NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using zolbetuximab with chemotherapy in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 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?

Issue date: September 2024

Note that this document is not NICE's final guidance on zolbetuximab with chemotherapy. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using zolbetuximab with chemotherapy in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 27 September 2024
- Second evaluation committee meeting: 8 October 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Zolbetuximab with fluoropyrimidine- and platinum-based chemotherapy is not recommended, within its anticipated marketing authorisation, for untreated locally advanced, unresectable or metastatic claudin 18.2-positive, HER2-negative, gastric or gastro-oesophageal junction adenocarcinoma in adults.

1.2 This recommendation is not intended to affect treatment with zolbetuximab with fluoropyrimidine- and platinum-based chemotherapy that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this

guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Standard care for gastric or gastro-oesophageal junction adenocarcinoma includes chemotherapy by itself, or with nivolumab or pembrolizumab. Zolbetuximab with fluoropyrimidine- and platinum-based chemotherapy (from now, zolbetuximab with chemotherapy) is a treatment option for people whose cancer expresses a protein called claudin 18.2.

Evidence suggests that people who have zolbetuximab and chemotherapy have longer before their cancer gets worse and live longer than people who have placebo and chemotherapy. 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.

There are uncertainties in the economic model used to estimate the cost effectiveness of zolbetuximab. These include:

- the long-term survival estimates
- how the efficacy of each treatment was estimated, and the data used to do this.

Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates for zolbetuximab plus chemotherapy compared with chemotherapy alone are above what NICE considers an acceptable use of NHS resources. Analysis of the economic model shows that zolbetuximab plus chemotherapy is not cost effective compared with nivolumab or pembrolizumab plus chemotherapy. So, it is not recommended.

2 Information about zolbetuximab

Marketing authorisation indication

2.1 Zolbetuximab (Vyloy, Astellas) in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for 'the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for zolbetuximab.

Price

2.3 The list price of zolbetuximab is £410 per 100-mg vial (excluding VAT; company submission).

2.4 The company has a commercial arrangement, which would have applied if zolbetuximab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Astellas, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Unmet need

3.1 Gastric and gastro-oesophageal junction cancers are the most common types of stomach cancer. In England, around 5,000 people were diagnosed with gastric cancer each year between 2016 and 2018. Most diagnoses in the UK are either in men, or people 75 years and older. In

the advanced stage, symptoms can include a lack of appetite with subsequent weight loss, fluid in the abdomen, abdominal pain, gastric obstruction, vomiting blood, or having blood in the stool. The approximate 5-year survival for people diagnosed between 2013 and 2017 was 21.6%, reducing to 13.9% in people 75 years and older. The patient experts explained that because of the low survival rates, it is important to have treatment options that are more effective and with manageable side effects. They added that an increasing number of younger people are also affected by these cancers. A patient expert noted the large impact on quality of life. For example, having difficulties with swallowing solids over many months, as well as having to use a feeding tube for most of the hours in the day. A clinical expert added that current treatment options improve median progression-free survival by 1 to 2 months in the first line, and a median of 2 to 3 months for overall survival. But, the clinical expert highlighted that there is an unmet need for people who can only have doublet chemotherapy as a first-line treatment option. The committee agreed that there is an unmet need in this population, which zolbetuximab with chemotherapy can address.

Clinical management

Treatment pathway

3.2 Current standard care for people with HER2-negative, locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma is:

- doublet chemotherapy (see NICE's guideline on oesophago-gastric cancer: assessment and management in adults)
- nivolumab with doublet chemotherapy for people whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more (see NICE's technology appraisal guidance on nivolumab, from here referred to as TA857)

- pembrolizumab with doublet chemotherapy for people with gastro-oesophageal junction cancer, whose tumours express PD-L1 with a CPS of 10 or more (see NICE's technology appraisal guidance on pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer)
- pembrolizumab with doublet chemotherapy for people with gastric or gastro-oesophageal junction adenocarcinoma, whose tumours are HER2-negative and express PD-L1 with a CPS of at least 1 (see NICE's technology appraisal guidance on pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma).

