncology.org/issue/S0923-7534(21)X0014-2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC:	https://www.scottishmedicines.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH:	https://www.cadth.ca/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant sources			

EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D	www.euroqol.org	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA:	http://www.inahta.org	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review (October 2023)			
Conference proceedings			
ISPOR Europe 2022	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2023	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2023	https://site2.convention.co.jp/igcc2023/program/	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2023	https://ascopubs.org/toc/jco/41/16_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2023	https://ascopubs.org/toc/jco/41/4_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2023	https://onlinelibrary.wiley.com/toc/10991069/2023/41/S2	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2022	https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	31/10/2023	Gastric cancer, Gastroesophageal junction cancer,

			GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2023	https://www.sciencedirect.com/journal/annals-of-oncology/vol/34/suppl/S2	18/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant Sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

Table 22: Appendix I: Cost & Resource use studies

Original review			
Conference proceedings			
Name of the conference	**Website**	**Date accessed**	**Search terms**
ISPOR 2018, Baltimore USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia pacific 2018, Japan	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2018, Barcelona, Spain	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, New Orleans, USA	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Latin America	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2019, Europe	https://www.ispor.org/heorresources/presentations-database/search	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2019	https://www.igca.info/	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2018	https://meetings.asco.org/abstracts-presentations/search?q=*&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22Gastrointestinal%20Cancers%20Symposium%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:%222018%22%7D%5D%7D	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2019	https://ascopubs.org/toc/jco/37/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

ASCO-Gastrointestinal Cancers Symposium, 2020	https://ascopubs.org/toc/jco/38/4_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2018	https://ascopubs.org/toc/jco/36/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2019	https://ascopubs.org/toc/jco/37/15_suppl	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Annual Meeting International Conference on Malignant Lymphoma (ICML), 2019	https://onlinelibrary.wiley.com/toc/10991069/2019/37/S2	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2018	https://www.annalsofoncology.org/issue/S0923-7534(18)X6800-8	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ESMO, 2019	https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0	08/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA Submissions			
NICE	https://www.nice.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other relevant sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	05/10/2020	Gastric cancer, Gastroesophageal

			junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	05/10/2020	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review August 2022			
Conference proceedings			
ISPOR 2020, Orlando, FL, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Asia Pacific 2020, Seoul, South Korea	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2020, Milan, Italy	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2021, Montreal, Canada	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR Europe 2021, Copenhagen, Denmark	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2022, Washington, DC, USA	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR ASIA Pacific 2022, virtual	https://www.ispor.org/heorresources/presentations-database/search	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial	https://www.igca.info/	08/09 /2022	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Gastrointestinal Cancers Symposium, 2021	https://ascopubs.org/toc/jco/38/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer

Gastrointestinal Cancers Symposium, 2022	https://ascopubs.org/toc/jco/40/4_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2020	https://ascopubs.org/toc/jco/38/15_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2021	https://ascopubs.org/toc/jco/39/3_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2022	https://ascopubs.org/toc/jco/40/16_suppl	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2021	https://onlinelibrary.wiley.com/toc/10991069/2021/39/S2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2020	https://www.annalsofoncology.org/issue/S0923-7534(20)X0014-7	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2021	https://www.annalsofoncology.org/issue/S0923-7534(21)X0014-2	08/09 /2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC:	https://www.scottishmedicines.org.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH:	https://www.cadth.ca/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D	www.euroqol.org	10/10/2022	Gastric cancer

			Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA:	http://www.inahta.org	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	10/10/2022	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
Update Review (October 2023)			
Conference proceedings			
ISPOR Europe 2022	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ISPOR 2023	https://www.ispor.org/heorresources/presentations-database/search	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Gastric Cancer Association (IGCC) – Biennial, 2023	https://site2.convention.co.jp/igcc2023/program/	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
American Society of Clinical Oncology (ASCO), 2023	https://ascopubs.org/toc/jco/41/16_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
ASCO-Gastrointestinal Cancers Symposium, 2023	https://ascopubs.org/toc/jco/41/4_suppl	31/10/2023	Gastric cancer Gastroesophageal junction cancer, GEJC, Stomach cancer
International Conference on Malignant Lymphoma (ICML), 2023	https://onlinelibrary.wiley.com/toc/10991069/2023/41/S2	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2022	https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	31/10/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
European Society for Medical Oncology (ESMO), 2023	https://www.sciencedirect.com/journal/annals-of-	18/11/2023	Gastric cancer, Gastroesophageal junction cancer,

	oncology/vol/34/suppl/S2		GEJC, Stomach cancer
HTA submissions			
NICE	https://www.nice.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
SMC	https://www.scottishmedicines.org.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
CADTH	https://www.cadth.ca/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Other Relevant Sources			
EconPapers within Research Papers in Economics (RePEc)	http://repec.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
EQ-5D:	www.euroqol.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
Cost Effectiveness Analysis Registry:	https://cear.tuftsmedicalcenter.org/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
INAHTA	http://www.inahta.org	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer
NIHR HTA	https://www.nihr.ac.uk/	1/11/2023	Gastric cancer, Gastroesophageal junction cancer, GEJC, Stomach cancer

TECH-VER checklist

Completeness and Consistency

- Some Named ranges had errors. These relate to the PSA and to formatting in the Pre-Prog Trt Cost sheet
    - *This error has been resolved*
- No hidden sheets
- Blank series are included in Chart 4:
    - *This was to account for the fact that the included comparators changes depending on the population of interest chosen in cell E13 in 'Settings' sheet – this avoided having to use VBA and so helps with transparency.*
- chartTornado horizontal axis did not display all results as needed
    - *This error has been resolved*
- Results are transparently reported in the Base Case sheet; OWSA, scenario analysis and PSA results are reported in DSA_Figures, DSA_Tables, PSA_Figures and PSA_Tables
- Sheets beginning with "Raw_" contain the inputs which are fed through to front end summaries of inputs as applied in the traces, after passing through phub.
- Sheets beginning with "tx_" contain traces for each model arm which are set up consistently and transparently

An overview of the results of black box tests is provided in Table 23. Following the results of these, there was no need to perform any further validation tests

Table 23: List of Black-box tests

Test description (Please document how the test is conducted, as well)	Expected result of the test
Pre-analysis calculations	
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes Increasing the value in cell Raw_TxCost!G6 increases pre-progression treatment costs in cell 'Base Case'!E69
Does the drug acquisition cost increase for higher weight or body surface area?	Yes Increasing the value in cell Raw_Demographics!J101 or Raw_Demographics!J30 increases increases pre-progression treatment costs in cells 'Base Case'!E69
Does the probability of an event, derived from an odds ratio (OR)/ relative risk (RR) / hazard ratio (HR) and baseline probability, increases with higher OR/RR/HR?	Yes Hazard ratios are not used in the base case. When changing values in Effectiveness!M23:M32, corresponding PFS curves move appropriately When changing values in Effectiveness!M63:M72, the corresponding OS curves move appropriately
In a partitioned survival model, does the progression free survival curve or the time on treatment curve crosses the overall survival curve?	No Effectiveness_calc sheet: A cap is in place for the PFS curves in columns FR:GC to prevent PFS>OS. DoT_Calc sheet: DoT can be capped by PFS as a user setting (Columns W:AN) and does not exceed OS.
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	An example of the calculations used can be found in cell Q26 on sheet 'Effectiveness_Calc'. From the formulae, it can be verified that the exponential is a special case of both the Weibull and gamma distributions. From the formulae it can also be seen that the generalized gamma contains the gamma as a special case
Is hazard ratio calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	Hazard ratios are applied to parametric chemotherapy extrapolations, see for example column CW of sheet 'Effectiveness_Calc'
For the treatment effect inputs, if the model uses outputs from WINBUGs, are the OR, HR and RR values all within plausible ranges? (should be all non-negative and the average of these WINBUGs outputs should give the mean treatment effect)	Not applicable The analysis does not use any CODA output

Event-state calculations	
Calculate the sum of the number of patients at each health state	Yes For each trace sheet the sum of each row in N16:Q2096=1
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes In all traces, health state occupancies are greater than or equal to zero
Check if all probabilities are smaller than or equal to one	Yes In all traces, health state occupancies are greater than or equal to zero
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Yes The number of patients in the Dead state is greater than or equal to the number in the previous cycle, for all cycles in all traces
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	In the zolbetuximab + chemotherapy, nivolumab + chemotherapy and pembrolizumab + chemotherapy traces a small number of patients remain alive at the end of the 40-year time horizon. This is partially explainable because the model does not continue until patients are 100 years old (rather until 98.5 years). The number of patients left alive in the final cycle is 0.075% and this will therefore have a minimal impact on results.
Discrete event simulation specific: sample one of the "time to event" types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	N/A Model is not a discrete event simulation
Set all utilities to one Set all utilities to zero	Setting all cells in Raw_Utility!D5:D10 to 1 and all cells in Raw_Safety!F248:F253, Raw_Safety!C265:C308 and Raw_Safety!F316 to 0, and turning off age-adjustment for utilities: life years equal QALYs for all cycles in all traces Setting all cells in Raw_Utility!D5:D10 to 0 results in total QALYs=0.
Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Setting all cells in Raw_Utility!D5:D10 to 0.5 reduces QALYs accumulated in every model arm
Set all costs to zero	Setting all costs in Raw_Safety; Raw_TxCost and Raw_MedCost to 0 results in no costs accumulated in the model at any time
Put mortality rates to 0	Setting OS to 1 (Effectiveness_Calc!GH:GS), and general population mortality (Raw_Life_Table columns D and J) to 0 results in 0 occupancy of the 'Dead' health state
Put mortality rate extremely high	Setting OS in cycle 0 to 0.01 results in all patients patients being dead by 18 months

Set the effectiveness, utility and safety related model inputs for all treatment options equal	For Nivolumab+chemotherapy and pembrolizumab+chemotherapy, effectiveness is already equal to zolbetuximab+chemotherapy. Copying over the PFS, and OS values for zolbetuximab+chemotherapy (Effectiveness_Calc columns FT and GJ) to the chemotherapy columns (Effectiveness_Calc columns FW and GM) In sheet DoT_Calc zolbetuximab + chemotherapy DoT (column K) is copied over into columns L,M,N,O, T and AF. Copying Raw_SafetyC5:C15 to the corresponding cells in the same table. Results in QALYs and LYs being equal across treatment arms
In addition to the inputs above, set cost related model inputs for all treatment options equal	Same costs, life years and QALYs should be accumulated for all treatment at any time As above, with the addition of: DoT_Calc!BK12:BT20 copied over the corresponding tables for comparators Setting all administration costs equal to DoT_Calc!BV14 Set Raw_MedCost!C39 to 0 Set Raw_TxCost!C36:C44 equal to Raw_TxCost!C35
Change around the effectiveness, utility and safety related model inputs between two treatment options	Swapping Raw_SafetyE5:E15 with H5:H15 and swapping Swapping over the PFS, and OS values for zolbetuximab+chemotherapy (Effectiveness_Calc columns FT and GJ) with the chemotherapy columns (Effectiveness_Calc columns FW and GM) Results in LYs and QALYs for each arm swapping
Check if the number of alive patients estimate at any cycle is in line with general population life table statistics	'General Population'! column AC values are greater or equal to Column Q in every trace for each cycle in the time horizon
Check if the QALY estimate at any cycle is in line with general population utility estimates	'General Population'! column W values are greater than model traces (column AF) at corresponding ages for each cycle in the time horizon. Modelled QALYs are appropriately age-adjusted
Set the inflation rate of the previous year higher	Increasing the pay and price index for 2023 (Raw_CPI!C22) results in increases of total costs for each reported category. Individual cost inputs were not checked due to time constraints The testing cost does not increase which is expected as it is taken at current prices.

Calculate the sum of all ingoing and outgoing transition probabilities	N/A As it is an AUC type model, no conventional transition probabilities were used
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	N/A No tunnel states are used in the model
Check if the time conversions for probabilities were conducted correctly.	No rates being converted to probabilities or vice versa were identified
Decision tree specific: calculate the sum of the expected probabilities of the terminal nodes	N/A The model is not a decision tree
Patient-level model specific: check if common random numbers are maintained for sampling for the treatment arms?	N/A the model is not a patient-level simulation
Patient-level model specific: check if correlation in patient characteristics is taken into account when determining starting population?	N/A the model is not a patient-level simulation
Increase the treatment acquisition cost	Increasing the unit cost (Raw_TxCost!G6), for zolbetuximab results in increased pre-progression treatment costs in the zolbetuximab arm ('Base Case'!E69) and has no impact on results for any other treatment arms
Population model specific: set the mortality and incidence rates to zero	N/A The model is not a population model
Result calculations	
Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	QALYs gained are not treatment-specific, QALY gained are therefore only based on the time spent in the health state. Life years are higher in treatment with higher efficacy (columns AA and AF in each tx_ sheet). Considering the efficacy (HR) is better for the intervention, the incremental LYs and QALYs are sensible.
Check the incremental cost results. Are they in line with the treatment costs?	In sheet “Pre-prog Trt Cost”, cell I21, if the treatment cost for Zolbe is increased to £500, the incremental costs increase accordingly.
Total life years > total quality adjusted life years	Yes
Undiscounted results > discounted results	Yes Undiscounted results are not reported in the Base Case results sheet, however in the traces, undiscounted results > discounted results
Divide undiscounted total QALYs by undiscounted life years.	For zolbe+chemotherapies, if the total undiscounted QALYs are divided by the total undiscounted LYs, the result is within the range of the utilities presented in the model, and aligned with the utilities presented for the pre-progressed

	health state. For chemotherapy we also get a result which is within the bounds.
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	N/A Subgroups are only used to determine the included comparator(s)
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes When a lower time horizon is selected in Settings!E29, total costs, QALYs and LYs reduce
Is the reporting and contextualization of the incremental results correct?	Cells F29 and F30, the formula in the model show that if the incremental costs are below 0, and the incremental QALYs are over 0, then the intervention will be dominant. If the incremental costs are above 0, and the incremental QALYs are below 0, then the intervention will be dominated. Results have been varied to ensure the label is inline with the results (inc. costs: -£2500, inc QALYs as 1.5 showed as dominant; inc costs: -£2500, inc QALY; -1, showed as dominated; inc costs -£2500 and inc QALYs; -1, showed 2500 (SW Quadrant). Results are presented in a pairwise fashion, so no strong dominance and extended dominance are presented.
Are the reported ICERs in the fully incremental analysis non-decreasing?	N/A Fully incremental analysis is not provided for the analysis as only one comparator is relevant for each population analyses
If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes There is a small difference in totals and disaggregated costs presented in the Base Case sheet. The discrepancy does not appear until the 14^{th} decimal place and will therefore not impact the ICER as it will represent rounding in Excel and hence does not constitute an error. The Total Costs are calculated as a total of each category per cycle and then discounted and summed separately.
Check if half cycle correction is implemented correctly (total life years with half cycle correction should be lower than without)	Half-cycle correction is calculated appropriately by taking the average between each cycle. It is applied to the total drug costs (i.e. acquisition and administration) in the pre-progression health and to the post-progression (disease management) cost (columns AH-AM in tx_ sheets)
Check the discounted value of costs/QALYs after 2 years	Yes

Set discount rates to zero	Yes, same ICER if discount is set to 0% or if the switch for the discounting is set to “No” in the “Settings” sheet
Set mortality rate to zero	Setting OS to 1 (Effectiveness_Calc!GH:GS), and general population mortality (Raw_Life_Table columns D and J) to 0 leads to 40 life years gained, in line with the 40 years time horizon in the base case.
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	Excluding the AE costs and disutility in the model by turning off the switches in D10 and D13 in the “safety” sheet of the model has the same impact as setting the incidence of grade 3+ AEs to 0 in table starting in E16:N26, in the “safety” sheet.
Divide total undiscounted treatment acquisition costs by the average duration on treatment.	Undiscounted pre-progression treatment cost for zolbetuximab + chemotherapy/(median DoT for zolbetuximab + chemotherapy, which occurs at cycle 25) = very similar to the monthly treatment cost of zolbetxumiab + CAPOX.
Set discount rates to a higher value	Increasing the discount rate to 50% reduced the incremental costs. Increasing the discount rate to 50% reduced the QALYs as well.
Set discount rates of costs/effects to an extremely high value	Setting the discount rate for costs and QALYs to 99% results in total costs and QALYs being almost the same as undiscounted costs when the time horizon is set to 1 year
Put adverse event/discontinuation rates to zero and then to extremely high level.	Incidence was first set to 0% for all AEs in table starting in E16:N26, in the “safety” sheet., which results in a decrease in costs and an increase in utilities. If the AE incidence is increased (tested at 70% incidence in the model), costs are increased and QALYs are decreased.
Double the difference in efficacy and safety between new intervention and comparator and report the incremental results.	In the model, the survival curves are modelled using independent extrapolations, for both OS and PFS. Therefore, it means that OS and PFS are modelled independently, with the treatment effect not being quantified using either a HR or OR. Hence, this check is not applicable.
Do the same for a scenario in which the difference in efficacy and safety is halved.	In the model, the survival curves are modelled using independent extrapolations, for both OS and PFS. Therefore, it means that OS and PFS are modelled independently, with the treatment effect not being quantified using either a HR or OR. Hence, this check is not applicable.
Uncertainty analysis calculations	
Are all parameters subject to uncertainty included in the one-way sensitivity analysis (OWSA)? Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of	Yes

a utility regression equation, survival curves with multiple parameters).	
Are the upper and lower bounds used in the one-way sensitivity analysis used confidence intervals based on the statistical distribution assumed for that parameter? Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower bound) - standard error and not standard deviation used in sampling - Lognormal / gamma distribution for hazard ratios and costs/ resource use - Beta for utilities and proportions/probabilities - Dirichlet for multinomial - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) - Normal for other variables as long as samples don't violate requirement to remain positive when appropriate	Yes
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No – mean results of the PSA are close to the deterministic base case
If you take new PSA runs from the excel model do you get similar results?	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes All PSA runs (vs. chemotherapy) are in the North East quadrant with just over half under the WTP threshold which aligns with the CEAC showing that at the willingness-to-pay threshold, the majority of PSA runs suggest zolbetuximab + chemotherapy is cost-effective
Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape?	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes All rows in AS26:AT226 sum to 1.
Are the explored scenario analyses provide a balanced view on the structural uncertainty?	Yes

(i.e. not always looking at more optimistic scenarios)	Scenario analyses increase and decrease the ICER compared to the base case. Scenarios have been added as requested by the EAG.
Are the scenario analysis results plausible and in line with a priori expectations?	Yes Scenarios reducing the effectiveness of the zolbetuximab arm (waning scenarios, hazard ratio approach) increase the ICER. Scenarios expected to increase costs for the zolbetuximab arm (vial sharing) increase the ICER Scenarios increasing the effectiveness of the chemotherapy arm (log-logistic chemotherapy OS and PFS) increase the ICER As expected scenarios surrounding AE costs and testing costs have minimal impact as these make up a small proportion of total model costs. Increasing the starting age of the model increases the ICER due to the modelled plateau in zolbetuximab + chemotherapy PFS and OS meaning that clinical benefit is modelled at the end of the time horizon for whichever patients may still be alive Note that it is not always possible to predict the impact of some scenarios as changes can impact both zolbetuximab + chemotherapy and chemotherapy
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are they scattered evenly between 0-1 when they are plotted?	Yes Random numbers used appear to be evenly distributed between 0 and 1
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter, use graphical methods to examine distributions, functions	Due to time constraints this was not checked. However, similarity of deterministic and probabilistic results suggests this is fine
Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon).	Structural uncertainty is tested in scenarios
Value of information analysis if applicable: Was this implemented correctly? Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions? Is EVPI larger than all individual EVPPI?	N/A, EVPI analysis is not included in the model

Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)? Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected)	Yes No errors were detected
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Plots of total costs and total QALYs are provided. For total costs a correlation is observed, which is because some costs are shared between arms. For total QALYs there is no real correlation. This is likely because the clinical effectiveness of zolbetuximab + chemotherapy is sampled separately to the effectiveness of chemotherapy.  
OWSA=one-way sensitivity analysis; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; WTP = willingness to pay; CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; LY = life years; QALYs = Quality adjusted life years; OR = odds ratio; RR= relative risk; HR = hazard ratio	

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Single technology appraisal

Zolbetuximab with chemotherapy for untreated CLDN18.2-positive HER2-negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Clarification questions addendum

May 2024

File name	Version	Contains confidential information	Date
ID5123 EAG Addendum 02052024_CIC_redacted	**1.0**	**No**	**02/05/2024**

Contents

Tables and figures

Abbreviations

AE	Adverse event
CAPOX	Capecitabine and oxaliplatin
CLDN18.2	Claudin 18.2
CI	Confidence interval
CPS	Combined positive score
DoR	Duration of response
DoT	Duration of treatment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EORTC QLQ-OG25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Oesophago-Gastric 25
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels
FAS	Full analysis set
G/GEJ	Gastric/gastro-oesophageal junction
IRC	Independent review committee
mFOLFOX6	Modified folinic acid, fluorouracil and oxaliplatin
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
SAE	Serious adverse event
SAS	Safety analysis set
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale

Clinical effectiveness

B.1. Clinical effectiveness results of the relevant trials

B.1.1. SPOTLIGHT

In this section, efficacy results are presented for SPOTLIGHT with a data cut of 8 September 2023.[1] In summary, the results of this update are similar to those of the first interim analysis and 29 June 2023 update. Of note:

- Zolbetuximab + modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX6) was associated with a statistically significant and clinically meaningful progression-free survival (PFS) benefit compared to placebo + mFOLFOX6 (hazard ratio [HR] 0.734 [95% confidence interval [CI]: 0.591, 0.910]; one-sided p = 0.0024), which is consistent with the HR observed in the 29 June 2023 datacut (HR 0.730 [95% CI 0.587, 0.907]; one-sided p = 0.0022) – see Section B.1.1.2.
- Zolbetuximab + mFOLFOX6 was associated with a statistically significant and clinically meaningful overall survival (OS) benefit compared to placebo + mFOLFOX6 (HR 0.784 [95% CI 0.644, 0.954]; one-sided p = 0.0075), which is consistent with the HR observed in the 29 June 2023 datacut (HR 0.778 [95% CI: 0.637, 0.949]; p = 0.0067) – see Section B.1.1.3.1.

B.1.1.1. Participant flow

Table 1 presents the summary of disposition events in SPOTLIGHT.

Table 1: Summary of disposition events in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)	Overall (n = 565)
Disposition phase, n (%)			
Treatment ongoing	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin.
Notes: Data cut-off: 8 September 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.1.2. Primary efficacy endpoint: progression-free survival

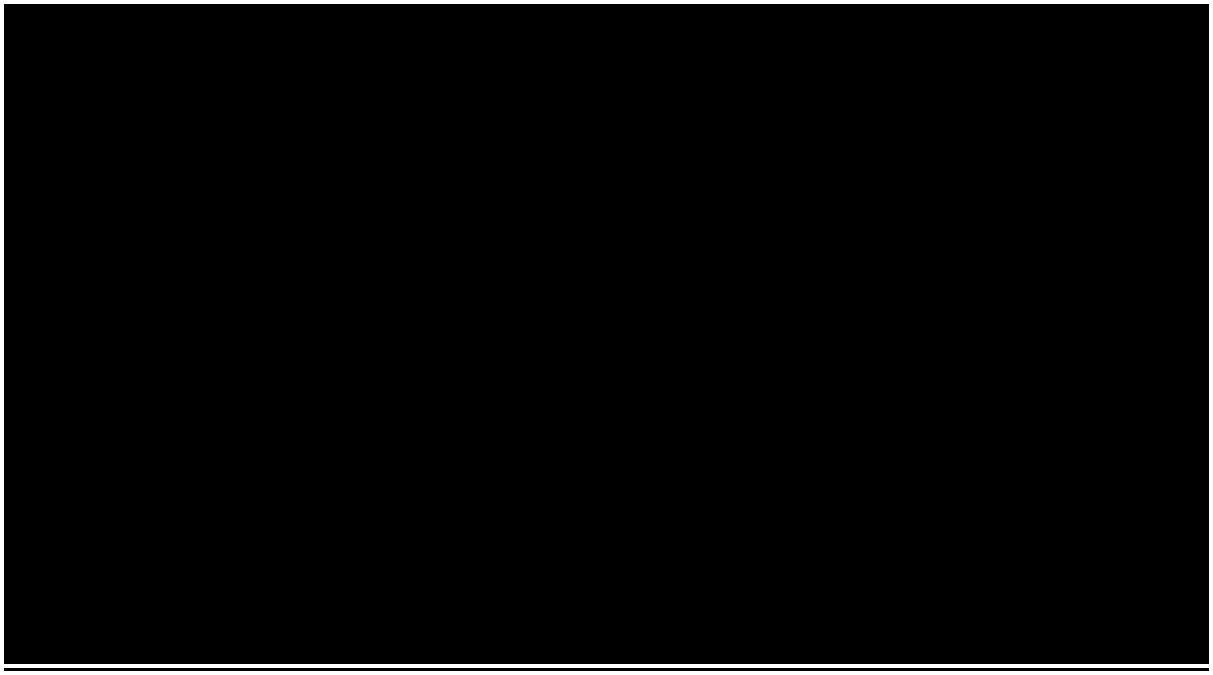
A summary of PFS assessed by independent review committee (IRC) is presented in Table 2 and the Kaplan–Meier plot is presented in Figure 1.[1]

Table 2: SPOTLIGHT: PFS assessed by IRC (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Median Follow-Up Time, Months (95% CI)	[redacted]	[redacted]
PFS Events, n (%)	[redacted]	[redacted]
Median PFS (95% CI), Months	11.04 [redacted]	8.94 [redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	0.734 (0.591, 0.910)	
1-sided P-value**	0.0024	
PFS Rate, % (95% CI)		
At 6 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival.
Notes: Data cut-off: 8 September 2023. * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test.
Source: SPOTLIGHT final data cut, 2024[1]; Shitara et al. 2024.[2]

Figure 1: SPOTLIGHT: Kaplan–Meier plot of PFS assessed by IRC (FAS)



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.1.3. Secondary efficacy endpoints

B.1.1.3.1. Overall survival

A summary of OS is presented in Table 3 and the Kaplan–Meier plot is presented in Figure 2.[1]

Table 3: SPOTLIGHT: Summary of OS (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Median Follow-Up Time, Months (95% CI)	33.28 [redacted]	31.38 [redacted]
Deaths, n (%)	[redacted]	[redacted]
Median OS (95% CI), Months	18.23 [redacted]	15.57 [redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	0.784 (0.644, 0.954)	
1-sided P-value**	0.0075	

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
PFS Rate, % (95% CI)		
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]
At 48 months	[redacted]	[redacted]

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival.
Notes: Data cut-off: 8 September 2023. * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test.
Source: SPOTLIGHT final data cut, 2024[1]; Shitara et al. 2024.[2]

Figure 2: SPOTLIGHT: Kaplan–Meier plot of OS (FAS)

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; OS, overall survival.
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.1.3.2. Objective response rate

A summary of objective response rate (ORR) assessed by IRC is presented in Table 4.[1]

Table 4: SPOTLIGHT: summary of ORR assessed by IRC – unconfirmed responses (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Best overall response, n (%)†	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/non-progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
No disease	[redacted]	[redacted]
Not available‡	[redacted]	[redacted]
ORR, n (%)	136 (48.1)	134 (47.5)
95% CI for ORR (%)§	(42.11, 54.05)	(41.56, 53.52)
Stratified one-sided p-value¶	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR (%)§	[redacted]	[redacted]
Stratified one-sided p-value¶	[redacted]	

Key: CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 8 September 2023. † The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm. ‡ No post-baseline imaging assessment. § Using exact method based on binomial distribution (Clopper–Pearson). ¶ Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. †† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease.
Source: SPOTLIGHT final data cut, 2024[1]; Shitara et al. 2024.[2]

B.1.1.3.3. Duration of response

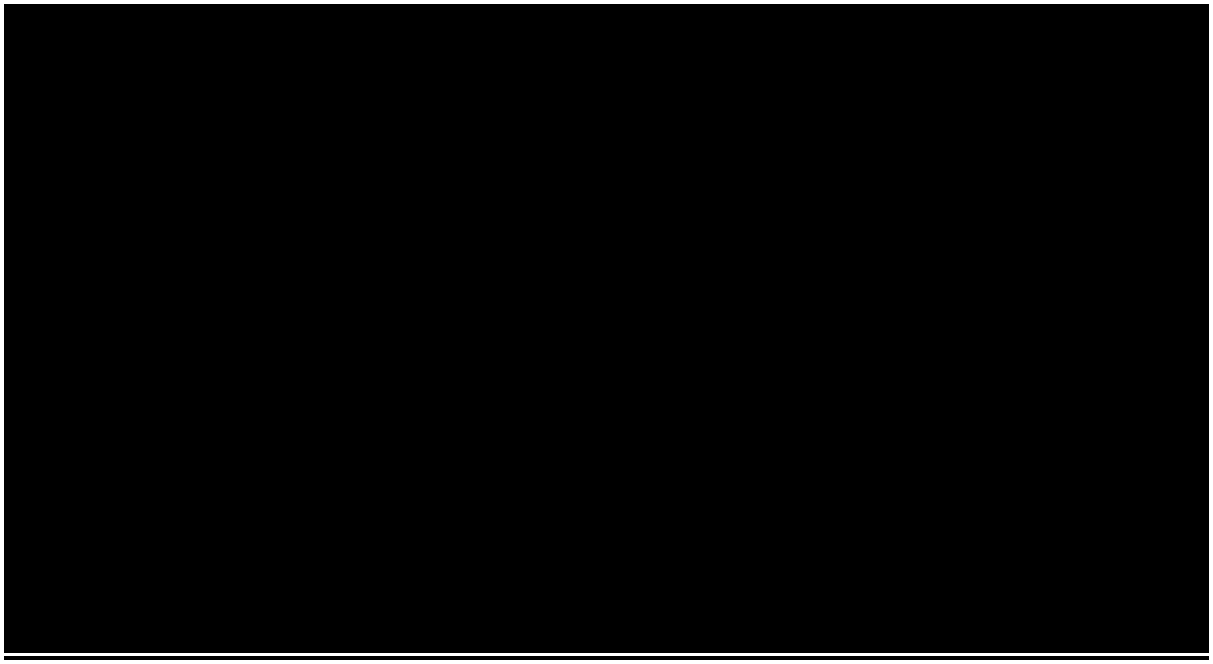
A summary of duration of response (DoR) is presented in Table 5 and the Kaplan–Meier plot is presented in Figure 3.[1]

Table 5: SPOTLIGHT: Summary of DoR by IRC (FAS)

	Zolbetuximab + mFOLFOX6 (n = 136)	Placebo + mFOLFOX6 (n = 134)
Events, n (%)	[redacted]	[redacted]
Median DoR (95% CI), Months	[redacted]	[redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival.
Notes: Data cut-off: [redacted]. * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test.
Source: SPOTLIGHT final data cut, 2024.[1]

Figure 3: SPOTLIGHT: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)



Key: CI, confidence interval; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients.
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.1.4. Health-related quality of life

At the time of this addendum, longitudinal analysis of the pre-specified patient-reported outcomes had not yet been completed, and is therefore not provided.

However, descriptive analysis of these results are similar to those from the previous data-cut.[1]

B.1.1.4.1. Time to confirmed deterioration

A summary of time to confirmed deterioration for global health status (GHS)/ quality of life (QoL), physical function (PF), and pain assessment in oesophago-gastric module (OG-25-Pain) is presented in Table 6.[1]

Table 6: SPOTLIGHT: TTCD for GHS/QoL, PF and OG25-Pain (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
EORTC QLQ-C30 PF (deterioration threshold = 13†)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
OG25-Pain (deterioration threshold = 16.7†)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
HR (95% CI)††	[redacted]	
EORTC QLQ-C30 GHS/QoL (deterioration threshold = 13†)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	15.44 (7.06, 23.89)	11.83 (9.23, 15.08)
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	

Key: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items); FAS, full analysis set; GHS, global health status; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; NE, non-estimable; NYR, not yet reached; OG25-Pain, pain assessment in oesophago-gastric module; PF, physical function; QoL, quality of life; TTCD, time to confirmed deterioration.
Notes: Data cut-off: 8 September 2023. † The threshold values of 13 for PF and GHS/QoL is based on Cocks et al. 2012[3], and 16.7 for OG25-Pain is based on Norman et al. 2003[4] and Sloan et al. 2005.[5] ‡ TTCD = date of first confirmed clinically meaningful deterioration/censored date – randomisation date +1. § Stratification factors were region, number of organs with metastatic sites, and prior gastrectomy. ¶ Based on 1-sided log-rank test. †† Based on stratified Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a HR < 1 indicates a reduction in the hazard rate in favour of the treatment arm.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.2. GLOW

In this section, efficacy results are presented for GLOW with a data cut-off of [redacted][6] In summary, the results of this update are similar to those of the first interim analysis and 29 June 2023 update. Specifically:

- Zolbetuximab + capecitabine and oxaliplatin (CAPOX) was associated with a statistically significant and clinically meaningful PFS benefit compared to placebo + CAPOX (HR [redacted] [95% CI [redacted]; one-sided p = [redacted]); for comparison, the HR observed in the 29 June 2023 datacut (HR 0.682 [95% CI: 0.545, 0.854], one-sided p = 0.0004) – see Section B.1.2.2.
- Zolbetuximab + CAPOX was associated with a statistically significant and clinically meaningful OS benefit compared to placebo + CAPOX (HR [redacted] [95% CI [redacted]; one-sided p = [redacted]); for comparison, the HR observed in the 29 June 2023 datacut ((HR 0.771 [95% CI: 0.624, 0.952]; one-sided p = 0.0079) – see Section B.1.2.3.1.

B.1.2.1. Participant flow

Table 7 presents the summary of disposition events in GLOW.

Table 7: Summary of disposition events in GLOW

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)	Overall (n = 507)
Disposition phase, n (%)			
Treatment ongoing	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

B.1.2.2. Primary efficacy endpoint: progression-free survival

A summary of PFS assessed by IRC is presented in Table 8 and the Kaplan–Meier plot is presented in Figure 4.[6]

Table 8: GLOW: of PFS assessed by IRC (FAS)

	Zolbetuximab + CAPOX (n =)	Placebo + CAPOX (n =)
Median Follow-Up Time, Months (95% CI)	[redacted]	[redacted]
PFS Events, n (%)	[redacted]	[redacted]
Median PFS (95% CI), Months	[redacted]	[redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	
PFS Rate, % (95% CI)		
At 6 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]
At 48 months	[redacted]	[redacted]

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival.
Notes: Data cut-off: [redacted]. * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test.
Source: GLOW final data cut, 2024.[6]

Figure 4: GLOW: Kaplan–Meier plot of PFS assessed by IRC (FAS)

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.
Notes: Data cut-off: [redacted] Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.
Source: GLOW final data cut, 2024.[6]

B.1.2.3. Secondary efficacy endpoints

B.1.2.3.1. Overall survival

A summary of OS is presented in Table 9 and the Kaplan–Meier plot is presented in Figure 5.[6]

Table 9: GLOW: Summary of OS (FAS)

	Zolbetuximab + CAPOX (n = 254)	**Placebo + CAPOX (n = 253)**
Median Follow-Up Time, Months (95% CI)	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]
Median OS (95% CI), Months	[redacted]	[redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	
OS Rate, % (95% CI)		

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]
At 48 months	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
Notes: Data cut-off: [redacted] * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test.
Source: GLOW final data cut, 2024.[6]

Figure 5: GLOW: Kaplan–Meier plot of OS (FAS)

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; N, number of patients; OS, overall survival.
Notes: Data cut-off: [redacted] Median follow-up = 26.09 months (zolbetuximab + CAPOX) versus 26.18 months (placebo + CAPOX). Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.
Source: GLOW final data cut, 2024.[6]

B.1.2.3.2. Objective response rate

A summary of ORR assessed by IRC is presented in Table 10.[6]

Table 10: GLOW: summary of ORR assessed by IRC – (FAS)

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
Best overall response, n (%)†	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/non-progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
No disease	[redacted]	[redacted]
Not available‡	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]
95% CI for ORR§	[redacted]	[redacted]
p-value*	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR§	[redacted]	[redacted]
p-value*	[redacted]	

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: [redacted]. † The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm. ‡ No post-baseline imaging assessment. § Using exact method based on binomial distribution (Clopper–Pearson). Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of metastatic sites and prior gastrectomy. * Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy. †† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).
Source: GLOW final data cut, 2024.[6]

B.1.2.3.3. Duration of response

A summary of DoR is presented in Table 11 and the Kaplan–Meier plot is presented in Figure 6.[6]

Table 11: GLOW: Summary of DoR by IRC (FAS)

	Zolbetuximab + CAPOX (n = 108)	Placebo + CAPOX (n = 99)
Events, n (%)	[redacted]	[redacted]
Median DoR (95% CI), Months	[redacted]	[redacted]
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
Notes: Data cut-off: [redacted]. * Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT. ** Based on 1-sided log-rank test. Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.
Source: GLOW final data cut, 2024.[6]

Figure 6: GLOW: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)

[redacted]

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: [redacted] Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.
Source: GLOW final data cut, 2024.[6]

B.1.2.4. Health-related quality of life

At the time of this addendum, longitudinal analysis of the pre-specified patient-reported outcomes had not yet been completed, and is therefore not provided.

However, descriptive analysis of these results are similar to those from the previous data-cut.[6]

B.1.2.4.1. Time to confirmed deterioration

A summary of time to confirmed deterioration for GHS/QoL, PF, and OG-25-Pain is presented in Table 12.[6]

Table 12: GLOW: TTCD for GHS/QoL, PF and OG25-Pain (FAS)

	Zolbetuximab + CAPOX (n = 254)	**Placebo + CAPOX (n = 253)**
PF (deterioration threshold = 13†)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
OG25-Pain (deterioration threshold = 16.7†)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
GHS/QoL (deterioration threshold = 13†)		

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	9.40 (7.36, 24.80)	7.49 (6.11, 9.86)
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	

Key: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; GHS, global health status; HR, hazard ratio; n, number of patients; NE, non-estimable; NYR, not yet reached; OG25-Pain, pain assessment in oesophago-gastric module; PF, physical function; QoL, quality of life; TTCD, time to confirmed deterioration.
Notes: Data cut-off: [redacted] † The threshold values of 13 for PF and GHS/QoL is based on Cocks et al. 2012[3], and 16.7 for OG25-Pain is based on Norman et al. 2003[4] and Sloan et al. 2005.[5] ‡ TTCD = date of first confirmed clinically meaningful deterioration/censored date – randomisation date +1. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. ¶ Based on 1-sided log-rank test. †† Based on stratified Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a HR < 1 indicates a reduction in the hazard rate in favour of the treatment arm.
Source: GLOW final data cut, 2024.[6]

B.1.3. Indirect and mixed treatment comparisons

As reported in the company evidence submission (Document B), section B.2.9. Indirect and mixed treatment comparisons, a network meta-analysis (NMA) was conducted to compare zolbetuximab + chemotherapy and nivolumab + chemotherapy vs chemotherapy in patients with PD-L1 CPS ≥ 5. This NMA has now been updated with the final datacuts of the SPOTLIGHT and GLOW trials (dated 8 September 2023 and [redacted] respectively) and the latest published datacut of the CheckMate 649 trial (29 May 2023).[7]

Additionally, to inform the scenario including pembrolizumab in patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1, an

additional two trials (identified through the SLR reported in the Document B Appendices of the company submission) were added following the company evidence submission: KEYNOTE-859 and KEYNOTE-062. Both trials investigated pembrolizumab + chemotherapy versus chemotherapy:

- KEYNOTE-062 was a randomized, partially blinded, Phase III clinical trial of pembrolizumab as monotherapy (not a relevant comparator for this scenario analysis) and in combination with fluorouracil + cisplatin (CF) or capecitabine + cisplatin (CX) versus placebo + CF/CX as first-line treatment in patients with advanced gastric/gastro-oesohpageal junction (G/GEJ) cancer and PD-L1 CPS ≥ 1
- KEYNOTE-859 was a Phase III, randomized, double-blind clinical study of pembrolizumab plus CF or CAPOX versus placebo + CF/CAPOX as first-line treatment in patients with previously untreated, unresectable or metastatic G/GEJ adenocarcinoma

The six trials now included in the network are summarised in Table 13 to Table 15.

Table 13: Comparative summary of studies considered for indirect treatment comparison

	SPOTLIGHT	GLOW	FAST	CheckMate 649	KEYNOTE-859	KEYNOTE-062
Study design	Phase III, double-blind RCT	Phase III, double-blind RCT	Phase II, randomised, open-label	Phase III, randomised, open-label	Phase III, randomised, double-blind	Phase III, randomised, partially blinded
Population	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	CLDN18.2-positive (≥ 40% of tumour cells with 2+ or 3+ staining intensity), advanced G/GEJ and oesophageal adenocarcinoma	Previously untreated, unresectable advanced or metastatic HER2-negative, G/GEJ, or oesophageal adenocarcinoma, regardless of PD-L1 expression	Previously untreated histologically or cytologically confirmed locally advanced or metastatic HER2-negative G/GEJ adenocarcinoma	Untreated, locally advanced/unresectable or metastatic G/GEJ cancer with PD-L1 CPS of 1 or greater
Intervention	Zolbetuximab + mFOLFOX6 (n = 283)	Zolbetuximab + CAPOX (n = 254)	Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 77)	Nivolumab + CAPOX/FOLFOX (n = 789)	Pembrolizumab + CAPOX/CF (n = 790)	Pembrolizumab + CX/CF (n = 257)
Comparator	mFOLFOX6 (n = 282)	CAPOX (n = 253)	EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 84)	CAPOX/FOLFOX (n = 792)	CAPOX/CF (n = 789)	CX/CF (n = 250)
Primary endpoint	PFS	PFS	PFS	PFS and OS	OS	PFS and OS
Median follow-up duration	[redacted] months*	[redacted] months*	54.7 months	Not reported (minimum follow up 48.1 months)	31 months	54.3 months

Key: CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; CF, fluorouracil + cisplatin; CPS, combined positive score; EOX, epirubicin, oxaliplatin and capecitabine; CX, capecitabine + cisplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCT, randomised controlled trial.
Note: * Median follow-up for OS differed between treatment arms; therefore a range has been included.
Source: Ajani et al. 2023[8]; Astellas, data on file 2023[9]; Lordick et al. 2023[10]; Astellas, data on file 2023[11]; SPOTLIGHT final data cut, 2024[1] ; GLOW final data cut, 2024[6] ; Sahin et al. 2021[12]; Shitara et al. 2024[7]; Rha, 2023[13]; Wainberg, 2022.[14]

Table 14: Patient characteristics at baseline for studies considered for indirect treatment comparison

	SPOTLIGHT		GLOW		FAST		CheckMate 649		KEYNOTE-859		KEYNOTE-062	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)	Nivolumab + CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)	Pembrolizumab + CF/CAPOX (n = 790)	CF/CAPOX (n = 789)	Pembrolizumab + CF/CX (n = 257)	CF/CX (n = 250)
Age (years), median	62.0	60.0	61.0	59.0	59.0	57.0	62.0	61.0	61	62	62	63
Male gender, %	62.0	62.0	63.0	62.0	61.0	67.0	68.0	71.0	67	69	76	72
Race, %												
White	49.0	48.0	37.0	36.0	NR	NR	70.0	68.0	54	55	NR	NR
Asian	34.0	34.0	62.0	62.0	NR	NR	24.0	24.0	34	34	NR	NR
ECOG, %												
0	44.0	41	43.0	43.0	30.0	30.0	41.0	42.0	36	38	NR	NR
1	54.0	58.0	57.0	56.0	70.0	70.0	59.0	57.0	64	62	53.7	54.0
2	< 1.0	0.0	0.0	0.0	0.0	0.0	< 1.0	< 1.0	NR	NR	NR	NR
Tumour location, %												
Oesophagus	0.0	0.0	0.0	0.0	3.0	5.0	13.0	14.0	NR	NR	NR	NR
GEJ	23.0	26.0	14.0	17.0	17.0	14.0	17.0	16.0	19	23	33	27
GC	77.0	74.0	86.0	83.0	81.0	81.0	70.0	70.0	81	76	66.1	72.4
HER2 status, %												

	SPOTLIGHT		GLOW		FAST		CheckMate 649		KEYNOTE-859		KEYNOTE-062	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)	Nivolumab + CAPOX/ FOLFOX (n = 789)	CAPOX/ FOLFOX (n = 792)	Pembrolizumab + CF/CAPOX (n = 790)	CF/CAPOX (n = 789)	Pembrolizumab + CF/CX (n = 257)	CF/CX (n = 250)
Positive	0.0	0.0	0.0	0	0.0	0.0	0.0	0.0	0	0	0	0
Negative	100.0	100.0	100.0	100.0	0.0	0.0	NR	NR	100	100	100 [a]	100 [a]
Unknown	0.0	0.0	0.0	0.0	100.0	100.0	~40.0	~40.0	0	0	0	0
CPS score, %												
unknown	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	0	0.1	NR	NR	0	0
≥ 1	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	82.1	84.0	78.2	78.2	100	100
≥ 5	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	60.0	61.0	48.0	41.2	NR	NR

Key: CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CPS, combined positive score; CX, capecitabine + cisplatin; ECOG, Eastern Cooperative Oncology Group; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; SmPC, summary of product characteristics.
Notes: [a] based on elibiility criteria.
Source: Ajani et al. 2023[8]; Astellas, data on file 2023[9]; Lordick et al. 2023[10]; Astellas, data on file 2023[11]; Sahin et al. 2021[12]; Janjigian et al. 2023;[15] Astellas, data on file 2023[16]; Nivolumab SmPC 2024[17]; Pembrolizumab SmPC. 2024.[18]

Table 15: Summary of outcomes used for clinical studies considered for indirect treatment comparison

	SPOTLIGHT	GLOW	FAST	CheckMate 649	KEYNOTE-859	KEYNOTE-062
Median OS	• Zolbetuximab + mFOLFOX6: 18.23 months • mFOLFOX6: 15.57 months	• Zolbetuximab + CAPOX: [redacted] months • CAPOX: [redacted] months	• Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 16.5 months • EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 8.9 months	• Nivolumab + CAPOX/FOLFOX PD-L1 CPS ≥ 5: 14.4 months • CAPOX/FOLFOX PD-L1 CPS ≥ 5: 11.1 months • Nivolumab + CAPOX/FOLFOX ITT: 13.7 months • CAPOX/FOLFOX ITT: 11.6 months	• Pembrolizumab + CAPOX/CF PD-L1 CPS ≥ 1: 13.0 months • CAPOX/CF PD-L1 CPS ≥ 1: 11.4 months	• Pembrolizumab + CX/CF PD-L1 CPS ≥ 1: 12.5 months • CX/CF PD-L1 CPS ≥ 1: 11.1 months
Median PFS	• Zolbetuximab + mFOLFOX6: 11.04 months • mFOLFOX6: 8.94 months	• Zolbetuximab + CAPOX: [redacted] months • CAPOX: [redacted] months	• Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 9.0 months • EOX (CLDN18.2 expression in ≥ 70% of tumour cells): 5.7 months	• Nivolumab + CAPOX/FOLFOX PD-L1 CPS ≥ 5: 8.3 months • CAPOX/FOLFOX PD-L1 CPS ≥ 5: 6.1 months • Nivolumab + CAPOX/FOLFOX ITT: 7.7 months • CAPOX/FOLFOX ITT: 6.9 months	• Pembrolizumab + CAPOX/CF PD-L1 CPS ≥ 1: 6.9 months • CAPOX/CF PD-L1 CPS ≥ 1: 5.6 months	• Pembrolizumab + CX/CF PD-L1 CPS ≥ 1: 6.9 months CX/CF PD-L1 CPS ≥ 1: 6.4 months

Key: CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CLDN18.2, claudin 18.2; CX, capecitabine + cisplatin; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ITT, intention-to-treat; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Source: Ajani et al. 2023[8]; Astellas, data on file 2023[9]; Lordick et al. 2023[10]; Astellas, data on file 2023[11]; Sahin et al. 2021[12]; Janjigian et al. 2023[15]; Shitara et al. 2024.[7]

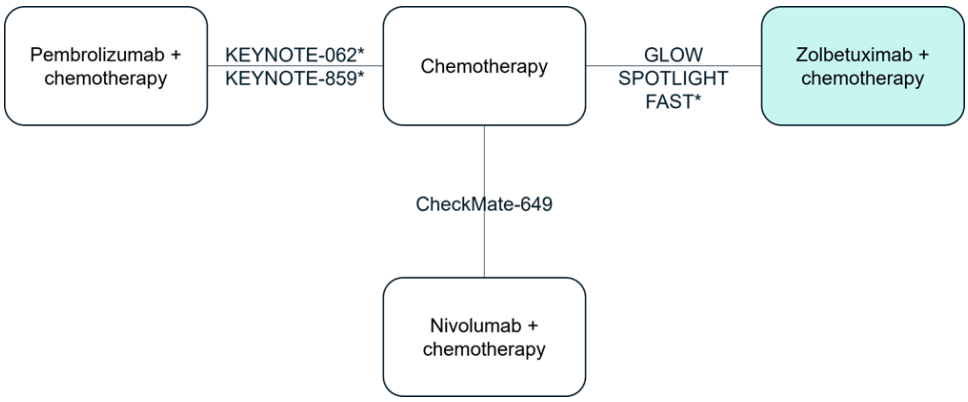
B.1.3.1. Non-proportional hazards network meta-analysis – methods

The methods follow the same approach as in the original company submission, as described in Appendix to document B section D.1.4. Methods of analysis of studies included in the indirect or mixed treatment comparison.

All studies compared two treatment regimens: one of zolbetuximab, nivolumab or pembrolizumab in addition to chemotherapy, compared to chemotherapy with placebo. Under the assumptions that the new regimens' relative efficacy is similar irrespective of the chemotherapy backbone and irrespective of the chemotherapy comparator, a network can be formed with chemotherapy being the common comparator arm.

Figure 7 presents the overall network of evidence, which contains all four studies in the evidence base.

Figure 7: Overall network diagram



Key: CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CLDN18.2, claudin 18.2; CX, capecitabine + cisplatin; EOX, epirubicin + oxaliplatin + capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; PD-L1, programmed death-ligand 1.
Note: The chemotherapy node in the network represents CAPOX, FOLFOX, EOX, CF or CX. * FAST was explored in sensitivity analyses as EOX is used infrequently in the UK, and a different test method was used for CLDN18.2; KEYNOTE-062 and KEYNOTE-859 were explored in scenario analyses as pembrolizumab has had a licence extension to PD-L1 CPS ≥ 1 patients.

Spline NMAs using one, two and three knots were explored for the primary analysis scenario. The best-fitting model for each endpoint and scenario was selected based on the deviance information criterion (DIC) statistic. For both OS and PFS endpoints, the primary scenario included:

- The intention-to-treat (ITT; all-comers) population for the SPOTLIGHT and GLOW trials
- The PD-L1 CPS ≥ 5 subgroup for the nivolumab trial CheckMate 649

Results from the primary scenario are presented in B.1.3.2.1.1 and B.1.3.2.2.1 and have been used in the base case economic analysis (See B.2 Clinical effectiveness results of the relevant trials).

Scenario analyses were carried out using the best-fitting model from the primary analysis. The following scenario analyses were performed:

1. Include FAST (CLDN18.2 ≥ 70% population) was explored in a scenario analysis due to the different CLDN18.2 test used compared with SPOTLIGHT and GLOW, and the infrequent use of the chemotherapy backbone EOX in the UK
2. Include the PD-L1 CPS ≥ 1 subgroup of the pembrolizumab trial KEYNOTE-859 and the ITT population of the pembrolizumab trial KEYNOTE-062 (as PD-L1 CPS ≥ 1 was an inclusion criterion).
3. Include FAST (CLDN18.2 ≥ 70% population) and the relevant populations (see point 2 above) from pembrolizumab trials KEYNOTE-062 and KEYNOTE-859.

The scenario including pembrolizumab + chemotherapy in the PD-L1 CPS ≥ 1 subgroup should be interpreted with caution, as nivolumab + chemotherapy is included in the network using data from the PD-L1 CPS ≥ 5 subgroup. PD-L1 CPS is a treatment effect modifier for pembrolizumab and nivolumab. Differences in the PD-L1 CPS cut-off, and consequently the distribution of PD-L1 CPS of the subgroup, are therefore likely to affect the relative efficacy of the checkpoint inhibitors compared to chemotherapy. As the network of evidence was star-shaped, no trial provided indirect evidence which would confound the results of any treatment versus chemotherapy. Therefore, comparisons between each treatment and chemotherapy are considered reliable. However, any comparisons between checkpoint inhibitors should be made with caution given that the they refer to different PD-L1 CPS cut-offs. For the same reason, if the NMA results are to be used to infer effectiveness of nivolumab + chemotherapy vs chemotherapy in PD-L1 CPS ≥ 5 population and pembrolizumab + chemotherapy vs chemotherapy in the PD-L1 CPS ≥ 1 population,

the implicit assumption is that the PD-L1 CPS distribution in the CheckMate 649 and KEYNOTE-062 and -859 are generalisable. Importantly, as there is no evidence to suggest PD-L1 CPS affects the efficacy of zolbetuximab + chemotherapy vs chemotherapy or the outcomes with chemotherapy, this issue does not affect the estimated HRs of zolbetuximab + chemotherapy vs chemotherapy.

These analyses are presented in B.1.3.2.1.2 - B.1.3.2.1.4 and B.1.3.2.2.2 - B.1.3.2.2.4.

B.1.3.2. Non-proportional hazards network meta-analysis – results

B.1.3.2.1. Progression-free survival

B.1.3.2.1.1. Primary analysis (2-knot model)

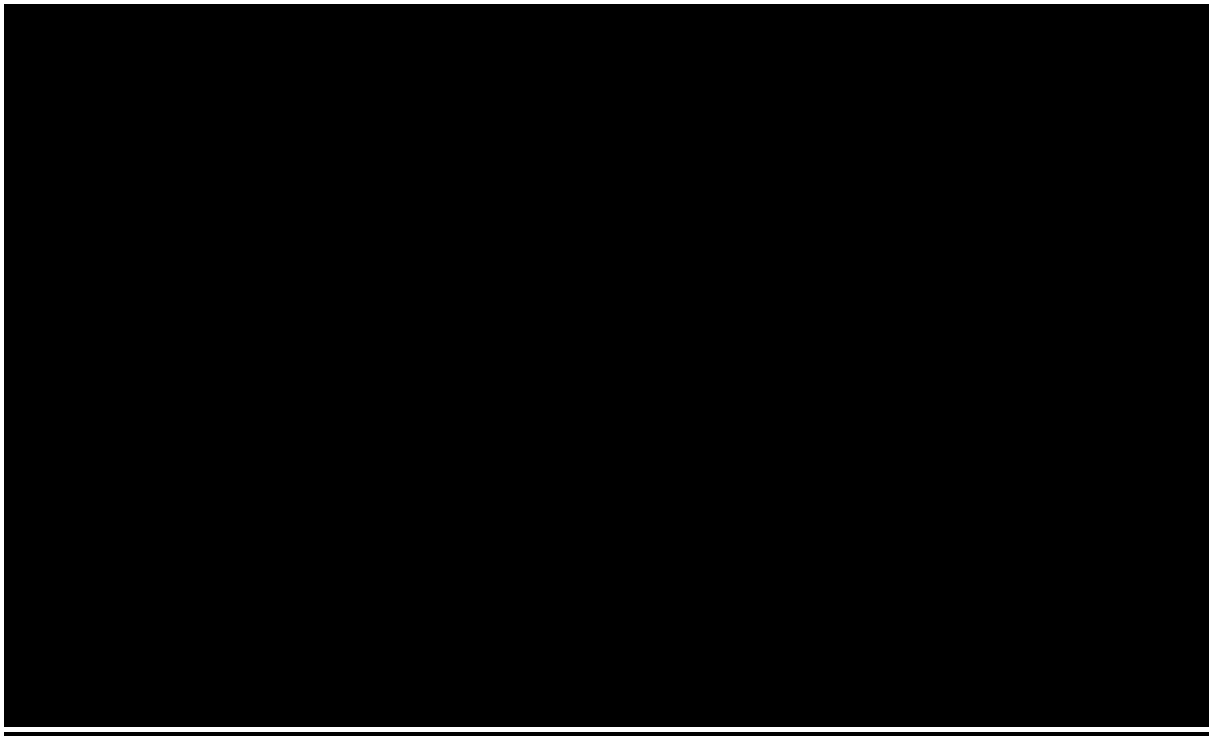
There was little difference (< 5 points) in the DIC values between the 2- and 3-knot spline NMAs of PFS (see Table 16), suggesting both models provide a similar fit to the data. Since the 2-knot spline model is a simpler model, it was selected as the base case model.

Table 16: DIC per model (1, 2, 3 knots) for the primary analysis of PFS

Number of knots	DIC
1	5,007.91
2	4,952.23
3	4,951.65
Key: DIC, deviance information criterion; PFS, progression-free survival.	

Figure 8 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the primary analysis of PFS (2-knot model). The results indicate that the NMA model provides a good fit to the observed data for all trials.

Figure 8: Study-specific survival – primary analysis of PFS (2-knot model)



Key: CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 9 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 9: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: Interpretation of HR plots for OS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649. The dashed lines show the empirical HRs estimated from the trial data.

Table 17 shows the estimated HRs versus chemotherapy at 6 months then yearly up to 5 years.

Table 17: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]

Key: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates reduced progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

B.1.3.2.1.2. Include FAST CLDN18.2 ≥ 70% subgroup (2-knot model)

Figure 10 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the scenario analysis of PFS including the FAST CLDN18.2 ≥ 70% subgroup. The results indicate that the NMA model provides a good fit to the observed data for all trials expect the FAST CLDN18.2 ≥ 70% subgroup. This is likely due to the relative treatment effects for zolbetuximab + chemotherapy versus chemotherapy primarily being driven by the larger GLOW and SPOTLIGHT trials.

Figure 10: Study-specific survival – including FAST CLDN18.2 ≥ 70% subgroup scenario analysis of PFS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

Figure 11 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 11: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup scenario analysis of PFS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The dashed lines show the empirical HRs estimated from the trial data. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

Table 18 shows the estimated HRs versus chemotherapy at specific time points (6 months, then yearly up to 5 years).

Table 18: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup scenario analysis of PFS

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]

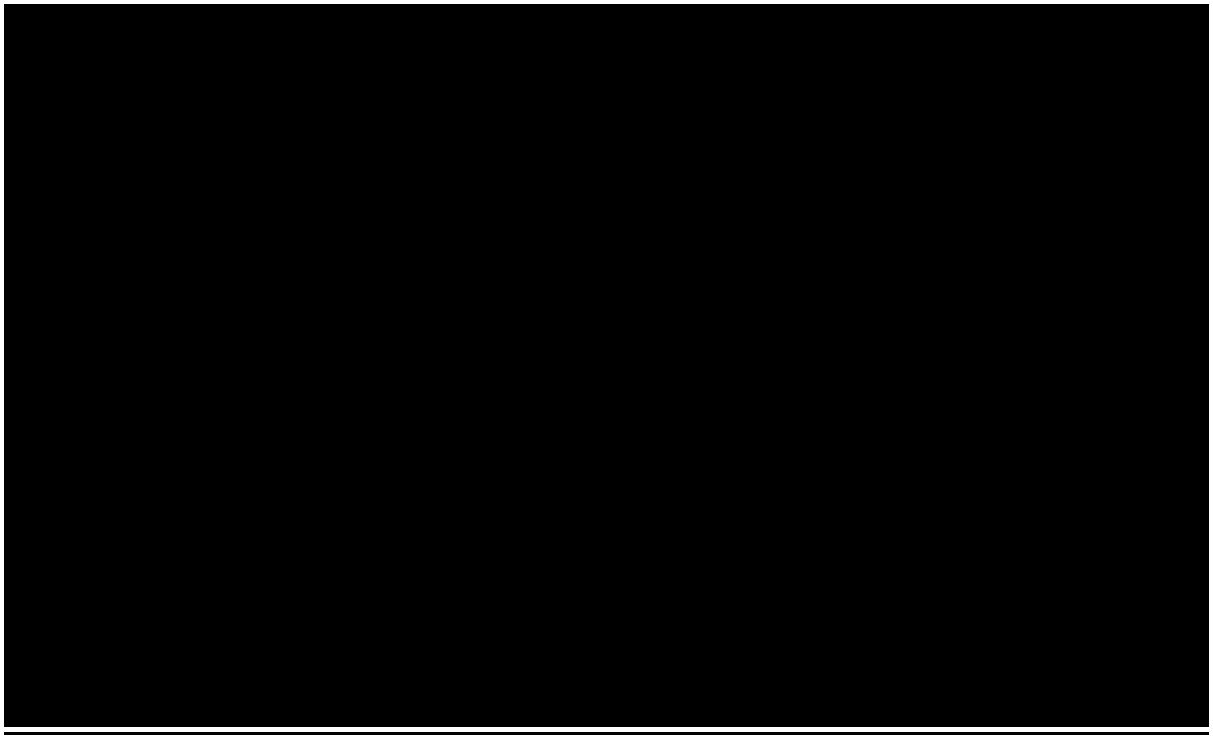
260	5	[redacted]	[redacted]

Key: CLDN18.2, claudin 18.2; CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates lower progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

B.1.3.2.1.3. Include pembrolizumab trials (PD-L1 CPS ≥ 1) (2-knot model)

Figure 12 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the scenario analysis of PFS including the relevant patient populations from the pembrolizumab trials (KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup). The results indicate that the NMA model provides a good fit to the observed data for all trials.

Figure 12: Study-specific survival – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)



Key: CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS≥1 subgroup) of the pembrolizumab trials.

Figure 13 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 13: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.
Notes: Interpretation of HR plots for PFS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS≥1 subgroup) of the pembrolizumab trials. The dashed lines show the empirical HRs estimated from the trial data.

Table 19 shows the estimated HRs versus chemotherapy at specific time points (6 months, then yearly up to 5 years).

Table 19: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5CPS ≥ 1	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1PS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Key: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates lower progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

B.1.3.2.1.4. Include FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) (2-knot model)

Figure 14 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the scenario analysis of PFS including the relevant patient populations from the pembrolizumab trials (KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup) and the FAST CLDN18.2 ≥ 70% subgroup. The results indicate that the NMA model provides a good fit to the observed data for all trials except FAST CLDN18.2 ≥ 70% subgroup (likely due to the relative treatment effects for zolbetuximab + chemotherapy versus chemotherapy primarily being driven by the larger GLOW and SPOTLIGHT trials).

Figure 14: Study-specific survival – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, , and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

Figure 15 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

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Figure 15: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.
Notes: Interpretation of HR plots for PFS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, and the CLDN18.2 ≥ 70% subgroup of the FAST trial. The dashed lines show the empirical HRs estimated from the trial data.

Table 20 shows the estimated HRs versus chemotherapy at specific time points (6 months, then yearly up to 5 years).

Table 20: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Key: CLDN18.2, claudin 18.2; CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates lower progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

B.1.3.2.2. Overall survival

B.1.3.2.2.1. Primary analysis (2-knot model)

The DIC values for the 2- and 3-knot spline NMAs of OS were the same (to 1 decimal place, see Table 21), suggesting both models provide a similar fit to the data. Therefore, since the 2-knot spline model is a simpler model, it was selected as the base case model.

Table 21: DIC per model (1, 2, 3 knots) for the primary analysis of OS

Number of knots	DIC
1	5,530.15
2	5,471.51
3	5,471.52

Key: DIC, deviance information criterion; OS, overall survival.

Figure 16 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the primary analysis of OS (2-knot model). The results indicate that the 2-knot spline NMA model provides a good fit to the observed data.

Figure 16: Study-specific survival – primary analysis of OS (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; OS, overall survival. PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 17 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 17: HRs over time for each treatment versus chemotherapy – primary analysis of OS (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; Nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Notes: Interpretation of HR plots for OS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649. The dashed lines show the empirical HRs estimated from the trial data.

Table 22 shows the estimated HRs versus chemotherapy at 6 months then yearly up to 5 years.

Table 22: HRs over time for each treatment versus chemotherapy – primary analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]

Key: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

B.1.3.2.2.2. Include FAST CLDN18.2 ≥ 70% subgroup (2-knot model)

Figure 18 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the OS scenario analysis including FAST CLDN18.2 ≥ 70% subgroup. The results indicate that the NMA model provides a good fit to the observed data for all trials except FAST CLDN18.2 ≥ 70% subgroup. This is likely due to the relative treatment effects for zolbetuximab + chemotherapy versus chemotherapy primarily being driven by the larger GLOW and SPOTLIGHT trials.

Figure 18: Study-specific survival – Include FAST CLDN18.2 ≥ 70% subgroup scenario analysis of OS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

Figure 19 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 19: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup analysis of OS (2-knot model)

Key: CLDN18.2, claudin 18.2; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: Interpretation of HR plots for OS - the lower the curve the higher the efficacy of treatment versus chemotherapy. Analysis includes PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and PD-L1 CPS ≥ 1 subgroup for the pembrolizumab trials. The dashed lines show the empirical HRs estimated from the trial data.

Table 23 shows the estimated HRs versus chemotherapy at 6 months then yearly up to 5 years.

Table 23: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy (PD-L1 CPS ≥ 5)
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]

Key: CLDN18.2, claudin 18.2; CPS, combined positive score; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

B.1.3.2.2.3. Include pembrolizumab trials (PD-L1 CPS ≥ 1) (2-knot model)

Figure 20 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the OS scenario analysis including the relevant patient populations from the pembrolizumab trials (KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup). Results indicate that the 2-knot spline NMA model provides a good fit to the observed data.

Figure 20: Study-specific survival – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

Figure 21 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 21: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Key: CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Notes: Interpretation of HR plots for OS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials. The dashed lines show the empirical HRs estimated from the trial data.

Table 24 shows the estimated HRs versus chemotherapy at specific time points (6 months then yearly up to 5 years).

Table 24: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5CPS ≥ 1	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1PS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Key: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

B.1.3.2.2.4. Include FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) (2-knot model)

Figure 22 shows the study-specific survival overlaid with the Kaplan–Meier curve for each trial in the OS scenario analysis including the relevant patient populations from the pembrolizumab trials (KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup) and the FAST CLDN18.2 ≥ 70% subgroup. Results indicate that the NMA model provides a good fit to the observed data for all trials except FAST CLDN18.2 ≥ 70% subgroup. This is likely due to the relative treatment effects for zolbetuximab + chemotherapy versus chemotherapy primarily being driven by the larger GLOW and SPOTLIGHT trials.

Figure 22: Study-specific survival – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, , and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

Figure 23 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 23: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Key: CLDN18.2, claudin 18.2; CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Notes: Interpretation of HR plots for PFS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, and the CLDN18.2 ≥ 70% subgroup of the FAST trial. The dashed lines show the empirical HRs estimated from the trial data.

Table 25 shows the estimated HRs versus chemotherapy at specific time points (6 months then yearly up to 5 years).

Table 25: HRs over time for each treatment versus chemotherapy – including FAST CLDN18.2 ≥ 70% subgroup and pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy PD-L1 CPS ≥ 5	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Key: CLDN18.2, claudin 18.2; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649, the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials, and the CLDN18.2 ≥ 70% subgroup of the FAST trial.

B.1.3.3. Proportional hazards network meta-analysis – results

This used the same methods and data sources as the original company submission.

Relevant results are provided below in Table 26.

Table 26: Results of proportional hazards network meta-analysis updated with final SPOTLIGHT and GLOW datacuts

Analysis	Intervention	HR (95% CrI) versus chemotherapy
Overall survival		
PD-L1 CPS ≥ 5 [1]	Zolbetuximab + chemotherapy	[redacted]
	Nivolumab + chemotherapy	[redacted]
PD-L1 CPS ≥ 1 [2]	Zolbetuximab + chemotherapy	[redacted]
	Nivolumab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]
PD-L1 CPS 1-9 [3]	Zolbetuximab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]
PD-L1 CPS 5-9 [4]	Zolbetuximab + chemotherapy	[redacted]
	Nivolumab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]
Progression-free survival		
PD-L1 CPS ≥ 5 [1]	Zolbetuximab + chemotherapy	[redacted]
	Nivolumab + chemotherapy	[redacted]
PD-L1 CPS ≥ 1 [2]	Zolbetuximab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]
PD-L1 CPS 1-9 [3]	Zolbetuximab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]
PD-L1 CPS 5-9 [4]	Zolbetuximab + chemotherapy	[redacted]
	Pembrolizumab + chemotherapy	[redacted]

Key: CLDN18.2, claudin 18.2; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1.
All analyses used the ITT population of the final SPOTLIGHT datacut (dated 8 September 2023), final GLOW datacut (dated [redacted])
[1] CheckMate 649 efficacy inputs were based on data with minimum follow-up time of 4 years, reported in Shitara 2024.[7]
[2] CheckMate 649 efficacy inputs were based on data cutoff date of May 31, 2022, reported in Janjigian 2023.[19] KEYNOTE-859 efficacy inputs were based on data cutoff date of October 3, 2022, reported in Rha 2023.[13]
[3] KEYNOTE-859 efficacy inputs were based on data cutoff date of October 3, 2022, reported in pembrolizumab European public assessment reports.[18]
[4] CheckMate 649 efficacy inputs were based on data cutoff date of May 27, 2020, reported in nivolumab European public assessment reports.[17] KEYNOTE-859 efficacy inputs were based on data cutoff date of October 3, 2022, reported in pembrolizumab European public assessment reports.[18]

B.1.3.4. Uncertainties in the indirect and mixed treatment comparisons

The update to the NMA using the final datacuts of the SPOTLIGHT and GLOW trials, and the latest publicly available data of the Checkmate 649 PD-L1 CPS ≥ 5 subgroup showed consistent results with those of the original analysis: zolbetuximab + chemotherapy has similar efficacy to nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 for PFS and OS outcomes. The new scenario comparing zolbetuximab + chemotherapy to pembrolizumab + chemotherapy in patients with PD-L1 CPS ≥ 1 shows that their efficacy is similar in terms of PFS and OS. The results are consistent across scenarios and with the proportional hazards NMA.

The key uncertainties and limitations are in line with those discussed in the original company submission (see Document B B.2.9.4. Uncertainties in the indirect and mixed treatment comparisons). In brief, these are (1) the analyses were conducted under a fixed effects framework, which may underestimate uncertainty (although would not affect point estimates); (2) the analyses assume that the chemotherapy regimens (in the backbone and as a comparator) were equivalent to enable a connected network, this creates uncertainty in the comparisons against pembrolizumab given the use of cisplatin in KEYNOTE-062; (3) the spline model may have underestimated the relative effectiveness of zolbetuximab + chemotherapy vs chemotherapy in the FAST CLDN18.2 ≥ 70% subgroup, given its poor fit. Furthermore, and specifically related to the scenario including pembrolizumab in patients with PD-L1 CPS ≥ 1, the results for pembrolizumab and nivolumab should be interpreted with caution given that nivolumab + chemotherapy uses the PD-L1 CPS ≥ 5 subgroup data and PD-L1 CPS is an effect modifier for pembrolizumab and nivolumab.

As discussed in the responses to clarification question B3, this NMA assumes that the distribution of PD-L1 CPS in the patients considered for zolbetuximab, nivolumab and pembrolizumab is the same as in the trials informing the analysis. If PD-L1 CPS is lower in clinical practice than in the trials, the effectiveness of nivolumab + chemotherapy and pembrolizumab + chemotherapy vs chemotherapy may be

overestimated (i.e., the HRs may be higher in the clinical practice population than the NMA results).

B.1.4. Adverse reactions

B.1.4.1. SPOTLIGHT

In this section, safety data are presented for SPOTLIGHT with a data cut of 8 September 2023.[1]

B.1.4.1.1. Treatment exposure

The extent of exposure to zolbetuximab or placebo in SPOTLIGHT is presented in Table 27.[1]

Table 27: Summary of extent of exposure in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Total population (n = 557)
Duration of zolbetuximab or placebo (days)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Cumulative actual dose (mg)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Relative dose intensity[a] (%)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Relative dose intensity category, n (%)			
< 50	[redacted]	[redacted]	[redacted]
≥ 50 to < 80	[redacted]	[redacted]	[redacted]
> 80	[redacted]	[redacted]	[redacted]
Number of infusions administered[b]			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Total population (n = 557)
Duration of zolbetuximab or placebo (days)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Average dose per infusion[c] (mg/m2)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; N, number; SD, standard deviation.
Notes: Data cut-off: 8 September, 2023. a(Actual cumulative dose/planned cumulative dose)* 100%. Planned dose intensity is protocol specified (see Section 5.1.1.1. of the SPOTLIGHT protocol; [b] Number of infusions per subject over the entire study period; [c] Sum of [(stop infusion)-(start infusion time) over different cycles]/(number of infusions administered). For infusions with overnight interruptions, the corresponding time will be excluded
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.4.1.2. Treatment-emergent adverse events

Table 28 presents any grade treatment-emergent adverse events (TEAEs) occurring in ≥ 10% of patients in either treatment arm.[1]

Table 28: Any grade TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)
Any TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + mFOLFOX6 (n = 279)**	**Placebo + mFOLFOX6 (n = 278)**
Abdominal pain	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypoalbuminemia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)
Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event. **Notes:** Data cut-off: 8 September, 2023. **Source:** SPOTLIGHT final data cut, 2024.[1]		

B.1.4.1.3. Grade ≥ 3 treatment-emergent adverse events

Table 29 presents any Grade ≥ 3 TEAEs occurring in ≥ 10% of patients in either treatment arm.[1]

Table 29: Grade ≥ 3 TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)
All Grade ≥ 3 TEAEs	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event. **Notes:** Data cut-off: 8 September, 2023. **Source:** SPOTLIGHT final data cut, 2024.[1]		

B.1.4.1.4. Study intervention-related treatment-emergent adverse events

Table 30 presents any grade study intervention-related TEAEs occurring in ≥ 10% of patients in either treatment arm.[1]

Table 30: Any grade zolbetuximab- or placebo-related TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6

	(n = 279)	(n = 278)
Any zolbetuximab- or placebo-related TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: 8 September, 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.4.1.5. Grade ≥ 3 study intervention-related treatment-emergent adverse events

Table 31 presents any Grade ≥ 3 study intervention-related TEAEs that occurred in > 10% of patients in either treatment arm.[1]

Table 31: Grade ≥ 3 study intervention-related TEAEs in > 10% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + mFOLFOX6 (n = 279)**	**Placebo + mFOLFOX6 (n = 278)**
All Grade ≥ 3 zolbetuximab- or placebo-related TEAEs	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Vomiting	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: 8 September, 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.4.1.6. Serious adverse events

Table 32 presents any grade study intervention-related SAEs occurring in ≥ 5% of patients in either treatment arm.[1]

Table 32: Any grade study intervention-related SAEs in ≥ 5% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)
Any SAE	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAE, serious adverse event; SAS, safety analysis set.
Notes: Data cut-off: 8 September, 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.4.1.7. Discontinuation and/or dose modifications due to treatment-emergent adverse events

Discontinuation and/or dose modifications of any study drug due TEAEs are presented in

Table **33** and in

Table **34**, respectively.[1]

Table 33: Discontinuation of zolbetuximab or placebo due to TEAEs in ≥ 5% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + mFOLFOX6 (n = 279)**	**Placebo + mFOLFOX6 (n = 278)**
Any TEAE	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: 8 September, 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

Table 34: Dose interruption of zolbetuximab or placebo due to TEAEs in ≥ 5% of patients in either treatment arm in SPOTLIGHT (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + mFOLFOX6 (n = 279)**	**Placebo + mFOLFOX6 (n = 278)**
Any TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: 8 September, 2023.
Source: SPOTLIGHT final data cut, 2024.[1]

B.1.4.1.8. Deaths

The number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms

([redacted] vs [redacted], respectively).[1] The primary cause of death was due to disease progression, occurring in [redacted] patients in the zolbetuximab + mFOLFOX6 arm and [redacted] patients in the placebo + mFOLFOX6 arm. TEAEs that led to death and were considered by the investigator as possibly related to zolbetuximab + mFOLFOX6 or placebo + mFOLFOX6 occurred in [redacted] ([redacted]) of patients in both treatment arms.

B.1.4.2. GLOW

In this section, safety data are presented for GLOW with a data cut of [redacted].[6]

B.1.4.2.1. Treatment exposure

The extent of exposure to zolbetuximab and placebo in GLOW is presented in Table 35.[6]

Table 35: Summary of extent of exposure in GLOW

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Total population (n = 503)
Duration of zolbetuximab or placebo (days)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]
Cumulative actual dose (mg)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Relative dose intensity[a] (%)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Relative dose intensity category, n (%)			
< 50	[redacted]	[redacted]	[redacted]
≥ 50 to < 80	[redacted]	[redacted]	[redacted]
> 80	[redacted]	[redacted]	[redacted]
Number of infusions administered[b]			

N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Average dose per infusion[c] (mg/m2)			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Key: mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; N, number; SD, standard deviation.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

B.1.4.2.2. Treatment-emergent adverse events

Table 36 presents any grade TEAEs occurring in ≥ 10% of patients in either treatment arm.[6]

Table 36: Any grade TEAEs in ≥ 10% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Investigations	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Hypoalbuminemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Hypoesthesia	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Palmar-plantar erythrodysesthesia syndrome	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

B.1.4.2.3. Grade ≥ 3 treatment-emergent adverse events

Table 37 presents any Grade ≥ 3 TEAEs occurring in ≥ 10% of patients in either treatment arm.[6]

Table 37: Grade ≥ 3 TEAEs in > 10% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
All Grade ≥ 3 TEAEs	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]

Vomiting	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

B.1.4.2.4. Study intervention-related treatment-emergent adverse events

Table 38 presents any grade study intervention-related TEAEs occurring in ≥ 10% of patients in either treatment arm.[6]

Table 38: Zolbetuximab or placebo-related TEAEs occurring in ≥ 10% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
Any zolbetuximab or placebo-related TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Notes: Data cut-off: [redacted] **Source:** GLOW final data cut, 2024.[6]		

B.1.4.2.5. Grade ≥ 3 study intervention-related treatment-emergent adverse events

Table 39 presents any Grade ≥ 3 study intervention-related TEAEs that occurred in > 10% of patients in either treatment arm.[6]

Table 39: Grade ≥ 3 study intervention-related TEAEs in ≥ 10% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
All Grade ≥ 3 zolbetuximab- or placebo-related TEAEs	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event. **Notes:** Data cut-off: [redacted] **Source:** GLOW final data cut, 2024.[6]		

B.1.4.2.6. Serious adverse events

Table 40 presents any grade study intervention-related SAEs occurring in ≥ 5% of patients in either treatment arm.[6]

Table 40: Any grade study intervention-related SAEs in ≥ 5% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Any SAE	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event. **Notes:** Data cut-off: [redacted] **Source:** GLOW final data cut, 2024.[6]		

B.1.4.2.7. Discontinuation and/or dose modifications due to treatment-emergent adverse events

Discontinuation and/or dose modifications of any study drug due to TEAEs are presented in Table 41 and Table 42, respectively.[6]

Table 41: Discontinuation of zolbetuximab or placebo due to TEAEs in ≥ 2% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
Any TEAE	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

Table 42: Dose interruption of zolbetuximab or placebo due to TEAEs in ≥ 5% of patients in either treatment arm in GLOW (SAS)

System Organ Class, n (%) Preferred term, n (%)	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**
Any TEAE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]

Key: CAPOX, capecitabine and oxaliplatin; n, number of patients; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: Data cut-off: [redacted]
Source: GLOW final data cut, 2024.[6]

B.1.4.2.8. Deaths

The number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + CAPOX and placebo + CAPOX arms ([redacted]

[redacted] vs [redacted], respectively).[6] The primary cause of death was due to disease progression, occurring in [redacted] patients in the zolbetuximab + CAPOX arm and [redacted] patients in the placebo + CAPOX arm. In total, [redacted] patients in the zolbetuximab + CAPOX arm and [redacted] patients in the placebo + CAPOX arm had TEAEs leading to death that the investigator considered to be related to zolbetuximab or placebo.

B.2. Cost-effectiveness

To reliably inform decision-making, it is important that accurate estimates of long-term survival are obtained for both OS and PFS. Because of this, the approach to survival extrapolation seeks to make the best use of all the available evidence by incorporating evidence on long-term chemotherapy outcomes from CheckMate-649 and using real-world evidence to inform the expectations about long-term survival with chemotherapy in the long-term – this is discussed in detail in Document B Section B.3.3.1.1. The importance of using external evidence to strengthen extrapolations is emphasised in the both NICE TSD 14 and 21, and the 'Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies' which was developed by several international experts in extrapolation and technology appraisal. [20] [21]

The use of pooled CAPOX and FOLFOX evidence is consistent with the approach taken in the appraisal of Nivolumab with chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (TA857), for which CheckMate-649 was the key source of clinical evidence. In TA857, CAPOX and FOLFOX were assumed to have equivalent effectiveness outcomes, reflecting the trial design of CheckMate-649, which was investigator choice between CAPOX and FOLFOX. This assumption of similar outcomes was confirmed by clinical experts in the appraisal committee meeting, who agreed that CAPOX and FOLFOX are broadly equivalent.[22] Hence outcomes for the chemotherapy arm of CheckMate-649 may be viewed as equivalent to the outcomes for the chemotherapy arms from SPOTLIGHT and GLOW, supporting the use of pooled outcomes from all three trials in the base case.

In addition to improving the sample size available for statistical estimation, use of evidence from CheckMate-649 has the key benefit of longer follow-up than either zolbetuximab trial. For the chemotherapy arms of SPOTLIGHT and GLOW follow-up is to [redacted] months for both trials (based on the last time at which at least one individual is at risk for OS), with less than ten people at risk by [redacted] and [redacted] months, respectively. CheckMate-649 has follow-up to 66 months, with at least 10 people at risk out to 60

months. Because of this, base case decision making should incorporate chemotherapy outcomes from CheckMate-649 to reduce the extrapolation uncertainty.

With this approach, to maintain randomisation and appropriately synthesise the relative efficacy of zolbetuximab, survival outcomes for zolbetuximab are derived from the spline-NMA, as detailed in Section B.1.3. This approach is in line with the recommendations in the NICE TSD 1, as the natural history of the target population with the comparator is modelled separately from the treatment effects relative to that comparator. [23]

As per the approach in the original company submission, and given that the updated NMA had similar results to the original NMA (in that the estimates of treatment effectiveness were very similar between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5), OS and PFS with nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5 were assumed equivalent to OS and PFS with zolbetuximab + chemotherapy. Since the estimates of treatment effectiveness were very similar between zolbetuximab + chemotherapy and pembrolizumab + chemotherapy in patients with PD-L1 CPS ≥ 1, the same approach was taken for this scenario.

This section presents updated cost-effectiveness results using the SPOTLIGHT data cut of 8 September 2023, the GLOW data cut of [redacted], and the latest published datacut of the CheckMate 649 trial (29 May 2023). [7]

Details of the survival modelling for the updated pooled data from SPOTLIGHT, GLOW and CheckMate-649 are provided below.

B.2.1. Overall survival

As survival models were only fit to the chemotherapy group, it was not necessary to test the proportional hazards assumption. Figure 24 shows the overall survival Kaplan Meier data in the chemotherapy group.

