NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Zolbetuximab with fluoropyrimidine- and platinum-based chemotherapy is not recommended, within its 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

Usual treatment for gastric or gastro-oesophageal junction adenocarcinoma includes chemotherapy alone, or with nivolumab or pembrolizumab. Zolbetuximab plus fluoropyrimidine- and platinum-based chemotherapy (from here, zolbetuximab plus chemotherapy) is a treatment option for cancer that makes a protein called claudin 18.2.

Clinical trial evidence shows that people who have zolbetuximab plus chemotherapy have longer before their cancer gets worse and live longer than people who have placebo plus chemotherapy. Zolbetuximab plus chemotherapy has not been directly compared with nivolumab plus chemotherapy or pembrolizumab plus chemotherapy. But results of an indirect comparison suggest that zolbetuximab may not work as well as either of these treatments.

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. The most likely cost-effectiveness estimates for zolbetuximab plus chemotherapy compared with nivolumab plus chemotherapy or pembrolizumab plus chemotherapy showed that zolbetuximab was less costly, but also less effective. So, zolbetuximab 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 over. In the advanced stage, symptoms can include loss of appetite and 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 over. The patient experts explained that because of the low survival rates, it is important to have treatment options that are more effective and have 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 (PFS) by 1 to 2 months in the first line, and a median of 2 to 3 months for overall survival (OS). 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 plus

fluoropyrimidine- and platinum-containing chemotherapy (from here referred to as zolbetuximab plus 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 tumours that 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 tumours that express PD-L1 with a CPS of 1 or more (see NICE's technology appraisal guidance on pembrolizumab, from here referred to as TA997).

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. Tests for these biomarkers 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 is also linked to outcomes for people having these treatments. 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. 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 plus chemotherapy for use 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 plus chemotherapy for PD-L1 CPS of at least 5
- pembrolizumab plus chemotherapy for PD-L1 CPS of at least 10, and for gastro-oesophageal junction adenocarcinoma only
- pembrolizumab plus 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 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. So they are more likely to be used while the clinical community develops more understanding of how zolbetuximab works. 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 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. Between the first and the second committee meeting, TA997 was published, which recommends pembrolizumab for people with PD-L1 CPS of at least 1. During the second committee meeting, the NHS Cancer Drugs Fund clinical lead explained that, following this recommendation, the uptake of pembrolizumab in the PD-L1 CPS 1 to 4 subgroup had rapidly increased. The committee concluded that both nivolumab and pembrolizumab in combination with chemotherapy are relevant comparators. People eligible for either or both of these according to their PD-L1 CPS would most likely have an immunotherapy 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 (n=565) and GLOW (n=507) 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 PFS, and the key secondary outcomes included OS. 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 plus chemotherapy is associated with a statistically significant improvement in PFS and OS compared with placebo plus chemotherapy. For SPOTLIGHT, this was a hazard ratio of 0.73 (95% confidence interval 0.59 to 0.91) for PFS, and 0.78 (95% confidence interval 0.64 to 0.95) for OS. For GLOW, this was a hazard ratio of 0.69 (95% confidence interval 0.54 to 0.87) for PFS, and 0.77 (95% confidence interval 0.62 to 0.97) for OS. The committee noted that SPOTLIGHT and GLOW were large-scale trials that provided head-to-head efficacy data. The committee concluded that, based on these trials, zolbetuximab plus chemotherapy shows a benefit at improving survival outcomes compared with placebo and chemotherapy.

Indirect treatment comparison

3.5 Zolbetuximab plus chemotherapy has not been directly compared with immunotherapies plus chemotherapy. 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 PD-L1 CPS of 5 or more subgroup from CheckMate 649 to inform the comparison with nivolumab 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 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 additional heterogeneity by including more studies into the network meta-analysis. The company also explained that PD-L1 CPS status does not affect outcomes for zolbetuximab plus 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 agreed that even when assuming that PD-L1 CPS status is not a treatment-effect modifier, there are additional differences between the trials to consider, such as trial design and background chemotherapy regimens used.

In response to the draft guidance consultation, the company stated that any differences between trials included in the network meta-analysis were not expected to favour zolbetuximab. The company explained that there is no known mechanism by which PD-L1 expression can affect zolbetuximab's action. It provided evidence showing similar OS between PD-L1 CPS subgroups for chemotherapy. It also provided evidence from SPOTLIGHT and GLOW by PD-L1 CPS subgroup that showed consistent

OS compared with the intention-to-treat population. Similar evidence was not provided for PFS. The company also highlighted that clinical experts in TA857 and TA997 supported assuming equivalence between different background chemotherapy regimens. At the second committee meeting, the committee still considered that there were underlying methodological issues present within the trials forming the network for the network meta-analysis. But, it concluded that it was the best available evidence for comparisons with the immunotherapies.

