Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Astellas**

2. **Consultee and commentator comments on the Draft Guidance from Merck Sharpe and Dohme**

3. **Comments on the Draft Guidance from experts – Ceri Steele, Patient expert, nominated by Together Support Group**

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. • The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Astellas Pharma Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Section 3.5 and 3.9 - Indirect Treatment comparison: degree of heterogeneity and likely direction of any bias in estimated relative treatment effects** We are concerned that the committee's current preferred approach to the indirect treatment comparison mis-characterises the likely direction of bias caused by the heterogeneity in the evidence base and is overly conservative against zolbetuximab. The draft guidance document states: "*The committee agreed that the network meta-analysis included considerable heterogeneity. It considered that even assuming that PD-L1 CPS status is not a treatment-effect modifier, there are additional differences between*

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	the trials to take into account. It concluded that the heterogeneity in the network meta-analysis adds to uncertainty." (section 3.5); and earlier in the same paragraph "*The EAG highlighted that there was considerable heterogeneity between the trials included in the network meta-analysis. This included having different PD-L1 CPS baseline status across the trials, as well as different features of the trials such as the study designs, and types of chemotherapy used. It was also unclear if PD-L1 CPS status is a treatment-effect modifier in this population.*" In brief, our interpretation is that the committee concluded that there was considerable heterogeneity due to differences in the proportion of patients expressing PD-L1 CPS, differences in the chemotherapy regimens, and differences in trial design. **We consider that the heterogeneity is most likely to bias the indirect treatment comparison against zolbetuximab + chemotherapy. Therefore, assuming equivalence is an appropriate simplifying assumption, and likely an under-estimate of the true cost-effectiveness of zolbetuximab + chemotherapy compared to the checkpoint inhibitors**. As outlined further below, this is because: 1) evidence from the SPOTLIGHT & GLOW trials, CheckMate-649, KEYNOTE-859 and other studies supports that heterogeneity in PD-L1 expression does <u>not</u> modify the effectiveness of either chemotherapy or zolbetuximab plus chemotherapy; 2) there is precedence from previous NICE appraisals (TA857 and TA997) in addition to clinical support to consider equivalence between the different background chemotherapies and therefore the impact of any heterogeneity on this dimension is likely to be negligible; 3) differences in the trial design are unlikely to be a major source of heterogeneity, and finally, 4) differences between the population likely to be actively considered for zolbetuximab and the trial data used for nivolumab and pembrolizumab will more likely lead to an overestimation of their effectiveness relative to zolbetuximab. ***1) Heterogeneity in PD-L1 CPS expression does not modify the effectiveness of either chemotherapy or zolbetuximab plus chemotherapy*** As noted in the draft guidance, the available evidence supports that PD-L1 CPS expression does not affect the outcomes of patients receiving either chemotherapy or zolbetuximab plus chemotherapy: • **There is no known mechanism of action by which PD-L1 expression can affect zolbetuximab's action on cancer cells.** Zolbetuximab is a monoclonal antibody directed against the tight junction molecule claudin 18.2 (CLDN18.2). In contrast, checkpoint inhibitors such as nivolumab and pembrolizumab are

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

Draft guidance comments form

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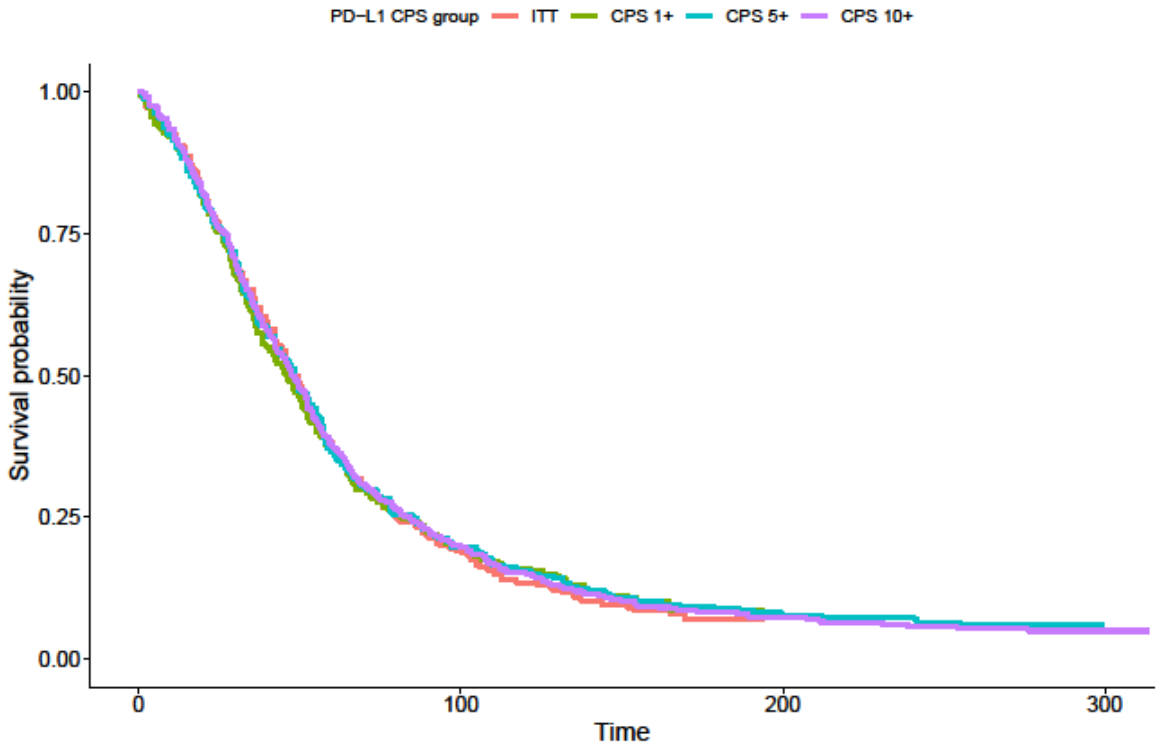
monoclonal antibodies that bind to the programmed death-1 (PD-1) receptor and block its interaction with PD-L1 and PD-L2.[1, 2]

- **Evidence from CheckMate-649, KEYNOTE-590, KEYNOTE-859 and external literature shows that the survival outcomes with chemotherapy are similar between PD-L1 CPS subgroups.[3-5]** Figure 1 below demonstrates that the outcomes of an 'all-comers' chemotherapy population can be expected to be equivalent to a patient population with CPS ≥10, CPS ≥5 or CPS ≥1.
  This evidence is consistent with the findings of a targeted literature review, which included additional studies.[6] This review concluded that there was no clear association between PD-L1 expression and outcomes, and there was no evidence supporting that PD-L1 expression affects chemotherapy efficacy.

Figure 1: Chemotherapy overall survival by PD-L1 CPS status (pooled data of CheckMate-649, KEYNOTE-859 and KEYNOTE-590) [3-5]



Note: The Figure shows the pooled chemotherapy arms of CheckMate-649, KEYNOTE-859 and KEYNOTE-590, by PD-L1 CPS subgroup[3-5].

- **The post-hoc analysis of SPOTLIGHT and GLOW by PD-L1 CPS subgroup shows consistent relative effectiveness results compared to the ITT analysis**. There were various analyses across the combination of trials

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

(SPOTLIGHT only, GLOW only, both), outcomes (PFS, OS), and PD-L1 CPS threshold (i.e., PD-L1 CPS unknown, PD-L1 CPS < 5 or ≥ 5, and PD-L1 CPS < 1 or ≥ 1). In all analyses, there was overlap of the 95% confidence intervals for hazard ratios (HRs) between the groups above and below different PD-L1 thresholds. The subgroups above the CPS thresholds did not have a consistently higher or lower HR, which would be the case if PD-L1 CPS were an effect modifier for zolbetuximab. We note the uncertainty in these results given that sample sizes, particularly in the PD-L1 CPS ≥ 5 subgroups are small, less than [redacted] (i.e., [redacted] patients in SPOTLIGHT and [redacted] in GLOW, across both arms); CPS results are not available for approximately [redacted] of all randomised patients (because patients in some geographies and sites could not be tested) and there is risk of imbalances between treatment arms within the subgroups [redacted]

- **The conclusion that PD-L1 status is not a treatment effect modifier for zolbetuximab or chemotherapy has received consistent clinical support from the clinical experts consulted by the company and also by the clinical expert present at the appraisal committee meeting**. This is noted in the draft guidance: "*The clinical expert added that there is no clear association between PD-L1 CPS and effectiveness of zolbetuximab*." (Section 3.5)."

2) ***There is precedence from previous NICE appraisals and clinical support to consider equivalence between the different background chemotherapies.*** The draft guidance document highlights the different types of chemotherapy used in the trial network as an additional source of heterogeneity. SPOTLIGHT used folinic acid, fluorouracil and oxaliplatin (FOLFOX) as the chemotherapy regimen while GLOW used capecitabine with oxaliplatin (CAPOX). The other studies included in the network also used these regimens and have each been considered in prior NICE appraisals (TA857 and TA997). In neither of these appraisals was the varied mix of chemotherapy regimens highlighted as a key source of heterogeneity that would lead to increased uncertainty. Instead, **there was clear support in both appraisals for the equivalent efficacy of the differing chemotherapy regimens allowed within the clinical trials**:

a. TA857 was based on the CheckMate-649 trial, in which the chemotherapy regimen was investigators' choice of CAPOX or FOLFOX. TA857 states "*Clinical experts also confirmed the company's approach and noted that dual chemotherapy regimens have similar efficacy*." (section 3.3).[7]

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

b. TA997 used the KEYNOTE-859 trial, which used investigators choice of CAPOX or cisplatin and 5-fluorouracil as the chemotherapy regimen. TA997 states "*The committee heard from the clinical expert that each of the doublet chemotherapy combinations are considered clinically equivalent*." (section 3.2).[8]

The assumption of equal efficacy was also validated by clinicians for this submission, as described in the company submission (Section B.3.3.1.1).

3) Differences in trial design are unlikely to be a major source of heterogeneity

A source of heterogeneity noted in the draft guidance was differences in trial design. The key differences in trial design are (i) CheckMate 649 being an unblinded study whereas the zolbetuximab studies are blinded, and (ii) CheckMate 649 included patients with oesophageal adenocarcinoma (12% of PD-L1 CPS ≥ 5 subgroup).[3]

Regarding (i), the purpose of blinding is to ensure the effectiveness of the novel therapy is not over-estimated versus the comparator arm. Other things equal the lack of blinding in CheckMate 649 could result in an overestimation of nivolumab plus chemotherapy's efficacy vis a vis the chemotherapy arm and therefore an underestimation of zolbetuximab plus chemotherapy's relative efficacy versus nivolumab plus chemotherapy. However, the results used within the network meta-analysis (NMA) were based on the independently-assessed radiological assessment. The independent radiologists in each study were blinded to treatment assignment.

Regarding (ii), as shown in Chau et al, patients with oesophageal adenocarcinoma have very similar outcomes to patients with gastric or gastro-oesophageal junction adenocarcinoma.[9] Additionally, the CheckMate-649 subgroup analysis shows similar HRs irrespective of specific cancer location.[3] Therefore, this difference is unlikely to increase heterogeneity in the indirect treatment comparison.

