NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Zanidatamab for treating HER2-positive advanced biliary tract cancer after 1 or more systemic treatments

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using zanidatamab 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?

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Note that this document is not NICE's final guidance on this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using zanidatamab in the NHS in England.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: 3 February 2026
- Second evaluation committee meeting: 3 March 2026
- Details of the evaluation committee are given in section 4.

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1 Recommendations

1.1 Zanidatamab should not be used to treat HER2-positive (defined as immunohistochemistry 3 [IHC3] positive) unresectable locally advanced or metastatic biliary tract cancer in adults after at least 1 line of systemic treatment.

1.2 This recommendation is not intended to affect treatment with zanidatamab 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.

What this means in practice

Zanidatamab is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to suggest that zanidatamab is value for money in this population.

Why the committee made these recommendations

Usual treatment for HER2-positive (IHC3 positive) unresectable advanced biliary tract cancer after at least 1 line of systemic treatment varies. If further anticancer treatment is suitable, people usually have FOLFOX chemotherapy with active symptom control (ASC). If this is not suitable, people usually have ASC only.

Zanidatamab has not been directly compared in a clinical trial with usual treatment. Indirect comparisons suggest that it is likely to increase how long people have until their condition gets worse and how long people live compared with usual treatment. But, it is uncertain how much extra benefit people would get with zanidatamab.

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There are uncertainties in the economic model, particularly about how much zanidatamab may improve health-related quality of life compared with usual treatment.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for zanidatamab and more analyses are needed. So, zanidatamab should not be used.

2 Information about zanidatamab

Anticipated marketing authorisation indication

2.1 Zanidatamab (Ziihera, Jazz Pharmaceuticals) does not have a marketing authorisation in Great Britain yet. It received a marketing authorisation by the European Commission for 'the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for zanidatamab.

Price

2.3 The list price per pack of 2 vials of 300-mg zanidatamab is currently confidential.

2.4 The company has an approved commercial arrangement (simple discount patient access scheme), which would have applied if zanidatamab had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Jazz Pharmaceuticals will be included here when guidance is published.

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3 Committee discussion

The evaluation committee considered evidence submitted by Jazz Pharmaceuticals, 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

3.1 Biliary tract cancer includes bile duct cancer (cholangiocarcinoma), gallbladder cancer and ampullary cancer. The committee noted that only ampullary cancer arising from the ampulla of Vater was within the scope of this evaluation. This evaluation focuses on biliary tract cancer that has excessive expression of the human epidermal growth factor receptor 2 (HER2) protein. HER2 acts as a stimulant that encourages cancer cells to grow quickly. HER2 alterations are identified in about 5% to 10% of cholangiocarcinomas and up to 20% of gallbladder cancers. The patient experts described how biliary tract cancer can have vague, non-specific symptoms, and is often misdiagnosed as other conditions. This means that most biliary tract cancers are diagnosed at a late stage when the cancer is usually inoperable. In England, fewer than one-third of people survive for 1 year after diagnosis. The patient experts described how the poor prognosis of advanced biliary tract cancer causes significant shock and has a huge emotional impact on people with the condition and their families. They further explained that, for the minority of people whose cancer is operable, the risk of recurrence after surgery is very high, and this remains a constant worry. The patient experts noted that the recent availability of first-line durvalumab (see NICE's technology appraisal guidance on durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer) has been a step-change in treatment. But, they emphasised that it is not effective for everyone, and may only extend survival by a few months. For people whose cancer has progressed on first-line treatment, the patient experts explained that second-line treatment options are limited and depend on the type of genetic alterations that the cancer has. The committee concluded that

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biliary tract cancer can have a substantial psychological, social and physical impact on people with the condition and their families.