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 increase quality-adjusted life years (QALYs) through increasing OS and PFS. 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. It explained that CAPOX is the most commonly used chemotherapy in the UK and has broadly equivalent effectiveness with folinic acid, fluorouracil and oxaliplatin (FOLFOX). At the first committee meeting, the National Speciality Adviser for the Cancer Drugs Fund noted that 70% of clinical practice uses CAPOX rather than FOLFOX. The committee concluded that the company's model is appropriate for decision making.

Treatments available according to PD-L1 CPS subpopulations

3.7 At the first committee meeting, the company's economic analyses included:

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

In response to the draft guidance consultation, the company presented results for the following:

- zolbetuximab plus chemotherapy compared with chemotherapy alone in the whole population
- zolbetuximab plus chemotherapy compared with nivolumab plus chemotherapy for the subgroup with PD-L1 CPS of 5 to 9
- zolbetuximab plus chemotherapy compared with pembrolizumab plus chemotherapy for the subgroup with PD-L1 CPS of 1 to 9.

The EAG noted that the company had only presented pairwise comparisons and not enabled a fully incremental analysis in the subgroups where there was more than 1 relevant comparator. The

committee concluded that, in general, incremental analysis is the preferred method. But pairwise analysis was justified in this case because the immunotherapies had similar efficacy in terms of QALYs generated in the model.

Data informing the chemotherapy arm

3.8 In its original submission, the company pooled chemotherapy outcomes from SPOTLIGHT, GLOW, and CheckMate 649 to estimate the outcomes in the chemotherapy arm. The company explained that including CheckMate 649 increased the sample size and follow up, because CheckMate 649 has a median follow up of 4 years. It added 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 equivalent efficacy for chemotherapy regimens, that is, the choice of chemotherapy regimen would not affect survival outcomes. The company added that its OS extrapolation for chemotherapy is supported by real-world evidence. It highlighted that in TA857, a small proportion of people were alive at 5 years and beyond, which suggests that long-term survival is plausible for people having chemotherapy. 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. At the first committee meeting, the committee considered that there were benefits to including evidence from CheckMate 649 as part of the

chemotherapy arm. But, it highlighted that naive pooling added 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.

In response to the draft guidance consultation, the company provided evidence comparing its OS extrapolations with survival in external cohorts. The company stated that its OS extrapolation was more aligned with external cohort estimates of OS at 5 years, than the EAGs. As suggested by committee, the company also used data from CheckMate 649 to derive an informative prior. The log-logistic model was selected by the company to model CheckMate 649 OS for chemotherapy. The shape parameter of this model was used as the informative prior for the company's chemotherapy OS extrapolation. This approach initially predicted higher OS than the company's original approach, but predicted similar OS from year 5 to 6 onwards. In its critique of the company's response, the EAG updated its base case parametric model from the gamma to the log-logistic model. This provided better alignment with observed OS in external cohorts. The EAG added that the company's selected informative prior overestimates OS compared with pooled SPOTLIGHT and GLOW data and most external cohorts. The EAG noted that the SPOTLIGHT and GLOW trials were already mature and questioned whether adding CheckMate 649 was necessary. At the second committee meeting, the committee acknowledged that the company had explored its suggested informative prior approach. It considered the outputs of the company's informative prior analysis and noted the unexplained difference between OS in CheckMate 649 and SPOTLIGHT in particular. The committee agreed that the main benefit of using an

informative prior in this instance would be if trial data was immature. SPOTLIGHT and GLOW data are reasonably mature. So, using an additional arm as the informative prior without accounting for heterogeneity in relevant treatment-effect modifiers between this arm and SPOTLIGHT or GLOW, likely increases uncertainty compared with using head-to-head data. It concluded that it preferred the EAG's approach of fitting a log-logistic parametric model to the chemotherapy arm of the pooled SPOTLIGHT and GLOW trials only.

Relative efficacy and survival extrapolations

Compared with chemotherapy (primary analysis)

3.9 Initially, the company considered both parametric and more flexible spline models. It used spline models in its base case because it expected a small proportion of long-term survivors. In its primary analysis, the company used a 3-knot hazard spline-based model to estimate OS and PFS for the pooled chemotherapy arm, which included SPOTLIGHT, GLOW and CheckMate 649 trials (see section 3.8). The company applied time-varying relative treatment effects (hazard ratios) to the chemotherapy outcomes to estimate OS and PFS for zolbetuximab plus chemotherapy. It presented scenarios using evidence from SPOTLIGHT and GLOW only to extrapolate OS and PFS. In the scenario for OS, selected extrapolations were the log-logistic for the zolbetuximab plus chemotherapy arm, and gamma for the chemotherapy arm. In the scenario for PFS, these were the 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 at the first committee meeting it used:

- a log-logistic extrapolation for zolbetuximab plus chemotherapy to estimate OS and PFS
- a gamma extrapolation for OS, and a log-logistic extrapolation for PFS for the chemotherapy arm

- a scenario using the log-logistic extrapolation for OS in the chemotherapy arm, because it better reflected 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 meant that anything that affected the chemotherapy arm will also affect the zolbetuximab arm. But this is not the case when using independent parametric curves, as used in the EAG's approach, 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 amount of heterogeneity between the studies.

