NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Zanidatamab for treating HER2-positive advanced biliary tract cancer after 1 or more lines of systemic treatment [ID6388]

1 Recommendation

1.1 Zanidatamab can be used, within its marketing authorisation, 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.

What this means in practice

Zanidatamab must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. Zanidatamab must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that zanidatamab provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made this recommendation

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

Issue date: April 2026

Zanidatamab has not been directly compared in a clinical trial with FOLFOX or ASC. 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.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, zanidatamab can be used.

2 Information about zanidatamab

Marketing authorisation indication

2.1 Zanidatamab (Ziihera, Jazz Pharmaceuticals) as monotherapy is indicated 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 is 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 a commercial arrangement (simple discount patient access scheme). This makes zanidatamab available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, Jazz Pharmaceuticals did not disclose its Carbon Reduction Plan for UK carbon emissions.

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, for ampullary cancer, only ampullary cancer arising from the ampulla of Vater was within the scope of this evaluation. This evaluation focuses on biliary tract cancer that overexpresses 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

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. Zanidatamab is the first HER2-targeted treatment available. The company explained that the marketing authorisation for zanidatamab specifies that the cancer must have a high expression of HER2. This is usually determined using immunohistochemistry (IHC). High HER2 expression is known as IHC3 positive. 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. They highlighted that further education for healthcare professionals would be needed if zanidatamab were to become available. 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.

The committee noted that biliary tract cancer is rare and only around 50 people per year in England would have zanidatamab if it became available. This is substantially fewer than the total number of people who have biliary tract cancer in England. The company explained that the expected number is small 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 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). When 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 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. Survival with FOLFOX is typically less than 6 months; only about 1 month more than with ASC alone. Despite this, 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 that a treatment with better outcomes and reduced toxicity would allow them to live longer and better lives. The clinical experts also explained that zanidatamab is administered less frequently than FOLFOX and does not need an implanted central venous access device, which may release

capacity at 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 after 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), and the median overall survival was 18.1 months (95% CI 12.2 to 22.9). 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. Survival outcomes were not reported for the study done in England. In the study done in France,

median progression-free survival was 8.0 months with zanidatamab. Median overall survival had not yet been reached. The 1-year overall survival rate was 90.9% and the 2-year rate was 79.6%. The committee concluded that HERIZON-BTC-01 was the key clinical evidence source for zanidatamab for HER2-positive IHC3-positive advanced biliary tract cancer. It acknowledged that the real-world sources provided important evidence that the trial data was likely to reflect outcomes in clinical practice.

Comparators: ABC-06

3.5 The clinical evidence for FOLFOX plus ASC, and 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]). 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 the cancer to be HER2 positive. The committee questioned whether HER2 is a prognostic factor in biliary tract cancer. The clinical experts explained that, although there is not good quality evidence for this, current clinical opinion is 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. At the second meeting, the committee noted a comment on the draft guidance from an NHS healthcare professional. This comment described as-yet unpublished evidence that HER2 status was a prognostic factor for poorer outcomes in this population. The committee noted that its ability to consider this evidence was limited given that it was not yet published. But, the committee thought that this evidence could mean that the comparative effectiveness of zanidatamab was underestimated. This was because all people in HERIZON-BTC-01 were HER2 positive, and so would be expected to have worse outcomes, whereas HER2 status was not assessed in ABC-06.

The committee 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 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 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 company considers the proportion of the IHC3-positive only population to be confidential so it 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 most people now have durvalumab at first line, its treatment benefit remains modest. For the second meeting, the company submitted evidence that showed similar survival in HERIZON-BTC-01 across people who had and did not have durvalumab as a first-line treatment.

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 company considers the exact proportion of people who had subsequent treatment to be confidential so it cannot be reported here. But the committee noted that the proportion was substantially higher than the proportion who had subsequent treatments in ABC-06. 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 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 done analyses that adjusted for treatment switching. But, the committee acknowledged that given the sample size of the trial, this may not fully resolve the uncertainty. At the second meeting, the company presented evidence from HERIZON-BTC-01 that compared survival of people who had chemotherapy and people who had treatment other than chemotherapy as a first subsequent treatment. The EAG highlighted that this analysis was based on a small number of people. The committee concluded that HERIZON-BTC-01 and ABC-06 were sufficiently generalisable to inform this evaluation, but that some uncertainty remained, and this would be taken 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 company considers the exact number of people in this second-line only subpopulation to be confidential so it cannot be reported here). The company identified 4 key prognostic factors:

