Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Jazz Pharmaceuticals**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. AMMF – The Cholangiocarcinoma Charity, authored by Paul Howard, patient expert nominated by AMMF

3. **Comments on the Draft Guidance from experts:**
   a. John Bridgwater - clinical expert, nominated by Jazz Pharmaceuticals

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 **Comments on the Draft Guidance received through the NICE website**

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 **External Assessment Group critique of company comments on the Draft Guidance**

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

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Jazz Pharmaceuticals (Jazz) are disappointed that the committee's draft guidance does not recommend zanidatamab for the treatment of HER2-positive (immunohistochemistry 3 [IHC3]-positive) unresectable locally advanced or metastatic biliary tract cancer in adults after at least 1 line of systemic treatment, in line with the expected marketing authorisation. In response to the uncertainties and preferences noted by the committee in the draft guidance, Jazz highlight the following: • In HERIZON-BTC-01, the majority of patients were given no further treatment, or were treated with systemic chemotherapy (which has minimal impact on overall survival); therefore, the observed overall survival in the trial is expected to be highly reflective of the overall survival that would be seen in clinical practice. This is supported by the real-world evidence (full response in Comment number 4) • The log-logistic curve chosen by Jazz to inform overall survival for zanidatamab is more aligned with the 5 year survival estimates (7.4%) of other targeted treatments which are expected to have similar impacts on overall survival, compared with the committee's preferred gamma curve (2.5%), which also lacks face validity (full response in Comment number 6) • Results of the additional utility scenario analyses conducted for this consultation response show that whichever approach is taken to utilities, the effect on the incremental cost-effectiveness ratio is relatively small (full response in Comment number 8) • The impact of biliary tract cancer on caregivers is an extremely important consideration, and Jazz welcome the committee's acknowledgement of this. The company base case has been revised to reflect this and other considerations presented in the draft guidance (full responses in Comment numbers 9 to 16)

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	As detailed by patient and clinical experts in the appraisal committee meeting and noted in the draft guidance, biliary tract cancer is an aggressive and devastating disease with a high unmet need and limited treatment options; *"…the poor prognosis of advanced biliary tract cancer causes shock and has a huge emotional impact on people with the condition and their families"*. Zanidatamab represents a step-change in the second line treatment of locally advanced or metastatic biliary tract cancer. The only treatment option currently available to this patient population is systemic chemotherapy with FOLFOX, which is associated with substantial toxicity concerns and minimal survival benefit compared with active symptom control (1). As noted in the draft guidance *"…chemotherapy can cause pain, exhaustion, nerve damage, infections, and sepsis…these greatly contribute to a reduced quality of life, an increased dependency on carers and families, and a reduced ability to work"* and *"…people with HER2-positive advanced biliary tract cancer would highly value a HER2-targeted, effective, and well-tolerated treatment option"*. Zanidatamab would address this unmet need in this patient population, providing a much-needed chemotherapy-free targeted treatment option that substantially increases the median overall survival and has a tolerable safety profile (2). To highlight this, as noted in the draft guidance, patient experts described how *"[zanidatamab] would be more effective and better tolerated than FOLFOX, alleviating the burden on carers and allowing people to return to work"* and provided feedback from people treated with zanidatamab who described it as *"life-altering"*, noting *"…the boost to their mental health and wellbeing from having a life-extending treatment was "indescribable""*. Jazz do not believe that the provisional recommendations are a sound and suitable basis for guidance to the NHS based on the following comments and responses to this consultation: • has all of the relevant evidence been taken into account? No. Jazz believe the committee have not taken into account the totality of the clinical evidence for zanidatamab for second line HER2-positive biliary tract cancer, which is important in the context of a very rare cancer with a high unmet need. The draft guidance noted that *"…the real-world sources provided important supportive evidence"*; however, it is unclear how the UK and France real-world evidence, as provided in the company's submission, in addition to the evidence from the Phase 1 ZWI-ZW25-101, trial has been considered from the draft guidance. Jazz believe it is essential to consider this supporting evidence to minimise any perceived uncertainty from the committee in outcomes from the HERIZON-BTC-01 trial (as detailed in Comments number 2 and 3). Furthermore, since the company's submission to NICE, AMMF have published a survey relating to the patient and carer experience of biliary tract cancer (3), which is highly relevant for this appraisal and should be taken into account; where relevant, outcomes from this survey have been included and referenced in the answers below. • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. Jazz believe that in considering the uncertainty of the clinical evidence, the committee have not been mindful that second line HER2-positive biliary tract cancer is a very rare disease and that zanidatamab is an innovative technology that can address a high unmet need in a population that experiences health inequalities. Jazz note that the draft guidance does not mention the rare or aggressive nature of biliary