4) Differences between the population likely to be actively considered for zolbetuximab and the trial data used for nivolumab and pembrolizumab will more likely lead to an overestimation of their effectiveness relative to zolbetuximab.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	As highlighted briefly in the draft guidance document in Section 3.3, clinical experts have consistently indicated that if zolbetuximab were to be approved by NICE, patients with high PD-L1 CPS (e.g., CPS ≥ 10) are likely to still receive nivolumab or pembrolizumab if they are able to tolerate a checkpoint inhibitor. PD-L1 CPS is a treatment modifier for the checkpoint inhibitors and patients with higher CPS scores tend to have better outcomes on checkpoint inhibitors compared to patients with lower CPS scores.[1, 2] The relationship between PD-L1 expression and checkpoint inhibitor effectiveness has been recently reviewed by the US Federal Drug Administration (our bold): "*The current US FDA approvals of ICIs [immune checkpoint inhibitors] in combination with chemotherapy for the first line treatment of gastric/GEJ adenocarcinoma is agnostic of PD-L1 expression status; however, consistently across 3 different applications, FDA's patient-level pooled population, and in a trial level meta-analysis (Yoon et al. 2022),* ***a predictive role of PD-L1 expression emerged*** *and approvals for all randomized patients may not be in the best interest of patients with tumors with low PD-L1 expression. Addition of ICIs to standard of care chemotherapy for the treatment of patients with PD-L1 < 1 does not appear to result in benefit.* ***Benefit for patients with PD-L1 ≥10 have the greatest magnitude of benefit. Benefit is unclear in patients with PD-L1 levels less than 10 across the class; however, data interpretation is challenging. If patients with low or no PD-L1 expression are not expected to benefit based on the available data, then administering anti-PD1 therapy has the potential for harm including serious immune related adverse events on top of a malignancy that can markedly affect a patient's quality of life.*** **"** (page 33 (3.1.1. Summary) of FDA Briefing Document to the Oncology Advisory Committee Meeting of September 26, 2004 on Immune checkpoint inhibitors in patients with metastatic or unresectable HER2-negative gastric adenocarcinoma, available at https://www.fda.gov/media/182138/download). Given this expected approach to treatment, the average PD-L1 CPS in the patient population considered for zolbetuximab, nivolumab and pembrolizumab in clinical practice is likely to be lower than the average PD-L1 CPS in the PD-L1 CPS ≥ 5 subgroup in CheckMate 649 and the PD-L1 CPS ≥1 subgroups in KEYNOTE-062 and KEYNOTE-859. For the population likely to be considered for zolbetuximab in clinical practice, (e.g., low to intermediate CPS, particularly as clinical experience with zolbetuximab develops), the efficacy of nivolumab vs chemotherapy is likely to be similar to that observed for the PD-L1 CPS 5-9 population in CheckMate 649, and the efficacy of pembrolizumab vs chemotherapy is likely to be similar to that observed for the PD-L1 CPS 1-9 population in KEYNOTE-062 and KEYNOTE-859.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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Our submission presented a proportional hazards network meta-analysis comparing zolbetuximab, nivolumab, pembrolizumab (all + chemotherapy), and chemotherapy using the ITT results from the zolbetuximab trials, and the PD-L1 subgroups of the nivolumab and pembrolizumab trials (see section B.1.3.3 of Addendum to responses to clarification questions). Kaplan–Meier data were not available for these populations, precluding the use of a time-varying NMA. The table below shows that, as would be expected, the relative efficacy of zolbetuximab versus nivolumab and pembrolizumab (all + chemotherapy) improves when efficacy data from the most relevant population is used.

Table 1: Hazard ratios of OS and PFS for zolbetuximab plus chemotherapy versus pembrolizumab plus chemotherapy and nivolumab plus chemotherapy across PD-L1 CPS subgroups

Subgroup analysis, HR (95% CrI)	Zolbetuximab + chemotherapy versus pembrolizumab + chemotherapy		Zolbetuximab + chemotherapy versus nivolumab + chemotherapy	
	PD-L1 CPS ≥ 1	PD-L1 CPS 1–9	PD-L1 CPS ≥ 5	PD-L1 CPS 5–9
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]

Key: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; NR, not reported; OS, overall survival, PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.
Notes: Results showed median and 95% CrI of HR. A HR < 1 indicate a favourable result of zolbetuximab + chemotherapy versus the comparator. Results from a fixed effects model.
All analyses used the ITT population of the final SPOTLIGHT datacut (dated 8 September 2023), final GLOW datacut (dated 12 January 2024).

These results were used to inform scenarios of the cost-effectiveness analyses, under the company amended EAG base case – assumptions and results shown in the Appendix. As the HR for PFS for the comparison zolbetuximab + chemotherapy versus nivolumab + chemotherapy was not available, the HR for OS was used instead. This is likely a conservative assumption based on a comparison of the HRs for OS and PFS in Table 1, for which the PFS HR is always smaller than the corresponding OS HR. **Results demonstrate that zolbetuximab at the confidential discount dominates pembrolizumab and nivolumab (all + chemotherapy) at list price. At list price, zolbetuximab has a very low ICER compared to nivolumab and dominates pembrolizumab (all + chemotherapy).**

We are also concerned about the **contrast in the committee preferring the EAG's approach of using the numerical results of the indirect treatment comparison to model the outcomes of nivolumab and pembrolizumab (which**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	imply some degree of certainty in the numerical results), despite considering the heterogeneity (hence uncertainty) to be high: "*The committee noted the uncertainty with using the results from the network meta-analysis that imply clinical equivalence for zolbetuximab plus chemotherapy and nivolumab plus chemotherapy. It concluded that for the secondary analysis, it preferred the EAG's approach because it used direct evidence from the trials for the chemotherapy arm, and this also excluded the pooling of CheckMate 649*." (section 3.9). Furthermore, we are concerned that the conclusion in Section 3.13 that: "*In the analysis for the population where nivolumab plus chemotherapy is also a comparator (PD-L1 CPS of at least 5), the committee concluded that zolbetuximab plus chemotherapy did not show equivalent or greater effectiveness than nivolumab plus chemotherapy*. " **is a direct contradiction to the earlier statement** in the section "*Why the committee made these recommendations*" that: "*Zolbetuximab plus chemotherapy has been indirectly compared with pembrolizumab plus chemotherapy and nivolumab plus chemotherapy. The results found no differences in effectiveness between zolbetuximab and the other 2 treatments*." Based on the latter statement, the committee concluded that there were no differences in effectiveness between zolbetuximab and the checkpoint inhibitors, therefore the rationale for assuming otherwise later in the guidance is unclear. **Given the likely direction of any bias in the comparisons to nivolumab and pembrolizumab, assuming equivalence is an appropriate simplifying assumption, and likely an under-estimate of the true cost-effectiveness of zolbetuximab + chemotherapy**. Assuming that nivolumab or pembrolizumab are superior to zolbetuximab would be unreasonably pessimistic. If the NICE committee would like to explore the impact of assuming differential efficacy on the cost-effectiveness of zolbetuximab versus nivolumab and pembrolizumab, hazard ratios from the standard NMA, using population subgroups akin to clinical practice (PD-L1 CPS 1-9 for pembrolizumab; 5-9 for nivolumab), should be considered alongside assuming equivalent efficacy based on the time-varying NMA of the PD-L1 CPS ≥ 1 and CPS ≥ 5 subgroups, which uses less relevant comparative efficacy data despite its more nuanced analytic approach.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

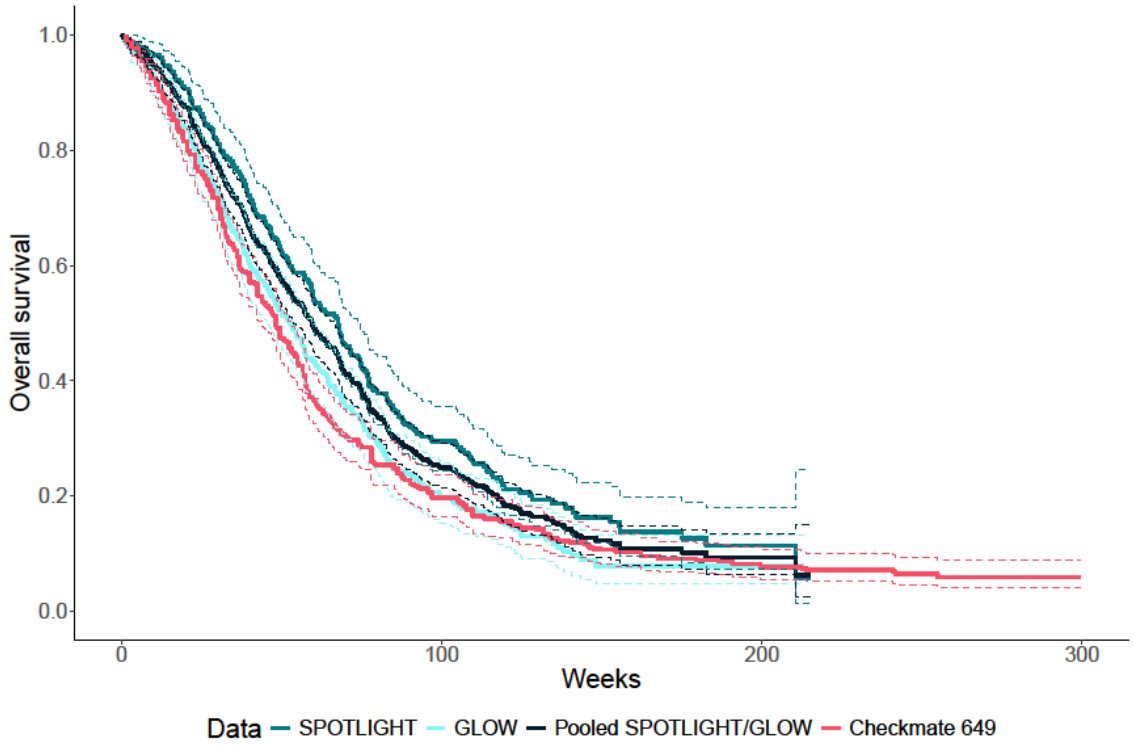
2	**Section 3.7 – Clinical trial data informing the model: discrepancy between the EAG report's proposed approach and methodological guidance from both NICE and the literature** We are concerned that the EAG report's approach to generate long-term estimates of survival is inconsistent with good practice approaches – including from NICE – because it does not use relevant external evidence and does not consider a sufficient range of extrapolation approaches. ***1) The exclusion of CheckMate 649 discards a valuable source of evidence that can reduce the uncertainty in long-term chemotherapy outcomes.*** As outlined in the first comment, differences by trial are not expected to differentially affect chemotherapy outcomes, hence there is no reason to exclude CheckMate 649. Instead, **its inclusion is aligned with the principles of evidence-based medicine and NICE guidance whereby all relevant evidence should be used.** For example, the NICE real-world evidence (RWE) framework highlights that external evidence may be used both when trial follow-up is limited and to inform baseline event rates.[10] It is further noted that the recent renal cell carcinoma pathway model commissioned by NICE used real-world evidence as their preferred methodological approach.[11] As the external CheckMate 649 evidence is from a trial, it is expected to have patient inclusion criteria and reporting of outcomes that are more aligned with the zolbetuximab trials than RWE. Figure 2 shows the similarity of chemotherapy outcomes in the SPOTLIGHT, GLOW and CheckMate 649 studies, further supporting the appropriateness of collectively considering these trials.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Figure 2: SPOTLIGHT, GLOW and CheckMate 649 chemotherapy outcomes



The inclusion of CheckMate 649 leads to a reduction in extrapolation uncertainty due to its longer follow-up and increased sample size. These benefits more than outweigh the uncertainties associated with incorporating this external evidence. Under this approach, estimates for zolbetuximab + chemotherapy need to be obtained via relative treatment effects compared to chemotherapy, with the best source of these being the time-varying estimates.

We note that **separating out the estimation of the baseline risk and applying a relative treatment effect is consistent with the NICE manual for health technology evaluations**, which states: "*Quantifying the baseline risk of health outcomes and how the condition would naturally progress with the comparator(s) can be a useful step when estimating absolute health outcomes in the economic analysis. This can be informed by observational studies. Relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes for the populations or subgroups of interest. State and justify the methods used to identify and critically evaluate sources of data for these estimates.*" (section 4.6.16).[12]

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Finally, we note that one of the EAG's preferred assumptions is to use the BSA from CheckMate 649,[3] which further supports this being a relevant and generalisable trial to the zolbetuximab trial populations.

2) The EAG report preferred extrapolation approach has results inconsistent with external evidence.

The EAG report stated that the use of recreated data for CheckMate 649 leads to uncertainty. However published studies have shown that reconstruction of oncology survival curves results in "excellent accuracy".[13] Furthermore, the NICE manual for health technology evaluations recommends using this method when individual patient level data is not available (see Section 4.6.21).[12]

The draft committee guidance also states that "*The EAG added that with spline modelling, there is a concern that the tail of the extrapolation may be overemphasised*". However published studies demonstrate that overfitting is not an issue with splines, and instead the additional flexibility of spline models (compared to standard parametric models) is required to provide an acceptable fit to the data.[14-17] This is reflected in our submission, where spline models were required to adequately capture the tail of survival and provide extrapolations with face validity when compared to relevant external evidence, as demonstrated in Table 2.