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

The company was able to adjust the population of HERIZON-BTC-01 to match ABC-06 on these factors. But, it 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
- overall survival compared with ASC alone (progression-free survival was not available for ASC alone 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 used a large, US-based patient database (Flatiron) which included people 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 was also observed in 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 used 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 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 it 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 evaluations for biliary tract cancer. 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 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 and EAG 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 and preferred 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 was also plausible and so would consider it as an optimistic scenario. The EAG observed that using the gamma curve to model overall survival and retaining the company approach to model progression-free survival resulted in the curves crossing at around 5 years, which should not be possible. So, the committee suggested using the log-normal curve for zanidatamab progression-free survival. This had better statistical fit and similar survival landmarks to the log-logistic curve, but was more pessimistic in the long term, so largely avoided the crossing issue.

At the second meeting, the company responded that the gamma curve

was too pessimistic and gave long-term survival estimates that were substantially lower than in comparable NICE evaluations of second-line targeted treatments for other molecular subtypes of biliary tract cancer. The company explained that it had received clinical advice that suggested these different targeted treatments are expected to have similar long-term survival. Furthermore, the company noted that using the log-normal progression-free survival curve did not avoid the crossing issue, rather it just occurred later in the time horizon. The company reiterated its preference to use log-logistic curves for progression-free and overall survival. The committee recalled that it thought using the log-normal curve was also plausible and noted the consultation comment that new evidence suggested that HER2 is a prognostic factor in biliary tract cancer, and that this was likely to be favourable to zanidatamab (see section 3.6). The committee considered implied hazard ratios between the different plausible overall survival curves for zanidatamab and the curves used for the comparators. It noted that, in the long term, the hazard ratio for the gamma curve rose above 1; that is, it predicted worse survival for zanidatamab than for the comparators. The clinical experts explained that although they would expect some treatment waning in the long term, people who have zanidatamab are typically healthier than people who have FOLFOX, even after progression. So, it was unlikely for people who have zanidatamab to have a higher long-term risk of death. The committee concluded that the log-normal curve should be used to extrapolate zanidatamab overall survival and retained its preference for modelling progression-free survival using the log-normal curve.

Time on treatment

3.10 The company fitted 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 company considers the exact time to be confidential so it 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 used 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. At the first meeting, the committee concluded that the log-normal curve was appropriate to extrapolate zanidatamab time on treatment. At the second meeting, the company highlighted that each of the time-on-treatment extrapolations exceeded progression-free survival at some point and that the purpose of capping in the model was to prevent this. The company also noted that all people in HERIZON-BTC-01 had stopped treatment by 3 years, largely because of cancer progression. So, the company maintained its preference for the gamma curve. The EAG also maintained its preference for the log-normal curve, citing zanidatamab's favourable toxicity profile and the lack of a stopping rule as reasons for people continuing treatment while progression free. The clinical expert agreed that the primary reason for stopping treatment was progression, and that they would expect people on zanidatamab to remain on treatment while progression free. The committee concluded that the log-normal time-on-treatment curve was more appropriate in the model because it meant that more people in the progression-free health state remained on treatment for longer.

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 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. 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

Application of utility values in the model

3.11 At the first meeting, 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 company considers the exact values to be considered confidential so they cannot be reported here). 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 was modelled as constant over time and did 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 began to decrease for a period of time before death (irrespective of whether the cancer had progressed). Then, utility decreased 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 suggested that this approach was problematic because people on zanidatamab were 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 meant that quality-adjusted life years (QALYs) generated in the progression-free health state were affected by the lower utility values (that came from being close to death) in the comparator arms, but the same was not true for zanidatamab. 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.

At the second meeting, the company responded that high-utility observations close to death are a known phenomenon and do not undermine the time-to-death approach. One of the patient experts also responded that people with biliary tract cancer report that utility tends to remain stable throughout the condition, and there is rapid deterioration before death. The EAG repeated its arguments from the first meeting and restated its preference for the progression-based approach. The committee recognised the merits of both approaches to calculating utility values. But, it agreed with the EAG that the appropriateness of the time-to-death approach was limited by the difference in time in progressed disease between the treatments, and the implications of that for QALY accrual in the progression-free health states of the comparator arms. The committee also agreed with the EAG that using progression-based utility values meant that the model was more internally consistent. For these

reasons, the committee concluded that progression-based utility values were more appropriate for the model.