Draft guidance comments form

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	tract cancer, which Jazz consider extremely relevant in this appraisal. In line with section 6.2.33 of the NICE methods guide, in these specific circumstances, the committee can make recommendations accepting a higher degree of uncertainty, so the interpretation of the clinical evidence is not reasonable. In addition, Jazz believe the committee decision-making in considering the uncertainty and innovation is not in line with previous decision-making for targeted treatments for biliary tract cancer, so the interpretations are not reasonable. In addition to the comments below, Jazz are pleased to be able to provide further supporting data in the Appendices to this response: Appendix 1: Landmark survival analysis Appendix 2: Subsequent treatment subgroup analysis Appendix 3: ABC-06 treatment-specific utility values (as requested by committee) Appendix 4: Revised company base case Appendix 5: Scenario analysis Appendix 6: Health inequity report Appendix 7: Health-related quality of life studies identified in the systematic literature review
2. Clinical effectiveness evidence	In Section 3.4 of the draft guidance, the 2 real-world studies were noted as important supportive evidence by the committee (4, 5), but it is unclear how these important real-life data were considered in line with the NICE real world evidence framework. In the context of second line HER2-positive biliary tract cancer as a very rare disease, it is important that the totality of the evidence be considered appropriately, which should include the results of these real-world studies. This evidence provides clarity on the positive impact of zanidatamab for patients treated outside of clinical trials, with demographics expected to align with NHS practice. In particular, uncertainty around survival benefit and previous PD-1/PD-L1 use may be alleviated when taking into account this evidence, as detailed in Comment number 3 below. Further supportive data of the long-term response, survival benefit, and safety profile were also provided by case studies from the AMMF patient survey, which included UK patients treated with zanidatamab (3, 6). In addition, in the committee appraisal meeting, no discussion of other clinically relevant outcomes such as objective response rate, or duration of response were included. Appendix 1 provides a new landmark HERIZON-BTC-01 analysis of responder data to highlight the survival benefit offered by zanidatamab (7). Taking into account all the evidence, the strong HERIZON-BTC-01 clinical trial data in combination with the real-world evidence and supporting data from the AMMF patient survey should help reduce any clinical uncertainty around the survival benefit. Currently, the approach taken by the committee is very pessimistic and an unreasonable interpretation in light of the real-world evidence and in the context of a very rare disease with low patient numbers and an innovative treatment addressing a high unmet need for a population that lives with health

Draft guidance comments form

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	inequalities. Only around 50 patients per year in England would be eligible for treatment with zanidatamab and, as highlighted by the patient testimony reported in the draft guidance, these patients could benefit from the positive, *"life-altering"*, impact of zanidatamab.
3. Generalisability of the trials (previous PD-1 use)	In Section 3.6 of the draft guidance, the committee noted *"…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…".* Figure 1 presents an additional analysis of HERIZON-BTC-01 by prior PD-L1 use. It should be noted that results include low patient numbers, and the uncertainty should be considered appropriately in the context of this very rare disease. However, results strongly support the views of the clinical experts stated at the committee that prior PD-L1 use is unlikely to impact the overall survival outcome observed in the IHC3-positive subpopulation of HERIZON-BTC-01. As shown in Figure 1, there is no statistical difference in overall survival between prior PD-L1 use (n=16) and the IHC3-positive subpopulation (n=62). Jazz would also like to highlight that the submitted supporting real-world evidence from France (5) included 20 patients with IHC2- or IHC3-positive HER2-positive biliary tract cancer, of which 75% were previously treated with durvalumab and systemic chemotherapy. Despite low patient numbers reflective of an early access programme in this rare cancer, the results strongly support the overall effectiveness of zanidatamab reported in HERIZON-BTC-01, and corroborate the positive clinical expert opinion expressed in the appraisal committee meeting. In particular, the overall survival probability at 12 months in the France real-world evidence study was 90% (95% confidence interval: 0.51, 0.98) in patients with HER2-positive IHC3-positive biliary tract cancer (5), which is numerically greater than that seen in similar patients in HERIZON-BTC-01 (12-month overall survival probability: [redacted]% [95% confidence interval: [redacted]]) (8). Although there are expected variations between the pivotal zanidatamab clinical trial and real-world evidence, these data suggest that prior PD-1/PD-L1 treatment may not substantially impact the efficacy of zanidatamab and may actually improve outcomes in the NHS, where durvalumab and chemotherapy is standard of care. This should reduce the uncertainty of the long-term overall survival extrapolations, and shows the pessimistic curves chosen by the committee are unreasonable. Jazz Pharmaceuticals ask that the supporting real-world evidence presented in the company's submission is fully taken into consideration in interpretation of the totality of the evidence to reduce any uncertainty in these outcomes.