Clinical management

Treatment options and positioning of zanidatamab

3.2 The clinical experts explained that, in the NHS, most people with unresectable advanced biliary tract cancer have durvalumab with gemcitabine and cisplatin as first-line treatment. The clinical experts described that the cancer is screened for different genetic alterations at diagnosis to determine eligibility for targeted second-line treatment. There are already targeted second-line treatments available for some other types of genetic alterations, but zanidatamab is the first HER2-targeted treatment available. The company explained that the marketing authorisation for zanidatamab specifies cancer with a high expression of HER2. This is usually determined using immunohistochemistry (IHC). The costs of additional IHC tests were included as part of the company submission. The clinical experts highlighted that, although HER2 screening is common in the NHS for other cancers, its use for biliary tract cancer is inconsistent across the NHS. They highlighted that further education for healthcare professionals would be needed if zanidatamab were to become available. Only cancers with high HER2 expression (IHC3 positive) are eligible for zanidatamab; cancers with lower expression (IHC1 positive or IHC2 positive) or no expression (IHC0) are not eligible. The clinical experts explained that people with cancer that has high expression of HER2 are not expected to have worse outcomes than people whose cancer has low or no expression. The company highlighted that about 80% of biliary tract cancers with HER2 alterations are IHC3 positive. However, only about 50 people per year in England would have zanidatamab if it became available. This is because of the low prevalence of HER2 alterations, the late diagnosis associated with biliary tract cancer, and the modest outcomes of first-line treatment. The clinical experts noted that HER2-positive biliary tract cancer is currently treated in

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the same way as cancer with no targetable genetic alterations. Standard care depends on whether the person with the condition is willing and able to have treatment. The clinical experts explained that, for people for whom further treatment is suitable, standard care is a combination of chemotherapies (folinic acid, fluorouracil and oxaliplatin [FOLFOX]) with active symptom control (ASC). For people for whom further chemotherapy is not suitable, usual management is ASC alone. This may include a range of supportive measures such biliary drainage, antibiotics, analgesia, steroids, antiemetics, palliative radiotherapy, and transfusion of blood products. The committee concluded that FOLFOX plus ASC, or ASC alone, were the relevant comparators for zanidatamab. The committee also noted that the eligible population for zanidatamab was small.

Unmet need

3.3 Both the patient and clinical experts stressed that FOLFOX is associated with substantial toxicity. The patient experts noted how chemotherapy can cause pain, exhaustion, nerve damage, infections and sepsis. They noted that these contribute to a greatly reduced quality of life, an increased dependency on carers and families, and a reduced ability to work. The patient and clinical experts explained that this toxicity must be balanced against the modest survival benefit that FOLFOX offers. This is typically less than 6 months, which is only about 1 month more than with ASC alone. Despite this modest survival benefit, people often choose to have FOLFOX because of the lack of other treatment options. The clinical experts also noted that FOLFOX administration takes around 2 days through a long-term implanted central venous access device. This creates an additional burden for people with the condition and their families. The patient experts described how highly they would value zanidatamab. They explained it would be more effective and better tolerated than FOLFOX, alleviating the burden on carers and allowing people to return to work. The clinical experts also explained that zanidatamab is administered less frequently than FOLFOX and does not require an implanted central venous access device, which reduces the burden on those with biliary

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tract cancer and on hospitals providing care. The patient experts provided feedback from people who had had zanidatamab and who described the treatment as “life-altering”. They said that the boost to their mental health and wellbeing from having a life-extending treatment was “indescribable”. The committee concluded that people with HER2-positive advanced biliary tract cancer would highly value a HER2-targeted, effective, and well-tolerated treatment option.