The clinical expert noted that clinical management aims to use treatments that target specific biomarkers that may be linked to different outcomes and prognoses. Biomarkers can help to inform judgements on the suitability of a treatment and how a person's condition is likely to respond. These biomarkers have tests, and include mismatch repair status and the expression of the proteins HER2 and PD-L1. The clinical experts explained that PD-L1 CPS status can predict a cancer's response to immunotherapies like nivolumab or pembrolizumab, and it is also linked to treatment outcomes for this condition. But, this is not an absolute association and the PD-L1 CPS test can be subjective. Zolbetuximab is a monoclonal antibody that targets the protein claudin 18.2 in cells. The company have a diagnostic test in development for claudin 18.2, with positivity defined as expression in at least 75% of tumour cells. The company positioned zolbetuximab with chemotherapy irrespective of PD-L1 CPS status, in line with its marketing authorisation.

Comparators

3.3 The comparators in the NICE scope were:

- chemotherapy, including doublet treatment with fluorouracil or capecitabine with cisplatin or oxaliplatin
- nivolumab with chemotherapy for PD-L1 CPS of at least 5
- pembrolizumab with chemotherapy for PD-L1 CPS of at least 10, and for gastro-oesophageal junction adenocarcinoma only
- pembrolizumab with chemotherapy for PD-L1 CPS of at least 1, for gastric or gastro-oesophageal junction adenocarcinoma (subject to NICE evaluation).

Initially, the company did not provide a comparison of zolbetuximab plus chemotherapy compared with pembrolizumab plus chemotherapy. The company highlighted that for a PD-L1 CPS of at least 1, there was no recommendation for pembrolizumab at the time of submission. For PD-L1 CPS of at least 10, there was a lack of similarity between people with gastric or gastro-oesophageal junction adenocarcinoma eligible for zolbetuximab and pembrolizumab. Also, a cancer with higher PD-L1 CPS may be more likely to be treated with a checkpoint inhibitor, such as nivolumab or pembrolizumab, rather than zolbetuximab. The company added that although the population for zolbetuximab is not restricted by PD-L1 CPS, clinical experts reported that at higher PD-L1 CPS, checkpoint inhibitors are predicted to have better outcomes. They are therefore more likely to be used as more understanding of how zolbetuximab works is developed by the clinical community. The clinical expert explained that currently, most people with PD-L1 CPS of at least 10 would have a checkpoint inhibitor. The clinical expert suggested that for people with a PD-L1 CPS of less than 5, zolbetuximab is likely to be considered. This is because, currently, this population is not eligible for an immunotherapy. But, when considering the treatment options, there are characteristics that can lead to immunotherapy treatment not being considered a suitable treatment option (contraindicated). For example, some autoimmune conditions, fitness levels, and the treatment's toxicities may rule out using immunotherapies. The main infusion-related toxicity for zolbetuximab is nausea and vomiting, which can be managed well,

compared with those of immunotherapies. So, people who can have chemotherapy are likely to be fit enough to have zolbetuximab too. Following the EAG request, the company included pembrolizumab plus chemotherapy in its indirect treatment comparison with zolbetuximab plus chemotherapy for cancers with a PD-L1 CPS of at least 1 (see section 3.5). The EAG noted that this subgroup can be further divided into additional subgroups such as PD-L1 CPS of at least 10. The committee concluded that both nivolumab and pembrolizumab in combination with chemotherapy are relevant comparators to consider. 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.