Table 2: Observed and predicted chemotherapy outcomes

Study / approach		**60 months**
Company approach: pooled SPOTLIGHT & GLOW & CheckMate 649 PD-L1 CPS ≥ 5 subgroup, spline-model	Predicted OS (%)	[redacted]
EAG approach: SPOTLIGHT & GLOW, parametric models	Predicted OS (%)	[redacted]
Marsden Cohort[18]	Observed OS (%)	3%
BECOME cohort[19]	Observed OS (%)	11%
Flatiron cohort[20]	GC observed OS (%)	4%
	GEJC observed OS (%)	6%
Merchant cohort[21]	Observed OS (%)	5%
Chau cohort[9]	Observed OS (%)	4%

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

TA857 ERG correction to company approach[7]	Predicted OS (%)	3.8%

Key: GC, gastric cancer; GEJC, gastro-oesophageal junction cancer; NR, not reported; OS, overall survival.

As shown in Table 2, the EAG report preferred extrapolations underestimate those reported in the external literature using real-world data. If external data is not used, implicitly it is assumed that the only relevant evidence is that of the SPOTLIGHT and GLOW trials. However the NICE guidance states: "*The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources, such as historical cohort data sets or other relevant studies*." (section 4.6.20, page 88).[12]

In TA857, the committee's decision was based on incremental cost-effectiveness ratios (ICERs) using extrapolations that predicted longer term OS rate with chemotherapy of 1.5% at 10 years, and 0.9% at 20 years.[7] This compares well with our longer term predictions of [redacted]% at 10 years, and [redacted]% at 20 years, while the EAG report predictions are [redacted]% at 10 years, and [redacted]% at 20 years.

3) The EAG report preferred extrapolation approaches lead to inconsistent decision making

We note that, in the EAG report primary analysis, the effectiveness of zolbetuximab + chemotherapy is based on parametric survival models fit to the zolbetuximab trials, while in its secondary analysis (including nivolumab), the effectiveness of zolbetuximab + chemotherapy is based on the results of the NMA. For both zolbetuximab + chemotherapy and chemotherapy, the same population was used in both analyses. Despite this, these approaches to extrapolations mean that **for the same comparison using the same data, the EAG report produces two different estimates for the cost-effectiveness of zolbetuximab + chemotherapy compared to chemotherapy.**

4) *Our new analysis shows that the committee's suggested approach to extrapolation produces results that are consistent with the original company base-case*

In the draft guidance consultation for zolbetuximab, the committee noted that there was uncertainty in the appropriateness of pooling chemotherapy survival outcomes from CheckMate 649, SPOTLIGHT and GLOW. "*Instead, the committee preferred to explore the feasibility of using evidence from CheckMate 649 as an informative prior*

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

for the overall survival extrapolation." (section 3.8) We agree that CheckMate 649 is relevant external evidence that should be formally incorporated when generating survival extrapolations and thank the committee for this suggestion.

Below we outline the results of analyses exploring the use of CheckMate 649 as an informative prior.

Methods

This approach uses external evidence as an informative prior in a Bayesian framework to extrapolate outcome data.[22-24] It provides a principled approach to incorporating external evidence and can overcome the limitations associated with naïve pooling. To implement this approach the following steps were taken:

- Fit standard parametric survival models to the 'internal' data (pooled SPOTLIGHT and GLOW). The results of this exercise were already reported in detail in the 'Clarification questions addendum' so only top-level results are reported here.
- Fit standard parametric survival models to the 'external' data (CheckMate 649).
- Based on the results of the first two steps, identify a parametric survival model that provides a good fit to both the internal and external data. For this model, the parameter estimates resulting from fitting to CheckMate 649 are used to construct an informative prior which is then used when fitting the same parametric model to the pooled SPOTLIGHT and GLOW data.

An informative prior was only used for the shape parameter, consistent with previous applications.[22-24] This is motivated by noting that the shape parameter generally controls the 'shape' of the hazard distribution (for example, for the Weibull the shape parameter determines if the hazard distribution is increasing or decreasing) while the scale parameter determines the magnitude of the hazard distribution. Allowing for study-specific estimates of the scale parameter allows for differences in outcomes between the internal and external evidence, while still allowing CheckMate 649 to influence outcomes for pooled SPOTLIGHT and GLOW via the shape parameter. Model fitting used the code made available by Bullement et al. and was implemented in R-Stan.[22, 25] When defining the informative priors, a choice is required for the standard deviation to use, with smaller values indicating that more weight is given to the external data. There is no consensus on what value to use for the standard deviation. One study used the empiric standard deviation of the shape parameter from the external evidence, another fixed the standard deviation at 5% of the mean, and the third study did not state the approach.[22-24] As the empiric standard deviation of the shape from CheckMate 649 was 4% of the mean, this value was used.

Six standard survival models were considered: Weibull, Gompertz, gamma, log-logistic, log-normal and generalised gamma. For the three-parameter generalised gamma, informative

priors were used for the shape and scale parameters. The exponential was not considered as it has only one parameter which implies the Bayesian prior approach would give near-identical results to naïve pooling.

This analysis uses the SPOTLIGHT data cut of 8 September 2023[26], the GLOW data cut of 12 January 2024,[26] and the latest published data cut of the CheckMate 649 trial (29 May 2023).[27]

An overview of the Kaplan–Meier estimates of OS for each dataset is provided in Figure 2 and Table 3. Of the three datasets, CheckMate 649 is the largest and most mature, having both the highest proportion of deaths – 90% compared to approximately [redacted]% in both the zolbetuximab trials, along with an additional 85 to 87 weeks of follow-up. The same chemotherapy regimens are used across the three trials, reflected by the similar shape of the survival curves. This supports the approach of formally incorporating CheckMate 649 as a valuable additional evidence source when generating extrapolations.

Table 3: Overview of datasets used

Dataset used	Sample size	Percent of patients with an event	Last observed event time (weeks)
SPOTLIGHT	282	[redacted]%	[redacted]
GLOW	253	[redacted]%	[redacted]
CheckMate 649	482	90%	300

Results

Fit to pooled SPOTLIGHT and GLOW

The fit of standard parametric models to the pooled SPOTLIGHT/GLOW chemotherapy arms is presented in Figure 3, with goodness of fit values provided in Table 4. The lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values are for the gamma model. Based on AIC both the log-logistic, Weibull and generalised gamma models provide within-sample fit that is similar to that of the gamma (based on values within 5 points of the best fitting model), whilst based on BIC the log-logistic and Weibull (but not the generalised gamma) provides similar fit. Of these models, both the gamma and generalised gamma fail to fit the tail of the observed Kaplan–Meier estimates, suggesting that they may result in implausible extrapolations.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Figure 3: Fit of standard parametric models to pooled SPOTLIGHT/GLOW chemotherapy overall survival

Table 4: Fit statistics of standard parametric models, pooled SPOTLIGHT/GLOW chemotherapy arm, overall survival

	AIC	BIC
Weibull	4536.00	4544.56
Log-normal	4578.86	4587.42
Log-logistic	4534.83	4543.39
Gompertz	4558.73	4567.29
Gamma	4532.36	4540.93
Generalised gamma	4534.10	4546.95
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

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

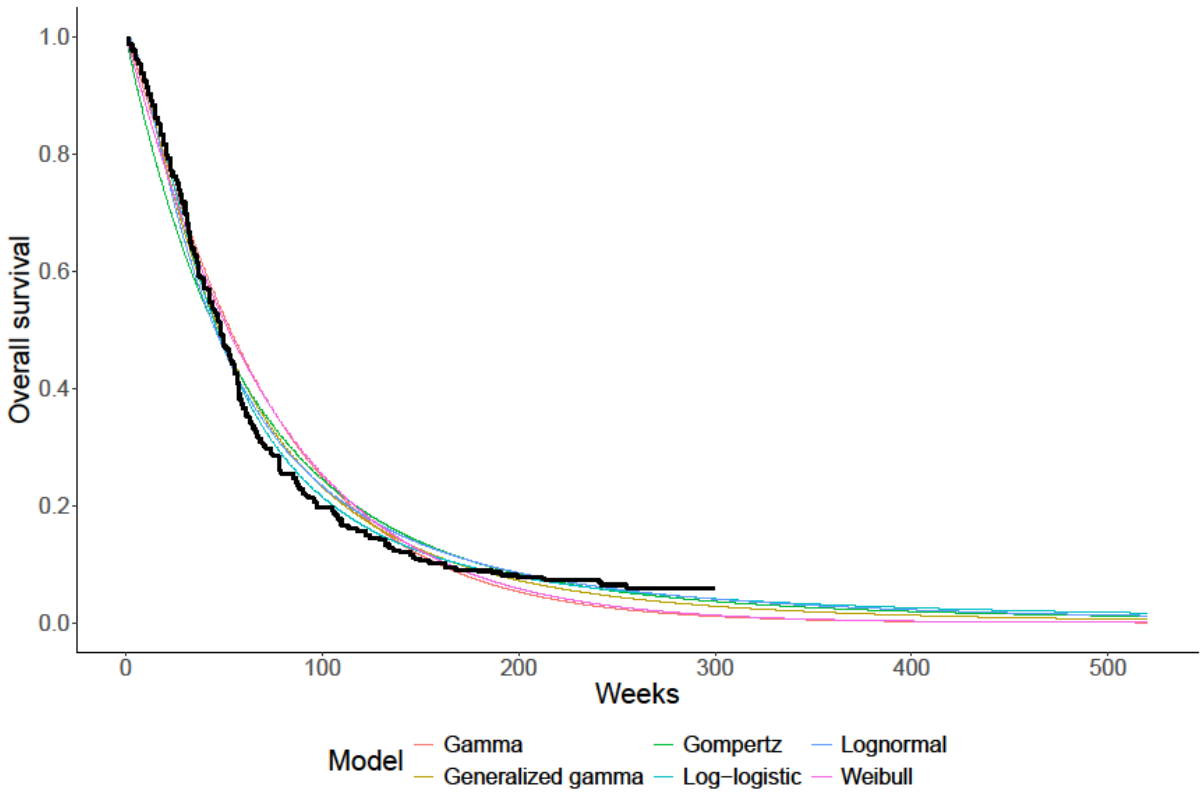
Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Fit to CheckMate 649

The fit of standard parametric models to the CheckMate 649 (PD-L1 CPS ≥5 subgroup) chemotherapy arm is presented in Figure 4, with goodness of fit values provided in Table 5. In contrast to the pooled SPOTLIGHT/GLOW chemotherapy arm, for CheckMate 649 there is much closer agreement in model estimates and extrapolations across the six parametric survival models. This likely reflects the larger sample size and longer follow-up, further reinforcing the importance of considering this source of evidence on chemotherapy outcomes. None of the models capture the potential long-term tail in the observed Kaplan–Meier estimates. For both AIC and BIC, the lowest values are for the log-logistic model. The second-best fitting model based on both measures is the generalised gamma. However, this has AIC and BIC values > 20 points above that for the log-logistic, suggesting that the log-logistic is the only model to provide a satisfactory fit to the data. As the log-logistic model also provides a good fit to the pooled SPOTLIGHT/GLOW chemotherapy arm, the log-logistic is used for the informative prior analysis.

Figure 4: Fit of standard parametric models to CheckMate 649 (PD-L1 CPS ≥5 subgroup) chemotherapy overall survival



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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Table 5: Fit statistics standard parametric models, CheckMate 649 (PD-L1 CPS ≥5 subgroup) chemotherapy, overall survival

	AIC	BIC
Weibull	3318.20	3326.56
Log-normal	3285.12	3293.48
Log-logistic	3260.55	3268.90
Gompertz	3310.04	3318.39
Gamma	3312.06	3320.41
Generalised gamma	3280.79	3293.32

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Results from the informative prior approach

The extrapolations from the log-logistic model with formal incorporation of CheckMate 649 (PD-L1 CPS ≥5 subgroup) as an informative prior ("informative prior approach") and from the original company base-case using the spline extrapolation fitted to the pooled SPOTLIGHT, GLOW and CheckMate 649 (PD-L1 CPS ≥5 subgroup) ("original approach") are shown in Figure 5 (together with Kaplan–Meier estimates from the two pooled SPOTLIGHT/GLOW chemotherapy arms and CheckMate 649 (PD-L1 CPS ≥5 subgroup) for reference). Table 6 shows the landmark estimates.

There are small differences between the new "informative prior approach" and the "original approach" (i.e., the difference between the OS rates estimated by each approach ranges between 0%-5% depending on the year). In the earlier years, the new "informative prior approach" estimates slightly higher OS values than the "original approach". From year 5-6 onwards, the two approaches predict similar OS rates.

In the pooled SPOTLIGHT/GLOW chemotherapy arm, the latest observable Kaplan-Meier OS rate is 9% at 4-years, which is between the "informative prior approach" at [redacted]% and the "original approach" at [redacted]%. The EAG's preferred approach is lower ([redacted]%) at 4-years.