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Draft guidance comments form

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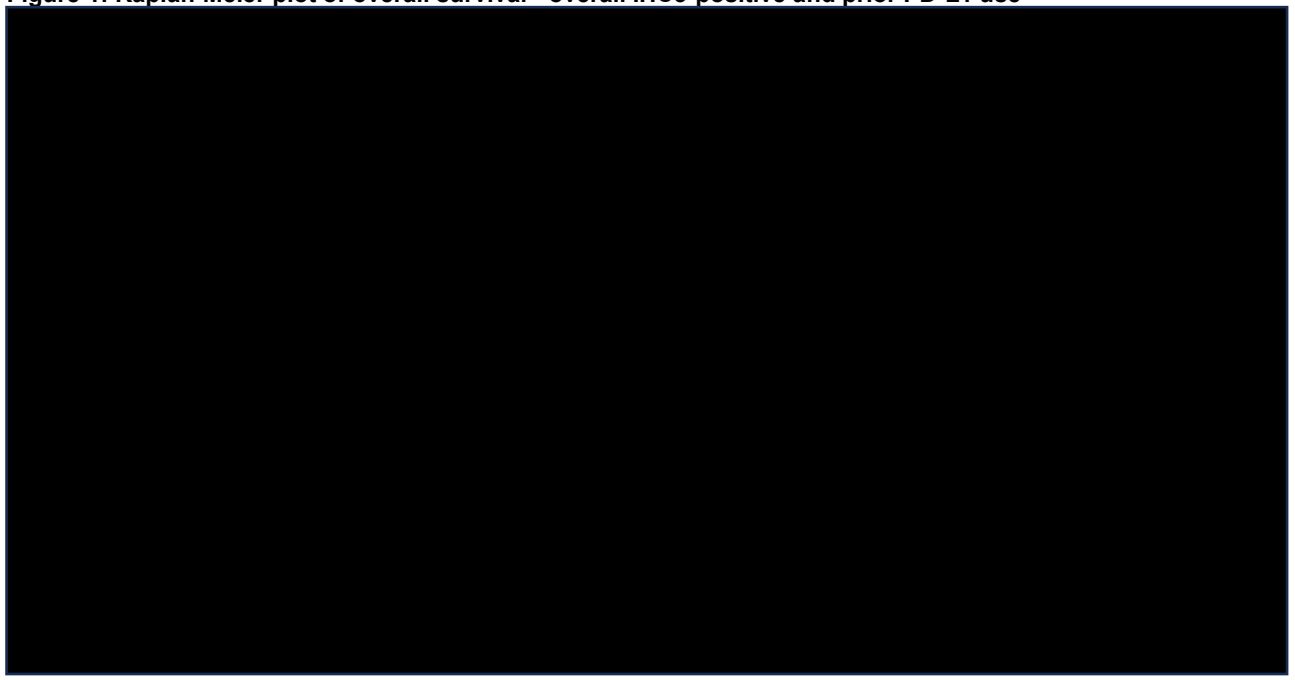
	Figure 1: Kaplan-Meier plot of overall survival - overall IHC3-positive and prior PD-L1 use  Abbreviations: 1L, first line; CI, confidence interval; IHC3+, immunohistochemistry 3-positive; PD-L1, programmed death-ligand 1.
4. Generalisability of trials (subsequent treatments in HERIZON-BTC-01)	In Section 3.6 of the draft guidance, the committee noted *"…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)."* and questioned *"whether the availability of many different subsequent treatments contributed to the overall survival benefit associated with zanidatamab."* Jazz note that time to second progression after subsequent treatment was not collected in HERIZON-BTC-01. However, in line with the clinical trials conducted for other targeted treatments, the majority of patients who received a subsequent treatment in HERIZON-BTC-01 received systemic chemotherapy, which aligns with NHS practice (9): • The majority n=33 (53.2%) received no subsequent treatment; only 29 of 62 patients received further lines of therapy:

Draft guidance comments form

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	○ 17 of 29 (58.6%) received subsequent systemic chemotherapy as their first subsequent treatment after zanidatamab ○ Only 4 of 29 received subsequent PD-1 or PD-L1 inhibitors ○ Only 3 patients received a subsequent HER2-directed therapy As the majority of patients were given no further treatment, or were treated with systemic chemotherapy, which has minimal impact on overall survival, the observed overall survival in HERIZON-BTC-01 is expected to be highly reflective of the overall survival that would be seen in UK clinical practice. To reassure the committee on the minimal impact of subsequent treatment following progression with zanidatamab, and for transparency, Jazz have provided a further analysis of overall survival by subsequent treatment (Appendix 2). Patients who received subsequent chemotherapy and non-chemotherapy as their next subsequent regimen were split into their respective groups at the point of receiving first subsequent treatment (Figure 9). The analyses demonstrate that there is no evidence to show that patients receiving subsequent treatment, or the type of subsequent treatments received, impacted the overall survival after treatment with zanidatamab and there was no significant difference between treatment groups. The impact of subsequent treatments on efficacy and inclusion of costs in the cost-effectiveness model align with previous technology appraisals in biliary tract cancer (ivosidenib; TA948 (10), durvalumab TA944 (11)) and clinical expert opinion elicited through the Delphi study conducted by the company for the submission and in line with NICE Decision Support Unit: Technical Support Document 26 (12, 13). As such, the uncertainty around overall survival benefit with zanidatamab should be minimal in the context of a very rare disease. The impact of subsequent treatments in previous appraisals was not considered by the committee (10, 11, 14, 15), including in the durvalumab appraisal, a first-line treatment for advanced biliary tract cancer; in TOPAZ-1, 42.5% of patients who received durvalumab had subsequent treatments (11). HER2-positive (IHC3-positive) biliary tract cancer is a very rare and aggressive disease, which is devastating to patients and their families or caregivers. As highlighted by the clinical experts in the appraisal committee meeting, *"…people who have zanidatamab are often healthier and more able to tolerate further treatment than people who have FOLFOX."* Therefore, the substantial improvement in wellbeing provided by zanidatamab may offer more hope for patients through the ability to cope better with current subsequent treatment options, which have substantial toxicity concerns (1), and in future clinical trials during their extended lifespan.
5. Indirect treatment comparisons	In Section 3.7 of the draft guidance, the committee noted: *"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."*

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	Jazz wish to highlight that many different approaches were provided to help reduce uncertainty in the analyses of zanidatamab compared with FOLFOX or active symptom control, including a matching-adjusted indirect comparison, an external control arm from the Flatiron database, and the naive comparison. Compared with standard of care, zanidatamab consistently showed substantial improvement in overall survival and progression-free survival, with a tolerable safety profile (1, 2, 8, 16-18). Due to the limitations of the other indirect comparisons, and in line with the pemigatinib technology appraisal (TA722) (14), Jazz considers, in alignment with the EAG preferences, the naive comparison to be the best and most consistent approach to minimise uncertainty in analyses of this very small patient population. Due to the rarity of advanced HER2-positive IHC3-positive biliary tract cancer, it is necessary to interpret the evidence in the context of a very rare disease and an innovative technology that can address a high unmet need, in a population that experiences health inequalities.
6. Survival analysis extrapolations	In Section 3.9 of the draft guidance, the committee noted that: *"[the log-normal and log-logistic] curves aligned with clinical expectation of survival but was concerned that the log-logistic curve was too optimistic in the long term. The committee therefore felt that the gamma curve was more appropriate for extrapolating zanidatamab overall survival"*. Jazz believes that the gamma curve is too pessimistic to be reasonable considering this contradicts the enhanced survival shown in supporting real-world evidence (4, 5) and the plausible potential for long-term survival that was highlighted by the clinical experts at committee (at least [redacted]% of patients with HER2-positive IHC3-positive biliary tract cancer in HERIZON-BTC-01 were still alive at the final trial data cut-off (19)). In addition, and as noted in the draft guidance, the log-logistic and log-normal curves align more with the EAG conclusions in the assessment report, and structured expert elicitation using a Delphi study of 11–14 UK experts, in line with NICE Decision Support Unit: Technical Support Document 26 (12, 13). The draft guidance states that "*The clinical experts further explained there may be variation in patient outcomes, but many people would progress quickly on treatment. The committee therefore felt the gamma curve was more appropriate for extrapolating zanidatamab OS*". Jazz would like to note that this conclusion does not consider the evidence or clinical opinion that patients treated with zanidatamab (and other targeted treatments) live for a substantial period of time post-progression, and substantially longer than those treated with FOLFOX. This is reflected in the real-world evidence, clinical trial, and clinical expectation, but has not been reasonably interpreted in the draft guidance for the choice of overall survival curve. The median progression-free survival and overall survival of zanidatamab in HERIZON-BTC-01 was 7.2 and 18.1 months, respectively, compared with 4.2 and 6.2 months for FOLFOX in ABC-06, suggesting a much longer duration post-progression for zanidatamab. As discussed in Comment number 4, subsequent treatment has been shown to not significantly impact the overall survival of patients after zanidatamab (Appendix 2), as such the longer benefit of survival after zanidatamab in HERIZON-BTC-01 is not anticipated to be due to subsequent therapy. In addition, the committee's choice of the gamma curve for overall survival meant that overall survival and progression-free survival curves crossed at around 5 years so the committee concluded that *"the log-normal curve should be used to extrapolate zanidatamab progression-free*