Clinical effectiveness

Zanidatamab: HERIZON-BTC-01 and real-world sources

3.4 The clinical evidence for zanidatamab came from HERIZON-BTC-01. This was a phase 2b, open-label, multicentre, international, single-arm trial. HERIZON-BTC-01 was done in 32 sites across 9 countries, including 1 UK site. The trial population included people with HER2-amplified unresectable locally advanced or metastatic biliary tract cancer previously treated with 1 or more lines of treatment. People in the trial had to have had cancer progression after previous gemcitabine-based treatment, or had to have developed intolerance to treatment. The trial included 87 people. Of these, 80 people had IHC2- or IHC3-positive cancer (referred to as cohort 1 from here), and of those, 62 people had IHC3-positive cancer. The company noted that the marketing authorisation for zanidatamab specified IHC3-positive cancer, so this was the main cohort presented in its submission. The primary outcome of HERIZON-BTC-01 was confirmed objective response rate. The company reported data from the final data cut (July 2024). In the IHC3-positive cohort, the median progression-free survival (as assessed by independent central review) was 7.2 months (95% confidence interval [CI] 5.4 to 9.4 months), and the median overall survival was 18.1 months (95% CI 12.2 to 22.9 months). The company also referenced 2 real-world studies of zanidatamab, 1 that reported treatment response in 20 people in England, and 1 that reported survival of 20 people (of which 12 had IHC3-positive cancer) in France. The committee concluded that HERIZON-BTC-01 was the key clinical

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evidence source for zanidatamab for HER2-positive IHC3-positive advanced biliary tract cancer, but acknowledged that the real-world sources provided important supportive evidence.

Comparators: ABC-06

3.5 The clinical evidence for FOLFOX plus ASC, or ASC alone, came from ABC-06. This was a phase 3, open-label, multicentre, randomised controlled trial. ABC-06 was done in 20 sites across the UK. The trial included 162 people with unresectable locally advanced or metastatic biliary tract cancer that progressed on first-line treatment with cisplatin and gemcitabine. The ABC-06 population was not assessed for HER2 expression. The primary outcome was overall survival. The trial found that people who had FOLFOX plus ASC had a statistically significant improvement in overall survival compared with people who had ASC alone (median 6.2 months versus 5.3 months, hazard ratio 0.69, p=0.031). The trial only reported median progression-free survival for the FOLFOX plus ASC arm (4.0 months [95% CI 5.4 to 7.6 months]). The committee concluded that ABC-06 was the most relevant evidence source available to inform estimates of the clinical effectiveness of the comparators.

Generalisability of the trials

3.6 The committee noted that there was no requirement in ABC-06 for HER2-positive cancer. The committee questioned whether HER2 is a prognostic factor in biliary tract cancer. The clinical experts explained that, while there is not good quality evidence for this, current clinical opinion suggested that HER2 is not a prognostic factor in biliary tract cancer. So, the clinical experts thought the lack of HER2 testing in ABC-06 did not prevent HERIZON-BTC-01 and ABC-06 from being compared in an indirect treatment comparison. The committee further noted that the mix of biliary tract cancer types differed between the trials, with HERIZON-BTC-01 having a higher proportion of gallbladder cancer, and ABC-06 having a higher proportion of cholangiocarcinoma. The committee questioned whether different types of biliary tract cancer had different outcomes. It

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noted that the company had submitted longitudinal UK data that showed similar overall survival for people with cholangiocarcinoma or gallbladder cancer. The clinical experts agreed with this and explained that all types of biliary tract cancer have a generally poor prognosis. The committee also highlighted that both HERIZON-BTC-01 and ABC-06 were done before durvalumab became standard care for first-line treatment of biliary tract cancer. Only about a quarter of the cohort 1 population (IHC2- or IHC3-positive) in HERIZON-BTC-01 had previous PD-1 or PD-L1 inhibitor treatment (such as durvalumab) before zanidatamab (the proportion of the IHC3-positive only population is considered confidential by the company and cannot be reported here). In ABC-06, nobody had first-line PD-1 or PD-L1 inhibitor treatment. The committee questioned whether people who experience progression on first-line durvalumab might have more aggressive cancer than the people in the trials, and whether this limited the generalisability of the trials to current clinical practice. The clinical experts explained that they did not know of any reason to suspect this, and clarified that, although durvalumab is now used by most people at first line, its treatment benefit remains modest. Finally, the committee noted that some people in HERIZON-BTC-01 had a range of subsequent treatments that would not be offered in the NHS. This included further PD-1 or PD-L1 inhibitors (such as pembrolizumab) and other HER2-targeted treatments (such as trastuzumab). The exact proportion of people who had subsequent treatment is considered confidential by the company and cannot be reported here. The committee questioned whether the availability of many different subsequent treatments contributed to the overall survival benefit associated with zanidatamab. The clinical experts explained that the only subsequent treatment that would be permitted in the NHS is FOLFOX. They emphasised that the reason so many people in HERIZON-BTC-01 could have a variety of subsequent treatments is that people who have zanidatamab are often healthier and more able to tolerate further treatment than people who have FOLFOX. But, there was limited evidence on the efficacy of any of the subsequent treatments so