A comparison of parameter estimates is provided in Figure 6, which presents for both parameters the posterior distribution arising from the informative prior approach, along with reference lines indicating the estimates from the individual data sources. As expected, the informed shape parameter is approximately mid-way between the two individual sources, whilst the scale parameter (which is not informed) is essentially unchanged.

Cost-effectiveness results incorporating the informative prior approach are provided in Table 10 through to Table 11 (all cost-effectiveness results are presented at the end of this

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	document). Results incorporated the revised confidential discount for zolbetuximab (confidential net price= £[redacted] per 100mg vial). The analyses use the External Assessment Group's (EAG's) base case assumptions with the following changes: • As suggested by the committee and described above, the survival outcomes with chemotherapy are based on pooled SPOTLIGHT/GLOW chemotherapy arm data with CheckMate 649 (PD-L1 CPS ≥5 subgroup) chemotherapy arm incorporated as an informative prior (i.e., the "informative prior approach"). • The effectiveness of zolbetuximab + chemotherapy is based on the time-varying network meta-analysis (NMA). This is because, when using an informative prior for chemotherapy, use of survival models fitted to the pooled SPOTLIGHT/GLOW for zolbetuximab + chemotherapy will not provide a 'like-for-like' comparison. Instead, relative treatment effects should be used. As outlined in the first and third consultation comments, it is appropriate to use these NMA results as (1) heterogeneity in PD-L1 CPS expression does not modify the effectiveness of either chemotherapy or zolbetuximab + chemotherapy; and (2) results are not influenced by the inclusion of CheckMate 649 in the network. • Two approaches are explored for treatment effect waning. When treatment effect waning is included, it begins at 5 years (as per the EAG base case) but does not reach 100% until 7 years. This approach is to ensure consistency with the implementation of treatment effect waning in previous appraisals.[7, 8] In the second approach, treatment effect waning is not included for zolbetuximab + chemotherapy, to reflect the lack of stopping rules for this intervention (see comment 4 for further discussion of treatment waning). When incorporating the revised confidential discount for zolbetuximab + chemotherapy, the incremental cost-effectiveness ratio (ICER) is £[redacted] when assuming treatment effect waning; and £[redacted] when assuming that the effect is sustained over time (i.e., excluding treatment effect waning). These demonstrate that the addition of zolbetuximab to chemotherapy is cost-effective. Assuming treatment effect waning already penalises for uncertainty in the economic evaluation, warranting the upper bound of the cost-effectiveness threshold at £30,000. If uncertainty is considered within the cost-effectiveness threshold, the ICER excluding treatment waning is more informative – this is discussed in more detail in comment 5. Collectively, the results support the appropriateness of using the CheckMate 649 trial to inform extrapolations for the pooled SPOTLIGHT/GLOW chemotherapy outcomes, either pooled or with the informative prior approach. Standard parametric models fit only to SPOTLIGHT/GLOW data do not adequately capture the expected subset of long-term

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	survivors, observed both in CheckMate 649 and additional studies (see Section B.3.13.2 of the company submission). This new informative prior approach, as well as being recommended by the committee, is consistent with first-principles best practice to incorporate external data to inform chemotherapy hazards, with zolbetuximab + chemotherapy hazards additively combined with these via the NMA results (which also has the benefit of providing an explicit treatment effect).[28, 29] This may be seen as a natural extension to the incorporation of general population mortality as a relevant form of external evidence.[30] *Figure 5: Overall survival estimates; log-logistic model with and without informative prior* 

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Figure 6: Distribution of parameter estimates from the informative prior approach (solid line = estimate from pooled SPOTLIGHT/GLOW, dashed line = estimate from CM-649)

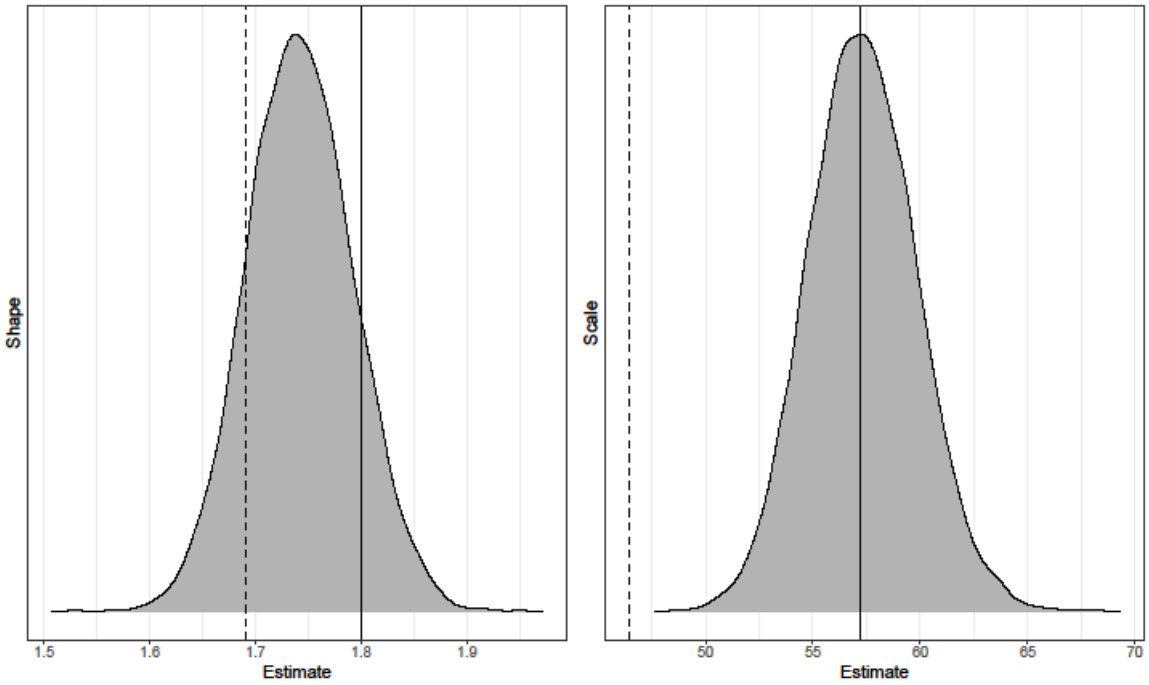

Table 6: Landmark estimates of survival

	OS estimates at each year, % (95% CI)		
Year	**Kaplan–Meier (pooled SPOTLIGHT/GLOW)**	**Log-logistic, informative prior**	**Spline; SPOTLIGHT, GLOW CheckMate 649 pooled, 3-knot hazard**
1	56% (52% to 60%)	[redacted]	[redacted]
2	24% (21% to 29%)	[redacted]	[redacted]
3	11% (8% to 15%)	[redacted]	[redacted]
4	9% (6% to 14%)	[redacted]	[redacted]
5	NA	[redacted]	[redacted]
6	NA	[redacted]	[redacted]
7	NA	[redacted]	[redacted]
8	NA	[redacted]	[redacted]
9	NA	[redacted]	[redacted]
Key: CI, confidence interval; NA, not applicable; OS, overall survival			

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

3	**Section 3.8 Appropriateness of indirect treatment comparison to synthesise SPOTLIGHT and GLOW trials** We are concerned that the committee may have considered that the potential heterogeneity in the indirect treatment comparison between zolbetuximab, pembrolizumab and nivolumab would also affect the comparison between zolbetuximab and chemotherapy. The draft guidance states: "*The committee noted the uncertainties associated with the network meta-analysis, which included the heterogeneity between the studies. The committee concluded that it prefers pooling evidence from SPOTLIGHT and GLOW, and extrapolating survival using parametric curves in line with the EAG's approach*." (section 3.8). **As the evidence network has a star-shape, the zolbetuximab vs chemotherapy node, which synthesises the evidence of SPOTLIGHT and GLOW, is minimally affected by the nodes comparing nivolumab and pembrolizumab to chemotherapy.** This is shown in Table 7, where the results of the zolbetuximab vs chemotherapy node are very similar with and without the inclusion of the pembrolizumab vs chemotherapy node. Table 7 also shows that, when incorporated in NMAs (both proportional hazards and time-varying) the results are similar to the HRs obtained from the within-trial analysis of pooled SPOTLIGHT and GLOW, with the advantage of the spline-based NMA capturing the change in hazard ratios over time. SPOTLIGHT and GLOW have identical/similar inclusion/exclusion criteria and trial design, apart from the chemotherapy regimen, which, as aforementioned, can be considered to be clinically equivalent. **Therefore the heterogeneity in the SPOTLIGHT and GLOW node is minimal.** Furthermore, **synthesising the two trials in terms of relative effectiveness and applying the relative effect to a baseline risk is aligned with NICE guidance and best practice** (see NICE health technology evaluations manual section 4.6.16 mentioned above).[12] For these reasons, it is appropriate to apply the estimated HRs to the chemotherapy baseline to predict PFS and OS with zolbetuximab, as done in the company's base-case.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Table 7: Hazard ratios of zolbetuximab vs chemotherapy by evidence source

Source	PFS (HR [95% CI])	OS (HR [95% CI])
SPOTLIGHT	0.73 (0.59, 0.91)	0.78 (0.64, 0.95)
GLOW	0.69 (0.55, 0.86)	0.76 (0.62, 0.94)
Pooled SPOTLIGHT and GLOW	0.71 (0.61, 0.83)	0.77 (0.67, 0.89)
Proportional hazards NMA (Pooled SPOTLIGHT and GLOW)*	[redacted]	[redacted]
Time-varying NMA primary analysis including nodes for zolbetuximab vs chemotherapy and nivolumab vs chemotherapy	1 year: [redacted] 2 years: [redacted] 3 years: [redacted] 4 years: [redacted] 5 years: [redacted]	1 year: [redacted] 2 years: [redacted] 3 years: [redacted] 4 years: [redacted] 5 years: [redacted]
Time-varying NMA primary analysis including nodes for zolbetuximab vs chemotherapy and nivolumab vs chemotherapy	1 year: [redacted] 2 years: [redacted] 3 years: [redacted] 4 years: [redacted] 5 years: [redacted]	1 year: [redacted] 2 years: [redacted] 3 years: [redacted] 4 years: [redacted] 5 years: [redacted]

Key: CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.
Note: *The same values and 95% CI were observed when different CPS subgroups were explored

4

Section 3.10 Treatment effect waning

We are concerned that the assumption that zolbetuximab's treatment effect stops abruptly at 5 years is overly pessimistic, given that (1) it is not supported by the available evidence and has poor face validity, and (2) is inconsistent with the assumptions on treatment waning of a recent appraisal in this indication (TA997).

(1) The assumption that zolbetuximab's treatment effect stops abruptly at 5 years is not supported by the available evidence and has poor face validity

As noted in the draft guidance document (our bold): "***The EAG agreed that the evidence did not show treatment-effect waning for zolbetuximab*** *but highlighted the limited follow up of overall and progression-free survival in SPOTLIGHT and GLOW. So it modelled scenarios using treatment-effect waning after 3 and 4 years. But the EAG base case applied the company's scenario and used a treatment-effect waning at 5 years. This was because the scenarios at 3 and 4 years were too pessimistic,* ***because the observed hazard ratios***

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

showed no sign of treatment-effect waning at 3 years *(although the number of people was small).*"

The continuation of the treatment effect is evident in the Figures below, which show the empirical HRs of SPOTLIGHT and GLOW trials, alongside with the predicted HRs from the indirect treatment comparison, and the treatment effect waning as applied by the EAG.

Figure 7: Comparison of hazard ratios of zolbetuximab vs chemotherapy

The poor face validity of this abrupt waning is shown in the EAG's base-case trace, where the proportion of patients alive with zolbetuximab has a kink at 5 years – see Figure 7.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Figure 8: Overall survival from the EAG base-case: zolbetuximab + chemotherapy

(2) The assumption that zolbetuximab's treatment effect stops abruptly at 5 years is inconsistent with the assumptions on treatment waning of a recent appraisal in this indication (TA997)

We note that, in TA997, "*The committee concluded that it was appropriate to apply treatment-effect waning for pembrolizumab for the CPS of 1 or more subgroup. It agreed that scenarios in which waning starts at either 5 years, 6 years or 7 years after starting treatment and reduces to the same as the comparator after 2 years, were all plausible*." (section 3.8). . Therefore, if effect waning is to be considered, we ask the committee to consider our proposed approach of applying it gradually as was conducted in TA997.