Clinical effectiveness

Clinical trials

3.4 The pivotal clinical-effectiveness evidence comparing zolbetuximab plus chemotherapy with placebo plus chemotherapy, came from the SPOTLIGHT and GLOW trials. These were both international, phase 3, multicentre, double-blind, randomised controlled trials. They included adults with claudin 18.2-positive, HER2-negative, untreated, locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. The primary outcome was progression-free survival, and the key secondary outcomes included overall survival. The trials differed in terms of the type of chemotherapy used. In SPOTLIGHT, the intervention was zolbetuximab plus modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX). This was compared with placebo plus mFOLFOX. In GLOW, the intervention was zolbetuximab plus capecitabine and oxaliplatin (CAPOX), compared with placebo plus CAPOX. The results suggest that zolbetuximab with chemotherapy is associated with a statistically significant improvement in progression-free survival and overall survival compared with placebo with chemotherapy. For SPOTLIGHT, this was a hazard ratio of 0.73 (95% confidence interval 0.59 to 0.91) for progression-free survival, and 0.78 (95% confidence

interval 0.64 to 0.95) for overall survival. The results for GLOW are considered confidential and cannot be reported here. The committee concluded that zolbetuximab with chemotherapy shows some benefit at improving survival outcomes compared with placebo and chemotherapy.

Indirect treatment comparison

3.5 Zolbetuximab plus chemotherapy has not been directly compared with immunotherapy, so the company did an indirect treatment comparison. It used a fixed-effects spline network meta-analysis to identify the relative treatment effect of:

- zolbetuximab plus chemotherapy and nivolumab plus chemotherapy for a PD-L1 CPS of at least 5, and
- pembrolizumab plus chemotherapy for a PD-L1 CPS of at least 1.

The network meta-analysis included:

- the intention-to-treat population from SPOTLIGHT and GLOW to inform the comparison with zolbetuximab plus chemotherapy
- the intention-to-treat population from KEYNOTE-062 and PD-L1 CPS of 1 or more subgroup from KEYNOTE-859 to inform the comparison with pembrolizumab plus chemotherapy
- the PD-L1 CPS of 5 or more subgroup from CheckMate 649 to inform the comparison with nivolumab plus chemotherapy.

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. The company explained that assuming equivalence for the chemotherapy regimens simplifies the analysis and avoids adding additional heterogeneity by having to add more studies into the network meta-analysis. The company also explained

that PD-L1 CPS status does not affect outcomes for zolbetuximab with chemotherapy and chemotherapy alone. The clinical expert noted that in the UK, it is expected that 30% to 40% of everyone with gastric or gastro-oesophageal junction adenocarcinoma would have a PD-L1 CPS of 5 or more. In SPOTLIGHT and GLOW, there was a lower proportion of people with a PD-L1 CPS of 5 or more. The clinical expert added that there is no clear association between PD-L1 CPS and effectiveness of zolbetuximab. 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 the trials to take into account. It concluded that the heterogeneity in the network meta-analysis adds to uncertainty.

Economic model

Company's modelling approach

3.6 The company presented a 3-state partitioned survival model, with mutually exclusive health states: pre-progression, post-progression, and death. The population in the model was adults with untreated claudin 18.2-positive (expression in at least 75% of cells), HER2-negative, locally advanced, unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Zolbetuximab plus chemotherapy was modelled to improve the quality-adjusted life years (QALYs) through increased overall survival and survival in the progression-free health state. It was also modelled to have greater acquisition costs compared with chemotherapy alone and include a cost for claudin 18.2 testing. The baseline characteristics, including the starting age, proportion of women, average weight, and body surface area, were from SPOTLIGHT and GLOW. Health-related quality of life was also from SPOTLIGHT and GLOW. The model used a 4-week cycle with half-cycle correction, over a lifetime time horizon of 40 years. In its base case, the company assumed CAPOX costing for chemotherapy, explaining that it is the most commonly used chemotherapy in the UK and has broadly equivalent effectiveness

with folinic acid, fluorouracil and oxaliplatin (FOLFOX). The National Speciality Adviser for the Cancer Drugs Fund noted that 70% of clinical practice is using CAPOX rather than FOLFOX. The company's analyses were:

- a primary analysis comparing zolbetuximab plus chemotherapy with chemotherapy alone, applied to the whole population
- a secondary analysis comparing zolbetuximab plus chemotherapy with chemotherapy alone, and with nivolumab plus chemotherapy for the population with PD-L1 CPS of at least 5.