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they were uncertain whether subsequent treatment would have clinical benefit. The company noted that participants in HERIZON-BTC-01 were followed-up to death, so any benefit of subsequent treatments would be captured in the overall survival outcome. But, the company did not present any information on time to second progression. The committee thought that data on time to second progression could have provided more information to explore and understand the effect of subsequent treatment. The committee noted that the company could have considered analyses which adjust for treatment switching. But, the committee acknowledged that, given the sample size of the trial, this may not fully resolve the uncertainty. The committee concluded that HERIZON-BTC-01 and ABC-06 were sufficiently generalisable to inform this evaluation. But, it considered that there was uncertainty about the extent to which subsequent treatments contributed to the overall survival outcomes in HERIZON-BTC-01. The committee agreed to take this uncertainty into account in its decision making.

Indirect treatment comparisons

3.7 The company did 3 indirect treatment comparisons to estimate the comparative efficacy of zanidatamab. Firstly, the company did an unanchored matching-adjusted indirect comparison (MAIC). This reweighted the population of HERIZON-BTC-01 to increase similarity with ABC-06, based on identified prognostic factors and treatment effect modifiers. The company used the second-line only population from HERIZON-BTC-01 to match ABC-06. This second-line only population was a subset of the 62-person IHC3-positive population in HERIZON-BTC-01 (the exact number of people in this second-line only subpopulation is considered confidential by the company and cannot be reported here). The company identified 4 key prognostic factors:

- Eastern Cooperative Oncology Group (ECOG) performance status
- line of treatment (second line compared with third line or later)
- primary tumour site

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- locally advanced cancer.

The company was able to adjust the population of HERIZON-BTC-01 to match ABC-06 on these factors. But, the company was unable to match the populations on other factors, including HER2 status. The matching process reduced the effective sample size used in the MAIC. The company presented both weighted (using the HERIZON-BTC-01 second-line only population after adjustment) and unweighted (using the unadjusted HERIZON-BTC-01 second-line only population) comparisons. In both the weighted and unweighted comparisons, zanidatamab showed a statistically significant improvement in progression-free survival and overall survival compared with FOLFOX plus ASC, and a statistically significant improvement in overall survival compared with ASC alone (progression-free survival was not available for ASC from ABC-06). The results of the weighted and unweighted comparisons were similar. The company cited several uncertainties in the MAIC, including being unable to match on all criteria, the limited effective sample size after matching, and uncertainty about whether the criteria selected for matching were truly prognostic.

The company also presented an external control arm analysis. This identified people in a large, US-based patient database (Flatiron) who had HER2-positive IHC3-positive locally advanced or metastatic biliary tract cancer and who had second-line treatment with 6 months or more of potential follow-up and 2 or more distinct visits. A total of 12 people met the inclusion criteria, and most had FOLFOX. To account for potential imbalance of key prognostic factors at baseline, standardised mortality ratio weighting was applied to the Flatiron cohort to increase similarity with HERIZON-BTC-01. Zanidatamab showed a statistically significant improvement in progression-free survival compared with the external control arm (median 7.26 months versus 2.30 months, hazard ratio 0.47, 95% CI 0.23 to 0.95). A statistically significant improvement

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was also observed for overall survival (median 18.07 months versus 3.29 months, hazard ratio 0.29, 95% CI 0.13 to 0.63). The company noted that this analysis was limited by the small sample size available for the external control arm, and by the different prescribing practices in the US and UK.