We recognise that the NICE manual for health technology evaluations advises for the routine considerations of scenarios about the duration of treatment effects (section see 4.6.20). However we note that whether these scenarios are incorporated in the committee's base-case for decision-making varies across appraisals. A recent review of NICE appraisals published between 20-Oct-2021 and 20-Sep-2023 found that the committee had excluded waning assumptions in 40/72 (68%) of oncology appraisals, and with those where waning was applied, various methods were explored.[31] This indicates variation and potential inconsistency in the application of these assumptions for decision-making, which has important consequences for the perceived cost-effectiveness of new drugs, hence patients' access to them.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

5	**Section 3.12 Acceptable incremental cost-effectiveness ratios: Risk of 'double-counting' uncertainty by adopting an unreasonable approach to the evidence** We are concerned that the EAG and committee's approach to handling uncertainty in the base case assumptions has been pessimistic, particularly in areas such as extrapolation methods, waning of zolbetuximab's treatment effect, and the use of point estimates for hazard ratios (HRs) that favour pembrolizumab and nivolumab. This pessimism is further compounded by the application of a lower threshold to accommodate uncertainty. **Such a dual approach—being conservative in base case assumptions while also applying a lower threshold—appears unreasonable and could be seen as to 'double count' for uncertainty.** The uncertainty associated with the proposed approach is lower than that considered in many NICE technology appraisals.[32, 33] In the first consultation comment, we show that any bias in the indirect treatment comparison is likely to lead to an underestimate of zolbetuximab's clinical and cost-effectiveness. Additionally, the extrapolations are based on SPOTLIGHT & GLOW, for which the data that is [redacted]% mature and are further informed by extensive external evidence with up to 4.5 years of follow-up; and in CheckMate 649, the data is 90% mature and has up to 6 years' follow-up. The assumptions regarding the extrapolation of treatment effects have been: compared to external data sources, validated by clinical experts, and aligned with both committee methodological precedence in prior appraisals (TA857 and TA997) and good practice guidance from NICE.[12] Given these comprehensive measures, it is challenging to envision an oncology appraisal where the uncertainty could be substantially lower. The wider issue of equitable access to innovative oncology therapies is particularly pressing for gastric cancer patients, especially those unable to tolerate checkpoint inhibitors. The removal of end-of-life criteria, which previously facilitated access to treatments for severe conditions, coupled with lowering the threshold as a result of perceived uncertainty is disrupting the ability of the UK healthcare system to have access to innovative oncology medicines that would benefit patients. As one of the comparators in this appraisal, nivolumab + chemotherapy, was approved using end of life criteria, this further compounds the approach taken by the committee. **The threshold of £25,000 per QALY (or the implicit threshold of £30,000 once the severity multiplier is considered) implied by the draft consultation document is unreasonable given several factors.** Firstly, **every reasonable attempt has been made to mitigate uncertainty**, including using mature data from two randomised controlled trials (RCTs), incorporating relevant long-term external evidence, employing numerous methods to explore the impact of structural uncertainty, clinical and economic validation, and maintaining consistency with prior appraisals in gastric cancer. Secondly, **the extent of the**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	remaining uncertainty is likely on the lower bound of what NICE committees typically face, further supported by external data source validation and clinical expert input. Lastly, **any residual uncertainty likely results in an underestimation of zolbetuximab's clinical and cost-effectiveness**, making the current threshold unreasonably conservative for this innovative therapy.
6	**Section 3.13 Committee's request for zolbetuximab to be compared to pembrolizumab in patients with PD L1 CPS of at least 10 – now redundant given the recently published NICE TA997** We are concerned that the recently published NICE guidance TA997 on pembrolizumab for patients with PD-L1 CPS of at least 1 was not considered when making this request. This guidance was published on 29-Aug-2024, and partially replaces TA737 with respect to patients with gastro-oesophageal junction adenocarcinoma, for whom TA737 recommended pembrolizumab + chemotherapy if patients had PD L1 CPS of at least 10. **As patients with PD L1 CPS of at least 10 are necessarily included in the group of patients with PD L1 CPS of at least 1, our understanding is that this request is fulfilled by our previously presented analysis on the clinical effectiveness and cost-effectiveness comparison zolbetuximab + chemotherapy vs pembrolizumab + chemotherapy in patients with PD L1 CPS of at least 1**.
5	
6	

Insert extra rows as needed

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Appendix: Cost-effectiveness results

The results presented therein use the company-amended EAG base-case, as follows:

- Chemotherapy survival outcomes: based on the prior pooled SPOTLIGHT/GLOW with log-logistic extrapolation. For OS extrapolation, this uses an informative prior based on CheckMate-649 PD-L1 CPS ≥5 as recommended by the committee (details in section 2, page 15-22).
- Zolbetuximab + chemotherapy survival outcomes: based on the spline-based network meta-analysis, applied to the chemotherapy reference.
- Treatment effect waning, when applied, applied gradually from year 5 to year 7 post-treatment initiation.
- As per EAG base-case: wastage is included (i.e., no vial sharing), the mean body surface area is 1.77 m^2, utility is based on the mixed effects model.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Table 8: Cost-effectiveness results vs nivolumab PD-L1 CPS 5-9 subgroup based on the company amended EAG base-case, with gradual treatment effect waning

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 or £36,000[1]
With severity modifier 1.2								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Nivolumab + chemotherapy PD-L1 CPS 5-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.43	[redacted]	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	-	–	–
Nivolumab + chemotherapy PD-L1 CPS 5-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.43	Zolbetuximab dominates	[redacted]
Without severity modifier								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–	[redacted]
Nivolumab PD-L1 CPS 5-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.35	[redacted]	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

With PAS price applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	–	[redacted]
Nivolumab PD-L1 CPS 5-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.35	Zolbetuximab dominates	[redacted]

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

The survival outcomes with nivolumab + chemotherapy are based on the hazard ratios estimates from the proportional hazards network meta-analysis comparing nivolumab + chemotherapy in PD-L1 CPS 5-9 vs chemotherapy (see Table 1, page 8), applied to the chemotherapy reference.

[1]The willingness to pay threshold used with severity modifier is £30,000/QALY; without severity modifier it is £36,000/QALY.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

Table 9: Cost-effectiveness results vs pembrolizumab PD-L1 CPS 1-9 subgroup based on the company amended EAG base-case, with gradual treatment effect waning, and a severity modifier

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 or £36,000[1]
With severity modifier 1.2								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Pembrolizumab PD-L1 CPS 1-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.22	Zolbetuximab dominates	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	-	–	–
Pembrolizumab PD-L1 CPS 1-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.22	Zolbetuximab dominates	[redacted]
Without severity modifier								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	–	[redacted]
Pembrolizumab PD-L1 CPS 1-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.19	Zolbetuximab dominates	[redacted]

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

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With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	–	[redacted]
Pembrolizumab PD-L1 CPS 1-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.19	Zolbetuximab dominates	[redacted]

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

The survival outcomes with nivolumab + chemotherapy are based on the hazard ratios estimates from the proportional hazards network meta-analysis comparing pembrolizumab + chemotherapy in PD-L1 CPS 1-9 vs chemotherapy (see Table 1, page 8), applied to the chemotherapy reference.

[1]The willingness to pay threshold used with severity modifier is £30,000/QALY; without severity modifier it is £36,000/QALY.

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Table 10: Cost-effectiveness results based on the company amended EAG's base case, with gradual treatment effect waning

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 or £36,000[1]
With severity modifier 1.2								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]	[redacted]
Without severity modifier								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.48	[redacted]	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.48	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.
[1]The willingness to pay threshold used with severity modifier is £30,000/QALY; without severity modifier it is £36,000/QALY.

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Table 11: Cost-effectiveness results based on the company amended EAG base case, without treatment effect waning

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 or £36,000[1]
With severity modifier x 1.2								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.71	[redacted]	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.71	[redacted]	[redacted]
Without severity modifier								
At list price								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.59	[redacted]	[redacted]
With new PAS applied to zolbetuximab								
Zolbetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.59	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.[1]The willingness to pay threshold used with severity modifier is £30,000/QALY; without severity modifier it is £36,000/QALY.

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck, Sharp & Dohme (MSD)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Pembrolizumab as a comparator and ITC vs pembrolizumab** **Page 6, paragraph 3.3 and page 9 paragraph 3.5 of the Draft guidance document** Zolbetuximab with chemotherapy has not been compared with pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy in the ongoing ID5123 appraisal despite the latter being listed

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	as a relevant comparator in the final scope. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (TA997) (1). The TA997 guidance was based on the KEYNOTE-859 trial (2). MSD agrees that data from KEYNOTE-859 trial should be used for the indirect treatment comparison (ITC) versus zolbetuximab in patients with untreated locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. MSD noted that the ID5123 submission does not include the most recent data cut (August 2023) of the KEYNOTE-859 trial. The median follow-up from randomisation to data cutoff is 41.6 months in Rha et al. 2024 (2). The August 2023 KEYNOTE-859 data informed the TA997 recommendation. The NICE TA737 guidance (3) was based on the KEYNOTE 590 clinical trial (4). As per the ID5123 final scope (5), the subgroup of patients with untreated locally advanced unresectable or metastatic HER2-negative GOJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 was a relevant comparator at the time when the final scope for ID5123 was issued. In August 2024, TA737 was partially updated by TA997 (specifically with respect to the HER2-negative gastro-oesophageal junction adenocarcinoma population). The KEYNOTE-062 trial (6) was included in the ITC network as a relevant evidence source, however it should be noted that KEYNOTE-062 did not inform marketing authorisation or HTA recommendations for pembrolizumab included in the final scope for the ID5123 appraisal. MSD noted a comment regarding a lower proportion of people with a PD-L1 CPS of 5 or more in SPOTLIGHT and GLOW trials. According to the trial publication (7), based on the ad hoc analysis, 225 of 288 (78.1%) patients were determined to have tumours with a PD-L1 CPS <5; in GLOW, 21.9% of assessed patients had tumours with a PD-L1 CPS ≥5, and, in SPOTLIGHT, 13.2% of assessed patients had tumours with a PD-L1 CPS ≥5. The number of patients with PD-L1 CPS ≥1 was not reported. MSD acknowledges challenges associated with comparison across different biomarker cuts, however MSD believes that if feasible, scenario analysis in a subgroup of patients with PD-L1 CPS ≥1 from SPOTLIGHT and GLOW trials could help inform a relative effectiveness comparison between zolbetuximab and pembrolizumab.
2	**Assumptions on equivalence** **Pages 15-16, paragraph 3.9 and page 18 paragraph 3.13 of the Draft guidance document** MSD notes the EAG and committee view that nivolumab and zolbetuximab should not be assumed to have equivalent efficacy. Consequently, cost-effectiveness results using ITC results for survival outcomes should be presented for the comparisons with pembrolizumab (using the KEYNOTE-859 trial) and nivolumab. When both are relevant comparators, fully incremental cost-effectiveness results should be presented.
3	**Approach to model subsequent treatments** **Page 533 and 669 of 783, of the Committee Papers** MSD is unclear if Astellas' approach to model subsequent treatments results in a discrepancy between subsequent treatments which are costed and those which contribute to OS benefit. Like ID4030 (TA997), a scenario analysis costing the most used subsequent treatments in the pivotal

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 27 September 2024. Please submit via NICE Docs.

	trial (SPOTLIGHT and GLOW) would be helpful to understand the direction and magnitude of this assumption.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Ceri Steele]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	This treatment offers an alternative treatment to patients who cannot have surgery with fewer side effects than the current standard of care, meaning that patients have a better quality of life during treatment

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2	This treatment offers an alternative to current standard of care for the increasing number of younger patients who are presenting with this condition
3	Survival rates for this cancer need to improve and this offers an opportunity to work towards that
4	How to put a price on a life?
5	
6	

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

Please return to: **NICE DOCS**

Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

"In September 2016 I was sitting in a delicatessen in Manhattan when I received an email from my dad. Ever fond of understatement, the words he used were to the effect of ""Son, I'm afraid I'm not well"".

My immediate thoughts were ""No, this can't be. We have so much left undone"".

Dad had been diagnosed with stage 4 cancer of the stomach. As it was at such an advanced stage, it became clear very early that he was in serious trouble. The tumour was considered inoperable as it was also attached to the pancreas. Two gruelling rounds of chemotherapy followed, and radiotherapy also. Dad attended each appointment on his bicycle, to the faint amazement of the hospital staff. Dad wasn't fond of fuss or ostentation.