Draft guidance comments form

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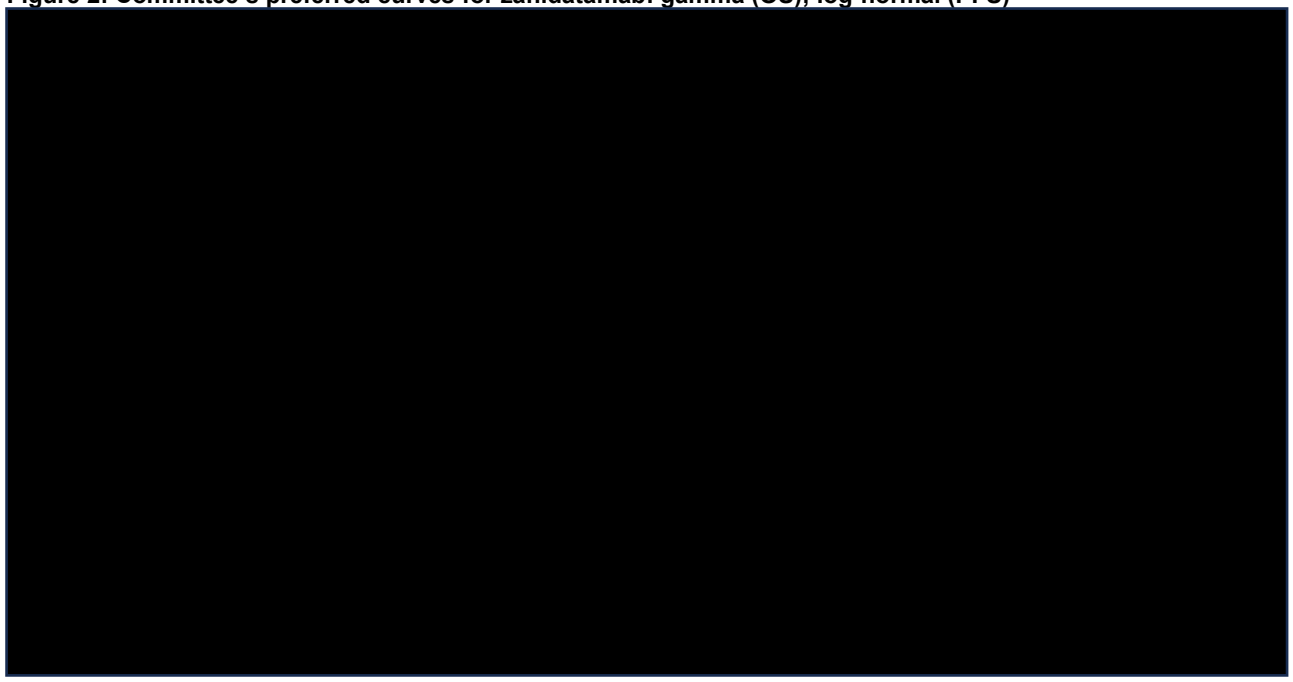
survival and the gamma curve should be used to extrapolate zanidatamab overall survival" as this *"largely avoided the crossing issue".* However, using the gamma overall survival curve and the log-normal progression-free survival curve still results in the curves crossing at around 5 years, which should not be feasible (Figure 2). Therefore, the gamma curve for zanidatamab overall survival lacks face validity and is not considered a plausible survival extrapolation.