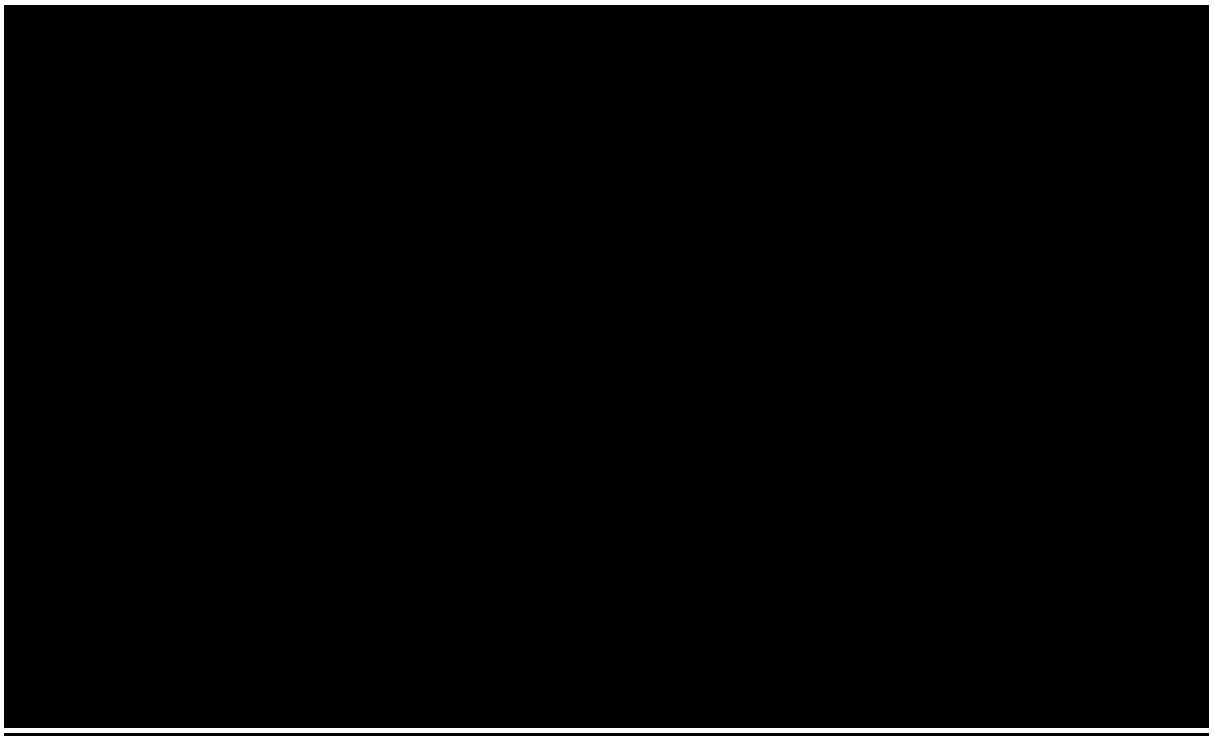
Figure 25 and Figure 26 show the Kaplan Meier overall survival data from the chemotherapy arms of each trial separately and the corresponding log-cumulative hazard plots, respectively. The chemotherapy arm of CheckMate-649 PD-L1 CPS ≥ 5 subgroup had visually similar survival to the chemotherapy arm of the GLOW trial, whilst the log-cumulative hazard plot demonstrates that neither the Weibull nor exponential are likely to be suitable models.

Figure 24 Pooled chemotherapy Kaplan Meier OS data (pooled GLOW, SPOTLIGHT and CheckMate-649 PD-L1 CPS ≥ 5)

Figure 25 Kaplan Meier OS data from the chemotherapy arms of GLOW, SPOTLIGHT and CheckMate-649 PD-L1 CPS ≥ 5

Key: CM-649, CheckMate 649.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 26 Log-cumulative hazards plot of OS in the chemotherapy arms of GLOW, SPOTLIGHT and CheckMate-649



Key: CM-649, CheckMate 649.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

An overview of the number of patients at risk for the pooled SPOTLIGHT, GLOW and CheckMate 649 chemotherapy data is provided in Table 43.

Table 43: A summary of the numbers of patients at risk for the pooled chemotherapy data (SPOTLIGHT, GLOW, CheckMate 649) - OS

Time (Years)	Numbers at risk
0	[redacted]
0.25	[redacted]
0.5	[redacted]
0.75	[redacted]
1	[redacted]
1.25	[redacted]
1.5	[redacted]

1.75	[redacted]
2	[redacted]
2.25	[redacted]
2.5	[redacted]
2.75	[redacted]
3	[redacted]
3.25	[redacted]
3.5	[redacted]
3.75	[redacted]
4	[redacted]
4.25	[redacted]
4.5	[redacted]
4.75	[redacted]
5	[redacted]

B.2.1.1. Parametric survival models

The following parametric survival models were considered:

- Exponential
- Weibull
- Gompertz
- Gamma
- Log-logistic
- Log-normal
- Generalised gamma

Landmark survival at select time points are presented in Table 44 alongside the standard parametric extrapolations (Figure 27) and corresponding hazards (Figure 28). Statistical fit according to AIC and BIC of each model is presented in Table 45. The empirical hazard rates in Figure 28 show that the hazard rate with chemotherapy increases then decreases; i.e., there is a clear turning point in the hazards. The standard parametric distributions that are potentially able to capture

these turning points are the log-normal and the log-logistic. Visual examination suggests that the log-logistic curve has the turning point closer to the empirical hazards, whereas the log-normal curve has a poorer visual fit. The log-logistic distribution is also the best statistically fitting distribution according to AIC and BIC, with no other models having values within five points. Nevertheless, visually the log-logistic distribution may overestimate hazard rates compared to the empirical hazards, hence the log-logistic distribution may underestimate survival with chemotherapy in the longer term. This prompted the exploration of spline-based survival models, described in the next section.

Table 44 Standard parametric model landmark OS for pooled chemotherapy

Time (Years)	0	1	2	3	4	5	10
Number at risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 27 OS parametric survival curves for pooled chemotherapy

Figure 28 OS parametric survival curve hazard plots for pooled chemotherapy

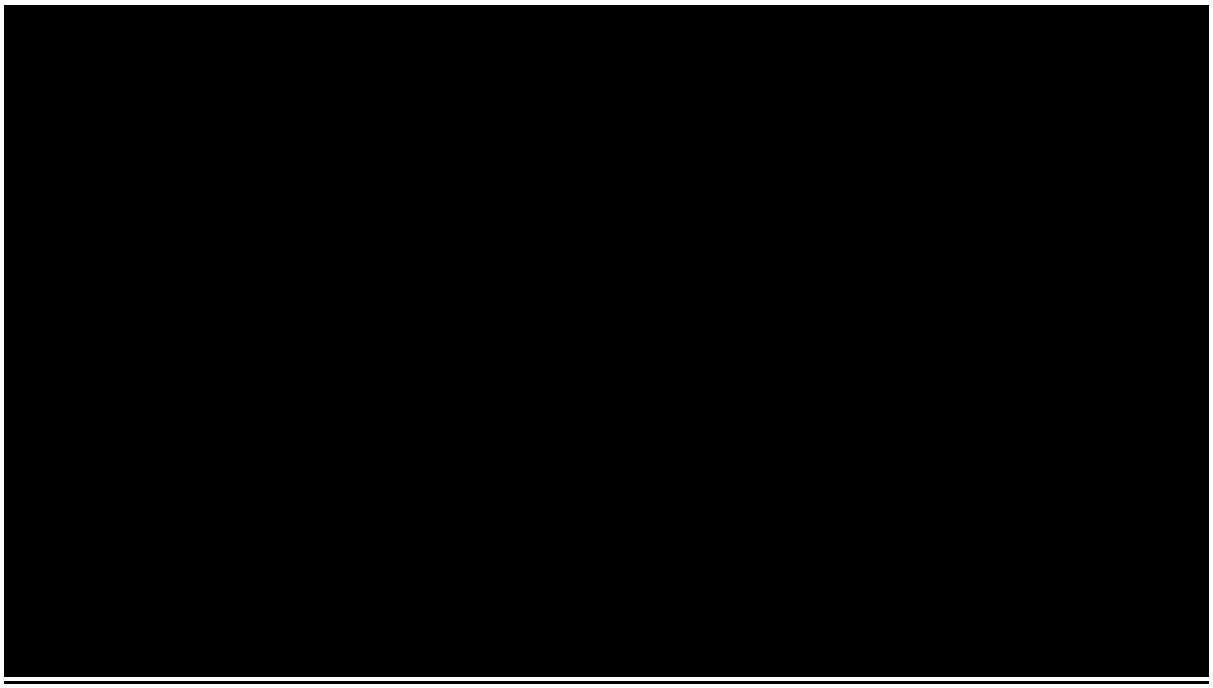


Table 45 Fit statistics of OS standard parametric extrapolations for pooled chemotherapy

Model	AIC	AIC_rank	BIC	BIC_rank
Exponential	9,165	6	9,170	6
Gamma	9,126	3	9,135	3
Gen.gamma	9,105	2	9,119	2
Gompertz	9,167	7	9,177	7
Log-logistic	9,079	1	9,089	1
Log-normal	9,144	5	9,154	5
Weibull	9,141	4	9,151	4
Key: AIC, Akaike's information criteria; BIC, Bayesian information critera				

B.2.1.2. Spline-based models

Landmark survival at select time points are presented in Table 46 alongside the spline-based extrapolations (Figure 29). Statistical fit according to AIC and BIC of each model is presented in Table 47.

Table 46 Spline model landmark OS for pooled chemotherapy

Time (Years)	0	1	2	3	4	5	10
Number at risk	1017	[redacted]					
Observed survival	100%	[redacted]					
1 knot hazards	100%	[redacted]					
1 knot odds	100%	[redacted]					
1 knot normal	100%	[redacted]					
2 knot hazards	100%	[redacted]					
2 knot odds	100%	[redacted]					
2 knot normal	100%	[redacted]					
3 knot hazards	100%	[redacted]					
3 knot odds	100%	[redacted]					
3 knot normal	100%	[redacted]					

Figure 29 OS spline-based model curves for pooled chemotherapy

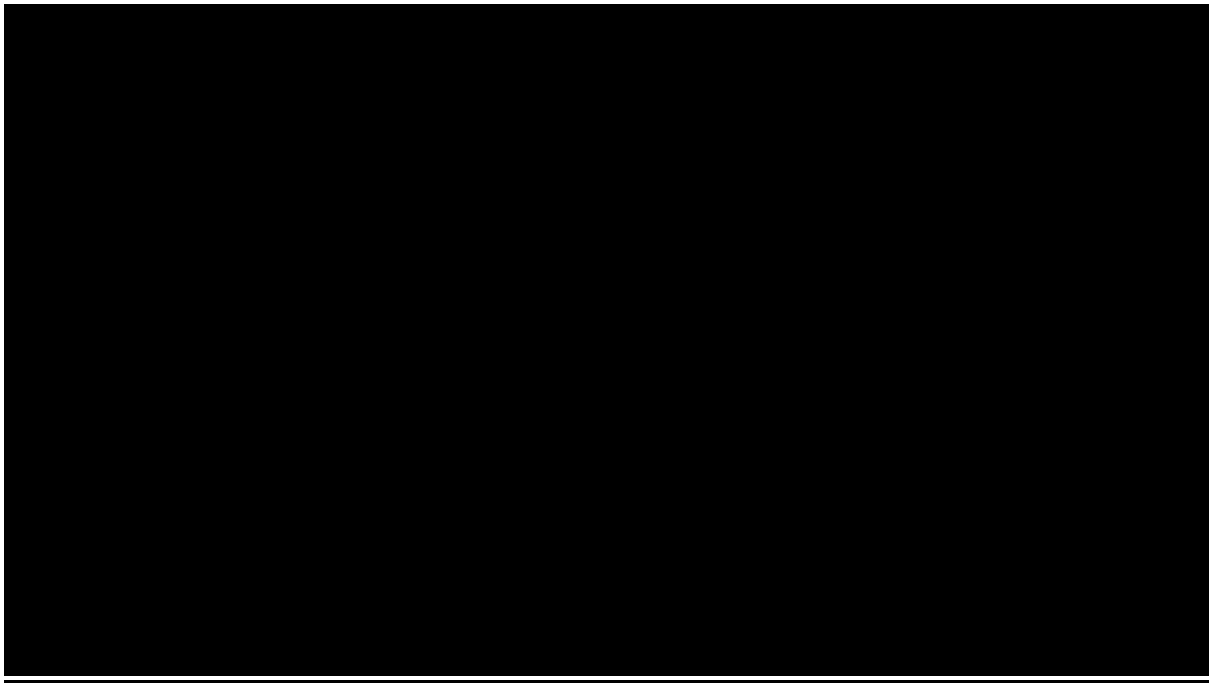


Table 47 Fit statistics of overall survival spline-based models for pooled chemotherapy

Model	AIC	AIC_rank	BIC	BIC_rank
1 knot hazards	9,106.3	9	9,121.1	9
1 knot odds	9,069.9	6	9,084.6	1
1 knot normal	9,090.4	8	9,105.2	8
2 knot hazards	9,067.6	3	9,087.3	2
2 knot odds	9,068.4	5	9,088.1	3
2 knot normal	9,075.1	7	9,094.8	7
3 knot hazards	9,066.2	1	9,090.8	4
3 knot odds	9,066.5	2	9,091.1	5
3 knot normal	9,067.9	4	9,092.5	6
Key: AIC, Akaike's information criteria; BIC, Bayesian information critera				

All of the spline-based models provide visually good fit to the majority of the observed data. The generally similar extrapolations are consistent with the real-world external evidence that there is a small proportion of long-term survivors with chemotherapy (see Document B B.3.3.1.1.1. Supportive evidence on survival outcomes of chemotherapy from real-world studies). There is some variation in the fit of the spline-based models, with 3-knot models fitting the tail of the Kaplan-Meier better. Based on AIC, the 3-knot hazard has the best fit, with near-identical values

for the other 3-knot models. The BIC favours more parsimonious models, with the 1-knot odds having the lowest score, followed by the 2-knot hazard. However, the 3-knot models are the only models to adequately capture survival in the tail of the Kaplan-Meier, suggesting that these are the most appropriate to use for extrapolation.

When comparing model types, the log-logistic is the only parametric model with an acceptable fit, as previously discussed. Based on AIC, spline-based models provide a better fit than standard parametric models. Visually, they are also better able to match the empirical hazard function. The log-logistic model has a lower BIC than the 3-knot spline models, but there remain three other spline models with lower BIC. As discussed previously, the BIC may be overly-penalising model complexity. Hence, the 3-knot hazard spline model is used in the base case (Figure 30), with use of the log-logistic used in a scenario analysis. The OS smoothed hazards and 3-knot hazard model hazards are presented in Figure 31. Use of alternative spline-based models was not explored as the similarity of extrapolations arising from these suggests that the impact on cost-effectiveness results would be minimal (Figure 32), though the model has the functionality to explore this if required. The OS smoothed hazards and top 3 best-fitting model hazards are presented in Figure 32. Landmark overall survival estimates for zolbetuximab and chemotherapy capped by general population mortality using the spline-based extrapolation (base case) are presented in Table 48.

Figure 30 Pooled chemotherapy OS, 3-knot hazard spline

Figure 31: OS smoothed hazards and 3-knot hazard model hazards

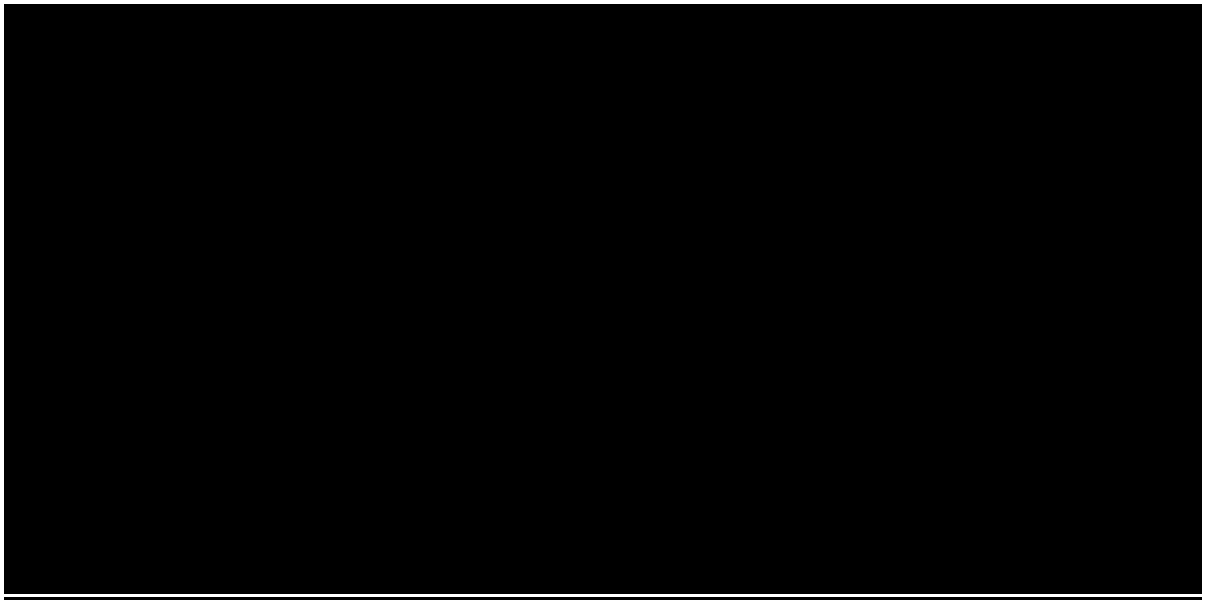


Figure 32: OS smoothed hazards and top 3 best-fitting model hazards

Table 48: Landmark overall survival estimates for zolbetuximab and chemotherapy capped by general population mortality – base case using spline-based extrapolation

Months		Zolbetuximab and chemotherapy	Chemotherapy
OS (%)	Month 6	82.27%	78.19%
	Month 12	59.02%	50.86%
	Month 18	40.60%	31.12%
	Month 24	30.14%	20.93%
	Month 36	20.14%	12.12%
	Month 60	12.37%	6.17%
Key: OS, overall survival			

B.2.1.3. Scenario: evidence from just SPOTLIGHT and GLOW

A Schoenfeld plot, log-log cumulative hazards plot and the observed and modelled hazards of the overall survival data from the SPOTLIGHT and GLOW trials are presented in Figure 33 to Figure 35. Figure 35 shows the observed and estimated OS hazards from parametric survival models fitted to the pooled data of GLOW and SPOTLIGHT. Figure 36 shows the smoothed and empirical OS hazards. Figure 37

shows the log survival odds plot for OS, and Figure 38 the QQ plot for OS, all for pooled SPOTLIGHT and GLOW data.

The extrapolated overall survival curves for the pooled chemotherapy arms of SPOTLIGHT and GLOW, and the pooled zolbetuximab + chemotherapy arms of SPOTLIGHT and GLOW are presented in Figure 39 and Figure 40. For both arms there is uncertainty as to the best parametric survival model to use for extrapolations. Differing models provide different fit towards the end of the observed follow-up; however due to the inherent uncertainty at these time points (due to a small number of patients being at risk) it is unclear which model is the most appropriate. This uncertainty can be reduced by increasing the sample size (which increases the number of patients at risk over time), further motivating the inclusion of external evidence from CheckMate 649. There is also uncertainty in the appropriateness of the proportional hazards assumption, as the log-log cumulative hazard plot shows potential convergence (Figure 34). Goodness of fit values are provided in Table 49. For zolbetuximab + chemotherapy there is support from both the AIC and BIC to use the log-logistic, as this has the lowest values for both. Similarly, for chemotherapy there is support from both the AIC and BIC to use the gamma, as this has the lowest values for both.

Figure 33 OS - Schoenfeld plot of residuals, SPOTLIGHT and GLOW

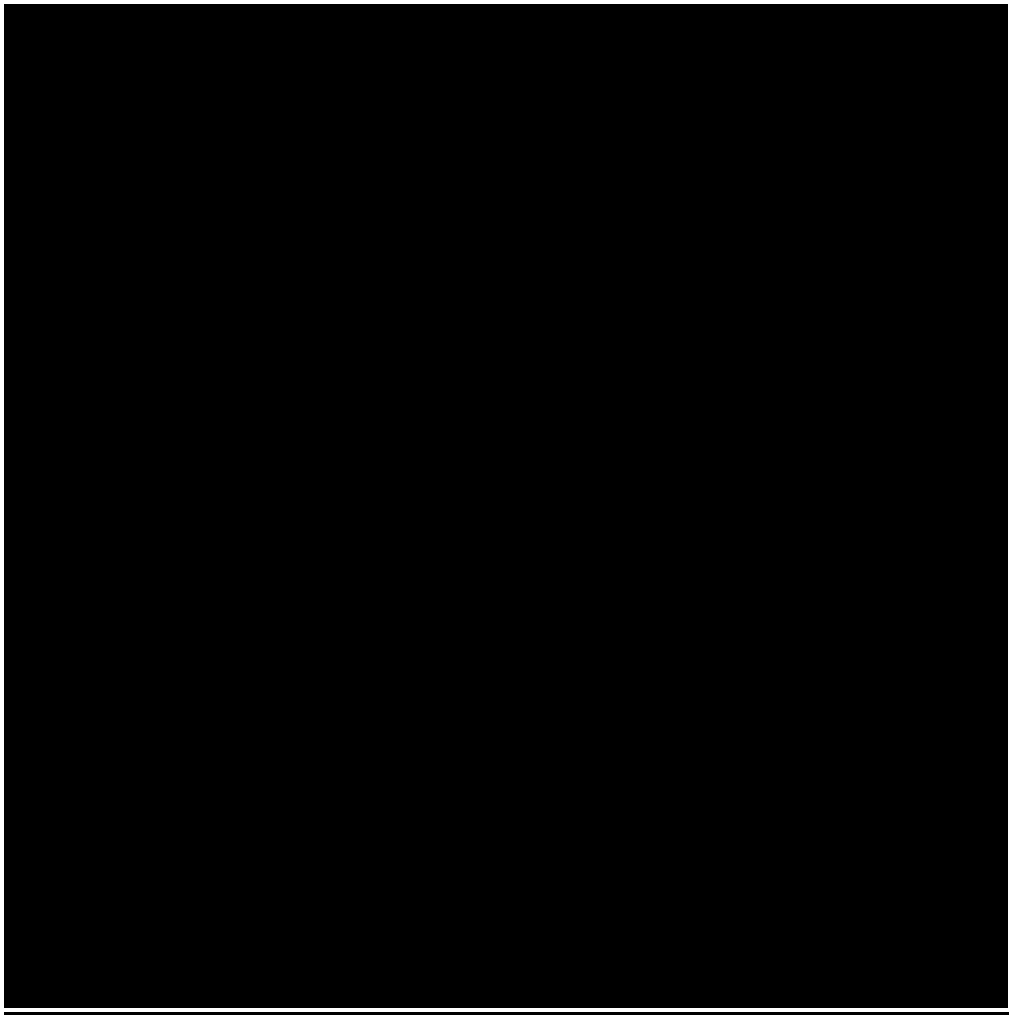


Figure 34 Log-log cumulative hazard plots of OS from both pooled zolbetuxumab + chemotherapy arms and pooled chemotherapy arms of SPOTLIGHT and GLOW

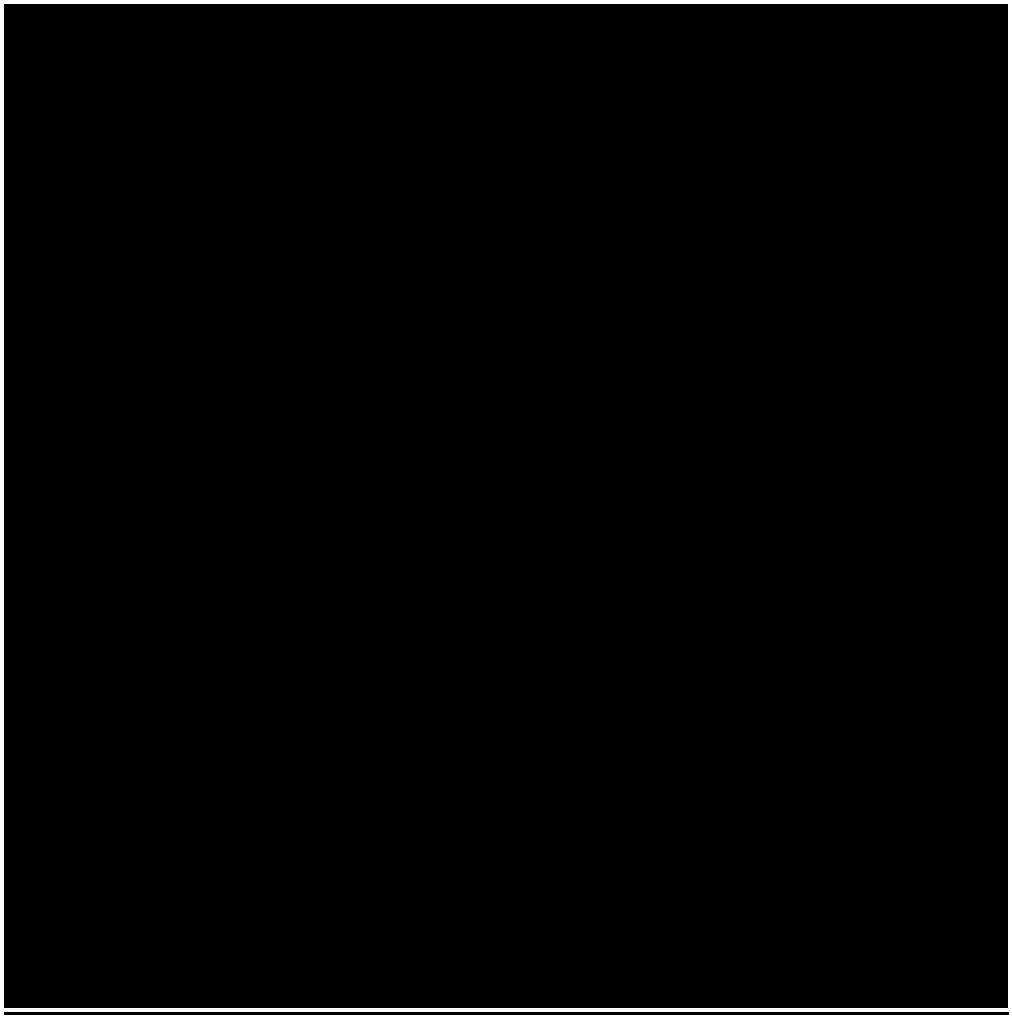


Figure 35 Observed and estimated OS hazards from parametric survival models of GLOW and SPOTLIGHT

Figure 36: OS smoothed and empirical hazards

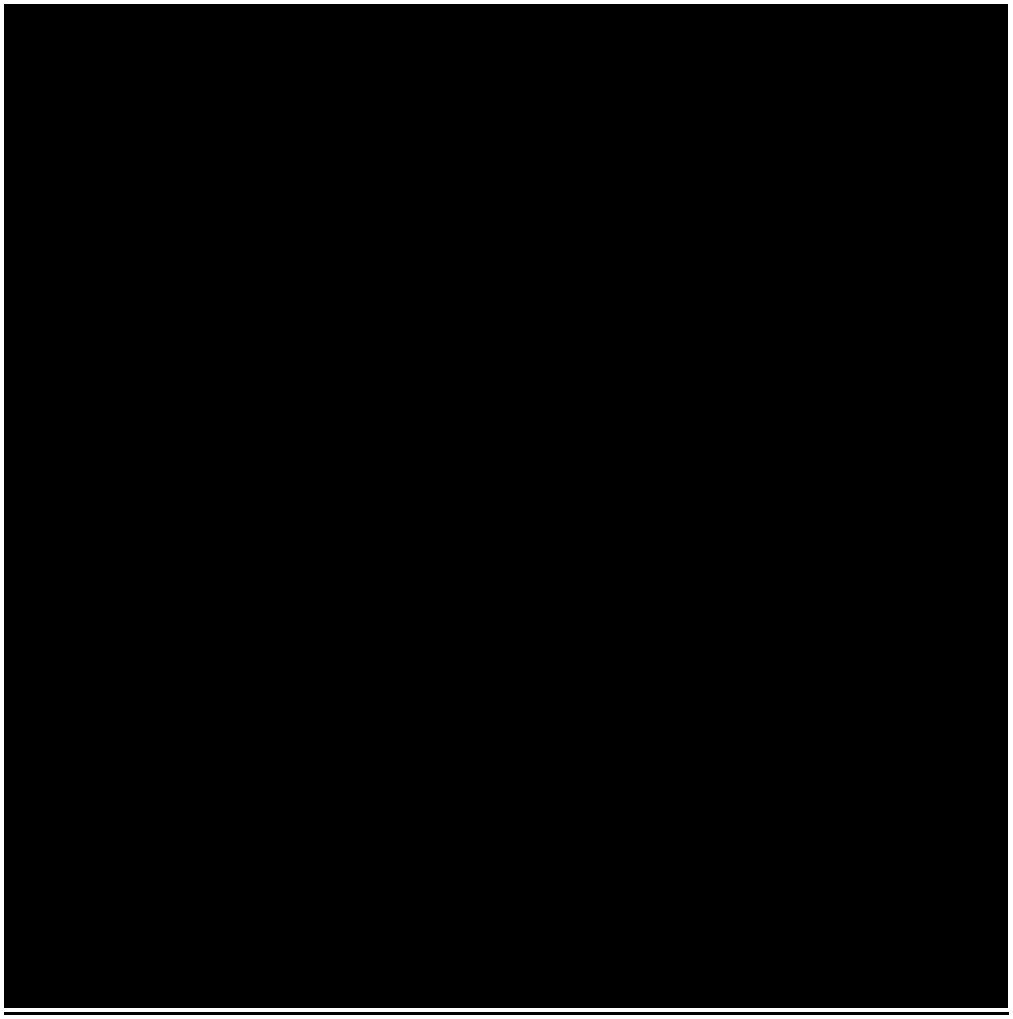


Figure 37: OS log survival odds plot

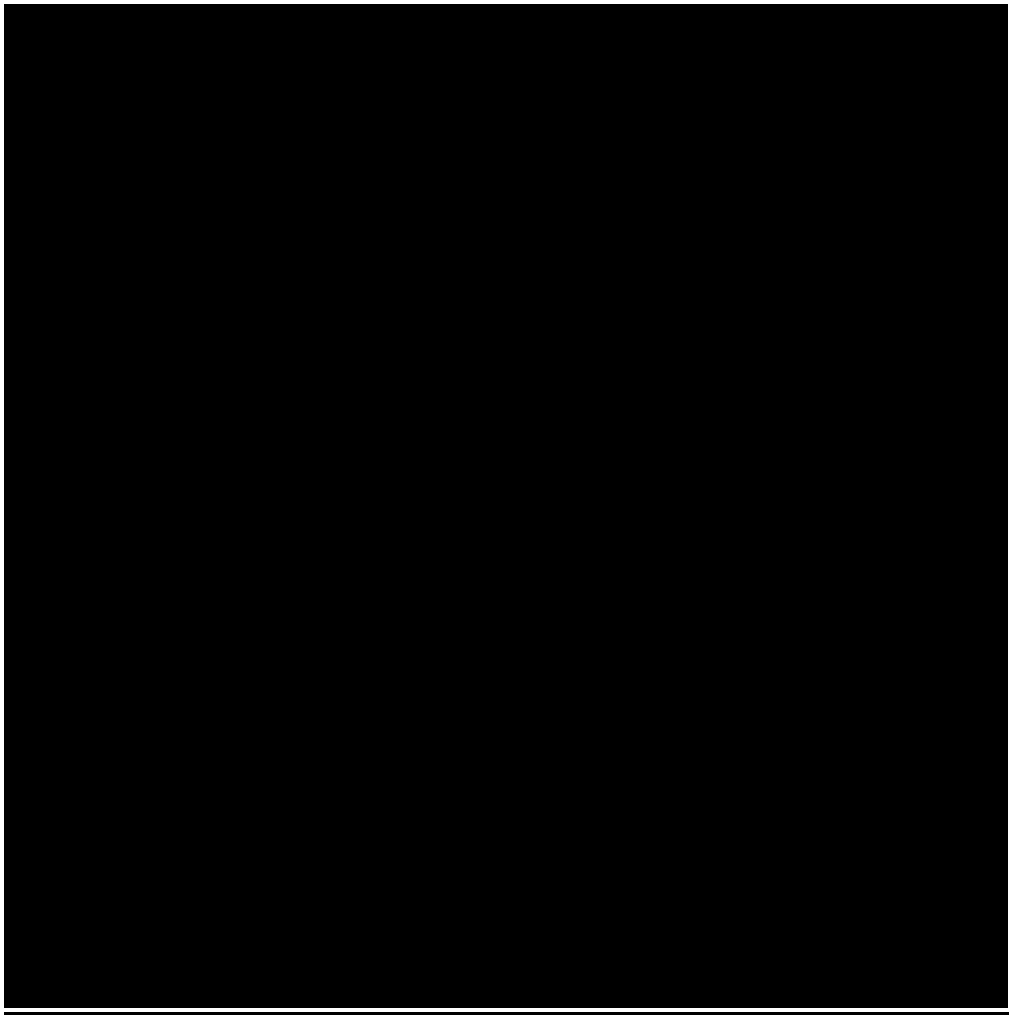


Figure 38: OS QQ plot

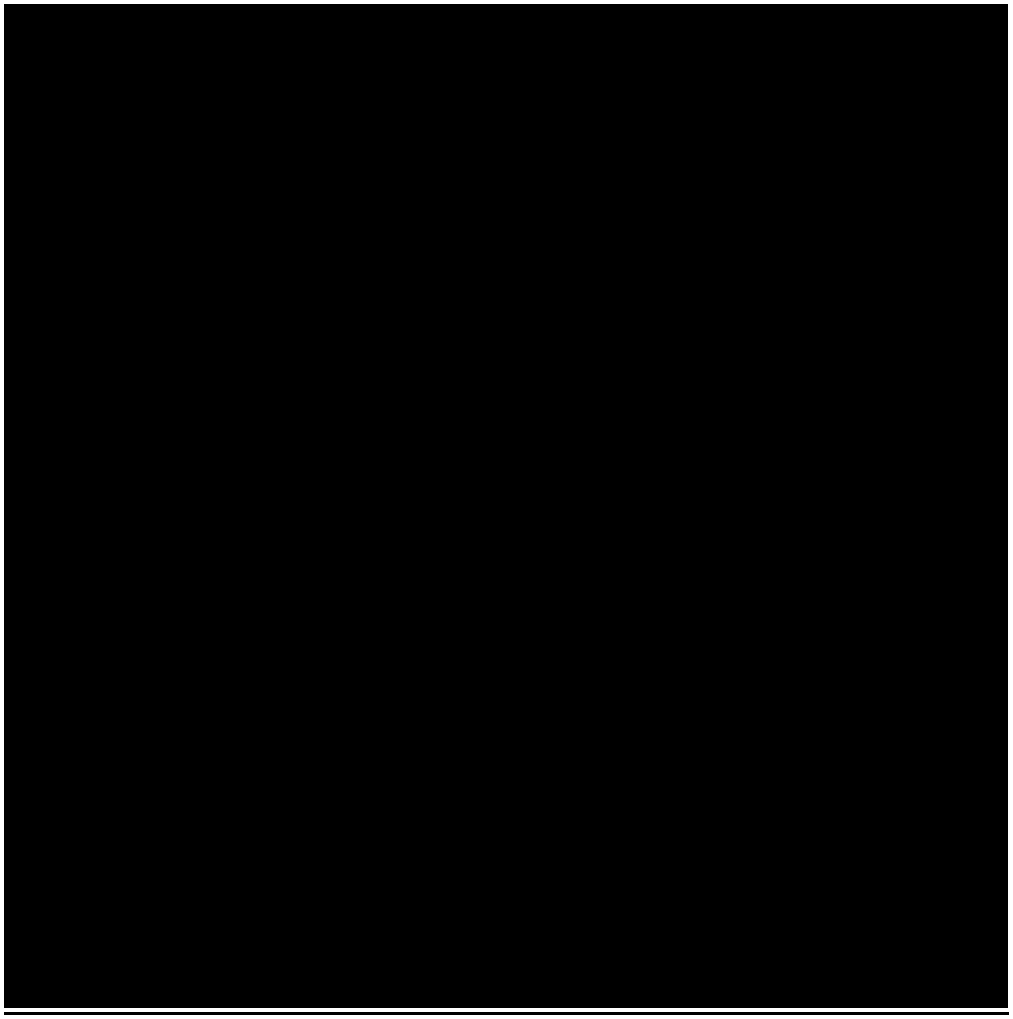


Figure 39 OS standard parametric models and KM data from chemotherapy arms of SPOTLIGHT and GLOW pooled

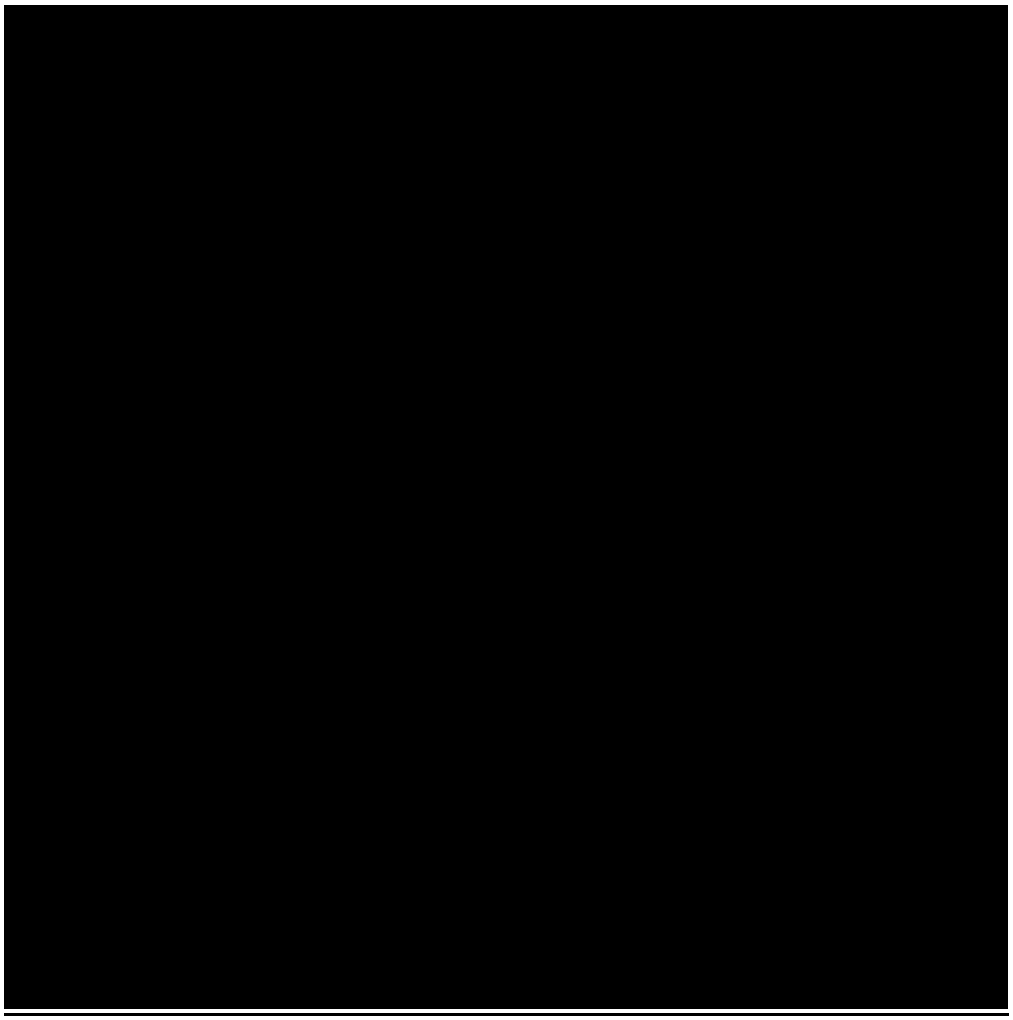
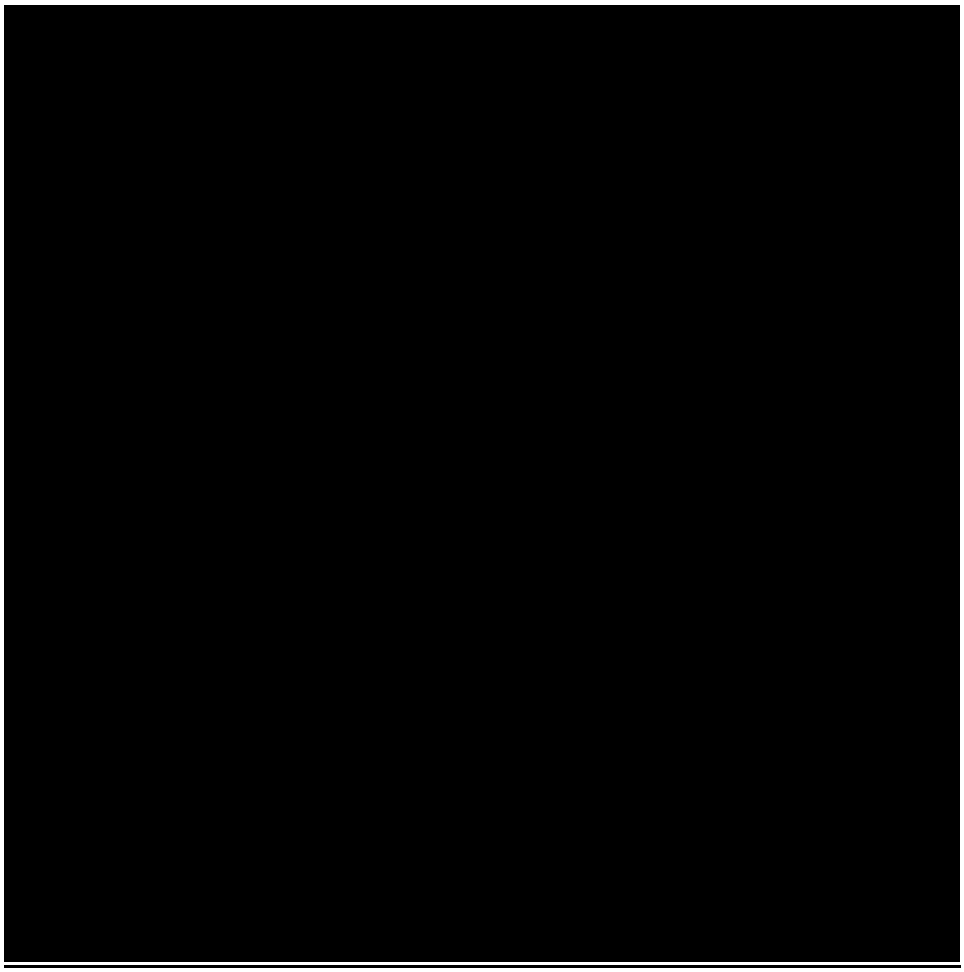


Table 49 Fit statistics of OS standard parametric models, SPOTLIGHT and GLOW

	Zolbetuximab + chemotherapy		Chemotherapy	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	4245.21	4249.49	4571.14	4575.42
Weibull	4222.94	4231.51	4536.00	4544.56
Log-normal	4225.05	4233.62	4578.86	4587.42
Log-logistic	4210.51	4219.09	4534.83	4543.39
Gompertz	4241.21	4249.78	4558.73	4567.29
Gamma	4217.52	4226.09	4532.36	4540.93
Generalised gamma	4214.73	4227.59	4534.10	4546.95
Key: AIC, Akaike information critia; BIC Bayesian information criteria				

Figure 40 OS standard parametric models and KM data from Zolbetuximab + chemotherapy arms of SPOTLIGHT and GLOW pooled



B.2.2. Progression-free survival

As survival models were only fit to the chemotherapy group, it was not necessary to test the proportional hazards assumption. Figure 41 shows the progression-free survival Kaplan Meier data in the chemotherapy group.

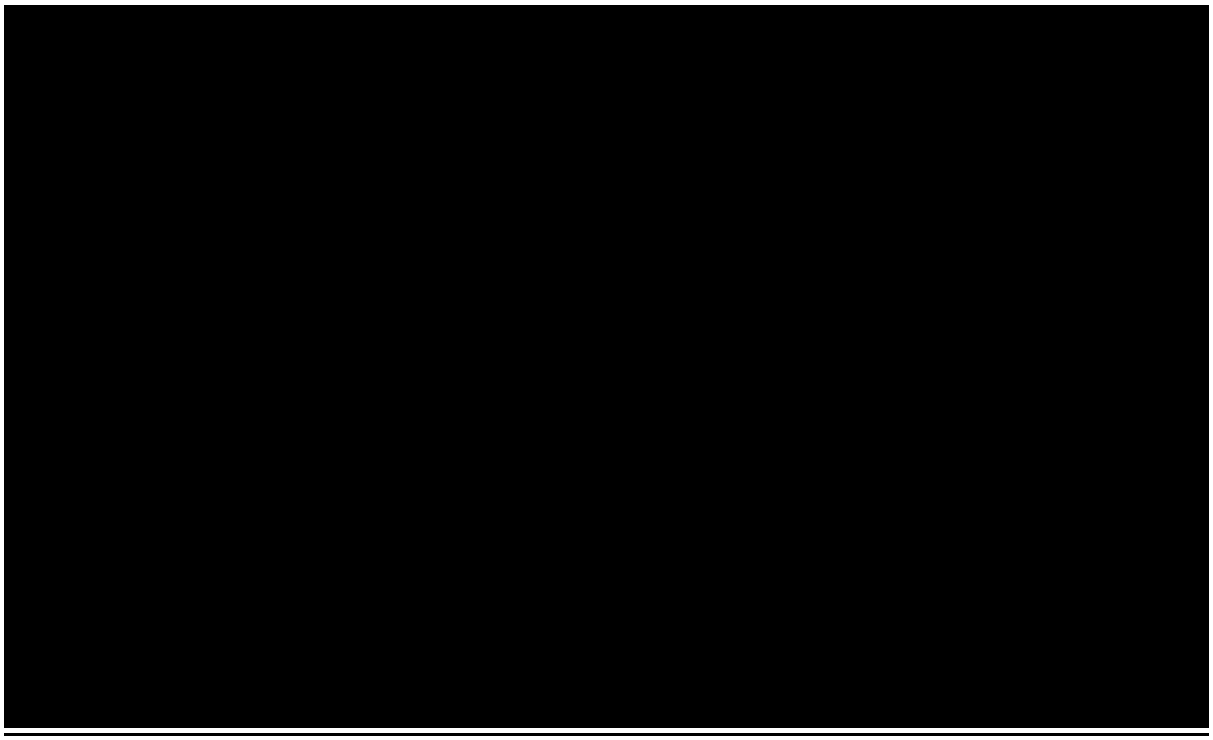
Figure 42 and Figure 43 show the Kaplan Meier progression-free survival data from the chemotherapy arms of each trial separately and the corresponding log-cumulative hazard plots, respectively. Findings are similar to those for OS, supporting the inclusion of CheckMate 649 PD-L1 CPS ≥ 5.

Figure 41 Pooled chemotherapy Kaplan Meier PFS data (pooled GLOW, SPOTLIGHT and CheckMate-649 PD-L1 CPS ≥ 5)

Figure 42 Kaplan Meier PFS data from the chemotherapy arms of GLOW, SPOTLIGHT and CheckMate-649 PD-L1 CPS ≥ 5

Key: CM-649, CheckMate 649.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 43 Log-cumulative hazard plot of PFS data from the chemotherapy arms of GLOW, SPOTLIGHT and CheckMate-649 PD-L1 CPS ≥ 5



An overview of the number of patients at risk for the pooled SPOTLIGHT, GLOW and CheckMate 649 chemotherapy data is provided in Table 50.

Table 50: A summary of the numbers of patients at risk for the pooled chemotherapy data (SPOTLIGHT, GLOW, CheckMate 649) - PFS

Time (Years)	Numbers at risk
0	[redacted]
0.25	[redacted]
0.5	[redacted]
0.75	[redacted]
1	[redacted]
1.25	[redacted]
1.5	[redacted]
1.75	[redacted]
2	[redacted]
2.25	[redacted]

2.5	[redacted]
2.75	[redacted]
3	[redacted]
3.25	[redacted]
3.5	[redacted]
3.75	[redacted]
4	[redacted]
4.25	[redacted]
4.5	[redacted]
4.75	[redacted]
5	[redacted]

B.2.2.1. Parametric survival models

Landmark survival at select time points are presented in Table 51, alongside the standard parametric extrapolations (Figure 44) and corresponding hazards (Figure 45). Statistical fit according to AIC and BIC of each model is presented in Table 54. The log-logistic provides the best within-sample fit based on both measures. However, as with the OS parametric models, the visual comparison between the empirical hazard and the estimated hazard suggests that all the parametric curves, including the log-logistic, overestimate hazard rates from around 2-years onwards.

Table 51 Standard parametric model landmark PFS for pooled chemotherapy

Time (Years)	0	1	2	3	4	5	10
Number at risk	1017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 44 PFS parametric survival curves for pooled chemotherapy

Figure 45 PFS parametric survival curve hazard plots for pooled chemotherapy

Table 52 Fit statistics of PFS standard parametric extrapolations for pooled chemotherapy

Model	AIC	AIC_rank	BIC	BIC_rank
Exponential	7,278	7	7,283	6
Gamma	7,261	5	7,270	5
Gen.gamma	7,179	2	7,194	3
Gompertz	7,255	4	7,265	4
Log-logistic	7,143	1	7,153	1
Log-normal	7,180	3	7,190	2
Weibull	7,276	6	7,286	7
Key: AIC, Akaike's information criteria; BIC, Bayesian information critera				

B.2.2.2. Spline-based models

Landmark survival at select time points (Table 53) are presented in alongside the spline-based extrapolations (Figure 46). Statistical fit according to AIC and BIC of each model is presented in Table 54. As with OS, the 3-knot spline models give best fit to tail, with little difference in estimates between these three models. For both AIC and BIC, the two best-fitting models from both measures are always the 3-knot odds followed by the 3-knot normal, with the 3-knot hazard also within one point of the best-fitting model. Collectively, this supports the use of a 3-knot model.

Table 53 Spline model landmark OS for pooled chemotherapy

Time (Years)	0	1	2	3	4	5	10
Number at risk	1017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed survival	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 knot hazards	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 knot odds	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 knot normal	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knot hazards	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knot odds	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knot normal	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knot hazards	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knot odds	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knot normal	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 46 PFS spline-based model curves for pooled chemotherapy

Table 54 Fit statistics of PFS standard spline-based models for pooled chemotherapy

Model	AIC	AIC_rank	BIC	BIC_rank
1 knot hazards	7,165.0	8	7,179.8	8
1 knot odds	7,145.2	7	7,159.9	7
1 knot normal	7,175.8	9	7,190.5	9
2 knot hazards	7,129.5	4	7,149.2	3
2 knot odds	7,136.4	5	7,156.1	5
2 knot normal	7,139.9	6	7,159.6	6
3 knot hazards	7,124.8	3	7,149.4	4
3 knot odds	7,124.0	1	7,148.7	1
3 knot normal	7,124.2	2	7,148.8	2
Key: AIC, Akaike's information criteria; BIC, Bayesian information critera				

In summary, log-logistic is the only parametric model with an acceptable fit. Based on both AIC and BIC, the 3-knot spline-based models provide a better fit. Overall, based on AIC, there are six of the nine spline-based models providing a better fit than the log-logistic with four providing a better fit based on BIC. Hence, the 3-knot odds spline model is used in the base case (Figure 47), with use of the log-logistic used in a scenario analysis. The PFS smoothed hazards and 3-knot odds model hazards are presented in Figure 48Figure. Use of alternative spline-based models

was not explored as the similarity of extrapolations arising from these suggests that the impact on cost-effectiveness results would be minimal (Figure 49)- the model has the functionality to explore this if required. The PFS smoothed hazards and top three best-fitting model hazards are presented in Figure 49.

Figure 47 Pooled chemotherapy PFS, 3-knot odds spline

Figure 48: PFS smoothed hazards and 3-knot odds model hazards

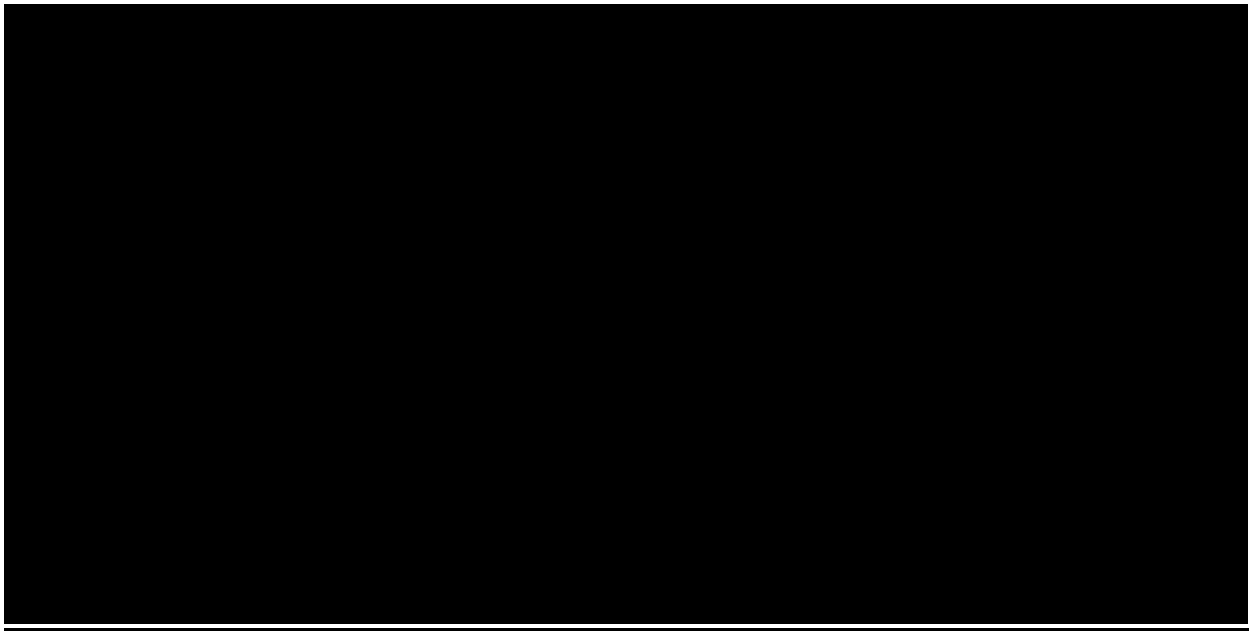
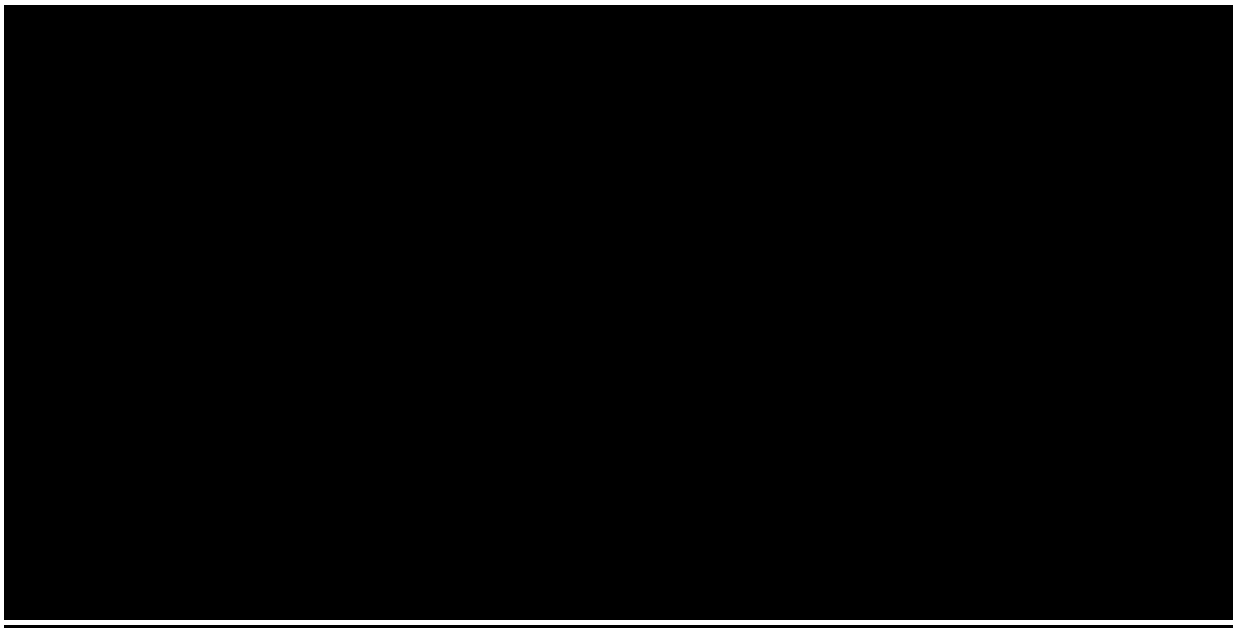


Figure 49: PFS smoothed hazards and top 3 best-fitting model hazards



B.2.2.3. Scenario: evidence from just SPOTLIGHT and GLOW

A Schoenfeld plot, log-log cumulative hazards plot and the observed and modelled hazards of the PFS data from the pooled SPOTLIGHT and GLOW trials are presented in Figure 50 to Figure 52. Figure 53 to Figure 55 show the observed hazards, log survival plot, and QQ plots related to the same data. The PFS curves

for the pooled chemotherapy arms of SPOTLIGHT and GLOW, and the pooled zolbetuximab + chemotherapy arms of SPOTLIGHT and GLOW are presented in Figure 56 and Figure 57. Table 55 shows the fit statistics.

As with OS, convergence of the log-log cumulative hazard plot for PFS suggests that an assumption of proportional hazards may not be met. When fitting separate parametric models to both treatments, all models notably fail to capture the observed plateau that occurs at the end of follow-up. This is likely due to a combination of insufficient follow-up to reliably estimate the long-term survival, low patient numbers, and insufficiently flexible survival models. These limitations are all addressed by the use of flexible spline-based models and the incorporation of external evidence from CheckMate 649.

Figure 50 PFS - Schoenfeld plot of residuals, SPOTLIGHT and GLOW

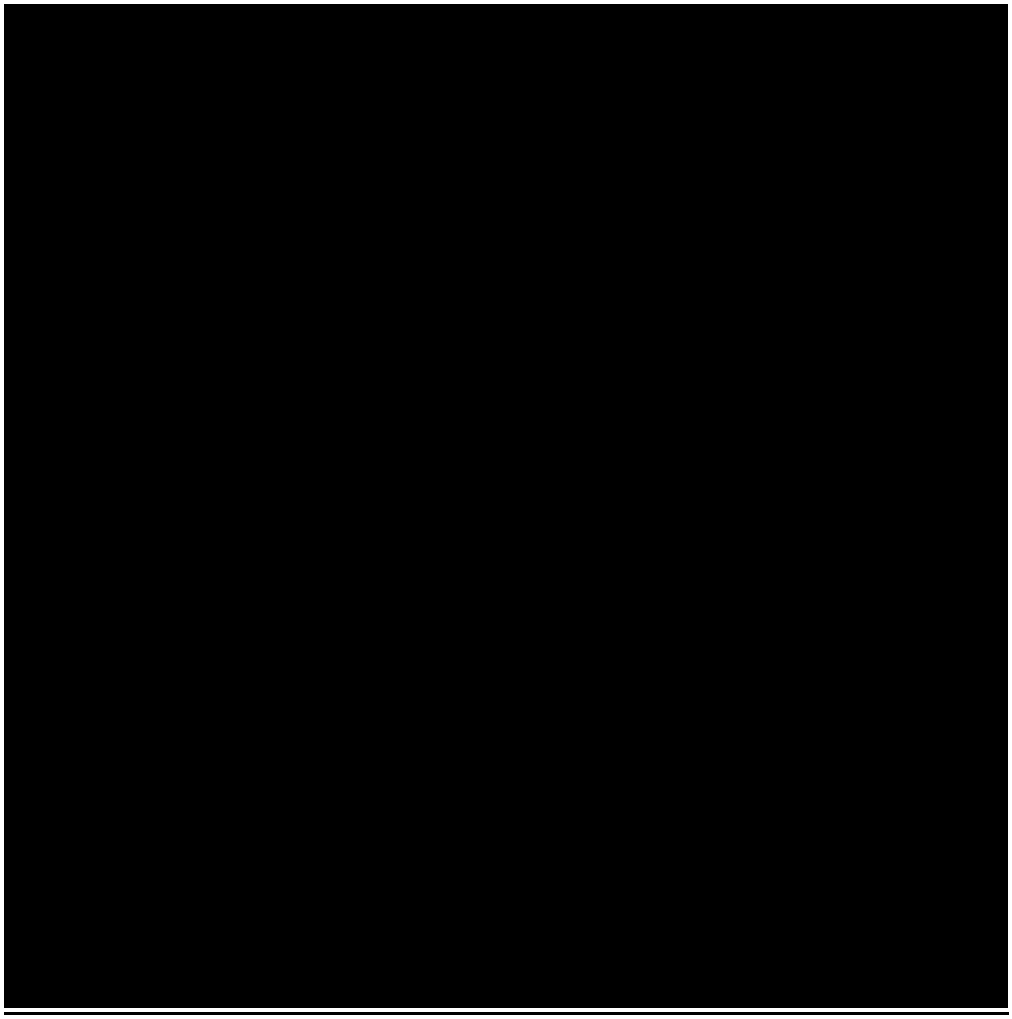


Figure 51 Log-log cumulative hazard plots of PFS from both pooled zolbetuxumab + chemotherapy arms and pooled chemotherapy arms of SPOTLIGHT and GLOW

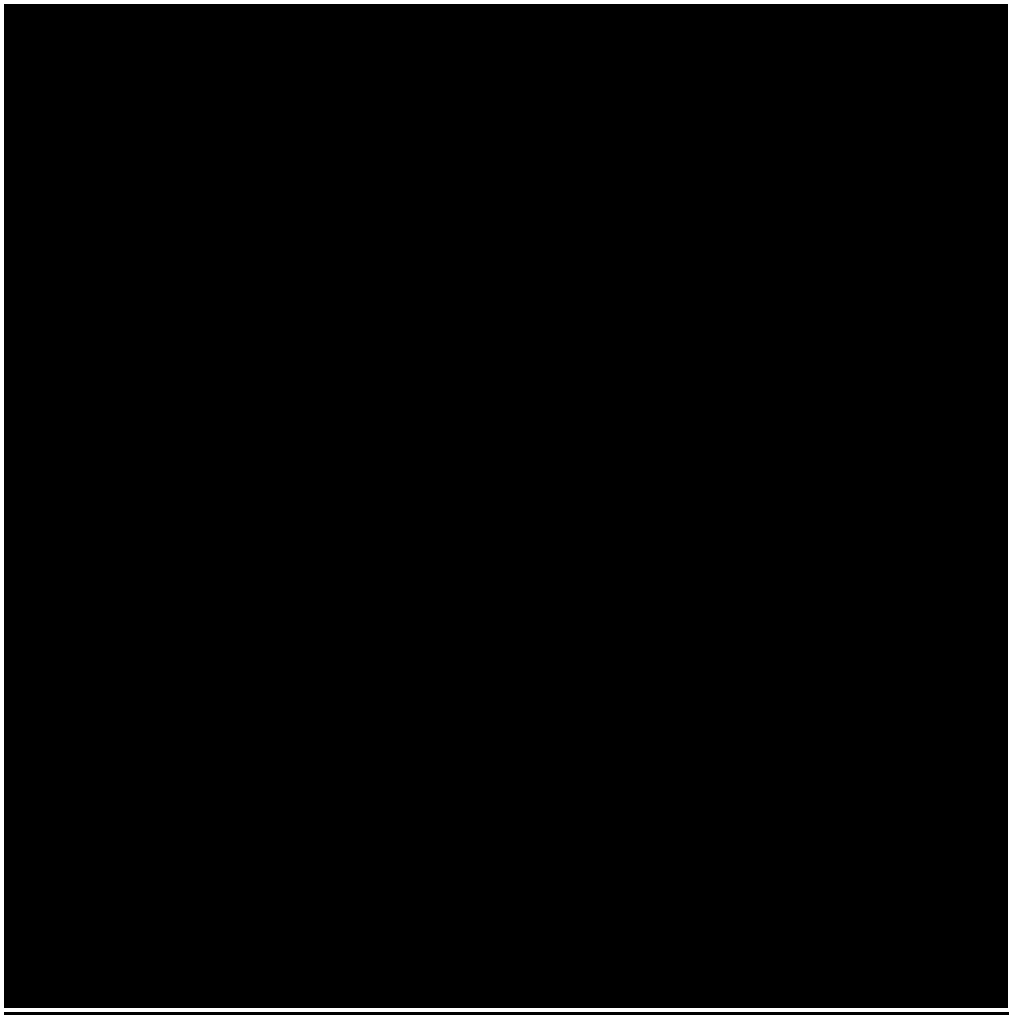


Figure 52 Observed and estimated PFS hazards from parametric survival models of GLOW and SPOTLIGHT

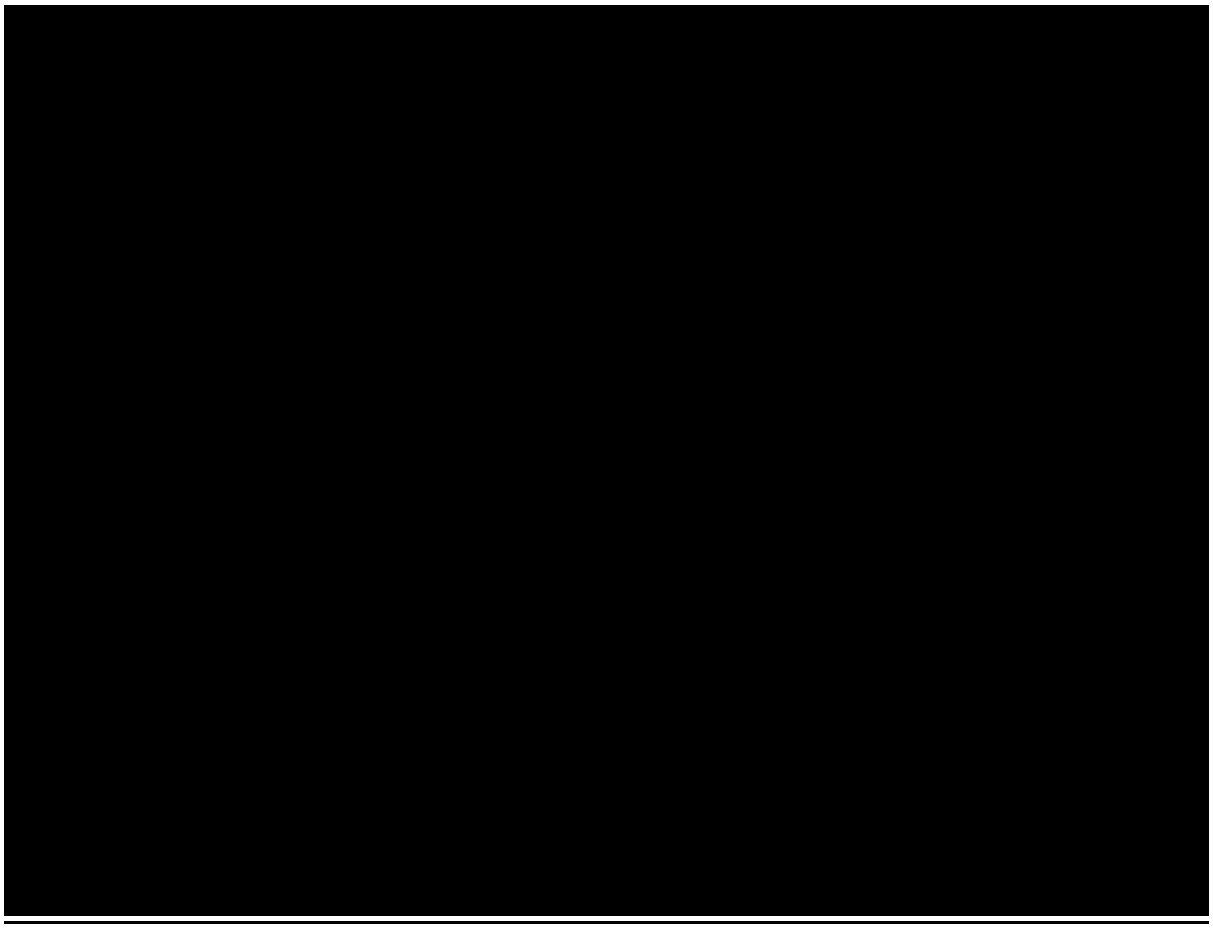


Figure 53: PFS smoothed and empirical hazards

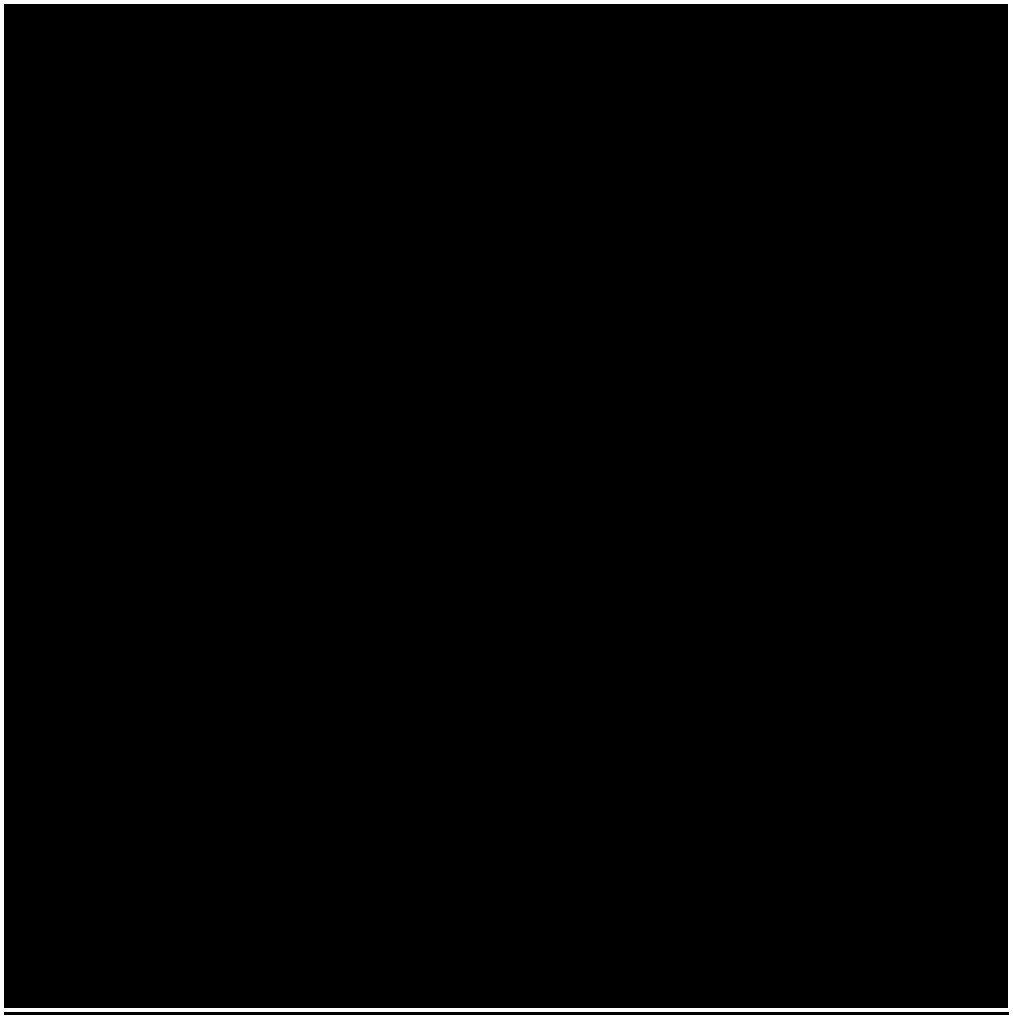


Figure 54: PFS log survival odds plot

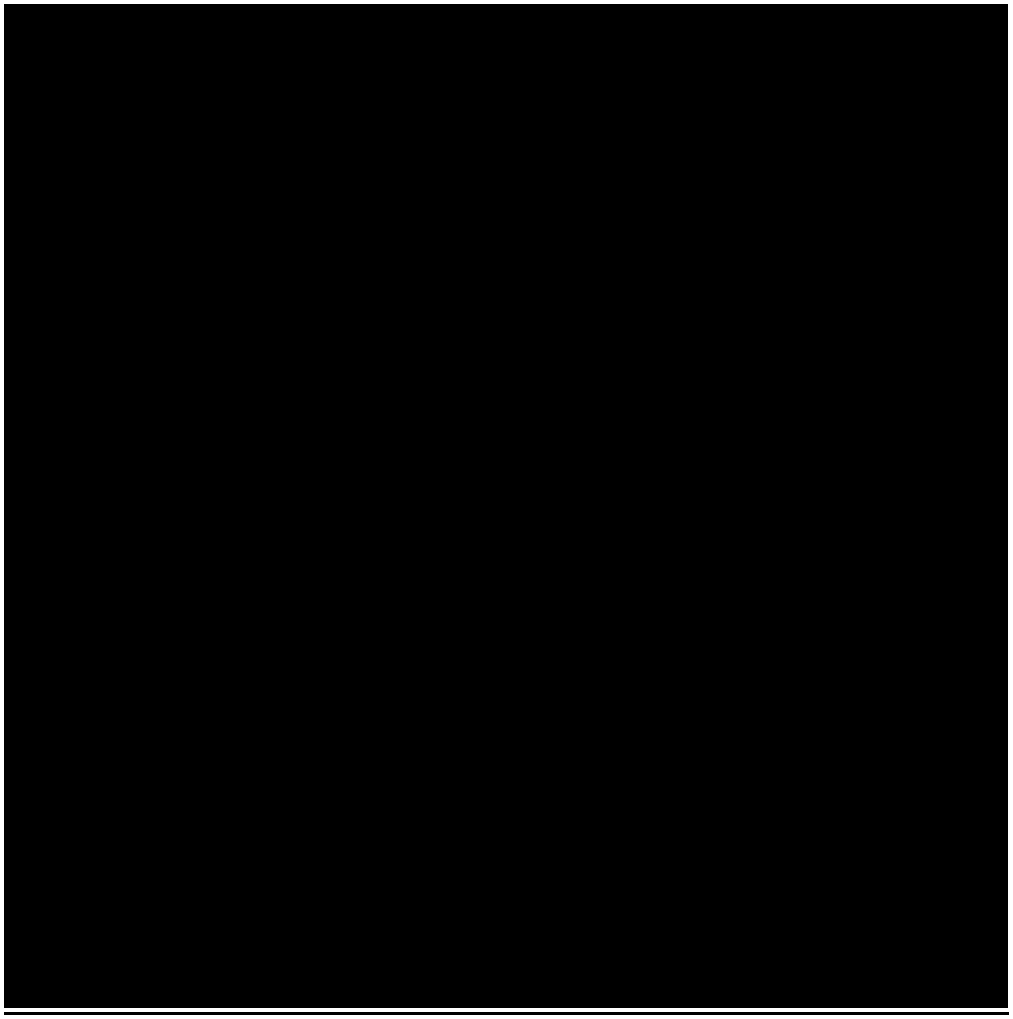


Figure 55: PFS QQ plot

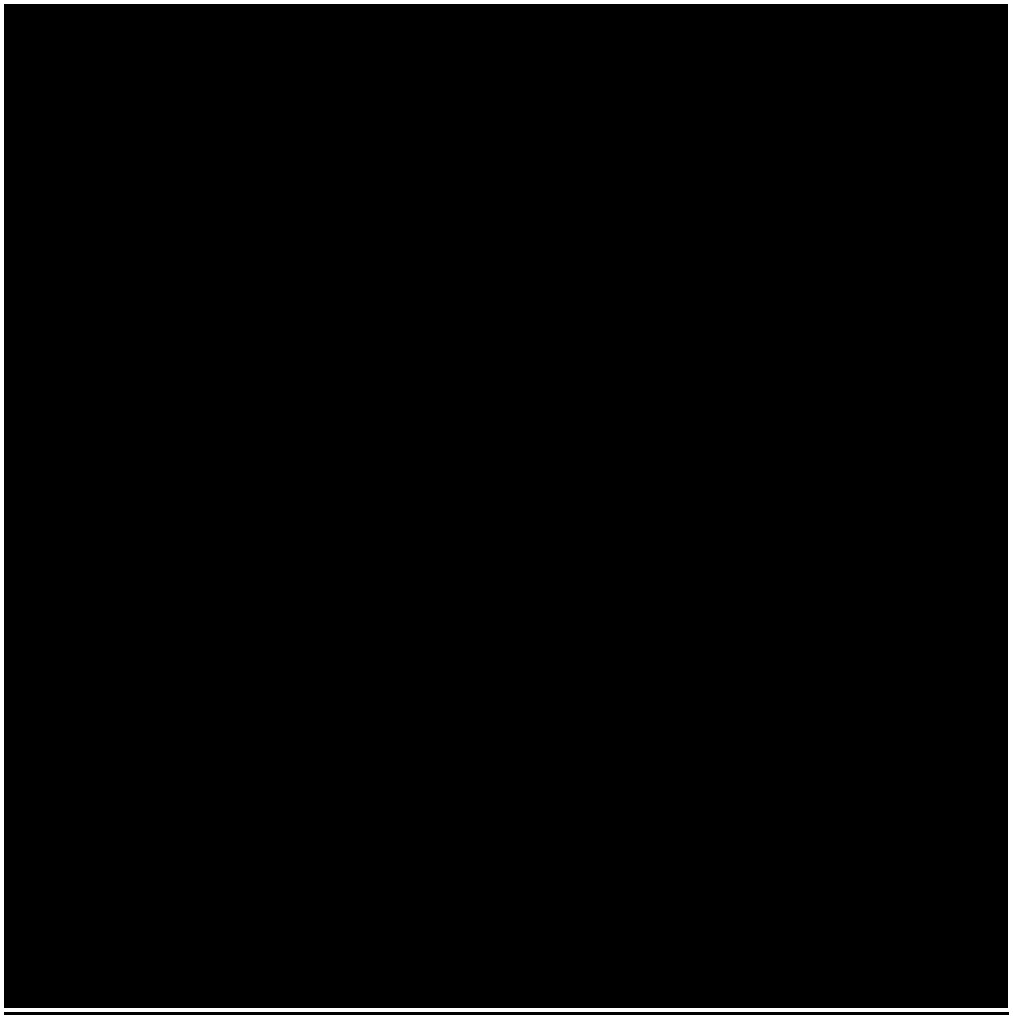


Figure 56 PFS standard parametric models and KM data from chemotherapy arms of SPOTLIGHT and GLOW pooled

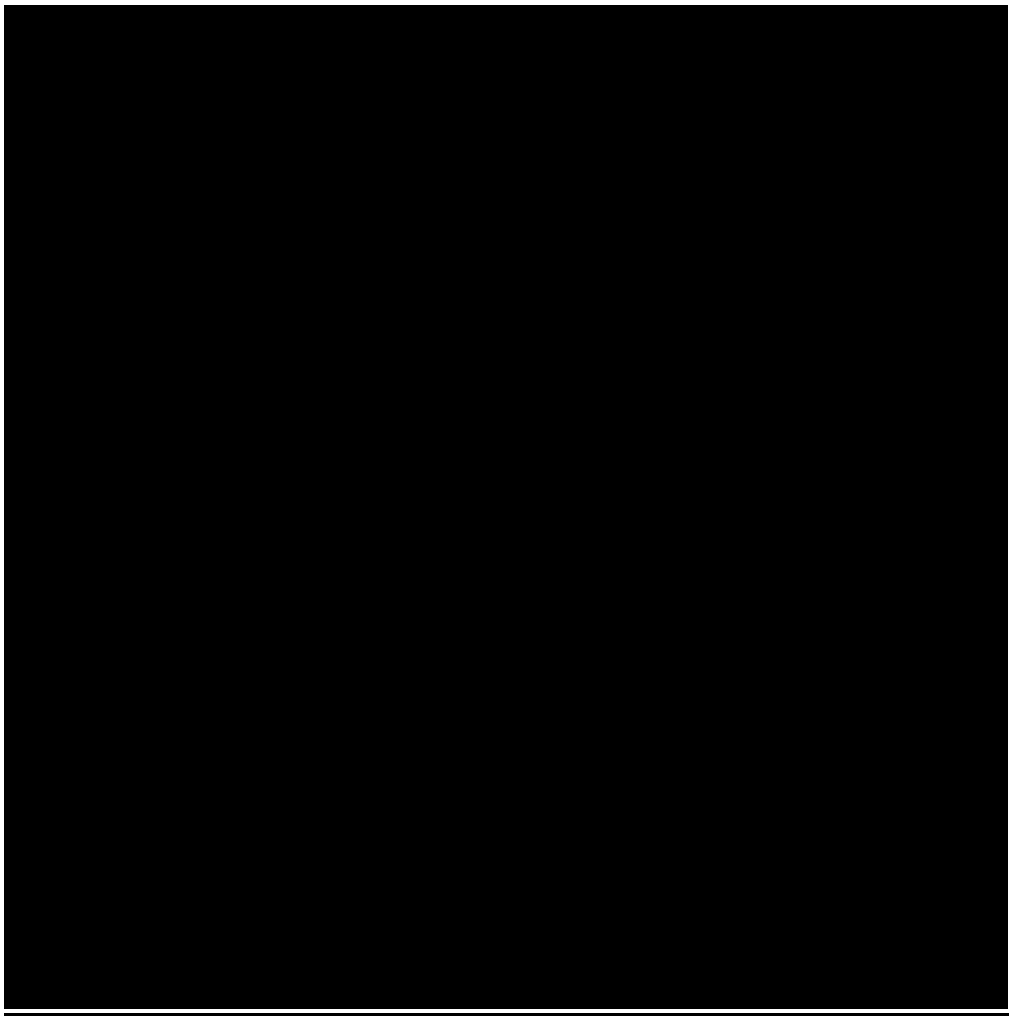


Figure 57 PFS standard parametric models and KM data from Zolbetuximab + chemotherapy arms of SPOTLIGHT and GLOW pooled

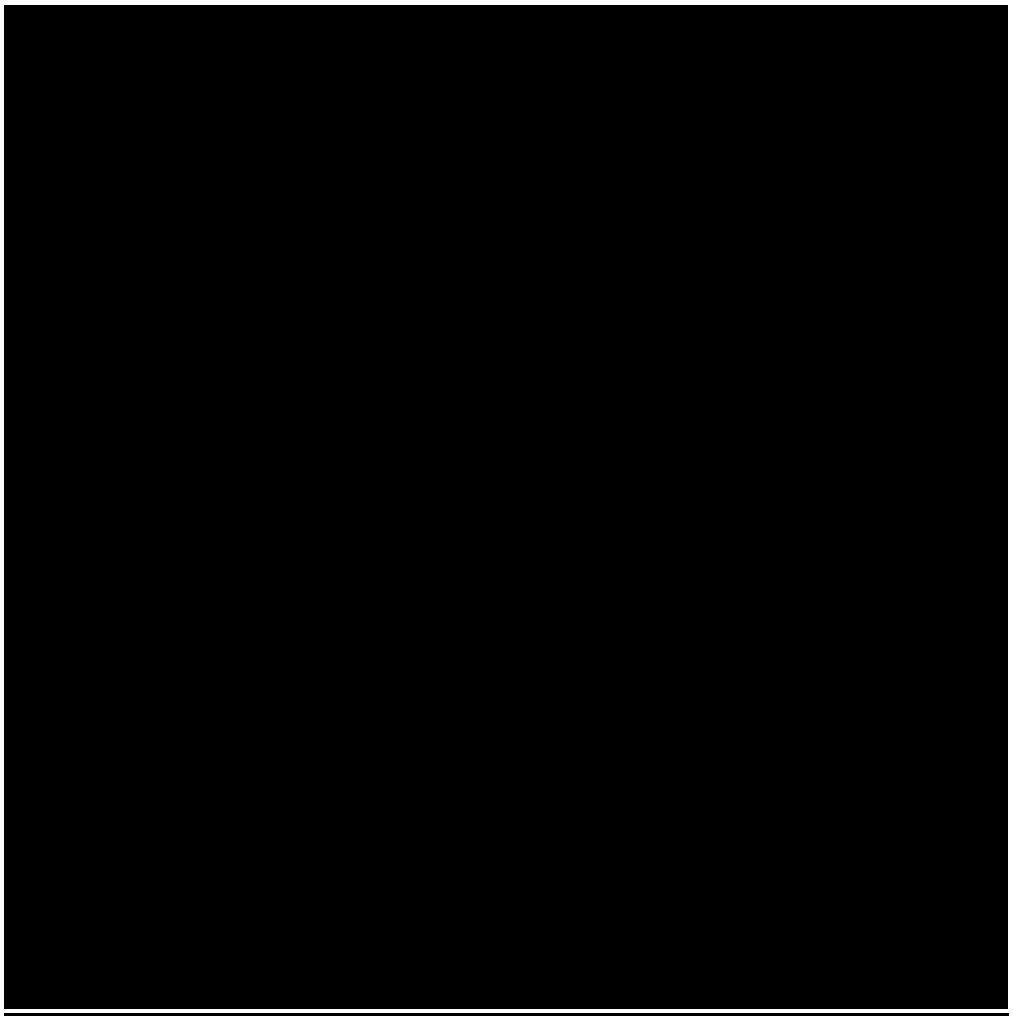


Table 55 Fit statistics of PFS standard parametric models, SPOTLIGHT and GLOW

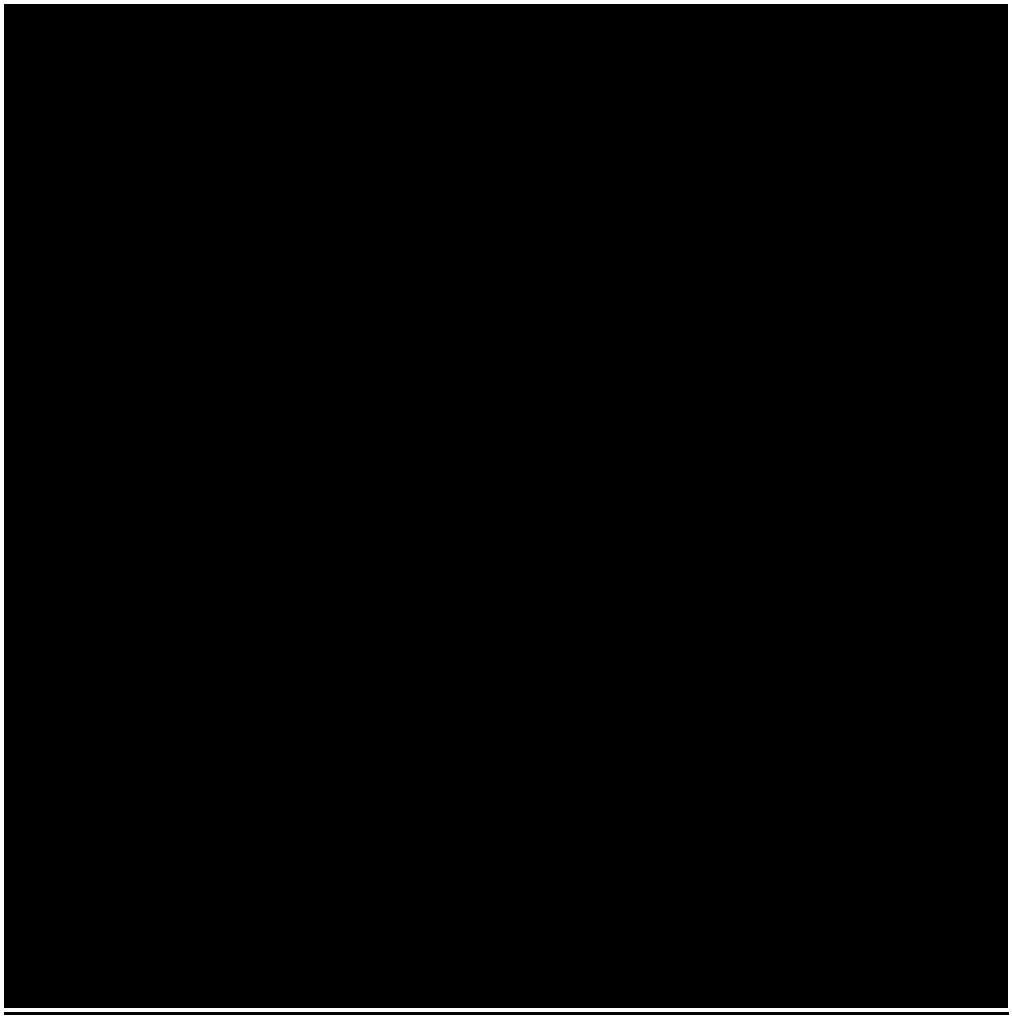
	Zolbetuximab + chemotherapy		Chemotherapy	
	AIC	BIC	AIC	BIC
Exponential	3302.38	3306.66	3651.95	3656.23
Weibull	3298.64	3307.21	3630.46	3639.02
Log-normal	3249.56	3258.13	3631.49	3640.05
Log-logistic	3247.84	3256.41	3598.64	3607.21
Gompertz	3300.20	3308.77	3652.99	3661.56
Gamma	3290.64	3299.21	3620.73	3629.29
Generalised gamma	3250.74	3263.60	3613.75	3626.59

B.2.3. Duration of treatment

B.2.3.1. SPOTLIGHT & GLOW (Pooled)

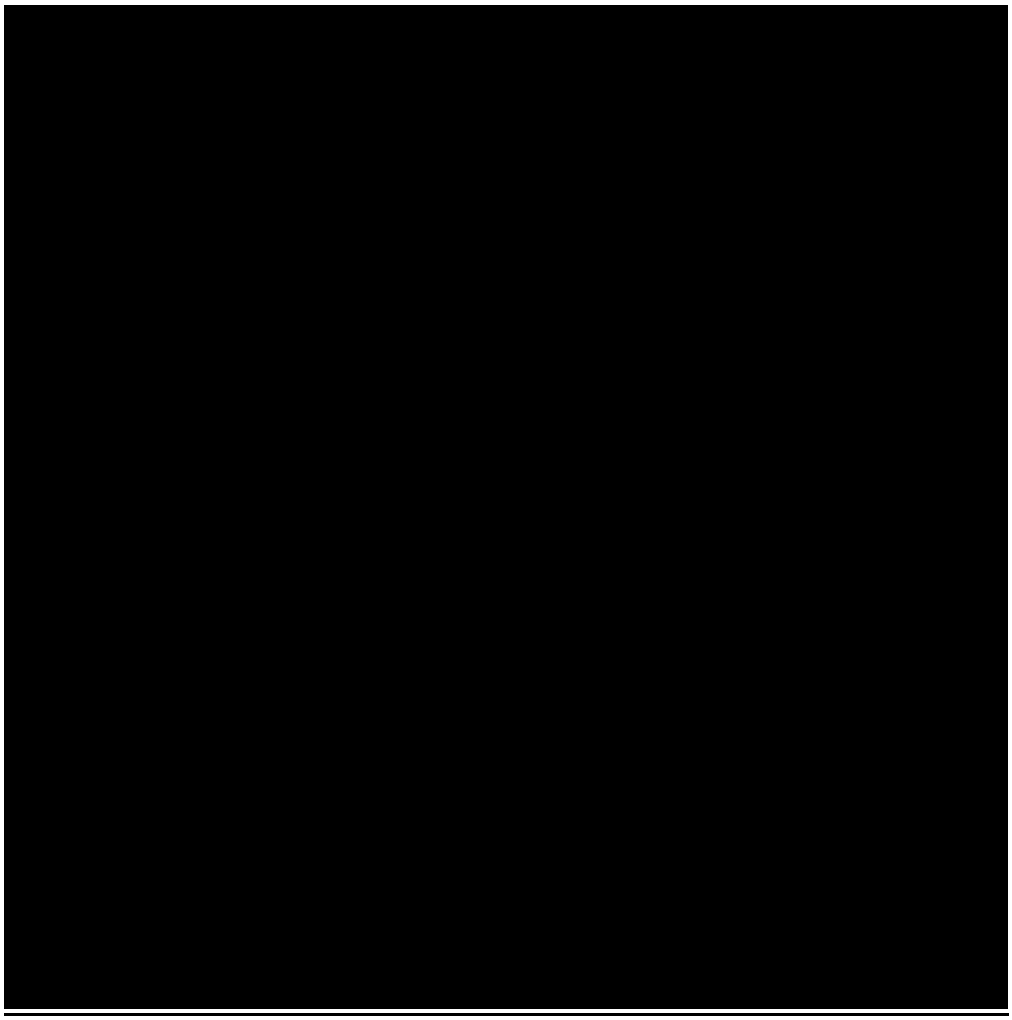
Supportive plots are provided in the following Figures (Figure 58 to Figure 66; Table 56). These are for the pooled SPOTLIGHT and GLOW evidence (data cut-off 8 September 2023 and [redacted], respectively). They demonstrate that the assumption of proportional hazards is violated, motivating the use of separately fitted models.