Because of the limitations with the MAIC and external control arm comparison, the company chose to use a naive comparison of HERIZON-BTC-01 and ABC-06 to estimate the clinical benefit of zanidatamab. The EAG agreed that the naive comparison was the best approach of those presented. But it was concerned about the robustness of the naive comparison and emphasised to the committee that the derived comparative treatment effect estimates may be unreliable. The committee concluded that the naive comparison was appropriate to use in the economic model. But, the committee thought that there was a high degree of uncertainty associated with using a naive comparison and agreed to account for this in its decision making.

Economic model

Company's modelling approach

3.8 The company developed a partitioned survival model with 3 discrete health states: progression-free, progressed disease, and death. The progression-free health state was further divided into on-treatment and off-treatment substates. The EAG agreed that the structure of the economic model was appropriate and consistent with previous NICE appraisals in this disease area. The committee concluded that the economic model was acceptable for decision making.

Survival analysis

3.9 The company fitted independent standard parametric survival models to the unadjusted progression-free survival and overall survival data from HERIZON-BTC-01 and ABC-06. Because progression-free survival data

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for ASC was not available from ABC-06, the company applied the hazard ratio for overall survival derived from the MAIC (see section 3.7) to the zanidatamab progression-free survival curve to estimate ASC progression-free survival. The committee thought the company's progression-free and overall survival curve selections for the comparators were reasonable. For zanidatamab progression-free survival, the company and EAG agreed that the log-logistic curve was appropriate. For zanidatamab overall survival, the company chose the log-logistic curve. It explained that the log-logistic curve had the second-best statistical fit to the data and aligned with clinical expectation of survival. The EAG thought that the log-logistic curve was optimistic over the long term. So, the EAG chose the log-normal curve because it had a similar statistical fit to the data, but slightly less optimistic long-term survival predictions. The committee noted that both curves aligned with clinical expectation of survival but was concerned that the log-logistic curve was too optimistic in the long term. The clinical experts explained that they would not expect people who had zanidatamab to survive much longer than 5 years, but cautioned that zanidatamab has not been available long enough to confirm this prediction. The clinical experts further explained that there may be variation in patient outcomes, but many people would progress quickly on treatment. The committee therefore felt that the gamma curve was more appropriate for extrapolating zanidatamab overall survival. The gamma curve had similar statistical fit to the data but had more pessimistic long-term survival estimates and tended to zero more quickly. The committee thought that the log-normal curve could also be plausible and so would consider it as an optimistic scenario. The EAG observed that using the gamma curve meant that the overall survival and progression-free survival curves crossed beyond 5 years, which should not be possible. So, the committee suggested using the log-normal curve for zanidatamab progression-free survival. This had similar statistical fit and survival landmarks to the log-logistic curve, but was more pessimistic in the long term, so largely avoided the crossing issue. The committee

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agreed that using the gamma curve for overall survival helped to reduce some of the uncertainty in the evaluation. The committee concluded that the log-normal curve should be used to extrapolate zanidatamab progression-free survival and the gamma curve should be used to extrapolate zanidatamab overall survival.

Time on treatment

3.10 The company fit standard parametric survival models to the zanidatamab time-on-treatment data from HERIZON-BTC-01. The company chose the gamma curve in its base case because this gave the shortest time on treatment, consistent with the observed data. The EAG noted that using the gamma curve meant that the time on treatment curve exceeded progression-free survival in the model for a substantial period of time, before steeply decreasing (the exact time is considered confidential by the company and cannot be reported here). The EAG explained that the time-on-treatment curve was capped to progression-free survival in the company's model, which avoided this implausible situation, but it thought that this implied that the gamma curve lacked face validity. Instead, the EAG chose to use the log-normal curve. This exceeded progression-free survival for a shorter period, and meant that a higher proportion of the progression-free cohort remained on treatment throughout the model. The committee concluded that the log-normal curve was appropriate to extrapolate zanidatamab time on treatment.