In response to the draft guidance consultation, the company stated that any heterogeneity in the network meta-analysis would not affect the comparison of zolbetuximab plus chemotherapy with chemotherapy. In its critique, the EAG acknowledged that the company's approach allowed longer-term data to be used but increased uncertainty. So it preferred to use trial data only. The committee agreed that the network meta-analysis was not necessary for the comparison with chemotherapy. This was because there was robust, randomised, mature data from 2 large-scale trials already available to inform this comparison (see section 3.4). Aligned with section 3.8, the committee concluded that it preferred the EAG's approach to modelling the relative efficacy of zolbetuximab plus chemotherapy and chemotherapy. This used independent log-logistic models fit to direct data from the pooled SPOTLIGHT and GLOW trials only.

Compared with immunotherapies (secondary analysis)

3.10 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 (see section 3.9). At the time of the first committee meeting, results for the secondary analysis only included the comparison with nivolumab plus chemotherapy. This was because the technology appraisal for pembrolizumab (TA997) was published between the first and second committee meetings. For the comparison with nivolumab plus chemotherapy, the company explored applying the time-varying relative treatment effects from its network meta-analysis to the chemotherapy outcomes. But, in its base case, the company assumed equal effectiveness between zolbetuximab and nivolumab. That is, that the survival outcomes were the same between both treatments and outcomes differed based on differences in adverse events only (see section 3.5). 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. As described in section 3.9 for the chemotherapy arm, the EAG's base case in the secondary analysis initially used a gamma extrapolation for OS and log-logistic for PFS. But for the OS and PFS extrapolation for the zolbetuximab plus chemotherapy arm, it used the hazard ratio from the network meta-analysis applied to the baseline survival curve for chemotherapy. The EAG disagreed with assuming equal effectiveness between zolbetuximab with chemotherapy and nivolumab with chemotherapy because the time-varying relative effects from the network meta-analysis did not favour zolbetuximab (the exact time-varying relative effects are considered confidential by the company so cannot be reported here). It added that the differences should be reflected in the model outcomes, as per the EAG's base case, which used the time-varying relative effects. At the first meeting, the committee agreed that nivolumab and zolbetuximab should not be assumed to have equivalent efficacy and noted that a lack of statistical significance in the results of the network meta-analysis does not show clinical equivalence. So, 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.

In response to the draft guidance consultation, the company explained that, if anything, the network-meta-analysis would bias against zolbetuximab (see section 3.5). This is because the relative efficacy of zolbetuximab improves when data from most relevant PD-L1 CPS subgroups is used. The company presented an analysis comparing hazard ratios for OS in the whole population with the population with a lower CPS. The company presented results for zolbetuximab plus chemotherapy compared with nivolumab in the PD-L1 CPS 5 to 9 subgroup and pembrolizumab in the PD-L1 CPS 1 to 9 subgroup. Results showed a benefit for zolbetuximab in subgroups with a lower CPS. So, the company stated that assuming clinical equivalence between zolbetuximab, nivolumab and pembrolizumab is an appropriate simplifying assumption. At the second committee meeting, the company explained that constant (rather than time-varying) relative effects were used for the lower CPS subgroups because Kaplan–Meier data was not available to estimate time-varying relative effects. The EAG explained that there was some evidence to show that the proportional hazards assumption did not hold for all studies. This supported the EAG's base case, which used time-varying relative effects for the whole population, irrespective of PD-L1 CPS. The EAG's pairwise comparisons showed incremental QALYs that favoured nivolumab and pembrolizumab over zolbetuximab. At the second committee meeting, the committee considered whether zolbetuximab would be expected to have the same long-term benefits as immunotherapies. It agreed with the EAG that the proportional hazards assumption may not hold, supporting the EAG's time-varying approach. Given that the committee considered the company's network-meta-analysis suitable for decision making (see section 3.5), it preferred the EAG's approach using time-varying relative treatment effects from the network meta-analysis for the secondary analysis.