Figure 58: Duration of treatment log-log cumulative hazard plot based on SPOTLIGHT & GLOW trials (pooled data)



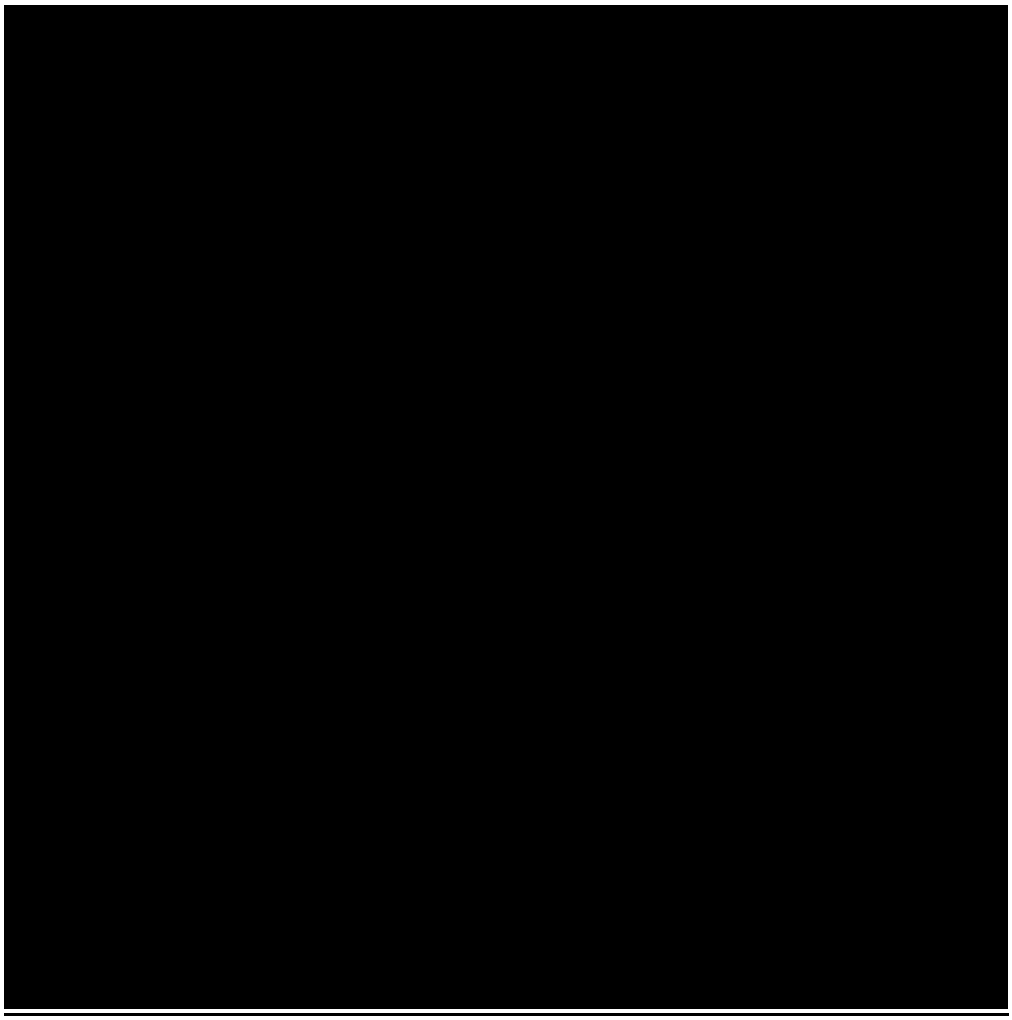
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 59: Duration of treatment schoenfeld residuals plot based on SPOTLIGHT & GLOW trials (pooled data)



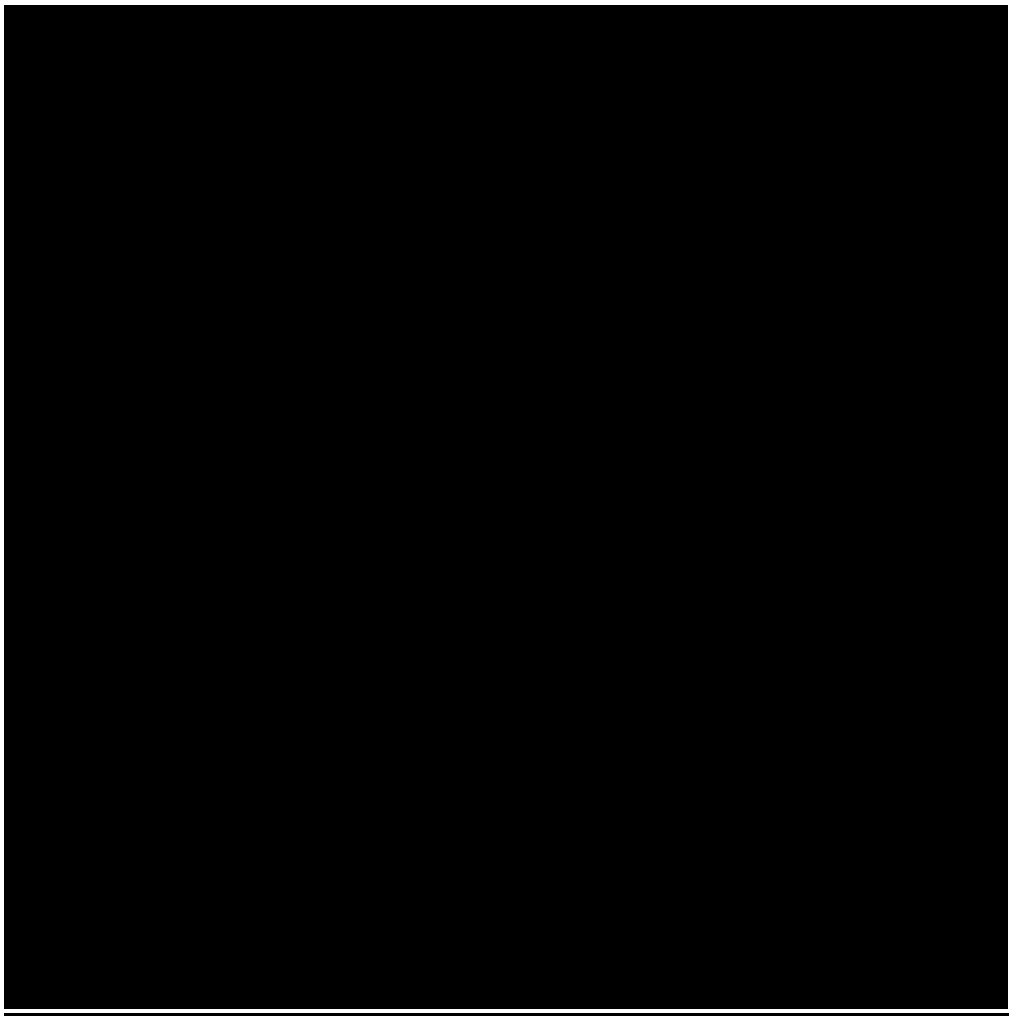
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 60: Duration of treatment hazard plots based on SPOTLIGHT & GLOW trials (pooled data)



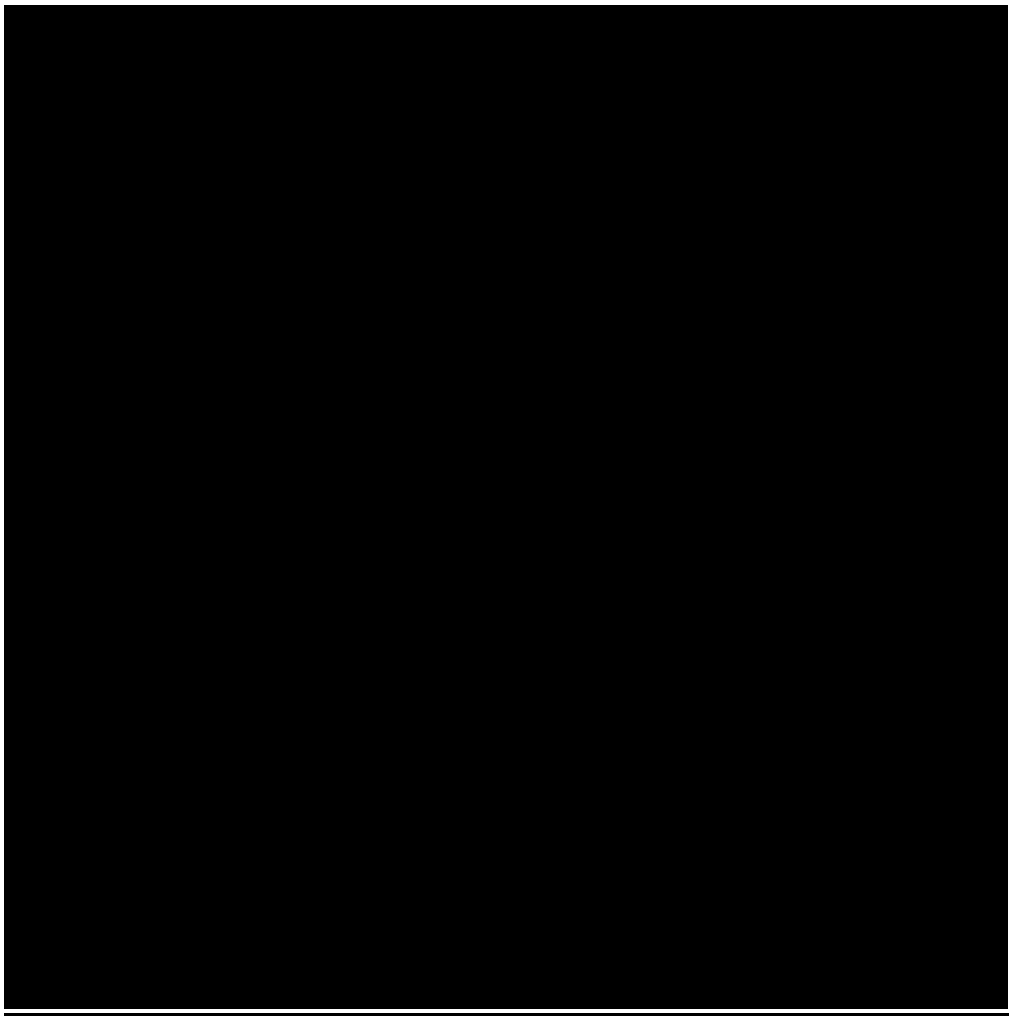
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 61: Duration of treatment log survival odds plot based on SPOTLIGHT & GLOW trials (pooled data)



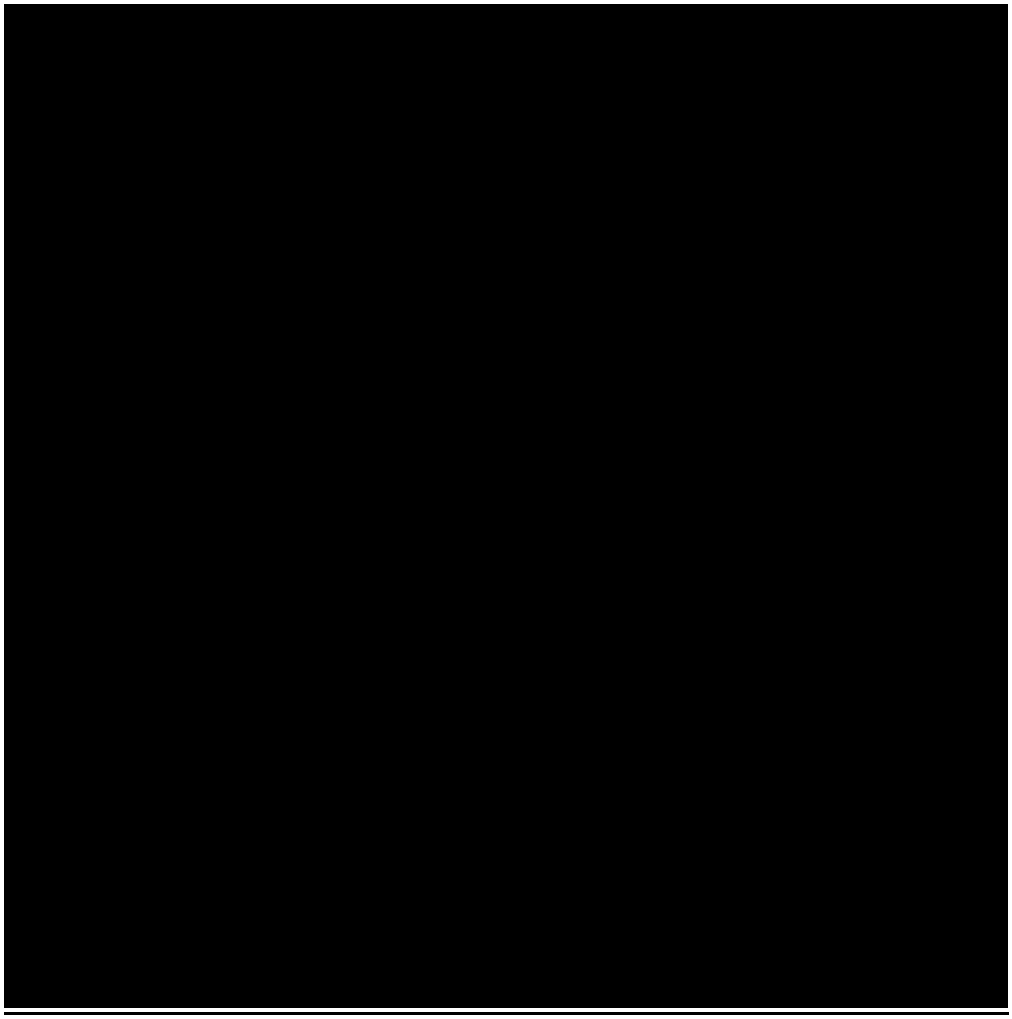
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 62: Duration of treatment QQ plot based on SPOTLIGHT & GLOW trials (pooled data)



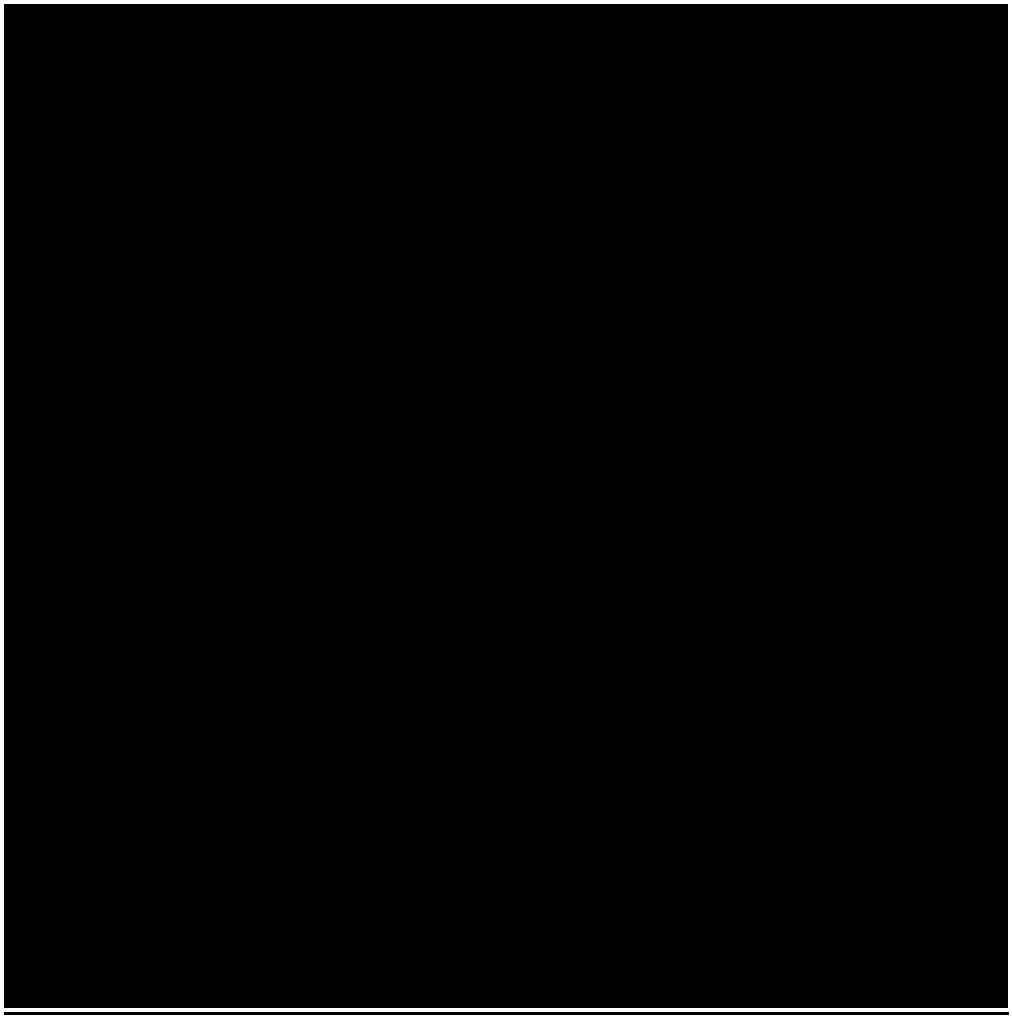
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 63: Fit of parametric survival models, duration of treatment: zolbetuximab + chemotherapy based on SPOTLIGHT & GLOW trials (pooled data)



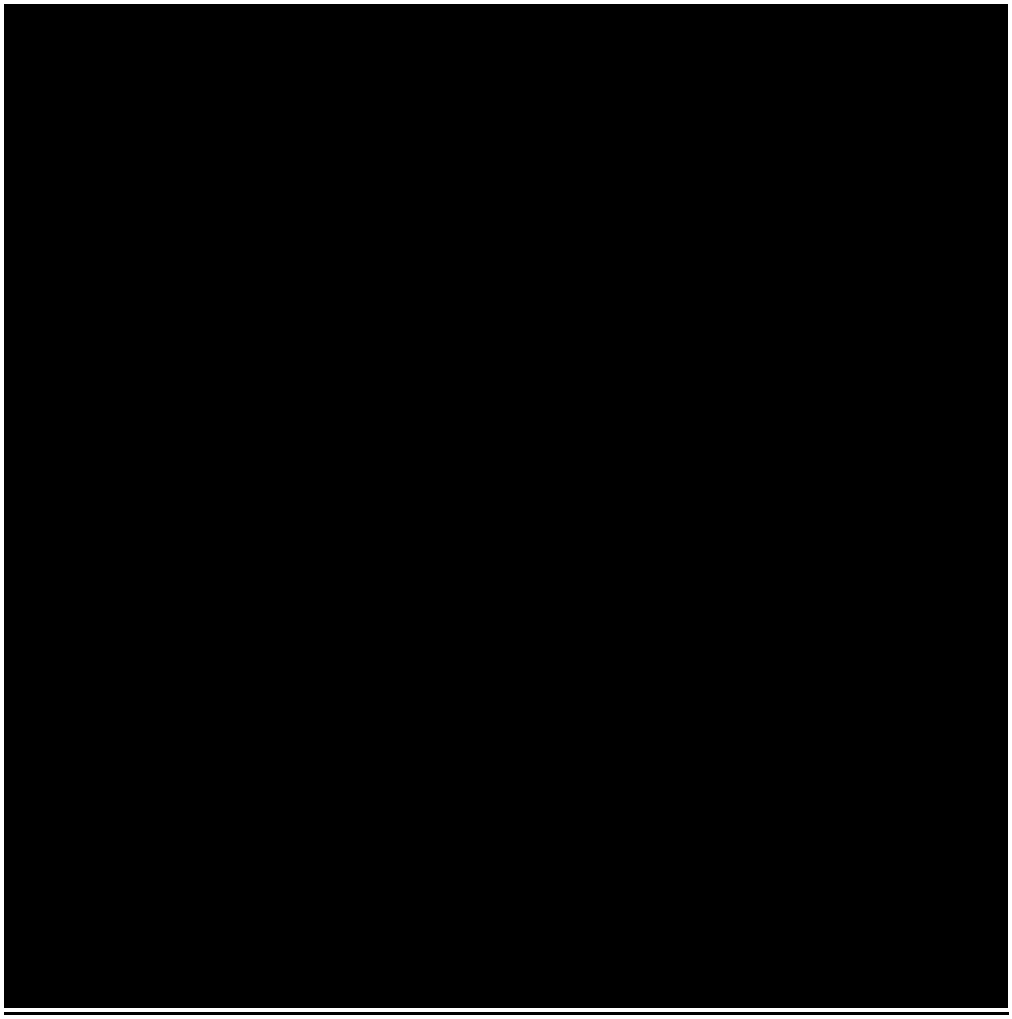
Note: Duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm.

Figure 64: Fit of parametric survival models, duration of treatment: zolbetuximab + chemotherapy (zolbetuximab) based on SPOTLIGHT & GLOW trials (pooled data)



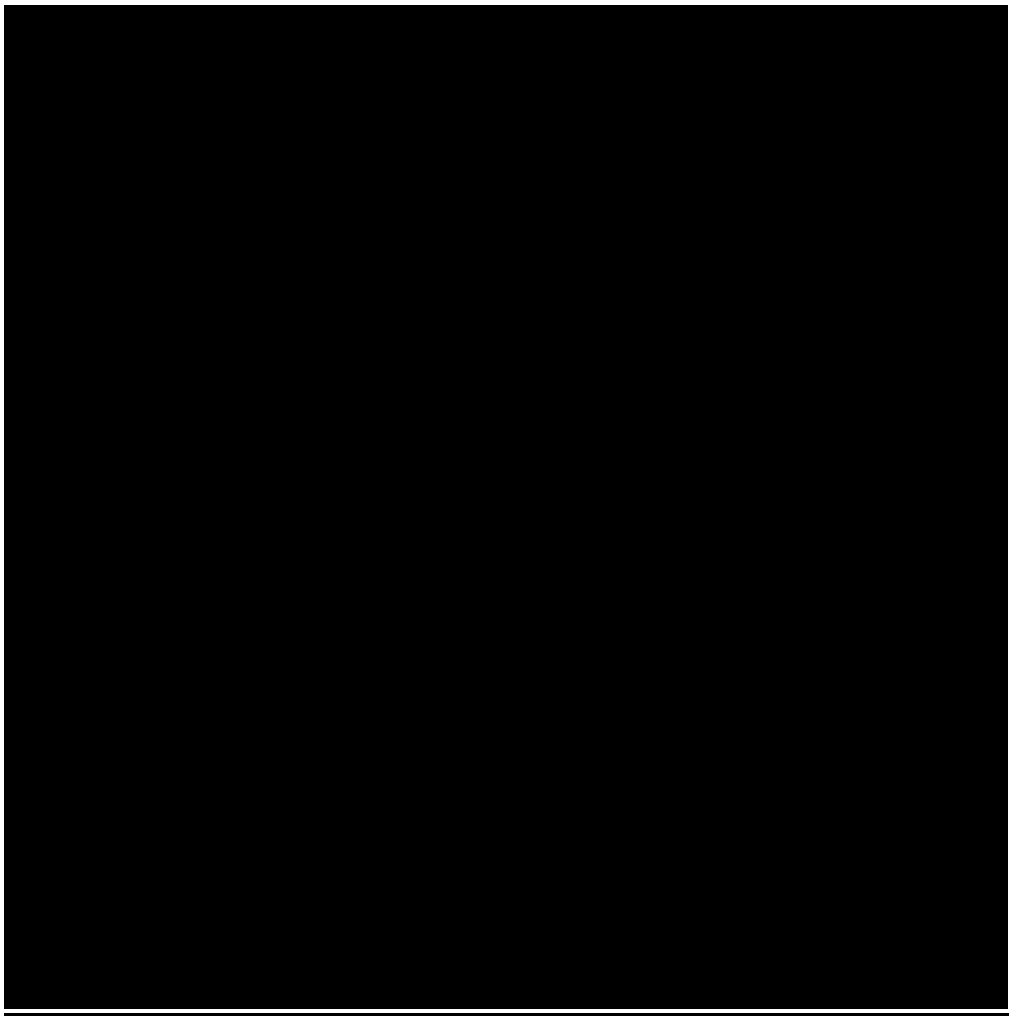
Note: Duration of treatment refers to the duration of the zolbetuximab component in the zolbetuximab + chemotherapy arm.

Figure 65: Fit of parametric survival models, duration of treatment: zolbetuximab + chemotherapy (chemotherapy) based on SPOTLIGHT & GLOW trials (pooled data)



Note: Duration of treatment refers to the maximum duration of any of the chemotherapy components in the zolbetuximab + chemotherapy arm.

Figure 66: Fit of parametric survival models, duration of treatment: chemotherapy based on SPOTLIGHT & GLOW trials (pooled data)



Note: Duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

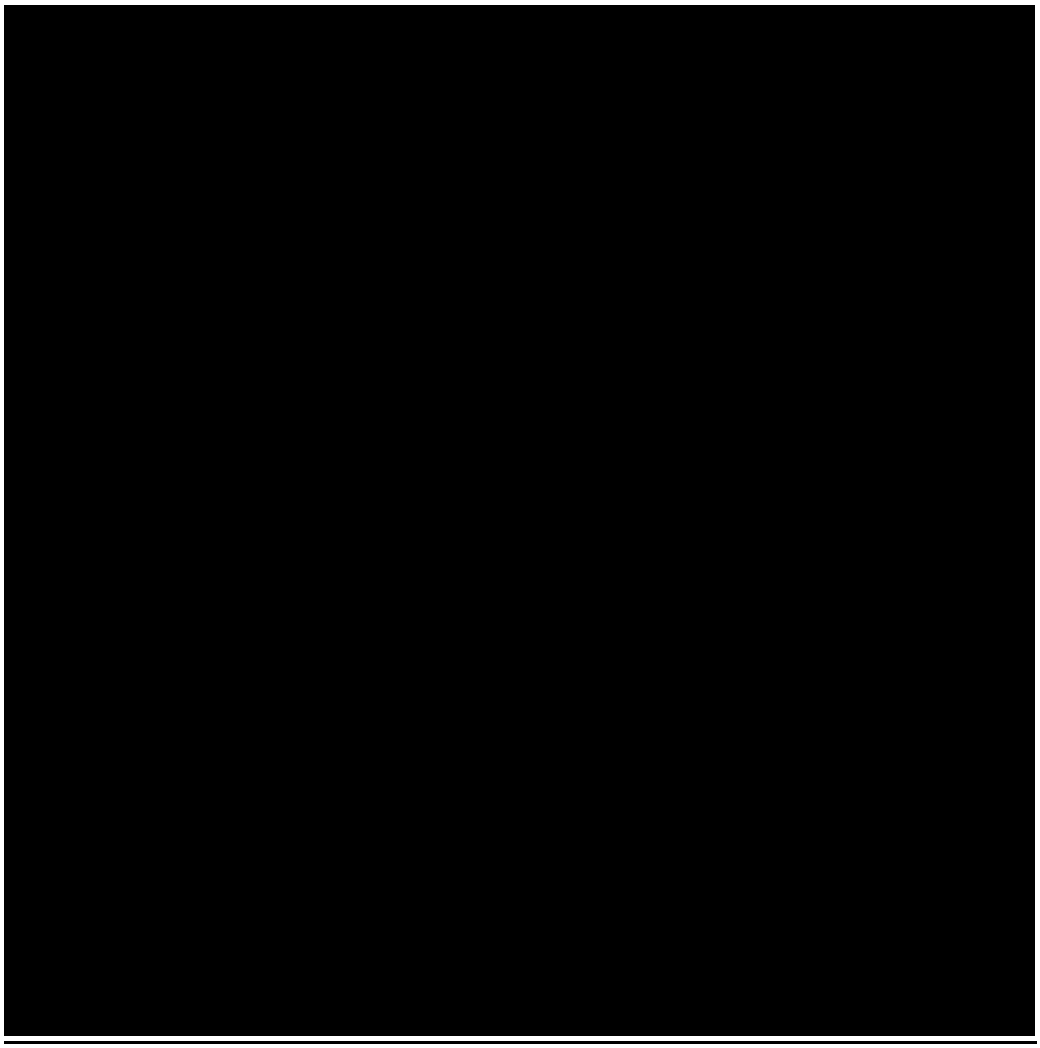
Table 56 Fit statistics of DoT standard parametric models, based on SPOTLIGHT and GLOW (pooled data)

	Zolbetuximab + chemotherapy		Zolbetuximab + Chemotherapy (Zolbetuximab)		Zolbetuximab + Chemotherapy (Chemotherapy)		Chemotherapy	
	AIC	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	4573.13	4577.40	4683.09	4687.37	4640.31	4644.57	4565.96	4570.23
Weibull	4575.13	4583.68	4613.09	4621.65	4637.35	4645.87	4558.93	4567.47
Log-normal	4736.78	4745.34	4744.37	4752.92	4716.11	4724.64	4646.55	4655.08
Log-logistic	4666.83	4675.39	4686.09	4694.64	4659.58	4668.10	4559.72	4568.25
Gompertz	4573.73	4582.29	4645.49	4654.04	4628.90	4637.42	4567.58	4576.11
Gamma	4574.51	4583.07	4606.93	4615.48	4638.85	4647.37	4555.04	4563.58
Generalised gamma	4568.60	4581.43	4608.86	4621.69	4638.15	4650.95	4555.26	4568.07

B.2.3.2. GLOW

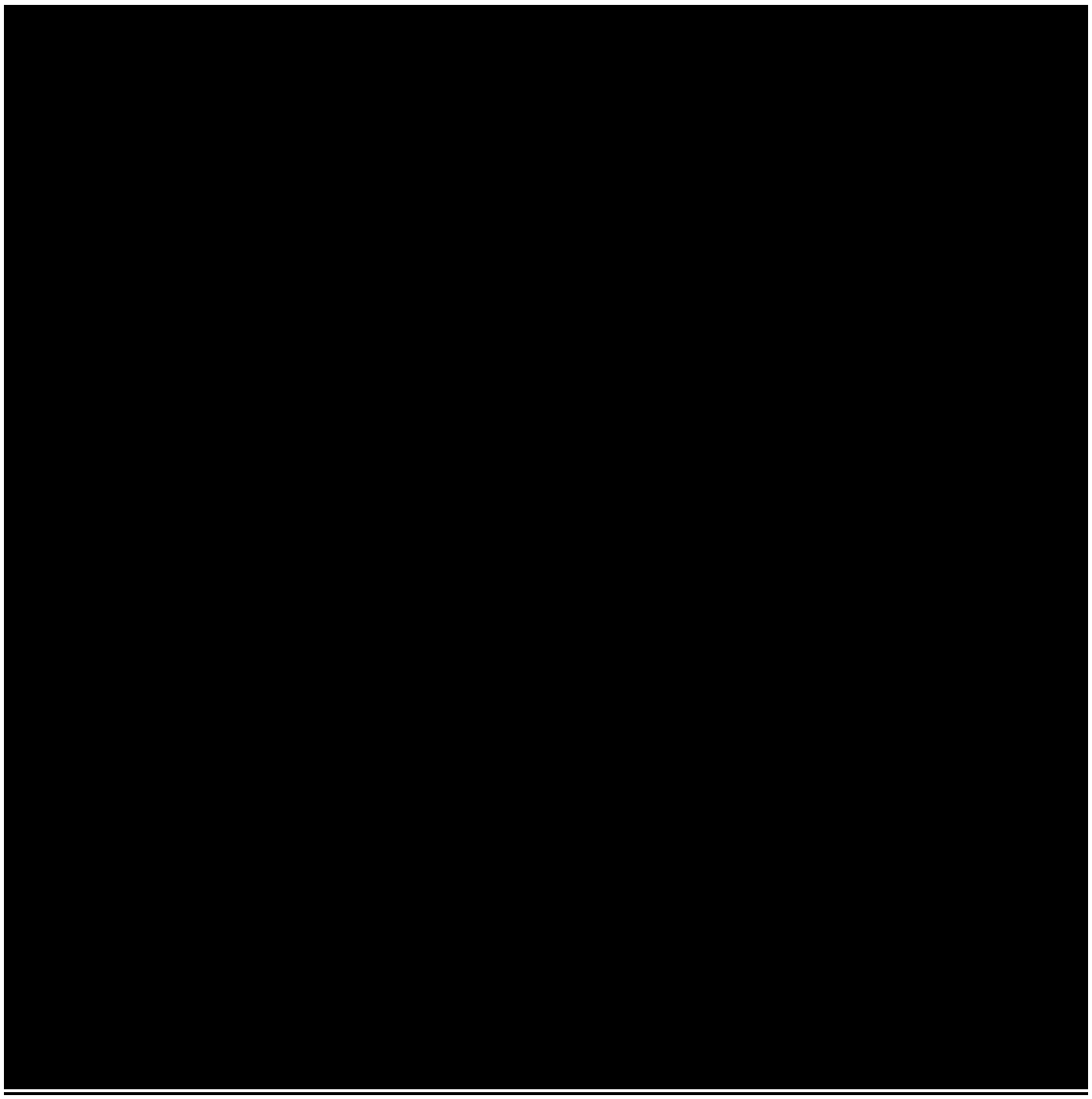
Supportive plots for the extrapolation of duration of treatment based on the GLOW trial (data cut-off [redacted]) are provided in the following Figures (Figure 67 to Figure 75; Table 57).

Figure 67: Duration of treatment log-log cumulative hazard plot based on GLOW trial only



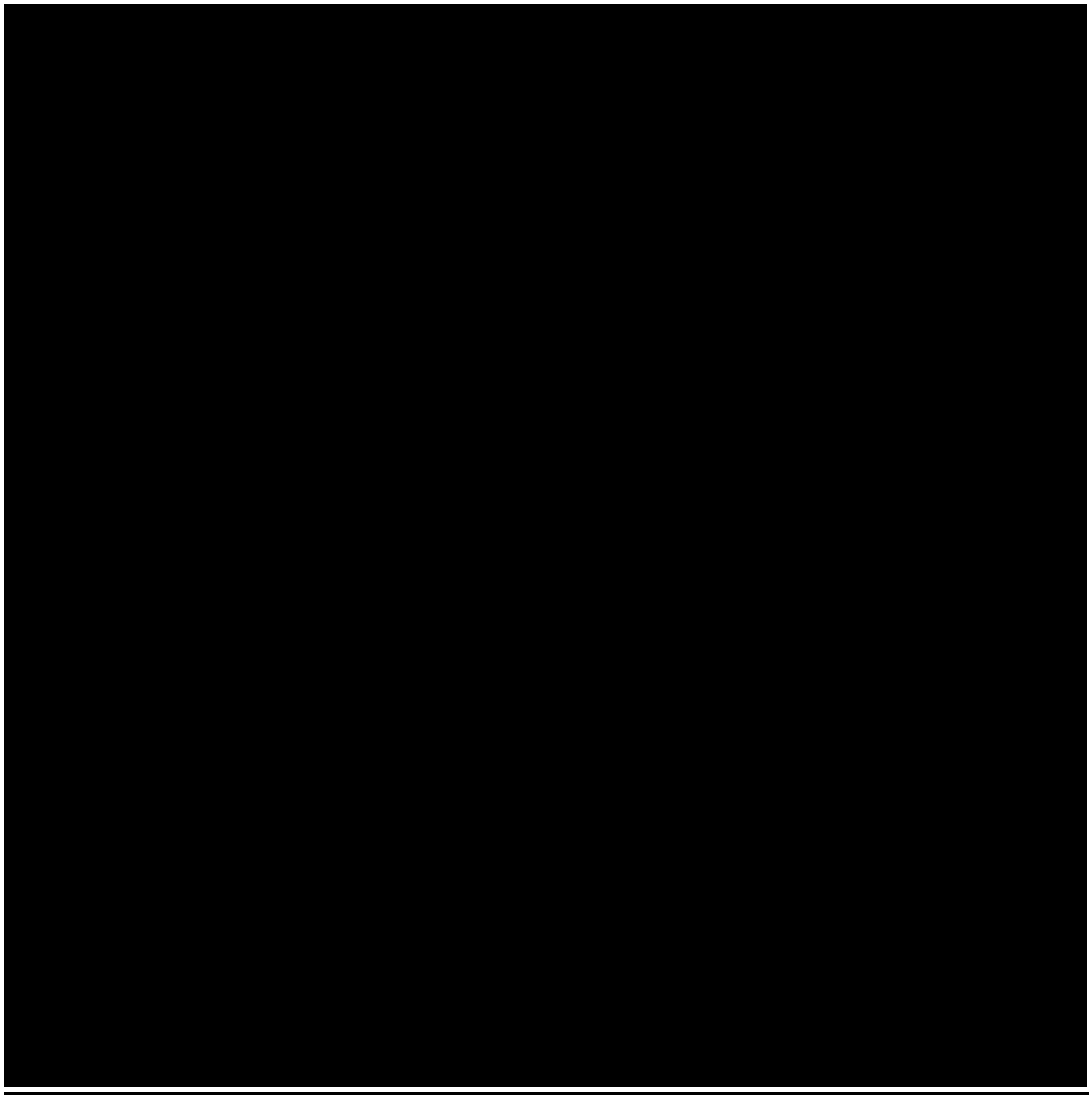
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 68: Duration of treatment schoenfeld residuals plot based on GLOW trial only



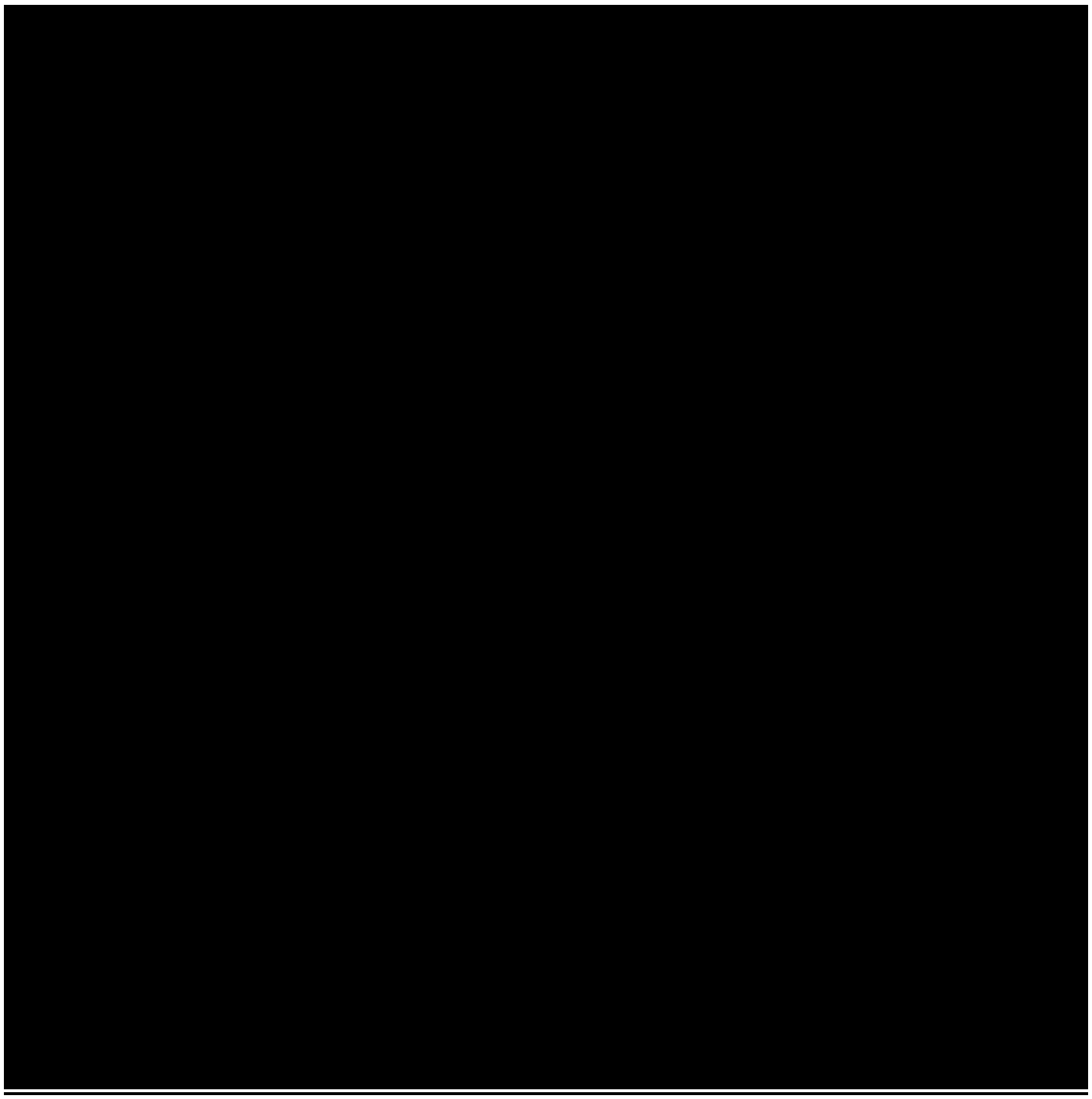
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 69: Duration of treatment hazard plots based on GLOW trial only



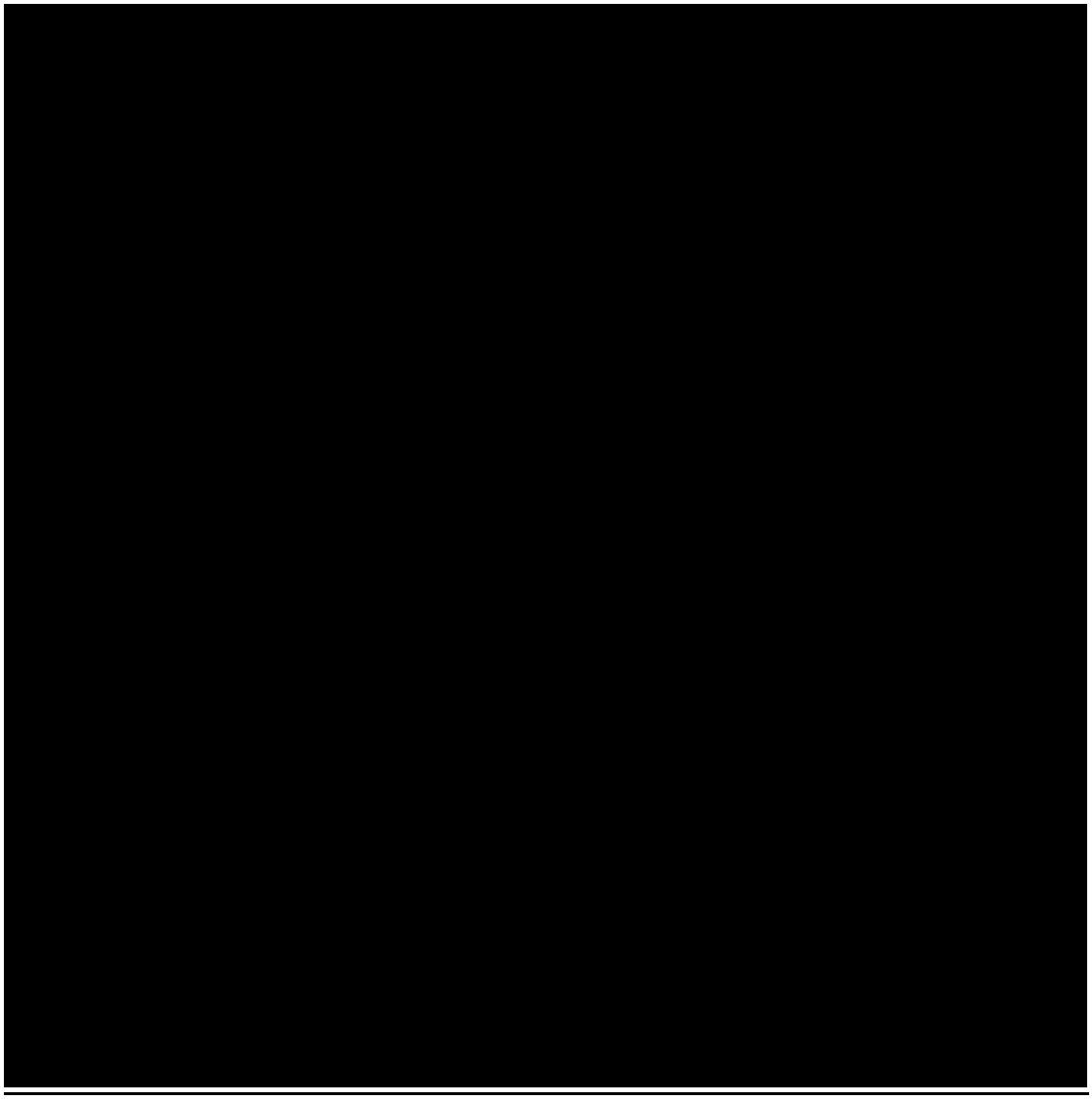
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 70: Duration of treatment log survival odds plot based on GLOW trial only



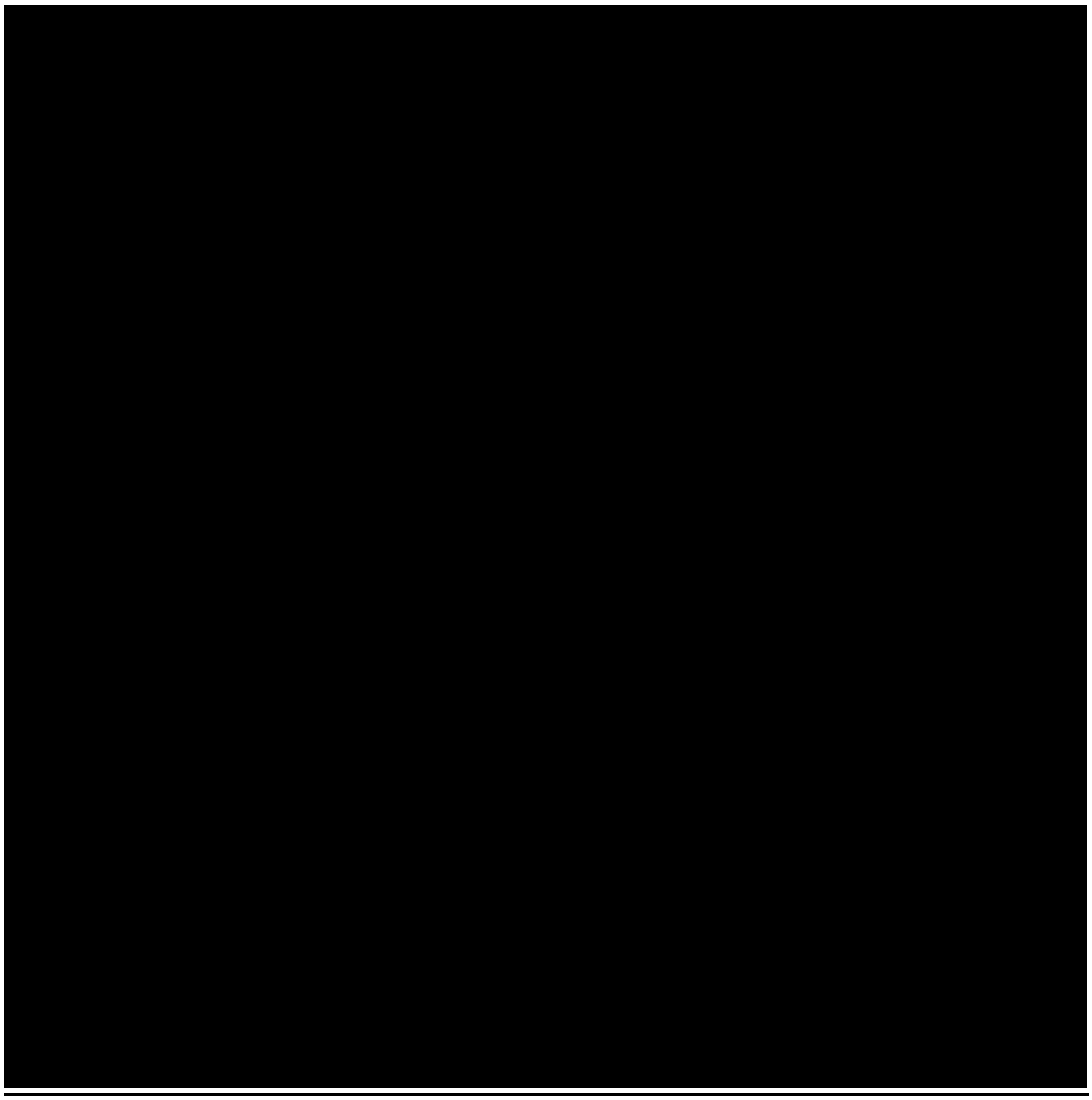
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 71: Duration of treatment QQ plot based on GLOW trial only



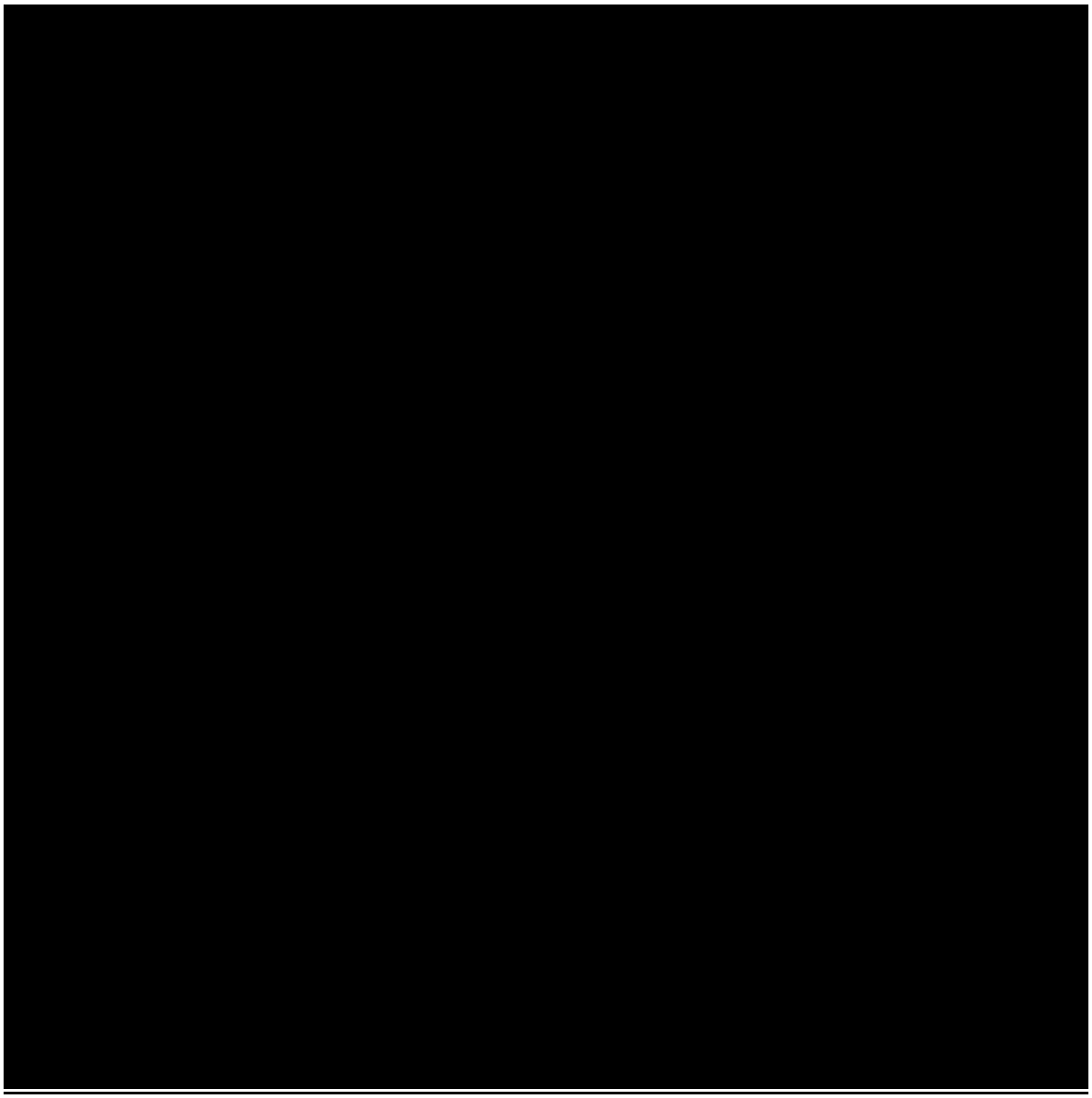
Note: For zolbetuximab + chemotherapy, duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm. For chemotherapy, duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Figure 72: Fit of parametric survival models, duration of treatment based on GLOW trial only: zolbetuximab + chemotherapy



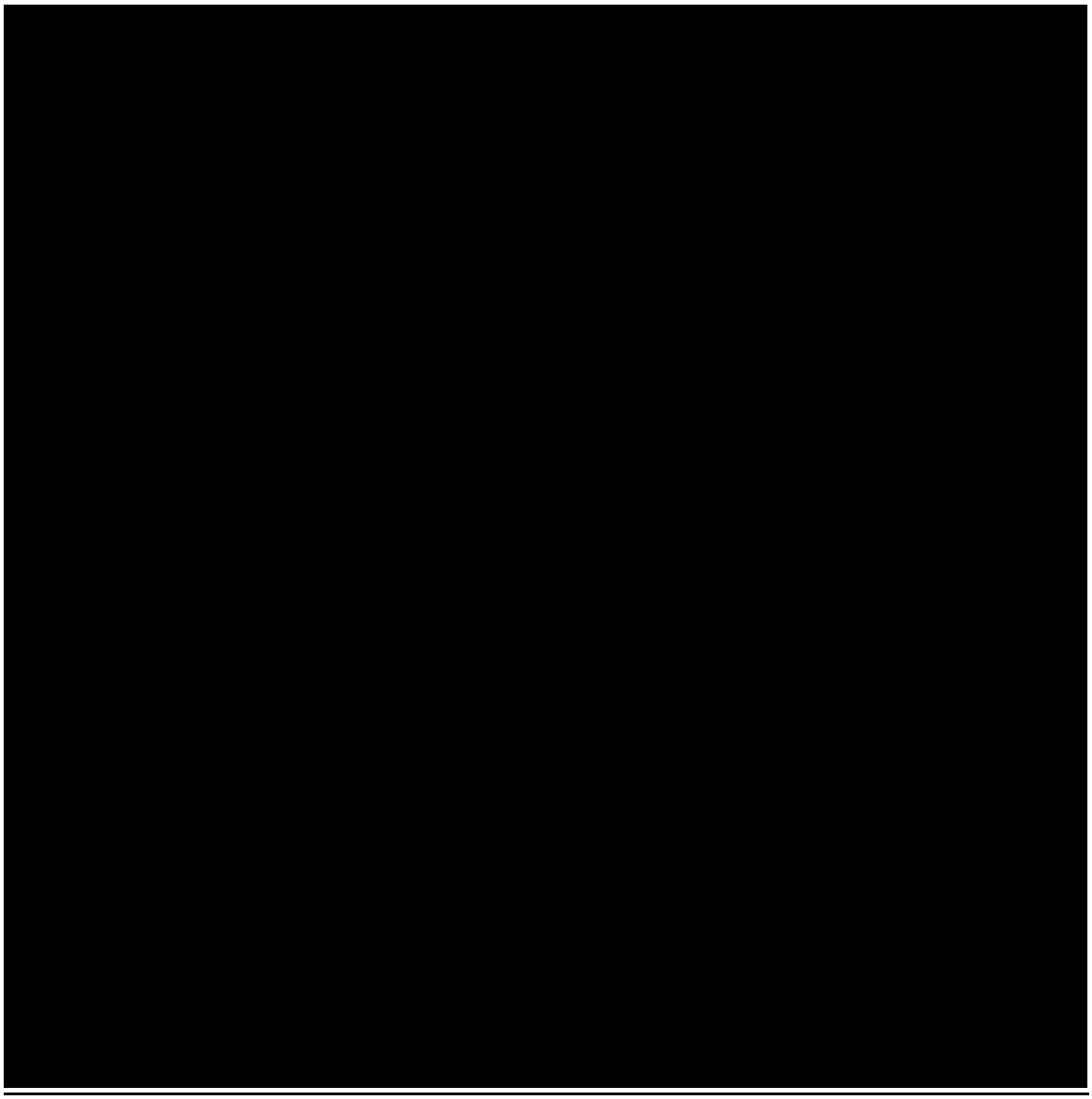
Note: Duration of treatment refers the maximum duration of any component in the zolbetuximab + chemotherapy arm.

Figure 73: Fit of parametric survival models, duration of treatment based on GLOW trial only: zolbetuximab + chemotherapy (zolbetuximab)



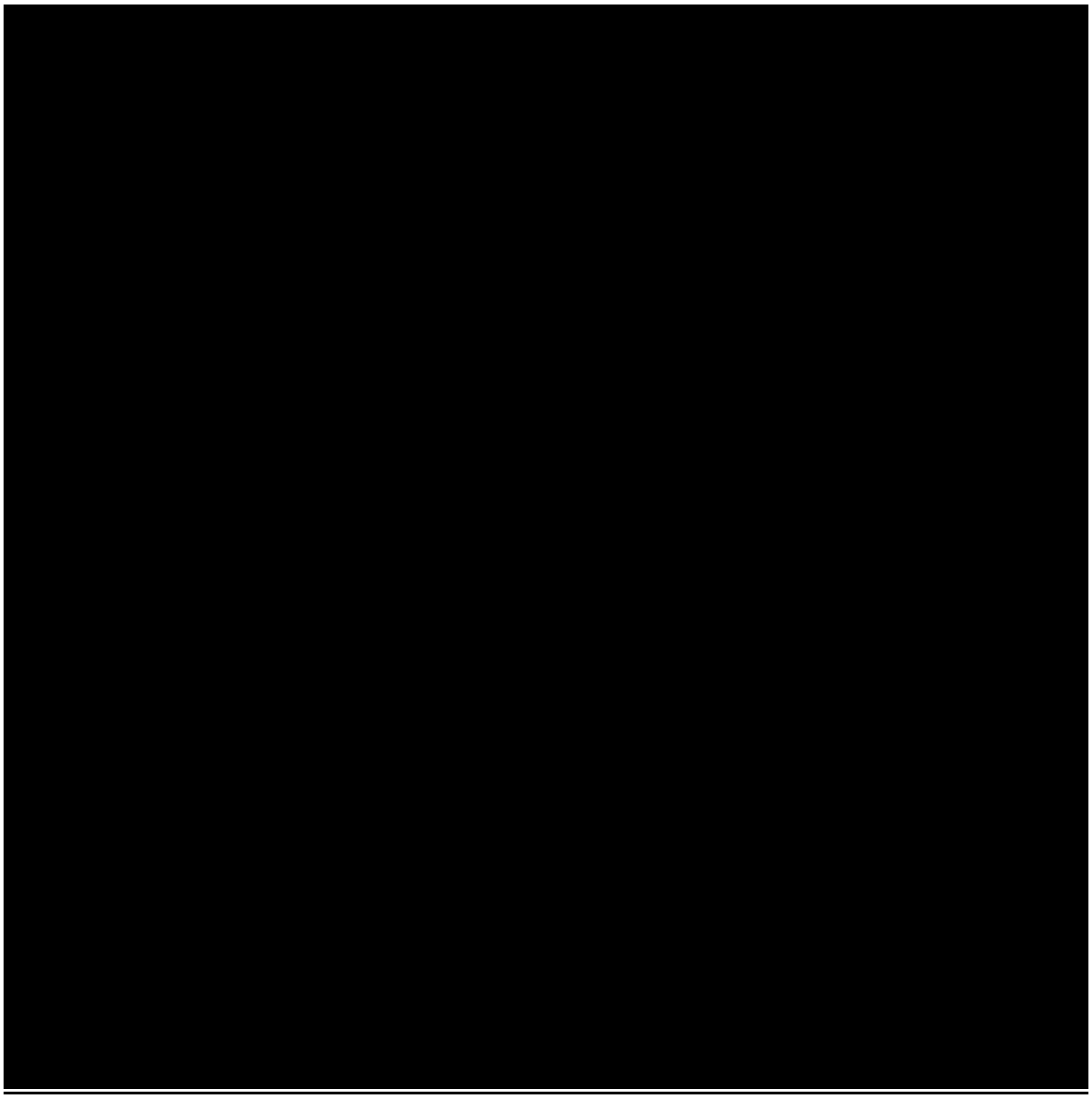
Note: Duration of treatment refers to the duration of the zolbetuximab component in the zolbetuximab + chemotherapy arm.

Figure 74: Fit of parametric survival models, duration of treatment based on GLOW trial only: zolbetuximab + chemotherapy (chemotherapy)



Note: Duration of treatment refers to the maximum duration of any of the chemotherapy components in the zolbetuximab + chemotherapy arm.

Figure 75: Fit of parametric survival models, duration of treatment based on GLOW trial only: chemotherapy



Note: Duration of treatment refers to the maximum duration of any of the chemotherapy components in the chemotherapy arm.

Table 57: Fit statistics of DoT standard parametric models, GLOW

	Zolbetuximab + chemotherapy		Zolbetuximab + chemotherapy (Zolbetuximab)		Zolbetuximab + chemotherapy (Chemotherapy)		Chemotherapy	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	2152.80	2156.33	2197.72	2201.26	2165.96	2169.49	2103.82	2107.33
Weibull	2154.34	2161.41	2161.81	2168.87	2164.81	2171.87	2096.84	2103.88
Log-normal	2229.01	2236.08	2226.07	2233.14	2205.72	2212.77	2155.17	2162.20
Log-logistic	2200.41	2207.48	2202.24	2209.31	2178.79	2185.84	2117.96	2124.99
Gompertz	2154.61	2161.67	2179.90	2186.96	2159.18	2166.23	2104.43	2111.46
Gamma	2153.47	2160.54	2158.77	2165.84	2165.83	2172.88	2096.60	2103.64
Generalised gamma	2152.59	2163.19	2160.76	2171.36	2166.05	2176.63	2098.47	2109.03

B.2.4. Measurement and valuation of health effects

B.2.4.1. Health-related quality-of-life data from clinical trials

The current analysis presented here used data from SPOTLIGHT and GLOW trial (data cut-off 8 September 2023 and [redacted] for SPOTLIGHT and GLOW, respectively) [1, 6], using the methods as reported in the original submission (see Document B B.3.4.1. Health-related quality-of-life data from clinical trials). Results are presented in B.2.4.3 Health-related quality-of-life data used in the cost-effectiveness analysis.

B.2.4.2. Adverse reactions

Safety data from the SPOTLIGHT[1], GLOW[6], CheckMate 649[24] and KEYNOTE-859[13] trials were used within the economic model to explore the impact of AEs on patient utility. Treatment-related Grade 3+ AEs with an incidence of ≥ 5% in any arm of the GLOW, SPOTLIGHT, CheckMate 649 and KEYNOTE-859 trials were included.

Table 58 provides a summary of intervention-related Grade 3+ AE incidence rates used in the model, and the total QALY decrement for each treatment. The intervention-related Grade 3+ AE incidence rates for the individual SPOTLIGHT and GLOW trials are provided in Section B.1.4. The loss in utility due to AEs was accounted for within the economic model as a lump sum upon treatment initiation for each treatment arm as described in the original submission (Document B section B.3.4.4. Adverse reactions).

Table 58: Intervention-related Grade 3+ AEs with incidence ≥ 5%

Adverse event	Used in model base case			
	Zolbetuximab + chemotherapy	**Chemotherapy**	**Nivolumab + chemotherapy**	**Pembrolizumab + Chemotherapy**
Nausea	[redacted]	[redacted]	2.6%	3.00%
Diarrhoea	[redacted]	[redacted]	4.5%	5.00%
Abdominal pain	[redacted]	[redacted]	0.0%	0.00%
Vomiting	[redacted]	[redacted]	2.2%	4.00%
Anaemia	[redacted]	[redacted]	6.0%	8.00%
Decreased appetite	[redacted]	[redacted]	1.8%	2.00%
Platelet count decreased	[redacted]	[redacted]	2.6%	7.00%
Neutrophil count decreased	[redacted]	[redacted]	10.6%	9.00%
White blood cell count decreased	[redacted]	[redacted]	2.9%	0.00%
Neutropenia	[redacted]	[redacted]	15.1%	7.00%
Lipase increased	[redacted]	[redacted]	5.8%	0.00%
Reference	SPOTLIGHT and GLOW	SPOTLIGHT and GLOW	Janjigian et al. (2021)	Rha et al. (2023)
Total QALY decrement	-0.0020	-0.0015	-0.0012	-0.0011

Key: AE, adverse event; QALY, quality-adjusted life year.
Notes: The adverse event incidence for Zolbetuximab + chemotherapy is derived from the weighted average of the individual SPOTLIGHT and GLOW trials, based on the primary analysis data cut of 8 September 2023 for SPOTLIGHT and [redacted] for GLOW.

B.2.4.3. Health-related quality-of-life data used in the cost-effectiveness analysis

Evidence on the number of observations per trial and health state is provided in Table 59. The estimated pre- and post-progression health state utilities from GLOW, SPOTLIGHT, and the pooled analysis are presented Table 60.

Table 59: Number of patients and observations with non-missing EQ-5D data

Data source	All subjects			
	Pre-progression		Post-progression	
	Number of patients	Number of observations	Number of patients	Number of observations
SPOTLIGHT[1]	[redacted]	[redacted]	[redacted]	[redacted]
GLOW[6]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]
Note: The analysis presented here uses the SPOTLIGHT final data cut (data cut off from 8 September 2023) and the GLOW final data cut (data cut off from [redacted]).				

Table 60: Utility inputs using GEE model [1, 6]

Health state	Mean	Standard error	Reference
Pre-progression	[redacted]	[redacted]	Pooled SPOTLIGHT and GLOW as used in the base case
Post-progression	[redacted]	[redacted]	
Pre-progression	[redacted]	[redacted]	GLOW
Post-progression	[redacted]	[redacted]	
Pre-progression	[redacted]	[redacted]	SPOTLIGHT
Post-progression	[redacted]	[redacted]	
Key: GEE, generalised estimating equation. **Note:** The analysis presented here uses the SPOTLIGHT final data cut (data cut off from 8 September 2023) and the GLOW final data cut (data cut off from [redacted]).			

B.2.5. Cost and healthcare resource use identification, measurement and valuation

B.2.5.1. Intervention and comparators' costs and resource use

The costs of the model interventions and comparators, including drug procurement and administration, are applied each cycle based on acquisition costs detailed in

Table 61. RDIs for pre-progression treatments were obtained from relevant clinical trials (Table 62) or assumed to be 100% where information was not available, in the case of nivolumab and pembrolizumab.

Table 61: Drug acquisition unit cost

Drug	mg per unit	Unit cost* (2023 GBP)	Discount	Reference	Use in model
Zolbetuximab	100	375.00	[redacted]	Astellas	Model base case: CAPOX is chemotherapy backbone for zolbetuximab arm and chemotherapy comparator
Capecitabine	150	0.11	N/A	eMIT (2023)[25]	
Oxaliplatin	100	24.44	N/A	eMIT (2023) [25]	
Nivolumab	240	2,633.00	N/A	BNF (2023) [26]	Comparator in model for those eligible for Nivolumab
Pembrolizumab	100	2,630.00	N/A	MIMS (2023) [27]	Comparator in model for those eligible for Pembrolizumab
Docetaxel	160	15.67	N/A	eMIT (2023) [25]	Used in model base case as post-progression treatments
Paclitaxel	100	8.49	N/A	eMIT (2023) [25]	
Fluorouracil (bolus)	500	6.08	N/A	BNF (2023) [26]	Used in scenario analyses
Fluorouracil (infuser)	1,000	3.93	N/A	eMIT (2023) [25]	

Key: BNF, British National Formulary; CAPOX, capecitabine and oxaliplatin; eMIT, electronic market information tool; MIMS, monthly index of medical specialities; N/A, not applicable.
Notes: * The lowest cost per mg unit was chosen if multiple strengths were available.

Table 62: Relative dose intensity

Treatment	Regimen	Drug	Relative dose intensity	Reference	Use in model
Zolbetuximab + chemotherapy	Zolbetuximab + chemotherapy	Zolbetuximab (loading)	[redacted]	SPOTLIGHT & GLOW	Model base case as a combined zolbetuximab + chemotherapy arm using the weighted average from SPOTLIGHT and GLOW for zolbetuximab. Chemotherapy components using the RDI from GLOW (CAPOX)
		Zolbetuximab (maintenance)	[redacted]		
		Oxaliplatin	[redacted]		
		Capecitabine	[redacted]		
Chemotherapy	CAPOX	Oxaliplatin	[redacted]	GLOW	Model base case as a combined chemotherapy arm using GLOW (CAPOX) RDI
		Capecitabine	[redacted]		
Nivolumab + chemotherapy	Nivolumab + CAPOX	Nivolumab	100%	RDI was unavailable so an RDI of 100% was assumed	Comparison made to nivolumab as part of secondary analyses for those eligible to Nivolumab
		Oxaliplatin	100%		
		Capecitabine	100%		
Pembrolizumab + chemotherapy	Pembrolizumab + CAPOX	Pembrolizumab	100%	RDI was unavailable so an RDI of 100% was assumed	Comparison made to pembrolizumab as part of secondary analyses for those eligible to Pembrolizumab
		Oxaliplatin	100%		
		Capecitabine	100%		
Zolbetuximab + FOLFOX	Zolbetuximab + FOLFOX	Zolbetuximab (loading)	[redacted]	SPOTLIGHT	Explored in scenario analysis as part of trial-specific costing
		Zolbetuximab (maintenance)	[redacted]		
		Oxaliplatin	[redacted]		
		Leucovorin	[redacted]		

Treatment	Regimen	Drug	Relative dose intensity	Reference	Use in model
		Fluorouracil (bolus)	[redacted]		
		Fluorouracil (infuser)	[redacted]		
FOLFOX	FOLFOX	Oxaliplatin	[redacted]	SPOTLIGHT	Explored in scenario analysis as part of trial-specific costing
		Leucovorin	[redacted]		
		Fluorouracil (bolus)	[redacted]		
		Fluorouracil (infuser)	[redacted]		

Key: CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; RDI, relative dose intensity.
Notes: [1]RDI's presented here are from the updated data cut

B.2.5.2. Health-state unit costs and resource use

B.2.5.2.1. Pre-progression treatment costs

Pre-progression treatment costs were calculated based on the drug acquisition cost per administration, drug administration cost per administration, number of administrations per week, and proportion of patients remaining on treatment at each week according to DoT curves. A summary of the intervention and comparator dosing and acquisition costs (with PAS applied) is presented in Table 63.

Table 63: Intervention and comparator dosing and acquisition cost without discounting at list price and following application of PAS

Treatment	Treatment components	Treatment cycle	Acquisition cost per administration (with PAS discount)	Total pre-progression drug costs per arm (with PAS)	Use in model
Zolbetuximab + chemotherapy	Zolbetuximab loading	Q3W	[redacted]	[redacted]	Model base case as zolbetuximab + chemotherapy arm, with CAPOX costing applied
	Zolbetuximab maintenance	Q3W	[redacted]		
	Oxaliplatin (high dose)	Q3W	£51.40		
	Capecitabine	BID Days 1–14 Q3W	£1.00		
Chemotherapy	Oxaliplatin (high dose)	Q3W	£51.43	[redacted]	Model base case as chemotherapy arm, with CAPOX costing applied
	Capecitabine	BID Days 1–14 Q3W	£1.03		

Treatment	Treatment components	Treatment cycle	Acquisition cost per administration (with PAS discount)	Total pre-progression drug costs per arm (with PAS)	Use in model
Nivolumab + chemotherapy	Nivolumab	Q3W	£3,949.50	£51,367.39	Comparison made with nivolumab as part of secondary analyses for those eligible to Nivolumab
	Oxaliplatin (high dose)	Q3W	£54.08		
	Capecitabine	BID Days 1–14 Q3W	£1.21		
Pembrolizumab + chemotherapy	Pembrolizumab	Q3W	£5,260.00	£66,673.74	Comparison made with pembrolizumab as part of secondary analyses for those eligible to Pembrolizumab
	Oxaliplatin (high dose)	Q3W	£54.08		
	Capecitabine	BID Days 1–14 Q3W	£1.21		

Key: BID, twice daily; CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; PAS, patient access scheme; Q3W, every 3 weeks. The total pre-progression drug costs per arm are discounted to present values.

B.2.5.2.2. Post-progression treatment costs

The total post-progression treatment cost per patient was calculated as the product of the proportion of progressed patients receiving post-progression treatments, distribution of post-progression treatments, weekly cost of each treatment, and mean duration of each treatment. The lump sum cost of post-progression treatment by pre-progression treatment is presented in Table 64.

Table 64: Post-progression treatment costs by pre-progression treatment

Pre-progression treatment	Percentage of patients receiving post-progression treatment	Lump sum cost (2023 GBP)	Reference for proportion of patients receiving post-progression treatment	Use in model
Zolbetuximab + chemotherapy	[redacted]	[redacted]	Pooled SPOTLIGHT and GLOW	Model base case as a combined zolbetuximab arm and CAPOX as the chemotherapy backbone
Chemotherapy	[redacted]	[redacted]	Pooled SPOTLIGHT and GLOW	
Nivolumab + chemotherapy	37%	2,301.18	Janjigian et al. 2021	Comparison made with nivolumab as part of secondary analyses for those eligible to Nivolumab
Pembrolizumab + chemotherapy	45%	2,782.99	Rha et al. 2023	Comparison made with pembrolizumab as part of secondary analyses for those eligible to Pembrolizumab
Key: CAPOX, capecitabine and oxaliplatin.				

B.2.5.3. Adverse reaction costs

The lump sum cost due to AEs for each treatment arm is shown in Table 65.

Table 65: Total AE cost for each treatment arm

Treatment arm	Total AE cost (2023 GBP)	Use in model
Zolbetuximab + chemotherapy	801.57	Model base case as a combined zolbetuximab arm and CAPOX as the chemotherapy backbone
Chemotherapy	695.64	
Nivolumab + chemotherapy	666.28	Comparison made with nivolumab as part of secondary analyses for those eligible to Nivolumab
Pembrolizumab + chemotherapy	487.60	Comparison made with pembrolizumab as part of secondary analyses for those eligible to Pembrolizumab
Key: AE, adverse event; CAPOX, capecitabine and oxaliplatin.		

B.2.6. Base case results

B.2.6.1. Base case incremental cost-effectiveness analysis results of zolbetuximab + chemotherapy versus chemotherapy

The base case considers zolbetuximab + chemotherapy versus chemotherapy alone. The fully incremental cost-effectiveness results when using list prices and with the patient access scheme (PAS) discount applied for zolbetuximab are presented in Table 66 whilst results incorporating the severity modifier for zolbetuximab are presented in Table 67.

There was an incremental life year gain of [redacted] years, and a quality-adjusted life year (QALY) gain of 0.54 for patients receiving zolbetuximab + chemotherapy versus chemotherapy alone. This translates to an incremental cost-effectiveness ratio (ICER) at list price of [redacted] per QALY, and [redacted] when incorporating the PAS.

In line with the TSD23 guidance on severity shortfall calculations, it is appropriate to apply a 1.2 QALY modifier. This reduces the list and PAS ICERs to [redacted] per QALY, and [redacted] per QALY, respectively. The modified PAS ICER is below the willingness to pay (WTP) threshold of £30,000 per QALY and demonstrates that

zolbetuximab provides substantial clinical benefit for a justifiable cost in a population facing a substantial unmet need. Results without the severity modifier are compared to a modified WTP threshold of £36,000 per QALY, which represents the WTP threshold with the 1.2 severity modifier.

Table 66: Base case results (deterministic) of zolbetuximab + chemotherapy versus chemotherapy alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £36,000
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.54	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	– -	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.54	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 67: Base case results with the severity modifier applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.65	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	-	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.65	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.2.6.2. Base case results of the secondary analysis to Nivolumab

Table 68 shows the deterministic cost-effectiveness results of zolbetuximab + chemotherapy versus nivolumab + chemotherapy in the patients with PD-L1 CPS ≥ 5, and Table 69 shows the same results with the severity modifier applied.

Table 68: Base case results (deterministic) of zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £36,000
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Nivolumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	– -	–	–
Nivolumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 69: Base case results with the severity modifier applied of zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Nivolumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	-	–	–
Nivolumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.2.6.3. Base case results of the secondary analysis to Pembrolizumab

Table 70 shows the deterministic cost-effectiveness results of zolbetuximab + chemotherapy versus pembrolizumab + chemotherapy in the patients with PD-L1 CPS ≥ 1, and Table 71 shows the same results with the severity modifier applied.