Utility values and disutilities

3.12 The company applied several disutilities in the original model:

- An adverse event disutility was applied to zanidatamab and FOLFOX plus ASC as a one-off QALY reduction. The company explained that this was to account for the frequency of grade 3 and 4 adverse events.
- A treatment-specific disutility was applied to FOLFOX plus ASC, and ASC alone, was applied to the per-cycle time-to-death utility values. The company 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 and 2 adverse events. For ASC, this treatment-specific disutility accounted for lack of disease control. The company calculated this disutility by using the baseline and 4-month utility values from ABC-06 to calculate a relative utility decrement that was then applied to HERIZON-BTC-01 utility values.
- A further disutility to account for the relative proportions of people on FOLFOX who have a peripherally inserted central catheter 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 that the company's calculation was based on a naive comparison of utility values reported in 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 in the application of the separate 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 further treatment (see section 3.6). So, it also requested that the company provide a scenario including post-progression treatment-specific utility values. This scenario should account for some people having FOLFOX after zanidatamab and the potential lower utility that might be associated with FOLFOX compared with ASC only after zanidatamab.

At the second meeting, the company simplified its application of disutilities so that only the treatment-specific disutility was applied in its base case. The EAG thought that this was appropriate and reduced the risk of double counting. In response to the committee's request, the company noted that it could not calculate true treatment-specific utility values because it did not have access to the individual patient data for ABC-06. But the company noted that these could be estimated given that the baseline and 4-month utility values were published for ABC-06. The company's method was based on the assumptions that the published baseline value was equivalent to the progression-free utility, and that the 4-month value was a combination of the progression-free and progressed utility. Under these assumptions, the company calculated the progressed utility for FOLFOX plus ASC as 0.41 and for ASC alone as 0.47. The published baseline (assumed equal to progression-free) utility was 0.77 for FOLFOX plus ASC and 0.75 for ASC alone. The EAG noted that the assumption that baseline utility was equal to progression-free utility could be inappropriate because it

was assessed before treatment started. So, it would not capture any benefits (such as remaining progression free) or drawbacks (such as adverse events) of treatment. The committee noted that this method predicted a substantial decrease in utility for people whose cancer progressed on FOLFOX plus ASC or ASC alone, but a similar decrease was not modelled for zanidatamab. The clinical and patient experts reiterated that people who have zanidatamab are much healthier and have a far better quality of life than people who have FOLFOX, and that this benefit appears to last beyond cancer progression. The committee also noted that people on the comparators in the model spent a short time in the progressed disease health state, so the impact of this assumption on the cost-effectiveness estimates was limited. So, the committee concluded that the company's calculated treatment-specific utility values were appropriate to use in the model. But the committee recognised that the company's calculation introduced further naive comparison between HERIZON-BTC-01 and ABC-06. So, it agreed to account for this uncertainty in its decision making.

Costs

Relative dose intensity

3.13 The company applied the relative dose intensity for zanidatamab from HERIZON-BTC-01 to account for missed doses, reductions and interruptions (the company considers the exact relative dose intensity to be confidential so it 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 than 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, and that relative dose intensity should be applied to both treatment acquisition and administration costs.

Cardiac monitoring

3.14 The company noted that the marketing authorisation for zanidatamab requires regular assessment of left ventricular ejection fraction during treatment. So, it included the cost of regular echocardiography for zanidatamab. The company also explained that the marketing authorisations for fluorouracil and oxaliplatin include requirements to regularly monitor cardiac function (fluorouracil) or the QT interval (oxaliplatin). The company included the costs of monitoring using echocardiography for 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 best reflected 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.

At the second meeting, the company updated its model to include the NHS cost collection reference cost for all ECGs. This was £118. The EAG noted that this may be an overestimate and instead chose to use the cost for directly accessed diagnostic services only (£54). The clinical expert and Cancer Drugs Fund clinical lead explained that often scheduling

pressures mean that people cannot have an ECG at the same appointment as the treatment administration. For this reason, the committee thought that the company's cost, which was the average cost for an ECG in all settings, was more appropriate for the model. The committee preferred that this cost was applied twice per course of FOLFOX.

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 QALYs, known as 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 technology appraisal and highly specialised technologies guidance manual. Both the company and EAG estimated the proportional shortfall to be greater than 95%. The committee agreed it was appropriate to apply a severity weight of 1.7 to the incremental QALYs.