The EAG had different definitions of the primary and secondary analyses, to better match the clinical data. These were:

- a primary analysis comparing zolbetuximab plus chemotherapy with chemotherapy alone, for the population with PD-L1 CPS less than 5 gastric and gastro-oesophageal junction adenocarcinoma
- a secondary analysis, comparing zolbetuximab plus chemotherapy with chemotherapy alone, and with nivolumab plus chemotherapy, the population with PD-L1 CPS of 5 or more but less than 10 for gastric and gastro-oesophageal junction adenocarcinoma.

The committee concluded that the company's model is appropriate for decision making, and the committee considered both sets of primary and secondary analyses.

Clinical trial data informing the model

3.7 Because the follow up from SPOTLIGHT and GLOW was limited, the company pooled chemotherapy outcomes from SPOTLIGHT, GLOW, and CheckMate 649 to estimate the outcomes in the chemotherapy arm. Including CheckMate 649 increased the sample size and follow up, because CheckMate 649 has a median follow up of 4 years. The company explained that because CheckMate 649 has a longer follow up, it would capture the tails of the Kaplan–Meier curves, which would have smaller

patient numbers with shorter follow up. The company added that in TA857, CheckMate 649 was considered generalisable to the NHS, so including it adds more power to the extrapolation. The company recreated individual patient-level data from CheckMate 649 by digitising the survival curves using an algorithm by Guyot et al. (2012). Then, patient-level data from CheckMate 649, SPOTLIGHT and GLOW was combined into a single dataset. The company did not adjust for patient characteristics and expected any numerical differences in survival outcomes to be caused by chance and variability in trial populations. The company also assumed an equivalent efficacy for chemotherapy regimens and assumed that it would not affect survival outcomes. The EAG highlighted the methodological uncertainty of naive pooling of chemotherapy outcomes by not adjusting for differences in patient characteristics and using recreated data from CheckMate 649. So, the EAG excluded CheckMate 649 in its base case. Including CheckMate 649 in the chemotherapy arm results in greater predicted 5- and 10-year overall survival estimates. The company added that this outcome is supported by real-world evidence. It highlighted that in TA857, a small proportion of people remained alive at 5 years and beyond, which suggests that long-term survival is plausible. The committee agreed that there are benefits to including evidence from CheckMate 649 as part of the chemotherapy arm. But, it highlighted that using naive pooling adds to uncertainty. It suggested that the company should explore the feasibility and appropriateness of using other methods to include more mature evidence from CheckMate 649 in the survival outcomes for chemotherapy. For example, using data from CheckMate 649 to derive an informative prior for the shape parameters of extrapolation models based on SPOTLIGHT and GLOW. The committee noted that, although CheckMate 649 has a longer follow up, it also has low patient numbers at the tails of the Kaplan–Meier curves, which adds uncertainty. It concluded that in absence of appropriate pooling of the evidence, it favours using the direct evidence from the trial.

Survival extrapolations for the primary analyses

3.8 The company considered both parametric and more flexible spline models in its base case because it expected a small proportion of long-term survival. In its primary analysis, the company used a 3-knot hazard spline-based model to estimate overall survival and progression-free survival for the pooled chemotherapy arm. The company applied time-varying relative treatment effects to the chemotherapy outcomes based on its 2-knot spline network meta-analysis to estimate overall survival and progression-free survival for zolbetuximab with chemotherapy. Therefore, survival curves were only fitted to the pooled chemotherapy arm. The company did scenarios using evidence from SPOTLIGHT and GLOW to extrapolate overall survival and progression-free survival. For overall survival, these were log-logistic for the zolbetuximab plus chemotherapy arm, and gamma for the chemotherapy arm. For progression-free survival, these were log-logistic for both the zolbetuximab plus chemotherapy arm and the chemotherapy arm. The EAG preferred to use parametric survival modelling. The EAG excluded CheckMate 649 in its base case, so for its primary analysis it used:

- a log-logistic extrapolation for zolbetuximab plus chemotherapy to estimate overall and progression-free survival
- a gamma extrapolation for overall survival, and a log-logistic extrapolation for progression-free survival for the chemotherapy arm
- a scenario using the log-logistic extrapolation for overall survival in the chemotherapy arm because it may better reflect the proportion of long-term survival, but with a reduced fit compared with the gamma extrapolation.

The EAG noted that the company's approach using the time-varying relative treatment effects means that anything that affects the chemotherapy arm, will affect the zolbetuximab arm. But this is not the case when using independent parametric curves, as used in the EAG's

primary analysis, before treatment-effect waning is taken into account. The EAG added that with spline modelling, there is a concern that the tail of the extrapolation may be overemphasised. 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. This is because of uncertainties in the assumptions with using the network meta-analysis to inform the survival modelling, and because of its preference to exclude CheckMate 649 in the pooled chemotherapy arm (see section 3.7). Instead, the committee preferred to explore the feasibility of using evidence from CheckMate 649 as an informative prior for the overall survival extrapolation.

Survival extrapolations for the secondary analyses

3.9 In its secondary analysis, the company also considered both parametric and more flexible spline-based modelling. It used the same assumptions as described for its primary analysis when chemotherapy was a comparator. That is, using a 3-knot hazard spline-based model to estimate overall survival and progression-free survival for the pooled chemotherapy arm of SPOTLIGHT, GLOW and CheckMate 649. For the comparison with nivolumab plus chemotherapy, the company applied the time-varying relative treatment effects to the chemotherapy outcomes based on its 2-knot spline network meta-analysis, as described for the primary analysis. But, the results from zolbetuximab plus chemotherapy were also used for nivolumab plus chemotherapy. Therefore, the company assumed that the survival outcomes were the same between the 2 treatment options, differing in adverse events only. In its secondary analysis, the EAG considered that the evidence from SPOTLIGHT and GLOW was appropriate to estimate the survival extrapolation in the chemotherapy arm using the best-fitting parametric survival curves. The EAG's base case in the secondary analysis also used a gamma

extrapolation for overall survival and log-logistic for progression-free survival for the chemotherapy arm. But for the zolbetuximab plus chemotherapy arm, it used the hazard ratio from the network meta-analysis applied to the baseline survival curve for chemotherapy for the zolbetuximab with chemotherapy extrapolation. The EAG highlighted that, in the economic model, the results from the network meta-analysis for nivolumab plus chemotherapy are not used. Instead, the results from the zolbetuximab plus chemotherapy arm were applied to the nivolumab plus chemotherapy arm, implying equal treatment effectiveness. The EAG disagreed with assuming equal effectiveness because the time-varying relative effects from the network meta-analysis were different for the zolbetuximab plus chemotherapy and nivolumab plus chemotherapy analyses, so it should be reflected in the model outcomes. The committee agreed that nivolumab and zolbetuximab should not be assumed to have equivalent efficacy and noted that a lack of statistical significance in network meta-analysis results does not show clinical equivalence. 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.

Treatment-effect waning

3.10 In its base case, the company did not apply treatment-effect waning to the zolbetuximab with chemotherapy arm. The company explained that there is no time-based stopping rule for zolbetuximab and there is no evidence that the observed treatment effect reduces over time. But, after the clarification stage, the company provided scenarios that applied treatment-effect waning to the zolbetuximab with chemotherapy arm after 5, 6, and 7 years. This was done by applying the chemotherapy hazard ratios to the zolbetuximab with chemotherapy arm. 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 showed no sign of treatment-effect waning at 3 years (although the number of people was small). The committee concluded that, because of a lack of long-term follow-up overall survival data, it would include a treatment-effect waning at 5 years in its preferred assumptions.