Table 70: Base case results (deterministic) of zolbetuximab + chemotherapy versus pembrolizumab + chemotherapy in the patients with PD-L1 CPS ≥ 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £36,000
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	– -	–	–
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 71: Base case results with the severity modifier applied vs. pembrolizumab + chemotherapy in the patients with PD-L1 CPS ≥ 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £30,000
At list price								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]
With PAS applied to zolbetuximab								
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	–	–	-	–	–
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.00	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.2.7. Exploring uncertainty

B.2.7.1. Probablistic sensitivity analysis

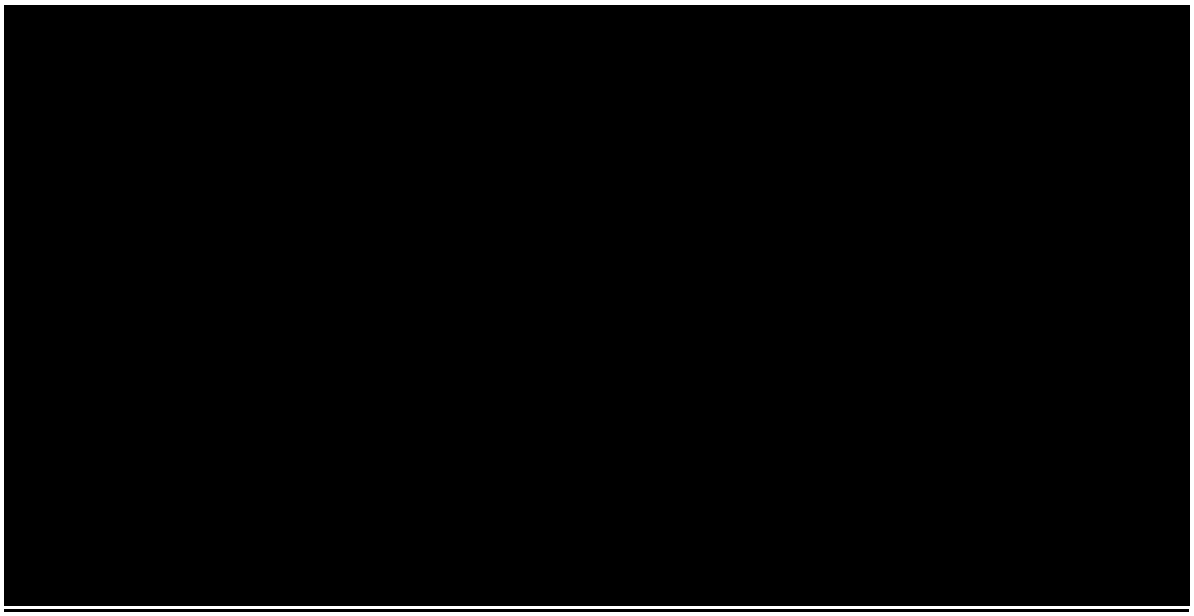
The ICER scatterplots for the base case analysis at list price and with confidential discount, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 76 to Figure 79. The cost-effectiveness acceptability curve with confidential discount is presented in Figure 80, although this plot should be interpreted with caution as nivolumab + chemotherapy is only recommended in patients with PD-L1 CPS ≥ 5, and pembrolizumab + chemotherapy is only recommended in patients with PD-L1 CPS ≥ 1, and PD-L1 CPS is a treatment effect modifier for both checkpoint inhibitors. These figures do not incorporate the severity modifier of 1.2. Instead a modified WTP threshold of £36,000 is used to reflect the severity modifier.

Figure 76: ICER scatterplot: zolbetuximab + chemotherapy versus chemotherapy at PAS

Figure 77: ICER scatterplot: zolbetuximab + chemotherapy versus chemotherapy at list price

Figure 78: ICER scatterplot: zolbetuximab + chemotherapy versus nivolumab + chemotherapy at PAS

Figure 79: ICER scatterplot: zolbetuximab + chemotherapy versus pembrolizumab + chemotherapy at PAS



Based on this analysis, the probability that zolbetuximab + chemotherapy is cost-effective versus chemotherapy (incorporating PAS discount) is estimated to be [redacted]% at a modified WTP threshold of £36,000 per QALY.

Figure 80 Cost-effectiveness acceptability curve of all treatments with PAS applied

B.2.7.2. Deterministic sensitivity analysis

Results of the deterministic sensitivity analysis are presented in Figure 81 and Figure 82 for zolbetuximab + chemotherapy vs chemotherapy, at list price and PAS, respectively, representing the impact of specific parameters on ICER estimates. These figures do not incorporate the severity modifier of 1.2. Instead a modified WTP threshold of £36,000 is used to reflect the severity modifier. The tornado diagrams below show the parameters the ICER is most sensitive to; while there is movement in the ICER estimate, this is modest and relatively stable. The factors with the greatest impact on the ICER were post-progression disease management costs, and – to a smaller extent – pre-progression disease management costs and utility pre- and post-progression. The widest ICER range was in the analysis varying pre-progression disease management costs off treatment for zolbetuximab + chemotherapy, at between [redacted] per QALY (at PAS prices).

Figure 81: Deterministic sensitivity analysis for zolbetuximab + chemotherapy versus chemotherapy – impact on ICER at list price

Figure 82: Deterministic sensitivity analysis for zolbetuximab + chemotherapy versus chemotherapy – impact on ICER at PAS price for zolbetuximab

B.2.7.3. Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. A summary of the scenarios explored with justification is presented in Table 72. Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price and with PAS applied are presented in Table 73 and Table 74 , respectively. Corresponding tornado plots using the results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price and with PAS applied are presented in Figure 83 and Figure 84, respectively.

Table 72: A summary of scenarios explored as part of sensitivity analysis

#	Base case	Scenario	Justification
1.	Chemotherapy OS and PFS based on pooled chemotherapy arms of SPOTLIGHT, GLOW and CheckMate 649 PD-L1 CPS ≥ 5 subgroup trials, extrapolated with splines Zolbetuximab + chemotherapy OS and PFS based on relative efficacy estimates from spline-based NMA applied to chemotherapy reference	Chemotherapy OS & PFS based on the pooled chemotherapy arms of the SPOTLIGHT and GLOW trials; parametric function - Log-logistic; zolbetuximab + chemotherapy outcomes based on spline NMA as per base-case	Assess the impact of using alternative extrapolating models and using only the zolbetuximab trials; log-logistic chosen as the best-fitting that also models a small subset of long-term survivors for OS and PFS
2.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy Pooled spline chemotherapy trials for estimation of OS and PFS for chemotherapy	Zolbetuximab + chemotherapy and chemotherapy OS & PFS based on the pooled SPOTLIGHT and GLOW trials; Statistically best fitting survival curves for extrapolation for both arms.	This assumes that the two pooled trials represent the outcomes in clinical practice in their relative proportions, and the statistically best fitting survival curves represent the most appropriate extrapolations.
3.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy	Zolbetuximab + chemotherapy outcomes based on proportional hazards NMA	As time-varying hazard ratios were near-constant, use of a constant hazard ratio
4.	Chemotherapy OS and PFS based on pooled chemotherapy arms of SPOTLIGHT, GLOW and CheckMate 649 649 PD-L1 CPS ≥ 5 subgroup trials, extrapolated with splines	Chemotherapy OS and PFS based on the three pooled chemotherapy trials; Best fitting survival curves for extrapolation (log-logistic); zolbetuximab + chemotherapy outcomes based on spline NMA as per base-case	To assess the impact of using alternative extrapolation models, specifically standard parametric models for OS and PFS for the chemotherapy arm.
5.	Spline estimation of OS and PFS for Zolbetuximab + chemotherapy Pooled spline chemotherapy trials	Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted	The outcomes are the weighted average of the individual trials at 80% GLOW and 20% SPOTLIGHT (representing the approach that 80% of patients have CAPOX as per GLOW and 20% have FOLFOX as per

#	Base case	Scenario	Justification
	for estimation of OS and PFS for chemotherapy CAPOX costing	average of chemotherapy with 80% CAPOX, 20% FOLFOX	SPOTLIGHT), with parametric extrapolation and trial specific costing
6.	Discounting of cost and health outcomes at 3.5%	No discounting	As per NICE methods guide
7.	Cost of managing treatment-related Grade 3+ AEs with an incidence of ≥ 5%	No AE cost	As per NICE methods guide
8.	Vial sharing: remaining amount in vials used for one patient are assumed to be used for another patient	Vials are not shared between patients	To explore the impact if vial sharing is not feasible
9.	100% of patients receive CAPOX	80% receive CAPOX and 20% receive FOLFOX	The ERG report for the nivolumab appraisal (TA857) stated that at least 80% of patients received CAPOX based on clinical opinion.
10.	100% of patients receive CAPOX	80% receive CAPOX and 20% receive FOLFOX with Q2W zolbetuximab dosing	The ERG report for the nivolumab appraisal (TA857) stated that at least 80% of patients received CAPOX based on clinical opinion. Q2W is used to reflect that when zolbetuximab is used with a FOLFOX backbone, Q2W dosing is used for zolbetuximab.
11.	GEE utility model (See Section B.2.4.3)	Mixed-effects utility model Pre-progression=[redacted] Post-progression=[redacted]	There is uncertainty over the best statistical model to apply to longitudinal utility data
12.	Age at treatment start – 58.5 years	64.15 years	This was explored in the TA857[28, 29], due to concerns that the patients' age in the trial was younger than in NHS clinical practice

#	Base case	Scenario	Justification
13.	Including CLDN18.2 testing costs for zolbetuximab	Removing CLDN18.2 testing costs for zolbetuximab	As per NICE methods guide
14.	GEE utility model (See Section B.2.4.3)	Utility source – Literature (ToGa trial) Pre-progression = 0.797 Post-progression = 0.577	Alternative values for pre- and post-progression that have been used in existing analyses[30]
15.	Duration of treatment: Chemotherapy - Parametric model (Weibull from GLOW), Zolbetuximab + Chemotherapy - Apply PFS HR to chemotherapy DoT, Nivolumab + chemotherapy - Apply PFS HR to chemotherapy DoT, Pembrolizumab + chemotherapy - Apply PFS HR to chemotherapy DoT	Use the DoT observed in GLOW for CAPOX (Gamma extrapolation) to inform DoT with chemotherapy (including chemotherapy when used with another treatment); and use the DoT observed in GLOW for zolbetuximab (Gamma extrapolation) for zolbetuximab. Nivolumab and pembrolizumab DoT both set equal to zolbetuximab DoT.	Company suggested alternative approach to modelling DoT. For consistency with the chemotherapy arm, which uses GLOW CAPOX DoT, all the other treatments (zolbetuximab + chemotherapy, nivolumab + chemotherapy, pembrolizumab + chemotherapy) use the GLOW zolbetuximab + chemotherapy DoT. This has the benefit of simplicity, however it does not account for the disconnect between the trial populations used in the NMA and the populations used for DoT modelling (the base case appproach attempts to account for this).
EAG requested scenarios			
16.	Post-progression treatment costs were represented by a lump sum cost based on taxane treatment, but representing a basket of post-progression treatments, to	Post-progression treatment costs set to £0.	As the duration of post progression survival is shorter for zolbetuximab than for chemotherapy, the EAG suggested that subsequent treatment costs should not have a major impact on the ICER. As such, a scenario was provided where post-progression treatment costs are set to 0 for both Zolbetuximab + chemotherapy and chemotherapy.

#	Base case	Scenario	Justification
	represent the costs of post-progression in clinical practice. Total post-progression costs: • Zolbetuximab + chemotherapy = £[redacted] • Chemotherapy = £[redacted]		
17.	RDI for zolbetuximab + chemotherapy as follows: • Zolbetuximab (loading): [redacted]% • Zolbetuximab (maintenance): [redacted] • Oxaliplatin: [redacted]% • Capecitabine: [redacted]% RDI for Nivolumab was unavailable so an RDI of 100% was assumed	RDI of zolbetuximab set equal to that of nivolumab (i.e. both = 100%)	As RDI was not available for the nivolumab arm, a RDI of 100% was assumed by the company. As such, the EAG requested a scenario where both nivolumab and zolbetuximab have the same RDI.
18.	Treatment waning was not included for zolbetuximab + chemotherapy as there is no time-based stopping rule for zolbetuximab	Explore treatment waning of zolbetuximab + chemotherapy, with waning to chemotherapy. This is implemented by using the chemotherapy hazards after 5 years	The EAG requested a scenario where treatment effect waning was assumed at different time points.
19.	Treatment waning was not included for zolbetuximab + chemotherapy as there is no time-based stopping rule for zolbetuximab	Explore treatment waning of zolbetuximab + chemotherapy, with waning to chemotherapy. This is implemented by using the chemotherapy hazards after 6 years	The EAG requested a scenario where treatment effect waning was assumed at different time points.
20.	Treatment waning was not included for zolbetuximab + chemotherapy as there is no time-based stopping rule for zolbetuximab	Explore treatment waning of zolbetuximab + chemotherapy, with waning to chemotherapy. This is implemented by using the chemotherapy hazards after 7 years	The EAG requested a scenario where treatment effect waning was assumed at different time points.

#	Base case	Scenario	Justification
21.	Dosing regimen was based on BSA from the pooled SPOTLIGHT and GLOW at $1.70m^2$	BSA of $1.73m^2$, based on data reported in ID4030	This scenario explores the impact of alternative sources of data to inform BSA, by using the data reported by the company of ID4030 in response to clarification questions – a large cancer centre in London reported a mean BSA of $1.73m^2$.

Key: AE, adverse event; BSA, body surface area; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; DoT, duration of treatment; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year; RDI, relative dose intensity

Table 73: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price

Scenario	ICER (∆Cost/∆QALY)	% Change vs. Basecase
Base-case	[redacted]	-
1. Chemotherapy OS & PFS Parametric function - Log-logistic	[redacted]	7.6%
2. Zolbetuximab + Chemotherapy & Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) - Best fitting	[redacted]	17.5%
3. Zolbetuximab + Chemotherapy (Hazard ratio)	[redacted]	15.3%
4. Chemotherapy OS & PFS Parametric Function (Pooled chemotherapy trials) - Best fitting	[redacted]	-3.6%
5. Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted average of chemotherapy with 80% CAPOX, 20% FOLFOX	[redacted]	4.5%
6. No discounting	[redacted]	-21.7%
7. No AE cost	[redacted]	-0.2%
8. Vial sharing	[redacted]	3.8%
9. 80% receiving CAPOX	[redacted]	0.9%
10. 80% receiving CAPOX - Q2W Zolbe dosing	[redacted]	1.0%
11. Utility - Mixed effects model	[redacted]	-0.1%
12. Age at treatment start (years)	[redacted]	0.9%
13. No CLDN18.2 testing costs	[redacted]	-0.4%
14. Utility source - ToGA trial	[redacted]	-4.1%
15. Use GLOW DoT for all treatments	[redacted]	-2.7%

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. Basecase
Base-case	[redacted]	-
EAG requested scenarios		
16. Subsequent treatment costs set to £0	[redacted]	1.0%
17. RDI of Nivo equal to Zolbe	[redacted]	1.9%
18. Zolbetuximab + chemotherapy treatment waning - from 5 years	[redacted]	27.6%
19. Zolbetuximab + chemotherapy treatment waning - from 6 years	[redacted]	21.3%
20. Zolbetuximab + chemotherapy treatment waning - from 7 years	[redacted]	16.8%
21. BSA based on data reported in ID4030	[redacted]	1.5%
Key: AE, adverse event; BSA, body surface area; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; DoT, duration of treatment; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year; RDI, relative dose intensity		

Table 74 Results from the scenario analyses vs chemotherapy (with PAS)

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. base case
Basecase	[redacted]	-
1. Chemotherapy OS & PFS Parametric function - Log-logistic	[redacted]	8.5%
2. Zolbetuximab + Chemotherapy & Chemotherapy OS & PFS Parametric function (SPOTLIGHT/GLOW) - Best fitting	[redacted]	25.7%
3. Zolbetuximab + Chemotherapy (Hazard ratio)	[redacted]	14.0%
4. Chemotherapy OS & PFS Parametric Function (Pooled	[redacted]	-3.6%

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. base case
Basecase	[redacted]	-
chemotherapy trials) - Best fitting		
5. Zolbetuximab + Chemotherapy & Chemotherapy - OS & PFS Parametric Function (Pooled SPOTLIGHT/GLOW) - Best fitting with weighted average of chemotherapy with 80% CAPOX, 20% FOLFOX	[redacted]	11.4%
6. No discounting	[redacted]	-19.0%
7. No AE cost	[redacted]	-0.6%
8. Vial sharing	[redacted]	3.1%
9. 80% receiving CAPOX	[redacted]	0.3%
10. 80% receiving CAPOX - Q2W Zolbe dosing	[redacted]	0.2%
11. Utility - Mixed effects model	[redacted]	-0.1%
12. Age at treatment start (years)	[redacted]	0.8%
13. No CLDN18.2 testing costs	[redacted]	-1.0%
14. Utility source - ToGA trial	[redacted]	-4.1%
15. Use GLOW DoT for all treatments	[redacted]	-2.1%
EAG requested scenarios		
16. Subsequent treatment costs set to £0	[redacted]	2.8%
17. RDI of Nivolumab equal to Zolbetuximab	[redacted]	1.7%
18. Zolbetuximab + chemotherapy treatment waning - from 5 years	[redacted]	25.2%
19. Zolbetuximab + chemotherapy	[redacted]	19.5%

Scenario	ICER (ΔCost/ΔQALY)	% Change vs. base case
Basecase	[redacted]	-
treatment waning - from 6 years		
20. Zolbetuximab + chemotherapy treatment waning - from 7 years	[redacted]	15.4%
21. BSA based on data reported in ID4030	[redacted]	1.2%
Key: AE, adverse event; BSA, body surface area; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; DoT, duration of treatment; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year; RDI, relative dose intensity		

Figure 83: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy at list price

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; DoT, duration of treatment; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

Figure 84: Results from the scenario analyses of zolbetuximab + chemotherapy vs chemotherapy with PAS applied

Key: AE, adverse event; CAPOX, capecitabine + oxaliplatin; CLDN18.2, claudin 18.2; DoT, duration of treatment; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; Q2W, every 2 weeks; QALY, quality-adjusted life year.

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Single Technology Appraisal

Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Part 1: Treating untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Martin SCOTT-BROWN
2. Name of organisation	University Hospital Coventry and Warwickshire
3. Job title or position	Consultant Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma? ☒ A specialist in the clinical evidence base for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No past or current, direct or indirect links to, or funding from, the tobacco industry
8. What is the main aim of treatment for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To control the cancer to improve symptoms caused by the cancer. To maintain quality of life by delaying the development of progressive cancer and the symptoms associated with this and also to prolong life expectancy. To keep the patient "as well as possible for as long as possible"
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	We are currently offering patients additional drugs on top of chemotherapy for improvements in Median PFS of 1-2 months in the first line setting and improvements in Median OS of 2-3 months. Given the mode of action of some of these drugs we are also seeing improvements in longer term survival not adequately represented by Median OS, in terms of improvements in 2 year and 3 years survivors (of the order of a doubling in the percentage of patients reaching these time points, which is a very clinically meaningful outcome for our patients, who for many years have had very poor outcomes from our current standard of care chemotherapy treatments).
10. In your view, is there an unmet need for patients and healthcare professionals in untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma?	We are striving to move to personalised cancer treatment, to target the right treatment to the right patient, adding targeted therapy to those who will benefit and avoiding unnecessary toxicity and costs in patients who will not respond to treatment. Recently in Gastro-oesophageal cancer we are finding new biomarkers for treatment (Her-2, MMR, CPS and now Claudin 18.2, with other biomarkers on the horizon e.g. FGFR2). There are still a subset of patients who only receive first line chemotherapy (i.e. Her-2 negative, CPS negative). There is an unmet need to be able to offer these patients biomarker selected targeted agents to improve their clinical outcomes. Zolbetuximab is only suitable for patients with Her-2 negative disease and Claudin 18.2 positivity is more common in patients with a CPS<5, who until recently were ineligible for any other treatment other than chemotherapy alone.

11. How is untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	In patients fit enough for first line chemotherapy treatment, the backbone of treatment is with first line chemotherapy (Oxaliplatin 5-FU – either CAPOX or FOLFOX) In patients with a positive CPS score (CPS >1 or CPS >5) addition of Immunotherapy to chemotherapy (either Nivolumab or Pembrolizumab) would be considered as per NICE guidance The most accepted clinical guidelines for treatment would be the ESMO Clinical practice guidelines published in 2022. The pathway of care for treatment is well defined, with little variety between professionals across the NHS. The addition of Immunotherapy to chemotherapy is standard for patients with a CPS>5. Whether all patients will receive immunotherapy in the CPS 1-4 group following the recent approval by NICE of Pembrolizumab in patients with a CPS>1 will have to be seen. Approval of Zobetuximab for Claudin 18.2 positive gastric or gastro-oesophageal junction adenocarcinoma will add a novel treatment option for many patients with no treatment option other than doublet chemotherapy (CPS<1). Questions remain as to the relative merits of Zolbetuximab versus immunotherapy in patients with a CPS >5 and now that Pembrolizumab has been approved in patients with a CPS >1 the clinical community will have to make decisions in the CPS 1-4 group as well.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Zolbetuximab will be given in secondary care in specialised chemotherapy units alongside standard systemic chemotherapy, so there will be no change in patient care from current standard clinical practice. Clinical staff (Nursing, medical and pharmacy staff) will need training in the preparation and administration of Zolbetuximab with chemotherapy and medical staff will need training in the management of patients on Zolbetuximab. The additional infusion time will have some impact on chair times in chemotherapy units. This treatment is biomarker selective, so all biopsies will need analysis for Claudin 18.2 expression in specialist pathology departments with appropriate

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	quality control of testing. Testing pathways will need to be set up from all treating units to have access to the testing within appropriate time windows (a new test, but pathways are already in place for Her-2, MMR and CPS testing)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The data from SPOTLIGHT and GLOW trials indicates an improvement in median Progression Free and Overall Survival, so I expect Zolbetuximab to provide clinically meaningful benefits compared with current care. Zolbetuximab is generally well tolerated with the on treatment effect of Infusion related Nausea and vomiting being the most common significant treatment related adverse event. With appropriate management this can be controlled in the vast majority of patients within 1-2 cycles of starting treatment, especially with more experience of using this drug. Without other significant increases in toxicity and the improved PFS and OS I would expect Zolbetuximab to increase health related quality of life more than current standard of care, however I have not seen any definitive data from the trials to support this expectation.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Zolbetuximab would only be appropriate for those patients with the appropriate Biomarker – i.e. Her-2 negative Claudin 18.2 positive Gastric or Gastro-oesophageal adenocarcinoma. In the first line setting clinicians may make judgements as to the suitability of patients for Zolbetuximab or Immunotherapy based on their CPS score. This is not that there is any evidence for less effectiveness of Zolbetuximab in CPS high tumours, however patients may be felt to gain increased benefit from Immunotherapy rather than Zolbetuximab in the CPS high category.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The addition of Zolbetuximab will require: Biomarker testing, requiring additional testing on the biopsy in specialised pathology units (on top of current standard of care testing) Preparation of the drug in aseptic units linked with chemotherapy units Administration will add additional time to infusion times for patients receiving chemotherapy (impacting on chemotherapy unit capacity)

	Management of infusion related Nausea and vomiting may require additional administration of antiemetics at the time of infusion. The addition of Zolbetuximab will NOT require any additional clinic time for medical professionals, nor any extra monitoring (i.e. no extra imaging, as imaging would be as standard of care for systemic chemotherapy)
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There would be no "special" rules for starting or stopping treatment with Zolbetuximab. Patients will be started on Zolbetuximab with chemotherapy if they have unresectable or metastatic Her-2 negative Claudin 18.2 positive gastric or gastro-oesophageal adenocarcinoma and are considered fit for combination chemotherapy and Zolbetuximab. In my experience all patients deemed fit enough for standard of care chemotherapy would be considered suitable for the addition of Zolbetuximab. Patients will remain on treatment until they experience disease progression (on standard of care follow up imaging – as per current practice with chemotherapy alone) or toxicity or if the patient chooses to stop treatment.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No, the benefit of Zolbetuximab is likely to be best assessed by the quality-adjusted life year (QALY) calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	In cancer treatment we are always looking at incremental gains, finding new treatments that make a difference to a new subset of patients (in this case Her-2 negative Clauding 18.2 positive gastric and gastro-oesophageal adenocarcinoma patients). This is an innovative scientifically driven process. Developing a drug to target a novel biomarker and proving a clinically significant

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	improvement in survival in the patients expressing this biomarker. For many patients with Her-2 negative Claudin 18.2 positive gastric and gastro-oesophageal adenocarcinoma we have no other treatment than the blunt tool of systemic chemotherapy, using targeted therapy is a "step-change" in their management. Improving control of cancer (Progression free survival) and survival (Overall survival) is an unmet need in Gastric and gastro-oesophageal cancer, particularly in those without any additional treatment over and above doublet systemic chemotherapy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The major toxicity of Zolbetuximab is infusion related nausea and vomiting. This is an on treatment effect of the drug and is now well recognised. With prompt recognition and appropriate management these symptoms can usually be very well managed, data from the trials indicates that the vast majority of patients have good control of Nausea and Vomiting (not significantly greater than standard of care chemotherapy) within 3 weeks of starting treatment. Should Zolbetuximab be approved, the education of treating clinicians and chemotherapy nursing staff regarding this toxicity and it's prevention will be vital to the smooth introduction of Zolbetuximab to standard clinical practice.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials of Zolbetuximab (both GLOW and SPOTLIGHT) do reflect current UK clinical practice. SPOTLIGHT and GLOW were both international clinical trials, with good recruitment to SPOTLIGHT in a number of UK centres. SPOTLIGHT predominantly recruited non-Asian patients (70%), whilst GLOW had 60% Asian patients. Both showed similar improvements in survival. The predominant location of the primary was within the stomach in both trials, although Gastro-oesophageal tumours are more common in the UK setting. The most important outcomes are those measured in the trials, Progression Free Survival (prevention of progression of the cancer) and Overall Survival. It is also important to see that the survival benefit seems to last, with a significant improvement in Survival persisting at 24 and 36 months. Surrogate outcome measures were not used.

	I am not aware of adverse events that have subsequently come to light. In the combined SPOTLIGHT and GLOW trials over 500 patients have received treatment with Zolbetuximab (and previous patients in early phase treatments).
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	There is limited real world data for Zolbetuximab as licensing is ongoing around the world and therefore few patients have received treatment outside of SPOTLIGHT and GLOW
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	Gastric an gastro-oesophageal cancer does not discriminate on the grounds of "age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex and sexual orientation or people with any other shared characteristics". Patients with these characteristics may not access health care equally, however should they be found to have a Her-2 negative Claudin 18.2 positive gastric or gastro-oesophageal adenocarcinoma there would be no bar to them receiving Zolbetuximab should it receive NICE approval (this is no different to standard of care doublet systemic chemotherapy).

• lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

We must strive to improve treatment options for patients with gastric and gastro-oesophageal adenocarcinoma

Zolbetuximab has been shown to significantly improve clinically meaningful outcomes for patients with Her-2 negative Claudin 18.2 gastric and gastro-oesophageal adenocarcinoma in two large randomised controlled trials that reflected standard UK practice

Toxicities from the addition of Zolbetuximab are manageable, usually being controlled in the first 2-3 weeks of treatment

The addition of Zolbetuximab will not significantly alter the patient pathway, as in Gastro-oesophageal Oncology we have commonly treated patients with a chemotherapy backbone with the addition of targeted therapies (e.g. Herceptin, Nivolumab, Pembrolizumab)

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Single Technology Appraisal

Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma or caring for a patient with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 26 July 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with this condition or caring for a patient with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma

Table 1 About you, untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma, current treatments and equality

1. Your name	Ceri Steele
2. Are you (please tick all that apply)	☐ A patient with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma ? ☐ A patient organisation employee or volunteer? X Other (please specify): squamous cell oesophageal cancer patient (don't know if claudin 18.2 positive or HER2 negative)
3. Name of your nominating organisation	OG Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) X Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement X I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	X I am drawing from personal experience X I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: other patients in the support group X I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma? **If you are a carer (for someone with untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma) please share your experience of caring for them**	I didn't have claudin 18.2 positive HER2 negative gastro-oesophageal junction adenocarcinoma but had squamous cell carcinoma (unknown if HER2 negative or claudin 18.2 positive) – treatment for adenocarcinoma and squamous cell carcinoma are comparable – I had chemo and radiotherapy followed by surgery
7a. What do you think of the current treatments and care available for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. Treatment is mainly palliative and side effects can affect quality of life to quite a large degree b. I don't know
8. If there are disadvantages for patients of current NHS treatments for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma (for	If taken in tablet form, this can present difficulties if swallowing is impaired (a common symptom of OC)

example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I don't know, other than it is given intravenously so no swallowing As stated, it is given intravenously so no swallowing
10. If there are disadvantages of Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma over current treatments on the NHS please describe these. For example, are there any risks with Zolbetuximab with chemotherapy? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't know
11. Are there any groups of patients who might benefit more from Zolbetuximab with chemotherapy or any	OC is presenting in increasing numbers of younger patients whose symptoms are often dismissed until the cancer is at a later stage so more treatment options offers more hope and potentially increases life expectancy

who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma and Zolbetuximab with chemotherapy? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No
13. Are there any other issues that you would like the committee to consider?	Oesophageal cancer is one of the few cancers with an unchanged survival rate (currently less than 20% survive beyond 5 years) making it increasingly important that more effective treatments are found with manageable side effects

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- OC survival rates need to be improved
- This cancer is presenting with increasing frequency in a younger population
- Quality of life needs to be considered
- Inability to swallow is one of the side effects of this cancer so method of delivery needs to take this into account.
- Options need to be there so that, if one line of treatment proves to be unsuccessful, patients still have hope

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Zolbetuximab with chemotherapy for untreated CLDN18.2-positive HER2-negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma [ID5123]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Mirre Scholte acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm and Andrea Fernandez Coves acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian and Nigel Armstrong acted as systematic reviewers as well as health economists on this assessment. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

5-FU	Flourouracil
AE	Adverse event
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPOX	Capecitabine and oxaliplatin
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CF	Fluorouacil + cisplatin
CI	Confidence interval
CLDN18.2	Claudin 18.2
CM-649	CheckMate649
CPS	Combined positive score
CR	Complete response
CrI	Credible interval
CS	Company submission
CX	Capecitabine + cisplatin
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DIC	Deviance information criterion
DoR	Duration of response
DOR	Duration of response
DoT	Duration of treatment
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EED	Economic Evaluation Database
EEPRU	Economic Evaluation of Health and Social Care Interventions
eMIT	Electronic market information tool
ESMO	European Society for Medical Oncology
EOX	Epirubicin, oxaliplating and capecitabine
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions 5-Levels
EAG	Evidence Assessment Group
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FE	Fixing errors
FV	Fixing violations
GC	Gastric cancer
GEE	Generalised estimating equation
GEJ	Gastro-oesophageal junction
GEJC	Gastro-oesophageal junction cancer
GHS	Global health status
GLMM	Generalised linear mixed model
HER2	human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio

ICML	International Conference on Malignant Lymphoma
ICTRP	International Clinical Trials Register Platform
IDMC	Independent Data Monitoring Committee
IGCC	International Gastric Cancer Association
IHC	Immunohistochemistry
IQR	Interquartile range
IRC	Independent review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan Meier
KSR	Kleijnen Systematic Reviews Ltd
LS	Least squares
LYs	Life years
LYG	Life years gained
MeSH	Medical subject headings
mFOLFOX6	Modified folinic acid in combination with fluorouracil and oxaliplatin
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mITT	modified intention-to-treat
MJ	Matters of judgement
MMRM	Mixed model repeated measures
N	Number of patients
N/A	Not applicable
NE	Non-estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
Nivo	Nivolumab
NL	The Netherlands
NMA	Network meta-analysis
NYR	Not yet reached
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD-L1	Programmed death ligand 1
PF	Physical functioning
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SD	Standard deviation

SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single Technology Appraisal
TA	Technology Assessment
TEAE	Treatment emergent adverse event
TSD	Technical Support Document
TTCD	Time to confirmed deterioration
UK	United Kingdom
UMC+	University Medical Center+
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organization
WTP	Willingness-to-pay
Zolbe	Zolbetuximab

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary in presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

#	Summary of issue	Report Sections
1	There was a lack of evidence on the comparator of pembrolizumab with chemotherapy for patients with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 10.	2.3
2	There was limited comparability of patients' baseline characteristics in terms of PD-L1 CPS status between included trials in the indirect treatment comparison (ITC) analysis.	3.3, 3.4
3	There was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis.	3.3, 3.4
4	Relevant comparators in different sub-populations.	4.2.4
5	Uncertainty regarding the appropriateness of including the CheckMate 649 trial to estimate chemotherapy outcomes.	4.2.6
6	Appropriateness of assuming equal treatment effectiveness for zolbetuximab + chemotherapy and nivolumab + chemotherapy.	4.2.6
7	Selection of extrapolation curves to estimate treatment effectiveness in the PD-L1 CPS populations.	4.2.6
8	Uncertainty regarding the existence and onset of treatment effectiveness waning.	4.2.6
9	Uncertainty regarding the estimated utility values.	4.2.8
10	Post-progression treatments not being representative of UK clinical practice.	4.2.9

EAG = Evidence Assessment Group; CPS = combined positive score; ITC = indirect treatment comparison; PD-L1 CPS = programmed death-ligand 1 combined positive score; UK = United Kingdom

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased survival in the progression-free and overall survival (OS) health states

Overall, the technology is modelled to affect costs by:

- Its higher drug acquisition costs as compared to chemotherapy
- The need for CLDN18.2 testing (£176 per patient)

The parameters that have the greatest effect on the ICER (based on the company's one-way sensitivity analyses) are:

- Post-progression disease management costs
- Pre-progression disease management costs
- Utility values pre- and post-progression

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following company submission (CS) scenarios that have a substantial impact on the ICER:

- Varying the method of progression-free survival (PFS) and OS extrapolation modelling (scenarios using parametric functions based on the zolbetuximab trials)
- Including treatment effect waning for zolbetuximab

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

The decision problem addressed in the CS is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on the comparator of pembrolizumab with chemotherapy for patients with PD-L1 CPS ≥ 10 (see Table 1.2).

Table 1.2: Key issue 1: Lack of evidence on the comparator of pembrolizumab with chemotherapy for patients with PD-L1 CPS ≥ 10

Report Section	**2.3**
Description of issue and why the EAG has identified it as important	The NICE final scope included pembrolizumab with chemotherapy (PD-L1 CPS ≥ 10 GEJ only and PD-L1 CPS ≥1) as a comparator for patients whose tumours express PD-L1. In the company submission (CS), the company's decision problem excluded pembrolizumab plus chemotherapy as a comparator for the subgroup of patients with PD-L1 CPS ≥1 given that this is subject to an ongoing NICE appraisal. It also excluded PD-L1 CPS ≥ 10 based on the lack of overlap between patients with gastric cancer/gastro-oesophageal junction (GEJ) adeno-carcinoma who are eligible for both zolbetuximab with chemotherapy (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with PD -L1 CPS ≥ 10). However, it is unclear if the small overlap [redacted] between patients with gastric cancer/GEJ adenocarcinoma eligible for both zolbetuximab plus chemotherapy (CLDN18.2 positivity in ≥75% of tumour cells) and pembrolizumab with chemotherapy (with PD-L1 CPS ≥ 10) would be similar to those in clinical practice. The EAG requested the company to provide further justification on this exclusion in the clarification letter. Responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also provided additional network meta-analysis (NMA) results by incorporating

Report Section	2.3
	pembrolizumab plus chemotherapy as a comparator for patients with PD-L1 CPS ≥1. The EAG notes that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators.
What alternative approach has the EAG suggested?	Pembrolizumab plus chemotherapy should be included as a comparator for patients with PD-L1 CPS ≥ 10.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	Either the company should clarify that patients with PD-L1 CPS ≥10 are ineligible for zolbetuximab or the clinical effectiveness and cost effectiveness for the subgroup of patients with PD-L1 CPS ≥10 should be assessed by using pembrolizumab plus chemotherapy as a comparator.
CPS = combined positive score; CS = company submission; EAG = Evidence Assessment Group; GEJ = gastro-oesophageal junction; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PD-L1 = programmed death ligand 1	

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

The EAG identified two major concerns with the evidence presented on the clinical effectiveness: limited comparability of patients' baseline characteristics in terms of PD-L1 CPS status between included trials in the ITC analysis (see Table 1.3) and the lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis (see Table 1.4).

Table 1.3: Key issue 2: Limited comparability of patients' baseline characteristics in terms of PD-L1 CPS status between included trials in the ITC analysis

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The NICE final scope highlighted the subgroup of patients with PD-L1 CPS ≥ 5. However, the company submission provided data for the base-case ITC analysis between the overall population of SPOTLIGHT and GLOW trials and the subgroup of patients with PD-L1 CPS ≥5 from the CheckMate-649 trial. Therefore, EAG requested the company to provide the ITC results for the subgroup of patients with PD-L1 CPS ≥5 from all included trials. In responding to the EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, and because the company claimed that PD-L1 CPS does not affect outcomes for zolbetuximab with chemotherapy and chemotherapy alone, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC analysis but the company used the overall population with mixed status of PD-L1 CPS from the included trials (SPOTLIGHT and GLOW) in the ITC analysis. While the EAG acknowledged that the results of the post-hoc subgroup analysis should be treated with caution, it is important

Report Section	3.3 and 3.4
	to ensure the comparability of patients' baseline characteristics between included trials for the purpose of ITC analysis. It is also unclear whether PD-L1 status is a treatment effect modifier for zolbetuximab with chemotherapy versus chemotherapy alone.
What alternative approach has the EAG suggested?	The feasibility assessment for the populations in the scope of ITC analysis (PD-L1 CPS ≥5 and PD-L1 CPS ≥1 populations) should be properly conducted.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends the comparison of baseline characteristics for the PD-L1 CPS≥5 and PD-L1 CPS ≥1 populations between included trials in the ITC where data are available.
CPS = combined positive score; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death ligand 1	

Table 1.4: Key issue 3: Lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	Given that the ITC analysis was based on the overall population with mixed status of PD-L1 CPS from the zolbetuximab trials (SPOTLIGHT and GLOW) and the PD-L1 CPS ≥5 subgroup from the CheckMate-649 trial and the PD-L1 CPS ≥1 subgroup from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859), there was considerable heterogeneity in patients' PD-L1 CPS status between included trials in the ITC and it is unclear whether PD-L1 CPS status is a treatment effect modifier for chemotherapy versus zolbetuximab plus chemotherapy alone. Furthermore, following the assessment of heterogeneity and uncertainty, the differences in the features of the trials (including different blinding methods: double blind for SPOTLIGHT, GLOW and KEYNOTE-859 versus open label for CheckMate-649) also introduced limitations in the results of ITC analysis. Therefore, there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC analysis. Due to this issue, there were uncertainties in the validity of ITC results.
What alternative approach has the EAG suggested?	The assumption of exchangeability for the purpose of ITC analysis should be acceptable.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that sufficient evidence should be provided to support the assumption of exchangeability for the purpose of ITC analysis.
CPS = combined positive score; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death ligand 1	

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

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary

and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in Tables 1.5 to 1.12 below.

Table 1.5: Key issue 4: Relevant comparators in different sub-populations

Report Section	**4.2.4**
Description of issue and why the EAG has identified it as important	The CS explored different comparators that become relevant in different sub-populations but did not provide cost-effectiveness analyses (CEAs) for all of these.
What alternative approach has the EAG suggested?	The EAG considers that CEAs should the provided for the following sub-populations based on the comparators available in these: Primary analysis: PD-L1 CPS <5 gastric and GEJ– the only comparator is chemotherapy Secondary analysis: PD-L1 CPS ≥ 5 and <10 gastric and GEJ chemotherapy and nivolumab + chemotherapy are both comparators. Here, relative effectiveness from the NMA should be included by the company, even with the caveat that these may be conservative. With potential approval of treatments, potentially relevant future subgroups include: PD-L1 CPS ≥ 1 gastric and GEJ (subject to approval of pembrolizumab in this population) The subgroup of patients with PD-L1 CPS ≥ 10 gastric and GEJ may become relevant if zolbetuximab is considered an effective treatment and comparator to nivolumab and pembrolizumab in this subgroup.
What is the expected effect on the cost effectiveness estimates?	Not available.
What additional evidence or analyses might help to resolve this key issue?	It should be confirmed whether patients with PD-L1 CPS ≥ 10 (gastric or GEJ) are indeed not eligible for zolbetuximab unless pembrolizumab or nivolumab are contraindicated. If this is not the case, analyses should be provided for these populations, with inclusion of appropriate comparators in the CEAs; and NMA results should likely be used in the CEAs.
CEAs = cost effectiveness analyses; CS = company submission; EAG = Evidence Assessment Group; GEJ = gastro-oesophageal junction; NMA = network meta-analysis; PD-L1 = programmed death ligand 1	

Table 1.6: Key issue 5: Uncertainty regarding the appropriateness of including the CheckMate 649 trial to estimate chemotherapy outcomes

Report Section	**4.2.6**
Description of issue and why the EAG has identified it as important	The company includes the CheckMate 649 trial (nivolumab + chemotherapy compared to chemotherapy) to estimate outcomes in the chemotherapy arm. The benefit of this is mainly in the longer follow-up of the trial (approximately 5 years). This results in different extrapolations of the chemotherapy survival curves compared to when only the SPOTLIGHT and GLOW trials are used: higher 5-year and 10-year OS estimates for chemotherapy. Including CheckMate 649 might result in long-term outcomes in line with expert opinion, however the EAG highlights the methodological uncertainty caused by the naïve pooling of the SPOTLIGHT, GLOW and CheckMate 649 trials.
What alternative approach has the EAG suggested?	Excluding the CheckMate 649 trial.

Report Section	4.2.6
What is the expected effect on the cost effectiveness estimates?	Excluding the CheckMate 649 trial will increase the ICER, the extent depends on the selected survival curve extrapolations used.
What additional evidence or analyses might help to resolve this key issue?	The individual patient data of the CheckMate 649 trial might be suitable to obtain better long-term estimates, but a pooling method adjusting for differences in trial designs and patient selection should be used to obtain these estimates.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival	

Table 1.7: Key issue 6: Appropriateness of assuming equal treatment effectiveness for zolbetuximab + chemotherapy and nivolumab + chemotherapy

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	In the economic model, the NMA results for nivolumab + chemotherapy are absent. Instead, the NMA results for zolbetuximab are used, implying equal treatment effectiveness.
What alternative approach has the EAG suggested?	The EAG has asked for a full cost effectiveness comparison of zolbetuximab versus nivolumab (clarification question B3), however the company deems the cost-comparison approach to be most appropriate.
What is the expected effect on the cost effectiveness estimates?	As the HRs of nivolumab + chemotherapy versus chemotherapy at each time point are lower than the HRs of zolbetuximab + chemotherapy versus chemotherapy, the ICER is likely going to increase when the NMA results of nivolumab are included.
What additional evidence or analyses might help to resolve this key issue?	Provide a full cost-effectiveness analysis including the NMA results of nivolumab + chemotherapy
EAG = Evidence Assessment Group; HRs - hazard ratios; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis	

Table 1.8: Key issue 7: Selection of extrapolation curves to estimate treatment effectiveness in the PD-L1 CPS populations

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company uses spline modelling to extrapolate the OS and PFS survival curves for the chemotherapy and zolbetuximab + chemotherapy arms in the base-case primary analysis, and also in the secondary scenario to extrapolate chemotherapy OS and PFS. The EAG deems spline modelling to be inappropriate as parametric survival curves have a good fit (both visually and statistically). The company notes the poor fit of the parametric models for PFS because of an observed plateau, however the EAG highlights that this observed plateau (observed after approximately 2.5 years) is based on extremely low patient numbers.
What alternative approach has the EAG suggested?	Parametric survival modelling using the company's scenario 2 assumptions (chemotherapy: gamma for OS and log-logistic for PFS, zolbetuximab: log-logistic for both OS and PFS) for the primary analysis, and for the secondary analysis the same assumptions for chemotherapy (gamma for OS and log-logistic for PFS) and the NMA for extrapolation of zolbetuximab + chemotherapy and nivolumab + chemotherapy. A scenario analysis using the log-logistic curve for

Report Section	4.2.6
	chemotherapy OS was conducted by the EAG, as it could potentially better reflect the small proportion of long-term survivors.
What is the expected effect on the cost effectiveness estimates?	In the primary analysis the ICER increases with 25.8% to [redacted] and in the secondary analysis the ICER of zolbetuximab + chemotherapy versus chemotherapy alone increases with 120.0% to [redacted]
What additional evidence or analyses might help to resolve this key issue?	More evidence on the existence of a survival plateau with zolbetuximab + chemotherapy, however this is not available from the SPOTLIGHT and GLOW trials.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival	

Table 1.9: Key issue 8: Uncertainty regarding the existence and onset of treatment effectiveness waning

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Treatment effect waning is currently not implemented in the base-case analyses. Currently, the evidence does not show a treatment effectiveness waning for zolbetuximab, but follow-up is limited to approximately [redacted] for OS and PFS in the GLOW and SPOTLIGHT trials. Therefore, the EAG finds it important to explore treatment effect waning assumptions.
What alternative approach has the EAG suggested?	The company has modelled scenarios with treatment effect waning onset at 5, 6 and 7 years and the EAG has also modelled treatment effect waning at 3 and 4 years. In their base-case the EAG adopted an assumption of treatment effect waning onset at 5 years.
What is the expected effect on the cost effectiveness estimates?	The increase in the ICER varies between 48.6% and 15.4% (ICERs of [redacted] and [redacted], respectively) with treatment effect waning onset assumptions of 3 and 7 years, respectively. The EAG base-case assumption results in an increase of 25.2% to [redacted]
What additional evidence or analyses might help to resolve this key issue?	Ideally, long-term follow-up data is needed to assess if and when treatment waning occurs.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival	

Table 1.0: Key issue 9: Uncertainty regarding the estimated utility values.

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	No data imputation was performed for the EQ-5D data collected in the SPOTLIGHT and GLOW trials, despite data not being missing at random. Therefore, there is risk of bias in the utility estimates used in the economic model, which were on average higher than those from other TA from similar populations. The company provided utility estimates using GEE (base-case) and mixed-effects models. However, the mixed-effects model is considered more flexible and provided more realistic estimates.

Report Section	4.2.8
What alternative approach has the EAG suggested?	Using the utility estimates from the mixed effects model.
What is the expected effect on the cost effectiveness estimates?	Using a mixed effects model to estimate utility values decreases the ICER. The effect of data imputation on the ICER is unknown.
What additional evidence or analyses might help to resolve this key issue?	The company should perform data imputation on the collected EQ-5D data and calculate the utility estimates using the mixed effects model (GLMM).
EAG = Evidence Assessment Group; EQ-5D = European Quality of Life- 5 Dimensions GEE = generalised estimating equation; GLMM = generalised linear mixed model, ICER = incremental cost-effectiveness ratio; TA = Technical Appraisal	

Table 1.1: Key issue 10: Post-progression treatments not being representative of UK clinical practice

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	In the CS base-case, patients in the post-progression state received an equal split of docetaxel and paclitaxel, irrespective of the first-line of treatment. However, this differed from the subsequent treatments used in the SPOTLIGHT and GLOW trials, and in UK clinical practice, which mainly involves FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) in England, and docetaxel and irinotecan in Scotland.
What alternative approach has the EAG suggested?	Update the post-progression treatments in the economic model to those applied in UK clinical practice, including the expected percentage per treatment group, exact drug acquisition and administration costs, and treatment duration.
What is the expected effect on the cost effectiveness estimates?	The EAG is not able to assess the impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	The company should update the economic model and analyses to include treatments aligned with UK clinical practice (as suggested above).
CS = company submission, EAG = Evidence Assessment Group, ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

1.6 Summary of the EAG's view

The CS base-case ICERs (deterministic) were [redacted] versus chemotherapy in the primary analysis and [redacted] versus nivolumab + chemotherapy and [redacted] versus chemotherapy in the secondary analysis. This result does not include the application of a 1.2x QALY weight, instead a modified willingness-to-pay (WTP) threshold of £36,000 was used. The estimated EAG base-case ICERs (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1 were [redacted] versus chemotherapy in the primary analysis and [redacted] versus nivolumab + chemotherapy and [redacted] versus chemotherapy in the secondary analysis. The probabilistic EAG base-case primary analysis indicated a cost effectiveness probability of 1.9% for zolbetuximab + chemotherapy versus chemotherapy at a WTP threshold £36,000 per QALY gained. The secondary analysis indicated cost effectiveness probabilities of 0.6%

for zolbetuximab +chemotherapy versus chemotherapy and 0.0% for zolbetuximab + chemotherapy versus nivolumab + chemotherapy at a WTP threshold £36,000 per QALY gained. The most influential adjustments were related to the appropriate evidence used to inform treatment effectiveness, selection of survival curves to estimate treatment effectiveness and assumptions regarding treatment effect waning. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment effect waning and, in the secondary scenario, when the log-logistic curve for chemotherapy OS is used.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of zolbetuximab + chemotherapy, which can be partly resolved by the company by further clarification and conducting further analyses. Further clarification is needed on whether patients with programmed death ligand 1 (PD-L1) CPS ≥ 10 (gastric or GEJ) are indeed not eligible for zolbetuximab unless pembrolizumab or nivolumab are contraindicated. If this is not the case, analyses should be provided for these populations, with inclusion of appropriate comparators in the cost effectiveness analysis (CEA). Further analyses are potentially needed to appropriately include CheckMate 649, including the selection of most appropriate extrapolation curves in the model and further justification of the existence of a survival plateau. In addition, analysis are needed to obtain fully incremental cost effectiveness results for the comparison between zolbetuximab + chemotherapy and nivolumab + chemotherapy without the assumption of equal treatment effectiveness, to justify the assumption of no treatment waning, to obtain better utility estimates using data imputation and a mixed effects model, and to update the post-progression treatments included in the model. Therefore, the EAG believes that neither the CS nor the EAG report contain an unbiased ICER of zolbetuximab + chemotherapy compared with the relevant comparators.

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Population	First-line treatment of patients with advanced unresectable HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive	First-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive	Aligns with anticipated marketing authorisation	The population considered in the company submission is in line with the anticipated marketing authorisation for zolbetuximab.
Intervention	Zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy	As per final scope	Not applicable	The intervention is in line with the NICE scope.
Comparator(s)	Chemotherapy only, including: • Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin For patients whose tumours express PD-L1: • Nivolumab with chemotherapy (PD-L1 CPS ≥ 5) • Pembrolizumab with chemotherapy (with CPS of 10 or more and for gastro-oesophageal junction adenocarcinoma only) • Pembrolizumab with chemotherapy (with CPS 1 or more and for gastric or GEJ adenocarcinoma – subject to NICE evaluation	• Chemotherapy only, including: – Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin – For patients whose tumours express PD-L1 – Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)	Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a very small overlap [redacted] between patients with GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10). Therefore,	For patients whose tumours express PD-L1, the company included nivolumab with chemotherapy (PD-L1 CPS ≥ 5) in their evidence submission. However, the company excluded pembrolizumab with chemotherapy as a comparator. The EAG requested

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			because the overlap in the CPS ≥ 10 patient population is very small and pembrolizumab with chemotherapy is not recommended in patients with CPS ≥ 1 (NICE [ID4030], pembrolizumab with chemotherapy has not been included as a comparator	the company to provide further justification on this exclusion in the clarification letter. In responding to the EAG's request, the company provided additional NMA results by incorporating pembrolizumab with chemotherapy as a comparator for patients with PD-L1 CPS ≥ 1 for gastric or GEJ adenocarcinoma.
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per final scope	Not applicable	The outcomes reported are in line with the NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social	As per final scope	Not applicable	The assumption of equal effectiveness of zolbetuximab + chemotherapy and nivolumab + chemotherapy hampered a full cost-effectiveness

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. • The use of zolbetuximab is conditional on the presence of CLDN18.2. The economic modelling should include the costs associated with diagnostic testing for CLDN18.2 in people with gastric or gastro-oesophageal junction adenocarcinoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			analysis, see key issue 6.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	

Based on Table 1 of CS[1]

CS = company submission; CLDN18.2 = claudin 18.2; CPS = combined positive score; GC = gastric cancer; GEJ = gastro-oesophageal junction; GEJC = gastro-oesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; PSS = Personal Social Services

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) final scope is *"first-line treatment of patients with advanced unresectable HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive"*.[2] The population in the CS is *"first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive"*.[1]

According to the company the decision problem addressed in the company submission (CS) is slightly different from that specified in the final scope, which does not specify that the population will include metastatic human epidermal growth factor receptor (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are claudin (CLDN) 18.2 positive.

The Evidence Assessment Group (EAG) requested the company to clarify the difference between the population defined in the NICE final scope and the population in the CS.[1, 2] The EAG also request the company to elaborate on the impact of this difference on the standard of care in this population.[3] The company provided the following response: *"This is a minor difference in terminology, which has no impact on the standard of care in this population. In the NICE scope, the term "advanced unresectable" refers to patients with locally advanced unresectable adenocarcinoma as well as patients with metastatic adenocarcinoma. Furthermore, the patient population in the submission aligns with the expected marketing authorisation"*.[4] The EAG considers that the population addressed in the company submission is generally in line with the population defined in the NICE final scope.

The population considered in the CS is in line with the anticipated marketing authorisation for zolbetuximab.

The marketing authorisation application to the use of zolbetuximab in this indication has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) national (150-day) route with an expected marketing authorisation date of [redacted].[1]

2.2 Intervention

The intervention (zolbetuximab) is in line with the NICE final scope. Zolbetuximab is for an intravenous (IV) use. The recommended dose is administered by IV infusion over a minimum of 2 hours. Zolbetuximab must not be administered as an IV push or bolus injection.

If zolbetuximab and fluoropyrimidine- and platinum-containing chemotherapy are administered on the same day, zolbetuximab must be administered first. Zolbetuximab should be administered via IV infusion with the following dosing:[1]

- Single loading dose: 800 mg/m^2 IV on Cycle 1 Day 1
- Maintenance dose:
  - 600 mg/m^2 IV every 3 weeks, or
  - 400 mg/m^2 every 2 weeks

Duration of therapy is until disease progression or unacceptable toxicity. Zolbetuximab should be administered in combination with fluoropyrimidine- and platinum-containing chemotherapy.[1]

According to the company, a test of CLDN18.2 positivity is required prior to the administration of zolbetuximab. CLDN18.2 positivity (defined as ≥ 75% of tumour cells demonstrating moderate-to-

strong membranous CLDN18 immunohistochemistry staining) should be determined by a validated test. The VENTANA CLDN18 (43-14A) pharmaceutical diagnostic assay is an under-development companion diagnostic test for CLDN18.2. This companion diagnostic test specific to zolbetuximab is expected to be approved once the medicine is licensed.[1]

2.3 Comparators

The description of the comparators in the NICE final scope is as follows:[2]

"Chemotherapy only, including:

- *Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin*

For patients whose tumours express PD-L1:

- *Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)*
- *Pembrolizumab with chemotherapy (with CPS of 10 or more and for gastro-oesophageal junction adenocarcinoma only)*
- *Pembrolizumab with chemotherapy (with CPS 1 or more and for gastric or GEJ adenocarcinoma – subject to NICE evaluation".*

The company addressed the following comparators in the CS:

"Chemotherapy only, including:

- *Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin*

For patients whose tumours express PD-L1:

- *Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)".*[1]

The company states that *"Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a very small overlap ([redacted]) between patients with GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10). Therefore, because the overlap in the CPS ≥ 10 patient population is very small and pembrolizumab with chemotherapy is not recommended in patients with CPS ≥ 1 (NICE [ID4030]), pembrolizumab with chemotherapy has not been included as a comparator".*[1]

EAG comment: The company's decision problem omitted pembrolizumab with chemotherapy as a comparator for combined positive score (CPS) ≥1 because it has not been recommended by NICE yet, this being subject to an ongoing appraisal. It omitted it as a comparator for CPS ≥ 10 on the basis of the lack of overlap between patients with gastric cancer/GEJ adenocarcinoma who are eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10). However, it is unclear if the small overlap [redacted] between patients with gastric cancer/GEJ adenocarcinoma eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10) would be similar to those in standard practice. The EAG requested the company to provide further justification on this exclusion in the clarification letter. In responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also provided additional network meta-

analysis (NMA) results by incorporating pembrolizumab with chemotherapy as a comparator for patients with PD-L1 CPS ≥1 for gastric cancer or GEJ adenocarcinoma. The EAG notes that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators. In conclusion, the EAG recommends that either the company clarifies that patients with PD-L1 CPS ≥ 10 are ineligible for zolbetuximab or the clinical effectiveness and cost effectiveness for the subgroup of GEJ patients with PD-L1 CPS ≥ 10 should be assessed by using pembrolizumab plus chemotherapy as a comparator. Pembrolizumab + chemotherapy could also be included as a comparator for all subgroups should there be a positive recommendation by NICE for PD-L1 CPS ≥1.

2.4 Outcomes

The NICE final scope lists the following outcome measures:[2]

- Overall survival (OS)
- Progression-free survival (PFS)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The outcome measures included in the CS were consistent with those specified by the NICE final scope.

2.5 Other relevant factors

According to the company, no equality issues were related to the use of zolbetuximab plus chemotherapy for the first-line treatment of patients with advanced unresectable HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive.[1]

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) evidence relating to the efficacy and safety of zolbetuximab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction cancer (GEJC).

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1, 5] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[6, 7] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SLR conducted to identify relevant clinical evidence on the efficacy and safety of different treatments in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction cancer (GEJC).[5] Searches were conducted in September 2020, with updates conducted in August 2022 and October 2023. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1980-2020 week 38 1974-2022 week 31 1974-2023 week 43	22.9.20 11.8.22 30.10.23
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-21.9.20 1946-11.8.22 1946-27.10.23	22.9.20 11.8.22 30.10.23
The Cochrane Library (including CDSR, DARE and CENTRAL)	Ovid	All years	23.9.20 11.8.22 30.10.23
Conferences			
• ASCO ICML • ESMO • ISPOR • IGCC • ASCO Gastrointestinal Cancers Symposium	Internet	2017-2023	8.10.20 8.9.22 31.10.23

Resource	Host/Source	Date Ranges	Date searched
Trials registries			
• ClinicalTrials.gov • WHO ICTRP	Internet		
CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; CENTRAL: Cochrane Central Register of Controlled Trials; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Gastric Cancer Association; IGCC: International Gastric Cancer Association; ICML: International Conference on Malignant Lymphoma; WHO ICTRP: World Health Organization International Clinical Trials Registry			

EAG comments:

- Searches were undertaken in September 2020, with updates conducted in August 2022 and October 2023, to identify relevant clinical evidence on the efficacy and safety of different treatments in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction cancer. The CS, Appendix D and the Company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.[1, 4, 5, 8]
- A good range of bibliographic databases, conferences, websites and trials registers were searched. Reference checking was conducted.
- The database searches for the clinical effectiveness SLR combined a facet for gastric cancer with terms for zolbetuximab and its comparators. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. The study design filters were not referenced, so it was unclear whether the filters used were published objectively derived filters. The filters contained a combination of subject heading terms and free-text terms and the EAG considered them appropriate.
- Searches were well-structured, transparent and reproducible, and employed comprehensive use of both subject headings (MeSH/EMTREE) and free-text terms.
- Database searches were limited to studies from 2000-date. No language limit was applied to the searches.
- Conference proceedings were hand-searched for five key international conferences between 2017 and 2023. In addition to this, conference proceedings will have been retrieved by the Embase and CENTRAL searches.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for RCTs and non-RCTs is presented in Table 3.2.

On reviewing the criteria, the EAG sought clarification on whether it appropriately met the NICE final scope due to the inclusion of other checkpoint inhibitors that are not relevant to the NICE final scope. The company in their response to the request for clarification stated that *"the SLRs were conducted to meet the needs of health technology assessment agencies internationally, therefore include interventions that are not available in the UK. The wider inclusion criteria do not compromise the validity or the usefulness of the SLRs to inform the NICE appraisal of zolbetuximab, as all comparators relevant to the UK were included".*[4]

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Component	Inclusion	Exclusion
Population	Adult patients (≥ 18 years) with pathologically confirmed metastatic or locally advanced unresectable, or recurrent gastric or GEJ adenocarcinoma, who: • Have not received any previous first-line treatment (chemotherapy or targeted agent) for gastric or GEJ cancer (prior adjuvant or neo-adjuvant therapy is permitted) • Have HER2-negative status	• 18 years of age • HER2-positive status • Studies with mixed patient populations will be included if ≥ 80% of patients are eligible, or if eligible subgroups are reported
Interventions	Treatments currently used or in development for advanced or metastatic GC: Avelumab (Bavencio®) Bemarituzumab Camrelizumab* CAPOX (capecitabine + oxaliplatin) Cisplatin + 5-FU (fluorouracil) Cisplatin + capecitabine (CX) DCF (docetaxel, cisplatin, 5-FU) Durvalumab* ECF (epirubicin, cisplatin, fluorouracil) ECX (epirubicin, cisplatin, capecitabine) EOF (epirubicin, oxaliplatin, fluorouracil) EOX (epirubicin, oxaliplatin, capecitabine) FLOT (folinic acid, fluorouracil, oxaliplatin, docetaxel) FOLFIRI (folinic acid, fluorouracil, irinotecan) Ipilimumab (Yervoy®) mFOLFOX6 Nivolumab (OPDIVO®) Oxaliplatin + 5-FU (fluorouracil) Pamiparib Pembrolizumab	• Treatments not listed • Non-pharmacological therapies

Component	Inclusion	Exclusion
	Placebo Sintilimab* Spartalizumab* Tislelizumab Toripalimab* Zolbetuximab BSC	
Comparators	Treatments currently used or in development for advanced or metastatic GC: • Avelumab (Bavencio®) • Bemarituzumab • Camrelizumab* • CAPOX (capecitabine + oxaliplatin) • Cisplatin + 5-FU (fluorouracil) • Cisplatin + capecitabine (CX) • DCF (docetaxel, cisplatin, 5-FU) • Durvalumab* • ECF (epirubicin, cisplatin, fluorouracil) • ECX (epirubicin, cisplatin, capecitabine) • EOF (epirubicin, oxaliplatin, fluorouracil) • EOX (epirubicin, oxaliplatin, capecitabine) • FLOT (folinic acid, fluorouracil, oxaliplatin, docetaxel) • FOLFIRI (folinic acid, fluorouracil, irinotecan) • Ipilimumab (Yervoy®) • mFOLFOX6 • Nivolumab (OPDIVO®) • Oxaliplatin + 5-FU (fluorouracil) • Pamiparib • Pembrolizumab • Placebo • Sintilimab*	• Treatments not listed • Non-pharmacological therapies

Component	Inclusion	Exclusion
	• Spartalizumab* • Tislelizumab • Toripalimab* • Zolbetuximab BSC	
Outcomes	**Baseline characteristics** Patient and study characteristics (including age, race, country, % males, CLDN18.2 status etc.) **Efficacy** • Overall survival • Progression-free survival • Time to progression • Duration of response • Event-free survival • Response rates (complete response, partial response, stable disease) • Objective response rate • Disease control rate • Duration of treatment; duration of treatment beyond progression **Safety** • All-grade treatment related AE • Treatment related Grade 3 or 4 AEs • Treatment related SAEs Tolerability: dose reductions and interruptions, discontinuation (all-cause; due to AEs)	Outcome(s) not listed
Study design/setting	RCTs, any duration (irrespective of blinding)	Other study designs
Language restrictions	English language publications	Non-English language studies

Component	Inclusion	Exclusion
Geography	No restriction	-
Date of publication	Original SLR: 2000–22 September 2022 First SLR update: 22 September 2022–11 August 2022) Second SLR update: 11 August 2022–30 October 2023	Studies published prior to 2000

Based on Table 10 of the CS appendices[5]

*New treatments added for the 2022 update, for which relevant literature investigating these treatments was searched from 2000–11 August 2022 during the 2022 update. These interventions were not included in the original SLR.

AE = adverse event; BSC = best supportive care; CAPOX = capecitabine and oxaliplatin; CS = company submission; DCF = docetaxel = cisplatin = 5-FU; ECX = epirubicin, cisplatin, capecitabine; EOF = epirubicin, oxaliplatin, fluorouracil; FLOT = folinic acid, fluorouracil, oxaliplatin, docetaxel; FOLFIRI = folinic acid, fluorouracil, irinotecan; FU = fluorouracil; GEJ = gastro-oesophageal junction; GSRS = Gastrointestinal Symptom Rating Scale; HER2 = human epidermal growth factor receptor 2; RCT = randomised controlled trial; SAE = serious adverse event; SLR = systematic literature review

3.1.3 Critique of data extraction

While the CS confirms that screening was conducted in duplicate by two independent reviewers, data extraction was conducted by one reviewer and then checked by a second reviewer[1]. While this is a widely used approach, it is likely more prone to bias and error than two independent extractions that are then compared and discussed. The Company does confirm that any inconsistencies between the first and second reviewer were resolved through discussion or by the involvement of a third reviewer.

EAG comment: This approach is widely used and reported in the literature, however, it should be noted that it is more prone to error and bias than independent duplicate extractions. While we do not assert that this means there is a presence of error or bias across these data, we do highlight that there is an increased likelihood of it.

3.1.4 Quality assessment

The CS confirms that **'**SPOTLIGHT and GLOW were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies. A complete quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented'. In Tables 28-30 of the appendices, the quality appraisals for SPOTLIGHT, GLOW and FAST are presented.[5] While the CS emphasises the consistency of the critical appraisal with GCP ethical principles, it does not confirm the specific approach that was taken. The EAG in request for clarification asked the company to provide additional information on the number of reviewers that were involved in this process and whether such work was undertaken independently. In their response, the company confirmed that "*Quality assessments were performed for all the final studies included in the SLR by two reviewers independently to assess the likelihood of bias. Any disagreements were resolved by discussion and/or additional referees*".[4]

EAG comment: The Company confirmed that appraisals were undertaken with an approach that is appropriate for minimising error and bias.

3.1.5 Evidence synthesis

The company states that a formal meta-analysis was not performed.[1] However, the rationale for not performing meta-analysis was not stated. The EAG requested the rationale for not performing meta-analysis.[3] The company stated in their response that the zolbetuximab trials were not meta-analysed in a separate analysis but the trials were meta-analysed in the network meta-analysis.[4] Given this response, it was unclear about the rationale for not performing meta-analysis. However, data from another RCT (CheckMate-649) comparing nivolumab with chemotherapy versus chemotherapy were combined with the data of SPOTLIGHT and GLOW in the ITC base-case analysis. Further details are provided in Section 3.3 of this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Of the 90 studies identified by the SLR, the CS states that four studies were deemed relevant.[1] These relevant studies included three studies providing efficacy and safety evidence for zolbetuximab + chemotherapy, and one for nivolumab + chemotherapy. The CS presents the details of the SPOTLIGHT. GLOW and FAST trials in support of the submission and these will be summarised below.

3.2.1 Study retrieval

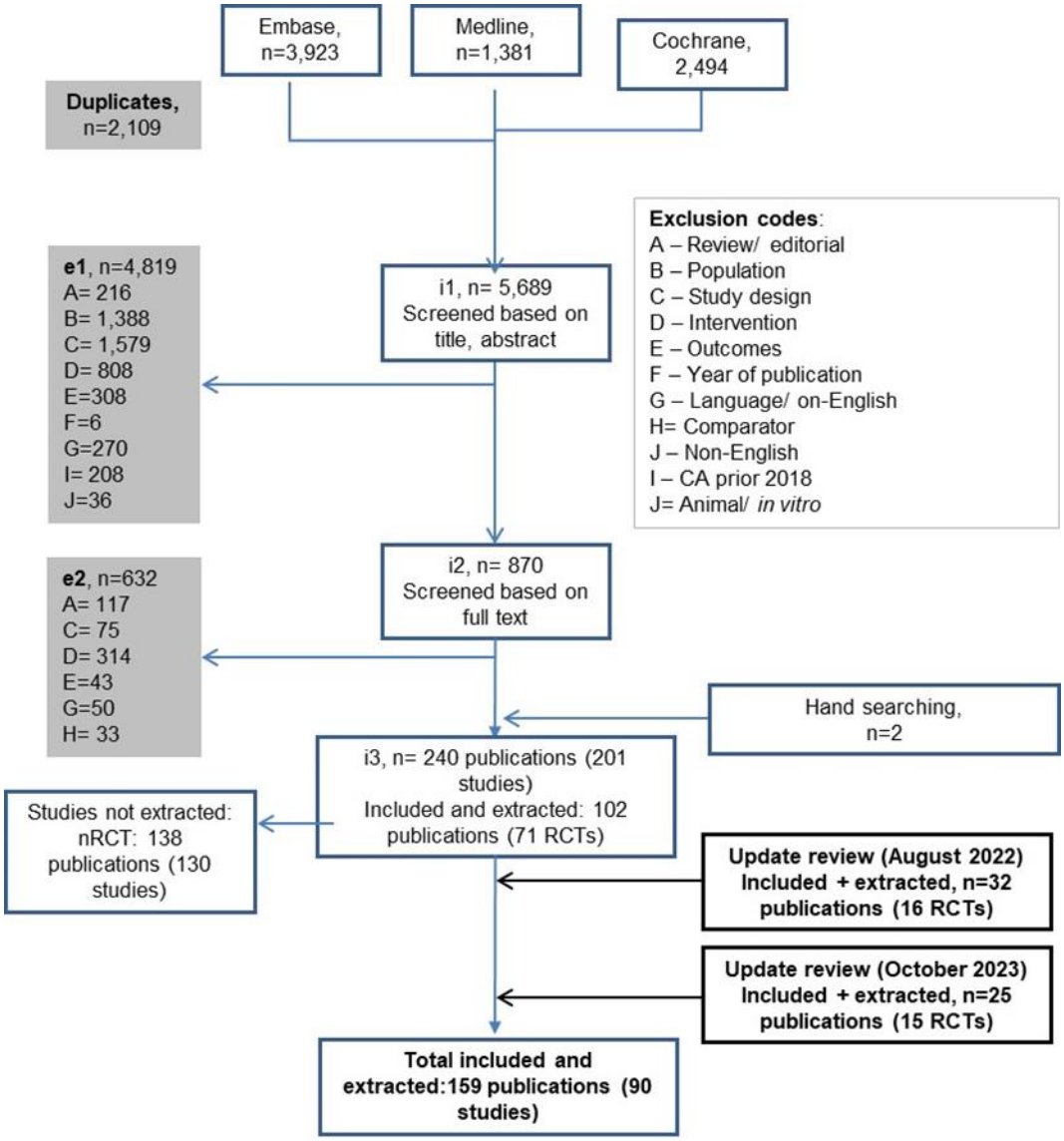
The SLR was conducted to identify relevant clinical studies in support of this submission. The CS appendices detail this process[5]. Evidence was identified from the systematic search and screen and two additional updates. Initially 5,689 records (see Figure 3.1 below) were identified that were obtained for screening after the removal of duplicates. This yielded 870 relevant records for further exploration. Of these, 632 records were then deemed irrelevant and excluded. Manual handsearching resulted in two further papers meaning that 240 records deemed eligible for inclusion.

An update to this was conducted in 2022 where 1,289 additional records were obtained for screening after removal of duplicates. One hundred and twenty-eight full texts were obtained for further exploration with 84 subsequently being excluded. Ten further records were identified through manual hand searching resulting in 54 records being included at the 2022 update.

Finally, an additional update was executed in 2023 and identified 977 records eligible for screening after duplicate removal. Ninety-five records were then obtained and reviewed through full-text screening. Seventy-two studies were excluded, leaving 23 records. Manual handsearching resulted in two additional studies, meaning 25 records were included.

The SLR therefore identified 159 records in total, comprising 90 RCTs. Four of these were deemed relevant and included three studies for zolbetuximab (SPOTLIGHT, GLOW and FAST), and one study for nivolumab (Opdivo®) (CheckMate 649). The study retrieval process is summarised in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart detailed below.

Figure 3.1: PRISMA flow diagram



Based on Figure 1 of the CS appendices[5] and Figure 1 of the response to the request for clarification[4]
CS = company submission; e1 = excluded publications after title/abstract screening stage; e2 = excluded publications after full-text review stage; i1 = publications to screen at title/abstract stage; i2 = publications to screen at full-text review stage; i3 = total included publications after full-text review stage for original report and 2022 search update; RCTs = randomised controlled trials; SLR = systematic literature review

3.2.2 Summary of SPOTLIGHT, GLOW and FAST trials

Two Phase III trials, SPOTLIGHT and GLOW are the pivotal trials for zolbetuximab in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable/metastatic G/GEJ adenocarcinoma. The FAST trial, a Phase II trial designed to assess the efficacy and tolerability of zolbetuximab in patients with advanced G/GEJ or oesophageal adenocarcinoma with moderate-to-strong CLDN18.2 expression in ≥ 40% tumour cells, provides supportive evidence. Each of these trials will be briefly summarised below.

Table 3.3: Overview of Study characteristics

Study	SPOTLIGHT	GLOW	FAST
Study design	Phase III, double-blind	Phase III, double-blind	Phase II, randomised,

Study	SPOTLIGHT	GLOW	FAST
	RCT	RCT	open-label trial
Population	Adults with CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	Adults with CLDN18.2-positive (≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining), HER2-negative locally advanced unresectable/metastatic G/GEJ adenocarcinoma	Adults with CLDN18.2-positive (≥ 40% of tumour cells with 2+ or 3+ staining intensity), HER2/neu-negative patients with HER2/neu-positive status, but not eligible for trastuzumab therapy by discretion of the investigator, advanced G/GEJ and oesophageal adenocarcinoma Relevant to this appraisal is the subgroup with CLDN18.2 expression in ≥ 70% of tumour cells
Intervention(s)	Zolbetuximab + mFOLFOX6 (n = 283)	Zolbetuximab + CAPOX (n = 254)	Zolbetuximab + EOX (n = 77)
Comparator(s)	mFOLFOX6 (n = 282)	CAPOX (n = 253)	EOX (n = 84)
Indicate if study supports application for marketing authorisation	Yes	Yes	No
Indicate if study used in the economic model	Yes	Yes	No
Rationale if study not used in the model	N/A	N/A	The relevant subgroup from FAST was included in a scenario of the indirect treatment comparison. As results were similar to the base-case analysis without the FAST subgroup, the scenario analysis was not taken forward to the economic model.
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rate • Adverse events • HRQL	• Overall survival • Progression-free survival • Response rate • Adverse events • HRQL	• Overall survival • Progression-free survival • Response rate • Adverse events
All other reported outcomes	• Time to confirmed deterioration • Pharmacokinetics • Immunogenicity	• Time to confirmed deterioration • Pharmacokinetics • Immunogenicity	• Time to progression
Based on Table 3 of the CS[1]			

Study	SPOTLIGHT	GLOW	FAST
Bolded outcomes are those used in the economic modelling. CAPOX = capecitabine and oxaliplatin; CLDN18.2 = claudin 18.2; CS = company submission; EOX = epirubicin, oxaliplatin and capecitabine; G/GEJ = gastric/gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQL = health-related quality of life; mFOLFOX6 = modified folinic acid in combination with fluorouracil and oxaliplatin; N/A = not applicable; RCT = randomised controlled trial			

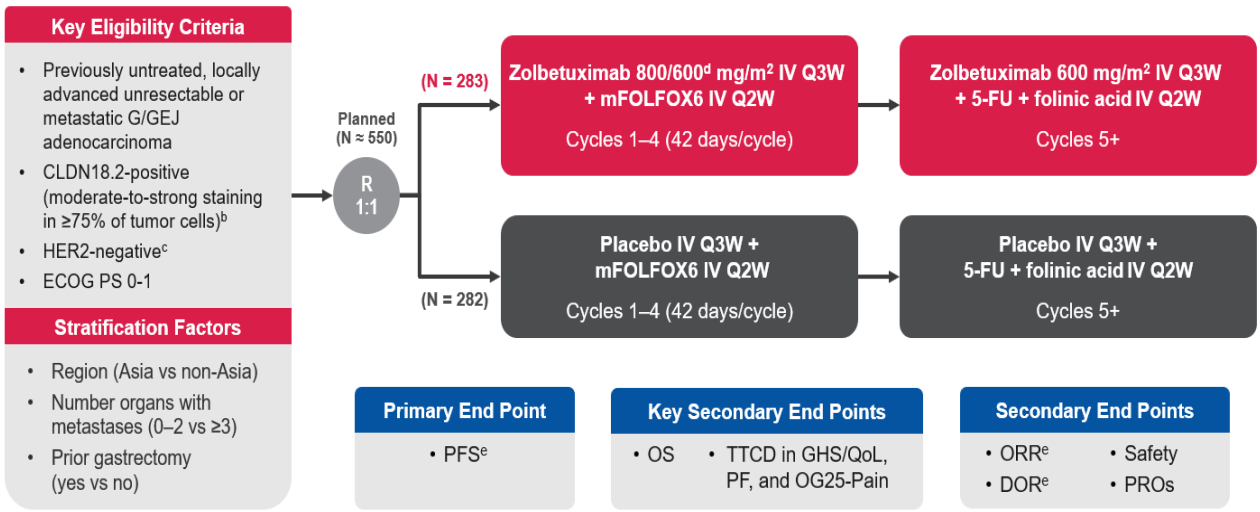
3.2.2.1 SPOTLIGHT overview

SPOTLIGHT was a Phase III, multicentre, double-blind, RCT conducted at 232 sites in 20 countries, with nine United Kingdom (UK) based sites[1]. This trial was implemented to evaluate the efficacy and safety of zolbetuximab + folinic acid in combination with fluorouracil and oxaliplatin (mFOLFOX6) versus placebo + mFOLFOX6 as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. The CS clarifies that "*The final database lock for the SPOTLIGHT trial took place on 08 September 2023. Data analysis is currently ongoing and is expected to be submitted with responses to clarification questions".*[1] The results from the final data-cut were submitted during the clarification response stage.

The study was conducted across six periods: (1) screening, (2) treatment, (3) safety follow-up, (4) post-treatment follow-up for PFS, (5) long-term follow-up for PFS following subsequent anti-cancer treatment (PFS2), and (6) OS. Please see Figure 3.2 for an overview of trial process.

The CS[1] clarifies that the SPOLTLIGHT primary efficacy endpoint consisted of PFS (per RECIST 1.1, as determined by an independent review committee (IRC). Secondary endpoints included OS and time to confirmed deterioration (TTCD), objective response rate (ORR), duration of response (DoR) and HRQoL. These are summarised in Figure 3.1 (SPOTLIGHT trial process) below.

Figure 3.2: SPOTLIGHT trial design



Adapted from Figure 3, CS[1]

5-FU, fluorouracil; CLDN18.2, claudin 18.2; CS, company submission; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G/GEJ, gastric/gastro-oesophageal junction; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRC, independent review committee; IV, intravenous; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; QoL, quality of life; R, randomised; RECIST, Response Evaluation Criteria In Solid Tumours; TTCD, time to confirmed deterioration.
Notes: [a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, North America and South. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m2 at Cycle 1 Day 1 followed by 600 mg/m2 on Cycle 1 Day 22 and Days 1 and 22 of subsequent cycles; [e]As per RECIST v1.1 by IRC.

3.2.2.1.1 SPOTLIGHT Eligibility criteria

To determine the effects of zolbetuximab + mFOLFOX6 compared with placebo + mFOLFOX6, 565 patients were randomised in a 1:1 ratio to either of the two arms: Arm A – zolbetuximab + mFOLFOX6, or Arm B – placebo + mFOLFOX6. The following criteria applied for inclusion of participant in the study:[1]

- ≥ 18 years of age
- CLDN18.2-positive (defined as ≥ 75% of tumour cells showing moderate-to-strong membranous CLDN18 staining, determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay)
- HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma.
- radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1, an ECOG PS score of 0 or 1, and adequate organ function.

3.2.2.1.2 SPOTLIGHT Baseline characteristics

Table 3.4 describes the baseline characteristics of both arms of the SPOTLIGHT trial as presented in the CS[1]. The characterises in both arms appear to be well balanced although if we are to assume a >5% difference is noteworthy then it is remarkable that 27% of placebo + mFOLFOX6 patients had a metastasis location in the liver compared to 22% of the patients in the Zolbetuximab + mFOLFOX6 arm. Additionally, 33% of patients in the zolbetuximab + mFOLFOX6 arm had a metastasis location of the peritoneum compared to just 27% of the patients in the placebo + mFOLFOX6 arm.

Table 3.4: SPOTLIGHT: patient demographics and baseline disease characteristics

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Median age (IQR), years	62.0 (51.0, 69.0)	60.0 (50.0, 69.0)
Sex, n (%)		
Male	176 (62.2)	175 (62.1)
Female	107 (37.8)	107 (37.9)
Region, n (%)		
Asia	88 (31.0)	89 (32.0)
Non-Asia	195 (69.0)	193 (68.0)
Ethnicity, n (%)		
Hispanic or Latino	36 (13.8)	37 (14.8)
Not Hispanic or Latino	225 (86.2)	213 (85.2)
Missing	22 (8.0)	32 (11.0)
Organs with metastases, n (%)		
0–1	219 (77.0)	219 (78.0)
≥ 3	64 (23.0)	63 (22.0)

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Location of metastases, n (%)*		
Lymph node	101 (36.0)	109 (39.0)
Peritoneum	94 (33.0)	76 (27.0)
Liver	62 (22.0)	75 (27.0)
Lung	36 (13.0)	33 (12.0)
Bone	28 (10.0)	23 (8.0)
Abdominal cavity	19 (7.0)	17 (6.0)
Ovary	16 (6.0)	19 (7.0)
Previous gastrectomy, n (%)		
Yes	84 (30.0)	82 (29.0)
No	199 (70.0)	200 (71.0)
Primary site, n (%)		
GC	219 (77.4)	210 (74.5)
GEJC	64 (22.6)	72 (25.5)
Lauren classification, n (%)		
Diffuse	82 (29.1)	117 (42.1)
Intestinal	70 (24.8)	66 (23.7)
Mixed	31 (11.0)	13 (4.7)
Unknown	49 (17.4)	40 (14.4)
Other	50 (17.7)	42 (15.1)
Missing	1 (< 1.0)	4 (1.0)
ECOG performance status score, n (%)		
0	125 (44.8)	115 (41.4)
1	153 (54.8)	163 (58.6)
2†	1 (0.4)	0 (0.0)
Missing‡	4 (1.0)	4 (1.0)
Measurable disease, n (%)		
Yes	211 (75)	211 (75)
No	72 (25)	71 (25)

Based on Table 4 of CS[1]
CS, company submission; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: *Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.
†Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment.
‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG PS score of 0 or 1 and were thus eligible for enrolment.

The EAG on reviewing the baseline characteristics of the SPOLIGHT trial (see Table 3.4 above) queried the relevance of such a sample to the clinical population in England and Wales. We asked the company to provide data detailing the patient characteristics from Europe and from the UK specifically and with

relevant breakdown by ethnicity within those populations. In their response to the request for clarification, the company provided the UK following data [4].

As can be seen in Table 3.5 below, the involvement of UK based participants in the SPOTLIGHT trial was minimal and because of this small sample ([redacted]), the differences between the two groups appear to be noteworthy (>5%). However, this reflects the small sample and therefore cannot be relied upon to necessarily represent any clinical difference. It would therefore be prudent simply to highlight that it would be difficult to discern the representativeness of this data to UK based patients, or to determine whether uneven matching would render any clinical differences at the outcome level.

Table 3.5: Baseline characteristics of UK patients in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 [redacted]	**Placebo + mFOLFOX6** [redacted]
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Bone	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ovary	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 [redacted]	Placebo + mFOLFOX6 [redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
ECOG PS score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2†	[redacted]	[redacted]
Missing‡	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Adapted from Table 4 of the response to the request for clarification[4]
ECOG PS, Eastern Cooperative Oncology Group Performace Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.
† Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG PS score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment.
‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG PS score of 0 or 1 and were thus eligible for enrolment.

In response, the company also provided the data on all European and UK patients combined.[4] As can be seen in Table 3.6 below, the distributions between groups and generally evenly matched, however some noteworthy differences concerned with the cancer status are evident. In the placebo + mFOLFOX6 group, the peritoneum as a site of metastasis is increased (>5%) compared to the zolbetuximab + mFOLFOX6 group. Additionally, the distribution of primary site locations are different between the groups with [redacted]% of tumours originating in the GC and [redacted]% in the GEJC in the zolbetuximab + mFOLFOX6 group compared to the placebo + FOLFOX6 group where [redacted]% of tumours had their origin the GC compared to [redacted]% which originated in the GEJC.