For FOLFOX plus ASC, time-on-treatment data was not available from ABC-06. So, the company assumed that time on treatment would be equal to progression-free survival. This was supported by clinical advice to the company that suggested that progression-free survival was a reasonable proxy for time on treatment and that treatment costs would not be overestimated. The committee recalled that FOLFOX treatment often comes with substantial toxicity (see section 3.3), which can lead to people stopping treatment before progression. So, it was not convinced that the model should assume time on treatment to be equal to progression-free

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survival for FOLFOX. The company had provided a scenario in which FOLFOX time on treatment was based on a hazard ratio applied to progression-free survival. This hazard ratio was estimated using the median number of FOLFOX cycles reported in ABC-06 (converted to months) divided by the median progression-free survival. This approach was preferred by the EAG. The committee concluded that FOLFOX time on treatment should be modelled by applying a hazard ratio to progression-free survival to account for people stopping treatment for reasons other than progression.

Utility values

3.11 The company presented 2 approaches for estimating utility values. First, the company estimated progression-based utility values using data from cohort 1 (IHC2- and 3-positive) of HERIZON-BTC-01 (see section 3.4). This approach estimated a utility value for people who were progression-free and another (lower) value for people whose cancer had progressed (the exact values are considered confidential by the company and cannot be reported here). The company explained that the progression-based approach was very common in previous NICE appraisals. But, the company noted that this approach is often limited by a small number of observations after progression. These observations are usually at or around the time of progression, when the negative effects of progression may not be fully realised. The company further explained that utility is modelled as constant over time and does not capture the expected decline in utility close to death. To overcome these limitations, the company also presented a time-to-death approach. This approach estimated utility based on the time to a person's death, rather than their progression status. In the time-to-death approach, utility begins to decrease for a period of time before death (irrespective of whether cancer has progressed). Then, utility decreases rapidly in the days before death. The company thought that the time-to-death approach better reflected the patient experience for biliary tract cancer. The EAG noted that the time-to-death approach calculated utility values from the zanidatamab HERIZON-

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BTC-01 data but also applied these to the FOLFOX plus ASC and ASC alone arms of the model. The EAG suggested that this was problematic because people on zanidatamab are modelled to have a significantly longer period in the progressed disease health state than people on the comparators. When using the time-to-death approach, this means that lower utility values (that come from being close to death) are applied in the comparator arms when many people are still progression-free. The EAG further noted that there were very few utility observations close to death, and that the average utility of these observations was higher than might be expected. This was especially true when using data from the IHC3-positive cohort, rather than cohort 1 as the company had done. The EAG questioned whether this limited the face validity of the time-to-death approach. Furthermore, the EAG noted that costs and treatments in the model were determined by progression status, so using progression-based utilities would mean that the model was more internally consistent. The committee recognised the merits of both approaches to calculating utility values. But, it thought that the small number of high-utility observations close to death created significant uncertainty and reduced face validity of the time-to-death approach. For this reason, the committee concluded that progression-based utility values were more appropriate for the model.

The company also applied several disutilities in the model. The company applied an on-treatment disutility to zanidatamab and FOLFOX to account for the frequency of grade 3 or 4 adverse events. This disutility was higher for FOLFOX. The company also applied a treatment-specific disutility to FOLFOX plus ASC, and ASC alone. The company calculated this disutility by using the baseline and 4-month utility values from ABC-06 to calculate a relative utility decrement which was then applied to HERIZON-BTC-01 utility values. This treatment-specific disutility was higher for ASC alone than FOLFOX plus ASC (the exact decrements are considered confidential by the company and cannot be reported here). The company