Severity

3.11 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company used pooled baseline characteristics from SPOTLIGHT and GLOW in its calculations. Its analysis resulted in a proportional QALY shortfall that meets the criteria for a 1.2 severity weight applied to the QALYs. The EAG did analyses for the primary and secondary analysis, with and without CheckMate 649. These analyses also resulted in a severity weight of 1.2 applied to the QALYs. The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.12 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an

effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of unresolved uncertainty, specifically the:

- heterogeneity of the trials informing the network meta-analysis for the indirect treatment comparison
- methodology by which data from CheckMate 649 is pooled with SPOTLIGHT and GLOW to inform the chemotherapy arm in the company's modelling approach
- assumption that nivolumab and zolbetuximab with chemotherapy have equivalent efficacy, and the associated survival modelling.

So, the committee concluded that an acceptable ICER would be towards the lower to middle of the range that NICE considers an acceptable use of NHS resources.

Committee preferred assumptions

3.13 The committee's preferred assumptions included:

- pembrolizumab as a relevant comparator for the population with a PD-L1 CPS of at least 10
- excluding CheckMate 649 from the pooled SPOTLIGHT and GLOW data informing the chemotherapy arm
- using parametric survival modelling to estimate overall and progression-free survival
- applying treatment-effect waning at 5 years
- using a severity modifier of 1.2 applied to the QALYs.

When considering the committee preferences and confidential discounts, the cost-effectiveness results for the population eligible for chemotherapy

only (PD-L1 CPS of less than 5), were above the range normally considered an acceptable use of NHS resources. The company considered the exact ICERs to be confidential so they cannot be reported here. 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. So, it did not accept the results of the company secondary analysis for this comparison. In the EAG's secondary analysis, there was 0% probability that zolbetuximab plus chemotherapy would be cost effective compared with nivolumab plus chemotherapy at the usually accepted ICER range, taking into account the severity modifier and confidential price of the comparator. The committee recalled that in people with PD-L1 CPS of at least 5, clinical experts are more likely to prefer using a checkpoint inhibitor in most scenarios. It concluded that zolbetuximab could not be considered cost effective as an addition to chemotherapy or as an alternative to a PD-1 inhibitor in combination with chemotherapy.

Equality

3.14 The committee did not identify any equality issues.

Uncaptured benefits

3.15 The committee considered whether there were any uncaptured benefits of zolbetuximab with chemotherapy. The committee noted that zolbetuximab with chemotherapy is novel and has an innovative mechanism of action by targeting claudin 18.2, which is an additional biomarker in this condition. So it recognised that this treatment would add a treatment option and address an unmet need particularly when chemotherapy alone is the only treatment option. It also noted from the clinical expert that zolbetuximab with chemotherapy is associated with side effects that are more manageable than those of the current treatment options. But, the committee did not identify additional benefits of zolbetuximab with

chemotherapy not captured in the economic modelling. So, the committee concluded that all additional benefits of zolbetuximab with chemotherapy have already been taken into account.

Conclusion

Recommendation

3.16 The committee's preferred cost-effectiveness estimates for zolbetuximab with chemotherapy were above the range that NICE considers an acceptable use of NHS resources. Compared with PD-1 inhibitors, the assumption of similarity was not justified and zolbetuximab plus chemotherapy was not shown to be cost effective relative to these comparators where they are relevant. So, the committee concluded that it could not recommend zolbetuximab with chemotherapy for treating claudin 18.2-positive, HER2-negative, unresectable, advanced, gastric or gastro-oesophageal junction adenocarcinoma in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A with the Chair standing in from Committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Summaya Mohammad

Technical lead

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Technical adviser

Jennifer Upton

Project manager

Janet Robertson

Associate director

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