Table 3.6: Baseline characteristics of European and UK combined patients in SPOTLIGHT

	Zolbetuximab + mFOLFOX6 (n = [redacted])	Placebo + mFOLFOX6 (n = [redacted])
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 (n = [redacted])	Placebo + mFOLFOX6 (n = [redacted])
Race, n (%)		
White	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Abdominal Cavity	[redacted]	[redacted]
Adrenal Gland	[redacted]	[redacted]
Bone	[redacted]	[redacted]
Chest	[redacted]	[redacted]
Colon	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Heart	[redacted]	[redacted]
Kidney	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Mediastinum	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ovary	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Rectum	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Spleen	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]

	Zolbetuximab + mFOLFOX6 (n = [redacted])	Placebo + mFOLFOX6 (n = [redacted])
Missing	[redacted]	[redacted]
ECOG PS score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2†	[redacted]	[redacted]
Missing‡	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Adapted from Table 3 of the response to the request for clarification[4]
ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.
† Baseline measurements were reported at Cycle 1 Day 1, at which time these patients had an ECOG PS score of 2; these patients had a score of 1 at screening and were thus eligible for enrolment.
‡ Baseline measurements were reported at Cycle 1 Day 1; patients reported as missing did not receive any treatment, and thus no baseline was defined, as per the statistical analysis plan. However, at screening these patients had an ECOG PS score of 0 or 1 and were thus eligible for enrolment.

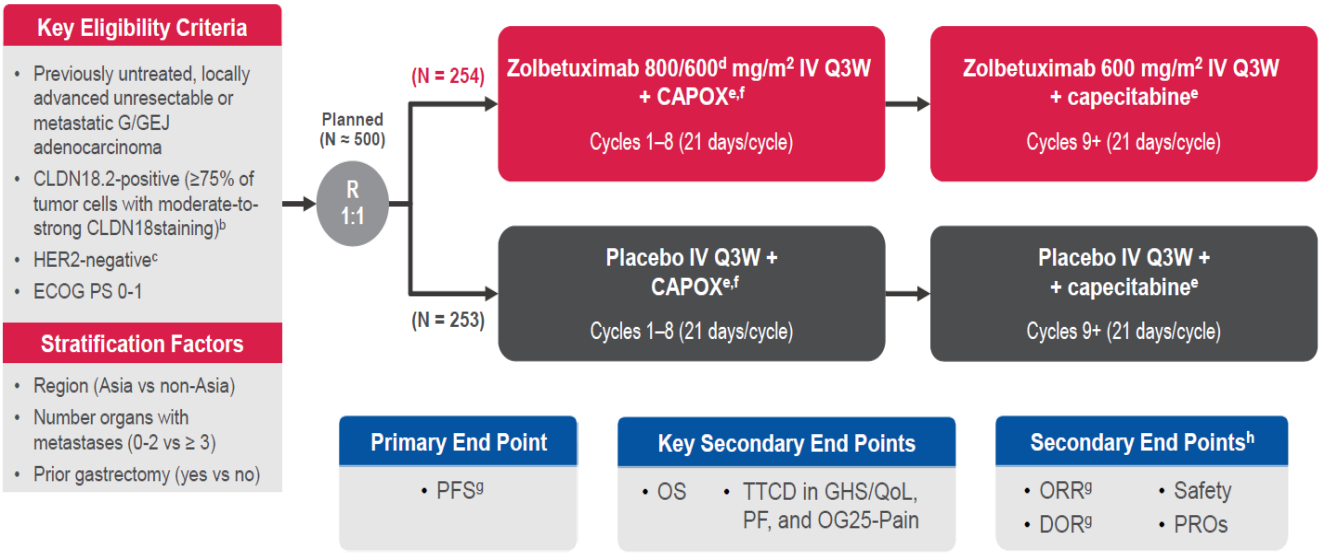
3.2.2.2 GLOW Overview

The GLOW trial is a Phase III, multicentre, double-blind RCT conducted at 176 sites in 18 countries, with four sites in the UK. It is designed to evaluate the efficacy and safety of zolbetuximab + CAPOX versus placebo + CAPOX as first-line treatment in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. The final database lock for the GLOW trial took place on 12 January 2024.[1] The results from the final datacut were submitted and are presented in subsequent sections.

The study consisted of six periods: (1) screening, (2) treatment, (3) safety follow-up, (4) post-treatment follow-up for PFS and (5) long-term follow-up for PFS2 and (6) OS. Please see Figure 3.3 for an overview of GLOW trial processes.

The primary efficacy endpoint of GLOW is PFS (per RECIST 1.1 by IRC). Key secondary endpoints include OS and TTCD, ORR, DoR and HRQoL. These are summarised in Figure 3.3 below.

Figure 3.3: GLOW trial design



Adapted from figure 4 of the CS[1]

CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18 isoform 2; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GHS, global health status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; OG25-Pain, European Organisation for Research and Treatment of Cancer Quality of Life Oesophago-Gastric; ORR, objective response rate; OS, overall survival; PF, physical functioning; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; QoL, quality of life; R, randomised; TTCD, time to confirmed deterioration.

Notes: [a]Study was conducted at 166 sites in 18 countries across Asia, Europe, North America, and South America.

[b]By central IHC using the VENTANA CLDN18.2 (43-14A) RxDx.

[c]By central or local HER2 testing (IHC 0–1, or IHC2/FISH-).

[d]800 mg/m2 on Day 1 of subsequent cycles.

[e]1,000 mg/m^2 capecitabine orally BID on Days 1–14 of each cycle.

[f]130 mg/m2 oxaliplatin IV on Day 1 of each cycle.

[g]RECIST V 1.1 per IRC assessment.

3.2.2.2.1 GLOW eligibility criteria

To determine the effects of zolbetuximab + CAPOX compared with placebo + CAPOX, 507 patients were randomised in a 1:1 ratio to either Arm A – zolbetuximab + CAPOX, or to Arm B – placebo + CAPOX. The following criteria applied for inclusion of participant in the study:[1]

- ≥ 18 years of age with CLDN18.2-positive (defined as ≥ 75% of tumour cells with moderate-to-strong membranous CLDN18 staining, determined by central IHC using the investigational VENTANA CLDN18 [43-14A] RxDx Assay)
- HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GEJC, with radiologically evaluable disease according to RECIST version 1.1
- ECOG PS score of 0 or 1
- Adequate organ function

3.2.2.2.2 GLOW baseline characteristics

The baseline characteristics for patients in both arms of GLOW are presented in Table 3.7 below. Generally, the arms are well balanced. However, like in the SPOTLIGHT trial, the EAG noted that over 60% of participants are from Asia with over 96% of participants having an ethnicity described as '*Not*

Hispanic or Latino'. The EAG requested that the company provide data detailing the patient characteristics from Europe and from the United Kingdom specifically and with relevant breakdown by ethnicity within those populations. In the response to the request for clarification[4], the company provided the additional data (see Tables 3.7 and 3.8 below).

Table 3.7: GLOW: patient demographics and baseline disease characteristics

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
Median age (range), years	61.0 (22, 82)	59.0 (21, 83)
Sex, n (%)*		
Male	159 (62.6)	156 (61.7)
Female	95 (37.4)	97 (38.3)
Region, n (%)		
Asia	157 (61.8)	158 (62.5)
Non-Asia	97 (38.2)	95 (37.5)
Ethnicity, n (%)		
Hispanic or Latino	10 (4.0)	7 (2.8)
Not Hispanic or Latino	242 (96.0)	241 (97.2)
Missing	2	5
Organs with metastases, n (%)		
0–2	189 (74.4)	188 (74.3)
≥ 3	65 (25.6)	65 (25.7)
Prior gastrectomy, n (%)		
Yes	75 (29.5)	75 (29.6)
No	179 (70.5)	178 (70.4)
Primary site, n (%)		
GC	219 (86.2)	209 (82.6)
GEJC	35 (13.8)	44 (17.4)
Lauren classification, n (%)		
Diffuse	87 (34.4)	100 (39.5)
Intestinal	36 (14.2)	41 (16.2)
Mixed	20 (7.9)	21 (8.3)
Unknown†	76 (30.0)	64 (25.3)
Other	34 (13.4)	27 (10.7)
Missing	1	0
ECOG performance status score, n (%)		
0	108 (42.7)	108 (43.2)
1	145 (57.3)	142 (56.8)
Missing‡	1	3
Measurable disease, n (%)**		
Yes	195 (76.8)	205 (81.0)
No	59 (23.2)	48 (19.0)

Adapted from table 4, CS[1]

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
CAPOX, capecitabine and oxaliplatin; CS, company submission; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; n, number of patients. Notes: *Sex was reported by study site staff through an interactive response technology system with options 'male' or 'female'. † Patients with Lauren classification 'unknown' had adenocarcinoma without Lauren classification. ‡ Baseline measurements were reported at Cycle 1, Day 1. Patients reported as 'Missing' did not receive any treatment, thus no baseline was defined per the statistical analysis plan. However, at screening, these patients had an ECOG PS score of 0 or 1 and were thus eligible for enrolment. ** Based on central assessment.		

Table 3.8 details patients' characteristics from those UK based participants.

Table 3.8: Baseline characteristics of UK patients in GLOW

	Zolbetuximab + CAPOX ([redacted])	Placebo + CAPOX ([redacted])
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Bone	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Omentum	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]

	Zolbetuximab + CAPOX ([redacted])	Placebo + CAPOX ([redacted])
ECOG PS score, n (%)		
0	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Adapted from Table 6 of the response to the request for clarification[4]
ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: * Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.

UK based participants are minimal with only [redacted] participants meaning that any characteristic differences (>5%) between the two arms of the UK participants cannot be determined to be due to the small sample or actual characteristics differences that could influence outcomes if these were represented in a larger sample. The company also provided the characteristics of UK and European participants combined, see Table 3.9.

Table 3.9: Baseline characteristics of European and UK patients in GLOW

	Zolbetuximab + CAPOX (n = [redacted])	Placebo + CAPOX (n = [redacted])
Median age (range), years	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Location of metastases, n (%)*		
Adrenal Gland	[redacted]	[redacted]
Bone	[redacted]	[redacted]
Oesophagus	[redacted]	[redacted]
Liver	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]
Mediastinum	[redacted]	[redacted]
Omentum	[redacted]	[redacted]

	Zolbetuximab + CAPOX (n = [redacted])	Placebo + CAPOX (n = [redacted])
Other	[redacted]	[redacted]
Ovary	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]
Pelvis	[redacted]	[redacted]
Pericardium	[redacted]	[redacted]
Peritoneum	[redacted]	[redacted]
Pleura	[redacted]	[redacted]
Retroperitoneum	[redacted]	[redacted]
Skin	[redacted]	[redacted]
Spleen	[redacted]	[redacted]
Stomach	[redacted]	[redacted]
Primary site, n (%)		
GC	[redacted]	[redacted]
GEJC	[redacted]	[redacted]
Lauren classification, n (%)		
Diffuse	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]
Mixed	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG PS score, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Measurable disease, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Adapted from Table 5 of the response to the request for clarification [4]
ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; IQR, interquartile range; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin.
Notes: *Locations of metastases that were identified in at least 5% of patients in either treatment group are presented.

Generally, the arms are comparable although some noteworthy differences are evident (>5%). Again, it must be noted that the total European/UK based participants combined and only constitute [redacted] participants in total from a trial that involved 507 participants representing only [redacted]% of total participants. The origin of tumours was different between arms with [redacted]% of those of the zolbetuximab and CAPOX group being located in GC and [redacted]% in the GEJC compared to [redacted]% and [redacted]% in the placebo and CAPOX group. Metastasis locations also varied, with the adrenal gland, liver and lymph nodes being more frequent (>5%) than in the zolbetuximab and CAPOX group than in the placebo and CAPOX group.

3.2.2.3 FAST Overview

The CS presents the FAST trial stating "*supportive evidence is provided by the earlier FAST trial, a Phase II trial designed to assess the efficacy and tolerability of zolbetuximab in patients with advanced G/GEJ or oesophageal adenocarcinoma with moderate-to-strong CLDN18.2 expression in ≥ 40% tumour cells*".[5]

The primary outcomes as described in Appendix M of the CS[5] are PFS and '*the safety and tolerability of zolbetuximab in combination with EOX*'. Additional outcomes include OS, survival status in 12 months, TTP defined as the time from randomisation to the first observation of confirmed disease progression, ORR, defined as the fraction of patients with a complete response (CR) or partial response (PR) according to RECIST 1.1, DCR, defined as the fraction of patients with CR, PR or standard deviation (SD), according to RECIST 1.1 and DOR, defined as the time when CR or PR were first met until the first date that recurrent disease, PD or death occurred, see Table 3.10.

Table 3.10 Summary of trial methodology in FAST

Trial number (acronym)	**FAST (NCT01630083)**
Location	A total of 46 sites across six countries (Russia, Ukraine, Germany, Bulgaria, Czech Republic, Latvia)
Trial design	Phase 2, multinational, multicentre, open label, randomised trial
Eligibility criteria for participants	**Key inclusion criteria:** • Participants were adults (e.g. ≥ 18 years in the US) according to local regulation • Participants must have had: – A histologically confirmed diagnosis of adenocarcinoma of the stomach, the oesophagus or the GEJ – Inoperable, locally advanced disease or resections with macroscopic residual disease at the resection margin, or recurrent or metastatic disease – Measurable and/or non-measurable disease as defined by according to RECIST 1.1 – A HER2-negative tumour (based on local or central evaluation) • Patients tumour expressed CLDN18.2 in ≥ 40% of cells, with a staining intensity of 2+ or 3+ (moderate to strong) confirmed by IHC testing • Adequate organ function **Key exclusion criteria:** • Prior severe allergic reaction or intolerance to a monoclonal antibody, including humanised or chimeric antibodies • Prior severe allergic reaction or intolerance to the chemotherapeutics used in this study or any excipient in the respective formulations • Previous chemotherapy for advanced disease • Previous perioperative chemotherapy with curative intention within 6 months of the start of study treatment. If the interval was longer than 6 months (counted from stop date of the perioperative chemotherapy), patients were allowed in the study • Radiotherapy within 4 weeks of start of study treatment (day 1 of cycle 1; 2-week interval was allowed if palliative radiotherapy was given to

Trial number (acronym)	FAST (NCT01630083)
	bone metastatic side peripherally and the patient recovered from acute toxicity) • Other investigational agents or devices used concurrently or within 4 weeks prior to this study (day 1 of cycle 1) • Known human immunodeficiency virus infection or known symptomatic hepatitis (A, B and/or C) • Clinical symptoms of cerebral metastases • Clinically significant (i.e., active) cardiac disease. History of myocardial infarction or hospitalisation for congestive heart failure within 12 months of enrolment • Other clinically significant disease or comorbidity which may have adversely affected the safe delivery of treatment within this study including, but not limited to any of the following: ongoing or active infection that required parenteral antibiotics, uncontrolled hypertension, present cardiac arrhythmia with serious hemodynamic consequences or unstable angina pectoris • Psychiatric illness or social situations that would preclude study compliance • Pregnancy or breastfeeding • Gastric bleeding within the last 2 weeks; symptomatic peptic ulcer • Concurrent systemic immunosuppressive therapy, in particular systemic corticoids were to be stopped 2 weeks prior to therapy (day 1 of cycle 1). Inhaled and topically-applied steroids were the exception and were allowed. Systemic steroids were to be avoided as long as the patient was being treated with study medication. An exception was in the case of uncontrollable nausea and/or vomiting. • Previous treatments with maximum cumulative doses of epirubicin > 500 mg/m2 and/or other anthracyclines and androstenediones • Treatment with sorivudine or analogs • Known peripheral neuropathy greater than grade 1 (absence of deep tendon reflexes as the sole neurological abnormality did not render the patient ineligible)
Settings and locations where data were collected	Patients received study intervention directly from the investigator or designee, under medical supervision.
Trial drugs	• Arm 1: EOX chemotherapy alone (50 mg/m2 epirubicin intravenously on day 1 of each cycle, 130 mg/m2 oxaliplatin intravenously on day 1 of each cycle, 625 mg/m2 capecitabine orally twice daily on days 1 to 21 of each cycle). The first dose of capecitabine was to be taken in the evening of day 1 • Arm 2: EOX chemotherapy as described for Arm 1 in combination with zolbetuximab administered as loading dose of 800 mg/m2 intravenously on day 1 of cycle 1 followed by 600 mg/m2 intravenously on day 1 of each subsequent cycle. Zolbetuximab was administered prior to EOX chemotherapy • Arm 3: EOX chemotherapy as described for Arm 1 in combination with zolbetuximab 1000 mg/m2 intravenously on day 1 of each cycle. Zolbetuximab was administered prior to EOX chemotherapy

Trial number (acronym)	FAST (NCT01630083)
	In the follow-up phase, patients in Arms 2 and 3 were permitted to continue zolbetuximab monotherapy with 600 mg/m2 (Arm 2) or 1000 mg/m2 (Arm 3) administered intravenously as a 2-hour infusion once every 3 weeks until PD, withdrawal of consent or unacceptable toxicity
Concomitant medication	The following medications were prohibited: • Sorivudine or analogs • Other non-licensed, investigational drugs or anticancer treatment until the end of study treatment, with the exception of anticancer treatment for a malignancy other than advanced adenocarcinoma of the stomach, oesophagus or gastro-oesophageal junction. Anticancer treatment for a second malignancy may have been allowed during the study treatment period after consultation between the investigator and the sponsor's medical monitor • Use of cimetidine in patients who were receiving epirubicin
Primary outcome	The primary objectives of the study were: • To evaluate the efficacy of zolbetuximab in combination with EOX as determined by PFS • To determine the safety and tolerability of zolbetuximab in combination with EOX
Other outcomes used in the economic model/specified in the scope	• OS, defined as the time from randomisation to death from any cause or last contact, if alive • Survival status in 12 months • TTP, defined as the time from randomisation to the first observation of confirmed disease progression • ORR, defined as the fraction of patients with a CR or PR according to RECIST 1.1 • DCR, defined as the fraction of patients with CR, PR or SD, according to RECIST 1.1 • DOR, defined as the time when CR or PR were first met until the first date that recurrent disease, PD or death occurred
Pre-planned subgroups	If the evidence allows, the following subgroups will be considered: • Subgroups by tumour location

Based on Table 97, CS appendix M[5]
CLDN18.2, claudin 18 isoform 2; CR, complete response; CS = company submission; DCR, disease control rate; DOR, duration of response; EOX, epirubicin, oxaliplatin and capecitabine; G/GEJ, gastric/gastro-oesophageal junction cancer; GEJ, gastro-oesophageal cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; TTP, time to progression

3.2.2.3.1 FAST eligibility criteria

Participants were initially randomly assigned 1:1 to receive either EOX alone or zolbetuximab (600 mg/m^2) in combination with EOX. An additional third arm was added 15 months after the start of enrolment to evaluate a higher dose of zolbetuximab (1,000 mg/m^2) in combination with EOX resulting in an adjusted allocation of 1:1:7 to allow the third arm consisting of zolbetuximab (1,000 mg/m^2) in combination with EOX to enrol a similar number of patients.

The following criteria applied to all participants:

- ≥ 18 years of age with confirmed CLDN18.2-positive (defined as ≥ 40% of tumour cells with a staining intensity of 2+ or 3+ as determined by the CLAUDETECT™18.2 immunohistochemistry assay)
- HER2-negative inoperable, locally advanced, recurrent or metastatic G/GEJC
- radiologically evaluable disease (measurable or non-measurable) according to Response Evaluation Criteria in Solid Tumours Version 1.1
- ECOG PS score of 0 or 1
- adequate organ function.

3.2.2.3.2 FAST baseline characteristics

Table 3.11: Baseline characteristics are presented for the FAST trial in the CS addendum

	Zolbetuximab + EOX (n = 77)	**EOX (n = 84)**
Age (years), median	59.0	57.0
Male gender, %	61.0	67.0
Race, %		
White	NR	NR
Asian	NR	NR
ECOG, %		
0	30.0	30.0
1	70.0	70.0
2	0.0	0.0
Tumour location, %		
Oesophagus	3.0	5.0
GEJ	17.0	14.0
GC	81.0	81.0
HER2 status, %		
Positive	0.0	0.0
Negative	0.0	0.0
Unknown	100.0	100.0
CPS score, %		
unknown	NR	NR
≥ 1	NR	NR
≥ 5	NR	NR

Adapted from Table 14 of the CS addendum[8]
CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CPS, combined positive score; CX, capecitabine + cisplatin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; SmPC, summary of product characteristics

Characteristics between the two arms in the FAST trial are generally similar although it is noted that there are less reported data than is seen in the SPOTLIGHT and GLOW trials.

3.2.2.4 External validity

The EAG queried the representativeness of these data to the relevant clinical population in the UK (England and Wales) and asked the company to provide justification to this end. In their response to the request for clarification the company stated that *'There is limited recent evidence on the characteristics of patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma who receive first line treatment in the NHS. Patients included in SPOTLIGHT and GLOW have similar characteristics to those included in CheckMate 649, which was deemed generalisable to NHS clinical practice. Furthermore, patients included in SPOTLIGHT and GLOW have similar characteristics to those included KEYNOTE-859, which was used in ID4030[9]. To address the concerns raised in NICE TA857 that patients in the CheckMate 649 trial were younger than those in NHS clinical practice[10] scenario 12 of the company submission increased the age at treatment start from 58.5 years to 64.15 years; this had a negligible impact on cost-effectiveness results (ICER increased by 0.8%)[4].*

Four points are made in their response. 1) that there are limited data to confirm representativeness of those treated first line in the NHS; 2) that patient characteristics exhibit similarity between SPOTLIGHT/GLOW and CHECKMATE 649 which was itself deemed generalisable to NHS practice; 3) SPOTLIGHT/GLOW patients have similar characteristics to those in KEYNOTE-859; and 4) that any age range discordancy between CHECKMATE 649 and NHS practice was addressed in appropriate analysis and no meaningful impact was observed on the cost effectiveness data.

The EAG emphasises that where assumptions are to be made indirectly, appropriate considerations need to be made in any analysis or interpretation of results. We note the above points raised and the relevant responses but also emphasise the minimal involvement of UK (England and Wales) based participants in these contributory trials. While the recent evidence on patients in the NHS may be limited as per the company response (see above) it is still noteworthy that the trials in general have minimal participants drawn from the UK, Particularly England or Wales. It is with this in mind that we are cautious about data generalisability to the relevant population in England and Wales.

EAG comment: The EAG highlights the minimal involvement of patients from the UK and Europe and is uncertain that these data may be generalisable to the relevant clinical population of England and Wales.

3.2.3 Statistical analysis for the SPOTLIGHT trial

The CS details three defined analysis populations for the SPOTLIGHT trial:[1]

- Full analysis set consists of all patients who were randomised to one of the treatment arms. Patients were analysed according to the treatment arm to which they were randomised. The full analysis set was used for describing baseline characteristics and all efficacy analyses.
- Safety analysis set consists of all patients who received at least one dose of any study drug (zolbetuximab or placebo/mFOLFOX6). Patients were analysed according to the treatment arm they received. The safety analysis set was used for the summary of demographic and baseline characteristics and all safety and tolerability-related variables.
- Pharmacokinetic analysis set consists of a subset of the safety analysis set where at least one zolbetuximab concentration measurement was available. The pharmacokinetic analysis set was used for the description of pharmacokinetic data.

The company provided an overview of the plan for hypothesis testing in Section B 2.4.1.2 of the CS. The company made the following statement:[1]

- *"The hypothesis testing on the primary analysis was performed at an overall one-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in the zolbetuximab +*

mFOLFOX6 arm compared with the placebo + mFOLFOX6 arm (versus the alternative hypothesis that PFS is prolonged in the zolbetuximab + mFOLFOX6 arm compared with the placebo + mFOLFOX6 arm).”

Furthermore, the company made the following statements:[11]

- *“The primary endpoint is PFS assessed by the blinded IRC. For each subject, PFS is defined as the time from the date of randomization until the date of radiological disease progression (i.e., PFS) assessed by IRC, or until death due to any cause, whichever is earlier. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive new anticancer therapy before radiological progression will be censored at the date of the last radiological assessment before the new anticancer therapy started. If progression or death occurs after missing 2 or more scheduled radiological assessments, the subject will be censored at the date of last radiological assessment or at the date of randomization if no post-baseline radiological assessment is available. The primary analysis will be performed when approximately 300 PFS events have been observed. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI. The primary analysis will be performed using the FAS.*
- *A key secondary endpoint OS is defined as the time from the date of randomization until the documented date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject is still taking study drug or after the subject discontinue study drug. Subjects who are still alive at the time of analysis will be censored at the last day known to be alive. The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by the same stratification factors used for PFS analysis. To maintain the overall Type I error rate at the 0.025 significance level, the hypothesis testing on OS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 1-sided 0.025 significance level. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI.”*

The company states that one final analysis was planned for PFS while an interim analysis and final analysis were planned for OS.[1] The company further states that the OS interim and final analyses were performed only if the primary PFS analysis was significant. The OS interim analysis occurred at the same time as final PFS analysis after the pre-specified number of PFS events (300 events). The final OS analysis was performed on 08 September 2023 after the pre-specified number of OS events were observed.

3.2.4 Statistical analysis for the GLOW trial

The CS details three defined analysis populations for the GLOW trial:[1]

- Final analysis set consists of all patients who were randomised to one of the two treatment arms. Patients were analysed according to the treatment arm to which they were randomised. The final analysis set was used for the summary of demographic and baseline characteristics and all efficacy analyses.
- Safety analysis set consists of all patients who received at least one dose of any study drug (zolbetuximab or placebo/CAPOX). Patients were analysed based on the treatment they received. The safety analysis set was used for the summary of demographic and baseline characteristics and all safety and tolerability-related variables.
- Pharmacokinetic analysis set consists of a subset of the safety analysis set where at least one zolbetuximab concentration measurement was available. The pharmacokinetic analysis set was used for the description of pharmacokinetic data.

The company provided an overview of the plan for hypothesis testing in Section B 2.4.1.2 of the CS. The company made the following statement:[1]

- *"The hypothesis testing on the primary analysis was performed at an overall one-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in the zolbetuximab + CAPOX arm compared with the placebo + CAPOX arm (versus the alternative hypothesis that PFS is prolonged in the zolbetuximab + CAPOX arm compared with the placebo + CAPOX arm)."*

Furthermore, the company made the following statements:[12]

- *"The primary endpoint is PFS assessed by the blinded IRC. For each subject, PFS is defined as the time from the date of randomization until the date of radiological disease progression (i.e., PFS) assessed by IRC, or until death due to any cause, whichever is earlier. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive new anticancer therapy before radiological progression will be censored at the date of the last radiological assessment before the new anticancer therapy started. If progression or death occurs after missing 2 or more scheduled radiological assessments, the subject will be censored at the date of last radiological assessment or at the date of randomization if no post-baseline radiological assessment is available. The primary analysis will be performed when approximately 300 PFS events have been observed. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI. The primary analysis will be performed using the FAS.*
- *A key secondary endpoint OS is defined as the time from the date of randomization until the documented date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject is still taking study drug or after the subject discontinue study drug. Subjects who are still alive at the time of analysis will be censored at the last day known to be alive. The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by the same stratification factors used for PFS analysis. To maintain the overall Type I error rate at the 0.025 significance level, the hypothesis testing on OS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 1-sided 0.025 significance level. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI."*

The company states that one final analysis was planned for PFS while an interim analysis and final analysis were planned for OS. The OS interim analysis was performed at the same time as the final PFS analysis after the pre-specified number of PFS events (300 events). The final OS analysis was performed after the pre-specified number of OS events were observed if the interim OS was not statistically significant. The OS interim and final analyses were performed only if the primary PFS analysis was significant.[1]

Table 3.10 presents a summary of statistical analyses for SPOTLIGHT and GLOW.

EAG comment: The statistical methods appear to be satisfactory.

Table 3.10: Summary of statistical analyses for SPOTLIGHT and GLOW

	SPOTLIGHT	GLOW
Hypothesis objective	The hypothesis testing on the primary analysis will be performed at an overall 1-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in Arm A compared to Arm B versus the alternative hypothesis that PFS is prolonged in Arm A compared to Arm B.	The hypothesis testing on the primary analysis was performed at an overall 1-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in the zolbetuximab + CAPOX arm compared to the placebo + CAPOX arm versus the alternative hypothesis that PFS is prolonged in the zolbetuximab + CAPOX arm compared to the placebo + CAPOX arm
Statistical analysis	The IDMC could have recommended terminating the trial for favourable or unfavourable results using the final PFS and the interim OS analysis. If the PFS was not significant at 0.025 1-sided alpha, the study would have been terminated for failure. In the case of favourable results, the 1-sided significance level for superiority was 0.0082, assuming approximately 72% of the target number of OS events were obtained, for the interim OS analysis and 0.0225 for the final OS analysis. If the 1-sided p value of the interim OS analysis was less than the significance level (and PFS was also significant at 1-sided 0.025 alpha), the IDMC could recommend terminating the study for success. If the study was not stopped after the interim OS analysis, a final OS analysis would occur after 100% of the planned death events have been observed. At the time of interim OS analysis, 82.32% of the target OS event has been obtained, which corresponds to 1-sided significance level of 0.0135.	The OS interim analysis occurred at the same time as final PFS analysis (after the prespecified number of PFS events, i.e., 300) and final OS analysis was to be performed after the prespecified number of OS events are observed if interim OS is not statistically significant. The O'Brien-Fleming boundaries as implemented by alpha spending method were used for the OS interim analyses and for the final OS analyses. The OS interim and final analyses were to be performed only if primary PFS analysis was significant. All statistical tests of treatment effects were conducted at the 1-sided 0.025 level of significance unless otherwise specified. At the time of interim OS analysis, 1-sided 0.0135 level of significance was used with 82.38% information fraction
Sample size, power calculation	The planned 300 PFS events during the study will provide 93.4% power to detect a difference in PFS between Arm A (zolbetuximab + mFOLFOX6) with the assumption of 9 months median PFS time and Arm B (placebo + mFOLFOX6) with the assumption of 6 months median PFS time (HR = 0.67) at the overall 1-sided 0.025 significance level. Similarly, the planned 396 OS events during the study will provide 81% power to detect a difference in OS between	The planned 300 PFS events during the study provide 93.4% power to detect a difference in PFS between Arm A (zolbetuximab + CAPOX) with the assumption of 9 months median PFS time and Arm B (placebo + CAPOX) with the assumption of 6 months median PFS time (HR = 0.67) at the overall 1-sided 0.025 significance level. Similarly, the planned 386 OS events during the study provide 80% power to detect a difference in OS between Arm A (zolbetuximab +

	SPOTLIGHT	GLOW
	Arm A (zolbetuximab+mFOLFOX6) with the assumption of 14.7 months median survival time and Arm B (placebo + mFOLFOX6) with the assumption of 11 months median survival time (HR = 0.75) at the overall 1-sided 0.025 significance level.	CAPOX) with the assumption of 14.7 months median OS time and Arm B (placebo + CAPOX) with the assumption of 11 months median OS time (HR = 0.75) at the overall 1-sided 0.025 significance level.
Data management, patient withdrawals	All CRF data were entered by the study site in an electronic database provided by Astellas. To ensure the collection of accurate, consistent data, periodic site monitoring visits were conducted by designated representatives. Data were reviewed for accuracy and computer logic checks were performed to identify potential errors, which were subsequently reviewed with the study site and corrected accordingly in the database. Some of the clinical data were collected outside the Astellas electronic database. In these cases, the vendor provided data in an agreed upon format to Astellas. To ensure the collection of accurate and consistent data, these data were reconciled on key parameters and outlier checks were performed regularly upon receipt of new transfers. All PRO data were recorded in an electronic device. To ensure the collection of accurate and consistent data, checks were performed within the device during entry requiring review and confirmation of data by the participant. Periodic review was performed by the study site to ensure compliance. An audit trail to support data query resolution and any modification to the data was maintained.	All CRF data were entered by the study site in an electronic database provided by Astellas. In order to ensure the collection of accurate, consistent data, periodic monitoring site visits were conducted by designated representatives. Data were reviewed for accuracy, and computer logic checks were performed to identify potential errors, which were subsequently reviewed with the study site and corrected accordingly in the database. Some of the clinical data were collected outside the clinical data management system. In these cases, the vendor provided data in an agreed upon format to the sponsor. In order to ensure the collection of accurate and consistent data, these data were reconciled on key parameters and outlier checks were performed regularly upon receipt of new transfers. All PRO data were recorded in an electronic device. In order to ensure the collection of accurate and consistent data, these data were reconciled on key parameters upon receipt of new transfers. Periodic review was performed by the study site to ensure compliance. An audit trail to support data query resolution and any modification to the data was maintained.

Based on Table 88 of CS appendix[5]
CAPOX, capecitabine and oxaliplatin; CRF, case report form; CS, company submission; HR, hazard ratio; IDMC, Independent Data Monitoring Committee; mFOLFOX6, modified folinic acid, 5-fluorouracil and oxaliplatin; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcomes

3.2.5 Risk of bias assessments

The Company performed critical appraisals for the GLOW, SPOTLIGHT and FAST studies which were included in the Appendix D of the CS.[5] According to the CS, all studies were appraised "*in accordance with the ethical principles of Good Clinical Practice (GCP) and considered to be a high-quality study"*. Each study is assessed against a seven criteria checklist. The EAG also considered the studies against the same checklist and a summary of results for each trial can be seen in tables below. Where the EAG assessment was different, a comment is included in the relevant column. Where no comment is required 'N/A' is inserted.

3.2.5.1 SPOTLIGHT appraisal

Table 3.11: Critical appraisal of SPOTLIGHT

Author	Assessment	Decision	Justification	EAG
Shitara et al. 2023[13]	Was randomisation carried out appropriately?	Yes	Masked staff site via interactive response technology by block randomisation (block sizes of two)	N/A
	Was the concealment of treatment allocation adequate?	Unclear	No information	N/A
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There was no significant difference in the baseline characteristics reported between the two treatment arms	Generally comparable, but noticeable (>5%) differences in metastasis location, Lauren classification
	Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Double-blind (participant and investigator)	N/A
	Were there any unexpected imbalances in dropouts between groups?	Yes	Reported in Figure 1 of the trial profile	N/A
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The author has measured the same number of outcomes as reported	N/A
	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy included all patients, and safety included mITT population	N/A

Adapted from Table 28, Appendix D, CS[5]
CS = company submission; EAG = Evidence Assessment Group; ITT, intention-to-treat; mITT, modified intention-to-treat; N/A = not applicable

As can be seen, the study does not adequately describe the concealment of treatment allocation, and we consider that some baseline differences do exist between the populations, although we do not claim that

these differences may yield any meaningful clinical difference or reflect any physiological differences of impact between the groups. We note that when assessing risk of bias, where a particular criterion is inadequately/unclearly reported, the EAG typically takes a conservative view that we cannot then presume that it was conducted to the appropriate standard and so caution should be exercised. In this case treatment allocation concealment was not described to a level where one could be confident in the robustness of the process. For that reason, we would disagree with the company assessment and consider this to be at a moderate risk of bias, although we do acknowledge that this is a conservative assessment.

3.2.5.2 GLOW appraisal

Table 3.12: Critical appraisal of GLOW

Author	Assessment	Decision	Justification	EAG
Shah et al. 2023[14]	Was randomisation carried out appropriately?	Yes	Randomisation was performed by blinded site staff using interactive response technology by block randomisation with block sizes of two and was stratified according to: region (Asia versus non-Asia), number of organs with metastases (0–2 versus ≥ 3) and prior gastrectomy (yes versus no)	N/A
	Was the concealment of treatment allocation adequate?	Unclear		N/A
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There was no significant difference in the baseline characteristics reported between the two treatment arms	N/A
	Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Double-blind (participant and investigator)	N/A
	Were there any unexpected imbalances in dropouts between groups?	No	No imbalance with respect to drop-outs between groups	N/A
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The author has measured the same number of outcomes as reported	N/A
	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The efficacy included all patients, and safety included mITT population	N/A

Adapted from Table 29, Appendix D, CS[5]
CS = company submission; ITT = intention-to-treat; mITT = modified intention-to-treat; N/A = not applicable

Again, in the GLOW trial there is no masking of treatment allocation and so the risk of selection bias is present. This of course does not necessarily mean that there is indeed such a bias, or even that the robustness of the methodology is necessarily compromised, but where there is no treatment allocation

concealment, there is sufficient reason to consider that this poses a risk of bias and therefore this should be made clear. For this reason, the EAG considers this study possesses a moderate risk of bias.

3.2.5.3 FAST appraisal

Table 3.13: Critical appraisal of FAST

Author	Assessment	Decision	Justification	EAG
Sahin et al. 2021[15]	Was randomisation carried out appropriately?	No	Unclear information	N/A
	Was the concealment of treatment allocation adequate?	No	Unclear information	N/A
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	There was no significant difference in the baseline characteristics reported between the two treatment arms	N/A
	Were the care providers, participants and outcome assessors blind to treatment allocation?	No	Open label	N/A
	Were there any unexpected imbalances in dropouts between groups?	Unclear	Details regarding study withdrawals were not reported	N/A
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Author has measured same number of outcomes as reported in the protocol (NCT01630083)	N/A
	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All patients were included in the analysis	N/A

Adapted from Table 30, Appendix D, CS[5]
CS = company submission; EAG = Evidence Assessment Group; ITT = intention-to-treat; N/A = not applicable

As can be seen in Table 3.13 above, the FAST trial has some key criteria where information is limited. For this reason, the EAG does not agree that this trial is considered to be of low risk of bias. We in fact consider that any trial that does not meet a particular standard, or does indeed meet it, but does not adequately report it, has to have a conservatively rated high risk of bias. One has to exercise caution and to do so is appropriate when considering the application and interpretation of such research.

EAG comment: We consider that the trials appraised as 'low' risk by the company do not detail sufficient information to be reliably appraised as such and we are of the mind that the SPOTLIGHT and GLOW trials should be considered to be of a moderate risk of bias. We emphasise that conservative appraisals are appropriate and that where information is not reported we must assume that it is not reported because it did not happen.

3.2.6 Efficacy results of the SPOTLIGHT trial

Results were presented from the SPOTLIGHT trial with a data cut of 29 June 2023, which was not a pre-specified data cut. The CS stats that the final database lock for the SPOTLIGHT trial took place on

08 September 2023 and data analysis is ongoing.[1] The results from the final data-cut for this trial were submitted with the responses to clarification questions.

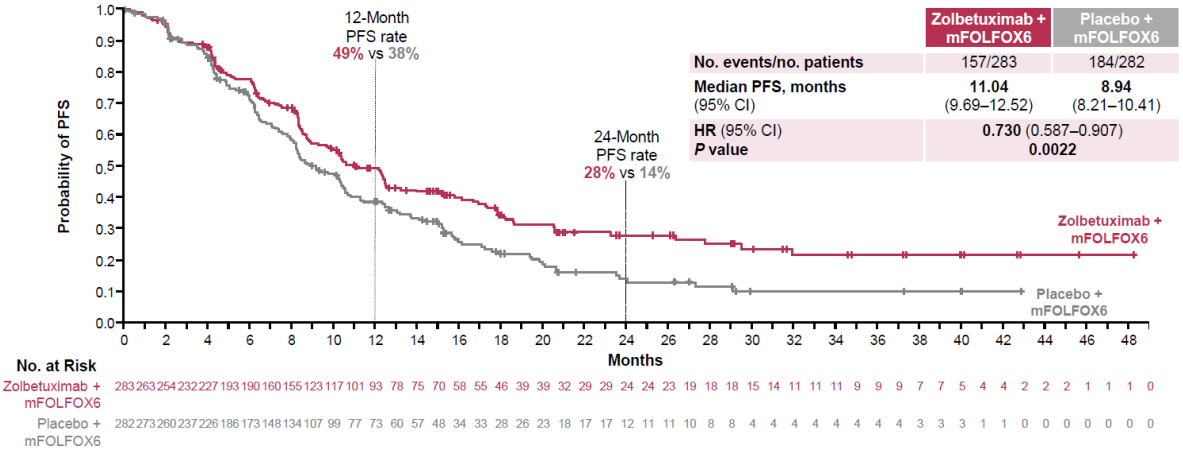
3.2.6.1 Progression free survival

As of the data cut-off date (29 June 2023), median duration of follow-up for PFS was 17.87 months (95% confidence interval [CI]: [redacted]) in the zolbetuximab plus mFOLFOX6 group and 15.18 months (95% CI: [redacted]) in the placebo plus mFOLFOX6 group.[1]

Zolbetuximab plus mFOLFOX6 was associated with a statistically significant improvement in PFS when compared with placebo plus mFOLFOX6 based on IRC assessment per RECIST 1.1: hazard ratio (HR) 0.73 (95% CI: 0.587, 0.907; p = 0.0022). The median PFS was 11.04 months (95% CI: 9.69, 12.52) and 8.94 months (95% CI: 8.21, 10.41) for the zolbetuximab plus mFOLFOX6 group and the placebo plus mFOLFOX6 group, respectively.[1]

The corresponding K-M survival plots of PFS are presented in Figure 3.4.

Figure 3.4: SPOTLIGHT: KM plot of PFS (per RECIST 1.1) assessed by IRC (FAS)



Based on Figure 5 of CS[1]

CI, confidence interval; CS, company submission; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; K-M, Kaplan-Meier; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1

Notes: Data cut-off: 29 June 2023

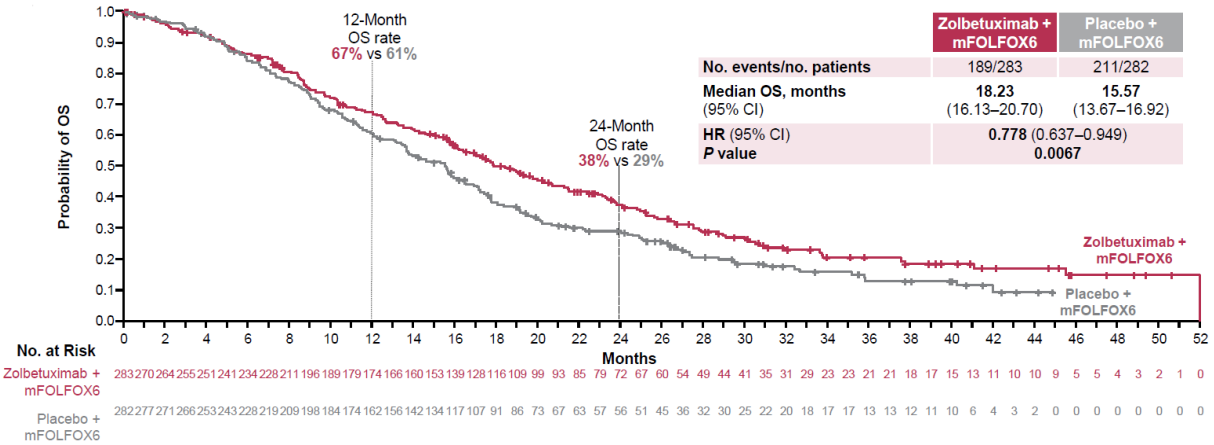
3.2.6.2 Overall survival

As of the data cut-off date of 29 June 2023, the median duration of follow-up for OS was 31.11 months (95% CI: [redacted]) in the zolbetuximab plus mFOLFOX6 group and 29.57 months (95% CI: [redacted]) in the placebo plus mFOLFOX6 group.

Zolbetuximab plus mFOLFOX6 was associated with a statistically significant improvement in OS when compared with the placebo plus mFOLFOX6 group: HR 0.778 (95% CI: 0.637, 0.949; p = 0.0067). The median OS was 18.23 months (95% CI: 16.13, 20.70) in the zolbetuximab plus mFOLFOX6 group while the median OS was 15.57 months (95% CI: 13.67, 16.92) in the placebo plus mFOLFOX6 group.

The corresponding K-M survival plots are presented in Figure 3.5.

Figure 3.5: SPOTLIGHT: K–M plot of OS (FAS)



Based on Figure 6 of CS[1]
CI, confidence interval; CS, company submission; FAS, full analysis set; HR, hazard ratio; K-M, Kaplan-Meier; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; OS, overall survival
Notes: Data cut-off: 29 June 2023.

3.2.6.3 Objective response rate

The ORR per IRC for the zolbetuximab plus mFOLFOX6 arm, was 48.1% (95% CI: 42.11, 54.05) and the disease control rate (DCR) was [redacted] (95% CI: [redacted]), compared with 47.5% (95% CI: 41.56, 53.52) and [redacted] (95% CI: [redacted]) in the placebo plus mFOLFOX6 arm.[1]

[redacted] patients had a CR and [redacted] patients had a PR in the zolbetuximab plus mFOLFOX6 group. [redacted] patients had a CR, and [redacted] patients had a PR in the placebo plus mFOLFOX6 group.

Table 3.14 provides an overview of the data on ORR.

Table 3.14: SPOTLIGHT: summary of ORR assessed by IRC – unconfirmed responses (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Best overall response, n (%)[†]	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	44 (15.5)	51 (18.1)
Non-CR/non-progressive disease	52 (18.4)	60 (21.3)
Progressive disease	15 (5.3)	17 (6.0)
Not evaluable	4 (1.4)	3 (1.1)
No disease	5 (1.8)	1 (0.4)
Not available[‡]	27	16
ORR, n (%)	136 (48.1)	134 (47.5)
95% CI for ORR (%)[§]	(42.11, 54.05)	(41.56, 53.52)
Stratified one-sided p-value[¶]	[redacted]	

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR (%)§	[redacted]	[redacted]
Stratified one-sided p-value¶	[redacted]	

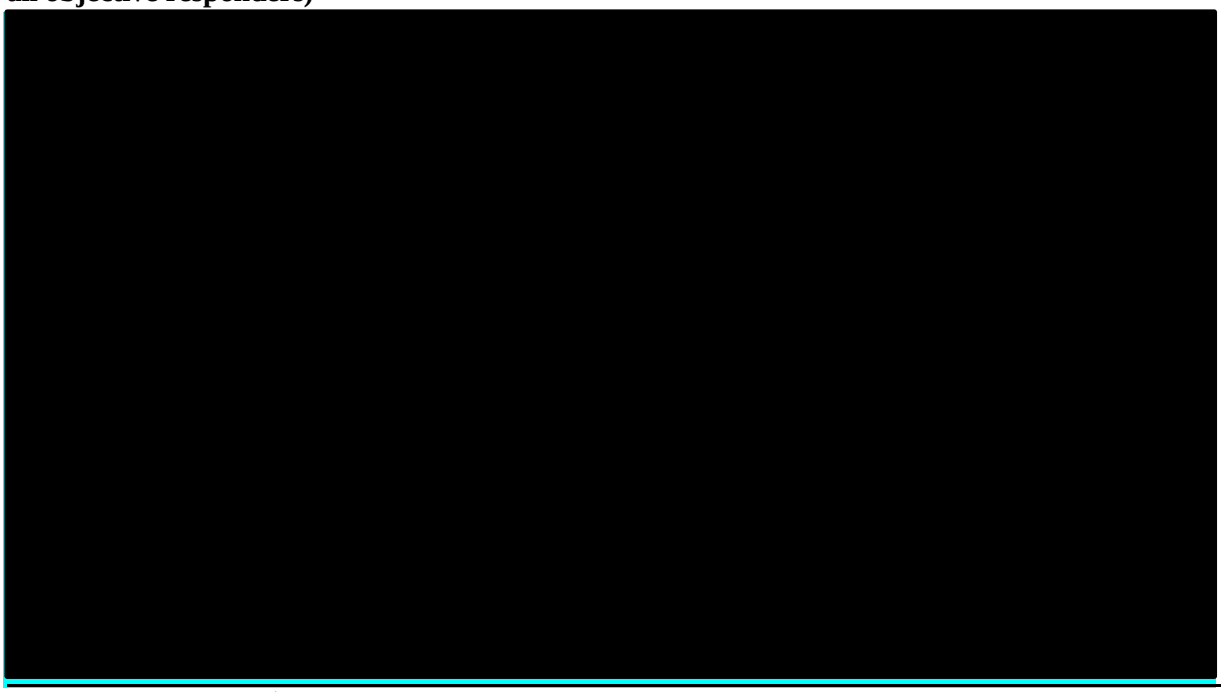
Based on Table 6 of CS[5]
CI, confidence interval; CR, complete response; CS = company submission; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1
Notes: Data cut-off: 29 June 2023.
† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm.
‡ No post-baseline imaging assessment.
§ Using exact method based on binomial distribution (Clopper–Pearson)
¶ Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy
†† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease

3.2.6.4 Duration of response

As of data cut date of 29 June 2023, the median DoR as assessed by the IRC was 9.00 months (95% CI: 7.49, 10.38) in the zolbetuximab plus mFOLFOX6 group and 8.11 months (95% CI: 6.47, 11.37) in the placebo plus mFOLFOX6 group [redacted]

The corresponding K-M survival plots are presented in Figure 3.6.

Figure 3.6: SPOTLIGHT: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)



Based on Figure 7 of CS[1]
CI, confidence interval; CS = company submission; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients

Notes: Data cut-off: 29 June 2023.

EAG comment: Given that the survival data and other efficacy outcomes from the CS are not relatively mature, in the clarification letter, the EAG requested more mature data from the SPOTLIGHT trial for all outcomes reported. In responding to EAG's request, the company provided more mature data (see Section 3.2.7) from the SPOTLIGHT trial at the clarification stage.

3.2.6.5 Health-related quality of life

Changes in HRQoL was assessed by using the European Quality of Life-5 Dimensions 5-Levels (EQ-5D-5L) visual analogue scale (VAS). The data cut-off date of 9 September 2023 (primary analysis data cut) was selected as the time point for analysing changes from baseline for the EQ-5D-5L.[1]

The EQ-5D-5L measures self-rated health state using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at five levels (no problems, slight problems, moderate problems, severe problems and extreme problem).

Baseline EQ-5D-5L VAS scores were comparable between treatment arms. There were no significant differences being observed for either treatment arm for the EQ-5D-5L VAS scores during the treatment and follow-up periods.[1]

However, the company states that no formal statistical testing was performed on these measures for the EQ-5D-5L questionnaire.[1]

Figure 3.7 presents longitudinal analysis of change from baseline in EQ-5D-5L questionnaire utility index score for the SPOTLIGHT trial. The mean change from baseline in EQ-5D-5L questionnaire is presented in Figure 3.8.

Figure 3.7: SPOTLIGHT: longitudinal analysis of change from baseline in EQ-5D-5L questionnaire utility index score – MMRM analysis

Based on Figure 41 of CS Appendix[5]
CI, confidence interval; CS, company submission; EQ-5D-5L, European Quality of Life-5 Dimensions 5-Levels; LS, least squares; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; MMRM, mixed model repeated measures.
Notes: Data cut-off: 9 September 2022.

Figure 3.8: SPOTLIGHT: mean change from baseline in EQ-5D-5L questionnaire VAS (FAS)

Based on Figure 42 of CS Appendix[5]
CI, confidence interval; CS, company submission; EQ-5D-5L, European Quality of Life-5 Dimensions 5-Levels; LS, least squares; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; MMRM, mixed model repeated measures; VAS, visual analogue scale
Notes: Data cut-off: 9 September 2022.

EAG comment:

- There was a lack of long-term follow-up data relating to HRQoL outcomes. Given that HRQoL outcomes from the CS are not relatively mature, in the clarification letter, the EAG requested more mature data from the SPOTLIGHT trial for all outcomes reported. In responding to the EAG's request, the company stated that at the time of the company response addendum, longitudinal analysis of the pre-specified patient-reported outcomes had not yet been completed and additional longitudinal analysis of HRQoL data were therefore not provided.[8]
- In responding to the EAG's request, the company provided other relevant longer-term HRQoL data (see Section 3.2.7.5) during the clarification response stage.

3.2.7 Updated efficacy results of the SPOTLIGHT trial

3.2.7.1 Progression-free survival

Based on the final data cut date (8 September 2023) of the SPOLTLIGHT trial, the updated results showed that zolbetuximab plus mFOLFOX6 was associated with a statistically significant improvement in PFS assessed by IRC compared to placebo plus mFOLFOX6 (HR 0.734, 95% CI: 0.591, 0.910).[8]

The updated results of PFS assessed by IRC for the SPOTLIGHT trial are presented in Table 3.15 and the K–M plot is presented in Figure 3.9.

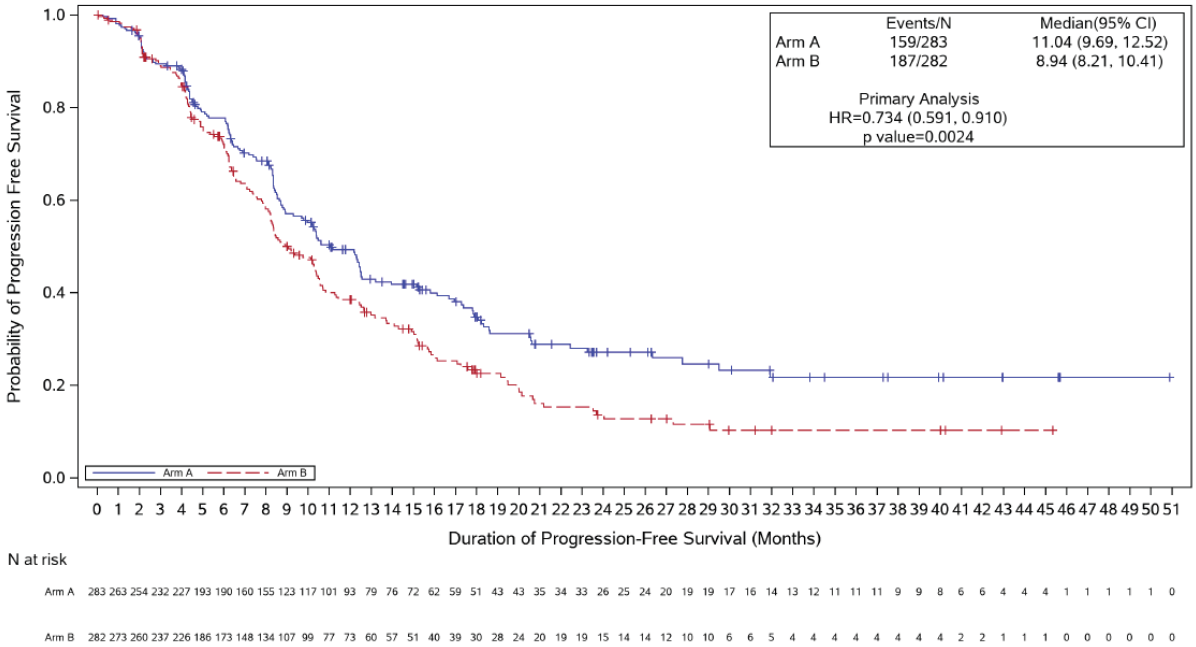
Table 3.15: SPOTLIGHT: PFS assessed by IRC (FAS)

	Zolbetuximab + mFOLFOX6 (n=283)	Placebo + mFOLFOX6 (n=282)
Median Follow-Up Time, Months (95% CI)	18.04 (15.28, 23.33)	17.91 (14.78, 23.75)
PFS Events, n (%)	159 (56.2)	187 (66.3)
Median PFS (95% CI), Months	11.04 (9.69, 12.52)	8.94 (8.21, 10.41)

	Zolbetuximab + mFOLFOX6 (n=283)	Placebo + mFOLFOX6 (n=282)
Stratified Analysis*		
HR (95% CI)	0.734 (0.591, 0.910)	
1-sided P-value**	0.0024	
PFS Rate, % (95% CI)		
At 6 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]

Based on Table 2 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival
Notes: Data cut-off: 8 September 2023.
*Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test

Figure 3.9: SPOTLIGHT: K–M plot of PFS assessed by IRC (FAS)



Based on Figure 1 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.

3.2.7.2 Overall survival

Based on the final data cut date (8 September 2023) of the SPOTLIGHT trial, the updated results showed that zolbetuximab plus mFOLFOX6 was associated with a statistically significant improvement in OS compared to placebo plus mFOLFOX6 (HR 0.784, 95% CI: 0.644, 0.954).[8]

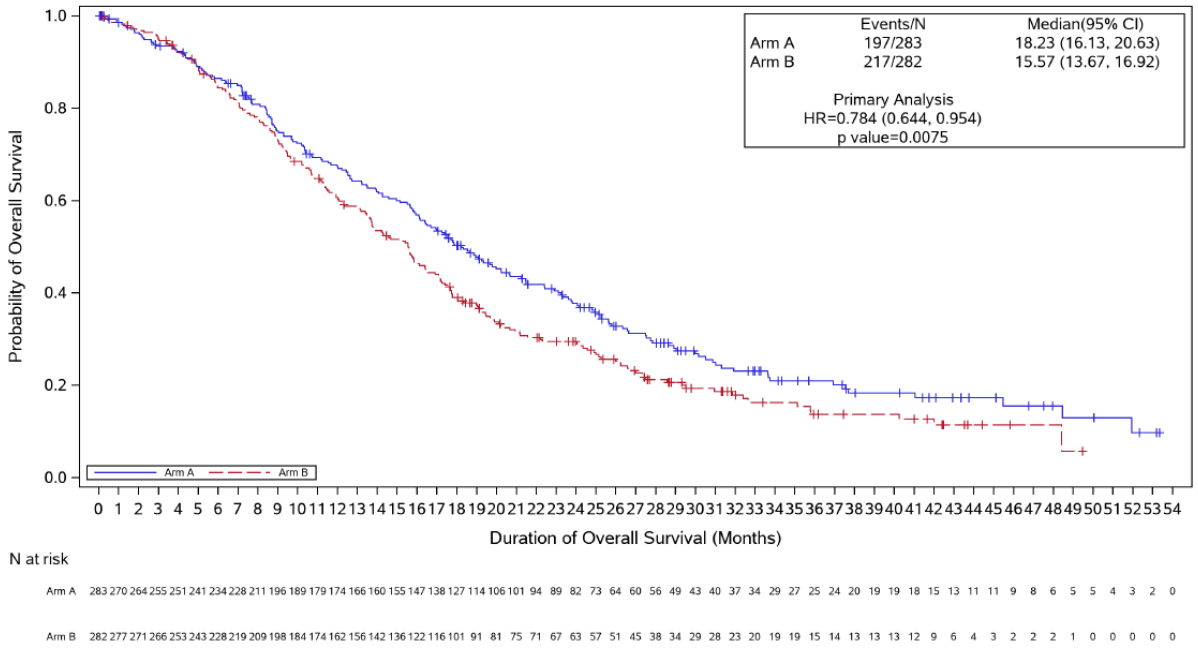
The updated result of OS is presented in Table 3.16 and the K-M plot is presented in Figure 3.10.

Table 3.16: SPOTLIGHT: Summary of OS (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
Median Follow-Up Time, Months (95% CI)	33.28 (29.27, 37.59)	31.38 (28.68, 36.17)
Deaths, n (%)	197 (69.6)	217 (77.0)
Median OS (95% CI), Months	18.23 (16.13, 20.63)	15.57 (13.67, 16.92)
Stratified Analysis*		
HR (95% CI)	0.784 (0.644, 0.954)	
1-sided P-value**	0.0075	
PFS Rate, % (95% CI)		
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]
At 48 months	[redacted]	[redacted]

Based on Table 3 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival.
Notes: Data cut-off: 8 September 2023.
* Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test.

Figure 3.10: SPOTLIGHT: K–M plot of OS (FAS)



Based on Figure 2 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients; OS, overall survival.
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.

3.2.7.3 Objective response rate

Based on the final data cut date (8 September 2023) of the SPOLTLIGHT trial, the updated results showed that the ORR assessed by IRC was 48.1% (95% CI: 42.11, 54.05) and the DCR was [redacted] (95% CI: [redacted]) in the zolbetuximab plus mFOLFOX6 arm, when compared with ORR ((47.5%; 95% CI: 41.56, 53.52) and DCR ([redacted]; 95% CI: [redacted]) in the placebo plus mFOLFOX6 arm. In addition, 21 (7.4%) patients had a CR and 115 (40.6%) patients had a PR in the zolbetuximab plus mFOLFOX arm. 13 (4.6%) patients had a CR and 121 (42.9%) patients had a PR in the placebo plus mFOLFOX arm.[8]

Table 3.17 presents the updated results of ORR assessed by IRC for the SPOTLIGHT trial.

Table 3.17: SPOTLIGHT: summary of ORR assessed by IRC – unconfirmed responses (FAS)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
Best overall response, n (%)†	[redacted]	[redacted]
CR	21 (7.4)	13 (4.6)
PR	115 (40.6)	121 (42.9)
Stable disease	44 (15.5)	51 (18.1)
Non-CR/non-progressive disease	52 (18.4)	60 (21.3)
Progressive disease	15 (5.3)	17 (6.0)
Not evaluable	4 (1.4)	3 (1.1)
No disease	5 (1.8)	1 (0.4)
Not available‡	27	16
ORR, n (%)	136 (48.1)	134 (47.5)
95% CI for ORR (%)§	(42.11, 54.05)	(41.56, 53.52)
Stratified one-sided p-value¶	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR (%)§	[redacted]	[redacted]
Stratified one-sided p-value¶	[redacted]	

Based on Table 4 of company response addendum[8]
CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 8 September 2023.
† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm.
‡ No post-baseline imaging assessment. Using exact method based on binomial distribution (Clopper–Pearson).
¶ Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. † DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease

3.2.7.4 Duration of response

Based on the final data cut date (8 September 2023) of the SPOLTLIGHT trial, the updated results showed that the median DoR as assessed by the IRC was 9.00 months (95% CI: 7.49, 10.38) in the zolbetuximab plus mFOLFOX6 arm and 8.11 months (95% CI: 6.47, 11.37) in the placebo plus mFOLFOX6 arm. There was no statistically significant difference in duration of response between the zolbetuximab plus mFOLFOX6 arm and placebo plus mFOLFOX6 arm ([redacted]).[8]

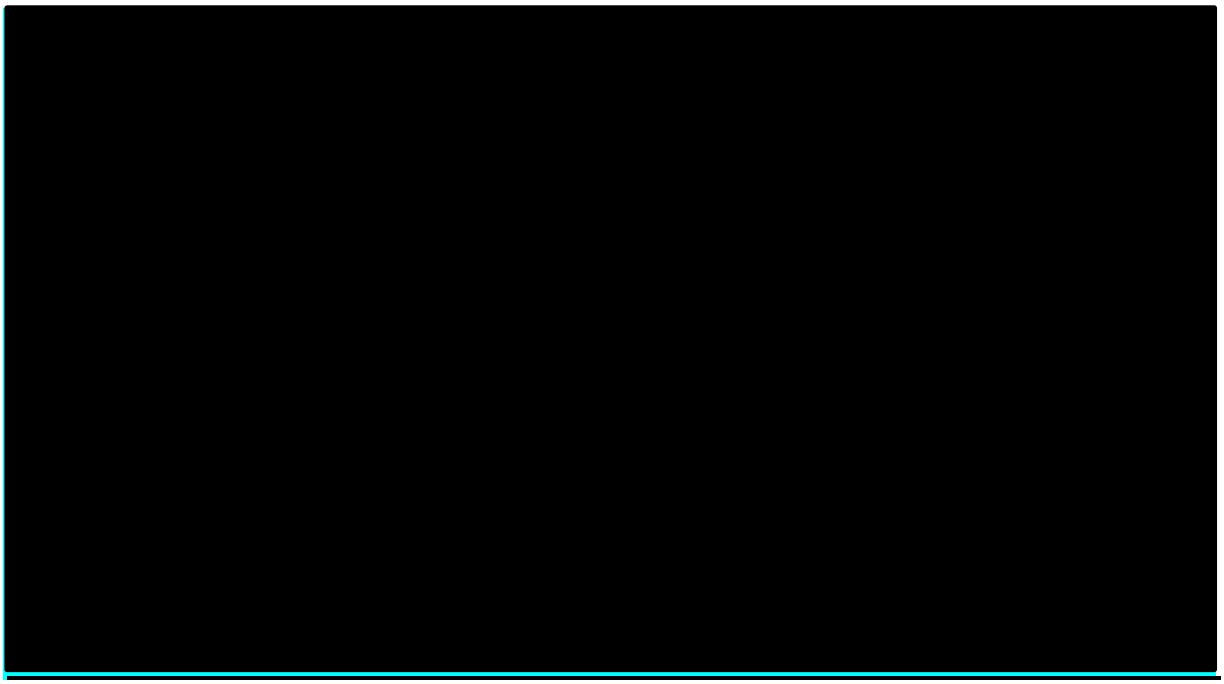
Table 3.18 presents the updated results of duration of response (DoR) for the SPOTLIGHT trial. The K–M plot is presented in Figure 3.11.

Table 3.18: SPOTLIGHT: Summary of DoR by IRC (FAS)

	Zolbetuximab + mFOLFOX6 (n = 136)	Placebo + mFOLFOX6 (n = 134)
Events, n (%)	[redacted]	[redacted]
Median DoR (95% CI), Months	9.00 (7.49, 10.38)	8.11 (6.47, 11.37)
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	0.0721	

Based on Table 5 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival.
Notes: Data cut-off: 8 September 2023.
* Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test.

Figure 3.11: SPOTLIGHT: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)



Based on Figure 3 of company response addendum[8]
CI, confidence interval; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; N, number of patients.
Notes: Data cut-off: 8 September 2023. Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.

3.2.7.5 Updated results of Health-related quality of life for the SPOTLIGHT trial

3.2.7.5.1 Time to confirmed deterioration

Based on the final data cut date (8 September 2023) of the SPOLTLIGHT trial, the results of time to confirmed deterioration for this trial showed that in terms of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items) (EORTC QLQ-C30) PF, the median of time to first confirmed deterioration was 10.71 months for the zolbetuximab plus mFOLFOX6 arm

while the median of time to first confirmed deterioration was 12.32 months for the placebo plus mFOLFOX6 arm. There was no statistically significant difference in time to first confirmed deterioration between the zolbetuximab plus mFOLFOX6 arm and the placebo plus mFOLFOX6 arm ([redacted]).[8]

In terms of EORTC QLQ-C30 GHS/QoL, the median of time to first confirmed deterioration was 15.44 months for the zolbetuximab plus mFOLFOX6 arm while the median of time to first confirmed deterioration was 11.83 for the placebo plus mFOLFOX6 arm. There was no statistically significant difference in time to first confirmed deterioration between the zolbetuximab plus mFOLFOX6 arm and placebo plus mFOLFOX6 arm ([redacted]).[8]

Table 3.19 presents a summary of time to confirmed deterioration for GHS/QoL, PF, and pain assessment in oesophago-gastric module (OG-25-Pain) for the SPOTLIGHT trial.

Table 3.19: SPOTLIGHT: TTCD for GHS/QoL, PF, and pain assessment in oesophago-gastric module (OG-25-Pain)

	Zolbetuximab + mFOLFOX6 (n = 283)	**Placebo + mFOLFOX6 (n = 282)**
EORTC QLQ-C30 PF (deterioration threshold = 13)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	10.71 (6.01, NE)	12.32 (9.26, NE)
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
OG25-Pain (deterioration threshold = 16.7)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	

	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = 282)
EORTC QLQ-C30 GHS/QoL (deterioration threshold = 13)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	15.44 (7.06, 23.89)	11.83 (9.23, 15.08)
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	

Based on Table 6 of company response addendum[8]
CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 items); FAS, full analysis set; GHS, global health status; HR, hazard ratio; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin; n, number of patients; NE, non-estimable; NYR, not yet reached; OG25-Pain, pain assessment in oesophago-gastric module; PF, physical function; QoL, quality of life; TTCD, time to confirmed deterioration
Notes: Data cut-off: 8 September 2023. ‡ TTCD = date of first confirmed clinically meaningful deterioration/censored date – randomisation date +1. § Stratification factors were region, number of organs with metastatic sites, and prior gastrectomy. ¶ Based on 1-sided log-rank test. †† Based on stratified Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.

3.2.8 Efficacy results of the GLOW trial

Results were presented from the GLOW trial with a data cut of 29 June 2023, which was not a pre-specified data cut. The CS states that the final database lock for the GLOW trial took place on 12 January 2024 and data analysis is ongoing.

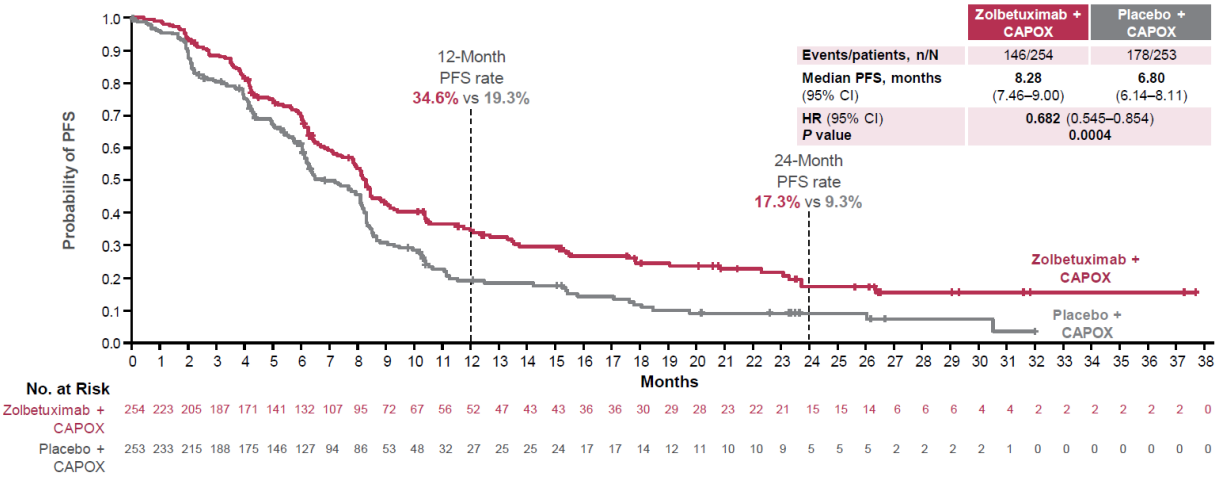
3.2.8.1 Progression free survival

As of the data cut-off date (29 June 2023), median duration of follow-up for PFS was 17.81 months (95% CI: [redacted]) in the zolbetuximab plus CAPOX arm and 15.05 months (95% CI: [redacted]) in the placebo plus CAPOX arm.[1]

Zolbetuximab plus CAPOX was associated with a statistically significant improvement in PFS when compared with placebo plus mFOLFOX6 based on IRC assessment per RECIST 1.1: HR 0.682 (95% CI: 0.545, 0.854), p = 0.0004). The median PFS was 8.28 months (95% CI: 7.46, 9.00) in the zolbetuximab plus CAPOX arm and 6.80 months (95% CI: 6.14, 8.11) in the placebo plus CAPOX arm.[1]

The corresponding K-M survival plots of PFS are presented in Figure 3.12.

Figure 3.12: GLOW: K–M plot of PFS assessed by IRC (FAS)



Based on Figure 8 of CS[1]

CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CS, company submission; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.

Notes: Data cut-off: 29 June 2023.

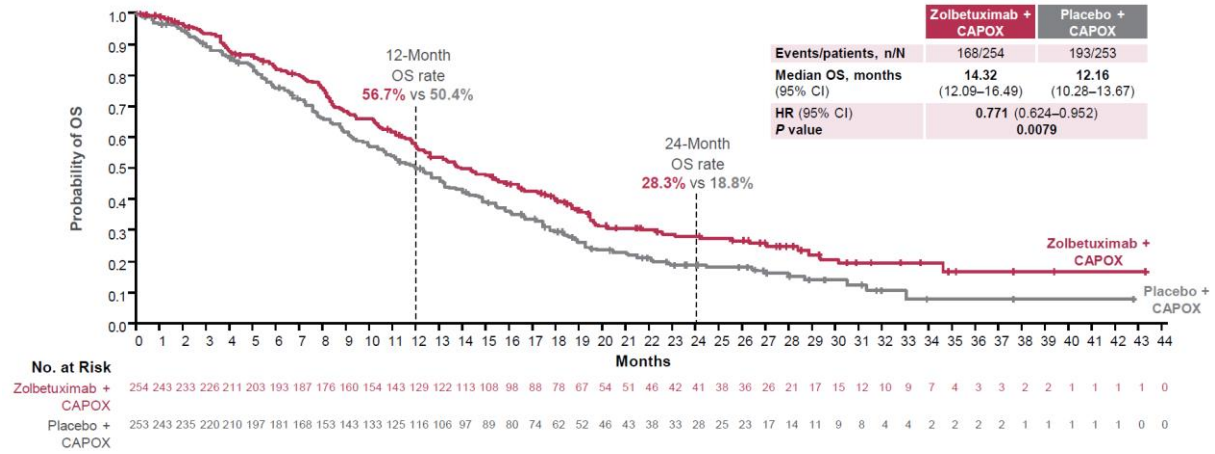
3.2.8.2 Overall survival

As of the data cut-off date of 29 June 2023, the median duration of follow-up for OS was 26.09 months (95% CI: [redacted]) in the zolbetuximab plus CAPOX arm and 26.18 months (95% CI: [redacted]) in the placebo plus CAPOX arm.[1]

Zolbetuximab plus CAPOX was associated with a statistically significant improvement in OS when compared with the placebo plus CAPOX group: HR 0.771 (95% CI: 0.624, 0.952; p = 0.0079). The median OS was 14.32 months (95% CI: 12.09, 16.49) in the zolbetuximab plus CAPOX arm and 12.16 months (95% CI: 10.28, 13.67) in the placebo plus CAPOX arm.[1]

The corresponding K-M survival plots are presented in Figure 3.13.

Figure 3.13: GLOW: K–M plot of OS (FAS)



Based on Figure 9 of CS[1]

CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CS, company submission; FAS, full analysis set; HR, hazard ratio; N, number of patients; OS, overall survival.

Notes: Data cut-off: 29 June 2023.

3.2.8.3 Objective response rate

The ORR per IRC was [redacted] (95% CI: [redacted]) and the DCR was [redacted] (95% CI: [redacted]) in the zolbetuximab plus CAPOX arm, when compared with ORR ([redacted]; 95% CI: [redacted]) and DCR ([redacted]; 95% CI: [redacted]) in the placebo plus CAPOX arm.[1]

[redacted] patients had a CR, and [redacted] patients had a PR in the zolbetuximab plus CAPOX arm. [redacted] patients had a CR, and [redacted] patients had a PR in the placebo plus CAPOX arm.

Table 3.20 provides an overview of the data on ORR.

Table 3.20: GLOW: Summary of ORR assessed by IRC – (FAS)

	Zolbetuximab + CAPOX (n = 254)	**Placebo + CAPOX (n = 253)**
Best overall response, n (%)†	[redacted]	[redacted]
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non-CR/non-progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]
No disease	[redacted]	[redacted]
Not available‡	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]
95% CI for ORR§	[redacted]	[redacted]
p-value*	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR§	[redacted]	[redacted]
p-value*	[redacted]	

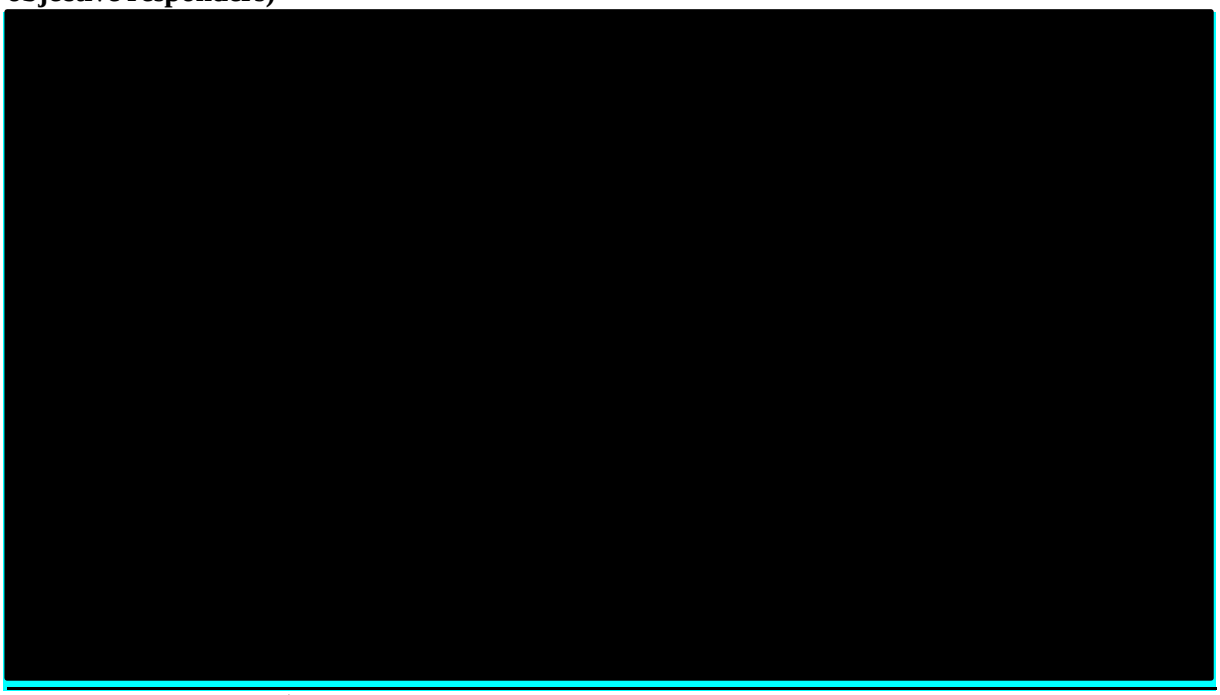
Based on Table 7 of CS[1]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; CS, company submission; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 29 June 2023.
† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm.
‡ No post-baseline imaging assessment.
§ Using exact method based on binomial distribution (Clopper–Pearson). Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of metastatic sites and prior gastrectomy.
* Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy.
†† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks)

3.2.8.4 Duration of response

As of data cut date of 29 June 2023, the median DoR as assessed by the IRC was 6.28 months (95% CI: 5.39, 8.28) in the zolbetuximab plus CAPOX arm and 6.08 months (95% CI: 4.44, 6.34) in the placebo plus CAPOX arm ([redacted].[1]

The corresponding K-M survival plots are presented in Figure 3.14.

Figure 3.14: GLOW: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)



Based on Figure 10 of CS[1]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; cs, company submission; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; N, number of patients; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 29 June 2023.

3.2.8.5 Health-related quality of life

Changes in HRQoL was assessed by using the EQ-5D-5L VAS. The data cut-off date of 7 October 2023 (primary analysis data cut) was selected as the time point for analysing changes from baseline for the EQ-5D-5L.[1]

The EQ-5D-5L measures self-rated health state using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at five levels (no problems, slight problems, moderate problems, severe problems and extreme problem).

Baseline EQ-5D-5L VAS scores were comparable between treatment arms. There were no significant differences being observed for either treatment arm for the EQ-5D questionnaire index score and EQ-VAS during the treatment and follow-up periods.[1] The company states that no formal statistical testing was performed on these measures of EQ-5D-5L VAS scores.[1]

Figure 3.15 presents longitudinal analysis of change from baseline in EQ-5D-5L questionnaire utility index score for the GLOW trial. Figure 3.15 presents longitudinal analysis of change from baseline in EQ-5D-5L VAS for the GLOW trial.

Figure 3.15: GLOW: longitudinal analysis of change from baseline in EQ-5D-5L questionnaire utility index score – MMRM analysis

Based on Figure 51 of CS appendix
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CS, company submission; EQ-5D-5L, EuroQoL 5-level EQ-5D; LS, least squares; MMRM, mixed model repeated measures.
Notes: Data cut-off: 7 October 2022.

Figure 3.16: GLOW: longitudinal analysis of change from baseline in EQ-5D-5L VAS – MRMM analysis

Based on Figure 52 of CS appendix
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CS, company submission; EQ-5D-5L, EuroQoL 5-level EQ-5D; LS, least squares; MMRM, mixed model repeated measures; VAS, visual analogue scale.
Notes: Data cut-off: 7 October 2022.

EAG comment:

- There was a lack of long-term follow-up data relating to HRQoL outcomes. Given that HRQoL outcomes from the CS are not relatively mature, in the clarification letter, the EAG requested more mature data from the GLOW trial for all outcomes reported. In responding to the EAG's request, the company stated that at the time of the company response addendum, longitudinal analysis of the pre-specified PROs had not yet been completed and additional longitudinal analysis of HRQoL data were therefore not provided.[8]
- In responding to EAG's request, the company provided other relevant longer-term HRQoL data (see Section 3.2.9.5) during the clarification response stage.

3.2.9 Updated efficacy results of the GLOW trial

3.2.9.1 Progression-free survival

Based on the final data cut date (12 January 2024) of the GLOW trial, the updated results showed that zolbetuximab plus CAPOX was associated with a statistically significant improvement in PFS assessed by IRC compared to placebo plus CAPOX (HR 0.689, 95% CI: 0.552, 0.860).[8]

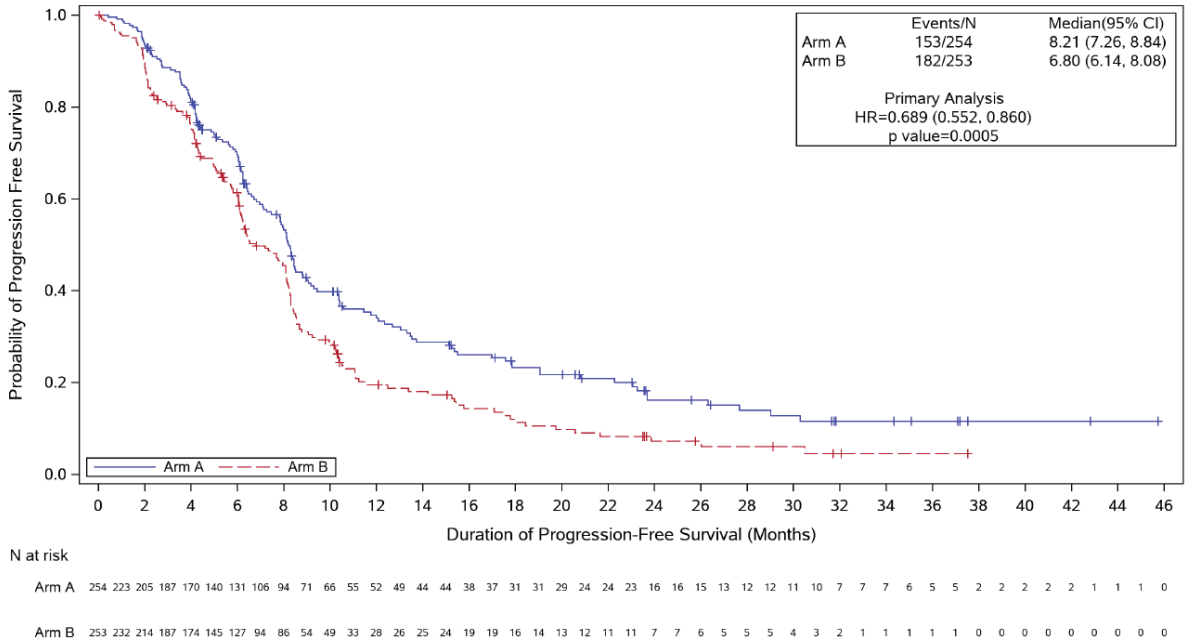
The updated results of PFS assessed by IRC for the GLOW trial are presented in Table 3.21 and the K–M plot is presented in Figure 3.17.

Table 3.21: GLOW: Summary of PFS assessed by IRC (FAS)

	Zolbetuximab + CAPOX	Placebo + CAPOX
Median Follow-Up Time, Months (95% CI)	20.57 (15.21, 23.62)	23.49 (10.38, 25.76)
PFS Events, n (%)	153 (60.2)	182 (71.9)
Median PFS (95% CI), Months	8.21 (7.26, 8.84)	6.80 (6.14, 8.08)
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	
PFS Rate, % (95% CI)		
At 6 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]
At 48 months	[redacted]	[redacted]

Based on Table 8 of company response addendum[8]
CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival.
Notes: Data cut-off: 12 January 2024.
* Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test.

Figure 3.17: GLOW: K–M plot of PFS assessed by IRC (FAS)



Based on Figure 4 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; K-M, Kaplan-Meier; N, number of patients; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1.
Notes: Data cut-off: 12 January 2024. Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.

3.2.9.2 Overall survival

Based on the final data cut date (12 January 2024) of the GLOW trial, the updated results showed that zolbetuximab plus CAPOX was associated with a statistically significant improvement in OS compared to placebo plus CAPOX (HR 0.763, 95% CI 0.622, 0.936).[8]

The updated result of OS is presented in Table 3.22 and the K–M plot is presented in Figure 3.18.