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explained that the rationale for this treatment-specific disutility for FOLFOX was the need for a long-term implanted central venous access device and the high incidence of grade 1 or 2 adverse events (which are not captured by the grade 3 or 4 adverse event disutility described above). For ASC, this treatment-specific disutility accounted for lack of disease control. Additionally, the company applied a further disutility to account for the relative proportions of people on FOLFOX who have a peripherally inserted central catheter (PICC) line versus a port-a-cath. This assumed an extra disutility associated with a port-a-cath. The EAG questioned whether a treatment-specific disutility was appropriate given the company's calculation was based on naive comparison of utilities between HERIZON-BTC-01 and ABC-06. It noted that it was not usual practice to include disutility associated with grade 1 or 2 adverse events in models, and said that assuming a consistent quality-of-life reduction from these events was not supported by evidence. The EAG also questioned whether there was double-counting present in the application of the separate adverse events, treatment-specific and administration disutilities. The committee was concerned that in the company's approach, grade 1 or 2 adverse events were being considered for the comparators but not for zanidatamab. The committee recalled the patient expert statements about the toxicity of FOLFOX and the tolerability of zanidatamab (see section 3.3). It thought that it was plausible that people would have better quality of life when on zanidatamab. So, it asked the company to consider providing treatment-specific utility values in the progression-free health state. It recalled the clinical expert statements that reported that people who have zanidatamab are typically healthier after progression and more able to tolerate subsequent treatment (see section 3.6). So, it also requested that the company provide a scenario that includes post-progression treatment-specific utility values. The committee noted that this scenario should account for some people having FOLFOX after zanidatamab and the potential lower utility that might be associated with

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FOLFOX compared with ASC only after zanidatamab. In summary, the committee requested that the company provide scenarios exploring:

- treatment-specific utility values that are fully justified, including:
  - providing adverse event decrements separately to explore face validity of these treatment-specific values
  - simplifying the utilities and disutilities to avoid double-counting
  - excluding disutility for grade 1 or 2 adverse events
- non-treatment-specific utility values with simplified disutilities to avoid double-counting and excluding disutility for grade 1 or 2 adverse events
- a comparison with utilities used in previous NICE evaluations in this disease area.

Costs

Relative dose intensity

3.12 The company applied the relative dose intensity for zanidatamab from HERIZON-BTC-01 to account for missed doses, reductions and interruptions (the exact relative dose intensity is considered confidential by the company and cannot be reported here). The company applied the same relative dose intensity for FOLFOX, citing a lack of data in biliary tract cancer to suggest otherwise. The EAG questioned whether this was appropriate. It recalled the patient expert statements (see section 3.3) that suggested that one of the perceived benefits of zanidatamab is fewer and less severe side effects compared with FOLFOX. So, the EAG sourced a lower relative dose intensity figure of 78% from a Korean real-world study. The clinical experts agreed that it was reasonable to assume lower relative dose intensity with FOLFOX because of its toxicity. So, the committee concluded that the model should include a relative dose intensity of 78% for FOLFOX.

Frequency of cardiac monitoring

3.13 The company noted that the marketing authorisation for zanidatamab requires regular assessment of the left ventricular ejection fraction during

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treatment. So, it included the cost of regular echocardiography for zanidatamab. The company also explained that the marketing authorisations for fluorouracil and oxaliplatin both include requirements to regularly monitor cardiac function (fluorouracil) or the QT interval (oxaliplatin). The company included the costs of monitoring via echocardiography for both zanidatamab and FOLFOX in its submission. At the first committee meeting the company explained that echocardiography was included by error for FOLFOX. The costs of electrocardiogram (ECG) monitoring should have been included instead. The clinical experts explained that they typically do an ECG when starting people on FOLFOX, and then only later on if indicated by symptoms. The company highlighted that the NHS reference costs for ECG and echocardiography were similar, but the committee questioned whether this accurately reflected NHS care for this condition. The committee asked that the company update the model with costs for ECG and echocardiography that were most reflective of NHS practice. In particular, the committee was interested to understand the applicability of NHS reference costs for ECG to people in this evaluation, many of whom would be already visiting hospital for treatment and seeing healthcare professionals able to use and interpret an ECG without an additional appointment.

Minor issues

3.14 The EAG's base case made several other minor adjustments. These were:

- using the HERIZON-BTC-01 IHC3-positive population as the source for adverse event rates and utility values (rather than cohort 1)
- excluding the company's end-of-life morphine cost (because this cost was likely captured in the company's end-of-life care cost).

The committee concluded that these changes were appropriate and

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should be reflected in updated scenario analyses provided by the company.