Figure 2: Committee's preferred curves for zanidatamab: gamma (OS); log-normal (PFS)



Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Considering other targeted therapies in biliary tract cancer, the curve chosen by Jazz to inform overall survival for zanidatamab (log-logistic) is more aligned with other targeted 5 year survival estimates. In NICE TA722 (pemigatinib), the committee chose the log-logistic overall survival curve for decision making, which gave a 5 year overall survival of 11% for pemigatinib (14). In NICE TA948 (ivosidenib), the committee concluded that both the log-normal and generalised gamma curves were plausible which gave 5 year estimates of 5.6% and 3.6%,

Draft guidance comments form

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	respectively (10). In TA1005 (futibatinib), the EAG's preferred model of Weibull was considered too pessimistic estimating 5 year survival of 1.5% (15). In TA1005, the company's preferred log-normal model estimated 5 year survival of 11%, which was in line with pemigatinib in TA722, and the committee concluded that there was no clear difference in efficacy between futibatinib and pemigatinib. Although Jazz acknowledges that ivosidenib, pemigatinib, and futibatinib are for different molecular populations within biliary tract cancer, the log-logistic curve chosen by Jazz to inform overall survival for zanidatamab is more aligned with the other targeted 5 year survival estimates (7.4%) compared to the committee's preferred gamma curve (2.5%). Clinical experts have stated that they would expect the targeted treatments to behave similarly in the long-term; as such, Jazz considers the gamma curve to be too pessimistic. The log-logistic curve, as per Jazz's original base case, is in line with accepted prior survival estimates in biliary tract cancer for targeted therapies, fits closely with expert elicitation using a Delphi study of 11–14 UK experts, and has the second best statistical fit. Jazz believes that the new evidence provided at consultation reduces much of the uncertainty in the treatment effect highlighted by the committee due to subsequent treatments and prior PD-L1 use. When considered in the context of a very rare disease and prior targeted therapies, real-world evidence, and strong clinical expert experience, this evidence should reassure the committee of the plausible potential of the long-term survival benefit of zanidatamab, and that the gamma curve is too pessimistic.
7. Time on treatment	In Section 3.10 of the draft guidance, the committee concluded that *"the log-normal curve was appropriate to extrapolate zanidatamab time on treatment".* This is because the EAG considered the gamma curve to lack face validity due to exceeding *"progression-free survival in the model for a substantial amount of time before steeply decreasing".* Jazz would like to highlight that all the time-on-treatment curves exceed the chosen progression-free survival at some point, which is a consequence of the curve fittings due to the Kaplan-Meier curves overlapping in the first 18 months. As the draft guidance correctly states *"the time-on-treatment curves was capped to progression-free survival in the company's model, which avoided this implausible situation"*; therefore, Jazz considers this to not be a reason for one of the curves to lack face validity. The EAG chose the log-normal curve as a *"higher proportion of the progression-free cohort remained on treatment throughout the model"* and the committee agreed with this choice. In the EAG report (Section 4.2.6), the EAG explained that they preferred the log-normal curve to inform zanidatamab's time-on-treatment as it predicts [redacted], and [redacted] of the progression-free cohort are on treatment at 1, 2, and 5 years respectively. In comparison to the gamma curve (company base case), which predicts [redacted], and [redacted] at 1, 2, and 5 years respectively. Jazz acknowledges that the choice of gamma curve results in a small proportion of the progression-free cohort on treatment at 5 years; however, the proportion of patients who are progression-free by that time is very small ([redacted]) i.e. it is a small proportion of a small proportion. As such, Jazz do not see this as a valid argument against the gamma curve as it seems plausible that when such a small proportion are progression-free, most patients would be off treatment.