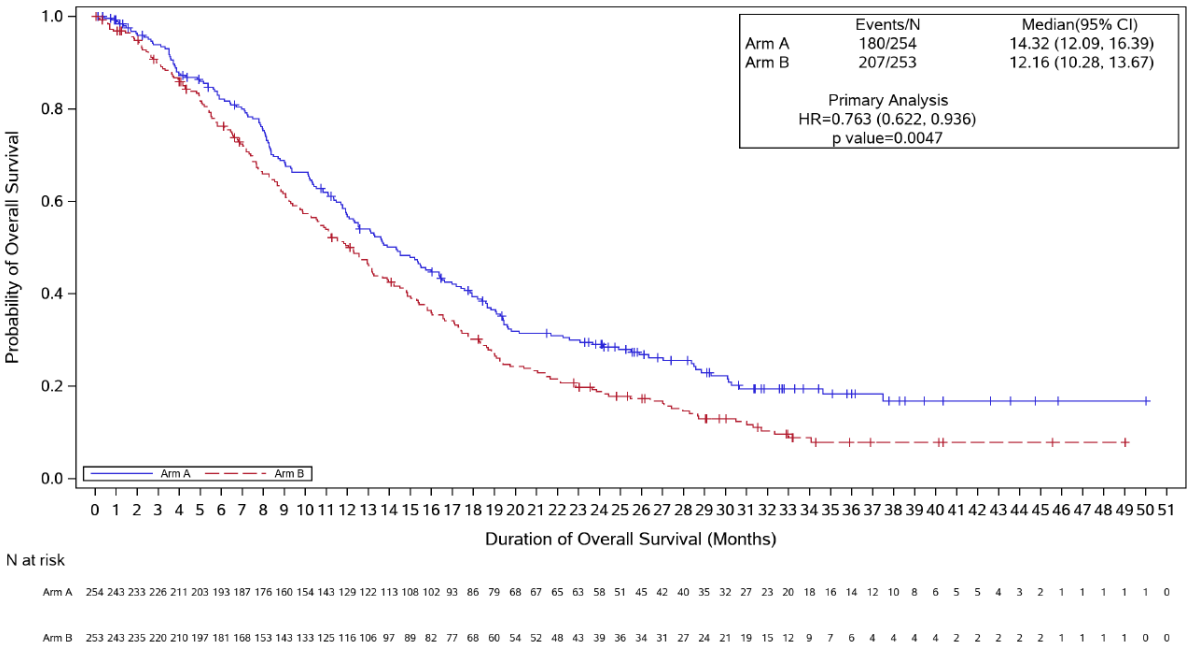
Table 3.22: GLOW: Summary of OS (FAS)

	Zolbetuximab + CAPOX (n = 254)	**Placebo + CAPOX (n = 253)**
Median Follow-Up Time, Months (95% CI)	31.70 (28.19, 33.71)	32.95 (29.70, 35.91)
Deaths, n (%)	180 (70.9)	207 (81.8)
Median OS (95% CI), Months	14.32 (12.09, 16.39)	12.16 (10.28, 13.67)
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	
1-sided P-value**	[redacted]	
OS Rate, % (95% CI)		
At 12 months	[redacted]	[redacted]
At 18 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]
At 30 months	[redacted]	[redacted]
At 36 months	[redacted]	[redacted]
At 42 months	[redacted]	[redacted]

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
At 48 months	[redacted]	[redacted]

Based on Table 9 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
Notes: Data cut-off: 12 January 2024.
* Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test.

Figure 3.18: GLOW: K–M plot of OS (FAS)



Based on Figure 5 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; K-M, Kaplan-Meier; N, number of patients; OS, overall survival.
Notes: Data cut-off: 12 January 2024. Median follow-up = 26.09 months (zolbetuximab + CAPOX) versus 26.18 months (placebo + CAPOX). Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.

3.2.9.3 Objective response rate

Based on the final data cut date (12 January 2024) of the GLOW trial, the updated results from the GLOW trial showed that the ORR per IRC was 42.5% (95% CI: 36.36, 48.85) and the DCR was [redacted] (95% CI: [redacted]) in the zolbetuximab plus CAPOX arm, when compared with ORR (39.1%; 95% CI: 33.08, 45.44) and DCR ([redacted]; 95% CI: [redacted]) in the placebo plus CAPOX arm.[8]

In addition, 11 (4.3%) patients had a CR and 97 (38.2%) patients had a PR in the zolbetuximab plus CAPOX arm, while 4 (1.6%) patients had a CR and 95 (37.5%) patients had a PR in the placebo plus CAPOX arm.[8]

Tables 3.23 provides an overview of the data on ORR.

Table 3.23: GLOW: summary of ORR assessed by IRC – (FAS)

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
Best overall response, n (%)†	[redacted]	[redacted]
CR	11 (4.3)	4 (1.6)
PR	97 (38.2)	95 (37.5)
Stable disease	47 (18.5)	57 (22.5)
Non-CR/non-progressive disease	39 (15.4)	35 (13.8)
Progressive disease	12 (4.7)	28 (11.1)
Not evaluable	1 (0.4)	5 (2.0)
No disease	3 (1.2)	1 (0.4)
Not available‡	44	28
ORR, n (%)	108 (42.5)	99 (39.1)
95% CI for ORR§	(36.36, 48.85)	(33.08, 45.44)
p-value*	[redacted]	
DCR, n (%)††	[redacted]	[redacted]
95% CI for DCR§	[redacted]	[redacted]
p-value*	[redacted]	

Based on Table 10 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; IRC, independent review committee; n, number of patients; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: 12 January 2024.
† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) is believed to be best response, the assessment should be at least 8 weeks after randomisation. For calculation of percentages, denominator included the total number of patients in each arm.
‡ No post-baseline imaging assessment.
§ Using exact method based on binomial distribution (Clopper–Pearson). Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were region, number of metastatic sites and prior gastrectomy.
* Based on one-sided Cochran–Mantel–Haenszel test. Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy.
†† DCR was defined as the proportion of patients who have a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).

3.2.9.4 Duration of response

Based on the final data cut date (12 January 2024) of the GLOW trial, the updated results of DoR from this trial showed that the median DoR as assessed by the IRC was 6.28months (95% CI: 5.39, 8.28) in the zolbetuximab plus CAPOX arm and 6.08 months (95% CI: 4.44, 6.34) in the placebo plus CAPOX arm. There was no statistically significant difference in duration of response between the zolbetuximab plus CAPOX arm and placebo plus CAPOX arm ([redacted]).[8]

Table 3.24 presents the updated results of DoR for the GLOW trial. The K–M plot is presented in Figure 3.19.

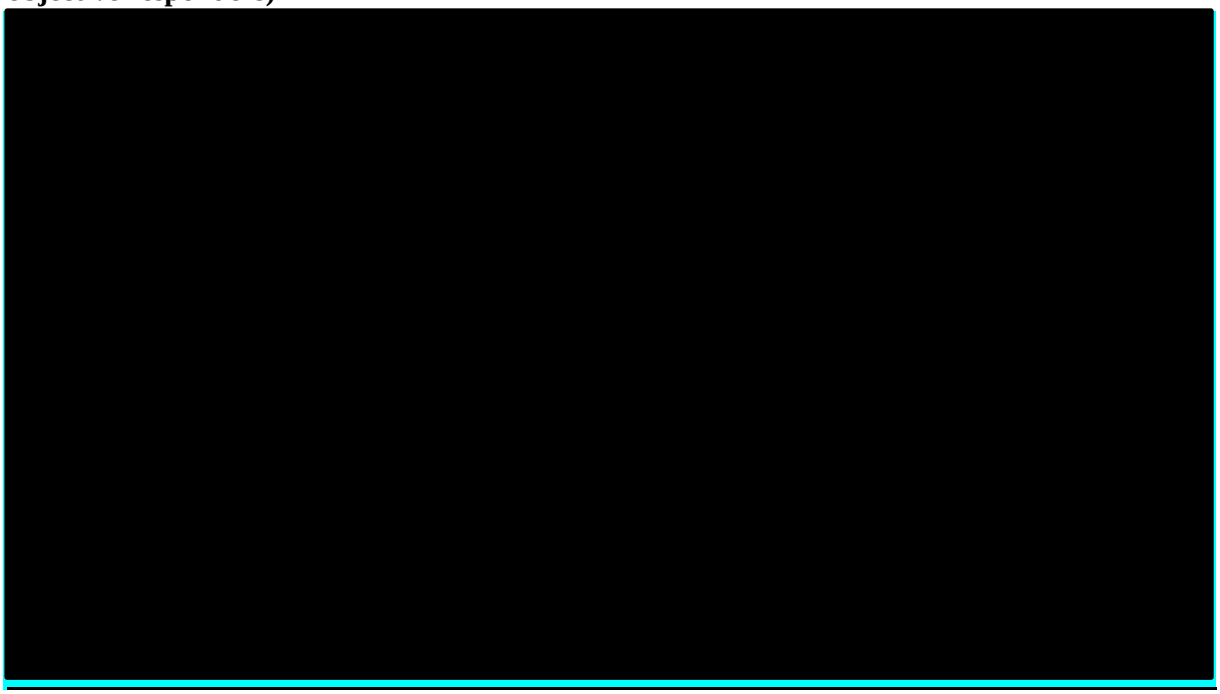
Table 3.24: GLOW: Summary of DoR by IRC (FAS)

	Zolbetuximab + CAPOX (n = 108)	Placebo + CAPOX (n = 99)
Events, n (%)	[redacted]	[redacted]
Median DoR (95% CI), Months	6.28 (5.39, 8.28)	6.08 (4.44, 6.34)
Stratified Analysis*		
Hazard Ratio (95% CI)	[redacted]	

	Zolbetuximab + CAPOX (n = 108)	Placebo + CAPOX (n = 99)
1-sided P-value**	[redacted]	

Based on Table 11 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; K-M, Kaplan-Meier; OS, overall survival.
Notes: Data cut-off: 12 January 2024.
* Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from IRT.
** Based on 1-sided log-rank test. Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.

Figure 3.19: GLOW: summary of DoR assessed by IRC – unconfirmed responses (FAS – all objective responders)



Based on Figure 6 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; CR, complete response; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; HRQoL = health-related quality of life; IRC, independent review committee; N, number of patients; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.
Notes: Data cut-off: [redacted]. Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.
Updated results of HRQoL for the GLOW trial

3.2.9.4.1 Time to confirmed deterioration

Based on the final data cut date ([redacted]) of the GLOW trial, the results of time to confirmed deterioration from the GLOW trial showed that for EORTC QLQ-C30 PF, the median of time to first confirmed deterioration was 8.31months for the zolbetuximab plus CAPOX arm while the median of time to first confirmed deterioration was 7.95 months for the placebo plus CAPOX arm. There was no statistically significant difference in time to first confirmed deterioration between the zolbetuximab plus CAPOX arm and the placebo plus CAPOX arm ([redacted]).[8]

In terms of EORTC QLQ-C30 GHS/QoL, the median of time to first confirmed deterioration was [redacted] months for the zolbetuximab plus CAPOX arm while the median of time to first confirmed deterioration was [redacted] months for the placebo plus CAPOX arm. There was no statistically significant difference in time to first confirmed deterioration between the zolbetuximab plus CAPOX arm and the placebo plus CAPOX arm ([redacted]).[8]

Table 3.25 presents a summary of TTCD for GHS/QoL, PF, and pain assessment in oesophago-gastric module (OG-25-Pain) for the GLOW trial.

Table 3.25: GLOW: TTCD for GHS/QoL, PF, and pain assessment in oesophago-gastric module (OG-25-Pain)

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
PF (deterioration threshold = 13)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	8.31 (5.88, 19.81)	7.92 (6.47, 11.30)
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
OG25-Pain (deterioration threshold = 16.7)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	
GHS/QoL (deterioration threshold = 13)		
Deterioration events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
No baseline score	[redacted]	[redacted]
No post-baseline score	[redacted]	[redacted]
No deterioration possible	[redacted]	[redacted]
No first deterioration	[redacted]	[redacted]
Time to first confirmed deterioration, months‡		
Median (95% CI)	[redacted]	[redacted]
1st quartile (95% CI)	[redacted]	[redacted]

	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 253)
3rd quartile (95% CI)	[redacted]	[redacted]
Stratified analysis§		
1-sided p-value¶	[redacted]	
HR (95% CI)††	[redacted]	

Based on Table 12 of company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FAS, full analysis set; GHS, global health status; HR, hazard ratio; n, number of patients; NE, non-estimable; NYR, not yet reached; OG25-Pain, pain assessment in oesophago-gastric module; PF, physical function; QoL, quality of life; TTCD, time to confirmed deterioration.
Notes: Data cut-off: 12 January 2024.
‡ TTCD = date of first confirmed clinically meaningful deterioration/censored date – randomisation date +1. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy.
¶ Based on 1-sided log-rank test.
†† Based on stratified Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.

3.2.10 Adverse events

The safety data were presented for SPOTLIGHT, GLOW and FAST with the finial data cut updated from the company response.[4]

3.2.10.1 Treatment-emergent adverse events

In the SPOTLIGHT trail, the company reported that *"the incidence of the most common TEAEs was similar in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms, with the exception of nausea (82.4% vs 61.5%), vomiting (67.4% vs 36.3%), and decreased appetite (48.7% vs 34.9%)"*.[1]

Similarly, in the GLOW trial, the company noted that *"the incidence of common TEAEs was similar in the zolbetuximab + CAPOX and placebo + CAPOX arms, with the exception (difference of ≥ 5%) of nausea (68.9% vs 50.2%, respectively), vomiting (66.1% vs 31.3%), decreased appetite (41.3% vs 34.5%), abdominal pain (16.1% vs 22.1%), hypoalbuminemia (22.4% vs 14.1%), constipation (15.7% vs 21.3%), neutropenia (19.7% vs 14.1%), weight decreased (19.7% vs 10.0%), and peripheral oedema (10.2% vs 2.4%)"*.[1]

A summary of any-grade TEAEs transpiring in ≥ 10% of patients in the SPOTLIGHT, GLOW and FAST study is provided in Table 3.26. Details of Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurring in > 10% of patients in the SPOTLIGHT, GLOW and FAST study are outlined in Table 3.27.

Table 3.26: Any grade TEAEs occurring in ≥ 10% of patients in either treatment arm in SPOTLIGHT, GLOW and FAST

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any TEAE	278 (99.6)	277 (99.6)	251 (98.8)	244 (98.0)	74 (96.1)	84 (100)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	53 (68.8)	50 (59.5)
Anaemia	106 (38.0)	107 (38.5)	93 (36.6)	92 (36.9)	35 (45.5)	30 (35.7)
Neutropenia	102 (36.6)	94 (33.8)	50 (19.7)	35 (14.1)	34 (44.2)	29 (34.5)
Thrombocytopenia	29 (10.4)	45 (16.2)	28 (11.0)	31 (12.4)	12 (15.6)	9 (10.7)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	76 (90.5)	70 (90.9)
Nausea	230 (82.4)	171 (61.5)	175 (68.9)	125 (50.2)	63 (81.8)	64 (76.2)
Vomiting	188 (67.4)	101 (36.3)	168 (66.1)	79 (31.7)	52 (67.5)	46 (54.8)
Diarrhoea	114 (40.9)	125 (45.0)	83 (32.7)	87 (34.9)	14 (18.2)	31 (36.9)
Constipation	101 (36.2)	113 (40.6)	40 (15.7)	53 (21.3)	[redacted]	[redacted]
Abdominal pain	70 (25.1)	87 (31.3)	41 (16.1)	56 (22.5)	14 (18.2)	10 (11.9)
Stomatitis	60 (21.5)	60 (21.6)	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	47 (16.8)	34 (12.2)	[redacted]	[redacted]	14 (18.2)	10 (11.9)
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	54 (70.1)	56 (66.7)
Fatigue	83 (29.7)	94 (33.8)	35 (13.8)	42 (16.9)	24 (31.2)	17 (20.2)
Asthenia	74 (26.5)	64 (23.0)	34 (13.4)	32 (12.9)	19 (24.7)	19 (22.6)
Pyrexia	59 (21.1)	50 (18.0)	36 (14.2)	23 (9.2)	9 (11.7)	17 (20.2)
Oedema peripheral	52 (18.6)	27 (9.7)	26 (10.2)	125 (50.2)	10 (13.0)	6 (7.1)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	41 (53.2)	47 (56.0)

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Neutrophil count decreased	96 (34.4)	91 (32.7)	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	57 (20.4)	56 (20.1)	[redacted]	[redacted]	25 (32.5)	26 (31.0)
Aspartate aminotransferase increased	50 (17.9)	47 (16.9)	[redacted]	[redacted]	7 (9.1)	11 (13.1)
White blood cell count decreased	51 (18.3)	46 (16.5)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	41 (14.7)	49 (17.6)	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	35 (12.5)	50 (18.0)	[redacted]	[redacted]	6 (7.8)	9 (10.7)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	24 (31.2)	23 (27.4)
Decreased appetite	136 (48.7)	97 (34.9)	[redacted]	[redacted]	15 (19.5)	19 (22.6)
Hypokalaemia	51 (18.3)	42 (15.1)	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminemia	46 (16.5)	18 (6.5)	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	9 (11.7)	17 (20.2)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	35 (45.5)	42 (50.0)
Peripheral sensory neuropathy	107 (38.4)	119 (42.8)	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	44 (15.8)	47 (16.9)	[redacted]	[redacted]	10 (13.0)	9 (10.7)
Dysgeusia	44 (15.8)	40 (14.4)	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	12 (15.6)	18 (21.4)

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	20 (23.8)	19 (24.7)
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	12 (14.3)	12 (15.6)
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 of Clarification response
For SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm.
CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 3.27: Grade ≥ 3 TEAEs in > 10% of patients in either treatment arm in SPOTLIGHT, GLOW and FAST

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any Grade ≥ 3 TEAE	[redacted]	[redacted]	[redacted]	[redacted]	54 (70.1)	54 (64.3)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	25 (32.5)	18 (21.4)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	5 (6.5)	4 (4.8)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	8 (10.4)	3 (3.6)
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 of Clarification response
For SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm.
CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event

3.2.10.2 Study intervention-related treatment-emergent adverse events

In the SPOTLIGHT trial, the company indicated that *"Zolbetuximab- or placebo-related TEAEs were more frequent in the zolbetuximab + mFOLFOX6 arm than in the placebo + mFOLFOX6 arm ([redacted] [redacted] vs [redacted] [redacted])".* [1]

Likewise, in the GLOW trial, the company reported that *"Zolbetuximab or placebo-related TEAEs were more frequent in the zolbetuximab + CAPOX arm versus the placebo + CAPOX arm ([redacted] vs [redacted], respectively)".*[1]

Table 3.28 outlined any-grade TEAEs related to study intervention transpiring in ≥ 10% of patients in SPOTLIGHT, GLOW and FAST trials. Table 3.29 presents Grade ≥ 3 study intervention-related TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT, GLOW and FAST trials.

Table 3.28: Any grade study intervention-related TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT, GLOW and FAST

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any intervention-related TEAE*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 of the response to the request for clarification[4]
For SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm.

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event						

Table 3.29: Grade ≥ 3 study intervention-related TEAEs in ≥ 10% of patients in either treatment arm in SPOTLIGHT, GLOW and FAST

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any Grade ≥ 3 intervention-related TEAEs*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 7 of the response to the request for clarification[4] For SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm. CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event						

3.2.10.3 Serious adverse events

In the SPOTLIGHT trial, the company noted that the number and percentage of patients encountering a serious adverse event (SAE) were similar between the zolbetuximab + mFOLFOX6 arm and the placebo + mFOLFOX6 arm ([redacted] versus [redacted] respectively).

Similarly, in the GLOW trial, the company observed that the number and proportion of patients experiencing an SAE were comparable between the zolbetuximab + CAPOX arm and the placebo + CAPOX arm ([redacted] versus [redacted] respectively).

Table 3.30 presents serious adverse events (SAEs) in ≥ 5% of patients in either treatment arm in either treatment arm in SPOTLIGHT, GLOW and FAST trials.

Table 3.30: SAEs in ≥ 5% of patients in either treatment arm in either treatment arm in SPOTLIGHT, GLOW and FAST

Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]	19 (24.7)	27 (32.1)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasm malignant	[redacted]	[redacted]	[redacted]	[redacted]	3 (3.9)	7 (8.3)

Based on Table 7 of the response to the request for clarification[4]
For SPOTLIGHT and GLOW, this includes data for zolbetuximab- or placebo-related TEAE. For FAST, these data include zolbetuximab-related TEAEs for the Zolbetuximab + EOX arm and non-zolbetuximab related TEAEs for the EOX arm.
CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event

3.2.10.4 Discontinuation and/or dose modifications due to treatment-emergent adverse events

Table 3.31 outlined summary of discontinuation and dose interruption of study drug across the SPOTLIGHT, GLOW, AND FAST trials.

Table 3.31: Discontinuation and dose interruption of study drug across the SPOTLIGHT, GLOW, AND FAST trials

System Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Discontinuation due to TEAEs in ≥ 5% of patients in either treatment arm						
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose interruption due to TEAEs in ≥ 5% of patients in either treatment arm						
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class, n (%) Preferred term, n (%)	SPOTLIGHT		GLOW		FAST	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + EOX (n = 77)	EOX (n = 84)
Based on Table 8 of the response to the request for clarification[4] CAPOX = capecitabine and oxaliplatin; EOX = epirubicin, oxaliplatin and capecitabine; mFOLFOX6 = modified folinic acid, fluorouracil and oxaliplatin; n = number of patients; TEAE = treatment-emergent adverse event						

3.2.10.5 Deaths

In the SPOTLIGHT trial, the company observed that *"the number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms ([redacted], respectively)"*.[1]

Similarly, in the GLOW trial, the company noted that *"the number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + CAPOX and placebo + CAPOX arms ([redacted], respectively)"*.[1]

EAG comment: The company did not provide advent event data by a comparison of the treatment arm versus the control arm in a Table in the CS. The EAG requested the company to provide all adverse event (AE) data for the comparison of the treatment arm versus the control arm of the SPOTLIGHT, GLOW and FAST trials in a Table. In responding to EAG's request, the company provided an overview of AEs in the SPOTLIGHT, GLOW and FAST trials in a Table in their clarification response.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Four trials were identified through an SLR that were considered for inclusion in an indirect treatment comparison (ITC) of interest to this appraisal. These trials investigated zolbetuximab and nivolumab. The company states that the ITC included three zolbetuximab studies (SPOTLIGHT, GLOW and FAST), and one trial that compared nivolumab plus chemotherapy with chemotherapy in patients with PD-L1 CPS ≥ 5 (PD-L1 CPS ≥ 5 subgroup from the CheckMate 649 trial).[1]

The company states that there was observed heterogeneity across studies with regard to trial design and patient population across included trials of the ITC. The company made the following statements in terms of the key differences across included trials:[1]

- *"The FAST trial did not include any Asian sites*
- *Chemotherapy regimens varied across the trials – however, CAPOX and FOLFOX are thought to be equivalent*
- *The median survival estimate for the chemotherapy arm was higher in SPOTLIGHT (15.5 month) compared with the other studies (8.9–11.1 months)*
- *A variation in the median follow-up was observed across trials, ranging from 15.1 months in GLOW to 36 months in CheckMate 649.*
- *CLDN18.2 expression status was not reported in non-zolbetuximab trials. However, this is not expected to be a limitation, as CLDN18.2 status has been shown not to affect outcomes with chemotherapy and is not expected to affect outcomes with CPIs."*

The company made the further following statement:[1]

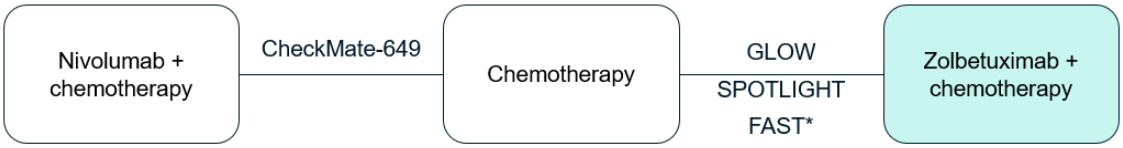
- "*All four studies compared two treatments, which allowed the selected studies to form a network through common comparator arms. However, as each study used a different chemotherapy control arm, there was no common comparator across trials – so a connected network of evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed."*

Furthermore, the company made the following statement:[1]

- *"as each study used a different chemotherapy control arm, there was no common comparator across trials – so a connected network of evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed."*

Figure 3.20 shows the overall network diagram for the ITC analysis.

Figure 3.20: Overall network diagram



Based on Figure 13 of CS[1]
CAPOX, capecitabine and oxaliplatin; CLDN18.2, claudin 18.2; CS, company submission; EOX, epirubicin + oxaliplatin + capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin.
Note: The chemotherapy node in the network represents CAPOX or FOLFOX. *****FAST CLDN18.2 ≥ 70% subgroup was explored in sensitivity analyses as EOX is used infrequently in the UK and a different test method was used for CLDN18.2.

Table 3.32 presents a summary of the patient characteristics at baseline for the ITT population in SPOTLIGHT and GLOW, and for patients with PD-L1 CPS ≥ 5 in CheckMate-649. There was considerable heterogeneity of PD-L1 CPS status for the included populations between SPOTLIGHT and GLOW trials and the PD-L1 CPS ≥ 5 subgroup in CheckMate-649. While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: [redacted] in zolbetuximab + mFOLFOX6 arm versus [redacted] in mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted] in Zolbetuximab + CAPOX arm versus [redacted] in CAPOX arm.[4] However, it should be noted that PD-L1 CPS might not be a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy. The company did present subgroup analyses for both GLOW and SPOTLIGHT for OS and PFS, one with a CPS threshold of 5 and the other with a CPS threshold of 1. For all analyses there was overlap of the 95% CIs for HR between the groups above and below the threshold. [redacted]
Therefore, although the EAG cannot speculate what the mechanism might be, it is unclear whether PD-L1 status is a treatment effect modifier.

Table 3.33 presents an overview of the PD-L1 CPS status of all randomised patients in the SPOTLIGHT and GLOW trials. Among those patients with known PD-L1 CPS of the SPOTLIGHT trial, [redacted] of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus mFOLFOX6 arm while [redacted] of patients had had PD-L1 CPS ≥ 1 in the placebo plus mFOLFOX6 arm. For those patients with known PD-L1 CPS of the GLOW trial, [redacted] of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus CAPOX arm while [redacted] of patients had PD-L1 CPS ≥ 1 in the placebo plus CAPOX arm.[4]

Table 3.32: Patient characteristics at baseline for studies considered for indirect treatment comparison.

	SPOTLIGHT (ITT)		GLOW (ITT)		CheckMate 649 (PD-L1 CPS ≥ 5)	
	Zolbetuximab + mFOLFOX6 (n = 283)	**mFOLFOX6 (n = 282)**	**Zolbetuximab + CAPOX (n = 254)**	**CAPOX (n = 253)**	**Nivolumab + CAPOX/ FOLFOX (n = 473)**	**CAPOX/ FOLFOX (n = 482)**
Age (years), median	62.0	60.0	61.0	59.0	63.0	62.0
Male gender, %	62.2	62.1	62.6	61.7	70.0	72.0
Race, %						
White	53.6	53.0	37.0	36.0	75.0	76.0
Asian	36.8	38.3	62.0	62.0	25.0	24.0
ECOG, %						
0	44.8	41.4	42.7	43.2	41.0	42.0
1	54.8	58.6	57.3	56.8	59.0	58.0
2	< 1.0	0.0	0.0	0.0	< 1.0	< 1.0
Tumour location, %						
Oesophagus	0.0	0.0	0.0	0.0	12.0	13.0
GEJ	22.6	25.5	13.8	17.4	18.0	18.0
GC	77.4	74.5	86.2	82.6	70.0	69.0
HER2 status, %						
Positive	0.0	0.0	0.0	0	0.0	0.0
Negative	100.0	100.0	100.0	100.0	NR	NR
Unknown	0.0	0.0	0.0	0.0	NR	NR
CPS score, % [1]						
≥ 5	[redacted]	[redacted]	[redacted]	[redacted]	100.0	100.0

Based on Table 2 of response to the request for clarification[4]

	SPOTLIGHT (ITT)		GLOW (ITT)		CheckMate 649 (PD-L1 CPS ≥ 5)	
	Zolbetuximab + mFOLFOX6 (n = 283)	mFOLFOX6 (n = 282)	Zolbetuximab + CAPOX (n = 254)	CAPOX (n = 253)	Nivolumab + CAPOX/ FOLFOX (n = 473)	CAPOX/ FOLFOX (n = 482)
CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOX, epirubicin, oxaliplatin and capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; G/GEJ, gastric/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; mFOLFOX6, modified folinic acid in combination with fluorouracil and oxaliplatin. **Notes:** [1] The proportion of patients with PD-L1 CPS ≥ 5 refers to those for whom the PD-L1 CPS result was known.						

Table 3.33: PD-L1 CPS status of the SPOTLIGHT and GLOW trials for all randomised patients

PD-L1 CPS subgroup, n (%)	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 283)	Placebo + mFOLFOX6 (n = [redacted])	Zolbetuximab + CAPOX (n = [redacted])	Placebo + CAPOX (n = [redacted])
Patients with known CPS	[redacted]	[redacted]	[redacted]	[redacted]
Patients with unknown CPS	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients (%) by PD-L1 CPS group in patients with known CPS				
PD-L1 CPS <1	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥1	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS <5	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥5	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS <10	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS ≥10	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 1 of response to the request for clarification[4] CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin; n, number of patients; PD-L1, programmed death-ligand 1. **Notes:** PD-L1 CPS results outside the 24-month cut-slide stability window and patients' samples that were not tested were labelled as "unknown". PD-L1 CPS results were accepted for analysis if the CPS results were within the established cut-slide stability window of 24 months and the patient was randomised.				

3.3.1 Methods for non-proportional hazards network meta-analysis

Proportionality of hazards was assessed for OS and PFS for all trials and endpoints with an available K–Mr curve. Log-cumulative hazard plots were used to evaluate the validity of the proportional hazard (PH) assumption. A plot of Schoenfeld residuals against survival times was also created. A formal Schoenfeld statistical test was used to test this PH assumption. The results showed some evidence that the PH assumption did not hold for all studies, thereby supporting the use of non-PH methods for the ITC analysis.[1]

The company made the following statement:[1]

- *"First- and second-order fractional polynomial NMA models were explored initially. However, the first-order models provided a poor fit to all trials in the evidence base (for both OS and PFS), and there were convergence issues with the second-order models, meaning relative effects could not be reliably estimated. Notably, the less flexible first-order models could not accurately model the long-term plateau in survival observed in the trials – not only of the new agents (i.e. zolbetuximab and nivolumab), but also the chemotherapy arms, leading to validity concerns. Given that the second-order models did not provide reliable results, these analyses used spline NMA as an alternative, flexible modelling approach.*
- *NMAs using spline methods were preferred for all outcomes, as this type of survival model has been recognised by NICE to adequately capture complex shapes, facilitating more realistic estimations of hazard and survivor functions.*
- *Spline NMAs using one, two and three knots were explored for the primary analysis scenario. The best-fitting model for each endpoint and scenario was selected based on the deviance information criterion statistic.*
- *For both OS and PFS endpoints, this included:*
  - *The intention-to-treat (ITT; all-comers) population for the SPOTLIGHT and GLOW trials*
  - *The CPS ≥ 5 subgroup for the nivolumab trial CheckMate 649."*

The company further states that a sensitivity analysis was conducted for ITC by including the FAST trial CLDN18.2 ≥ 70% subgroup. The FAST trial was not included in the base-case of ITC because this FAST study used a different CLDN18.2 test when compared with the SPOTLIGHT and GLOW trials, and the infrequent use of the chemotherapy backbone EOX in the UK.[1]

3.3.2 Results of non-proportional hazards network meta-analysis

3.3.2.1 Progression-free survival

The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy. The HR, which ranged from [redacted], was reasonably constant over time from 0.5 year to 5 years.[1]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 5 over time from 0.5 year to 4 year. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 4 years.[1]

Table 3.34 shows the estimated HR over time (up to 5 years) for each treatment versus chemotherapy from the primary PFS analysis (3-knot model).

Table 3.34: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (3-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]
Constant HR*		[redacted]	[redacted]

Based on Table 12 of CS[1]
CrI, credible interval; CS = company submission; HR, hazard ratio; PFS, progression-free survival.
Notes: * Constant HRs are taken from the global NMA presented in Appendix D.1.5.

Figure 3.21 also shows the estimated HR over time (up to 5 years) for each treatment versus chemotherapy from the primary PFS analysis (3-knot model).

Figure 3.21: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (3-knot model)

Based on Figure 16 of CS[1]
CS, company submission; HR, hazard ratio; Nivo, nivolumab; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

3.3.2.2 Overall survival

The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy. The HR, which ranged from [redacted], was reasonably constant over time from 0.5 year to 5 years.[1]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy in patients with PD-L1 CPS ≥ 5. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.[1]

Table 3.35 shows the estimated HR over time (up to 5 years) from the primary analysis of OS (3-knot model).

Table 3.35: HRs over time for each treatment versus chemotherapy – primary analysis of OS (3-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]
Constant HR*		[redacted]	[redacted]

Based on Table 13 of CS[1]
CrI, credible interval; CS, company submission; HR, hazard ratio; OS, overall survival
Notes: * Constant HRs are taken from the global NMA presented in Appendix D.1.5.

Figure 3.22 shows the estimated HR over time (up to 5 years) from the primary analysis of OS (3-knot model).

Figure 3.22: HRs over time for each treatment versus chemotherapy – primary analysis of OS (3-knot model)

Based on Figure 17 of CS[1]
CS, company submission; HR, hazard ratio; Nivo, nivolumab; OS, overall survival; Zolbe, zolbetuximab.
Note: The analysis includes CPS subgroup (CPS ≥ 5) for the nivolumab trial.

3.3.3 Updated results of non-proportional hazards network meta-analysis

In responding to the EAG's request, the company provided updated NMA results based on the final data cut of the SPOTLIGHT and GLOW trials (dated 8 September 2023 and 12 January 2024, respectively) and the latest published data cut off of the CheckMate 649 trial (29 May 2023).[8]

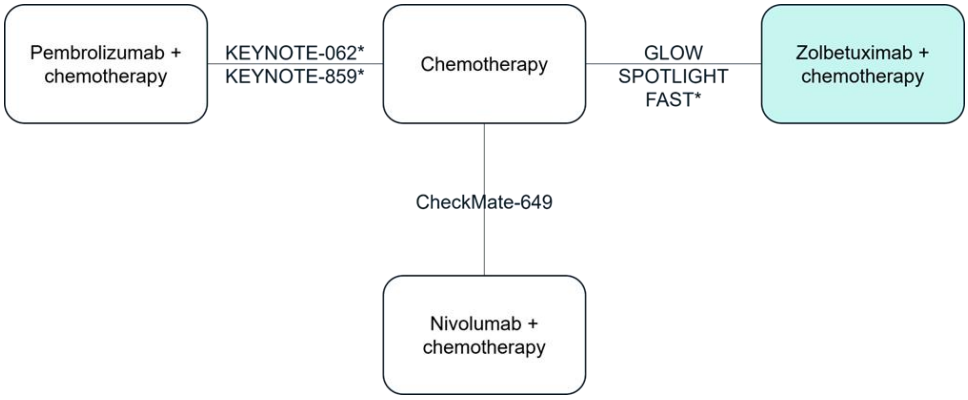
The company further stated that in order to inform the scenario including pembrolizumab in patients with PD-L1 CPS ≥ 1, an additional two trials were added to the updated NMA analysis: KEYNOTE-859 and KEYNOTE-062. Both trials investigated pembrolizumab plus chemotherapy versus chemotherapy.[8]

The company made the following statement:[8]

- *"All studies compared two treatment regimens: one of zolbetuximab, nivolumab or pembrolizumab in addition to chemotherapy, compared to chemotherapy with placebo. Under the assumptions that the new regimens' relative efficacy is similar irrespective of the chemotherapy backbone and irrespective of the chemotherapy comparator, a network can be formed with chemotherapy being the common comparator arm."*

Figure 3.23 shows the updated overall network diagram for the ITC analysis.[8]

Figure 3.23: Overall network diagram



Based on Figure 7 of the company response addendum[8]
CAPOX, capecitabine and oxaliplatin; CF, fluorouracil + cisplatin; CLDN18.2, claudin 18.2; CX, capecitabine + cisplatin; EOX, epirubicin + oxaliplatin + capecitabine; FOLFOX, folinic acid in combination with fluorouracil and oxaliplatin; PD-L1, programmed death-ligand 1.
Note: The chemotherapy node in the network represents CAPOX, FOLFOX, EOX, CF or CX. *FAST was explored in sensitivity analyses as EOX is used infrequently in the UK, and a different test method was used for CLDN18.2; KEYNOTE-062 and KEYNOTE-859 were explored in scenario analyses as pembrolizumab has had a licence extension to PD-L1 CPS ≥1 patients.

The updated NMA analysis used the same analysis approach as in the original CS. The company made the following statement:[8]

- *"Spline NMAs using one, two and three knots were explored for the primary analysis scenario. The best-fitting model for each endpoint and scenario was selected based on the deviance information criterion (DIC) statistic.*
- *For both OS and PFS endpoints, the primary scenario included:*
  - *The intention-to-treat (ITT; all-comers) population for the SPOTLIGHT and GLOW trials*
  - *The PD-L1 CPS ≥ 5 subgroup for the nivolumab trial CheckMate 649".*[8]

The company stated that scenario analyses were performed using the best-fitting model from the primary analysis.[8] The company further made the following statement in terms of a number of scenario analysis:[8]

- *"Include FAST (CLDN18.2 ≥ 70% population) was explored in a scenario analysis due to the different CLDN18.2 test used compared with SPOTLIGHT and GLOW, and the infrequent use of the chemotherapy backbone EOX in the UK*
- *Include the PD-L1 CPS ≥ 1 subgroup of the pembrolizumab trial KEYNOTE-859 and the ITT population of the pembrolizumab trial KEYNOTE-062 (as PD-L1 CPS ≥ 1 was an inclusion criterion).*
- *Include FAST (CLDN18.2 ≥ 70% population) and the relevant populations (see point 2 above) from pembrolizumab trials KEYNOTE-062 and KEYNOTE-859".*[8]

3.3.3.1 Progression free survival

Table 3.36 presents the deviance information criterion (DIC) per model (1, 2, 3 knots) for the primary analysis of PFS. There was little difference (< 5 points) in the DIC values between the 2- and 3-knot spline NMA results of the PFS outcome. This suggested that both models provided a similar fit to the data. Since the 2-knot spline model was a simpler model, the 2-knot spline model was selected as the base-case model.[8]

Table 3.36: DIC per model (1, 2, 3 knots) for the primary analysis of PFS

Number of knots	DIC
1	5,007.91
2	4,952.23
3	4,951.65

Based on Table of 16 of company response addendum[8]
DIC, deviance information criterion; PFS, progression-free survival.

Figure 3.24 shows the study-specific survival overlaid with the K-M curve for each trial in the primary analysis of PFS (2-knot model). The results suggested that the NMA model provides a good fit to the observed data for all trials.

Figure 3.24: Study-specific survival – primary analysis of PFS (2-knot model)

Based on Figure 8 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Table 3.37 shows the estimated HRs versus chemotherapy from 6 months to 5 years. The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy. The HR, which ranged from [redacted], was reasonably constant over time from 0.5 year to 5 years.[8]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 5. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.[8]

Table 3.37: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]

Based on Table 17 of company response addendum[8]
CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates reduced progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 3.25 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 3.25: HRs over time for each treatment versus chemotherapy – primary analysis of PFS (2-knot model)

Based on Figure 9 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Zolbe, zolbetuximab.
Note: Interpretation of HR plots for OS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649. The dashed lines show the empirical HRs estimated from the trial data.

3.3.3.1.1 Progression free survival: Include pembrolizumab trials (PD-L1 CPS ≥ 1) (2-knot model)

In responding to EAG's request, the company conducted additional NMA analysis by incorporating pembrolizumab trials (PD-L1 CPS ≥ 1).[4] Figure 3.26 shows the study-specific survival overlaid with the K-M curve for each trial in the scenario analysis of PFS including the relevant patient populations from the pembrolizumab trials (KEYNOTE-062 ITT and KEYNOTE-859 PD-L1 CPS ≥ 1 subgroup). The results indicate that the NMA model provides a good fit to the observed data for all trials.

Figure 3.26: Study-specific survival – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Based on Figure 12 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS≥1 subgroup) of the pembrolizumab trials.

Table 3.38 shows the estimated HRs versus chemotherapy at specific time points (from 6 months to 5 years). The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy. The HR, which ranged from [redacted], was reasonably constant over time from 0.5 year to 5 years.[8]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 5. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.[8]

In addition, the results showed that pembrolizumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 1. The HR, which ranged from [redacted] was also reasonably constant over time from 0.5 year to 5 years.[8]

Table 3.38: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Based on Table 19 of company response addendum
CPS, combined positive score; CrI, credible interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
Notes: HR < 1 indicates lower progression or death rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

Figure 3.27 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data.

Figure 3.27: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of PFS (2-knot model)

Based on Figure 13 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Pembro, pembrolizumab; Zolbe, zolbetuximab.

Notes: Interpretation of HR plots for PFS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS≥1 subgroup) of the pembrolizumab trials. The dashed lines show the empirical HRs estimated from the trial data.

3.3.3.2 Overall survival

Table 3.39 presents the DIC values for the 2- and 3-knot spline NMAs of OS. The DIC values for the 2- and 3-knot spline NMAs of OS were the same (to 1 decimal place). This suggested both models provided a similar fit to the data. Therefore, since the 2-knot spline model is a simpler model, the 2-knot spline model was selected as the base-case model.[8]

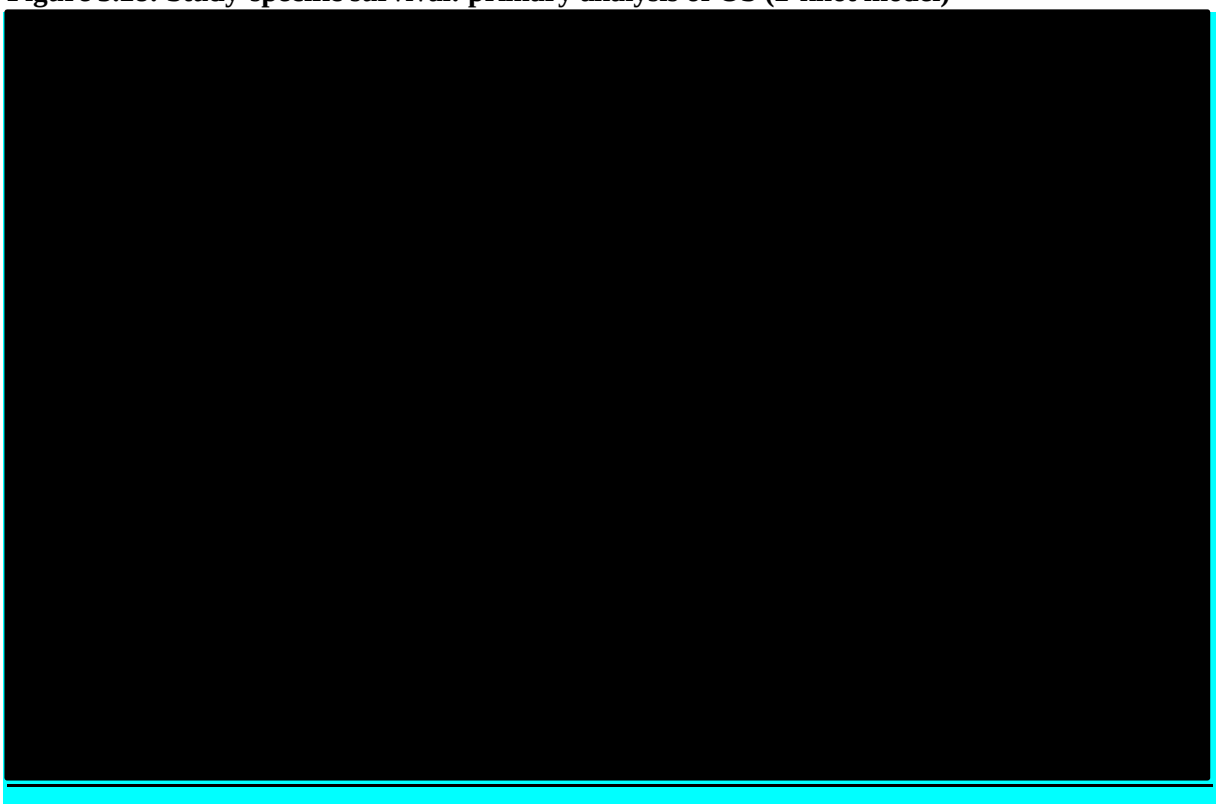
Table 3.39: DIC per model (1, 2, 3 knots) for the primary analysis of OS

Number of knots	DIC
1	5,530.15
2	5,471.51
3	5,471.52

Based on Table 21 of company response addendum[8]
DIC, deviance information criterion; OS, overall survival.

Figure 3.28 shows the study-specific survival overlaid with the K–M curve for each trial in the primary analysis of the OS outcome based on the 2-knot model. The results suggested that the 2-knot spline NMA model provided a good fit to the observed data.[8]

Figure 3.28: Study-specific survival: primary analysis of OS (2-knot model)



Based on Figure X of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; Nivo, nivolumab; OS, overall survival. PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649

Table 3.40 shows the estimated HRs versus chemotherapy at 6 months then yearly up to 5 years. The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy from 1 year to 5 years. The HR, which ranged from [redacted], was reasonably constant over time from 1 year to 5 years.[8]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy in patients with PD-L1 CPS ≥ 5 from 0.5 year to 5 years. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.[8]

Table 3.40: HRs over time for each treatment versus chemotherapy: primary analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy	
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5
26	0.5	[redacted]	[redacted]
52	1	[redacted]	[redacted]
104	2	[redacted]	[redacted]
156	3	[redacted]	[redacted]
208	4	[redacted]	[redacted]
260	5	[redacted]	[redacted]

Based on Table 22 of company response addendum[8]
CPS, combined positive score; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649.

Figure 3.29 shows the estimated HR over time for each treatment versus chemotherapy together with the empirical HRs estimated from the trial data based on the 2-knot model.

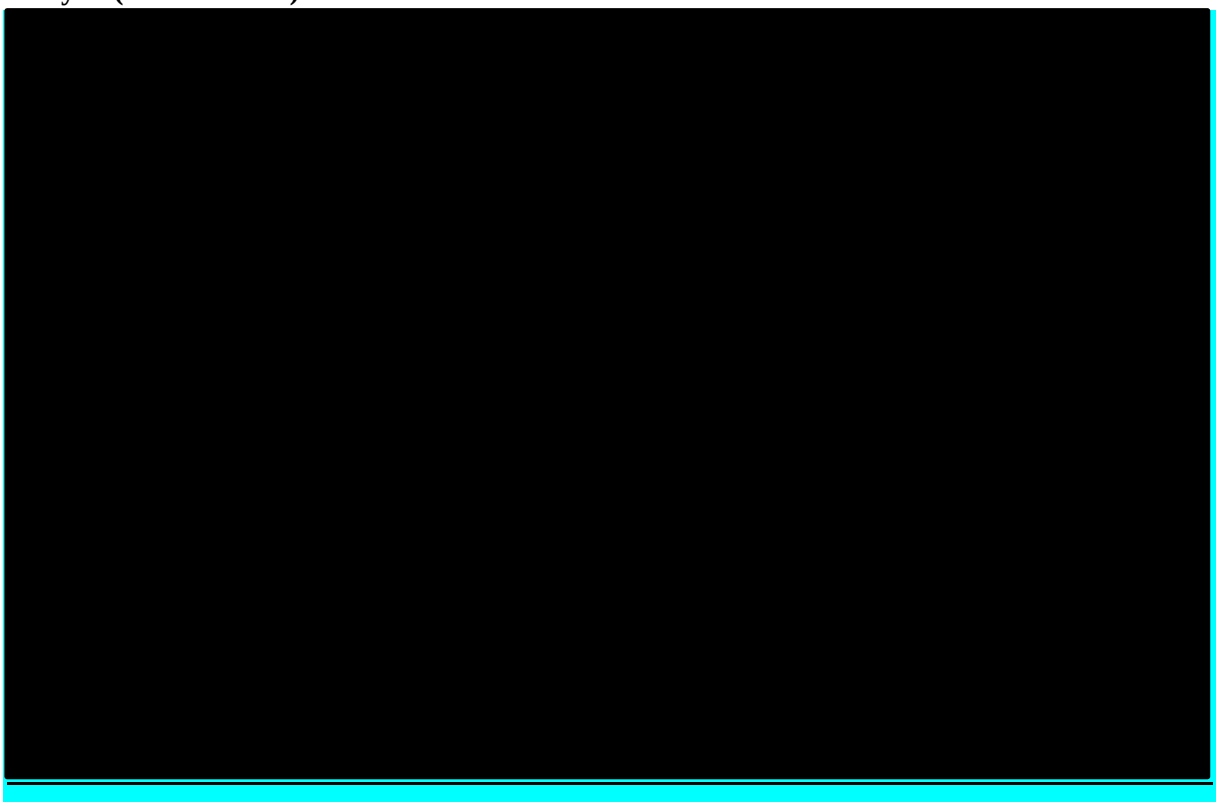
Figure 3.29: HRs over time for each treatment versus chemotherapy – primary analysis of OS (2-knot model)

Based on Figure 17 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; HR, hazard ratio; Nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab. Notes: Interpretation of HR plots for OS – the lower the curve the higher the efficacy of treatment versus chemotherapy. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649. The dashed lines show the empirical HRs estimated from the trial data.

3.3.3.2.1 Overall Survival: Include pembrolizumab trials (PD-L1 CPS ≥ 1)

Figure 3.30 shows the study-specific survival overlaid with the K–M curve for each trial in the OS scenario analysis including the relevant patient populations from the pembrolizumab trials of KEYNOTE-062 and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup). The results suggested that the 2-knot spline NMA model provided a good fit to the observed data.[8]

Figure 3.30: Study-specific survival – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis (2-knot model)



Based on Figure 20 of company response addendum[8]
CM-649, CheckMate 649; CPS, combined positive score; KN-062, KEYNOTE-062; KN-859, KEYNOTE-859; Nivo, nivolumab; OS, overall survival; Pembro, pembrolizumab; PD-L1, programmed death-ligand 1; Zolbe, zolbetuximab.
Note: The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

Table 3.41 shows the estimated HRs versus chemotherapy at specific time points (from 6 months to 5 years). The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy from 1 year to 5 years. The HR, which ranged from [redacted], was reasonably constant over time from 1 year to 5 years.[8]

The results further showed that nivolumab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy in patients with PD-L1 CPS ≥ 5 from 0.5 year to 5 years. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.[8]

The results also showed that pembrolizumab plus chemotherapy was associated with a statistically significant reduction in mortality rate compared with chemotherapy in patients with PD-L1 CPS ≥ 1 from 1 year to 5 years. The HR, which ranged from [redacted], was also reasonably constant over time from 1 year to 5 years.[8]

Table 3.41: HRs over time for each treatment versus chemotherapy – including pembrolizumab trials (PD-L1 CPS ≥ 1) scenario analysis of OS (2-knot model)

Time (weeks)	Time (years)	HR (95% CrI) versus chemotherapy		
		Zolbetuximab + chemotherapy	Nivolumab + chemotherapy CPS ≥ 5	Pembrolizumab + chemotherapy PD-L1 CPS ≥ 1
26	0.5	[redacted]	[redacted]	[redacted]
52	1	[redacted]	[redacted]	[redacted]
104	2	[redacted]	[redacted]	[redacted]
156	3	[redacted]	[redacted]	[redacted]
208	4	[redacted]	[redacted]	[redacted]
260	5	[redacted]	[redacted]	[redacted]

Based on Table 24 of company response addendum[8]
CPS, combined positive score; CrI, credible interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.
Notes: HR < 1 indicates lower mortality rate for each treatment versus chemotherapy. Results are considered statistically significant if the 95% CrI does not include 1. The analysis uses data from the PD-L1 CPS ≥ 5 subgroup of CheckMate 649 and the patients with PD-L1 CPS ≥ 1 of the KEYNOTE-062 (ITT) and KEYNOTE-859 (PD-L1 CPS ≥ 1 subgroup) of the pembrolizumab trials.

3.3.3.3 Uncertainties in the indirect and mixed treatment comparisons

The company discussed the uncertainties associated with the results of ITCs. The company stated that the updates to the NMA used the final data cuts of the SPOTLIGHT and GLOW trials, and the latest publicly available data of the Checkmate 649 PD-L1 CPS ≥ 5 subgroup.[8] The results from the updated NMA showed consistent results with those of the original analysis. The results showed that zolbetuximab plus chemotherapy had similar efficacy to nivolumab plus chemotherapy for PFS and OS outcomes in patients with PD-L1 CPS ≥ 5.[8]

The company further stated that the new scenario which compared zolbetuximab plus chemotherapy with pembrolizumab plus chemotherapy in patients with PD-L1 CPS ≥ 1 showed that their efficacy was similar in terms of PFS and OS outcomes.[8]

The company acknowledged that the analyses were conducted under a fixed effects framework, which may underestimate uncertainty (although this would not affect point estimates).[8] The company also acknowledged that the analyses assumed that the chemotherapy regimens (in the backbone and as a comparator) were equivalent to enable a connected network, this created uncertainty in the comparisons against pembrolizumab given the use of cisplatin in KEYNOTE-062.[8]

Furthermore, the company acknowledged that for the scenario including pembrolizumab in patients with PD-L1 CPS ≥ 1, the NMA results for pembrolizumab and nivolumab should be interpreted with caution given that the company used PD-L1 CPS ≥ 5 subgroup for nivolumab plus chemotherapy and PD-L1 CPS is an effect modifier for pembrolizumab and nivolumab.[8]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

EAG comment:

- The ITC base-case analysis in the company evidence submission was based on a NMA consisting of three RCTs (SPOTLIGHT, GLOW and CheckMate-649). Given that the data of the SPOTLIGHT and GLOW trial in the company evidence submission were not mature, the EAG requested the company to provide more mature data of the SPOTLIGHT and GLOW trial in the

clarification letter. In responding to the EAG's request, the company provided the updated results on the basis of the final data cut off dates of the SPOTLIGHT and GLOW trial at the clarification response stage. The updated results of OS and PFS based on the final data cut date of the SPOTLIGHT and GLOW trials were consistent with those results being presented in the company evidence submission. Following this the company also provided the updated results of ITC on the basis of final data cut dates of the SPOTLIGHT and GLOW trial during the clarification response stage.

- The ITC analysis in the company evidence submission did not include pembrolizumab plus chemotherapy as a comparator for patients whose tumours express PD-L1. However, the NICE final scope included pembrolizumab with chemotherapy (PD-L1 CPS ≥ 10 and PD-L1 CPS ≥1) as a comparator for patients whose tumours express PD-L1. In the CS, the company's decision problem excluded pembrolizumab plus chemotherapy as a comparator for the subgroup of patients with PD-L1 CPS ≥ 10 based on the lack of overlap between patients with gastric cancer/ GEJ adenocarcinoma who are eligible for both zolbetuximab with chemotherapy (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with PD -L1 CPS ≥ 10). However, it is unclear if the small overlap ([redacted]) between patients with gastric cancer/GEJ adenocarcinoma eligible for both zolbetuximab plus chemotherapy (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with PD-L1 CPS ≥ 10) would be similar to those in clinical practice. Given that the company excluded pembrolizumab plus chemotherapy as a comparator in their evidence submission, the EAG requested the company to provide further justification on this exclusion in the clarification letter.
- In responding to the EAG's request, the company provided additional NMA results by incorporating pembrolizumab plus chemotherapy as a comparator for patients with PD-L1 CPS ≥1 during the clarification response stage.
- The updated ITC base-case analysis being provided during the clarification response stage was based on a NMA consisting of three RCTs (SPOTLIGHT, GLOW and CheckMate-649) and two additional pembrolizumab RCTs (KEYNOTE-64 and KEYNOTE-859) were included in the scenario analysis. The updated ITC results were based on the final data cut off dates of the SPOTLIGHT and GLOW trials (8 September 2023 and 12 January 2024, respectively). The CheckMate-649 trial provided data of patients with PD-L1 CPS ≥ 5 who received the intervention of nivolumab with chemotherapy versus chemotherapy alone. The KEYNOTE-64 and KEYNOTE-859 trials provided data of patients with PD-L1 CPS ≥1 who received the intervention of pembrolizumab with chemotherapy versus chemotherapy alone.
- Given that the PHs assumptions for OS and PFS in the included populations may not be valid for studies in the ITC, the EAG considers that the time-varying method used by the company for ITC analysis seems to be an appropriate approach.
- The NICE final scope highlighted the subgroup of patients with PD-L1 CPS ≥ 5. However, the company provided data for the ITC analysis between the overall population of SPOTLIGHT and GLOW trials and the subgroup of patients with PD-L1 CPS ≥5 from the CheckMate-649 trial in the company evidence submission. Therefore, EAG requested the company to provide the results of ITC for the subgroup of patients with PD-L1 CPS ≥5 from all included trials in the clarification letter.
- In responding to the EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC analysis but the company used the overall population from the included trials (SPOTLIGHT and GLOW) in the ITC analysis.

- While the EAG acknowledged that the results of the post-hoc subgroup analysis should be treated with caution, it is important to ensure the comparability of patients' baseline characteristics between included trials for the purpose of NMA. The company used the overall population with mixed status of PD-L1 CPS from the zolbetuximab trials (SPOTLIGHT and GLOW) and the PD-L1 CPS ≥5 subgroup from the CheckMate-649 trial and the PD-L1 CPS ≥1 subgroup from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859) in the updated NMA.
- Heterogeneity of PD-L1 CPS status was observed for the included populations between SPOTLIGHT and GLOW trials and the PD-L1 CPS ≥ 5 subgroup in the CheckMate-649 trial. While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: [redacted]% in the zolbetuximab plus mFOLFOX6 arm versus [redacted]% in the placebo plus mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted]% in zolbetuximab plus CAPOX arm versus [redacted]% in the placebo plus CAPOX arm.[4] It should be noted that PD-L1 CPS might not be a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy. To show this, the company did present subgroup analyses for both GLOW and SPOTLIGHT for OS and PFS, one with a CPS threshold of 5 and the other with a CPS threshold of 1. For all analyses there was overlap of the 95% CIs for HR between the groups above and below the threshold. [redacted]
  Therefore, it appears that it is not entirely clear that PD-L1 status is not a treatment effect modifier.
- Furthermore, among those patients with known PD-L1 CPS of the SPOTLIGHT trial, [redacted]% of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus mFOLFOX6 arm while [redacted]% of patients had had PD-L1 CPS ≥ 1 in the placebo plus mFOLFOX6 arm. For those patients with known PD-L1 CPS of the GLOW trial, [redacted]% of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus CAPOX arm while [redacted]% of patients had PD-L1 CPS ≥ 1 in the placebo plus CAPOX arm.[4] However, all patients in the PD-L1 CPS ≥1 subgroups from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859) had PD-L1 CPS ≥ 1 in the updated NMA. Therefore, there was considerable heterogeneity in PD-L1 CPS status at baseline for the included populations between included trials in the updated NMA.
- Given that there was limited comparability of patients' baseline characteristics in terms of PD-L1 CPS status between included trials in the updated NMA (as acknowledged by the company), this limitation may have introduced uncertainties in the validity of ITC results.
- The EAG further notes that following the assessment of heterogeneity and uncertainty, the differences in the features of the trials (including different blinding methods: double blind for SPOTLIGHT, GLOW and KEYNOTE-859 versus open label for CheckMate-649) introduced limitations in the results of ITC. Therefore, given that there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC, there were uncertainties in the validity of ITC results.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification[1, 4, 5, 8] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of different treatments in patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction cancer. Searches were conducted in September 2020, with updates conducted in August 2022

and October 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings, websites and trials registers were searched. Overall, the EAG has no concerns about the literature searches conducted.

The study selection criteria for participants, interventions, comparators and outcomes in the systematic review of clinical effectiveness generally encompassed those specified by the NICE final scope.[2] Study selection was restricted to English language studies only and this may have meant that relevant evidence was missed. In addition, the restriction to RCTs only may have resulted in some relevant AE data that were overlooked.

The data extraction process was satisfactory and in line with recommended good practice in systematic reviews.[16]

The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The use of NICE-recommended checklist for RCT assessment of bias for included trials was appropriate.

Six unique RCTs were identified as being relevant to the NICE final scope. Two phase III RCTs (SPOTLIGHT and GLOW) provided the main source of evidence and one phase II RCT (FAST) provided additional source of evidence. Three additional RCTs (KEYNOTE-062, KEYNOTE-859 and CheckMate-649) provided comparative data for an ITC.

SPOTLIGHT was an international, phase III, double-blinded RCT that assessed the efficacy and safety of zolbetuximab in combination with chemotherapy in patients with untreated HER2-negative advanced or metastatic GC or GOJ adenocarcinoma whose tumours are CLDN18.2 positive.

Given that the data of the SPOTLIGHT trial in the company evidence submission were not mature, the EAG requested the company to provide more mature data of the SPOTLIGHT trial in the clarification letter. In responding to EAG's request, the company provided the updated results on the basis of the final data cut of 8 September 2023 of the SPOTLIGHT trial at the clarification response stage. The updated results of OS and PFS based on the final data cut date of the SPOTLIGHT trial were consistent with those results being presented in the company evidence submission.

Baseline variables in the SPOTLIGHT trial were generally comparable between the two treatment arms. At the final data cut date of 8 September 2023, OS was more favourable for zolbetuximab in combination with chemotherapy compared with chemotherapy for patients whose tumours are CLDN18.2 positive.

At the final data cut of 8 September 2023 of the SPOTLIGHT trial, IRC -assessed PFS was more favourable for zolbetuximab in combination with chemotherapy compared with chemotherapy in patients whose tumours are CLDN18.2 positive.

For the SPOTLIGHT trial, there were generally similar proportions of participants who experienced drug-related SAEs between the zolbetuximab with chemotherapy arm and the chemotherapy arm in patients whose tumours are CLDN18.2 positive.

GLOW was an international, phase III, double-blinded RCT that assessed the efficacy and safety of zolbetuximab in combination with chemotherapy in patients with untreated HER2-negative advanced or metastatic GC or GOJ adenocarcinoma whose tumours are CLDN18.2 positive.

Given that the data of the GLOW trial in the company evidence submission were not mature, the EAG requested the company to provide more mature data of the GLOW trial in the clarification letter. In responding to EAG's request, the company provided the updated results on the basis of the final data

cut of 12 January 2024 of the GLOW trial at the clarification response stage. The updated results of OS and PFS based on the final data cut date of the GLOW trial were consistent with those results being presented in the company evidence submission.

Baseline variables in the GLOW trial were generally comparable between the two treatment arms. At the final data cut of [redacted] for the GLOW trial, OS was more favourable for zolbetuximab in combination with chemotherapy compared with chemotherapy for patients whose tumours are CLDN18.2 positive.

At the final data cut of [redacted] for the GLOW trial, IRC-assessed PFS was more favourable for zolbetuximab in combination with chemotherapy compared with chemotherapy in patients whose tumours are CLDN18.2 positive.

For the GLOW trial, there were generally similar proportions of participants who experienced drug-related SAEs between the zolbetuximab with chemotherapy arm and the chemotherapy arm in patients whose tumours are CLDN18.2 positive.

The ITC base-case analysis was based on a NMA consisting of three RCTs (SPOTLIGHT, GLOW, CheckMate-649) and two additional pembrolizumab RCTs (KEYNOTE-64 and KEYNOTE-859) were included in the scenario analysis. The EAG requested the company to provide more mature data of SPOTLIGHT and GLOW trials in the clarification letter. In responding to EAG's request, the company provided the updated NMA results on the basis of the final data cut off dates of the SPOTLIGHT and GLOW trials (8 September 2023 and [redacted], respectively) during the clarification response stage. The CheckMate-649 trial provided data of patients with PD-L1 CPS ≥ 5 who received the intervention of nivolumab with chemotherapy versus chemotherapy alone. The KEYNOTE-62 and KEYNOTE-859 trials provided data of patients with PD-L1 CPS ≥1 who received the intervention of pembrolizumab with chemotherapy versus chemotherapy alone.

The NICE final scope highlighted the subgroup of patients with PD-L1 CPS ≥ 5. However, the company provided data for the ITC base-case analysis between the overall population of SPOTLIGHT and GLOW trials and the subgroup of patients with PD-L1 CPS ≥5 from the CheckMate-649 trial in the company evidence submission. Therefore, the EAG requested the company to provide the ITC results for the subgroup of patients with PD-L1 CPS ≥5 from all included trials.

In responding to EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, and because the company claimed that PD-L1 CPS does not affect outcomes for zolbetuximab with chemotherapy and chemotherapy alone, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC but the company used the overall population from the included trials (SPOTLIGHT and GLOW) in the ITC. However, the results of the subgroup analyses for OS and PFS for both trials show that it is unclear whether PD-L1 status is a treatment effect modifier.

While the EAG acknowledged that the results of the post-hoc subgroup analysis should be treated with caution, it is important to ensure the comparability of patients' baseline characteristics between included trials for the purpose of ITC. The company used the overall population with mixed status of PD-L1 CPS from the zolbetuximab trials (SPOTLIGHT, GLOW) and the PD-L1 CPS ≥5 subgroup from the CheckMate-649 trial and the PD-L1 CPS ≥1 subgroup from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859) in the updated NMA. Therefore, there was considerable heterogeneity in patients' PD-L1 CPS status at baseline between included trials in the updated NMA.

Fixed-effects models were used in the ITC analysis. As the PHs assumptions for OS and PFS in the included populations may not be valid for studies in the ITC, the EAG considers that the time-varying method used by the company for the ITC seems to be an appropriate approach.

As there was limited comparability of patients' baseline characteristics in terms of PD-L1 CPS status between included trials in the updated ITC analysis (as acknowledged by the company), this limitation introduced uncertainties in the results of ITC analysis. The EAG further notes that following the assessment of heterogeneity and uncertainty, the differences in the features of the trials (including different blinding methods: double blind for SPOTLIGHT, GLOW and KEYNOTE-859 versus open label for CheckMate-649) introduced limitations in the results of ITC analysis.

Given that there was a lack of sufficient evidence to support the assumption of exchangeability for the purpose of ITC, there were uncertainties in the validity of ITC results.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and resource use identification presented in the CS.[1, 5] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[6, 7] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provides details of an SLR was conducted to identify economic evaluation data from the published literature associated with patients with GC.[5] The searches were conducted in September 2020, with updates conducted in August 2022 and October 2023. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1980-2020 week 38 1980-2022 week 31 1980-2023 week 42	22.9.20 11.08.22 26.10.23
MEDLINE	Ovid	1946-21.9.20 1946-Aug Wk 1 2022 1946-25.10.23	22.9.20 11.8.22 26.10.23
The Cochrane Library (including CDSR, DARE and CENTRAL, HTA database, NHS EED)	Ovid	All years	23.9.20 11.8.22 26.10.23
EconLit	Ovid	1886-10.9.20 1886-4.8.22 1886-12.10.23	22.9.20 11.8.22 26.10.23
Additional resources			
CEA Registry	Internet	Not stated	5.10.20 10.10.22 1.11.23
RePEc	Internet	Not stated	5.10.20 10.10.22 1.11.23
EQ-5D Publications Database	Internet	Not stated	5.10.20 10.10.22 1.11.23
International HTA Database	Internet	Not stated	5.10.20 10.10.22 1.11.23
NIHR HTA	Internet	Not stated	5.10.20 10.10.22 1.11.23

Resource	Host/Source	Date Ranges	Date searched
HTA websites			
• NICE • SMC • CADTH	Internet	Not stated	5.10.20 10.10.22 1.11.23
Conferences			
• ASCO ICML • ESMO • ISPOR • IGCC • ASCO Gastrointestinal Cancers Symposium • ICML	Internet	2018-2023	8.10.20 8.9.22 31.10.23
CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; CENTRAL: Cochrane Central Register of Controlled Trials; HTA: Health Technology Assessment; NHS EED : NHS Economic Evaluation Database; CEA: Cost Effectiveness Analysis; RePEc: EconPapers within Research Papers in Economics; NIHR HTA: National Institute for Health and Care Research Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; CADTH: Canadian Agency for Drugs and Technology in Health; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; IGCC: International Gastric Cancer Association; ICML: International Conference on Malignant Lymphoma			

Appendix H of the CS provides details of an SLR was conducted to identify utility data from the published literature associated with patients with GC.[5] The searches were conducted in September 2020, with updates conducted in August 2022 and October 2023. A summary of the sources searched is provided in Table 4.2.

Table 4.2: Data sources searched for utility data (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1980-2020 week 38 1980-2022 week 31 1980-2023 week 43	22.9.20 09.08.22 30.10.23
MEDLINE	Ovid	1946-21.9.20 1946-8.8.22 1946-27.10.23	22.9.20 9.8.22 30.10.23
The Cochrane Library (including CDSR, DARE and CENTRAL, HTA database, NHS EED)	Ovid	All years	22.9.20 9.8.22 30.10.23
Additional resources			
CEA Registry	Internet	Not stated	5.10.20 10.10.22 1.11.23
RePEc	Internet	Not stated	5.10.20 10.10.22 1.11.23
EQ-5D Publications Database	Internet	Not stated	5.10.20

Resource	Host/Source	Date Ranges	Date searched
			10.10.22 1.11.23
International HTA Database	Internet	Not stated	5.10.20 10.10.22 1.11.23
NIHR HTA	Internet	Not stated	5.10.20 10.10.22 1.11.23
HTA websites			
• NICE • SMC • CADTH	Internet	Not stated	5.10.20 10.10.22 1.11.23
Conferences			
• ASCO ICML • ESMO • ISPOR • IGCC • ASCO Gastrointestinal Cancers Symposium	Internet	2018-2023	8.10.20 8.9.22 31.10.23

CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; CENTRAL: Cochrane Central Register of Controlled Trials; HTA: Health Technology Assessment; NHS EED : NHS Economic Evaluation Database; CEA: Cost Effectiveness Analysis; RePEc: EconPapers within Research Papers in Economics; NIHR HTA: National Institute for Health and Care Research Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; CADTH: Canadian Agency for Drugs and Technology in Health; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; IGCC: International Gastric Cancer Association; ICML: International Conference on Malignant Lymphoma

Appendix I of the CS provides details of an SLR conducted to identify cost and resource use data from the published literature associated with patients with GC. [5] The searches were conducted in September 2020, with updates conducted in August 2022 and October 2023. A summary of the sources searched is provided in Table 4.3.

Table 4.3: Data sources searched for cost and resource use data (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1980-2020 week 38 1980-2022 week 31 1980-2023 week 42	22.9.20 9.08.22 26.10.23
MEDLINE	Ovid	1946-21.9.20 1946-8.8.22 1946-25.10.23	22.9.20 9.8.22 26.10.23
The Cochrane Library (including CDSR, DARE and CENTRAL, HTA database, NHS EED)	Ovid	All years	22.9.20 9.8.22 26.10.23
EconLit	Ovid	1886-10.9.20	22.9.20

Resource	Host/Source	Date Ranges	Date searched
		1886-28.7.22 1886-12.10.23	9.8.22 26.10.23
Additional resources			
CEA Registry	Internet	Not stated	5.10.20 10.10.22 1.11.23
RePEc	Internet	Not stated	5.10.20 10.10.22 1.11.23
EQ-5D Publications Database	Internet	Not stated	5.10.20 10.10.22 1.11.23
International HTA Database	Internet	Not stated	5.10.20 10.10.22 1.11.23
NIHR HTA		Not stated	5.10.20 10.10.22 1.11.23
HTA websites			
• NICE • SMC • CADTH	Internet	Not stated	5.10.20 10.10.22 1.11.23
Conferences			
• ASCO ICML • ESMO • ISPOR • IGCC • ASCO Gastrointestinal Cancers Symposium	Internet	2018-2023	8.10.20 8.9.22 31.10.23

CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; CENTRAL: Cochrane Central Register of Controlled Trials; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Gastric Cancer Association; IGCC: International Gastric Cancer Association; WHO ICTRP: World Health Organization International Clinical Trials Registry; CEA: Cost Effectiveness Analysis; RePEc: EconPapers within Research Papers in Economics; HTA: CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; CENTRAL: Cochrane Central Register of Controlled Trials; HTA: Health Technology Assessment; NHS EED : NHS Economic Evaluation Database; CEA: Cost Effectiveness Analysis; RePEc: EconPapers within Research Papers in Economics; NIHR HTA: National Institute for Health and Care Research Health Technology Assessment; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; CADTH: Canadian Agency for Drugs and Technology in Health; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; IGCC: International Gastric Cancer Association; ICML: International Conference on Malignant Lymphoma

EAG comment:

- Searches was undertaken in September 2020, with updates conducted in August 2022 and October 2023 to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in

patients with GC. The CS, Appendices G-H and the Company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[1, 4, 5, 8]

- In addition to bibliographic database searches, a good range of Health Technology Assessment (HTA) organisation websites, grey literature resources and conferences proceedings were searched. Reference checking was conducted.
- Searches were well-structured, transparent and reproducible, and employed comprehensive use of both subject headings (MeSH/EMTREE) and free-text terms.
- Database searches were limited to studies published since 2000. Searches were not limited by language of publication.
- Conference proceedings were hand-searched for five key international conferences between 2018 and 2023. In addition to this, conference proceedings will have been retrieved by the Embase and CENTRAL searches.
- The cost effectiveness searches contained a population facet for GC. This was then combined with an intervention/comparator facet for zolbetuximab/comparators, and a study design filter containing terms for economic evaluations.
- The HRQoL searches contained a population facet for GC. This was then combined with a study design filter containing terms for HRQoL.
- The cost/resource use searches contained a population facet for GC. This was then combined with a study design filter containing terms for cost and resource use.
- None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

4.1.1 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies are presented in Table 4.4. For inclusion and exclusion criteria used for the identification of HRQoL studies and costs and resource use studies, see CS Appendix Tables 49 and 63.

Table 4.4: Eligibility criteria for the SLR

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (≥18 years) with pathologically-confirmed advanced gastric or GEJ adenocarcinoma	< 18 years of age Patients with any other disease Studies with mixed patient populations will be included if ≥ 80% of patients are eligible, or if eligible subgroups are reported
Intervention & comparators	Zolbetuximab mFOLFOX6 CAPOX (capecitabine) Cisplatin + 5-FU (fluorouracil) Oxaliplatin + 5-FU (fluorouracil) Cisplatin + capecitabine	Treatments not listed Non-pharmacological therapies

	Inclusion criteria	Exclusion criteria
	ECX (epirubicin, cisplatin, capecitabine) ECF (epirubicin, cisplatin, fluorouracil) EOX (epirubicin, oxaliplatin, capecitabine) EOF (epirubicin, oxaliplatin, fluorouracil) DCF (docetaxel, cisplatin, 5-FU) FOLFIRI (folinic acid, fluorouracil, irinotecan) FLOT (folinic acid, fluorouracil, oxaliplatin, docetaxel) Pembrolizumab Nivolumab (OPDIVO®) Ipilimumab (Yervoy®) Tislelizumab Pamiparib Bemarituzumab Avelumab (Bavencio®) Durvalumab* Toripalimab* Sintilimab* Spartalizumab* Camrelizumab* BSC Placebo	
Outcomes	ICERs Summary health outcomes (e.g. QALYs, LYG) Model summary (including perspective, time horizon and discounting) and structure Assumptions underpinning model structures Sources of clinical, cost and quality of life (transition probabilities) inputs Utilities derived using generic preference-based instruments (e.g. EQ-5D) for relevant health states	Outcome(s) not listed

	Inclusion criteria	Exclusion criteria
	Direct utility estimates (e.g. standard gamble, time trade off)	
Study design	Cost-effectiveness analysis (CEA) Cost-utility analysis (CUA) Cost-minimisation analysis (CMA) Cost-consequence analysis (CCA) Cost-benefit analysis (CBA)	Other study designs
Language	English language publications	Non-English language studies
Geography	No restriction	-
Date of publication	Last 20 years (2000– present)	Studies published prior to 2000
Table 31 of the CS Appendix[5] CS = company submission		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationale for excluding studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Fully incremental results were not included
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with reference case
Synthesis of evidence on health effects	Based on systematic review	In line with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	In line with reference case

Element of HTA	Reference case	EAG comment on CS
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with reference case
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	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

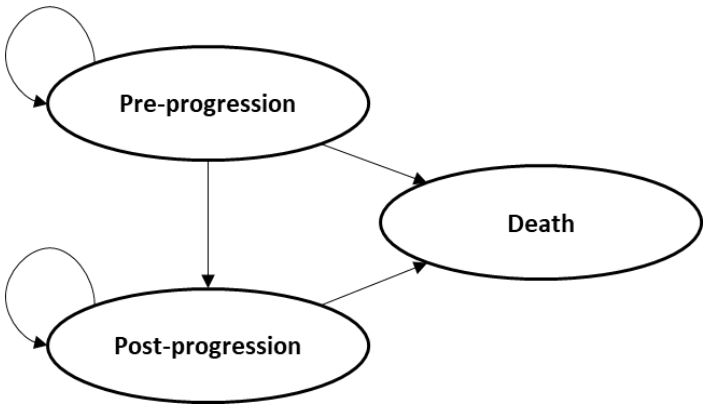
CS: company submission; EAG: Evidence Assessment Group; EQ-5D: EuroQol-5D; NHS: National Health Service; HTA: Health Technology Assessment; HRQoL: health-related quality of life; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services; QALY: quality adjusted life year; UK: United Kingdom.

4.2.2 Model structure

The CEA model used a three-state partitioned survival modelling approach. The model comprises three mutually exclusive health states: pre-progression, post-progression, dead. The model was programmed in MS Excel.

The partitioned survival modelling approach was selected because, amongst other considerations, it aligned well with the trial endpoints (PFS and OS).

Figure 4.1: Model structure



Based on Figure 18 of the CS[1]
CS = company submission

EAG comment: The NICE Decision Support Unit (DSU) Technical Support Document (TSD)19[17] recommends that state transition modelling be performed alongside partitioned survival analyses to assist in verifying the plausibility of the extrapolations. However, the EAG agrees with the company's assessment that the partitioned survival analysis approach is likely the most suitable to capture the disease, given the collected data on mortality and time to progression, and considers the company's model structure acceptable.

4.2.3 Population

Marketing authorisation had not yet been obtained at the date of the CS. The population included in the company's model was adult patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJC adenocarcinoma who have not previously been treated for advanced/metastatic disease with chemotherapy. CLDN18.2-positive was defined as patients' tumours expressing CLDN18.2 in ≥ 75% of tumour cells, demonstrating moderate-to-strong membranous staining as determined by central IHC testing. HER2-negativity is determined by local or central testing on a G/GEJC tumour specimen.

In accordance with the modelled population, the key trials, SPOTLIGHT[13] and GLOW[14], both included patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma. In both trials, patients were previously untreated. The phase II FAST study[15] included patients with advanced G/GEJ or oesophageal adenocarcinoma with moderate-to-strong CLDN18.2 expression in ≥ 40% tumour cells. CheckMate649[18] included previously untreated patients with unresectable advanced or metastatic HER2-negative, G/GEJ, or oesophageal adenocarcinoma, regardless of PD-L1 expression.

The key baseline patient characteristics in the economic model are listed in Table 4.6 below.

According to the company, the overall population consists of potentially distinct sub-populations for patients whose tumours express PD-L1, and according to the company have a:

- PD-L1 CPS ≥ 5
- CPS of 10 or more and for GEJ adenocarcinoma only
- CPS 1 or more and for gastric or GEJ adenocarcinoma – subject to NICE evaluation

The company performed a primary analysis on the whole population, and secondary analysis on the subgroup of patients whose tumours express PD-L1 (PD-L1 CPS ≥ 5). Note that the only comparator in the primary analysis was chemotherapy and both chemotherapy and nivolumab + chemotherapy were comparators in the secondary analysis. For both primary and secondary analyses, the company used the ITT populations from SPOTLIGHT and GLOW to inform the effectiveness of zolbetuximab. The company considered this appropriate also for the secondary analysis for the following three reasons:

- PD-L1 expression was not considered a prognostic factor or treatment effect modifier for chemotherapy according to literature
- The company is not aware of any biological mechanism by which PD-L1 status can affect the efficacy of zolbetuximab
- PD-L1 CPS was not a pre-specified subgroup analysis, and approximately one third of the patients enrolled in the trials could not be tested for PD-L1 CPS.

Table 4.6: Key baseline patient characteristics used in the economic model for primary and secondary analysis

Patient characteristics	Value	Measurement of uncertainty and distribution (SD)	Reference/source
Starting age (years)	58.50	12.49	SPOTLIGHT and GLOW
Proportion female (%)	37.9%	N/A	SPOTLIGHT and GLOW
Average patient weight (kg)	63.08	14.38	SPOTLIGHT and GLOW
Body surface area (m^2)	1.70	0.22	SPOTLIGHT and GLOW
Table 15 of the CS[1]			

EAG comment: The main concerns of the EAG relate to: a) the subpopulations that could be considered and b) the generalisability of the baseline characteristics to UK clinical practice.

a) The EAG notes that the subpopulations mentioned are not a requirement of the scope and that PDL-1 status might not be a treatment effect modifier for zolbetuximab nor chemotherapy (see Section 3.4). These subpopulations have been explored because of the availability of different comparators. As such, the EAG's critique of these subpopulations is located in Section 4.2.4.
b) Baseline characteristics of SPOTLIGHT and GLOW may not be generalisable to UK clinical practice. The age may be younger than that observed in the UK population as in Technology Assessment (TA) 857, a starting age of 64.15 was preferred by the committee, which was based on Cancer Research UK data. The impact of the starting age on model outcomes is, however, minimal. BSA in the CS may also not be representative of UK population as it differed from the one used in TA 857 (1.77 m^2). The company, in response to clarification question B21, provided the breakdown of BSA of the UK patients in SPOTLIGHT and GLOW, which was indeed higher than the average at [redacted] m^2 and [redacted] m^2 respectively (Table 17 of the response to POC), although sample sizes were small. The company also referenced data presented in ID4030 from a "large cancer centre in London" which reported similar BSA to the one in SPOTLIGHT and GLOW. However, the EAG wonders whether London is representative of the whole population. The company explored the impact of using an increased mean BSA of 1.73 m^2 in a scenario and found the impact to be limited. The EAG considers that the estimate for BSA of 1.77 m^2 used in TA857 may be more generalisable and used this in the EAG base-case.

4.2.4 Interventions and comparators

The model compares zolbetuximab + fluoropyrimidine- and platinum-based combination chemotherapy ('chemotherapy' for short) with chemotherapy alone. Chemotherapy could be CAPOX or FOLFOX. For effectiveness, the company pooled SPOTLIGHT and GLOW and therefore implicitly assumed an approximate 50/50 CAPOX/FOLFOX split. For cost calculations all patients received CAPOX as the chemotherapy backbone for zolbetuximab, and for the chemotherapy regimen as a comparator – given that (1) CAPOX is less costly than FOLFOX, and (2) clinical feedback and the conclusion of TA857[9] indicate that most patients receive CAPOX. The detailed dosing schedules were outlined in the CS and were in line with the CSRs of SPOTLIGHT and GLOW for zolbetuximab and with the summary of product characteristics (SmPC) for nivolumab.

The NICE scope listed the following comparators:

- Chemotherapy only, including doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin
- For patients whose tumours express PD-L1:
    - Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)
    - Pembrolizumab with chemotherapy (with CPS of 10 or more and for gastro-oesophageal junction adenocarcinoma only)
    - Pembrolizumab with chemotherapy (with CPS 1 or more and for gastric or GEJ adenocarcinoma – subject to NICE evaluation)

The company used chemotherapy only as comparator in their primary analysis. For their secondary analysis, in the subgroup of patients whose tumours express PD-L1 (PD-L1 CPS ≥ 5), the company provided a cost comparison with nivolumab + chemotherapy. A cost comparison was performed because *"nivolumab is considered broadly equivalent to zolbetuximab"*[1]. The company justified the selection of the comparators considered by stating that biomarker analysis of SPOTLIGHT and GLOW showed a small overlap ([redacted]) between patients with GC/GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10) and that no recommendation had been made on pembrolizumab with chemotherapy in patients with CPS ≥ 1 (NICE [ID4030][10]). No comparison with pembrolizumab was provided in the original submission.

For zolbetuximab no treatment stopping rule is recommended. However, for nivolumab and oxaliplatin stopping rules are in place for 2 years and 24 weeks respectively..