Treatment-effect waning

3.11 In its base case, the company did not apply treatment-effect waning to the zolbetuximab plus 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. At the clarification stage, the company provided scenarios that applied treatment-effect waning to the zolbetuximab plus chemotherapy arm after 5, 6, and 7 years after starting treatment. This was done by applying the chemotherapy hazard rates to the zolbetuximab plus chemotherapy arm. The EAG agreed that the evidence did not show treatment-effect waning for zolbetuximab but highlighted the limited follow up of OS and PFS in SPOTLIGHT and GLOW. The EAG modelled scenarios using treatment-effect waning after 3 and 4 years. But in its base case it used the company's scenario applying treatment-effect waning at 5 years. This was because it considered that scenarios where treatment-effect waning starts at 3 and 4 years were too pessimistic, because the observed hazard ratios showed no sign of treatment-effect waning at 3 years. But, it noted that the number of people still on treatment at 3 years was small. The committee concluded that, because of a lack of long-term follow-up OS data, it would include treatment-effect waning at 5 years in its preferred assumptions.

In response to the draft guidance consultation, the company presented results using 2 alternative approaches:

- applying treatment-effect waning gradually from 5 to 7 years, and
- not applying treatment-effect waning (the company confirmed this was its preferred base case before the second committee meeting).

The company reiterated that there is no evidence for treatment-effect waning. It added that the EAG's OS curve, which assumes treatment-effect waning, has poor face validity. It added that the assumption is also inconsistent with TA997. In that appraisal, waning was applied gradually

starting at either 5, 6 or 7 years after starting treatment, reducing to the same as the chemotherapy after 2 years. At the second committee meeting, the company explained that zolbetuximab would be expected to have a sustained treatment effect, but not to a greater extent than with immunotherapies. The committee considered that this supported using a more conservative assumption than in TA997. The committee noted that when applying treatment-effect waning, the hazards are the same between treatments from 5 years but zolbetuximab retains the benefit it has accrued up to 5 years. So, the committee concluded that its preference was to continue to use the EAG approach of applying treatment-effect waning at 5 years.

Severity

3.12 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 met 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

3.13 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 acknowledged that the data for zolbetuximab for the comparison with chemotherapy came from 2 large, randomised controlled trials with mature data (see section 3.4) and so uncertainty was low. So, the committee concluded that an acceptable ICER for the comparison with chemotherapy would be around £30,000 per QALY gained.

Committee-preferred assumptions

3.14 The committee's preferred assumptions included:

- using data from the pooled SPOTLIGHT and GLOW trials to inform the chemotherapy arm (see section 3.8)
- modelling the relative efficacy of zolbetuximab plus chemotherapy and chemotherapy alone using independent log-logistic models fit to the pooled SPOTLIGHT and GLOW trials only (see section 3.9)
- using time-varying relative treatment effects from the network meta-analysis for the comparisons with nivolumab plus chemotherapy and pembrolizumab plus chemotherapy (see section 3.10)
- applying treatment-effect waning at 5 years (see section 3.11)
- using a severity modifier of 1.2 applied to the QALYs (see section 3.12).

Cost-effectiveness estimates

3.15 When considering the committee preferences (see section 3.14), the ICER for zolbetuximab plus chemotherapy compared with chemotherapy alone was above the range normally considered a cost-effective use of NHS resources (see section 3.13). The company consider the ICER compared with chemotherapy to be confidential, so it cannot be reported here. The results for zolbetuximab plus chemotherapy compared with

nivolumab plus chemotherapy and pembrolizumab plus chemotherapy showed that zolbetuximab was less costly, but also less effective (in the southwest quadrant of the cost-effectiveness plane). Because of confidential comparator discounts, the ICERs compared with nivolumab and pembrolizumab are confidential, so cannot be reported here.

Equality

3.16 The committee did not identify any equality issues.

Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of zolbetuximab plus chemotherapy. The committee noted that zolbetuximab plus chemotherapy is novel and its targeting of claudin 18.2 is an innovative mechanism of action. So it recognised that zolbetuximab plus chemotherapy would add a treatment option and address an unmet need, particularly when chemotherapy is the only option available. It also noted from the clinical expert that zolbetuximab plus 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 plus chemotherapy not captured in the economic modelling. So, the committee concluded that all additional benefits of zolbetuximab plus chemotherapy had already been taken into account.

Conclusion

Recommendation

3.18 With the committee's preferred assumptions applied, zolbetuximab plus chemotherapy may not work as well as nivolumab plus chemotherapy or pembrolizumab plus chemotherapy. Although there was a benefit for zolbetuximab with chemotherapy compared with chemotherapy alone, cost-effectiveness estimates were above the range that NICE considers an acceptable use of NHS resources. So, it is not recommended 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.

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

James Fotheringham

Vice chair, technology appraisal committee A

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.

Anna Willis and Summaya Mohammad

Technical leads

Rufaro Kausi

Technical adviser

Jennifer Upton

Project manager

Janet Robertson

Associate director

ISBN: [to be added at publication]