Severity

3.15 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 quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company and EAG provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. Both the company and EAG estimated the proportional shortfall to be greater than 95%. The committee agreed it may be appropriate to apply a severity weight of 1.7 to the incremental QALYs. It recalled the patient and clinical expert testimony on the impact on quality of life and poor prognosis for people with current treatment. The committee was aware that it had not yet seen the shortfall associated with its preferred assumptions using different utility estimates. So, it will confirm the appropriate weighting when the requested additional analyses are available.

Other factors

Equality

3.16 The committee did not identify any equality issues in relation to characteristics protected by the Equality Act 2010. The company presented some evidence that there are socioeconomic differences in mortality rates for biliary tract cancer. The committee concluded that it was unclear to what extent, if any, that zanidatamab would reduce this health inequality, and so concluded that it could not take this into account in its decision making.

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Uncaptured benefits

3.17 The committee considered whether there were any uncaptured benefits of zanidatamab. It recalled that the patient experts spoke about the significant burden on carers for people with biliary tract cancer. The patient experts said they felt that zanidatamab had the potential to substantially reduce this carer burden. The committee recalled zanidatamab is thought to be a step-change in treatment, but that it is not curative and that people may have FOLFOX after zanidatamab. The committee was aware that effects on carers are not normally included in cancer evaluations. Given the nature of the condition and the effects of the treatment, the committee thought that there may be a justification for considering carer quality of life in this case. It felt that zanidatamab was likely to have a positive impact on carers. It noted that there was unlikely to be robust evidence to quantify this, but it would take this into account qualitatively in its decision making. The committee also recalled that zanidatamab is administered less frequently than FOLFOX and does not require an implanted central venous access device which may reduce the burden on hospitals providing care. So, the committee concluded that there were uncaptured benefits of zanidatamab and agreed to take these into account in its decision making.

Cost-effectiveness estimates

Acceptable ICER

3.18 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 that the uncertainties included that:

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- Subsequent treatments that would not be available in the NHS may have affected overall survival in HERIZON-BTC-01 (see section 3.6).
- A naive comparison of zanidatamab and the comparators was used to estimate the relative clinical effectiveness of zanidatamab (see section 3.7).
- It was unclear to what extent zanidatamab improved quality of life, given the multiple disutilities applied and the potential for double-counting (see section 3.11).

The committee also noted that:

- The decision risk is low given the small expected eligible population (see section 3.2).
- Use of the gamma curve for zanidatamab overall survival was more pessimistic in the long term than other plausible options (see section 3.9).
- There were uncaptured benefits of zanidatamab (see section 3.17).

The committee concluded that it could not set an acceptable ICER threshold until it had seen further analysis of utility values (see section 3.11).

Committee-preferred cost-effectiveness estimates

3.19 The committee recalled its preferred assumptions:

- using a naive indirect treatment comparison to compare zanidatamab with FOLFOX plus ASC and ASC alone (see section 3.7)
- extrapolating zanidatamab progression-free survival using the log-normal curve and overall survival using the gamma curve (see section 3.9)
- extrapolating zanidatamab time on treatment using the log-normal curve (see section 3.10)

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- applying a hazard ratio to FOLFOX progression-free survival to estimate time on treatment (section 3.10)
- using progression-based utilities in the model (see section 3.11)
- applying 78% relative dose intensity to FOLFOX (see section 3.12)
- using costs for ECG and echocardiography that are most reflective of NHS practice (see section 3.13)
- implementing the EAG's other adjustments to the model (see section 3.14).

The committee noted the additional analysis of utilities (see section 3.11) may substantially alter the estimates of cost effectiveness. So, it could not specify all its preferred assumptions until such analyses are available.

Conclusion

Recommendation

3.20 The committee concluded that zanidatamab should not be used for treating HER2-positive advanced biliary tract cancer after at least 1 line of systemic treatment. It noted the uncertainty in the clinical evidence and economic modelling for zanidatamab. The committee would like for the company to better reflect the utility benefits of zanidatamab in the economic modelling and requested further analyses on this.

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 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.

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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

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.

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Technical lead

Emily Leckenby

Technical adviser

Leena Issa

Project manager

Lorna Dunning

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