EAG comment: The main concern of the EAG is around the appropriate comparators and analysis types in the different subpopulations. As can be seen in Table 4.7, different comparators would be appropriate in different sub-populations, most notably nivolumab and pembrolizumab are appropriate comparators in some subpopulations:

- CPS ≥ 1 gastric and GEJ: this is a subgroup of patients with a currently ongoing NICE appraisal (ID4030) on pembrolizumab. In response to clarification question B3, the company provided a cost effectiveness analysis in this subgroup, but using effectiveness estimates from the zolbetuximab ITT population as PD-L1 CPS status was not measured in all patients in SPOTLIGHT and GLOW, and PD-L1 status is not a known treatment effect modifier for zolbetuximab. The company state that the NMA that this comparison is based on may underestimate the comparative efficacy of zolbetuximab + chemotherapy as a higher proportion of patients with higher PD-L1 CPS status are likely to have been included in the KEYNOTE trials than would be in the cohort of patients who in clinical practice are considered for zolbetuximab + chemotherapy. As such, the company expect the cost effectiveness analysis to be conservative and instead assumed equal effectiveness, resulting in [redacted] for zolbetuximab versus pembrolizumab (Table 70 in the addendum to the response to clarification letter).[8] It is also important to note that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators (see below).
- CPS ≥ 10 gastric: in this population, nivolumab is recommended by NICE. According to the company, zolbetuximab is unlikely to be used in this subgroup unless nivolumab is contraindicated. Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers that the company should provide further clarification on whether zolbetuximab should not be used in this population unless nivolumab is contra-indicated.
- CPS ≥ 10 GEJ: in this population, nivolumab and pembrolizumab are recommended. According to the company, zolbetuximab is unlikely to be used in this subgroup unless nivolumab or

pembrolizumab are contraindicated. A comparison against pembrolizumab has not been provided by the company despite the EAG's request in clarification question B3. Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers as above that the company should provide further clarification on whether zolbetuximab should not be used in this population unless nivolumab or pembrolizumab is contra-indicated.

- CPS ≥ 5 and <10 gastric and GEJ: in this population, the available comparators are chemotherapy and nivolumab and cost effectiveness is explored in the secondary analysis. The EAG requested a cost effectiveness analysis for the comparison between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5. The company provided a cost-effectiveness analysis where equal effectiveness for PFS and OS was assumed, with differences only in adverse events, leading to a minimal QALY difference. The company argued that the relative effectiveness estimate from the NMA was possibly biased in favour of nivolumab because the proportions of patients with higher CPS status were expected to be higher in CheckMate trials than in clinical practice – and that at a CPS status ≥ 10, checkpoint inhibitors would be preferred unless otherwise indicated. The company concluded *"that an NMA that compares zolbetuximab to nivolumab based on CheckMate 649 CPS ≥ 5 subgroup data is likely to overestimate the efficacy of nivolumab in the patient population likely to be considered for both treatments."* (clarification response B3). The EAG considers that this would imply that zolbetuximab should not be used in the population with PD-L1 CPS ≥ 10 unless checkpoint inhibitors are contra-indicated and would like further clarification and justification on this from the company. If this holds, the NMA may indeed be conservative for zolbetuximab. The EAG uses the cost effectiveness analysis in its base-case secondary analysis.
- CPS <5 gastric and GEJ: in this population, the available comparator is only chemotherapy. The evidence from SPOTLIGHT and GLOW broadly matches this population (as PD-L1 CPS status might not be a treatment effect modifier and, if it is, the treatment effect is probably higher for low CPS (see Section 3.4)) and this is therefore the population of interest for the EAG base-case primary analysis.

In summary, there are distinct analyses that can be performed, with each including different comparators and slight variations in the subpopulations of interest. The EAG's primary analysis differs slightly from the company's in that the EAG considers this analysis to be restricted only to CPS <5 gastric and GEJ, as above that, nivolumab would be an appropriate comparator and this is explored in the secondary analysis. Tertiary analysis in patients with CPS ≥ 10 status may be relevant conditional on the company's response. Quarternary analysis in patients with CPS ≥ 1 gastric and GEJ may become relevant if pembrolizumab were to be recommended for this subpopulation.

Table 4.7: Appropriate treatments per subpopulation (given PD-L1 status)

PD-L1 status	Chemotherapy	Nivolumab + chemotherapy	Pembrolizumab + chemotherapy	Zolbetuximab + chemotherapy	EAG comments
CPS ≥ 1 gastric and GEJ	X	-	?	X	Pembrolizumab is subject to NICE evaluation. This is also inappropriate given overlap between subgroup where nivolumab + chemotherapy and pembrolizumab + chemotherapy are comparators and where they are not comparators.
CPS ≥ 10 gastric	X	X	-	?	Eligibility for zolbetuximab to be confirmed.
CPS ≥ 10 GEJ	X	X	X	?	Eligibility for zolbetuximab to be confirmed.
CPS ≥ 5 and <10 gastric and GEJ	X	X	-	X	Secondary analysis: fully incremental cost effectiveness analysis results should be provided.
CPS < 5 gastric and GEJ	X	-	-	X	Primary analysis.

CPS: combined positive score, EAG: Evidence Assessment Group; GEJ: gastro-oesophageal junction; NICE: National Institute for Health and Care Excellence; PD-L1: programmed death ligand 1

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 4 weeks with a lifetime time horizon (40 years) and a half-cycle correction is applied.

EAG comment: No comment.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used are:

Zolbetuximab + chemotherapy: the SPOTLIGHT (chemotherapy regimen FOLFOX) and GLOW (chemotherapy regimen CAPOX) trials.[19, 20]

Nivolumab + chemotherapy: the CheckMate 649 trial PD-L1 CPS ≥ 5 subgroup (chemotherapy regimens were FOLFOX and CAPOX).[21]

Chemotherapy alone: the SPOTLIGHT (chemotherapy regimen FOLFOX), GLOW (chemotherapy regimen CAPOX) and CheckMate 649 PD-L1 CPS ≥ 5 subgroup (chemotherapy regimens were FOLFOX and CAPOX) trials.[19-21] In the CS[1], chemotherapy outcomes were obtained by pooling evidence from the SPOTLIGHT, GLOW, and CheckMate 649 trials, to increase the sample size for statistical estimation and to increase follow up (as the CheckMate-649 trial had longer follow-up compared to the SPOTLIGHT and GLOW trials). Assuming equivalent effectiveness outcomes for chemotherapy regimens was also done in TA857[9] and the ongoing ID4030.[10] After clarification, the company provided more detail on the pooling method: "*the survival curves from CheckMate 649 trial were digitised and the individual level data recreated using the Guyot et al*.[22] *algorithm. Data were pooled by combining the patient-level data from GLOW, SPOTLIGHT, and the recreated data from CheckMate 649 into a single dataset. No adjustment for differences in patient characteristics was made given the numerical differences in survival outcomes are expected to be due to chance*." [4]

The main outcomes regarding treatment effectiveness were OS and PFS. The survival extrapolation approach was informed by good practice guidance for selecting survival models to inform economic evaluations of cancer immunotherapies[23]. The methods used to decide on the best extrapolation approach were: review of external data to understand the likely shape of the survival curves, assessment of the proportional hazards assumption, examination of the shape of the hazard function and consideration of expert beliefs in TA857.[9] Various standard survival distributions were assessed (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, Weibull), and in addition spline modelling was considered.

4.2.6.1 Extrapolation of overall survival

Survival curves were only fitted to the pooled chemotherapy group, as the company used time-varying relative treatment effects from the NMA to obtain the OS curves for zolbetuximab + chemotherapy and nivolumab + chemotherapy. The company considered standard parametric survival models and more flexible spline models for the base-case because of the expectation of a small proportion of long-term survivors, which, as they stated, suggested a complex survival curve. The proportional hazards assumption was not tested as survival models were only fitted to the chemotherapy group. Of the standard parametric models, the company selected a log-logistic distribution based on the lowest AIC and BIC values (Table 45 Addendum to Response to clarification letter) and visual inspection of the hazard plots (Figure 28 Addendum to Response to clarification letter). The company subsequently argued that *"visually the log-logistic distribution may overestimate hazard rates compared to the*

empirical hazards, hence the log-logistic distribution may underestimate survival with chemotherapy in the longer term. This prompted the exploration of spline-based survival models.".[8] The company stated that all spline-based models provided visually good fits to the majority of the observed data (Figure 29 Addendum to Response to clarification letter). Based on AIC and BIC values (Table 47 Addendum to Response to clarification letter) the company concludes that: *"Based on AIC, the 3-knot hazard has the best fit, with near-identical values for the other 3-knot models. The BIC favours more parsimonious models, with the 1-knot odds having the lowest score, followed by the 2-knot hazard. However, the 3-knot models are the only models to adequately capture survival in the tail of the Kaplan-Meier, suggesting that these are the most appropriate to use for extrapolation"*.[8]

For zolbetuximab + chemotherapy and nivolumab + chemotherapy, the OS curves were obtained by applying time-varying relative treatment effects to the chemotherapy outcomes based on the 2-knot spline NMA. NMA results of zolbetuximab + chemotherapy were also used for nivolumab + chemotherapy.

The company also presented a scenario in which only evidence from the SPOTLIGHT and GLOW trials is used to extrapolate OS. The pooled individual patient data from both trials was used to fit standard parametric models to the two trial arms (zolbetuximab + chemotherapy and chemotherapy alone). To test the proportional hazards assumption, the company presented a Schoenfeld plot and a log-log cumulative hazards plot. The company stated that *"there is uncertainty in the appropriateness of the proportional hazards assumption, as the log-log cumulative hazard plot shows potential convergence"*.[8] Therefore, separate models were fitted for the chemotherapy and zolbetuximab + chemotherapy arm. For chemotherapy, the company selected the gamma model as the best fitting, based on lowest AIC and BIC values. For zolbetuximab + chemotherapy a log-logistic model was chosen, based on lowest AIC and BIC values.

4.2.6.2 Extrapolation of progression free survival

Survival curves were only fitted to the pooled chemotherapy group, as the company used time-varying relative treatment effects from the NMA to obtain the PFS curves for zolbetuximab + chemotherapy and nivolumab + chemotherapy. The company considered standard parametric survival models and more flexible spline models for the base-case. The proportional hazards assumption was not tested as survival models were only fitted to the chemotherapy group. Of the standard parametric models, the company selected a log-logistic distribution based on the lowest AIC and BIC values (Table 52 Addendum to Response to clarification letter). The company stated that *"as with the OS parametric models, the visual comparison between the empirical hazard and the estimated hazard suggests that all the parametric curves, including the log-logistic, overestimate hazard rates from around 2-years onwards."* The company stated that *"as with OS, the 3-knot spline models give best fit to tail, with little difference in estimates between these three models. For both AIC and BIC, the two best-fitting models from both measures are always the 3-knot odds followed by the 3-knot normal, with the 3-knot hazard also within one point of the best-fitting model. Collectively, this supports the use of a 3-knot model. (…) Hence, the 3-knot odds spline model is used in the base-case."*.[8]

For zolbetuximab + chemotherapy and nivolumab + chemotherapy the PFS curves were obtained by applying time-varying relative treatment effects to the chemotherapy outcomes based on the 2-knot spline NMA. NMA results of zolbetuximab + chemotherapy were also used for nivolumab + chemotherapy.

Similar to OS, the company presented a scenario in which only evidence from the SPOTLIGHT and GLOW trials is used to extrapolate PFS. To test the proportional hazards assumption, the company presented a Schoenfeld plot and a log-log cumulative hazards plot. The company stated that *"As with OS, convergence of the log-log cumulative hazard plot for PFS suggests that an assumption of*

proportional hazards may not be met." Therefore, separate models were fitted for the chemotherapy and zolbetuximab + chemotherapy arm. For both zolbetuximab + chemotherapy and chemotherapy, the company selected the log-logistic model as the best fitting, based on lowest AIC and BIC values. However, the company states that *"all models notably fail to capture the observed plateau that occurs at the end of follow-up. This is likely due to a combination of insufficient follow-up to reliably estimate the long-term survival, low patient numbers, and insufficiently flexible survival models. These limitations are all addressed by the use of flexible spline-based models and the incorporation of external evidence from CheckMate 649".*[8]

4.2.6.3 Treatment effect waning

In the base-case, the company considers treatment effect waning on OS and PFS for nivolumab only. The rationale is that nivolumab has a 2-year treatment stopping rule, and consequently patients are likely to experience treatment waning. These treatment waning assumptions for nivolumab were based on TA857.[9] The company argued that zolbetuximab does not have a time-based stopping rule and there is no evidence that the observed treatment effect would reduce over time, therefore the company considered treatment waning to not be applicable.

4.2.6.4 Extrapolation of duration of treatment

Evidence on duration of treatment (DoT) over time was available from both SPOTLIGHT and GLOW trials, but not from the CheckMate 649 and KEYNOTE trials. Hence, the company stated it was not possible to use pooled DoT from all trials. The company reasoned that there will be an association between DoT and PFS and found *"close agreement between GLOW PFS and the pooled PFS for the start of follow-up, when the majority of patients are at risk"*. Therefore, the GLOW DoT curves were selected to represent the pooled DoT curves. In the CS, the company selected the Weibull model to extrapolate GLOW DoT. Modelled DoT was capped to ensure modelled PFS was not exceeded "*given that zolbetuximab treatment should be discontinued upon progression*" (clarification response B12). For zolbetuximab + chemotherapy and nivolumab + chemotherapy, the DoT curves were obtained by applying time-varying relative treatment effects to the chemotherapy outcomes based on the 2-knot spline NMA for PFS. For nivolumab, a 2-year stopping rule was implemented.

EAG comment: The main concerns of the EAG relate to: a) including the CheckMate 649 trial to estimate chemotherapy outcomes, b) varying relative effectiveness of zolbetuximab as compared to CPI comparators depending on PD-L1 CPS, c) most appropriate extrapolations curves to estimate treatment effectiveness in the PD-L1 CPS populations, d) curves used and implementation of duration of treatment in the model, and e) treatment effect waning.

a) The company pools the trial data from the SPOTLIGHT and GLOW trials to estimate treatment effectiveness of zolbetuximab + chemotherapy. For the chemotherapy arm, they also use the CheckMate 649 trial: *"the survival curves from CheckMate 649 trial were digitised and the individual level data recreated using the Guyot et al. algorithm."* After clarification, the company provided more detail on their pooling method: *"Data were pooled by combining the patient-level data from GLOW, SPOTLIGHT, and the recreated data from CheckMate 649 into a single dataset. No adjustment for differences in patient characteristics was made given the numerical differences in survival outcomes are expected to be due to chance."* The EAG deems this method to be inappropriate because there was no adjustment for differences in patient characteristics nor differences between trials. Moreover, the data from the CheckMate 649 trial was recreated, adding to the uncertainty in the estimates. The benefit of using CheckMate 649 is mainly in the longer follow-up of the trial, as the maximum follow-up in the chemotherapy arm is increased from approximately 4 to 5 years by including this trial. This results in different extrapolations of the survival curves, with slightly better 5-year and 10-year OS estimates

(Table 4.8). Real world evidence[24-29] supports the existence of a small proportion of long-term survivors and in TA857 clinical experts indicated that *"about 4% of people could be expected to achieve long-term remission with chemotherapy"*[9]..

Table 4.8: Overview of long-term outcomes for the chemotherapy arm in- or excluding the CheckMate 649 trial

	Predicted 5-year OS	Predicted 10-year OS	Average LY gained
Pooled SPOTLIGHT, GLOW and CheckMate 649 (base-case 3-knot hazards spline extrapolation)	[redacted]	[redacted]	[redacted]
Pooled SPOTLIGHT, GLOW and CheckMate 649 (parametric log-logistic extrapolation)	[redacted]	[redacted]	[redacted]
Pooled SPOTLIGHT and GLOW (parametric gamma extrapolation, EAG base-case)	[redacted]	[redacted]	[redacted]
Pooled SPOTLIGHT and GLOW (parametric log-logistic extrapolation, EAG scenario analysis 13)	[redacted]	[redacted]	[redacted]
LY: life years, OS: overall survival			

. Including CheckMate 649 might result in long-term outcomes in line with expert opinion, however the EAG highlights the methodological uncertainty caused by the naïve pooling of the SPOTLIGHT, GLOW and CheckMate 649 trials. For these reasons, the EAG deems this to be a key issue and excludes the CheckMate 649 trial for the EAG base-case.

b) For the PD-L1 CPS ≥ 5 and <10 gastric and GEJ population, where nivolumab + chemotherapy and chemotherapy are relevant comparators, the available evidence regarding nivolumab comes from the CheckMate 649 trial which only provides results for the PD-L1 CPS score ≥ 5 subgroup. As a consequence, the effectiveness of nivolumab for the PD-L1 CPS score ≥ 5 and <10 subgroup specifically may be overestimated compared to zolbetuximab, as, according to the company, the effectiveness of nivolumab may increase in patients with higher CPS scores. Cost effectiveness estimates for zolbetuximab + chemotherapy versus nivolumab + chemotherapy for this subgroup may therefore be a conservative estimate and were not provided by the company. The EAG deems this approach to be inappropriate and has asked for a cost effectiveness comparison of zolbetuximab versus nivolumab (clarification question B3), however the company deems the cost-comparison approach to be most appropriate. This is a key issue as the time-varying relative effects from the NMA are different for zolbetuximab + chemotherapy and nivolumab + chemotherapy (Table 17 for PFS and 22 for OS Addendum to Response to clarification letter), and this should be reflected in the model outcomes. The EAG requests that this evidence be incorporated in the health economic model so that the full cost effectiveness analysis can be implemented.

c) The most appropriate evidence and extrapolation curves to estimate treatment effectiveness depends on the PD-L1 CPS status of the population:
    - The EAG considers the most appropriate evidence to compare zolbetuximab to chemotherapy in the PD-L1 CPS score <5 subgroup to be the evidence from the SPOTLIGHT and GLOW trials, as they directly compare zolbetuximab + chemotherapy to chemotherapy. The company uses pooled estimates from the SPOTLIGHT, GLOW and CheckMate 649 trials for the chemotherapy arm and the NMA to estimate the relative effectiveness of zolbetuximab + chemotherapy. Based on the reasoning in a) the EAG excludes the CheckMate 649 trial.

The company conducted a scenario using only the SPOTLIGHT and GLOW trials to obtain cost effectiveness outcomes for zolbetuximab versus chemotherapy. In this scenario parametric survival modelling is considered, using separate models for both treatment arms (PH assumption violated). The company notes the poor fit of the parametric models for PFS as "*all models notably fail to capture the observed plateau that occurs at the end of follow-up*", however the EAG highlights that this observed plateau (observed after approximately 2.5 years) is based on extremely low patient numbers (between [redacted] and [redacted] patients in the GLOW trial chemotherapy arm and between [redacted] and [redacted] patients in the SPOTLIGHT trial chemotherapy arm).[8] Before the plateau, the visual fit of the parametric curves seems good (Figure 57 Addendum to Response to clarification letter), therefore the EAG deems it appropriate to use parametric survival models. The EAG base-case therefore uses the company's scenario number 2 as their base-case (chemotherapy: gamma for OS and log-logistic for PFS, zolbetuximab: log-logistic for both OS and PFS). This scenario has a percentage of long-term survivors of [redacted] and [redacted] in the chemotherapy and zolbetuximab + chemotherapy arms at 10 years respectively. In addition, a scenario analysis using the log-logistic curve for chemotherapy OS was conducted by the EAG, as it might give a better reflection of the small proportion of long-term survivors, while only having slightly higher AIC and BIC values then the gamma extrapolation. In this scenario (EAG scenario analysis 13), percentages of long-term survivors of [redacted] and [redacted] in the chemotherapy and zolbetuximab + chemotherapy arms, respectively, were found at 10 years.

- For the PD-L1 CPS score ≥ 5 and <10 subgroup, the EAG considers the evidence from the SPOTLIGHT and GLOW to be appropriate for the survival extrapolations in the chemotherapy arm, for the reasons mentioned in a) and using the same extrapolation models as for the PD-L1 CPS <5 population. The EAG's base-case secondary analysis therefore uses the best-fitting parametric survival models (gamma for OS and log-logistic for PFS) for chemotherapy and the NMA for extrapolation of zolbetuximab + chemotherapy and nivolumab + chemotherapy. This is reflected in CS scenario 1, except that the company uses the log-logistic model for OS extrapolation while the gamma model is considered to be the best-fitting according to AIC and BIC. The "*log-logistic [was] chosen as the best-fitting that also models a small subset of long-term survivors for OS and PFS.*".[8] The EAG disagrees with the log-logistic as best-fitting, as it has higher AIC and BIC values compared to the gamma distribution, however does note the potentially better reflection of the small proportion of long-term survivors. The EAG's base-case secondary analysis therefore uses the best-fitting parametric survival models (gamma for OS and log-logistic for PFS) for chemotherapy, and the long-logistic extrapolation in a scenario analysis (EAG scenario 13). In the economic model, the NMA results for nivolumab + chemotherapy are absent. Instead, the NMA results for zolbetuximab are used, implying equal treatment effectiveness. The EAG deems this to be a key issue and has asked for a full cost effectiveness comparison of zolbetuximab versus nivolumab (clarification question B3).

d) It was unclear to the EAG how duration of treatment was modelled. After clarification and at the factual accuracy check, the company provided more information on duration of treatment. After factual accuracy check the EAG was able to assess DoT and concluded that the approach was largely appropriate. The EAG would have preferred to use the parametric DoT curve for zolbetuximab for the primary scenario instead of the DoT curve based on the NMA. This has, however, only a small impact on the ICER (decrease of [redacted], 2.1%), therefore the EAG did not alter its base-case.

e) The EAG requested scenario analyses that assumed treatment effect waning in their clarification letter, upon which the company provided three scenarios applying treatment effect waning of zolbetuximab + chemotherapy after 5, 6 and 7 years. When treatment waning occurred, the chemotherapy hazards were applied to the zolbetuximab + chemotherapy arm. Currently, the evidence does not show a treatment effectiveness waning for zolbetuximab (Figure 9 and 17 Addendum to Response to clarification letter), but follow-up is limited to approximately [redacted] for OS and PFS in the GLOW and SPOTLIGHT trials. As the duration of the treatment effect is uncertain at the end of follow-up and after the observed period, the EAG also modelled scenarios with treatment effect waning assumptions after 3 and 4 years. In TA857, the proportion of patients alive at 20 years was an important factor in the decision which treatment effectiveness waning scenario was most appropriate, with scenarios resulting in approximately 3% long-term survivors deemed most plausible by clinical experts and the committee. Table 4.9 shows the effect of the treatment effectiveness waning assumptions on the proportion of patients alive after 20 years for the PD-L1 CPS ≥ 5 and <10 subgroup using the treatment effectiveness extrapolations from the company base-case, the EAG base-case, and EAG scenario analysis 13, respectively. The EAG is uncertain which treatment effect waning scenario is most plausible but notes that this assumption has a large influence on the ICER (increasing with earlier onset of treatment effectiveness waning). Considering that at 3 years the observed hazard ratios show no sign of treatment effectiveness waning, although consisting of a small number of patients, the EAG deems treatment waning at 3 and 4 years to be too pessimistic. Therefore, as a base-case assumption, the EAG implements treatment effect waning for zolbetuximab + chemotherapy to occur at 5 years.

Table 4.9: Effect of treatment effectiveness waning assumptions on modelled long-term survival using the company base-case assumptions (including CheckMate 649) and the EAG base-case assumptions.

	Proportion of patients alive at 20 years in the chemotherapy arm	Proportion of patients alive at 20 years in the zolbetuximab + chemotherapy arm	Proportion of patients alive at 20 years in the nivolumab + chemotherapy arm
Company base-case (including CheckMate 649)			
No treatment effect waning	[redacted]	[redacted]	[redacted]
Treatment effect waning after 3 years	Treatment waning was not applied to chemotherapy	[redacted]	[redacted]
Treatment effect waning after 4 years		[redacted]	[redacted]
Treatment effect waning after 5 years		[redacted]	[redacted]
Treatment effect waning after 6 years		[redacted]	[redacted]
Treatment effect waning after 7 years		[redacted]	[redacted]

	Proportion of patients alive at 20 years in the chemotherapy arm	Proportion of patients alive at 20 years in the zolbetuximab + chemotherapy arm	Proportion of patients alive at 20 years in the nivolumab + chemotherapy arm
EAG base-case secondary analysis [without base case treatment waning setting]			
No treatment effect waning	[redacted]	[redacted]	[redacted]
Treatment effect waning after 3 years	Treatment waning was not applied to chemotherapy	[redacted]	[redacted]
Treatment effect waning after 4 years		[redacted]	[redacted]
Treatment effect waning after 5 years		[redacted]	[redacted]
Treatment effect waning after 6 years		[redacted]	[redacted]
Treatment effect waning after 7 years		[redacted]	[redacted]
EAG exploratory scenario analysis 13 for the secondary scenario [without base case treatment waning setting]			
No treatment effect waning	[redacted]	[redacted]	[redacted]
Treatment effect waning after 3 years	NA treatment waning was not applied to chemotherapy	[redacted]	[redacted]
Treatment effect waning after 4 years		[redacted]	[redacted]
Treatment effect waning after 5 years		[redacted]	[redacted]
Treatment effect waning after 6 years		[redacted]	[redacted]
Treatment effect waning after 7 years		[redacted]	[redacted]
EAG = Evidence Assessment Group			

4.2.7 Adverse events

The main sources of evidence on the incidence of AE used for intervention and comparators are the GLOW,[20] SPOTLIGHT,[19] CheckMate 649,[21] and KEYNOTE-859 [30] trials (Table 4.10). Only Grade 3+ AEs with an incidence of ≥ 5% were included in the economic model and analyses. Duration of AEs in weeks were derived from Shah et al. 2022.[31]

Table 4.10: Incidence of AEs per treatment arm and AEs estimated duration

Adverse event	Treatment arm				Duration (weeks)
	Zolbetuximab + chemotherapy	Chemotherapy	Nivolumab + chemotherapy	Pembrolizumab + chemotherapy	
Nausea	[redacted]	[redacted]	2.6%	3.00%	1.00
Diarrhoea	[redacted]	[redacted]	4.5%	5.00%	1.00
Abdominal pain	[redacted]	[redacted]	0.0%	0.00%	1.00
Vomiting	[redacted]	[redacted]	2.2%	4.00%	1.00
Anaemia	[redacted]	[redacted]	6.0%	8.00%	2.13
Decreased appetite	[redacted]	[redacted]	1.8%	2.00%	0.00
Platelet count decreased	[redacted]	[redacted]	2.6%	7.00%	1.70
Neutrophil count decreased	[redacted]	[redacted]	10.6%	9.00%	2.41
White blood cell count decreased	[redacted]	[redacted]	2.9%	0.00%	2.41
Neutropenia	[redacted]	[redacted]	15.1%	7.00%	1.89
Lipase increased	[redacted]	[redacted]	5.8%	0.00%	2.86
Source	SPOTLIGHT[20]	SPOTLIGHT[19, 20]	CheckMate649[21]	KEYNOTE-859[30]	Shah et al. 2022[31]

CS Addendum Table 58[8], CS Table 28.[1]
CS = company submission

EAG comment: The main concerns of the EAG relate to a) the expected duration of AEs was derived from a study in a different condition, b) error in AE duration implementation, and c) differences in original source for AE duration.

a) The effects of AE on QoL were calculated using the percentage of patients experiencing an AE with grade 3+ and incidence ≥ 5% and the expected AE duration in weeks. The percentage of patients experiencing an AE was derived from GLOW,[20] SPOTLIGHT,[19] CheckMate 649,[21] and KEYNOTE-859[30] trials. Duration of AEs was derived from Shah et al. (2022),[31] which reports on a different patient population than the population in this appraisal (i.e., adults with relapsed/refractory B-cell acute lymphoblastic leukaemia in the United States of America (USA) treated with either blinatumomab, inotuzumab ozogamicin, brexucabtagene autoleucel or chemotherapy). It is unclear to the EAG whether the duration of AEs for the population in Shah et al. can be extrapolated to the population used in this appraisal.[31] In addition, the duration of AEs in Shah et al. (2022) was also derived from multiple sources for multiple conditions (e.g., metastatic renal cell carcinoma, metastatic non-small cell lung cancer, among others). Therefore, it is also hard to assess whether the duration of the AEs is relative to the treatment cycle and should be, therefore, incorporated every time the modelled patients receive treatment, or if it depends on the unique AE and can be incorporated once. The EAG asked the company to provide AEs duration based on the SPOTLIGHT and GLOW trials in the clarification question B13[8]; however, the company stated that they could not conduct the analyses within the timelines of the clarification questions and that the duration of AEs had a negligible impact on the ICER. Ideally, the EAG would have preferred the use of trial data for the calculation of the AEs duration, as this would have provided more specific estimates for the studied population and clarified whether assuming that AEs could only happen once is correct. However, the EAG also notes the likely small impact of this issue on the cost effectiveness outcomes.
b) With the clarification response, the company provided an updated model. In this updated model, two AEs were added: abdominal pain and decreased white blood cell count. However, the duration of these AEs was not correctly incorporated in the model and the cells that should have included the duration of those in years appeared blank. Therefore, the effect of abdominal pain and decreased white blood cell count was not included in the QALY loss calculation. The EAG has corrected this error in their analyses, although its impact on the ICER was negligible.
c) Nausea and vomiting had a duration of 1 week. The company cited the duration of these AEs in Shah et al.; however, these were not specified in said publication.[31] Therefore, it is unclear for the EAG where these estimates were originally derived.

4.2.8 Health-related quality of life

The utility values were estimated based on progression status (pre-progression and post-progression) and TEAEs GRADE ≥ 3 status.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS,[1] the SLR identified 17 studies and five HTA submissions reporting EQ-5D utility data for patients with G/GEJC, either by progression status or time to death. The company did not include any of the 17 studies, arguing that it was unclear whether the health states were valued using UK societal preferences or if studies were representative of the UK population. Therefore, the company considered only three TAs reporting UK relevant utility values (TA191, TA208, and TA857)[9, 32, 33].

4.2.8.2 Health state utility values

The HRQoL used in the model was based on the EQ-5D-5L data collected in the SPOTLIGHT[19] and GLOW trials (12 January 2024 data cut).[20] EQ-5D values were estimated using the pooled data of both trials. No data imputation was performed for missing evaluations. EQ-5D data were mapped from EQ-5D-5L to EQ-5D-3L using the mapping function developed by the NICE DSU, with the Policy Research Unit in Economic Evaluation of Health and Social Care Interventions (EEPRU) dataset.[34, 35]

For the pre-progression health state, the company used the EQ-5D from patients in the PFS state (i.e., data collected before the date of progressive disease, death, or being censored following the rule for analysis of PFS). For the post-progression health state, the company used the EQ-5D of alive patients that were not in the pre-progression health state. For the post-progression, the EQ-5D measures collected after the censoring date of PFS among patients without progression or death event were excluded. If a patient has progressed, the post-progression EQ-5D measurements that were collected before their date of death were included in analyses.

A generalised estimating equation (GEE) model was developed to estimate utility scores and a mixed-effects model was explored in a scenario analysis in the original CS (Table 4.11).[1] The CS base-case included treatment independent utility values derived from the pooled treatment arms. The number of life years (LYs) gained per cycle in the pre- and post-progression state for every treatment arm were multiplied by the respective utility value and added together to obtain the total quality-adjusted life year (QALY) per treatment arm. The company's addendum[8] provided a new utility score using GEE with an exchangeable working correlation (Table 4.11), in addition to the independent working correlation used in the original CS. The update had a significant impact on the utilities ([redacted] of [redacted] for the pre-progression and of [redacted] for the post-progression) but no additional information was provided justifying the difference in outcomes. The mixed effects model was not further updated in the company addendum.[8]

Table 4.11: Health state utility values

Health state	Pre-progression	Post-progression	Use in the model
GEE (assumed exchangeable working correlation)	[redacted]	[redacted]	Base-case
GEE (assumed independent working correlation structure)	[redacted]	[redacted]	Previous base-case in CS
Mixed effects (original submission)	[redacted]	[redacted]	Scenario analysis
TA191	0.73	-	-
TA208	0.729	0.577	-
Shirowa et al. [36] (ToGA trial*)	0.797	0.577	Scenario analysis

CS Table 31,[8] CS, clarification response, TA191, TA208}, Addendum table 60.[8]
*Using the Japanese scoring algorithm

4.2.8.3 Disutility values

The main sources of evidence on treatment AE incidence were the GLOW,[20] SPOTLIGHT,[19] CheckMate 649,[21] and KEYNOTE-859[30] trials, TA857, and Shah et al. 2022. Likewise, the main sources of AE disutility and duration were TA857 and Shah et al 2022.[9, 31]

The impact on TEAEs on HRQoL is captured by a one-time QALY loss applied upon treatment initiation for each treatment arm (Table 4.12) using an additive approach. This utility decrement (or disutility) was calculated by taking the percentage of trial participants that experienced each Grade 3+ AE with an incidence of ≥ 5% (Table 4.10), the disutility value associated for each AE (CS, Table 28), and the assumed duration of the AE (Table 4.10). Utility decrements were based on TA857 and Shah et al 2022 (CS, Table 28).[9, 31]

Table 4.12: AE related disutility values per treatment arm

Treatment arm	Total QALY decrement due to AE
Zolbetuximab + chemotherapy	-0.00198
Chemotherapy	-0.00152
Nivolumab + chemotherapy	-0.00121
Pembrolizumab + chemotherapy	-0.00113
Economic model, sheet 'Safety', cells E29:N29 AE = adverse event, QALY = quality-adjusted life year	

An additional disutility was applied to account for patients ageing during the lifetime horizon. Age- and gender-matched general UK population utility values were used to adjust the health state utility values over time using a multiplicative approach.[37]

EAG comment: The main concerns of the EAG relate to: a) lack of data imputation, b) model choice for utility estimates, c) risk of underestimation of AE disutility, and d) scenario with values from the ToGA trial with the Japanese scoring algorithm.

a) HRQoL data were collected in the SPOTLIGHT and GLOW trials. However, as per the CS, no data imputation was performed for missing evaluations. The assumption that data were missing at random is questionable and may increase the risk of bias in the estimates. The company justified in clarification question B16 that the missingness of EQ-5D values was not substantial in either SPOTLIGHT or GLOW, and that there is no consensus in the literature on the best approach for dealing with missing EQ-5D data. However, it is uncertain whether the missingness of EQ-5D measures was "*small*", especially for the GLOW trial. Despite the fact that the average completeness was [redacted]% in GLOW, there was a significant decrease in the number of participants completing the questionnaire as the trial continued, as shown in Figure 6 of the clarification response,[4] therefore, calling into question the missing at random assumption. This could potentially incorporate bias, especially, as healthier patients would be more likely to stay in the trial, increasing the average utility value. Likewise, the company did not provide the number of respondents throughout time and the summary of missingness for the post-progression period, hindering the complete appraisal of the validity of the trial EQ-5D results. In addition, the argument of the lack of consensus for the best approach is not sufficient to not perform data imputation, but to explore different data imputation methods according to the possible mechanisms causing the data missingness [38]. Thus, the EAG would prefer the company to perform data imputation for the missing EQ-5D data from the trials
b) For the CS original base-case, a GEE model was developed to estimate the trials' utility scores (Table 4.11). In addition, the company used a pooled mixed-effects model in a scenario analysis, which resulted in slightly lower utility values than the base-case for both pre-progression (GEE: [redacted], mixed-effects: [redacted]) and post-progression (GEE:[redacted], mixed-effects: [redacted]). In Table 60 from the company addendum[8], the GEE model used in the base-case was updated with a different working correlation structure, using an exchangeable working correlation, instead of the independent one used in the original submission, which had a

significant impact on the utility values (pre-progression: [redacted], post-progression: [redacted]). The concerns of the EAG are:

a. In the clarification response B15, the company still refers to the old utility values of GEE ([redacted], and [redacted]). In addition, the values of the updated base-case are only included the updated values in Table 11 under the title: 'Health State Utility (GEE), exchangeable' and briefly mentioned that the difference between the two were that the original model assumed no correlation among observations, and the updated one assumed constant correlation. However, the company did not explain why they decided to change the original base-case utility values. The EAG would require further clarification from the company to solve the discrepancies between the clarification response and addendum. Moreover, the EAG would like further clarification on the rationale behind the choice of different working correlation structures.

b. The rationale for choosing the GEE model for the base-case was based on three points. First, the company stated that the GEE results were more comparable to the descriptive results (pre-progression: [redacted], post-progression: [redacted]) than the mixed effects. However, with the updated utility values, both GEE and mixed-effects results are similar for both pre-progression (GEE: [redacted], mixed-effects: [redacted]) and post-progression (GEE: [redacted], mixed-effects: [redacted]). Moreover, the similarity with the descriptive analysis results was not deemed a compelling argument, as they may misinterpret the effects over time and the possible variation in HRQoL data.[39] The second argument provided by the company was that GEE estimates could be considered '*conservative*', as the difference between the pre-, and post-progressed utilities was smaller in this model. Nonetheless, this difference increased with the updated data cut (difference in original GEE: [redacted], updated GEE: [redacted], mixed-effects: [redacted]). Third, the company preferred the GEE model, as it directly estimates cohort-level utilities, which aligns with the use of a cohort-level cost effectiveness model. However, the mixed-effects model can provide a more flexible framework and can account for individual and group-level variation.[40] As shown in table 4.7 of this report, all three utility estimates provided by the CS are higher than those from TAs in the same population. Likewise, the results from the GEE model using independent working correlations, produced utility pre-progression estimates higher than those from the UK general population in the same age group (male: 0.809, female: 0.791, average for the modelled population: 0.802).[37] Given that the population of this appraisal are patients with advanced unresectable adenocarcinoma, the EAG considers that assuming utilities higher than the UK general population lacks face validity and would prefer either the estimates from the updated GEE or the mixed-effects models. Given the limited rationale and information on the updated GEE, the EAG will use the mixed-effects model in their base-case.

c) Disutility values related to AEs were applied as a one off QALY loss in the first model cycle. AE QALY losses per treatment arm were obtained with the product of the AE incidence per arm from the trials, the disutility value and expected AE duration from the literature. The AE related disutility values (Table 4.12) obtained through this calculation were deemed low considering the impact of the AEs on the patients' QoL. As reported in the critique section of 4.2.7, it is unclear to the EAG whether the duration of the AEs is relative of the treatment cycle and should be incorporated every time the modelled patients receive treatment, or if it depends on the unique AE and can be incorporated once. The EAG considers the impact of this to be low, as multiplying the AE disutility by for example 20 treatment cycles had only a modest impact on the ICER.

d) The utility values from other TAs were generally [redacted] than the company's utility estimates (Table 4.11). However, the company argued that evidence from the literature showed [redacted] utility values than the ones provided by them, such as in Shirowa et al[36], which used EQ-5D data from the ToGA trial. Nonetheless, the values reported in Shirowa et al[36] (0.797 and 0.577) were obtained using the Japanese scoring algorithm. The utility values from the ToGA trial that were used in TA208, and approved by the committee, were lower than all the models provided by the company (pre-progression: 0.729, post-progression: 0.577). However, it should be noted that the pre-progression value used in TA208 increases over time, whilst the post-progression value is for patients who have progressed after two lines of treatment. Therefore, the EAG will run a scenario analysis with the utility values from TA208.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, medical costs (treatment administration, disease management, testing, terminal care), and costs of managing AEs.

Unit prices were based on the NHS reference prices,[41] British National Formulary (BNF),[42] Personal Social Services Research Unit (PSSRU) and Monthly Index of Medical Specialities (MIMS).[43]

4.2.9.1 Resource use and costs data identified in the review

According to the CS,[1] the SLR identified 29 studies reporting UK relevant resource use and cost information. Out of these, none were conducted in the UK and the company did not consider them of relevance to inform the model.

4.2.9.2 Treatment costs (with PAS)

Drug acquisition costs per administration were calculated based on dosage, unit drug costs, relative dose intensity (RDI), dosing schedules, and stopping rules (Tables 4.13 to 4.15). Vial sharing was assumed in the base-case and a scenario analysis without vial sharing was included. RDI was assumed to be 100% when not available from the trials (Table 4.15).

Table 4.13: Dosing schedules and stopping rules

Regimen	Component	Daily dose (mg/m^2)	Dosing schedule	Route of administration	Delay	Stopping rule
Zolbetuximab + CAPOX	Zolbetuximab (loading)	800	Q3W	IV	3	3 weeks
	Zolbetuximab (maintenance)	600	Q3W	IV	0	n/a
	Oxaliplatin (high dose)	130	Q3W	IV	0	24 weeks
	Capecitabine	1000	bid Days 1 - 14 Q3W	Oral	0	Beyond 8 treatment cycles can be continued at clinician's discretion

Regimen	Component	Daily dose (mg/m^2)	Dosing schedule	Route of adminis-tration	Delay	Stopping rule
Zolbetuximab + FOLFOX	Zolbetuximab (loading)	800	Q3W	IV	3	3 weeks
	Zolbetuximab (maintenance)	600	Q3W	IV	0	n/a
	Oxaliplatin (low dose)	85	Q2W	IV	0	24 weeks
	Leucovorin	400	Q2W	IV	0	Beyond 4 cycles can be continued at clinician's discretion
	Fluorouracil (bolus)	400	Q2W	IV	0	n/a
	Fluorouracil (infuser)	2400	Q2W	IV	0	Beyond 4 cycles can be continued at clinician's discretion
CAPOX	Oxaliplatin (high dose)	130	Q3W	IV	0	24 weeks
	Capecitabine	1,000	bid Days 1 - 14 Q3W	Oral	0	Beyond 8 treatment cycles can be continued at clinician's discretion
FOLFOX	Oxaliplatin (low dose)	85	Q2W	IV	0	24 weeks
	Leucovorin	400	Q2W	IV	0	n/a
	Fluorouracil (bolus)	400	Q2W	IV	0	n/a
	Fluorouracil (infuser)	2,400	Q2W	IV	0	n/a
Nivolumab + chemotherapy	Nivolumab	360*	Q3W	IV	0	104 weeks

Regimen	Component	Daily dose (mg/m^2)	Dosing schedule	Route of adminis-tration	Delay	Stopping rule
	Oxaliplatin (high dose)	130	Q3W	IV	0	24 weeks
	Capecitabine	1,000	bid Days 1 - 14 Q3W	Oral	0	Beyond 8 treatment cycles can be continued at clinician's discretion
Pembrolizumab + chemotherapy	Pembrolizumab	200*	Q3W	IV	0	104
	Capecitabine	1,000	bid Days 1 - 14 Q3W	Oral	0	n/a
	Oxaliplatin	130	Q3W	IV	0	n/a
Post-treatment	Docetaxel	75	Q3W	IV	0	Applied once
	Paclitaxel	80	Q4W	IV	0	Applied three times

CS Table 17, Table 36.[1]
*mg
CS = company submission; IV = intravenous; n/a = not applicable; Q2W = every 2 weeks; Q3W = every 3 weeks

The unit cost for zolbetuximab was provided by the company, which included a Patient Access Scheme (PAS) with a discount of [redacted] (Table 4.14), and the unit costs for other drugs were retrieved from the MIMS,[43] the BNF or the drugs and pharmaceutical electronic market information tool (eMIT; Table 4.10).[42, 44]

Table 4.14: Drug acquisition unit costs

Health state	Mg per unit	Unit costs	Discount
Zolbetuximab	100	£410 (with PAS: £[redacted])	[redacted]
Capecitabine	150	£0.11	N/A
Oxaliplatin	100	£24.44	
Leucovorin	100	£10.18	
Nivolumab	240	£2,633.00	
Pembrolizumab	100	£2,633.00	
Docetaxel	160	£15.67	
Paclitaxel	100	£8.49	
Fluorouracil (bolus)	500	£6.08	
Fluorouracil (infuser)	1000	£3.93	

Health state	Mg per unit	Unit costs	Discount
Docetaxel	160	£15.67	
Paclitaxel	100	£8.49	
Based on Table 32 of the CS[1] and clarification question addendum Table 61[8] CS: company submission; PAS: Patient Access Scheme			

The CS base-case assumed CAPOX costing for all patients regardless of their actual chemotherapy regimen, as it has lower acquisition and administration costs. The company argued that CAPOX is most used in the UK and that the effectiveness of CAPOX and FOLFOX is broadly equivalent.[1] For the base-case, the company stated that RDI for zolbetuximab was based on the pooled values from SPOTLIGHT and GLOW and its chemotherapy components (i.e., CAPOX) from GLOW.[20] For the comparator arm, RDI was sourced from GLOW. A distribution of 80% CAPOX and 20% FOLFOX was explored in a scenario analysis.

Table 4.15: RDI and drug acquisition costs per dosing schedule

Regimen	Treatment	RDI	Reference	Drug acquisition cost (£) per treatment cycle	Use in model
Zolbetuximab + chemotherapy	Zolbetuximab (loading)	[redacted]	Weighted SPOTLIGHT [19]and GLOW[20]	[redacted]	Model base-case
	Zolbetuximab (maintenance)	[redacted]		[redacted]	
	Oxaliplatin	[redacted]	GLOW[20]	[redacted]	
	Capecitabine	[redacted]		[redacted]	
Chemotherapy (CAPOX)	Oxaliplatin	[redacted]	GLOW[20]	[redacted]	Base-case
	Capecitabine	[redacted]		[redacted]	
Nivolumab + chemotherapy	Nivolumab	100%	Assumption	3,949.50	Comparison made to nivolumab as part of secondary analyses for those eligible to Nivolumab
	Oxaliplatin	100%		54.08	
	Capecitabine	100%		1.21	
Pembrolizumab + chemotherapy	Pembrolizumab	100%	Assumption	5,260.00	Comparison made to pembrolizumab as part of secondary analyses for those eligible to Pembrolizumab
	Capecitabine	100%		1.21	
	Oxaliplatin	100%		54.08	

Regimen	Treatment	RDI	Reference	Drug acquisition cost (£) per treatment cycle	Use in model
Zolbetuximab + CAPOX	Zolbetuximab (loading)	[redacted]	GLOW[20]	[redacted]	Scenario analysis
	Zolbetuximab (maintenance)	[redacted]		[redacted]	
	Oxaliplatin	[redacted]		[redacted]	
	Capecitabine	[redacted]		[redacted]	
Zolbetuximab + FOLFOX	Zolbetuximab (loading)	[redacted]	SPOTLIGHT[19]	[redacted]	Scenario analysis
	Zolbetuximab (maintenance)	[redacted]		[redacted]	
	Oxaliplatin	[redacted]		[redacted]	
	Leucovorin	[redacted]		[redacted]	
	Fluorouracil (bolus)	[redacted]		[redacted]	
	Fluorouracil (infuser)	[redacted]		[redacted]	
FOLFOX	Oxaliplatin	[redacted]	SPOTLIGHT[19]	[redacted]	Scenario analysis
	Leucovorin	[redacted]		[redacted]	
	Fluorouracil (bolus)	[redacted]		[redacted]	
	Fluorouracil (infuser)	[redacted]		[redacted]	
Chemotherapy (CAPOX)	Oxaliplatin	[redacted]	GLOW[20]	[redacted]	Scenario analysis
	Capecitabine	[redacted]		[redacted]	
Post-treatment	Docetaxel	100%	Assumption	12.50	Base-case
	Paclitaxel	100%		11.56	

Based on Tables 33 and 36 of the CS,[1] Clarification response addendum Table 63[8], and Clarification response excel model.
*On the clarification response addendum, the costs for zolbetuximab from the weighted GLOW and SPOTLIGHT, reported the values from zolbetuximab from CAPOX (£[redacted] and £[redacted]). However, the model used the values reported in this Table.CS = company submission

The unit administration costs were obtained from the National Cost Collection based on route of administration (CS, Table 34) and were inflated to 2023 cost year. The company assumed three possible administration paths: oral administration, in which they assumed a cost of £0; first attendance in an outpatient clinic (£452.70) and subsequent treatments in an outpatient clinic (£335.34). All treatments that required IV administration were assumed to happen in an outpatient setting.

4.2.9.3 Health state costs

The model calculated pre- and post-progression costs separately. Pre-progression costs (Table 4.16) included drug acquisition cost per administration, drug administration costs, number of administrations per week, and proportion of patients remaining on treatment based on the DoT curves. In the CS base-case, patients continued treatment until discontinuation, maximum treatment duration was achieved, progression, or death. The company base-case selected the DoT curve that belonged to the respective treatment (See Section 4.2.6. from this report). For the treatment arm with nivolumab and pembrolizumab, treatment costs were also estimated based on CAPOX, as that is cheaper than the other regimes.

Post-progression costs were applied as a lump sum when patients moved to the post-progression health state (Table 4.17). Post-progression costs were derived from the product of the proportion of patients progressed receiving treatment distribution of the post-progression treatments, weekly costs per treatment, and mean duration of each treatment. In the CS base-case, it was assumed that patients in the post-progression state would receive an equal split of docetaxel and paclitaxel, irrespective of the first-line of treatment. On average, patients received docetaxel for 9.21 weeks (lump sum cost of £2,060.41), and paclitaxel for 24.68 weeks (lump sum cost of £10,308.45).

Table 4.16: Pre-progression health state costs

Use	Treatment arm	Source	Cost per initial cycle (acquisition and administration)	Cost per subsequent cycles (acquisition and administration)**	Total drug costs	Total administration costs	Total costs
Base-case	Zolbetuximab + chemotherapy	Weighted SPOTLIGHT[19] + GLOW[20]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chemotherapy	GLOW[20]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pembrolizumab + chemotherapy	KEYNOTE-859[30]	5,783.73	5,783.73 + 16.96	62,608.03	5,353.29	67,961.33*
Scenarios	Nivolumab + chemotherapy (CAPOX)	CheckMate 649[21]	4,473.23	4,473.23 + 16.96	47,029.14	5,318.43	52,347.57*
	Zolbetuximab + CAPOX	GLOW[20]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Zolbetuximab +FOLFOX	SPOTLIGHT[19]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Chemotherapy FOLFOX	SPOTLIGHT[19]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SPOTLIGHT Zolbetuximab + CAPOX costing	GLOW[20] & SPOTLIGHT[19] (not pooled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Addendum model. *Total costs reported in the table were derived from the economic model, but do not align from the values reported in Addendum Table 63[8]
**Patients in subsequent cycles could incur two different costs, as some treatment arms require administrating drugs at different time points.

Table 4.17: Post-progression costs

Pre-progression treatment	Percentage of patients receiving post-progression treatment	Total costs	Source
Zolbetuximab + chemotherapy	[redacted]	[redacted]	Pooled SPOTLIGHT[19] and GLOW[20]
Chemotherapy	[redacted]	[redacted]	Pooled SPOTLIGHT[19] and GLOW[20]
Nivolumab + chemotherapy	37%	2,301.18	Janjigian et al. 2021[21]
Pembrolizumab + chemotherapy	47%	2,782.99	Rha et al. 2023[30]
Addendum Table 64.[8]			

4.2.9.4 Disease management costs

Modelled disease management costs included: visits to healthcare professionals, medical procedures, and hospitalisations. Resource use frequencies were obtained from NICE TA857 and were differentiated by pre-progression (on and off treatment) and post progression. Cost were inflated to 2023 using the approach of TA857. A summary of the disease management resource use and costs can be found in Table 4.18.

Table 4.18: Disease management resource use and costs

Health state	Procedure and monitoring service	Frequency	Unit cost	Total annual costs	Total annual costs per state
Pre-progression (on treatment)	Oncologist consultation	17.38	£227	£3,945.68	£3,945.68
Pre-progression (off treatment)	Oncologist consultation	8.69	£227	£1,972.84	£3,361.37
	Cardiac monitoring	4.00	£347	£1,388.53	
Post-progression	Nurse, home visit	52.14	£20	£1,017.66	£9,774.94
	Clinical nurse specialist	52.14	£56	£2,945.87	
	General practitioner	26.07	£166	£4,338.46	
	Therapist	26.07	£56	£1,472.94	
CS Table 41, 42,43,44, and economic model addendum[18] CS = company submission					

4.2.9.5 Testing costs

Patients require testing in order to determine eligibility for zolbetuximab (HER2, CLDN18.2 testing) and nivolumab and pembrolizumab (PD-L1 testing). The costs of HER2 and PD-L1 were not included in the economic model, as they were assumed to be standard of care (SoC) for all patients. Patients would incur in CLDN18.2 testing costs in the zolbetuximab + chemotherapy arm to identify those with CLDN18.2-positive expression.

The list price of the VENTANA CLDN18 (43-14A) RxDx Assay was not available; therefore, the company used an analogue (Agilent PD-L1 IHC 22C3 pharmDx test) to estimate the approximate cost (£74.48 per test). As 42.3% of patients in the SPOTLIGHT and GLOW trials tested positive for CLDN18.2, the company assumed that an average of 2.4 tests (obtained by 100/42.3) would be required to identify one patient with CLDN18.2 positive expression. Thus, the testing costs were £176.08 and included in the base-case. Scenario analysis were performed excluding the testing costs.

4.2.9.6 Adverse events costs

AE costs were applied as a lump sum upon treatment initiation for each treatment arm. The costs per AE (CS, Table 39) was sourced from NHS reference costs 2021-2022 and inflated to 2023. As NHS Cost Inflation Indices were only available to 2022, the company assumed that the inflation between 2021 and 2022 also applied between 2022 and 2023.

The unit costs per AE was assumed to be the same across treatment arms. Table 4.19 shows a summary of the AE incidence rates per arm. Unit costs per AE can be found in CS Table 39. The lump sum cost per treatment arm can be found in Table 4.19.

Table 4.19: AEs incidence rates and individual costs.

Treatment arm	Total costs due to AEs
Zolbetuximab + chemotherapy	£801.57
Chemotherapy	£695.64
Nivolumab + chemotherapy	£666.28
Pembrolizumab + chemotherapy	£487.60
Addendum Table 65	

4.2.9.7 Terminal care costs

All modelled patients incur in one-time terminal care cost before death of £5,131 to reflect the intensive palliative and hospice-related care that patients would require at the end of life.

EAG comment: The main concerns of the EAG relate to: a) vial sharing in the base-case, b) assuming an RDI of 100% when data was not available, c) post-progression costs not representing UK clinical practice, and d) discrepancies between clarification response and economic model.

a) Vial sharing is assumed in the company's base-case and no vial sharing is explored in a scenario analysis. The company justified the inclusion of vial sharing as it had been done previously in TA737 for pembrolizumab. However, the company did not provide further evidence supporting that vial sharing for zolbetuximab could be expected in UK clinical practice. Therefore, in line with the NICE guidelines, the EAG included no vial sharing in their updated base-case.
b) As the RDI values for nivolumab and pembrolizumab were unavailable, the company assumed a RDI of 100% for both treatment arms. After being asked in clarification question B20, the company provided a scenario analysis assuming 100% RDI for zolbetuximab, which increased the ICER by 1.9%. However, the EAG would prefer to assume the same RDI as

zolbetuximab ([redacted]) for nivolumab and pembrolizumab. Likewise, the EAG would also expect the same RDI as the intervention arm for the chemotherapy components of nivolumab and pembrolizumab (i.e., oxaliplatin: [redacted], capecitabine: [redacted]). Therefore, the EAG secondary analysis includes the same RDI values for nivolumab + chemotherapy as zolbetuximab + chemotherapy, as this would only be relevant for the cases in which nivolumab or pembrolizumab are used.

c) Post-progression costs were applied as a lump sum when patients moved to the post-progression health state. In the CS base-case, it was assumed that patients in the post-progression state would receive an equal split of docetaxel and paclitaxel, irrespective of the first-line of treatment. Nonetheless, in the SPOTLIGHT and GLOW trials, patients received paclitaxel (between 17.0% and 20.2%) and ramucirumab (between 8.3% and 12.4%). Likewise, in clarification response B6, the company stated that, according to clinical advice, the common distribution of second-line treatments in the UK would be FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) in England, and docetaxel and irinotecan in Scotland, and that third-line treatments would include any chemotherapy not used in second-line, trifluridine/tipiracil or nivolumab. In ID4030, the subsequent treatment distribution used was more aligned with the UK clinical pathway as it comprised a combination of FOLFIRI (60%), paclitaxel (30%) and irinotecan (10%); and for third-line, FOLFIRI (6%), paclitaxel (12%), and trifluridine/tipiracil (12%). In ID4030, the company also applied a lump sum upon progression of £16,779 for the pembrolizumab + chemotherapy arm and £35,203 for the chemotherapy arm, based on list prices. The company ran a scenario analysis using these cost estimates of £16,779 and £35,203 but for docetaxel and paclitaxel, respectively, which slightly decreased the ICER, and ensured that, therefore, assuming "*patients receive docetaxel or paclitaxel on progression is conservative against zolbetuximab + chemotherapy*". However, this simplistic assumption is flawed as it assumes that different treatments combinations (i.e., FOLFIRI, paclitaxel, irinotecan or trifluridine/tipiracil and docetaxel and paclitaxel), with diverse health effects, treatment duration, and costs are interchangeable. The company used a combination of docetaxel and paclitaxel based on TA857, however it is neither aligned with UK clinical practice, nor with SPOTLIGHT and GLOW. Therefore, this limits the validity of the assumed post-treatment costs and has been deemed a key issue by the EAG. Furthermore, as remarked by the EAG comments on ID4030, the assumption of a one-off cost upon progression, even with more appropriate distribution of treatments, may be too simplistic to capture the impact of the subsequent treatments.

d) The EAG found some minor discrepancies between the clarification response and the economic model. The values in Table 4.16 report the total acquisition and administration costs per treatment arm. The EAG obtained these results from the updated economic model; however, the values varied slightly from the ones reported by the company in table 63 from the addendum. The EAG has not been able to replicate these results.

4.2.10 Severity

The company's model was used for the QALY shortfall analysis. The expected general population QALYs for the modelled population were calculated in the model using the Office for National Statistics (ONS) Life Tables[45] and McNamara et al.[37] The QALY shortfall calculator by Schneider et al. 2022 was utilised to validate the absolute and proportional shortfall estimates. The informing sex distribution, starting age and discount rate were consistent with the company's base-case (Table 4.20). A severity modifier of x1.2 was applied to the threshold. The company confirmed that all PSA iterations resulted in a severity weight of x1.2.

Table 4.20: QALY shortfall analysis

QALY shortfall analysis: input factors	
Sex distribution	38% female
Starting age	58.5 years
Discount rate	3.5%
Total (discounted) QALYs for general population	12.28
QALY shortfall analysis: summary outputs	
Absolute QALY shortfall	[redacted]
Proportional QALY shortfall	[redacted]
QALY weight	x1.2

CS section B.3.6
CS = company submission; QALY = quality-adjusted life year

EAG comment: The EAG had no concerns regarding the QALY shortfall analysis.

4.2.11 Uncertainty

The company considers as the key areas of uncertainty:

- Data on OS and PFS from SPOTLIGHT and GLOW are not complete, which leads to uncertainty in the true long-term outcomes for both chemotherapy and zolbetuximab + chemotherapy.
- Both zolbetuximab, nivolumab and pembrolizumab are biologics with potentially complex mechanisms of action.
- There is no direct evidence comparing zolbetuximab with nivolumab and pembrolizumab.
- No UK-specific clinical data were available for any of the comparators.

EAG comment: The EAG largely agrees with the company's assessment of the key areas of uncertainty. In addition to the company's appraisal, the EAG highlights the following sources of uncertainty:

- Assuming equal effectiveness of the CAPOX and FOLFOX chemotherapy regimens, which anchors the NMA. This causes uncertainty in the generalisability of the NMA results.
- Appropriateness of comparators for different subgroups based on PD-L1 CPS status and evidence lacking to inform the comparisons in the appropriate subgroups.
- Assumptions regarding the waning of treatment effectiveness over time.
- Methodological uncertainty caused by naïve pooling of SPOTLIGHT, GLOW and CheckMate.
- Uncertainty in utility estimates due to missing data and lack of adjustment for it, and analysis method.
- Subsequent treatments in GLOW and SPOTLIGHT not in line with UK clinical practice, which may affect treatment effectiveness estimates.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The updated CS base-case cost effectiveness results (probabilistic [95% CI]), in response to the clarification letter, consider zolbetuximab + chemotherapy versus chemotherapy alone. Zolbetuximab + chemotherapy is more effective (incremental QALYs of 0.58 [ ], and more costly (additional costs of [-] with PAS) as chemotherapy amounting to an ICER of per QALY gained (Table 5.1). This result does not include the application of a 1.2x QALY weight, instead a modified WTPT threshold of £36,000 was used. The probability of zolbetuximab + chemotherapy being cost-effective, at thresholds of £30,000 and £36,000 per QALY gained, compared to chemotherapy are % and %, respectively.

Table 5.1: Probabilistic company base-case results, following clarification response

Intervention	Total life years	Total QALYs	Total Costs (£, with PAS)	Incr. QALYs	Incr. Costs (£)	ICER (£/QALY)
Zolbetuximab + chemotherapy						
Chemotherapy				0.58		
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year						

The company conducted a secondary deterministic CEA for zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5, in response to the clarification letter. Zolbetuximab + chemotherapy is as effective (incremental QALYs) and less costly (incremental costs of) as nivolumab + chemotherapy amounting to an ICER of .

Table 5.2: Deterministic secondary analysis results for zolbetuximab + chemotherapy versus nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5, following clarification response

Intervention	Total life years	Total QALYs	Total Costs (£, with PAS)	Incr. QALYs	Incr. Costs (£)	ICER (£/QALY)
Zolbetuximab + chemotherapy						
Nivolumab + chemotherapy				0.00		
Chemotherapy				0.69		
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; PAS: Patient Access Acheme; SW = South-West						

Overall, the technology is modelled to affect QALYs by:

- Increased survival in the progression free and OS health states

Overall, the technology is modelled to affect costs by:

- Its higher drug acquisition costs as compared to chemotherapy
- The need for CLDN18.2 testing (£176 per patient)

EAG comment: The main concerns of the EAG relate to: a) use of zolbetuximab NMA results for nivolumab in the economic model, b) not providing fully incremental results, and c) probabilistic results for the secondary analyses.

a) In the economic model, the NMA results for nivolumab + chemotherapy are absent. Instead, the NMA results for zolbetuximab are used, implying equal treatment effectiveness. The EAG deems this approach to be inappropriate and has asked for a cost effectiveness comparison of zolbetuximab versus nivolumab (clarification question B3), however the company deems the cost-comparison approach to be most appropriate. This is a key issue as the time-varying relative effects from the NMA are different for zolbetuximab + chemotherapy and nivolumab + chemotherapy (CS Addendum Table 17 for PFS and 22 for OS) are different, and this should be reflected in the model outcomes.
b) The NICE cost effectiveness manual dictates that fully incremental cost effectiveness results should be presented, however the company did not provide this.
c) The company has not provided probabilistic results in the Addendum for the secondary analyses.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The parameters that have the greatest effect on the ICER (based on the company's one-way sensitivity analyses) are:

- Post-progression disease management costs
- Pre-progression disease management costs
- Utility values pre- and post-progression

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER:

- Varying the method of PFS and OS extrapolation modelling (scenarios using parametric functions based on the zolbetuximab trials)
- Including treatment effect waning for zolbetuximab

EAG comment: The main concerns of the EAG relate to the PSA runtime, which is over 2 hours for 1,000 simulations. This hampers a thorough assessment of uncertainty as running the PSA for multiple scenarios is infeasible. Therefore, the EAG only conducted a PSA on the EAG base-case scenario and secondary scenario.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The relevance of the model structure and assumptions were validated through consultation with UK clinicians and health economists.

5.3.2 Technical verification

A technical review of the cost effectiveness model was conducted by an independent economist. A cell-by-cell verification process was also conducted to allow checking of all input calculation, formulae and Visual Basic code.

5.3.3 Comparisons with other technology appraisals

Cross validation with other TAs was performed for different input parameters, the model structure and other model features (see for example Table 16 of the CS).

5.3.4 Comparison with external data used to develop the economic model

Validation of extrapolation data was performed against observed survival rates from SPOTLIGHT and GLOW and reported in Appendix N.

5.3.5 Comparison with external data not used to develop the economic model

Validation was also conducted against real-world evidence and one meta-analysis on the OS rates at 5 years. The predicted OS rate at Year 5 for chemotherapy was similar to the reported OS rates from the real-world and historical evidence with sufficient follow-up.

EAG comment: The company's validation efforts were broadly appropriate. In response to clarification question B29, the company provided further evidence on their technical verification efforts, including the TECH-VER checklist. The EAG is satisfied that internal verification was sufficient. The company's cross validation efforts were hampered by the volume of redacted evidence in NICE documentation. Only higher-level assumptions such as the absence of treatment effect waning or assumptions relating to the model structure or incorporation of utility values could be compared – the impact on model outcomes could not be assessed. However, the EAG noted a lack of transparency in the company's methodology and discrepancies between the company's reporting and what was actually done in the model. This hampered the EAG's validation efforts. Examples include: i) modelling DoT, ii) use of the NMA, iii) utility values used, iv) use of ToGA trial estimates, v) total costs per treatment arm, and vi) unclear inflation adjustment for terminal care costs.

i) Regarding DoT, it is not clear which scenario was modelled and which curves were chosen based on what evidence, as the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values in CS Addendum Table 56 and 57 do not seem to correspond to the parametric curves chosen in the economic model (for example for chemotherapy, the exponential curve seems to be chosen in the model, while based on AIC and BIC for pooled SPOTLIGHT and GLOW, the gamma distribution would be a better fit). Next, it is unclear how DoT curves were derived for nivolumab + chemotherapy, i.e. it is unclear from the model whether this was based on the median DoT of nivolumab or based on the relative effects from the NMA.
ii) From the CS, it was unclear how the NMA was exactly used to obtain cost effectiveness outcomes. For the primary analysis, the NMA was not needed but was used by the company. For the secondary analysis, the NMA was needed to obtain relative effectiveness for zolbetuximab and nivolumab, however the company used the NMA results for zolbetuximab to obtain cost effectiveness estimates for both zolbetuximab + chemotherapy and nivolumab + chemotherapy.
iii) In the original CS, two models (i.e., GEE and mixed-methods) were used to estimate the utility values based on the trial EQ-5D data. The results from GEE were used to inform the base-case and those from mixed-methods for a scenario analysis. After the clarification response, in the addendum and model provided by the company, new estimates were provided for the base-case based on GEE. However, the company did not provide further information justifying the new values. Likewise, in the clarification response (questions B15 and B17), the company still referred to the old utility values of GEE and only described briefly the different method used to calculate the new estimates, without further inclusion on the rationale behind the different methodology used.

iv) The company provided a scenario analysis with utility values derived from Shirowa et al.[36] (0.797 and 0.577), which used EQ-5D data from the ToGA trial. The ToGA trial was used to inform the utilities in TA208 (0.729 and 0.577) using UK tariffs. The utilities from Shirowa et al.[36] were calculated with the Japanese algorithm, and would, therefore, not be preferred for a NICE Single Technology Assessment (STA). It was unclear to the EAG why the company used the values from Shirowa et al,[36] when the utilities approved in TA208 were also available.

v) The total pre-progression costs per treatment arm reported by the company in the clarification response addendum (Table 63) did not match those calculated in the model base-case (Table 4.16). The EAG was not able to replicate the results provided by the company and is, therefore, not able to assess whether it was a reporting mistake, or the company used different calculations.

vi) A one-off terminal care costs of £5,131 was applied in the model to patients who died at the end of each cycle, based on TA208 (£4,000) and inflated from 2010 to 2023.However, TA857, published in 2021, also based their calculation on TA208, but used a value of £5,387 for the one-off terminal care costs. The company was not able to explain the difference between their calculation and the one from the TA857.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020[46]:

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[47]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Duration of AEs (Section 4.2.7)
   The duration in years of two AEs (i.e., abdominal pain and decreased white blood cell count) was set at 0 years. The EAG corrected the AE duration by dividing the duration of the AE in weeks from the publication source by the number of cycles to obtain the duration in years so it could be used for the QALY loss calculation.

6.1.1.2 Fixing violations

No violations were identified.

6.1.1.3 Matters of judgement – Primary analysis (CPS <5 gastric and GEJ, chemotherapy as comparator)

2. Assuming no vial sharing in the base-case (Section 4.2.9)
   The EAG assumed that vial sharing would not occur in its base-case, while the company's base-case included vial sharing.
3. UK representative BSA (Section 4.2.3)
   The EAG used a BSA of 1.77 m^2 based on TA857, instead of 1.70 m^2 which was obtained from the SPOTLIGHT and GLOW trials.
4. Treatment effectiveness of chemotherapy based on SPOTLIGHT and GLOW trials (Section 4.2.6)
   The EAG included only the SPOTLIGHT and GLOW trials in its base-case, in contrast to the company's approach which included the SPOTLIGHT, GLOW and CheckMate 649 trials to obtain treatment effectiveness estimates for the chemotherapy arm. OS and PFS were modelled using gamma and log-logistic parametric functions, respectively.
5. Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials (Section 4.2.6)
   The EAG used the treatment effectiveness of zolbetuximab directly from the SPOTLIGHT and GLOW trials, instead of the using evidence from the NMA. OS and PFS were modelled using log-logistic parametric functions for both parameters.
6. Onset of treatment effect waning at 5 years (Section 4.2.6)
   The EAG assumed that treatment effect waning would start at 5 years, instead of assuming no treatment effect waning.
7. Mixed-effects model for utility values (Section 4.2.8)
   The EAG preferred the utility values obtained with the mixed-effects model instead of the GEE.

6.1.1.4 Matters of judgement – Secondary analysis (CPS ≥ 5 and <10 gastric and GEJ, chemotherapy and nivolumab + chemotherapy as comparators)

The secondary analysis uses the same matters of judgement as stated above but includes nivolumab + chemotherapy as comparator in the base-case.

8. Treatment effectiveness of zolbetuximab + chemotherapy and nivolumab + chemotherapy based on the NMA (Section 4.2.6)
   The EAG derived the relative effectiveness of zolbetuximab + chemotherapy and nivolumab + chemotherapy to be derived from the NMA, using the 2-knot spline NMA results. These relative effects are applied to the chemotherapy arm outcomes based on solely SPOTLIGHT and GLOW as in matter of judgement 4 above.
9. RDI for nivolumab + chemotherapy equal to zolbetuximab + chemotherapy (Section 4.2.9)
   The EAG assumed the same RDI for nivolumab + chemotherapy as for zolbetuximab + chemotherapy, instead of assuming 100% RDI for nivolumab + chemotherapy due to a lack of data.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

10. Treatment effect waning at 3 years (Section 4.2.6)
    Scenario analysis with treatment effect waning onset at 3 years, instead of 5 years.
11. Treatment effect waning at 4 years (Section 4.2.6)

Scenario analysis with treatment effect waning onset at 4 years, instead of 5 years.

12. AE utilities derived from TA208 (Section 4.2.8)
    Scenario analysis using the utility values of TA208, instead of the ones obtained from the mixed-effects model based on SPOTLIGHT and GLOW. However, it should be noted that the pre-progression value used in TA208 increases over time, whilst the post-progression value is for patients who have progressed after two lines of treatment.
13. Overall survival of chemotherapy modelled with log-logistic extrapolation curve (Section 4.2.6)
    Scenario analysis using the log-logistic extrapolation curve for chemotherapy OS instead of the gamma.

6.1.3 EAG subgroup analyses

The primary and secondary analyses were effectively subgroup analyses. No other subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Relevant comparators in different sub-populations (key issue 4)	4.2.4	Transparency	Primary analysis: PD-L1 CPS <5 gastric and GEJ Secondary analysis: PD-L1 CPS ≥ 5 and <10 gastric and GEJ. Here, relative effectiveness from the NMA should be included by the company, even with the caveat that these may be conservative.	+/-	No	For the comparison with nivolumab + chemotherapy a fully incremental cost-effectiveness analysis should be provided, using the relative treatment effects of zolbetuximab + chemotherapy and nivolumab + chemotherapy from the NMA. It should be confirmed whether patients with PD-L1 CPS ≥ 10 (gastric or GEJ) are indeed not eligible for zolbetuximab unless pembrolizumab or nivolumab are contraindicated. The subgroup of patients with PD-L1 CPS ≥ 10 gastric and GEJ may become relevant if zolbetuximab is considered an effective treatment and comparator to nivolumab and pembrolizumab in this subgroup.
Uncertainty regarding the appropriateness of including the CheckMate 649 trial to	4.2.6	Bias & indirectness	The EAG preferred to exclude the CheckMate 649 trial	+	Yes (EAG MoJ 4)	The individual patient data of the CheckMate 649 trial might be suitable to obtain better long-term estimates, but a pooling method adjusting for

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
estimate chemotherapy outcomes (key issue 5)						differences in trial designs and patient selection should be used to obtain these estimates.
Appropriateness of assuming equal treatment effectiveness for zolbetuximab + chemotherapy and nivolumab + chemotherapy (key issue 6)	4.2.6	Transparency, bias & indirectness	Full cost-effectiveness analysis including the NMA results of nivolumab + chemotherapy	+	No	Full cost-effectiveness analysis including the NMA results of nivolumab + chemotherapy
Selection of extrapolation curves to estimate treatment effectiveness in the PD-L1 CPS populations (key issue 7)	4.2.6	Methods	The EAG preferred to use parametric survival modelling in the primary analysis (chemotherapy: gamma for OS and log-logistic for PFS, zolbetuximab: log-logistic for both OS and PFS), and for the secondary analysis (chemotherapy: gamma for OS and log-logistic for PFS) and the NMA for extrapolation of zolbetuximab + chemotherapy and nivolumab + chemotherapy. The log-logistic extrapolation curve for chemotherapy OS was explored in a scenario, as it could potentially better reflect the small proportion of long-term survivors.	+	Yes (EAG MoJ 5 and 9 and scenario analysis 13)	More evidence on the existence of a survival plateau.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Uncertainty regarding the existence and onset of treatment effectiveness waning (key issue 8)	4.2.6	Methods	The EAG preferred to include treatment effect waning onset at 5 years in its base-case, and explored treatment effect waning onset at 3 and 4 years	+	Partly (EAG MoJ 6 and scenario analyses 10 and 11)	Ideally, long-term follow-up data is needed to assess if and when treatment waning occurs.
Uncertainty regarding the estimated utility values (key issue 9)	4.2.8	Bias & indirectness, methods	The EAG preferred to use the utility estimates from the mixed effects model	+/-	Partly (EAG MoJ 7)	Data imputation should be performed on the collected EQ-5D data.
Post-progression treatments not being representative of UK clinical practice (key issue 10)	4.2.9	Bias & indirectness	Use post-treatment treatments aligned with UK clinical practice.	+/-	No	Post-treatment treatments in UK clinical practice should be defined.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored
EAG = External Assessment Group; FE = Fixing errors; FV = fixing violations; MJ = matters of judgement; ICER = incremental cost effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.2 and 6.3 show how individual changes impact the results plus the combined effect of all changes simultaneously. Table 6.4 shows the probabilistic results of the EAG base-case primary and secondary analyses. The exploratory scenario analyses are presented in Tables 6.5 and 6.6. These are all conditional on the EAG base-case. The analyses numbers in Tables 6.2, 6.3, 6.5 and 6.6 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic EAG base-case primary analysis

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
CS base-case after clarification						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 1. Fixing error - Duration of AEs						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 2. Matter of judgment - Assuming no vial sharing						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 3. Matter of judgment – UK representative BSA						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 4. Matter of judgment - Treatment effectiveness of chemotherapy based on SPOTLIGHT and GLOW trials						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 5. Matter of judgment - Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 6. Matter of judgment - Onset of treatment effect waning at 5 years						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 7. Matter of judgment - Mixed effects model for utility values						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case (Primary analysis)						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs: adverse events; CS: company submission; EAG: Evidence Assessment Group; LY: Life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; UK: United Kingdom

Table 6.3: Deterministic EAG base-case secondary analysis

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
CS base-case after clarification						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
EAG analysis 8. Matter of judgment - EAG base-case primary analysis + Treatment effectiveness of zolbetuximab + chemotherapy and nivolumab + chemotherapy based on the NMA						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 9. Matter of judgment - EAG base-case primary analysis + Treatment effectiveness of zolbetuximab + chemotherapy and nivolumab + chemotherapy based on the NMA + RDI for nivolumab						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case secondary analysis						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs: adverse events; CS: company submission; EAG: Evidence Assessment Group; LY: Life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SW: south-west; UK: United Kingdom

Table 6.4: Probabilistic EAG base-case primary and secondary analyses

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
CS base-case primary analysis after clarification						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case primary analysis						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case secondary analysis						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs: adverse events; CS: company submission; EAG: Evidence Assessment Group; LY: Life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SW: south-west; UK: United Kingdom						

Table 6.5: Deterministic scenario analyses (conditional on EAG base-case primary analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
EAG base-case primary analysis						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 10. Exploratory scenario - Treatment effect waning at 3 years						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 11. Exploratory scenario - Treatment effect waning at 4 years						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
EAG analysis 12. Exploratory scenario – AE utilities derived from TA208						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 13. Exploratory scenario – log-logistic curve for chemotherapy OS						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs: adverse events; CS: company submission; EAG: Evidence Assessment Group; LY: Life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SW: south-west; UK: United Kingdom

Table 6.6: Deterministic scenario analyses (conditional on EAG base-case secondary analysis)

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
EAG base-case secondary analysis						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 10. Exploratory scenario - Treatment effect waning at 3 years						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 11. Exploratory scenario - Treatment effect waning at 4 years						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total LY	Total QALYs	Incremental costs zolbetuximab versus comparator	Incremental QALYs zolbetuximab versus comparator	ICER (£/QALY) zolbetuximab versus comparator
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 12. Exploratory scenario – AE utilities derived from TA208						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 13. Exploratory scenario – log-logistic curve for chemotherapy OS						
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs: adverse events; CS: company submission; EAG: Evidence Assessment Group; LY: Life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SW: south-west; UK: United Kingdom

6.3 EAG's preferred assumptions

The estimated EAG base-case primary analysis ICER (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained. For the secondary analysis, the ICERs were [redacted] versus nivolumab + chemotherapy and [redacted] versus chemotherapy. The probabilistic EAG base-case primary analysis indicated a cost effectiveness probability of 1.9% for zolbetuximab + chemotherapy versus chemotherapy at a willingness to pay threshold £36,000 per QALY gained. The secondary analysis indicated cost effectiveness probabilities of 0.6% for zolbetuximab +chemotherapy versus chemotherapy and 0.0% for zolbetuximab + chemotherapy versus nivolumab + chemotherapy at a willingness to pay threshold £36,000 per QALY gained. The most influential adjustments were related to the appropriate evidence and survival curves to estimate treatment effectiveness and assumptions regarding treatment effect waning. The ICER increased most in the scenario analyses with alternative assumptions regarding treatment effect waning and, in the secondary scenario, when the log-logistic curve for chemotherapy OS is used.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model complied with the NICE reference case, with the exception of the presentation of fully incremental results. The most prominent issues highlighted by the EAG are shown in the key issue tables in Section 1.5.

The first important issue is that different comparators are relevant in different sub-populations based on PD-L1 CPS score. The following populations were defined by the EAG: PD-L1 CPS <5 gastric and GEJ population where chemotherapy is the only relevant comparator and the PD-L1 CPS ≥ 5 and <10 gastric and GEJ population where chemotherapy and nivolumab + chemotherapy are comparators. Next to these two populations, the subgroup of patients with PD-L1 CPS ≥ 10 gastric and GEJ may become relevant if zolbetuximab is considered an effective treatment and comparator to nivolumab and pembrolizumab in this subgroup. With potential approval of treatments, potentially relevant future subgroups include: PD-L1 CPS ≥ 1 gastric and GEJ (subject to approval of pembrolizumab in this population). The company modelled a primary and secondary analysis: the primary analysis includes a comparison between zolbetuximab + chemotherapy versus chemotherapy in the whole gastric and GEJ population (regardless of PD-L1 status), and the secondary analysis includes a comparison between zolbetuximab + chemotherapy versus nivolumab + chemotherapy and chemotherapy in the population PD-L1 CPS ≥ 5. The EAG deems the primary analysis to be relevant in the PD-L1 CPS <5 gastric and GEJ population, where chemotherapy is the only relevant comparator to zolbetuximab + chemotherapy and the secondary analysis to be relevant in the PD-L1 CPS ≥ 5 and <10 gastric and GEJ population, where nivolumab + chemotherapy and chemotherapy are comparators to zolbetuximab + chemotherapy.

Besides the definition of eligible comparators in different sub-populations, there was uncertainty regarding the appropriateness of including the CheckMate 649 trial to estimate treatment effectiveness outcomes for chemotherapy. CheckMate 649 has the potential benefit of longer follow-up and 5-year and 10-year OS estimates for chemotherapy are higher., however the naïve pooling method of the trials is suboptimal. In addition, the selection of extrapolation curves to estimate treatment effectiveness in the primary and secondary analysis is likely inappropriate. In the primary analysis, the company uses spline modelling to extrapolate the OS and PFS survival curves for chemotherapy arm and the NMA for the zolbetuximab + chemotherapy arm. The EAG deems spline modelling to be inappropriate as parametric survival curves have a good fit (both visually and statistically) and deems the NMA to be unnecessary for the primary analysis. For the secondary analysis, the NMA is appropriate to obtain relative treatment effects, however the NMA results for nivolumab + chemotherapy are not used in the cost effectiveness model. Instead, the NMA results for zolbetuximab + chemotherapy are used for nivolumab + chemotherapy, assuming equal treatment effectiveness. Next, there was uncertainty regarding the existence and onset of treatment effectiveness waning for zolbetuximab. Treatment effectiveness waning was not implemented in the model in the base-case (but explored in scenarios) as the data does not show signs of treatment effectiveness waning, but follow-up is limited. There was also uncertainty regarding the estimation of utility values, as no data imputation was performed for the EQ-5D data that was collected, which could have introduced bias in the estimates. A GEE model was used to estimate utility values, which resulted in relatively high estimates as compared to published estimates in the same disease. Last, post-progression treatments included in the model (docetaxel and paclitaxel) were found to be not in line with UK clinical practice (mainly FOLFIRI (folinic acid, 5-fluorouracil, and irinotecan) in England, and docetaxel and irinotecan in Scotland).

The CS base-case ICERs (deterministic) were [redacted] versus chemotherapy in the primary analysis and [redacted] versus nivolumab + chemotherapy and [redacted] versus chemotherapy in the secondary scenario. This result does not include the application of a 1.2x QALY weight, instead a modified WTP threshold of £36,000 was used. The estimated EAG base-case ICERs (deterministic), based on the EAG preferred assumptions highlighted in Section 6.1 were [redacted] versus chemotherapy in the primary analysis and [redacted] versus nivolumab + chemotherapy and [redacted] versus chemotherapy in the secondary analysis. The probabilistic EAG base-case primary analysis indicated a cost effectiveness probability of 1.9% for zolbetuximab + chemotherapy versus chemotherapy at a willingness to pay threshold £36,000 per

QALY gained. The secondary analysis indicated cost effectiveness probabilities of 0.6% for zolbetuximab +chemotherapy versus chemotherapy and 0.0% for zolbetuximab + chemotherapy versus nivolumab + chemotherapy at a willingness to pay threshold £36,000 per QALY gained. The most influential adjustments were related to the appropriate evidence used to inform treatment effectiveness, selection of survival curves to estimate treatment effectiveness and assumptions regarding treatment effect waning. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment effect waning and, in the secondary scenario, when the log-logistic curve for chemotherapy OS is used..

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of zolbetuximab + chemotherapy, which can be partly resolved by the company by further clarification and conducting further analyses. Further clarification is needed on whether patients with PD-L1 CPS ≥ 10 (gastric or GEJ) are indeed not eligible for zolbetuximab unless pembrolizumab or nivolumab are contraindicated. If this is not the case, analyses should be provided for these populations, with inclusion of appropriate comparators in the CEA. Further analyses are potentially needed to appropriately include CheckMate 649, including the selection of most appropriate extrapolation curves in the model and further justification of the existence of a survival plateau. In addition, analysis are needed to obtain fully incremental cost effectiveness results for the comparison between zolbetuximab + chemotherapy and nivolumab + chemotherapy without the assumption of equal treatment effectiveness, to justify the assumption of no treatment waning, to obtain better utility estimates using data imputation and a mixed effects model, and to update the post-progression treatments included in the model. Therefore, the EAG believes that neither the CS nor the EAG report contain an unbiased ICER of zolbetuximab + chemotherapy compared with the relevant comparators.

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Single Technology Appraisal

Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma ID5123

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 24th June 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 PD-L1 status is not a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 14 The EAG report states 'In responding to the EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC analysis but the company used the overall population with mixed status of PD-L1 CPS from the included trials (SPOTLIGHT and GLOW) in the ITC analysis.'	Please could you amend this to read: 'In responding to the EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, and because evidence supports that PD-L1 CPS does not affect outcomes for zolbetuximab with chemotherapy and chemotherapy alone, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC analysis. Instead, the company used the overall population with mixed status of PD-L1 CPS from the included trials (SPOTLIGHT and GLOW) in the ITC analysis.'	The current statement omits factual evidence that informed the company's approach for the ITC, which is needed for the reader to make an informed judgement about the extent to which the company's methodology is approach, and which is consistent with the EAG's view on PD-L1 CPS ('*The EAG notes that the subpopulations mentioned are not a requirement of the scope and that PDL-1 status is not a treatment effect modifier for zolbetuximab nor chemotherapy*.' ; page 129).	Amended to increase accuracy.