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 evidence that there are socioeconomic differences in mortality rates for biliary tract cancer. At the first meeting, 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.

At the second meeting, the company presented a distributional cost-effectiveness analysis to quantify the benefit of zanidatamab on this health inequality. The company used the ICD-10 code C22 (malignant

neoplasm of liver and intrahepatic bile ducts) to stratify the population according to the Index of Multiple Deprivation (IMD). This distribution showed that 24% of people with the condition were in the most deprived quintile (IMD1) and 17% were in the least deprived (IMD5). About 20% were in each of the IMD2 to IMD4 quintiles. The committee noted that the small eligible population for zanidatamab meant that, when considering all people served by the NHS, the net health inequality benefit of zanidatamab was negligible and so would do little to address inequality or unfairness in the societal distribution of health. But the committee did recognise that the extended administration time needed for FOLFOX was likely to affect people in the most deprived social group disproportionately. Furthermore, the committee noted comments from the patient experts about how they were able to return to work during treatment with zanidatamab, something that was not possible with FOLFOX. The committee recognised NICE evaluations use an NHS and Personal Social Services perspective. The committee concluded that any improvement in quality of life for people on zanidatamab had already been captured by applying treatment-specific utility values.

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 of people with biliary tract cancer. The patient experts said they felt that zanidatamab had the potential to substantially reduce this carer burden. 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. It felt that zanidatamab was likely to have a positive impact on carers, but it noted that there was unlikely to be robust evidence to quantify this. For the second meeting, the company included a 16% multiplier for carer quality of life in its base case. The company had sourced this multiplier from Pennington et al. (2026). The EAG noted that this multiplier was taken

from a study that looked at quality of life of carers of people with long-term after-effects of meningitis. The EAG noted that Pennington et al. (2026) explored several different approaches for determining carer utility, and it was not clear why the chosen method and multiplier was most appropriate for this evaluation. The EAG was unsure whether multipliers would be transferable across conditions, and the EAG and company were unaware of any studies that considered carer quality of life in biliary tract cancer. The committee thought that this use of a multiplier had not been justified by the evidence presented. It had not seen robust evidence that would allow it to consider the impact on carers quantitatively and so decided to consider it qualitatively. The committee also recalled that zanidatamab may increase the capacity of hospitals providing care because of its quicker and easier administration. 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 technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 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 following uncertainties:

- the higher subsequent treatment use in HERIZON-BTC-01 than in ABC-06, which may have affected overall survival (section 3.6)

- using a naive comparison of HERIZON-BTC-01 and ABC-06 to estimate the relative clinical effectiveness of zanidatamab (see section 3.7).
- using a naive comparison of HERIZON-BTC-01 and ABC-06 to estimate the treatment-specific utility values for the treatments in the model (see section 3.11).

The committee also noted that:

- the decision risk was low given the small expected eligible population (see section 3.2)
- there were uncaptured benefits of zanidatamab, including benefits for the quality of life of carers (see section 3.17).

The committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

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 and overall survival using log-normal curves (see section 3.9)
- extrapolating zanidatamab time on treatment using the log-normal curve (see section 3.10)
- applying a hazard ratio to FOLFOX progression-free survival to estimate time on treatment (see section 3.10)
- using progression-based utilities in the model (see section 3.11)
- using the treatment-specific utility values calculated from ABC-06 for FOLFOX plus ASC and ASC alone (see section 3.12)

- applying 78% relative dose intensity to FOLFOX, and applying the relative dose intensity to both treatment acquisition and administration costs (see section 3.13)
- using the company's revised cost for an ECG, applied twice per course of FOLFOX treatment (see section 3.14)
- qualitatively considering the uncaptured benefits associated with zanidatamab (see section 3.17).

The committee was satisfied that its preferred assumptions produced an ICER that was within the range that NICE considers to be a cost-effective use of NHS resources.

Conclusion

Recommendation

3.20 The committee concluded that zanidatamab can be used, within its marketing authorisation, for treating HER2-positive advanced biliary tract cancer after at least 1 line of systemic treatment.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance,

whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced biliary tract cancer after 1 or more systemic treatments and the healthcare professional responsible for their care thinks that zanidatamab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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.

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.

Tom Palmer

Technical lead

Emily Leckenby

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

ISBN: [to be added at publication]