Draft guidance comments form

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	Furthermore, in the HERIZON-BTC-01 trial, all patients had stopped zanidatamab treatment by 3 years; therefore, there is no evidence to support patients still being on treatment at and beyond 5 years. Jazz therefore maintain that the gamma curve is the most appropriate curve to reflect zanidatamab's time-on-treatment as it is most consistent with the observed data. In Section 3.10 of the draft guidance, the committee note that *"that FOLFOX treatment often comes with substantial toxicity, which can lead to people stopping treatment before progression"* and therefore *"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."* Jazz acknowledges the substantial toxicity of FOLFOX and impact this can have on patients whilst receiving treatment. Therefore, in the revised base case, the time-on-treatment for FOLFOX uses the hazard ratio approach, which assumes some patients stop treatment before progression (Appendix 4).
8. Utility values (Suitability of the time-to-death modelling approach)	In Section 3.11 of the draft guidance, the committee "*recognised the merits of both approaches to calculating utility values*" but "*concluded that progression-based utility values were more appropriate in the model*". Jazz welcomes that the committee has recognised the merits of both approaches in the draft guidance. The following response provides further justification of why the time-to-death approach better reflects the quality of life over time experienced by patients with biliary tract cancer treated with second line therapies. This was evidenced at the committee by strong patient and clinical expert testimony, and by robust qualitative evidence in the AMMF survey consultation response, which has not been reasonably interpreted in the draft guidance when considering the utility approach. As evidenced in the AMMF survey, patients treated with zanidatamab experience a much-improved quality of life, which can allow them to return to normal activities, and even return to work: *"For me it has been life-altering and literally life-saving. I was out of options with current treatments and was given only a few months to live as my cancer was so aggressive. I have hardly any side effects compared to other treatments and feel better and better each day. My cancer is continuing to shrink in size... I am able to live a normal life and no longer feel completely defined by my cancer."* *"My mother has had 4 years of good quality life due to [zanidatamab]. She regained her independence... she has had some time to recover from her year on chemo... I was able to return to work and … able to maintain my job at 80% LTFT and look after my family."* *"My outlook on life has changed, as I can now see/hope for a long-term future. I don't worry so much about my wife becoming incidentally ill as this treatment is not so aggressive on the immune system compared to other treatments."* *"[Zanidatamab] gave me my life back. There are almost no side effects apart from mild gastric issues occasionally. I stay in excellent health and have done throughout my time on this treatment. I am back at work and feel strong mentally and physically. My quality of life is excellent: people would think there was nothing wrong with me..."*

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	"[Zanidatamab] changed everything for [my wife] and for our family. She was quickly independent again and everyone felt better. [My wife] is back to full strength and lives a normal life with a busy social life and family life: a thing we thought we had lost…She experiences little or no side effects." *"From our experience, [my partner] has less side effects than the Gem/Cis/Durva treatment. The infusion time is quicker … He has more energy, and our lives are far more 'normal' since he started the zanidatamab treatment. [He] has also been able to go back to work part-time."* *"I feel the advantage for this treatment is that there are a lot fewer side effects compared to chemotherapy alternatives... It has also improved my quality of life, reducing my tumour size significantly and improving my pain (I have reduced my pain medication significantly since starting zanidatamab)."* Also, Jazz wishes to highlight that although the time-to-death approach has not been used in previous biliary tract cancer appraisals, it is a well-recognised approach that has been previously accepted by committees when assessing therapies that have a substantial survival benefit in HER2-positive cancer, such as TA983 (pembrolizumab + trastuzumab) (20) and TA997 (pembrolizumab + chemotherapy) (21). In Section 3.11 of the draft guidance, the committee noted that *"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"* Patients in the comparator arms will incur lower utility values earlier in the model time horizon compared with patients treated with zanidatamab as they have much reduced survival. However, patients in the zanidatamab arm also incur the lower utility values at some point in the model time horizon, as it captures the patient's lifetime. The time-to-death utilities are applied **regardless of health-state,** as the time-to-death approach only considers survival and not progression status. To suggest in the draft guidance that more patients incur the lower utility values within the progression-free state is methodologically incorrect and is only reflective of the fact that patients in the comparator arms are closer to death despite being progression-free due to the poorer survival outcomes. Due to the nature of a partitioned survival model approach, it is not possible to determine a patient's time-to-death status by progression health state. To reassure the committee and to demonstrate the difference of utilities applied between treatment arms, Figure 3 and Figure 4 show the proportion of patients in each of the time-to-death categories using the grouping approach splitting time by <84 days, 84-196 days, and >196 days to death for zanidatamab and FOLFOX respectively. These show that a similar proportion of patients are receiving the lower utilities (at <84 days); however, given the poorer survival outcomes for the FOLFOX arms, these are applied earlier in the model time horizon compared to zanidatamab. A similar result will be happening using the continuous time-to-death model used in the company's base case, though this is more difficult to demonstrate in a plot.