EAG report page 15 The EAG report states 'Given that the ITC analysis was based on the overall population with mixed status of PD-L1 CPS from the zolbetuximab trials (SPOTLIGHT and GLOW) and the PD-L1 CPS ≥5 subgroup from the CheckMate-649 trial and the PD-L1 CPS ≥1 subgroup from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859), there was considerable heterogeneity in patients' PD-L1 CPS status between included trials in the ITC.'	Please could you amend this to read: 'Given that the ITC analysis was based on the overall population with mixed status of PD-L1 CPS from the zolbetuximab trials (SPOTLIGHT and GLOW) and the PD-L1 CPS ≥5 subgroup from the CheckMate-649 trial and the PD-L1 CPS ≥1 subgroup from the pembrolizumab trials (KEYNOTE-062 and KEYNOTE-859), there was considerable heterogeneity in patients' PD-L1 CPS status between included trials in the ITC (though it should be noted patients' PD-L1 CPS status is not a treatment modifier for chemotherapy or zolbetuximab plus chemotherapy).'	In its summary of heterogeneity, the EAG report omits mention that the primary dimension of heterogeneity (patients' PD-L1 CPS status) is not a treatment modifier for either chemotherapy or zolbetuximab plus chemotherapy. The amendment places this limitation of the evidence base in context, enabling the reader to make an informed judgement as to the extent heterogeneity undermines the assumption of exchangeability.	Amended to increase accuracy.
EAG report page 98 The EAG report states: 'Table 3.32 presents a summary of the patient characteristics at baseline for the ITT population in SPOTLIGHT and GLOW, and for patients with PD-L1 CPS ≥ 5 in CheckMate-649. There was	Please can you amend this to read: 'Table 3.32 presents a summary of the patient characteristics at baseline for the ITT population in SPOTLIGHT and GLOW, and for patients with PD-L1 CPS ≥ 5 in CheckMate-649. There was considerable heterogeneity of PD-L1 CPS status for the included populations between SPOTLIGHT and	Clarifying that PD-L1 CPS is not a treatment effect modifier for chemotherapy and zolbetuximab plus chemotherapy places this evidence in context enabling the reader to make an informed judgement as to the extent heterogeneity	Amended to increase accuracy.

considerable heterogeneity of PD-L1 CPS status for the included populations between SPOTLIGHT and GLOW trials and the PD-L1 CPS ≥ 5 subgroup in CheckMate-649.'	GLOW trials and the PD-L1 CPS ≥ 5 subgroup in CheckMate-649. However, it should be noted that PD-L1 CPS is not a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy.'	undermines the assumption of exchangeability.	
EAG report page 116 The EAG report states: 'Heterogeneity of PD-L1 CPS status was observed for the included populations between SPOTLIGHT and GLOW trials and the PD-L1 CPS ≥ 5 subgroup in the CheckMate-649 trial.'	Please can you amend to this to read: "Heterogeneity of PD-L1 CPS status was observed for the included populations between SPOTLIGHT and GLOW trials and the PD-L1 CPS ≥ 5 subgroup in the CheckMate-649 trial. However, it should be noted that PD-L1 CPS is not a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy."	Clarifying that PD-L1 CPS is not a treatment effect modifier for chemotherapy and zolbetuximab plus chemotherapy places this evidence in context enabling the reader to make an informed judgement as to the impact of this heterogeneity on the reliability of estimated treatment effects.	Amended to increase accuracy.
EAG report page 116 The EAG report states: 'Therefore, there was considerable heterogeneity in PD-L1 CPS status at baseline for the included populations between included trials in the updated NMA.'	Please can you amend to this to read: 'Therefore, there was considerable heterogeneity in PD-L1 CPS status at baseline for the included populations between included trials in the updated NMA. However, it should be noted that PD-L1 CPS is not a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy.'	Clarifying that PD-L1 CPS is not a treatment effect modifier for chemotherapy and zolbetuximab plus chemotherapy places this evidence in context enabling the reader to make an informed judgement as to the impact of this heterogeneity	Amended to increase accuracy.

		on the reliability of estimated treatment effects.	
EAG report page 115 and 118: The EAG report states: 'In responding to EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC but the company used the overall population from the included trials (SPOTLIGHT and GLOW) in the ITC.'	Please could you amend this to read: 'In responding to the EAG's request, the company stated that as the analysis of the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) was a post-hoc subgroup analysis (rather than a pre-specified subgroup analysis), the results from the post-hoc subgroup analysis should be treated with caution. Given this, and because evidence supports that PD-L1 CPS does not affect outcomes for zolbetuximab with chemotherapy and chemotherapy alone, the company did not use the PD-L1 CPS ≥5 subgroup from the included trials (SPOTLIGHT and GLOW) in the ITC analysis but the company used the overall population with mixed status of PD-L1 CPS from the included trials (SPOTLIGHT and GLOW) in the ITC analysis.'	The current statement omits factual evidence that informed the company's approach for the ITC, which is needed for the reader to make an informed judgement about the extent to which the company's methodology is approach.	Amended to increase accuracy.

EAG report page 118 The EAG report states: 'Therefore, there was considerable heterogeneity in patients' PD-L1 CPS status at baseline between included trials in the updated NMA.'	Please can you amend to this to read: 'Therefore, there was considerable heterogeneity in patients' PD-L1 CPS status at baseline between included trials in the updated NMA. However, it should be noted that PD-L1 CPS is not a treatment effect modifier for chemotherapy or zolbetuximab plus chemotherapy.'	Clarifying that PD-L1 CPS is not a treatment effect modifier for chemotherapy and zolbetuximab plus chemotherapy places this evidence in context enabling the reader to make an informed judgement as to the impact of this heterogeneity on the reliability of estimated treatment effects.	Amended to increase accuracy.

Issue 2 Pembrolizumab plus chemotherapy in patients with PD-L1 CPS ≥ 1 is a relevant subgroup

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 14 Table 1.2 of the EAG report states that 'Responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also	Please can you amend this to read: 'Responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also provided additional network meta-analysis (NMA) results by incorporating pembrolizumab plus chemotherapy as	The logic for stating that PD-L1 CPS ≥1 is not a relevant subgroup is unclear. As per the final scope, PD-L1 CPS ≥ 1 is an appropriate subgroup for pembrolizumab plus chemotherapy in patients with G/GEJ subject to NICE appraisal (ID4030[1]). The additional NMA provided at clarification questions was relevant to this comparator	Not a factual inaccuracy: the point is that the subgroup PD-L1 CPS ≥1 needs to be subdivided into the three subgroups each with a set of comparators that applies to all patients in each of those subgroups.

provided additional network meta-analysis (NMA) results by incorporating pembrolizumab plus chemotherapy as a comparator for patients with PD-L1 CPS ≥1. The EAG notes that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators.'	a comparator for patients with PD-L1 CPS ≥1.'	and was conducted in response to the EAG's request: '*B3 c) For patients with CPS 1 or more and for gastric or GEJ adenocarcinoma: the reason for not performing a comparison with pembrolizumab + chemotherapy was that it was not recommended by NICE(ID4030). The EAG notes that this guidance was not yet final, so it would prefer if a cost effectiveness analysis could be provided against pembrolizumab + chemotherapy*.' Furthermore, as discussed at the scoping meeting, due to the similarities in clinical outcomes, splitting CPS subgroups by primary cancer site (i.e. gastric or GEJ) was not considered appropriate. Related specifically to the statement: '*given that it is subdivided into three further subgroups, CPS ≥ 10 gastric,*	

		CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators', according to current NICE guidance the comparators in the PD-L1 CPS ≥ 10 gastric group and the PD-L1 CPS ≥ 5 and <10 gastric and GEJ group are the same, i.e., chemotherapy and nivolumab with chemotherapy via TA857.	
EAG report Page 27 The EAG report states 'In responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also provided additional network meta-analysis (NMA) results by incorporating pembrolizumab with	Please can this be amended to read: 'In responding to the EAG's request, the company stated that patients with high PD-L1 CPS are likely to receive a checkpoint inhibitor unless contraindicated, which might imply that patients with CPS ≥ 10 are ineligible for zolbetuximab. They also provided additional network meta-analysis (NMA) results by incorporating pembrolizumab with chemotherapy as a comparator for patients with PD-L1 CPS ≥1 for gastric cancer or GEJ adenocarcinoma. The EAG recommends that either the company	The logic for stating that PD-L1 CPS ≥1 is not a relevant subgroup is unclear. As per the final scope, PD-L1 CPS ≥ 1 is an appropriate subgroup for pembrolizumab plus chemotherapy in patients with G/GEJ subject to NICE appraisal (ID4030[1]). The additional NMA provided at clarification questions was relevant to this comparator and was conducted in response to the EAG's request: '*B3 c) For patients*	Not a factual inaccuracy: the point is that the subgroup PD-L1 CPS ≥1 needs to be subdivided into the three subgroups each with a set of comparators that applies to all patients in each of those subgroups.

chemotherapy as a comparator for patients with PD-L1 CPS ≥1 for gastric cancer or GEJ adenocarcinoma. The EAG notes that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators. In conclusion, the EAG recommends that either the company clarifies that patients with PD-L1 CPS ≥ 10 are ineligible for zolbetuximab or the clinical effectiveness and cost effectiveness for the subgroup of GEJ patients with PD-L1 CPS ≥ 10 should be assessed by using pembrolizumab plus chemotherapy as a comparator. Pembrolizumab + chemotherapy could also be included as a comparator for all subgroups should there be a positive	clarifies that patients with PD-L1 CPS ≥ 10 are ineligible for zolbetuximab or the clinical effectiveness and cost effectiveness for the subgroup of GEJ patients with PD-L1 CPS ≥ 10 should be assessed by using pembrolizumab plus chemotherapy as a comparator.'	*with CPS 1 or more and for gastric or GEJ adenocarcinoma: the reason for not performing a comparison with pembrolizumab + chemotherapy was that it was not recommended by NICE(ID4030). The EAG notes that this guidance was not yet final, so it would prefer if a cost effectiveness analysis could be provided against pembrolizumab + chemotherapy*.' Furthermore, as discussed at the scoping meeting, due to the similarities in clinical outcomes, splitting CPS subgroups by primary cancer site (i.e. gastric or GEJ) was not considered appropriate. Related specifically to the statement: '*given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their*	

recommendation by NICE for PD-L1 CPS ≥1.'		*comparators'*, according to current NICE guidance the comparators in the PD-L1 CPS ≥ 10 gastric group and the PD-L1 CPS ≥ 5 and <10 gastric and GEJ group are the same, i.e., chemotherapy and nivolumab with chemotherapy via TA857.	
EAG report page 130-131 The EAG report states 'As such, the company expect the cost effectiveness analysis to be conservative and instead assumed equal effectiveness, resulting in [redacted] for zolbetuximab versus pembrolizumab (Table 70 in the addendum to the response to clarification letter). It is also important to note that this subgroup is inappropriate given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10	Please can this be amended to read: 'As such, the company expect the cost effectiveness analysis to be conservative and instead assumed equal effectiveness, resulting in [redacted] for zolbetuximab versus pembrolizumab (Table 70 in the addendum to the response to clarification letter).'	The logic for stating that PD-L1 CPS ≥1 is not a relevant subgroup is unclear. As per the final scope, PD-L1 CPS ≥ 1 is an appropriate subgroup for pembrolizumab plus chemotherapy in patients with G/GEJ subject to NICE appraisal (ID4030[1]). The additional NMA provided at clarification questions was relevant to this comparator, and was conducted in response to the EAG's request: '*B3 c) For patients with CPS 1 or more and for gastric or GEJ adenocarcinoma: the reason*	Not a factual inaccuracy: the point is that the subgroup PD-L1 CPS ≥1 needs to be subdivided into the three subgroups each with a set of comparators that applies to all patients in each of those subgroups.

GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators (see below).'		*for not performing a comparison with pembrolizumab + chemotherapy was that it was not recommended by NICE(ID4030). The EAG notes that this guidance was not yet final, so it would prefer if a cost effectiveness analysis could be provided against pembrolizumab + chemotherapy*.' Furthermore, as discussed at the scoping meeting, due to the similarities in clinical outcomes, splitting CPS subgroups by primary cancer site (i.e. gastric or GEJ) was not considered appropriate. Related specifically to the statement: '*given that it is subdivided into three further subgroups, CPS ≥ 10 gastric, CPS ≥ 10 GEJ and CPS ≥ 5 and <10 gastric and GEJ, which differ in their comparators'*, according to current NICE guidance the comparators in the PD-L1	

		CPS ≥ 10 gastric group and the PD-L1 CPS ≥ 5 and <10 gastric and GEJ group are the same, i.e., chemotherapy and nivolumab with chemotherapy via TA857.	

Issue 3 Modelled population

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 25 The EAG report states: 'According to the company the decision problem addressed in the company submission (CS) is slightly different from that specified in the final scope, which does not specify that the population will include metastatic human epidermal growth factor receptor (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma	Please can this statement be removed or amended to clarify that there is a minor difference in terminology, with no impact to the population in the decision problem.	There is a minor difference in terminology between the NICE scope and the company submission, which has no impact to the population in the decision problem. While the NICE scope refers to "advanced unresectable" cancer, the company submission refers to "locally advanced unresectable or metastatic" cancer. As discussed in response to clarification question A8, the term "advanced unresectable"	Not a factual inaccuracy.

whose tumours are claudin (CLDN) 18.2 positive.'		refers to patients with locally advanced unresectable adenocarcinoma as well as patients with metastatic adenocarcinoma.	
EAG report page 128 The EAG report states: 'In both trials, patients were previously untreated.'	Please can you amend this to read: 'adult patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic G/GEJC adenocarcinoma who have not previously been treated for advanced/metastatic disease with chemotherapy'	The amendment aligns with the modelled population and the wording included in the company submission (see Document B Table 16).	Not a factual inaccuracy.
EAG report page 129 The EAG report states: 'For both primary and secondary analyses, the company used the ITT populations from SPOTLIGHT and GLOW to inform the effectiveness of zolbetuximab. The company considered this appropriate also for the secondary analysis for the following three reasons:	Please can you amend this to: 'For both primary and second analyses, the company used the ITT populations from SPOTLIGHT and GLOW to estimate the effectiveness of zolbetuximab + chemotherapy rather than restricting the zolbetuximab trial data by PD-L1 CPS score. This is for three reasons: • PD-L1 expression was not considered a prognostic factor or treatment-effect modifier for chemotherapy according to literature, and as such is only	The amendment aligns with the modelled population for both the primary and second analyses, and the wording included in the company submission and responses to clarification questions (e.g., see response to question A6).	Amended to increase accuracy.

• PD-L1 expression was not considered a prognostic factor or treatment effect modifier for chemotherapy according to literature • No evidence is known on PD-L1 status affecting the efficacy of zolbetuximab • PD-L1 CPS was not a pre-specified subgroup analysis, and approximately one third of the patients enrolled in the trials could not be tested for PD-L1 CPS.'	predictive of greater efficacy for nivolumab vs chemotherapy; • The company is not aware of any biological mechanism by which PD-L1 status can affect the efficacy of zolbetuximab; • PD-L1 CPS was not a pre-specified subgroup analysis, and approximately one third of the patients enrolled in the trials could not be tested for PD-L1 CPS, thereby increasing the risk of imbalance in baseline characteristics and uncertainty in the results. The company noted that the efficacy of zolbetuximab + chemotherapy should therefore not be influenced by PD-L1 CPS score; therefore breaking randomisation and using a CPS-based subpopulation for zolbetuximab will increase the uncertainty regarding its efficacy in this population.'		

EAG report page 130 The EAG report states, that for the comparison against nivolumab, 'A cost comparison was performed because *"nivolumab is considered broadly equivalent to zolbetuximab"'.*	Please amend this to: 'Given that there were no trials which directly compared nivolumab + chemotherapy (PD-L1 CPS ≥ 5) with zolbetuximab + chemotherapy, the relative effectiveness was estimated from the spline-based ITC. The ITC found that the estimates of treatment effectiveness were very similar between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5, for both OS and PFS. Given these results, recent clinical guidelines recommending both zolbetuximab + chemotherapy and checkpoint inhibitors should be considered in patients with PD-L1 CPS ≥ 5 [2] , and the NICE committee's preferred approach in the recent pembrolizumab appraisal (ID4030) whereby a cost-minimisation approach (comparing nivolumab + chemotherapy to pembrolizumab + chemotherapy) was adopted, with the evidence indicating no difference in efficacy, [1] the company used a simplifying assumption whereby the OS and PFS for nivolumab + chemotherapy in	This amendment aligns with the reasoning for conducting a cost-comparison for zolbetuximab + chemotherapy vs nivolumab + chemotherapy, and the wording included in the company submission and addendum (e.g., see, for example, Document B Section B.3.3.3.1 page 118).	Not a factual inaccuracy. In the CS document B, the company states: "As part of secondary analysis, a cost comparison was made between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients whose tumours express PD-L1 with a CPS of 5 or more"

	patients with PD-L1 CPS ≥ 5 were set equal to that for zolbetuximab + chemotherapy. ‘		
EAG report page 131 The EAG report incorrectly states that pembrolizumab is currently recommended in patients with PD-L1 CPS ≥ 10 and gastric cancer, and incorrectly states the analyses that were requested clarification question B3: • CPS ≥ 10 gastric: in this population, both nivolumab and pembrolizumab are recommended by NICE. According to the company, zolbetuximab is unlikely to be used in this subgroup unless pembrolizumab or	Please can you amend this to: • CPS ≥ 10 gastric: in this population, nivolumab is recommended by NICE. According to the company, zolbetuximab is unlikely to be used in this subgroup unless nivolumab is contraindicated. Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers that the company should provide further clarification on whether zolbetuximab should not be used in this population unless nivolumab is contra-indicated. • CPS ≥ 10 GEJ: in this population, nivolumab and pembrolizumab are recommended. According to the company, zolbetuximab is unlikely to be used in this subgroup unless	This amendment aligns with the current NICE recommendations for Nivolumab + chemotherapy (TA857)[4] pembrolizumab + chemotherapy (TA737)[5] and the analyses that were requested in clarification question B3.	Amended

nivolumab are contraindicated. Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers that the company should provide further clarification on whether zolbetuximab should not be used in this population unless nivolumab is contra-indicated. • CPS ≥ 10 GEJ: in this population, nivolumab is recommended. According to the company, zolbetuximab is unlikely to be used in this subgroup unless nivolumab is contraindicated. A comparison against nivolumab has not been provided by the company despite the EAG's request in clarification question B3.	pembrolizumab or nivolumab are contraindicated. A comparison against pembrolizumab has not been provided by the company despite the EAG's request in clarification question B3. Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers as above that the company should provide further clarification on whether zolbetuximab should not be used in this population unless pembrolizumab is contra-indicated.'		

Therefore, this subgroup of patients might not be eligible for zolbetuximab. The EAG considers as above that the company should provide further clarification on whether zolbetuximab should not be used in this population unless nivolumab is contra-indicated.'			
EAG report page 131 The EAG report states: 'CPS ≥ 5 and <10 gastric and GEJ: in this population, the available comparators are chemotherapy and nivolumab and cost effectiveness is explored in the secondary analysis. The EAG requested a cost effectiveness analysis for this comparison, but the company only provided one where equal effectiveness was assumed, with differences only in adverse events, leading to a minimal QALY difference. The company	Please amend this to: CPS ≥ 5 and <10 gastric and GEJ: in this population, the available comparators are chemotherapy and nivolumab and cost effectiveness is explored in the secondary analysis. The EAG requested a cost effectiveness analysis for the comparison between zolbetuximab + chemotherapy and nivolumab + chemotherapy in patients with PD-L1 CPS ≥ 5. The company provided a cost-effectiveness analysis where equal effectiveness for PFS and OS was assumed, with differences only in adverse events, leading to a minimal QALY difference. The company argued	The current statement is misleading because: 1. In their questions for clarification, the EAG did not request a cost-effectiveness analysis comparing zolbetuximab + chemotherapy to chemotherapy alone and nivolumab + chemotherapy in the subgroup with PD-L1 CPS ≥ 5 and <10 gastric and GEJ; the EAG questions A6 and B3 asked for a cost-	Amended for clarity.

argued that the relative effectiveness estimate from the NMA was possibly biased in favour of nivolumab because the proportions of patients with higher CPS status were expected to be higher in CheckMate trials than in SPOTLIGHT and GLOW – and that at a CPS status ≥ 10, checkpoint inhibitors would be preferred unless otherwise indicated.	that the relative effectiveness estimate from the NMA was possibly biased in favour of nivolumab because PD-L1 CPS is a treatment modifier for nivolumab, and the proportions of patients with higher CPS status were expected to be higher in CheckMate trials than in clinical practice, given that, at a CPS status ≥ 10, checkpoint inhibitors would be preferred unless otherwise indicated.	effectiveness analysis in the group with PD-L1 CPS ≥ 5, which the company provided. 2. In the company's response to question B3a, the company explained that the proportion of patients with high PD-L1 CPS in clinical practice, among those who are considered for either zolbetuximab and nivolumab, is likely to be lower than in the CheckMate 649 PD-L1 CPS ≥ 5 subgroup; the company did not compare to the proportion of patients with high PD-L1 CPS in the SPOTLIGHT and GLOW trials.	

EAG report Page 132 Table 4.7 of the EAG report incorrectly states that Nivolumab + chemotherapy is not a relevant comparator in CPS ≥10 GEJ and that pembrolizumab + chemotherapy is relevant comparator in CPS ≥10 gastric and CPS ≥10 GEJ.	Please can you amend Table 4.7 to state that nivolumab + chemotherapy is relevant comparator in CPS ≥10 gastric and CPS ≥10 GEJ and pembrolizumab + chemotherapy is only relevant comparator in CPS ≥10 GEJ.	This amendment aligns with the current NICE recommendations for nivolumab + chemotherapy (TA857)[4] pembrolizumab + chemotherapy (TA737).[5]	Amended.

Issue 4 Company approach to OS, PFS and DoT

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 16-17 The EAG report states 'Therefore, the relative effectiveness of zolbetuximab is likely overestimated in the 5-year estimates and underestimated in the long-term, however due to discounting and a greater proportion of the population being alive at 5 years compared to 20 years,	Please remove this sentence	The statement is factually incorrect because the relative effectiveness of zolbetuximab is estimated by the NMA, therefore it is not affected by chemotherapy outcomes. In addition, the rationale for the statement 'a greater proportion of the population being alive at 5 years compared to 20 years' is unclear as by definition	Amended.

including CheckMate 649 is likely optimistic.'		survival at 20 years cannot exceed survival at 5 years	
EAG report page 17 and 172 (the same statement is in both pages). The EAG report states 'The EAG deems spline modelling to be inappropriate as parametric survival curves have a good fit (both visually and statistically). The company notes the poor fit of the parametric models for PFS because of an observed plateau, however the EAG highlights that this observed plateau (observed after approximately 2.5 years) is based on extremely low patient numbers.'	Please can this be amended to read: 'The EAG deems spline modelling to be inappropriate under the criterion of internal fit, as parametric survival curves have a good fit (both visually and statistically). This is despite within-sample goodness of fit measures demonstrating that spline-based models have better statistical fit than parametric survival models, and external evidence demonstrating that a small proportion of patients remain alive over the long-term. The company notes the poor fit of the parametric models for PFS because of an observed plateau, which is consistent with external evidence on survival with chemotherapy, however the EAG highlights that this observed plateau	The statement is misleading because goodness-of-fit refers not only to internal fit to the observed data, but also fit to external evidence; and because within-sample statistical goodness of fit of the spline models is better than of the parametric models. Regarding fit to the external data, Section B.3.3.1.1.1. of the company submission provides evidence from several sources to demonstrate the existence of a small proportion of patients remaining alive for a long time. This external evidence	Not a factual inaccuracy

	(observed after approximately 2.5 years) is based on extremely low patient numbers.'	is used to justify the use of spline-based modelling as standard parametric survival models may not be sufficiently flexible to adequately model the observed data and provide plausible extrapolations. This information is relevant so that readers and the committee can form an informed judgement about the appropriateness of the company's approach. Regarding (internal) statistical fit, the addendum provides AIC and BIC values for both spline models and parametric survival models, and stated "*Based on AIC, spline-based models provide a better fit than standard parametric models. Visually, they are also better able to match the empirical hazard function*." (p85) for overall survival and "*In summary, log-logistic is the only parametric model with an acceptable fit. Based*	

		on both AIC and BIC, the 3-knot spline-based models provide a better fit." (p103) for progression-free survival.	
EAG report page 18 The EAG report states: 'More evidence on the existence of a survival plateau, however this is not available from the SPOTLIGHT and GLOW trials.'	Please amend this statement to: 'More evidence on the existence of a survival plateau with zolbetuximab + chemotherapy, however this is not available from the SPOTLIGHT and GLOW trials.'	This amendment improves clarity as evidence of a small proportion of long-term survivorship with chemotherapy is available from external real-world studies, which are summarised in the company submission (see Document B, section B.3.3.1.1.1. Supportive evidence on survival outcomes of chemotherapy from real-world studies).	Amended to improve clarity.

EAG report page 145. The EAG report states: 'The company selected the Weibull model to extrapolate GLOW DoT'	Please amend this to read: 'The company selected the gamma model to extrapolate GLOW DoT.'	Correction of a factual inaccuracy. The gamma model is used to extrapolate GLOW DoT in the company submitted model.	This is not a factual inaccuracy. In the CS Document B the company stated that the Weibull model was selected. In the CS Addendum, it was unclear which evidence and extrapolation model was chosen by the company to model DoT.
EAG report page 136 The EAG report states: 'As a consequence, the effectiveness of nivolumab for the PD-L1 CPS score ≥ 5 and <10 subgroup specifically may be overestimated compared to zolbetuximab, as, according to the company, the effectiveness of nivolumab may increase in patients with higher CPS scores.'	Please amend this to read: 'As a consequence, the effectiveness of nivolumab for the PD-L1 CPS score ≥ 5 and <10 subgroup specifically may be overestimated compared to zolbetuximab, as 3-year trial outcomes[6] demonstrate that the effectiveness of nivolumab increases in patients with higher CPS scores.'	This statement is misleading, as it is widely accepted that PD-L1 CPS is a treatment effect modifier for nivolumab, and published effectiveness shows that the hazard ratios for PFS and OS are lower (i.e., better) for higher PD-L1 CPS cut-offs [6].	Not a factual inaccuracy.

EAG report page 172. The EAG report states: 'CheckMate 649 has the potential benefit of longer follow-up and 5-year OS estimates for chemotherapy are lower while the stated improvement in the long-term predictions is uncertain.'	Please can this be amended to accurately reflect the impact of including CheckMate 649: 'CheckMate 649 has the potential benefit of longer follow-up and 5-year OS estimates for chemotherapy are higher, as are long-term predictions.'	The amendment corrects error in interpreting 5-year impact, and appropriately reflects the impact on long-term estimates.	Amended.

Issue 5 SPOTLIGHT & GLOW trial follow-up

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report Table 1.10 page 18. The EAG report states: 'Currently, the evidence does not show a treatment effectiveness waning for zolbetuximab, but follow-up is limited to approximately 1.5 and 2 years for PFS and to 2.5 and 3	Please can you amend this to: 'Currently, the evidence does not show a treatment effectiveness waning for zolbetuximab, with follow-up is limited to approximately [redacted] for OS and PFS in both trials. '	Follow-up differs by treatment arm of both SPOTLIGHT and GLOW trials. For OS, follow-up using the final data-cut is [redacted] for the chemotherapy arms of both SPOTLIGHT and GLOW trials and for the zolbetuximab arms it is 53 months and [redacted] for SPOTLIGHT and GLOW, respectively. For PFS, follow-up is 45 months and [redacted] for the chemotherapy	Amended to increase clarity.

years for OS in the GLOW and SPOTLIGHT trials, respectively.'		arms for SPOTLIGHT and GLOW, respectively. For the zolbetuximab arms of the trial, follow-up is 50 months and [redacted] for SPOTLIGHT and GLOW, respectively.	
EAG report page 138 The EAG states that: 'Currently, the evidence does not show a treatment effectiveness waning for zolbetuximab (Figure 9 and 17 Addendum to Response to clarification letter), but follow-up is limited to approximately 1.5 and 2 years for PFS and to 2.5 and 3 years for OS in the GLOW and SPOTLIGHT trials, respectively'	Please amend the text to read: 'follow-up is limited to approximately [redacted] in the chemotherapy arms of both trials'	Follow-up differs by treatment arm of both SPOTLIGHT and GLOW trials. For OS, follow-up using the final data-cut is [redacted] for the chemotherapy arms of both SPOTLIGHT and GLOW trials and for the zolbetuximab arms it is 53 months and [redacted] for SPOTLIGHT and GLOW, respectively. For PFS, follow-up is 45 months and [redacted] for the chemotherapy arms for SPOTLIGHT and GLOW, respectively. For the zolbetuximab arms of the trial, follow-up is 50 months and [redacted] for SPOTLIGHT and GLOW, respectively The EAG report refers to truncated figures for the trials' follow-up (Figure 9 and 17	Amended to increase clarity.

		Addendum to Response to clarification letter). Instead, follow-up should be inferred from Figures 39, 40, 56 and 57. This is consistent with EAG report page 136.	
EAG report page 138 The EAG report states: 'As the duration of the treatment effect is uncertain after the observed period, the EAG also modelled scenarios with treatment effect waning assumptions after 3 and 4 years.'	Please remove this statement or revise text to read: 'As the duration of the treatment effect is uncertain after the observed period, the EAG also modelled scenarios with treatment effect waning assumptions after 3 and 4 years which are within the observed period.'	This amendment reflects the correct observed follow-up of the GLOW and SPOTLIGHT trials.	Amended to increase clarity.
EAG report page 157 The EAG report states: 'Follow-up is limited to approximately 1.5 and 2 years for PFS	Please either remove the sentence or amend to: 'Follow-up is limited to approximately [redacted] for OS and PFS in both trials. Using the cost-effectiveness model provided alongside the addendum with response to clarification	Follow-up differs by treatment arm of both SPOTLIGHT and GLOW trials. For OS, follow-up using the final data-cut is [redacted] for the chemotherapy arms of both SPOTLIGHT and GLOW trials and for the	Point was removed as the observed versus extrapolated outcomes were no longer a concern to the EAG.

and to 2.5 and 3 years for OS in the GLOW and SPOTLIGHT trials, respectively. As a consequence, during the observed period (estimated to be 3 years) only 29% of total life years gained (LYG), 30% of total QALYs gained, and 48% of total costs were acquired. Hence, most QALYs and costs were obtained in the unobserved period and subject to uncertainty. ‘	questions, during the observed period (estimated to be 4 years), [redacted] of total life years gained (LYG), [redacted] of total QALYs gained, and [redacted] of total costs were accrued. Hence, the majority of QALYs and costs were obtained in the observed period.‘	zolbetuximab arms it is 53 months and [redacted] for SPOTLIGHT and GLOW, respectively. For PFS, follow-up is 45 months and [redacted] for the chemotherapy arms for SPOTLIGHT and GLOW, respectively. For the zolbetuximab arms of the trial, follow-up is 50 months and [redacted] for SPOTLIGHT and GLOW, respectively.	

Issue 6 Incorrect or missing data

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 19	Please can this be amended to read:	The statement is incorrect because Table	Amended

The EAG report states: 'Using a mixed effects model to estimate utility values increases the ICER. The effect of data imputation on the ICER is unknown.'	'Using a mixed effects model to estimate utility values decreases the ICER. The effect of data imputation on the ICER is unknown.'	6.2 of the EAG report demonstrates a decrease in the ICER (EAG analysis 7).	
EAG report page 20 The EAG report states: 'The EAG is not able to assess the impact on the ICER.'	Please can this be amended to read: 'The EAG is not able to assess the impact on the ICER. In the response to clarification question B6, the company explored use of subsequent therapies as used in the base-case of ID4030, which was based on clinical expert opinion. The second line treatments were FOLFIRI (60%), paclitaxel (30%) and irinotecan (10%). This led to a reduction in the ICER.'	The statement is misleading, because it omits an important analysis performed by the company which informs the question of how alternative post-progression treatment costs impact on cost-effectiveness results. This is important for readers and the committee to be able to form an informed judgement on the how alternative assumptions on post-progression treatment costs are likely to impact the ICER.	Not a factual inaccuracy. The EAG did not agree with the methodology used in the scenario provided by the company and reported its simplistic nature. Therefore, it remains true that the EAG was not able to perform an additional analysis with the preferred post-progression treatments and could not assess the impact on the ICER.

EAG report page 22 In the EAG report, the bullet point referring to 'For patients whose tumours express PD-L1' is under the bullet point referring to chemotherapy only: : • Chemotherapy only, including: – Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin – For patients whose tumours express PD-L1 – Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)	Please could you amend this so that the bullet point on 'For patients whose tumours express PD-L1' is at the same level as the bullet point on 'Chemotherapy only, including', as follows: • Chemotherapy only, including: – Doublet treatment with fluorouracil or capecitabine + cisplatin or oxaliplatin • For patients whose tumours express PD-L1 – Nivolumab with chemotherapy (PD-L1 CPS ≥ 5)	The amendment aligns with the decision problem table in the company submission.	Corrected.

EAG report page 27, Table 3.3. The EAG report states, in reference to the FAST trial: 'Zolbetuximab + EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 77) EOX (CLDN18.2 expression in ≥ 70% of tumour cells) (n = 84)'	Please amend table as follows: 'Zolbetuximab + EOX (n = 77) EOX (n = 84)'	We apologise that the reference to the FAST trial subgroup whose CLDN18.2 expression in ≥ 70% of tumour cells was incorrect in the company submission (Document B Table 3), as the number of patients refers to the entire FAST trial and not to the subgroup.	Corrected.
EAG report page 28 The EAG report states: 'The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) evidence relating to the efficacy and safety of	Please can you amend this to read: The company performed a systematic literature review (SLR) to identify and summarise the available randomised controlled trial (RCT) evidence relating to the efficacy and safety of zolbetuximab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction cancer (G/GEJC).	The amendment aligns with the wording and population included throughout the company submission and the rest of EAG report.	Amended

zolbetuximab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative gastric cancer (GC) or GOJ adenocarcinoma'.			
EAG report page 28 The EAG report states that the following conferences where searched as part of the clinical SLR: • ASCO Conference on malignant Lymphoma • ESMO • ISPOR • IGCC	Please can you amend this to read: • ASCO ICML • ESMO • ISPOR • IGCC • ASCO Gastrointestinal Cancers Symposium	The amendment aligns with the conferences that were searched and with the wording included in Appendix D.1.1 of the company submission.	Amended

• ASCO Gastrointestinal Cancers Symposium • ICML			
EAG report page 30 The EAG report states that the population inclusion criteria for the clinical SLR was: 'Adult patients (≥ 18 years) with pathologically confirmed metastatic or locally advanced unresectable, or recurrent gastric or GEJ adenocarcinoma, who:'	Please can you amend this to read: Adult patients (≥ 18 years) with pathologically confirmed metastatic or locally advanced unresectable, or recurrent gastric or GEJ adenocarcinoma, who: • Have not received any previous first-line treatment (chemotherapy or targeted agent) for gastric or GEJ cancer (prior adjuvant or neo-adjuvant therapy is permitted) • Have HER2-negative status	The amendment includes full details of the population inclusion criteria and aligns with the wording included in Table 10 in Appendix D.1.2 of the company submission.	Amended
EAG report page 30 The EAG report states that the population exclusion	Please can you amend this to read:	The amendment includes full details of the population exclusion criteria and aligns with	Amended

criteria for the clinical SLR was: • 18 years of age • HER2-positive status Studies with mixed patient populations will be included if ≥ 80% of patients are eligible, or if eligible subgroups are reported.	• < 18 years of age • HER2-positive status • Studies with mixed patient populations will be included if ≥ 80% of patients are eligible, or if eligible subgroups are reported	the wording included in Table 10 in Appendix D.1.2 of the company submission.	
EAG report page 35 The EAG report states: 'Initially 5,689 records (see Figure 3.1 below) were identified that were obtained for screening after the removal of duplicates. This yielded 870 relevant records for further exploration. Of these, 632 records were	Please can you amend this to read: 'Initially 5,689 records (see Figure 3.1 below) were identified that were obtained for screening after the removal of duplicates. This yielded 870 relevant records for further exploration. Of these, 632 records were then deemed irrelevant and excluded. Manual handsearching resulted in two further papers meaning that 240 records deemed eligible for inclusion.'	The amendment aligns with the correct number of publications identified in the original clinical SLR and number presented in Figure 3.1 of the EAG report and Figure 1 in Appendix D.1.2 of the company submission.	Amended

then deemed irrelevant and excluded. Manual handsearching resulted in two further papers meaning that 24 records deemed eligible for inclusion.'			
EAG report page 44 The EAG report states: 'The final database lock for the GLOW trial took place on 22 February 2024, and data analysis is currently ongoing.'	Please can you mark the final database lock date as confidential and remove that the data analysis is ongoing, as the company submitted results with the clarification responses. Therefore, the sentence should read: 'The final database lock for the GLOW trial took place on [redacted].'	The amendment aligns with the presentation of the results of the final datacut in the addendum to the responses to clarification questions.	Amended
EAG report page 50. The EAG report states: 'The origin of tumours was different between arms with 70.8% of those of the zolbetuximab and CAPOX group being located in GC and 29.1% in the GEJC	Please amend to: In the total European/UK based participants, the origin of tumours was different between arms with [redacted]% of those of the zolbetuximab and CAPOX group being located in GC and [redacted]% in the GEJC compared to [redacted] % and [redacted]% in the placebo and CAPOX group.	The amendment aligns with the EAG report Table 3.9 and with the Table 5 of the company's responses to clarification questions.	Amended

compared to 78.1 % and 29.2% in the placebo and CAPOX group. ‘			
EAG report page 61, Table 3.12 Critical appraisal of GLOW. The EAG report states: ‘The allocated treatments were not masked from the investigator and patients.’	Please remove this statement.	The publication reporting the GLOW trial states: ‘*The sponsor, investigators, clinical staff and patients remained blinded to treatment throughout the study. To maintain blinding, zolbetuximab and placebo, which were identical in appearance and form, were provided to investigators or designees by an unblinded pharmacist and administered in identical volumes, routes and schedules*.’ (Shah et al, Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nature	Amended

		Medicine, 2023, doi:10.1038/s41591-023-02465-7, page 11).	
EAG report page 91 The EAG report states: 'In the SPOTLIGHT trial, the company noted that the number and percentage of patients encountering a serious adverse event (SAE) were similar between the zolbetuximab + mFOLFOX6 arm and the placebo + mFOLFOX6 arm (47.0% versus 46.4%, respectively). Similarly, in the GLOW trial, the company observed that the number and proportion of patients experiencing an SAE were comparable between the	Please can you mark the data as confidential and amend the paragraph to include the correct data to read: 'In the SPOTLIGHT trial, the company noted that the number and percentage of patients encountering a serious adverse event (SAE) were similar between the zolbetuximab + mFOLFOX6 arm and the placebo + mFOLFOX6 arm ([redacted] versus [redacted], respectively). Similarly, in the GLOW trial, the company observed that the number and proportion of patients experiencing an SAE were comparable between the zolbetuximab + CAPOX arm and the placebo + CAPOX arm ([redacted] versus [redacted] respectively).'	The amendment aligns with the data and marking presented in Table 7 of the EAG clarification letter.	Amended

zolbetuximab + CAPOX arm and the placebo + CAPOX arm (48.0% versus 50.6%, respectively).'			
EAG report page 97 The EAG report states: 'In the SPOTLIGHT trial, the company observed that "*the number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms ([redacted], respectively)*".'	Please can you amend the paragraph to include the correct data to read: In the SPOTLIGHT trial, the company observed that "the number and proportion of patients experiencing a TEAE leading to death was comparable in the zolbetuximab + mFOLFOX6 and placebo + mFOLFOX6 arms ([redacted], respectively)".	The amendment aligns with the safety data from the final database lock presented in Section B.1.4.1.8 of the Addendum and aligns with the final database lock safety data presented in Table 3.26 to Table 3.31.	Amended
EAG report page 98 The EAG report states: 'While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5	Please can you amend this to read: 'While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of	The amendment aligns with the correct data for the CAPOX arm in GLOW presented in the company submission and in Table 3.32 of the EAG	Amended

subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: [redacted]% in zolbetuximab + mFOLFOX6 arm versus [redacted]% in mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted]% in Zolbetuximab + CAPOX arm versus [redacted]% in CAPOX arm.'	SPOTLIGHT: [redacted]% in zolbetuximab + mFOLFOX6 arm versus [redacted]% in mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted]% in Zolbetuximab + CAPOX arm versus [redacted]% in CAPOX arm.	report and Table 14 of the EAG Addendum.	
EAG report page 106 The EAG report states: 'Table 3.37 shows the estimated HRs versus chemotherapy from 6 months to 5 years. The results showed that zolbetuximab plus chemotherapy	Please can you amend this to read: 'Table 3.37 shows the estimated HRs versus chemotherapy from 6 months to 5 years. The results showed that zolbetuximab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy. The HR, which ranged from [redacted]) to [redacted]	The amendment aligns with the correct data for zolbetuximab + chemotherapy and nivolumab plus chemotherapy versus chemotherapy at year 5 presented in Table 3.37 of the EAG report and	Amended.

was associated with a statistically significant improvement in PFS compared with chemotherapy. The HR, which ranged from [redacted], was reasonably constant over time from 0.5 year to 5 years. The results further showed that nivolumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 5. The HR, which ranged from [redacted], was also reasonably	[redacted], was reasonably constant over time from 0.5 year to 5 years. The results further showed that nivolumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy in patients with PD-L1 CPS ≥ 5. The HR, which ranged from [redacted], was also reasonably constant over time from 0.5 year to 5 years.	Table 17 in the Addendum.	

constant over time from 0.5 year to 5 years.			
EAG report page 116 The EAG report states: 'While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: 9.5% in the zolbetuximab plus mFOLFOX6 arm versus 8.5% in the placebo plus mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: 13.8% in zolbetuximab plus CAPOX arm versus 9.8% in the placebo plus CAPOX arm.'	Please can you mark the data as confidential and amend the paragraph to include the correct data to read: 'While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: [redacted]% in zolbetuximab + mFOLFOX6 arm versus [redacted]% in mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted]% in Zolbetuximab + CAPOX arm versus [redacted]% in CAPOX arm.	The amendment aligns with the correct data for the CAPOX arm in GLOW presented in the company submission and in Table 3.32 of the EAG report and Table 14 of the EAG Addendum.	Amended

EAG report Table 4.1 on page 120 The EAG report incorrectly states the date searches for EconLit as part of the cost-effectiveness systematic literature review: • 22.9.20 • 9.8.22 • 26.10.23	Please can you amend Table 4.1 on page 120 to include the following dates searched for EconLit: • 22.9.20 • 11.08.22 • 26.10.23	The amendment aligns with the dates that EconLit was searched as reported in the company submission.	Amended
EAG report Table 4.1 on page 120 The EAG report states the date ranges for EconLit as part of the cost-effectiveness systematic literature review were: • 1886-10.9.20 • 1886-28.7.22 • 1886-12.10.23	Please can you amend Table 4.1 on page 120 to include the following dates searched for EconLit: • 1886-10.9.20 • 1886-4.8.22 • 1886-12.10.12	The amendment aligns with the dates that EconLit was searched as reported in the company submission.	Amended

EAG report Table 4.1 on page 120 The EAG report states the date searches for HTA websites as part of the economic evaluation SLR were: • 8.10.20 • 10.10.22 • 1.11.23	Please can you amend Table 4.1 on page 120 to include the following dates searched for HTA websites: • 5.10.20 • 10.10.22 • 1.11.23	The amendment aligns with the dates that the HTA websites were searched and with the wording included in the response to clarification questions.	Amended
EAG report Table 4.2 on page 121 The EAG report states the date searches for HTA websites as part of the health related quality of life SLR: • 8.10.20 • 10.10.22 • 1.11.23	Please can you amend Table 4.2 on page 121 to include the following dates searched for HTA websites: • 5.10.20 • 10.10.22 • 1.11.23	The amendment aligns with the dates that the HTA websites were searched and with the wording included in the response to clarification questions.	Amended

EAG report Table 4.3 on page 122 The EAG report states that the date searches for HTA websites as part of the cost and resource use SLR: • 8.10.20 • 10.10.22 • 1.11.23	Please can you amend Table 4.3 on page 123 to include the following dates searched for HTA websites: • 5.10.20 • 10.10.22 • 1.11.23	The amendment aligns with the dates that the HTA websites were searched and with the wording included in the response to clarification questions.	Amended
EAG report Table 4.4 on page 124 The EAG report does not have geography as one the eligibility criteria for the identification of cost-effectiveness studies as part of the economic evaluation SLR.	Please can you amend Table 4.4 on page 124 to include the inclusion criteria for geography, which is 'No restrictions'.	The amendment aligns with the eligibility criteria used to identify cost-effectiveness studies as part of the economic evaluation SLR and wording included in the company submission.	Amended.
EAG report page 130 EAG is unclear with their wording of 'The	Please can you amend the statement to: 'The company state that the NMA that this comparison is based on may underestimate the	The logic in the statement is unclear, and it is not correct when the EAG state that 'The	Amended to increase clarity.

company state that the NMA that this comparison is based on, suffers from may not be appropriate as proportions of patients with higher PD-L1 CPS status are likely higher in the KEYNOTE trials than in SPOTLIGHT and GLOW. ‘ and incorrectly states that ‘patients with higher PD-L1 CPS status are likely higher in the KEYNOTE trials than in SPOTLIGHT and GLOW.’	comparative efficacy of zolbetuximab + chemotherapy relative to pembrolizumab + chemotherapy as a higher proportion of patients with higher PD-L1 CPS status are likely included in the KEYNOTE trials than would be in the cohort of patients who in clinical practice are considered for zolbetuximab + chemotherapy’.	company state that the NMA that this comparison is based on, suffers from may not be appropriate as proportions of patients with higher PD-L1 CPS status are likely higher in the KEYNOTE trials than in SPOTLIGHT and GLOW.’. In the company’s response to clarification questions, it was noted that patients with higher PD-L1 CPS status are likely higher in the KEYNOTE trials than in the population considered for zolbetuximab in clinical practice rather than in reference to SPOTLIGHT and GLOW.	
Page 130 of the EAG report The EAG states: ‘But for nivolumab, CAPOX and FOLFOX, stopping	Please amend this to read: ‘But for nivolumab and oxaliplatin stopping rules are in place for 2 years and 24 weeks respectively.’	This amendment aligns with GLOW and SPOTLIGHT. 5-FU, folinic acid and capecitabine may be continued at the	Amended.

rules are in place for 2 years, 24 weeks and 24 weeks respectively.'		clinician's discretion beyond 24 weeks.	
EAG report page 136 Table 4.8 Predicted 5-year OS [redacted]	Please amend these to: [redacted]	Factual inaccuracy. The figures reported by the EAG are modelled 60-week survival for 5 years, rather than 60-month survival. The predicted 5-year OS shown here was obtained from sheet 'tx_Chemo' (=1-Q276).	Amended.
EAG report page 136 Table 4.8 Predicted 20-year OS [redacted]	Please amend these figures to: [redacted]	Factual inaccuracy. The figures reported by the EAG do not correspond to the cost-effectiveness model estimated OS. The predicted 5-year OS shown here was obtained from sheet 'tx_Chemo' (=1-Q1056).	Amended.
EAR report page 136 The EAG state: 'This results in different extrapolations of the	Please amend to 'This results in different extrapolations of the survival curves, with slightly increased 5-year OS and slightly higher long-term OS estimates (Table 4.8).'	Correct error in sentence	Amended.

survival curves, with slightly worse 5-year OS and slightly higher long-term OS estimates (Table 4.8).'			
EAG report page 137 The EAG report states: 'This scenario still accounts for a small proportion of long-term survivors, specifically [redacted] and [redacted] in the chemotherapy and zolbetuximab + chemotherapy arms at 20 years respectively.'	Please amend this text to read: This scenario estimates an extremely small proportion of patients will be long-term survivors - specifically [redacted] and [redacted] in the chemotherapy and zolbetuximab + chemotherapy arms at 20 years respectively.	Factual inaccuracy. The numbers quoted by the EAG do not correspond to the submitted cost-effectiveness model. The predicted 20-year OS shown here was obtained from sheet 'tx_Chemo' (=1-Q1056) and sheet 'tx_INT' (=1-Q1056).	Amended.
EAG report page 137 The EAG report states 'In addition, deeming the log-logistic as best fitting is in contradiction to the company's own	Please remove this statement.	This statement incorrectly interprets the wording included in company submission, where it was stated that log-logistic was the best-fitting model that also predicts a subset of long-term	Amended.

<table>
<tr>
<td>choices in scenario analysis 2.’</td>
<td></td>
<td>survivors, therefore there is no contradiction with the company’s choices for scenario analysis 2.</td>
<td></td>
</tr>
<tr>
<td>EAG report 138

The EAG report incorrectly states the effect of treatment effectiveness waning assumptions on modelled long-term survival in Table 4.9</td>
<td>Please amend Table 4.9 to the following:

<table>
<tr><th></th><th>Proportion of patients alive at 20 years in the chemotherapy arm</th><th>Proportion of patients alive at 20 years in the zolbetuximab + chemotherapy arm</th><th>Proportio patients a at 20 yea the nivoluma chemothe arm</th></tr>
<tr><td colspan="4">Company base-case (including CheckMate 649)</td></tr>
<tr><td>No treatment effect waning</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Treatment effect waning after 3 years</td><td rowspan="2">N/A – it is inappropriate to include chemotherapy as this is the reference curve for treatment waning</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Treatment effect waning after 4 years</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>This amendment aligns to the results of the EAG’s analyses in the cost-effectiveness model and accurately describes the EAG’s analyses</td>
<td>Amended.</td>
</tr>
</table>

	Treatment effect waning after 5 years		[redacted]	[redacted]			
	Treatment effect waning after 6 years		[redacted]	[redacted]			
	Treatment effect waning after 7 years		[redacted]	[redacted]			
	EAG base-case secondary analysis [without base case treatment waning setting]						
	No treatment effect waning	[redacted]	[redacted]	[redacted]			
	Treatment effect waning after 3 years [the EAG base case setting]	N/A – it is inappropriate to include chemotherapy as this is the reference curve for	[redacted]	[redacted]			

	Treatment effect waning after 4 years	treatment waning	[redacted]	[redacted]		
	Treatment effect waning after 5 years		[redacted]	[redacted]		
	Treatment effect waning after 6 years		[redacted]	[redacted]		
	Treatment effect waning after 7 years		[redacted]	[redacted]		
	EAG = Evidence Assessment Group; N/A, not applicable					
EAG report page 141 The EAG report states: 'c) Nausea and vomiting had a duration of 1 week and decreased appetite had no duration (i.e., 0	Please can this statement be amended to: 'c) Nausea and vomiting had a duration of 1 week. The company cited the duration of these AEs in Shah et al.; however, these were not specified in said publication.31 Therefore, it is unclear for the EAG where this estimate was originally derived.'				The amendment reflects that decreased appetite is referred to in the Shah et al publication, with an assumption of zero duration.	Amended.

days). The company cited the duration of these AEs in Shah et al.; however, these were not specified in said publication.31 Therefore, it is unclear for the EAG where these estimates were originally derived.'			
EAG report page 142 The EAG report states: 'The company's addendum provided a new utility score using GEE with an exchangeable working correlation (Table 4.7), instead of the independent working correlation used in the original CS.'	Table 4.7 outlines the appropriate treatments per subpopulation (given PD-L1 status). Please correct the table reference or remove the reference to this table. In addition, please amend this to: 'The company's addendum provided a new utility score using GEE with an exchangeable working correlation (Table 4.7), in addition to the independent working correlation used in the original CS.'	This amendment aligns with the information included in Table 11 of the company's response to clarification questions includes results when using the independent working correlation.	Amended.
EAG report page 143, Table 4.12.	Please amend to: -0.0020 for zolbetuximab + chemotherapy and	This amendment aligns with the information included in the	Amended.

The EAG report states that the total QALY decrement due to AE is -0.00148 for zolbetuximab + chemotherapy and -0.00104 for chemotherapy.	-0.0015 for chemotherapy.	Addendum to the responses to clarification questions (see Table 30 page 122) and the model file.	
EAG report page 144 The EAG report states: 'In the clarification response B15 and B17, the company still refers to the old utility values of GEE ([redacted], and [redacted]).'	Please can you amend this to: 'In the clarification response B15, the company still refers to the old utility values of GEE ([redacted], and [redacted]).'	This amendment aligns with the content included in the response to clarification questions.	Amended.
EAG report page 144. The EAG report states: 'The company was also asked to calculate the utility scores using the more common generalised linear	Please can this sentence be removed.	The EAG clarification question B15 did not ask the company to calculate utilities using GLMM, but to discuss the reasons for choosing GEE over GLM	Amended.

mixed model (GLMM) on clarification question B154: however, the company did not provide these estimates.'		or GLMM, which the company provided. For reference, question B15 was: '*B 15. Priority question: A generalised estimating equation (GEE) model was developed to estimate the trials' utility scores. Other commonly used methods are the generalized linear model (GLM) and the generalized linear mixed model (GLMM). The company provided a scenario analysis using a pooled mixed effects model, which resulted in slightly lower utility values than the base-case for both pre-progression (GEE: [redacted], mixed-effects: [redacted]) and post-progression (GEE: [redacted], mixed-effects: [redacted]). The company justified the bigger difference in the post-progression ([redacted])*	

		as compared to the pre-progression state ([redacted]) due to the fewer observations during post-progression (11,030 vs 1,149) and claimed that these were "inherently more uncertain". However, these differences could be due to the different models used and reflect some methodological uncertainty. *a) Please discuss the reasons for choosing the GEE over GLM or GLMM for the base-case.* *b) Please elaborate on the implications the different methods would have on the final utility values.* *c) The utility of the general population of this age group (male: 0.809, female: 0.791, average for the modelled*	

		population: 0.802) is lower than the average of the pre-progressed population, based on the GEE results ([redacted]). Please elaborate on the face-validity of this difference in utilities, especially given the significant low weight of the population considered in the appraisal in comparison with the general population.'	
EAG report page 145 The EAG report states: 'The utility values from the ToGA trial that were used in TA208, and approved by the committee, were lower than all the models provided by the company (pre-progression: 0.729,	Please amend to: 'The utility values from the ToGA trial that were used in TA208, and approved by the committee, were lower than all the models provided by the company (pre-progression: 0.729, post-progression: 0.577). However, these values cannot be directly compared as the pre-progression value used in TA208 increases over time, whilst the post-progression value is for patients who have progressed after two lines of treatment.'	As outlined the response to clarification question B17, it is not appropriate to use the TA208 utility values directly as (i) it omits the time-varying change in utility pre-progression and (ii) the post-progression utility is for patients who have progressed after two lines of treatment so is not comparable with the	Amended

post-progression: 0.577).'		patient population of this appraisal.	
EAG report page 148, Table 4.14. The EAG report states that the drug acquisition cost (£) per treatment cycle for zolbetuximab (loading) is [redacted] and for maintenance is [redacted], and notes in a footnote: 'On the clarification response addendum, the costs for zolbetuximab from the weighted GLOW and SPOTLIGHT, reported the values from zolbetuximab from CAPOX (£[redacted] and £[redacted]). However, the model used the values reported in this Table.'	Please remove footnote and report the costs £[redacted] and £[redacted] respectively.	According to the cost-effectiveness model submitted with clarification responses, in sheet 'Pre-Prog Trt Cost' cells Q62 and Q63, the drug acquisition costs are costs £[redacted] and £[redacted] respectively.	Not a factual inaccuracy. The values from sheet Pre-Prog Trt Cost' cells Q62 and Q63 report the costs of Zolbetuximab + CAPOX (i.e., only data from GLOW), as stated in cell E61. The estimates reported by the EAG in the table refer to Zolbetuximab + Chemotherapy, which used the RDI from the SPOTLIGHT and GLOW trials for Zolbetuximab and the RDI from GLOW for the oxaliplatin and capecitabine.
EAG report page 150	Please can you amend this to the following:	This amendment aligns with the approach for	Not a factual inaccuracy.

The EAG report has not stated the entire rationale for costing treatments with CAPOX for nivolumab and pembrolizumab: 'For the treatment arm with nivolumab and pembrolizumab, treatment costs were also estimated based on CAPOX, as that is cheaper than the other regimes. '	'For the treatment arm with nivolumab and pembrolizumab, treatment costs were also estimated based on CAPOX, given that (1) CAPOX is less costly than FOLFOX, and (2) clinical feedback and the conclusion of TA857 indicate that most patients receive CAPOX.'	including CAPOX costing for nivolumab and pembrolizumab and the wording used in the company submission.	
EAG report page 152, Table 4.17. For pre-progression (on treatment), this table refers to £3,945.26 as the total annual cost per state; £3,360.63 for pre-progression (off treatment); and £9,750.18 for post-progression.	Please amend to £3,945.68; £3,361.37; £9,774.94, respectively.	This amendment aligns with the excel model file, sheet 'Disease Management Costs', rows 15, 25 and 37, respectively.	Amended

EAG report page 153 The EAG report states: 'The company justified the inclusion of vial sharing as it had been done previously in TA737 for pembrolizumab. However, the company did not provide further evidence supporting that vial sharing for zolbetuximab could be expected in UK clinical practice.'	Please can you amend this to: 'The company justified the inclusion of vial sharing as it had been done previously in TA737 for pembrolizumab. In response to clarification question B.20, the company stated that this is also reflected the use of national dose banding for chemotherapies and other systemic cancer drugs such as nivolumab and pembrolizumab.'	This amendment aligns with the information included in the response to clarification questions.	Not a factual inaccuracy
EAG report page 154 The EAG report states: 'The company failed to explain why a combination of docetaxel and paclitaxel would be a good proxy to model subsequent therapies.'	Please can you remove this sentence or amend to the following: 'As part of their response to clarification question B.19, the company highlighted that the assumption of equal splitting between docetaxel and paclitaxel was the same as that used in TA857,[4] and accepted by the NICE committee as appropriate for decision making. '	Aligns with the justification given as part of response to clarification questions.	Amended to increase clarity.

EAG report page 20, page 156, page 172 The EAG state “This result does not include the application of a 1.2x QALY weight, instead the company uses a modified WPT threshold of £36,000.”	Please amend this sentence to provide results with and without the severity modifier applied and remove the text “instead the company uses a modified WPT threshold of £36,000”.	Results with the severity modifier have been provided by the company – see Addendum to clarification responses Table 66 and 67.	Amended to increase clarity.
EAG report page 157 The EAG incorrectly states that ‘The company has not provided probabilistic results for the secondary analyses.’	Please amend this to: The company provided probabilistic results for the secondary analyses both in the cost-effectiveness model, as well as providing ICER scatterplots and cost-effectiveness acceptability curves for the secondary analyses in both the company submission and addendum provided in response to clarification questions. For the base case probabilistic results vs pembrolizumab (with the PAS applied), the results from the cost-effectiveness model provided alongside the addendum in response to clarification questions are as follows:	This amendment aligns with the analyses provided in the cost-effectiveness model and the wording included in the company submission and addendum provided in response to clarification questions.	Not a factual inaccuracy as they were not provided in the Addendum.

Probabilistic Outcomes	Zolbetuximab + Chemotherapy	Pembrolizumab + Chemotherapy	Incremental	
Average Costs	[redacted]	[redacted]	[redacted]	
Average QALYs	[redacted]	[redacted]	[redacted]	
Average ICER (Cost/QALY)	[redacted]	[redacted]	[redacted]	

For the base case probabilistic results vs Nivolumab (with the PAS applied), the results from the cost-effectiveness model provided alongside the addendum are as follows:

Probabilistic Outcomes	Zolbetuximab + Chemotherapy	Nivolumab + Chemotherapy	Incre
Average Costs	[redacted]	[redacted]	[redacted]
Average QALYs	[redacted]	[redacted]	[redacted]
Average ICER (Cost/QALY)	[redacted]	[redacted]	[redacted]

EAG report page 162, The EAG includes scenario 12: 'AE utilities derived from TA208 (Section 4.2.8) Scenario analysis using the utility values of TA208, instead of the ones obtained from the mixed-effects model based on SPOTLIGHT and GLOW.'	Please amend to: 'AE utilities derived from TA208 (Section 4.2.8) Scenario analysis using the utility values of TA208, instead of the ones obtained from the mixed-effects model based on SPOTLIGHT and GLOW. It should be noted that the TA208 utility values cannot be directly compared to the ones from SPOTLIGHT and GLOW as the pre-progression value used in TA208 increases over time, whilst the post-progression value is for patients who have progressed after two lines of treatment.'	As outlined the response to clarification question B.17, it is not appropriate to use the TA208 utility values directly as (i) it omits the time-varying change in utility pre-progression and (ii) the post-progression utility is for patients who have progressed after two lines of treatment, hence it is not comparable with the patient population of this appraisal.	Amended.
EAG report page 163 Table 6.1 In Table 6.1, the EAG state that the expected impact on the ICER of 'Uncertainty regarding the estimated utility values (key issue 10)' is '+'	Please amend this marking to be '+/-'.	This amendment aligns with the results provided in Table 6.2 of the EAG report, whereby changing the utility estimates to using mixed effects models decreases the ICER. The EAG report does not provide a rationale for why data imputation would increase the ICER.	Amended.

Issue 7 Unclear or subjective language

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 13 and page 157 The EAG report states: 'The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) are: • Post-progression disease management costs • Pre-progression disease management costs	Please amend this to: 'Based on the company's one-way sensitivity analysis, the parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) are: • Post-progression disease management costs • Pre-progression disease management costs • Utility values pre- and post-progression'	This amendment aligns with the analyses provided in the cost-effectiveness model and the wording included in the addendum provided in response to clarification questions.	Amended to increase clarity.

• Utility values pre- and post-progression			
EAG report page 37 and page 63 The EAG report states: Page 37: 'The CS clarifies that "*The final database lock for the SPOTLIGHT trial took place on 08 September 2023. Data analysis is currently ongoing and is expected to be submitted with responses to clarification questions*".' EAG report page 63: 'The CS stats that the final database lock for the SPOTLIGHT trial took place on 08	Please amend this to: Page 37: 'The CS clarifies that "*The final database lock for the SPOTLIGHT trial took place on 08 September 2023. Data analysis is currently ongoing and is expected to be submitted with responses to clarification questions*". The results from the final datacut were submitted.' Page 63: 'The CS state that the final database lock for the SPOTLIGHT trial took place on 08 September 2023 and data analysis is ongoing. The results from the final datacut were submitted with the responses to clarification questions.'	This amendment aligns with the Addendum submitted with the company's responses to clarification questions, and clarifies to readers that the results with final datacut were submitted. Regarding specifically page 63, please amend the typo as per amended statement.	Amended

September 2023 and data analysis is ongoing.'			
EAG report page 44 The EAG report states: 'The final database lock for the GLOW trial took place on 22 February 2024, and data analysis is currently ongoing.''	Please amend this to: 'The final database lock for the GLOW trial took place on [redacted], and data analysis is currently ongoing. The results from the final datacut were submitted and are presented in subsequent sections.'	This amendment aligns with the Addendum submitted with the company's responses to clarification questions, and clarifies to readers that the results with final datacut were submitted.	Amended.
EAG report P136 The EAG report states: 'Including CheckMate 649 increases longer term OS but that effect is not as impactful due to discounting, and it decreases 5-year OS estimates and that effect has greater weight, leading to an overall	Please can you re-word this to accurately reflect the impact of including CheckMate 649: 'Including CheckMate 649 increases both 5-year OS estimates and longer-term OS as shown by the higher model estimates for both life years and QALYs.'	The logic in the previous statement is unclear appearing to alternate between stating the choice of including CheckMate 649 both improves and worsens aggregate estimates of chemotherapy's effectiveness. There is no need to speculate about the precise effects of discounting as the model output for discounted QALYs indicates that including CheckMate 649 leads to an overall increase in the QALYs associated with chemotherapy treatment.	Amended.

increase in LYs for the comparator arm when including CheckMate 649.'		Note also that, as highlighted previously, the stated impact on 5-year OS is incorrect, as the 5-year OS estimates increase if CheckMate-649 is included.	
EAG report page 136 The EAG are unclear when they state that 'Cost effectiveness for zolbetuximab + chemotherapy versus nivolumab + chemotherapy for this subgroup may therefore be a conservative estimate and were not provided by the company.'	Please can you amend this to: 'Cost effectiveness estimates for zolbetuximab + chemotherapy versus nivolumab + chemotherapy for this subgroup may therefore be a conservative estimate and were not provided by the company.'	This amendment enhances clarity.	Amended to increase clarity.
EAG report page 145 The EAG report states: 'The AE related disutility	Please can you remove this statement or add a definition of 'quite low' disutility values.	Statement should be removed or rephrase for clarity and objectivity.	Amended to increase clarity.

values (Table 4.8) obtained through this calculation were quite low considering the impact of the AEs on the patients' QoL'			
EAG report page 154 The EAG are unclear with their wording of 'However, this simplistic assumption is flawed as it compares different treatments, with diverse health effects, treatment duration, and costs are interchangeable. '	Please remove this sentence or reword so that the meaning becomes clear.	This sentence is unclear because, in calculating the post-progression treatment costs, no treatments were compared, and the treatment duration was incorporated in the calculation of cost.	Amended to increase clarity.
EAG report page 172. The EAG report states: 'For the	Please amend to: 'For the secondary analysis, the NMA is appropriate to obtain relative treatment effects, however the company assumed that	Amendment improves clarity. The original sentence could be interpreted to mean that the NMA was incorrectly implemented in the model,	Amended to increase clarity.

secondary analysis, the NMA is appropriate to obtain relative treatment effects, however the NMA was not correctly implemented in the model.'	nivolumab and zolbetuximab had similar effectiveness and used the estimates from zolbetuximab to inform both zolbetuximab and nivolumab.'	hence the cost-effectiveness results are incorrect, which is not the case.	
EAG report 172. The EAG report states: 'Treatment effectiveness waning was not implemented in the model as the data does not show signs of treatment effectiveness waning, but follow-up is limited.'	Please amend to: 'Treatment effectiveness waning was not implemented in the model in the base-case (but explored in scenarios) as the data does not show signs of treatment effectiveness waning, but follow-up is limited.'	Amendment improves clarity, as treatment effectiveness waning was implemented in the scenario analysis.	Amended to increase clarity.

Issue 8 Incorrect table or section cross-references

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 145 The EAG states 'The AE related disutility values (Table 4.8) obtained through this calculation were quite low considering the impact of the AEs on the patients' QoL'	Please correct the table reference or remove this statement.	Table 4.8 of the EAG report refers to predicted long-term OS in the chemotherapy arm. Table 4.12 refers to the AE-related disutility values per treatment arm.	Corrected.
EAG report page 145 The EAG report incorrectly refers to Table 4.9 when they state that 'Drug acquisition costs per administration were calculated based on dosage, unit drug costs,	Please correct the table reference or remove the reference to this table.	Table 4.9 refers to the effect treatment effectiveness waning assumptions. Treatment 4.14 refers to RDI and drug acquisition costs per dosing schedule.	Corrected.

relative dose intensity (RDI), dosing schedules, and stopping rules (Table 4.9).'			
EAG report page 153 The EAG incorrectly refer to Table 39 when they state that 'Individual costs per AE can be found in CS Table 39'	Please remove this reference or update the table reference to Table 40 of the CS.	This amendment aligns with the information provided in the company submission (Table 40 of CS).	CS Table 39 shows the adverse event unit costs, which the EAG refers to in this sentence.
EAG report page 154 The EAG report states: 'The values in table 4.13 report the total acquisition and administration costs per treatment arm.'	Please correct the table reference or remove the reference to this table.	Table 4.13 in the EAG report refers to dosing schedules and stopping rules, while Table 4.15 refers to pre-progression health state costs including costs per cycle, total drug costs, total administration costs, and total costs.	Point was removed as discrepancies between values were resolved.
EAG report page 156. The EAG report state: 'The need for	Please amend to: 'The need for CLDN18.2 testing (£176 per patient treated; £74.48 per patient tested).	This amendment improves clarity for readers.	

CLDN18.2 testing (£176 per patient).			
EAG report page 159 The EAG report states: 'The total costs per treatment arm reported by the company in the clarification response addendum did not match those calculated in the model base-case (Table 4.13). The EAG was not able to replicate the results provided by the company and is, therefore, not able to assess whether it was a reporting mistake, or the company used different calculations.'	Please correct the table reference.	Table 4.13 in the EAG report refers to dosing schedules and stopping rules, so it is unclear what the EAG is referring to.	Amended. The table mentioned was Table 4.16: Pre-progression health state costs

EAG report page 161 The EAG report states: ‘The EAG was unable to make adjustments for the violations that were identified, for example the issues pointed out in section 2.4.6.’	Please remove this subsection or amend to refer that no violations were found.	Section 2.4.6 does not exist in the report, and there are no instances of violations mentioned in the report.	Corrected.
EAG report page 161 The EAG incorrectly refers to Section 4.2.8: ‘2. Assuming no vial sharing in the base-case (Section 4.2.8). The EAG assumed that vial sharing would not occur in its base-case, while	Section 4.2.8 refers to health-related quality of life data rather than vial sharing, please remove reference to this section and update to Section 4.2.9.	This amendment aligns with the information included in the EAG report.	Corrected.

the company's base-case included vial sharing.'			
EAG report page 163 Table 6.1 In Table 6.1, the EAG report states: 'Uncertainty regarding the estimated utility values (key issue 10)' is resolved 'Partly (EAG MoJ 8)'	Please can you amend this to: 'Partly (EAG MoJ 7)'	This amendment aligns with the EAG matter of judgement analysis 7, where they explored Mixed-effects model for utility values.	Corrected.

Issue 9 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
EAG report page 17 Typos in: 'As the HRs of nivolumab + chemotherapy versus. chemotherapy at	Please can this be amended to read: 'As the HRs of nivolumab + chemotherapy versus chemotherapy at each time point are lower than the HRs of zolbetuximab + chemotherapy versus chemotherapy, the ICER is likely going to increase when the NMA results of nivolumab are included.'	Remove full stops that should not be included.	Corrected.

each time point are lower than the HRs of zolbetuximab + chemotherapy versus. chemotherapy, the ICER is likely going to increase when the NMA results of nivolumab are included.'			
EAG report page 20 An incorrect abbreviation is used: willingness-to-pay (WPT) threshold	Replace "WPT" with WTP (will apply to all instances of this abbreviation)	Fix typographical error	Corrected.
EAG report page 35 The EAG report states 'The SR was conducted to identify relevant clinical studies in support of this submission. The CS appendices detail this process.'	Please can you amend this to read: 'The SLR was conducted to identify relevant clinical studies in support of this submission. The CS appendices detail this process.'	The amendment aligns with correct acronym used throughout the EAG report and the company submission.	Corrected.
EAG report page 50, Table 3.10	Please amend the trial name in the first row in the table to 'FAST'.	The amendment corrects an error.	Corrected.

The EAG report states that the trial name is ‘GLOW’, when it should read ‘FAST’.			
EAG report page 60. The EAG report states: ‘The Company performed critical appraisals for the FLOW, SPOTLIGHT and FAST studies.’	Please amend to: ‘The Company performed critical appraisals for the GLOW, SPOTLIGHT and FAST studies.’	Typographical error	Corrected.
EAG report page 69, typographical error in: ‘Based on the final data cut date (8 September 2023) of the SPOLTLIGHT trial,’	Please amend to: ‘Based on the final data cut date (8 September 2023) of the SPOTLIGHT trial,’	Typographical error	Corrected.
EAG report page 97 The EAG report states ‘Four trials were identified through an SR that were considered for inclusion in an	Please can you amend this to read: ‘Four trials were identified through an SLR that were considered for inclusion in an indirect treatment comparison (ITC) of interest to this appraisal.	The amendment aligns with correct acronym used throughout the EAG report and the company submission.	Corrected.

indirect treatment comparison (ITC) of interest to this appraisal.			
EAG report page 97 The EAG report states: 'The company made further following statement: • "*All four studies compared two treatments, which allowed the selected studies to form a network through common comparator arms. However, as each study used a different chemotherapy control arm, there was no common comparator across trials – so a connected network of*	Please can you amend this to read: The company made the further following statement: • "*All four studies compared two treatments, which allowed the selected studies to form a network through common comparator arms. However, as each study used a different chemotherapy control arm, there was no common comparator across trials – so a connected network of evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed*."	The current two paragraphs state the same information, therefore the latter can be removed for clarity and brevity.	Corrected.

evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed." The company states that all four included studies compared two treatments that allowed the included studies to form a network through common comparator arms. Furthermore, the company made the following statement: "*as each study used a different chemotherapy control arm, there was no common*			

comparator across trials – so a connected network of evidence could not be formed. Therefore, equivalence of the two chemotherapy regimens (CAPOX, FOLFOX) in terms of relative effectiveness was assumed."			
EAG report page 118 The EAG report states: 'The KEYNOTE-859 trial provided data of patients with PD-L1 CPS ≥ 5 who received the intervention of nivolumab with chemotherapy versus chemotherapy alone.'	Please can you amend to: 'The CheckMate-649 trial provided data of patients with PD-L1 CPS ≥ 5 who received the intervention of nivolumab with chemotherapy versus chemotherapy alone.'	The KEYNOTE-859 was incorrectly referred to in this sentence.	Corrected.

EAG report page 118 The EAG report states: 'The KEYNOTE-64 and KEYNOTE-859 trials provided data of patients with PD-L1 CPS ≥1 who received the intervention of pembrolizumab with chemotherapy versus chemotherapy alone.'	Please can you amend to: 'The KEYNOTE-062 and KEYNOTE-859 trials provided data of patients with PD-L1 CPS ≥1 who received the intervention of pembrolizumab with chemotherapy versus chemotherapy alone.'	The trials included in the network meta-analysis to provide evidence on pembrolizumab were KEYNOTE-062 and -859.	Corrected.
EAG report page 129. The EAG report states: 'Chemotherapy could be CAPOX of FOLFOX.'	Please amend to: 'Chemotherapy could be CAPOX or FOLFOX.'	Typographical error.	Corrected.
EAG report page 136 The EAG report states: 'This is a key issue as the time-varying relative effects from the NMA	Please can you amend this to: 'This is a key issue as the time-varying relative effects from the NMA are numerically different for zolbetuximab + chemotherapy and nivolumab + chemotherapy (Table 17 for PFS and 22 for OS Addendum to Response	Typographical error, as 'are different' is duplicated. For clarity, the term 'numerically' should be added	Corrected.

are different for zolbetuximab + chemotherapy and nivolumab + chemotherapy (Table 17 for PFS and 22 for OS Addendum to Response to clarification letter) are different, and this should be reflected in the model outcomes.'	to clarification letter), and this should be reflected in the model outcomes.'	as the credible intervals overlap.	
EAG report page 145 The EAG report states: 'The EAG considers the impact of this to below, as multiplying the AE disutility by for example 20 treatment cycles had only a modest impact on the ICER.'	Please can you amend this to: The EAG considers the impact of this to be low, as multiplying the AE disutility by for example 20 treatment cycles had only a modest impact on the ICER.	Typographical error.	Corrected.
EAG report page 148, table 4.14. The cell in the first	Please amend to 'Regimen'.	Typographical error.	Corrected.

row/first column of the table states ‘Regiment’ whereas it should read ‘Regimen’.			
EAG report page 150 The EAG has included a spelling error in the following sentence: ‘For the treatment arm with nivolumab and pembrolizumab, treatment costs were also estimated based on CAPOX, as that is cheaper than the other regimes. ‘	Please can you amend this to: ‘For the treatment arm with nivolumab and pembrolizumab, treatment costs were also estimated based on CAPOX, as that is cheaper than the other regimens. ‘	Typographical error.	Corrected.

Errors in CIC markings

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
EAG report page 25	The expected marketing authorisation date should be marked CIC.	The marketing authorisation application to the use of zolbetuximab in this indication has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) national (150-day) route with an expected marketing authorisation date of [redacted].	Amended.
EAG report page 26	The percentage overlap should be marked CIC.	The company states that "Biomarker analysis of the two pivotal zolbetuximab Phase III studies (SPOTLIGHT and GLOW) demonstrated a very small overlap ([redacted]) between patients with GC / GEJC eligible for both zolbetuximab (CLDN18.2 positivity in ≥ 75% of tumour cells) and pembrolizumab with chemotherapy (with CPS ≥ 10). Therefore, because the overlap in the CPS ≥ 10 patient population is very small and pembrolizumab with chemotherapy is not recommended	Already marked CIC.

		in patients with CPS ≥ 1 (NICE [ID4030]), pembrolizumab with chemotherapy has not been included as a comparator”.	
EAG report page 41	The number of UK patients included in SPOTLIGHT should be marked CIC.	As can be seen in Table 3.5 below, the involvement of UK based participants in the SPOTLIGHT trial was minimal and because of this small sample ([redacted]), the differences between the two groups appear to be noteworthy (>5%).	Amended.
EAG report page 41	The number of UK patients included in SPOTLIGHT should be marked CIC in Table 3.5.	Please amend marking in the titles in Table 3.5 to the following: Zolbetuximab + mFOLFOX6 ([redacted]) Placebo + mFOLFOX6 ([redacted])	Amended.
EAG report page 42-43	The distribution of primary site locations in European patients in SPOTLIGHT should be marked CIC.	Additionally, the distribution of primary site locations are different between the groups with [redacted] of tumours originating in the GC and [redacted] in the GEJC in the zolbetuximab + mFOLFOX6 group compared to the placebo + FOLFOX6 group where [redacted] of tumours had their origin the GC	Amended.

		compared to [redacted] which originated in the GEJC.	
EAG report page 44	The date of the final database lock should be marked CIC.	The final database lock for the GLOW trial took place on [redacted].	Amended.
EAG report page 47	The number of UK patients included in GLOW should be marked CIC in Table 3.8.	Please amend marking in the titles in Table 3.8 to the following: Zolbetuximab + CAPOX ([redacted]) Placebo + CAPOX ([redacted])	Amended.
EAG report page 48	The number of UK patients included in GLOW should be marked CIC.	UK based participants are minimal with only [redacted] participants meaning that any characteristic differences (>5%) between the two arms of the UK participants cannot be determined to be due to the small sample or actual characteristics differences that could influence outcomes if these were represented in a larger sample.	Amended.
EAG report page 50	The number of European and UK patients and baseline characteristics percentages included in GLOW should be marked CIC.	Generally, the arms are comparable although some noteworthy differences are evident (>5%). Again, it must be noted that the total European/UK based participants combined and only	Amended.

		constitute [redacted] participants in total from a trial that involved 507 participants representing only [redacted] of total participants. The origin of tumours was different between arms with [redacted] of those of the zolbetuximab and CAPOX group being located in GC and [redacted] in the GEJC compared to [redacted] and [redacted] in the placebo and CAPOX group. Metastasis locations also varied, with the adrenal gland, liver and lymph nodes being more frequent (>5%) than in the zolbetuximab and CAPOX group than in the placebo and CAPOX group.	
EAG report page 56	The final analysis database lock date for SPOTLIGHT can now be unmarked.	The final OS analysis was performed on 08 September 2023 after the pre-specified number of OS events were observed.	Already marked CIC.
EAG report page 72	The hazard ratio, 95% CI and p-value for duration of response presented in Table 3.18 should be marked CIC.	Please amend marking in Table 3.18 to the following: [redacted]) [redacted]	Amended.

EAG report page 73	The hazard ratio and 95% CI for time to first confirmed deterioration in EORTC QLQ-C30 GHS/QoL should be marked CIC.	There was no statistically significant difference in time to first confirmed deterioration between the zolbetuximab plus mFOLFOX6 arm and placebo plus mFOLFOX6 arm ([redacted]).	Amended.
EAG report page 83	The median times to first confirmed deterioration should be marked as AIC. It is marked as confidential in Table 3.25. However, whilst cross-checking we have noticed it was unmarked in error in the clarification question responses addendum (ID5123 EAG Addendum 02052024_CIC.docx; p26, Table 12); we will email you as to next steps.	Please amend to: In terms of EORTC QLQ-C30 GHS/QoL, the median of time to first confirmed deterioration was [redacted] for the zolbetuximab plus CAPOX arm while the median of time to first confirmed deterioration was [redacted] for the placebo plus CAPOX arm	Amended.
EAG report page 90	The number of patients experiencing Zolbetuximab- or placebo-related TEAEs in the SPOTLIGHT final analysis should be marked AIC.	'In the SPOTLIGHT trial, the company indicated that "*Zolbetuximab- or placebo-related TEAEs were more frequent in the zolbetuximab + mFOLFOX6 arm ([redacted] vs [redacted])*".'	Amended.

EAG report page 90	The percentage of patients experiencing Zolbetuximab- or placebo-related TEAEs in the GLOW final analysis should be marked AIC.	'Likewise, in the GLOW trial, the company reported that "*Zolbetuximab or placebo-related TEAEs were more frequent in the zolbetuximab + CAPOX arm versus the placebo + CAPOX arm ([redacted] vs [redacted] respectively)*".'	Amended.
EAG report page 104	The final database lock data cut off date for GLOW should be marked CIC.	In responding to the EAG's request, the company provided updated NMA results based on the final data cut of the SPOTLIGHT and GLOW trials (dated 8 September 2023 and [redacted], respectively) and the latest published data cut off of the CheckMate 649 trial (29 May 2023).	Amended.
EAG report page 116	The PD-L1 CPS status from SPOTLIGHT and GLOW should be marked CIC.	While 100% of patients had PD-L1 CPS ≥ 5 from the PD-L1 CPS ≥ 5 subgroup of CheckMate-649 trial, a lower proportion of patients had PD-L1 CPS ≥ 5 from SPOTLIGHT and GLOW trials (PD-L1 CPS ≥ 5 of SPOTLIGHT: [redacted] in the zolbetuximab plus mFOLFOX6 arm versus [redacted] in the placebo plus mFOLFOX6 arm; PD-L1 CPS ≥ 5 of GLOW: [redacted] in zolbetuximab	Corrected.

		plus CAPOX arm versus [redacted] in the placebo plus CAPOX arm.	
EAG report page 116	The PD-L1 CPS status from SPOTLIGHT and GLOW should be marked CIC.	Furthermore, among those patients with known PD-L1 CPS of the SPOTLIGHT trial, [redacted]% of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus mFOLFOX6 arm while [redacted]% of patients had had PD-L1 CPS ≥ 1 in the placebo plus mFOLFOX6 arm. For those patients with known PD-L1 CPS of the GLOW trial, [redacted]% of patients had PD-L1 CPS ≥ 1 in the zolbetuximab plus CAPOX arm while [redacted]% of patients had PD-L1 CPS ≥ 1 in the placebo plus CAPOX arm.	Amended.
EAG report page 157	The percentage of LYG occurring in the observed follow-up of the SPOTLIGHT and GLOW trials should be marked, in addition to numbers being corrected as noted above. It may allow back-calculation of cost-effectiveness results.	'Follow-up is limited to approximately 4 years for OS and PFS in both trials. Using the cost-effectiveness model provided alongside the addendum with response to clarification questions, during the observed period (estimated to be 4 years), [redacted] of total life years gained (LYG), [redacted] of total QALYs gained, and [redacted] of total costs were accrued. Hence, the majority of QALYs and costs	Amended.

		were obtained in the observed period.‘	

References

1. National Institute for Health and Care Excellence. Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]. March 2024.
2. Muro K, Van Cutsem E, Narita Y, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. *Ann Oncol*. 2019; 30(1):19-33.
3. Astellas Pharma Global Development. Adhoc subgroup analysis of SPOLTIGHT and GLOW trials. December 2023 2023. Data on file
4. National Institute for Health and Care Excellence. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. TA857. 2023. (Updated: 11 January 2024) Available at: https://www.nice.org.uk/guidance/ta857. Accessed: 27 February 2024.
5. National Institute for Health and Care Excellence. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer. TA737. 2021. (Updated: 20 October 2021) Available at: https://www.nice.org.uk/guidance/ta737. Accessed: 2 November 2023.
6. Janjigian YY, Shitara K, Moehler MH, et al. Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate 649. American Society of Clinical Oncology, 2023.