Even though we remained optimistic throughout (I don't know what other mindset you could usefully adopt in such times), his condition deteriorated and he died on the [redacted]. Towards the end he suffered several strokes as that heinous disease slowly destroyed him. It was the most horrific thing that I have ever witnessed. He faced what was coming with a dignity that I found truly humbling. I miss this kindly and gentle man every day.

I do know that one of the few crumbs of comfort of his passing was that he was no longer in pain. If there were other options that could have extended his life and the quality of it, I would truly love other people to be able to access those options so that they could have extra time that I wasn't lucky enough to have."

Name	[redacted]
Comments on the DG:	

My name is [redacted] and I am a stage 2 stomach cancer survivor, but as we know most are not this fortunate and often get diagnosed at stage 4. Zolbetuximab is a promising new treatment for patients who are Claudin 18.2 positive. I am disheartened to read that NICE is rejecting its approval. Gastric cancer is already a massively underfunded area of cancer research and new treatments are essential to improving the quality of life of patients and to improve survival outcomes. In addition, patients who have signet ring gastric cancer, which is known for its chemoradio resistance could also massively benefit from this drug. This drug could also help multiple younger and older patients have longer to live. Signet ring carcinoma is massively increasing amongst the younger population, especially young women like myself.

Benefits of Zolbetuximab in Treating Claudin 18.2-Positive Stomach Cancer:

1. Improved Survival Outcomes:

Clinical trials have shown that zolbetuximab, when combined with chemotherapy, can significantly improve progression-free survival (PFS) (the time patients live without the cancer worsening) and overall survival (OS) compared to chemotherapy alone in patients with Claudin 18.2-positive stomach cancer.
In one trial, patients treated with zolbetuximab plus chemotherapy had median PFS of about 10.6 months, compared to 8.6 months for chemotherapy alone, and a median OS of 18.2 months versus 15.5 months.

2. Enhancing the Effectiveness of Chemotherapy:

When combined with standard chemotherapy (like oxaliplatin or capecitabine), zolbetuximab enhances the treatment's ability to shrink tumors and control disease progression, offering a more comprehensive attack on the cancer

3. Selective Targeting with Lower Toxicity:

Zolbetuximab specifically targets cancer cells that express Claudin 18.2, reducing the risk of harming normal cells that do not express this protein. This selective targeting typically results in fewer off-target side effects compared to more generalized cancer therapies.
Side effects from zolbetuximab, such as nausea, vomiting, and fatigue, are generally manageable and can be less severe than those seen with some traditional cancer treatments.

4. New Option for Advanced or Metastatic Disease:

For patients with advanced or metastatic gastric cancer, who have limited treatment options, zolbetuximab offers a promising new approach,

especially when their tumors are difficult to treat with surgery or other interventions.
It can also be beneficial in combination with chemotherapy as a first-line treatment, offering hope for better management of the disease from the outset.
Zolbetuximab is a promising new therapy for Claudin 18.2-positive stomach cancer due to its targeted mechanism of action, ability to improve survival outcomes, and relatively selective toxicity profile. It represents a step forward in precision oncology, where treatments are tailored to specific molecular characteristics of a patient's cancer, offering a more effective and personalized approach to care. This treatment should be approved by NICE.

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Zolbetuximab, in combination with chemotherapy, is now a guideline-endorsed therapy for patients with untreated advanced gastric cancer whose tumours express CLD18.2 at the requisite level. This treatment provides a robust, evidence-based alternative with manageable toxicity, surpassing chemotherapy alone, which typically results in a median survival of less than one year.

I would like to offer comments on the draft guidance.

1. The claim that all patients, irrespective of PD-L1 status, would receive zolbetuximab is highly questionable. Immune checkpoint inhibitors (ICIs) only demonstrate efficacy in patients with a CPS score of at least 5. Although pembrolizumab is approved for CPS 1-4 tumours, it is ineffective in this cohort. EPAR data indicates activity in CPS 1-4 but not CPS 5-9, a result widely dismissed as a false positive due to inadequate biomarker precision, and counter to that observed for other ICI. Consequently, zolbetuximab is likely to be favoured over pembrolizumab for CPS 1-4 patients, while CPS ≥5 patients may still receive pembrolizumab or nivolumab.

2. The committee has not adequately considered the latest evidence on zolbetuximab, particularly in relation to the control of nausea and vomiting through steroid use, and how this impacts on efficacy. This data, available in Japanese regulatory submissions and forthcoming in the EU EPAR, was also presented by Shitara et al. at GI ASCO 2024. A per-protocol analysis of the SPOTLIGHT trial revealed a survival benefit of over five months when steroids were utilized, suggesting that the real-world efficacy of zolbetuximab may be significantly greater.

3. Furthermore, the EAG's concerns about heterogeneity across trials are overstated. Variability in chemotherapy regimens (oxaliplatin vs. cisplatin) does not impact overall survival, and PD-L1 expression is neither prognostic nor influential in the interaction between CLD18.2 and zolbetuximab. If heterogeneity were a major factor, divergent outcomes would have been observed in ICI trials, yet the hazard ratios for ORR, PFS, and OS remain remarkably consistent across studies, underscoring that these concerns are not clinically relevant.

Name	[redacted]
Comments on the DG:	

From 2019 to 2023, I supported my brother-in-law through stage IV stomach cancer treatment until he passed away. He lived four years with stage IV because he was able to access private health care at The Marsden. I know the options he had as a private patient meant he lived longer and had more time with his family than he would have had under the NHS guidance at that time. He was able to have surgery because he responded well to chemotherapy instead of being told to wait until he had symptoms of recurrence. When he did sadly recur, he was able to get immunotherapy which was not available to NHS patients at the time. I am alerted to the fact that you are assessing the efficacy of zolbetuximab and that there are strong indicators that the FDA and EMA will approve its use within the coming months. It will be available to people in parts of the world where it has been approved but it will also be available to those who can pay in the UK. These treatments should not be available onto the most privileged and wealthy.
I recognise that there are financial constraints, but the recipients of the treatments are few. The commercial price appears comparable to that of other immunotherapies such as Nivolumab, although I am obviously not clear on the NHS discount or scheduling. I do know that having access to a treatment option at that point gave my family time and so many positive memories. I feel great sadness when I think of stomach cancer patients who were unable to afford all treatment options and were robbed of the time we were fortunate enough to have.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is important to look at patients who has Her2 neg and CPS<1 but are CLDN+ and who do not have any targetted therapy option.
Astellas should be able to supply that data.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are sound but don't think it has looked at all subset of patients who could potentially benefit.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Not on the aforementioned characteristics but I feel there is a biological group as mentioned who needs looking into.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Not sure

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not sure

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not sure

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As I am having difficulty in finding the correct place to put my comments, I've chosen to put my comments in this box.
My comments are:I was diagnosed with stage 4 cancer in 2017 when I turned 70 and I was given 12-18 months to live. I had total response to chemotherapy and had total gastrectomy. I am fit, well and working full time 7 years later.i understand I am one of 3%of stage 4 patients that survives. This drug should be approved for the other 97%that don't. Its shortsightedness on part of NICE to reject it. Not only they would be denying much needed medication in an underfunded cancer, they will be stifling grotesquely-needed innovation in this much neglected area of oncology. People in Britain deserve better. In the area of stomach cancer, Britain is already 25th in global outcomes and it doesn't do our reputation as a country any good.

Name	[redacted]

Comments on the DG:

Has all of the relevant evidence been taken into account?

NICE recognises the medical benefits of zolbetuximab and also how devastating and serious stomach cancer is, but nevertheless is looking to reject zolbetuximab on cost grounds, arguing that it's not a worthwhile allocation of NHS resources.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Zolbetuximab (made by Astellas) is a drug that targets claudin 18.2 which is a protein that is found in nearly half of all gastric cancers. Trials have shown improved overall survival and a longer time before progression (when the cancer comes back) and around the world, the medical community views this targeted therapy as a new standard of care. It is entirely possible that we will be one of the only developed countries in the world without access to this life-extending, even life-saving drug as the FDA, EMA are poised to approve it and it has already been approved in Japan.

Are the recommendations sound and a suitable basis for guidance to the NHS?

There are not many treatment options for stomach cancer and not everyone has the biomarkers necessary to get available drugs beyond chemotherapy. For many of these people, zolbetuximab will be their best hope.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As I lost my father to stomach cancer and there was not many hopeful treatment options, I feel this would give people a chance. I'm deeply affected by my experience and live in fear everyday that this could be genetic. Please consider this drug being approved to give people a chance. Stomach cancer has little treatment options currently, this really could make a difference.

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No.
1) NICE has failed to involve lay people who represent the interests of the people most directly affected by their recommendations which contravenes both their own Patient and Public Involvement Policy and the Health and Social Care Act (2012). See the heading 'compliance with NICE's Patient and Public Involvement Policy' in our comments.
2) Inadequate information about patients who are both CPS <1 and HER2 negative. Please refer to the heading in 'Zolbetuximab benefits all – but particularly those with the greatest unmet needs' in our comments.
3) Diffuse and SRCC are particularly aggressive and hard to treat subtypes of GC/GEJC and have a reduced response to immunotherapy, so would benefit from Zolbetuximab. Please refer to the comments under heading 'Zolbetuximab benefits all – but particularly those with the greatest unmet needs'.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No.
1) Zolbetuximab is the only targeted therapy option for many patients with the greatest unmet needs.
2) No targeted treatments currently approved for CPS<1 and HER2 negative cohort. The 5 year OS statistics on palliative double chemotherapy alone is only 2%-5% for this cohort.
3) Some PDL1 cohorts are unable to receive immunotherapy due to clinical reasons such as liver compromise or autoimmune disorders. Please refer to headings, 'Zolbetuximab benefits all – but particularly those with the greatest unmet needs' / 'Zolbetuximab, PDL1 and immunotherapy' and 'CPS 5-10, 10+' in our comments.

Comment from Gastric Cancer UK Ltd.

Compliance with NICE's Patient and Public Involvement Policy

As an organisation representing the voices of stomach cancer patients and carers, Gastric Cancer UK is aware of the Patient and Public Involvement policy for NICE as per the Health and Social Care Act (2012) and we want

to highlight that, in this instance, the standard process of patient and public involvement was not adequately met.

Your policy states: "that lay people, and organisations representing their interests, have opportunities to contribute to developing NICE guidance, advice and quality standards, and support their implementation, and that, because of this contribution, our guidance and other products have a greater focus and relevance for the people most directly affected by our recommendations".

Name	[redacted]
Comments on the DG:	
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? I'm not sure it's been adequately recognised that for many patients it isn't a case of having a choice between immunotherapy and zolbetuximab, or of them having having both. Not everyone is a candidate for immunotherapy so zolbetuximab would be their only hope beyond chemo. For these patients, should a cost comparison with immunotherapy be used when they can't access immunotherapy to start with? My father was diagnosed with stage IV stomach cancer in 2017 and he was one of the very few lucky ones as we still have him with us today, only because he had a super rare complete response to palliative chemo (FOLFOX) and was able to have surgery. The oncologist said this was something a doctor could only expect to see once or twice in their career. While he was unwell, I leaned heavily on peer support and got to know many patients and family members like myself. No one I got to know from that time is still alive apart from my dad. Not a single person. And in the following years as I've stayed with the stomach cancer communities both in the UK and internationally, I've lost count of the number of people we've lost. And the pattern has been the same. Folfox, capox or maybe flot, either no response or recurrence very soon after and no other meaningful options. Just ineffective chemo and no targeted therapies, if they're even strong enough to have it. I've noticed another pattern. In international groups, patients from other countries have so many more options than we do. People live longer in other countries than our patients do and it's unfair. It's not right that our loved ones don't have the same chances to survive just by virtue of where we live. It's just heartbreaking that of the few drugs available, NICE either delays approving them or outright rejects them.	

Name	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Are the recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

It is with considerable concern that we offer these comments, despite our absence from the committee proceedings, on what we see as a ruling that may have far-reaching negative consequences for gastroesophageal cancer patients. Many of these individuals, particularly those with advanced disease, are left with limited treatment options. For this cohort, zolbetuximab represents a significant advance. By not fully appreciating its potential benefit, we risk leaving these patients with little more than chemotherapy, a treatment that, in this context, offers a median survival of less than a year.

The committee's argument that all patients, regardless of PD-L1 status, would be treated with zolbetuximab is overly simplistic and not reflective of the clinical realities. Immune checkpoint inhibitors (ICIs), such as pembrolizumab or nivolumab, have demonstrated efficacy only in patients with a CPS score of 5 or higher. While pembrolizumab is funded for CPS 1-4 tumors, the evidence of its effectiveness in this population is highly questionable. Indeed, EPAR data suggests that any observed efficacy in CPS 1-4 is spurious—likely the result of poor biomarker precision—since it did not extend to CPS 5-9. Most leading oncologists would agree that this finding does not represent a genuine therapeutic benefit. Consequently, it is illogical to suggest that pembrolizumab or other ICIs would be preferred for CPS 1-4 patients. Zolbetuximab, by contrast, presents a more viable option for these patients, given its strong clinical evidence and tolerable side effect profile.

Moreover, the committee’s failure to properly weigh the most recent evidence supporting zolbetuximab is deeply concerning. Data presented by Shitara et al. at GI ASCO 2024, as well as findings included in Japanese regulatory submissions and soon to be reflected in the EU EPAR, provide a robust analysis of the SPOTLIGHT trial. This evidence demonstrates that when nausea and vomiting—two manageable side effects—are adequately controlled with steroids, zolbetuximab delivers a substantial improvement in

overall survival (OS), with a delta of more than five months. It is important to note that the use of steroids was not standard protocol in earlier trials, but is now routinely recommended in clinical practice. As a result, we can reasonably expect the real-world benefits of zolbetuximab to be even greater than what was initially observed.

This brings us to the issue of trial heterogeneity, which the Evidence Appraisal Group (EAG) raised as a central concern. Frankly, the committee's reliance on perceived variability across trials, particularly regarding chemotherapy regimens (oxaliplatin vs. cisplatin), is misguided. Current evidence clearly shows that the type of chemotherapy employed does not meaningfully affect overall survival. Additionally, PD-L1 expression, while often considered a key factor in immunotherapy decision-making, is neither prognostic nor relevant to the interaction between CLD18.2 and zolbetuximab. If heterogeneity were truly significant, we would expect to see considerable variation in outcomes across immune checkpoint inhibitor trials, yet the hazard ratios for objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) remain strikingly consistent across these studies. This consistency underscores the fact that the heterogeneity cited by the EAG does not translate into clinically meaningful differences.

In light of this, we would urge the committee to revisit its ruling. By discounting zolbetuximab as a key treatment option, we are effectively narrowing the therapeutic window for patients who, without this drug, face limited and largely ineffective alternatives. Chemotherapy alone is an unsatisfactory option for these patients, with survival rates that hover around one year at best. Zolbetuximab, on the other hand, offers not only hope but clear, evidence-based potential for improved outcomes. We fear that, without broader access to this drug, we are consigning patients with advanced gastric and gastroesophageal cancers to suboptimal care, with significant negative consequences for their survival and quality of life.

It is vital that, as clinicians, we do not lose sight of the human cost of these decisions. By incorporating the most up-to-date evidence and adopting a pragmatic approach to managing the manageable side effects of zolbetuximab, we have the opportunity to meaningfully extend survival for these patients. I would therefore strongly advocate for a re-evaluation of the ruling, with a view to ensuring that zolbetuximab remains a central part of our therapeutic arsenal for advanced gastroesophageal cancer.

Kind regards
[redacted]

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]

Draft guidance consultation – Additional evidence

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors

Huiqin Yang, Reviews Manager, KSR Ltd, United Kingdom (UK)
Sabine Grimm, Health Economist, Maastricht UMC+, NL
Andrea Fernández Coves, Health Economist, Maastricht UMC+, NL
Kevin McDermott, Systematic Reviewer, KSR Ltd, UK
Xiaoyu Tian, Systematic Reviewer & Health Economist, KSR Ltd
Lisa Stirk, Senior Information Specialist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK+

Correspondence to

Dr Huiqin Yang
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed

29 October 2024

1. Additional clinical evidence

1.1 Relative treatment effectiveness between zolbetuximab, pembrolizumab and nivolumab

In the EAG's report, the EAG stated that there was considerable heterogeneity in patients' PD-L1 CPS status between included trials in the indirect treatment comparison (ITC). 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.

The company in their response to the draft guidance presented the overall survival outcome of the pooled data of chemotherapy arm of Checkmate-649, KEYNOTE-859 and KEYNOTE-590 by PD-L1 CPS subgroups. However, only overall survival outcome of the pooled data of chemotherapy arm from these studies was presented. There were no relevant data of estimated hazard ratios between the relevant treatment and the chemotherapy arm based on the pooled data. Therefore, the EAG's opinion in terms of the uncertainty of ITC results remains. Furthermore, although the Kaplan-Meier curve showed that PD-L1 status may not be the treatment modifier for the pooled chemotherapy arm, PD-L1 status may have a potential impact on the zolbetuximab plus chemotherapy arm. Therefore, there was lack of supporting evidence on whether PD-L1 status would be a treatment effect modifier for the estimates of hazard ratios of overall survival and progression free survival of zolbetuximab plus chemotherapy versus chemotherapy. Therefore, the EAG's opinion that PD-L1 CPS might not be a treatment effect modifier for zolbetuximab plus chemotherapy versus chemotherapy also remains because there was a lack of further data to support this assumption. Also, the company have also not provided any further evidence to support an assumption of equal effectiveness, which would imply that the ITC, despite any questions regarding validity, continues to be a valid approach.

It should also be noted that based on the assessment of validity of the proportional hazard (PH) assumption, the results showed some evidence that the PH assumption did not hold for all studies, thereby supporting the use of time-varying approach for the ITC analysis. The company in their response to the draft guidance presented ITC results by using non-time varying ITC approach to estimate hazard ratios of overall survival and progression free survival for zolbetuximab plus chemotherapy versus pembrolizumab plus chemotherapy and nivolumab plus chemotherapy across PD L1 CPS subgroups. The EAG considers that, given that the company used the non-time varying ITC approach which appears not to be an appropriate approach, there were uncertainties on these results of the ITC analysis.

2. Additional Economic Evidence and Updated Cost-Effectiveness Results

2.1 Summary and critique of company's changes compared with the ACM 1 company base-case

2.1.1 The company's updated base-case

The EAG notes that the company used the EAG base-case settings with the exception of the log-logistic distribution instead of the gamma for OS (not requested by EAG or committee but acceptable to the EAG, see below), the inclusion of the informative prior based on Checkmate-649 (requested by committee), treatment effect waning applied gradually from 5-7 years onwards rather than at 5 years (not requested by EAG or committee, see critique below) and the use of the spline-based network meta-analysis, applied to the chemotherapy reference (not requested by EAG or committee, see critique below). The company also updated their PAS from [redacted]% to [redacted]% and continue to use a 1.2 severity modifier in its base-case.

2.1.2 Equal relative treatment effectiveness between zolbetuximab, pembrolizumab and nivolumab

Please see Section 1.1.

2.1.3 Inclusion of Checkmate-649

The EAG agrees with the company in principle that all appropriate evidence should be used. However, as before, it notes the uncertainties associated with naïve pooling of potentially heterogeneous studies and the relatively large impact of including Checkmate-649 on the ICER. In response to the company's comment on the EAG's use of BSA from Checkmate-640, the EAG notes that the generalisability of one patient characteristic in Checkmate-649 to the UK population (BSA) does not mean that naïve pooling of heterogeneous studies is appropriate. The company state that there is no considerable heterogeneity between trials, however, Figure 2 clearly shows large differences between Checkmate-649 and especially SPOTLIGHT in terms of OS, with barely overlapping confidence intervals. Reasons for this are not provided.

To address the committee's request, the company provided a new analysis using Checkmate-649 as an informative prior. This analysis assumes some generalisability of the shape parameter estimated from Checkmate-649 to SPOTLIGHT and GLOW trials. For this analysis, the company fitted parametric distributions to the pooled SPOTLIGHT and GLOW data and separately for the digitised Kaplan Meier curves for Checkmate-649. The company then selected a parametric model that had a good fit to both datasets. For this model, the shape parameter estimate for the Checkmate-649 data was used as the informative prior. Using only the shape parameter as informative prior was justified by it controlling the hazard distribution. The standard deviation was chosen to be 4% of the mean, in line with the standard deviation of the shape parameter from CheckMate-649. The company acknowledge that this choice is somewhat arbitrary. The EAG considers that it would have been interesting to observe alternative specifications of the standard deviation, especially considering that this directly

informs the weight that is given to the external data (the CheckMate-649 trial) and given that the resulting OS estimates are slightly above those associated with the company's original approach (naïve pooling), for example [redacted] vs [redacted] at 5 years.

The company chose the log-logistic distribution as it had the best statistical fit in Checkmate-649 and the second-best fit for SPOTLIGHT/GLOW. The EAG notes that the log-logistic model is the one that results in the highest possible OS estimates among all the curves in both datasets, and that it seems to over-estimate OS in the chemotherapy arm in SPOTLIGHT/GLOW (Company DG response Figures 3 and 4). The company did not provide the full detail on how the prior information was incorporated and also did not provide the updated shape parameter. Because the detailed steps were not shown, the EAG wondered whether the company followed the Soikkeli method[1] in which non-informative a priori distributions are first used for the shape and scale parameters, whereby the shape parameter is then updated with the external trial data (which would be the Checkmate-649 trial data in this case).

The EAG notes that the use of this prior in the model results in slightly increased life year gains for both zolbetuximab plus chemotherapy and chemotherapy arms (see EAG analyses below). The company's model estimates 5-, 10- and 20-year OS of [redacted] in the chemotherapy arm respectively, which is a slight increase compared with the company's original estimate at 5 years ([redacted]) and also higher than the observed 5-year OS in all cohorts except the BECOME, cohort and predicted 5-year OS in TA857 (Company's comments on DG, Table 2).

Given that GLOW and SPOTLIGHT data are [redacted] mature, and given that the EAG's scenario using trial data only and the log-logistic distribution results in better alignment of predicted versus observed OS (further substantiated in the next section), the EAG questions whether the addition of Checkmate-649 would substantially change or improve the estimation of survival outcomes, and whether any observed changes in survival predictions are not rather driven by heterogeneity between trials. The EAG therefore presents results without the use of the Checkmate-649 informed prior in its base-case.

The EAG notes the comment by the company that this leads to inconsistent estimates for LYG and QALY gains associated with zolbetuximab + chemotherapy between EAG primary and secondary analyses. The EAG believes that the best available evidence should be used for each decision. Given the multiple sources of uncertainty, especially indirectness given the differences in populations, using different estimates in different subpopulations for either the zolbetuximab + chemotherapy or comparator arms is difficult to avoid.

2.1.4 Use of spline models

The company insist that spline models are appropriate in this context, but no new arguments have been put forward. The risk of overfitting with spline models has been documented in the literature,[2, 3] and the EAG refers back to its original comment: *"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). 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."*[4]

The company provided further information on 5-year survival on chemotherapy from different real-world settings. The EAG acknowledges that its own base-case estimates are below those reported in these cohorts, and notes that the company's estimates are above those reported with the notable exception of the BECOME cohort which appears to be an outlier. The EAG also notes that the company's representation of the EAG's approach was inaccurate as it was not the EAG's approach using parametric models in general that resulted in an estimate of [redacted] alive at 5 years, but specifically using the gamma distribution for OS. The EAG refers to their scenario using the log-logistic instead of the gamma for extrapolating OS, which has [redacted] of patients alive at 5 years in the chemotherapy arm as an appropriate alternative as highlighted in the EAG report. This scenario results in proportions of [redacted] and [redacted] alive at 10 and 20 years respectively, which is in line with the company's estimates of [redacted] and [redacted] alive at 10 and 20 years respectively. The EAG also notes that the company used this distribution in their amended cost effectiveness analysis. The EAG therefore wishes to highlight that the company's conclusion *"Standard parametric models fit only to SPOTLIGHT/GLOW data do not adequately capture the expected subset of long-term survivors"* (Company's response to draft guidance) is inaccurate.

Based on the company's overview of chemotherapy outcomes and a review of modelling approaches, the EAG considers that spline models are not necessary to obtain plausible survival estimates for chemotherapy.

2.1.5 Estimation of relative treatment effect

The company continues to use the time-varying NMA for the estimation of the relative treatment effect instead of fitting curves independently. The company justified this stating: *"This is because, when using an informative prior for chemotherapy, use of survival models fitted to the pooled SPOTLIGHT/GLOW for zolbetuximab + chemotherapy will not provide a 'like-for-like' comparison. Instead, relative treatment effects should be used."* (Company response to Draft guidance) This was one reason for which the EAG preferred to use only the trial data for the primary analysis, as this will minimise any potential biases along these lines, albeit at the potential cost of not using slightly longer term data. The EAG thus considers that the base-case for the primary analysis could either be based on trial data only, as in the EAG's original base-case but using the log-logistic for OS to ensure external validity of the survival extrapolations for chemotherapy, or on the informative prior approach coupled with the relative effectiveness estimate from the NMA. The relative effects and thus the ICERs differ substantially between using trial data only and NMA relative effects; the incremental life years gained increase by almost [redacted] using the company's informative prior and time-varying NMA approach, compared to using trial data only (Table 1). The difference in ICERs is even more substantial when using the time-varying NMA. The advantages of the non-informative prior coupled with the time-varying NMA are the use of longer term data; the disadvantages include uncertainty caused by between trial heterogeneity as well as the use of splines in the time-varying NMA that may introduce bias by over-emphasizing the tail of the distribution that is subject to uncertainty. The latter bias can be mitigated by using treatment effect waning assumptions. On balance, the EAG prefers using trial data only for the primary analysis, but also presents the company's non-informative prior approach coupled with the time-varying NMA and with the fixed hazard ratio.

Table 1: Life year gains and ICERs with different model settings

	HR OS (where available)	LYG zolbetuximab	LYG chemotherapy	LYG incremental	ICER (without severity modifier, with new PAS)
No informative prior and parametric distributions fit independently (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informative prior and NMA fixed HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informative prior and time-varying NMA	1 year: [redacted] 2 years: [redacted] 3 years: [redacted] 4 years: [redacted] 5 years: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's treatment effect waning is included in producing LYG and ICER estimates; without them the scenario with the time-varying NMA would produce especially even larger incremental LYG HR = hazard ratio, LYG = life-years gained, NMA = network meta-analysis, OS = overall survival, PAS = patient access scheme					

2.1.6 Treatment effect waning

There is uncertainty about the prolonged treatment effect of zolbetuximab + chemotherapy and the company included two scenarios about this: one including treatment effect waning starting at 5 years and gradually reducing to match the comparator hazards by year 7, and one essentially excluding treatment effect waning. The EAG notes the committee's preferred assumptions that included modelling treatment effect waning at 5 years. In addition, treatment effect waning is a particularly important consideration when using the time-varying NMA that may produce optimistic hazard ratios towards the end of the trial period when patient number are low, as discussed above. Ultimately, there is no data supporting treatment effect waning or a prolonged treatment effect and any assumptions around this are uncertain. The EAG continues to use their 5-year treatment waning approach in line with committee preferences.

2.1.7 Comparisons with nivolumab and pembrolizumab

Since the last ACM1, pembrolizumab has been recommended as an option for untreated locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more.[5]

As stated by EAG in the Section 1.1, the company in their response to the draft guidance presented the results of ITC by using non-time varying approach to estimate hazard ratios of overall survival and progression free survival for zolbetuximab plus chemotherapy versus pembrolizumab plus chemotherapy and nivolumab plus chemotherapy across PD L1 CPS subgroups. The EAG considers that as the company used the non-time varying ITC approach which appears not to be an appropriate approach, there were uncertainties on these results of the ITC analysis. The EAG thus changes this in the model and uses the time-varying NMA results.

The company in their response to the draft guidance presented three different analyses: the analysis formerly known as the primary analysis, in which zolbetuximab + chemotherapy is compared with chemotherapy alone; an analysis compared with pembrolizumab for patients with PD-L1 CPS 1-9; and an analysis compared with nivolumab in the PD-L1 CPS 5-9 subgroup.

The company did not provide the comparison with pembrolizumab in patients with PD L1 CPS of at least 10 requested by the committee highlighting recently published NICE guidance TA997[5] on pembrolizumab in patients with PD L1 CPS of at least 1, stating: *"As patients with PD L1 CPS of at least 10 are necessarily included in the group of patients with PD L1 CPS of at least 1, our understanding is that this request is fulfilled by our previously presented analysis on the clinical effectiveness and cost-effectiveness comparison zolbetuximab + chemotherapy vs pembrolizumab + chemotherapy in patients with PD L1 CPS of at least 1."*[6]

The EAG notes that pembrolizumab may have different effects in the population with CPS of at least 10. However, it also noted the committee's statement in the draft guidance that *"People eligible for either or both of these according to their PD-L1 CPS would most likely have a PD-1 inhibitor as their first-line treatment."*[7]

The EAG notes that after pembrolizumab has been approved, there are four populations as detailed in Table 2. Two of these would warrant fully incremental analyses versus pembrolizumab + chemotherapy and / or nivolumab + chemotherapy and chemotherapy alone. The company should confirm whether chemotherapy is the only appropriate comparator when PD-L1 CPS status <1 and / or the patient is not eligible for treatment with pembrolizumab + chemotherapy or nivolumab + chemotherapy. It appears that patients with PD-L1 CPS status ≥ 10 are not eligible for zolbetuximab + chemotherapy unless when they are ineligible for treatment with pembrolizumab + chemotherapy or nivolumab + chemotherapy.

Table 2: 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 or not eligible for pembrolizumab or nivolumab	X	-	-	X	Primary analysis, criteria for which to be confirmed.
CPS ≥ 1 and < 5 gastric and GEJ	X	-	X	X	Fully incremental results should be provided.
CPS ≥ 5 and <10 gastric and GEJ	X	X	X	X	Fully incremental results should be provided.
CPS ≥ 10 gastric and GEJ	X	X	X	?	Eligibility for zolbetuximab unlikely / to be confirmed.

CPS: combined positive score, EAG: Evidence Assessment Group; GEJ: gastro-oesophageal junction; PD-L1: programmed death ligand 1

2.2 EAG analyses

2.2.1 EAG analyses

As per the critique points above, the EAG considered the following analyses plausible alternatives to the company's post ACM1 base-case in the primary analysis (Table X):

1. **EAG base-case**: Use only SPOTLIGHT + GLOW for OS and PFS, with log-logistic distributions for both, and separate parametric models, with treatment effect waning at 5 years in line with committee preferences
   - The EAG did not apply the prior approach
   - The EAG used the treatment effectiveness of zolbetuximab+chemotherapy directly from the SPOTLIGHT and GLOW trials. OS and PFS were modelled using log-logistic parametric functions for both parameters.
   - The EAG assumed that treatment effect waning would start at 5 years, instead of assuming no treatment effect waning or assuming that it would gradually reduce to match the comparator hazards by year 7.
2. **Alternative analysis #1.** Use Checkmate-649 informative prior approach, with log-logistic distributions for both, and time-varying NMA, with treatment effect waning at 5 years in line with committee preferences
   - The EAG used the treatment effectiveness of zolbetuximab+chemotherapy directly from the SPOTLIGHT and GLOW trials. OS and PFS were modelled using log-logistic parametric functions for both parameters.
   - The EAG assumed that treatment effect waning would start at 5 years, instead of assuming no treatment effect waning or assuming that it would gradually reduce to match the comparator hazards by year 7.
3. **Alternative analysis #2.** Use Checkmate-649 informative prior approach, with log-logistic distributions for both, and fixed hazard ratio, with treatment effect waning at 5 years in line with committee preferences
   - The EAG used the treatment effectiveness of zolbetuximab+chemotherapy based on the fixed hazard ratio.
   - The EAG assumed that treatment effect waning would start at 5 years, instead of assuming no treatment effect waning or assuming that it would gradually reduce to match the comparator hazards by year 7.

2.2.2 EAG secondary analysis

1. Comparison with nivolumab + chemotherapy in CPS ≥ 5 and <10 gastric and GEJ subgroup (pembrolizumab + chemotherapy and chemotherapy should be included here but not enabled by the company)
   - Based on the EAG base case (Section 2.2.1.)
   - The EAG used the time-varying NMA to inform the effectiveness of pembrolizumab and nivolumab

- The EAG assumed that treatment effect waning would start at 5 years, instead of assuming no treatment effect waning or assuming that it would gradually reduce to match the comparator hazards by year 7 for nivolumab (in line with TA857)

2. Comparison with pembrolizumab + chemotherapy in CPS ≥ 1 and < 5 gastric and GEJ subgroup (chemotherapy should be included here but not enabled by the company)
    - Based on the EAG base case (Section 2.2.1.)
    - The EAG used the time-varying NMA to inform the effectiveness of pembrolizumab and nivolumab
    - The EAG assumed that treatment effect waning would start at 5 years (in line with TA997)[5]

2.2.3 Subgroup analysis

No subgroup analysis was provided by the company.

2.2.4 Concerns regarding the model.

The EAG would like to highlight the different issues encountered while assessing the updated model provided by the company. 1) Replicability. Given that the EAG could not initially replicate the original base-case in the updated model, the company provided documentation describing the adjustments made on the model. However, this document did not specify the change in unit cost for zolbetuximab (from £[redacted] to £[redacted]) or the addition of treatment effect waning for pembrolizumab + chemotherapy and nivolumab + chemotherapy. 2) Technical verification. Technical verification was hampered by the use of large arrays which meant that it was more difficult to trace dependents or precedents. 3) Runtime. Originally, the PSA runtime was over 2 hours for 1,000 simulations. In the updated model, however, it increased to over 8 hours, which significantly limited a thorough assessment of uncertainty as running the PSA for multiple scenarios is not feasible. The EAG would like to highlight that multiple computers with the 64bit version of Microsoft Excel were used in an attempt to accelerate the analyses, however, all systems experienced similar processing times. Therefore, the EAG only conducted a PSA on the EAG base-case scenario. Likewise, the addition of the prior approach seemed to further slow down the model and further hinder the EAG analyses.

2.2.5 Cost-effectiveness results without severity modifier

Table 3: EAG amendments to post ACM1 company base-case (without severity modifier)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							

Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 1. Removing prior approach							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 2. Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 3. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG probabilistic base case.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated.
*Please note that eMIT prices were used.

Table 4: EAG alternative scenario #1 (without severity modifier)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							

Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 1. Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 2. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative scenario #1.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.							

Table 5: EAG alternative scenario #2 (without severity modifier)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #1. Treatment effectiveness of zolbetuximab+chemotherapy based on the fixed hazard ratio							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #1. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #2							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.

Table 6: EAG secondary analyses (without severity modifier) pairwise comparisons.

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (Zolbetuximab vs X) (£/QALY)
CS base-case*							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis #1. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis #2. Using time-varying NMA.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG secondary analysis.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.
Note. These are not fully incremental analyses, as this was not implemented in the company's CEM. Comparison with nivolumab + chemotherapy in CPS ≥ 5 and <10 gastric and GEJ subgroup. Comparison with pembrolizumab + chemotherapy in CPS ≥ 1 and < 5 gastric and GEJ subgroup.

2.2.1 Cost-effectiveness results with severity modifier

Table 7: EAG amendments to post ACM1 company base-case (with severity modifier)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							

Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 1. Removing prior approach							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 2. Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 3. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG probabilistic base case .							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.

Table 8: EAG alternative scenario #1 (with severity modifier).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 1. Treatment effectiveness of zolbetuximab + chemotherapy based on SPOTLIGHT and GLOW trials							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis 2. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative scenario #1.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.

Table 9: EAG alternative scenario #2 (with severity modifier).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case*							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #1. Treatment effectiveness of zolbetuximab+chemotherapy based on the fixed hazard ratio							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #2. Onset of treatment effect waning at 5 years with immediate effect							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG alternative analysis #2							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.							

Table 10: EAG secondary analyses (with severity modifier) pairwise comparisons.

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (Zolbetuximab vs X) (£/QALY)
CS base-case*							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case.							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis #1. Onset of treatment effect waning at 5 years with immediate effect for pembrolizumab and nivolumab							
Zolbetuximab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nivolumab + chemotherapy	[redacted]						
Pembrolizumab + chemotherapy	[redacted]						
EAG analysis #2. Using time-varying NMA.							
Zolbetuximab + chemotherapy	[redacted]						
Chemotherapy	[redacted]						
Nivolumab + chemotherapy	[redacted]						
Pembrolizumab + chemotherapy	[redacted]						
EAG secondary analysis.							
Zolbetuximab + chemotherapy	[redacted]						
Chemotherapy	[redacted]						
Nivolumab + chemotherapy	[redacted]						
Pembrolizumab + chemotherapy	[redacted]						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Results deterministic unless indicated. *Please note that eMIT prices were used.
Note. These are not fully incremental analyses, as this was not implemented in the company's CEM. Comparison with nivolumab + chemotherapy in CPS ≥ 5 and <10 gastric and GEJ subgroup. Comparison with pembrolizumab + chemotherapy in CPS ≥ 1 and < 5 gastric and GEJ subgroup.

3. References

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