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

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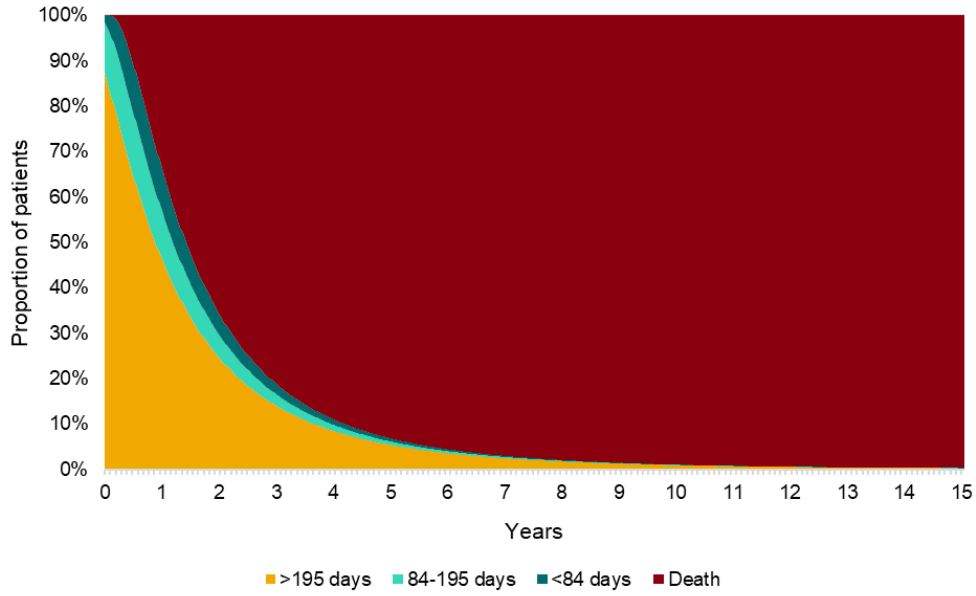
***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Figure 3: Zanidatamab time-to-death groupings over time



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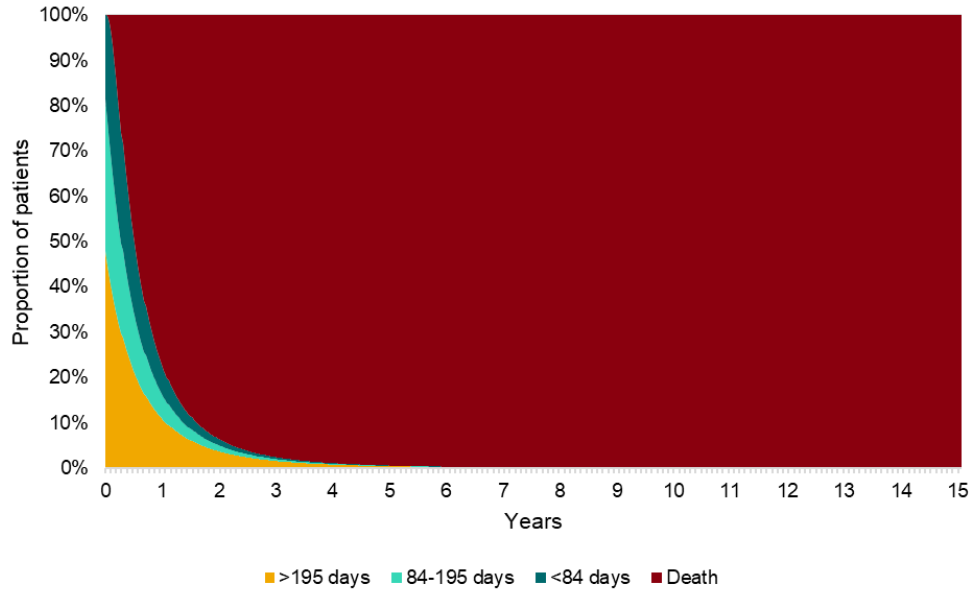
***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Figure 4: FOLFOX time-to-death groupings over time



In Section 3.11, the committee noted that "*the small number of high-utility observations close to death created significant uncertainty and reduced face validity of the time-to-death approach*".

High utility observations close to death (or within health states) is a common trait of trial utility analyses and those high observations would remain whether a time-to-death or progression-based approach is used. High observed utility values close to the time of death is not unusual and this can be seen in the publication by Hatswell (2023) (22). This study fitted time-to-death continuous models to non-small cell lung cancer utility data from two clinical studies. The data had minimum follow-up of 64.2 and 64.5 months in the two trials and included 4,850 EQ-5D-3L responses from 788 patients, which is substantial in the context of a very rare disease. Over the study period, 718 patients had died.

Figure 5 (from Hatswell [2023] (22)), shows the utility observations by time-to-death and demonstrates a large number of observations at the higher end despite being close to death. Given that this data set includes a large number of observations and is relatively mature (91% deaths), it can be concluded that high observations close to death is not uncommon and does not reduce the face validity of the data set.

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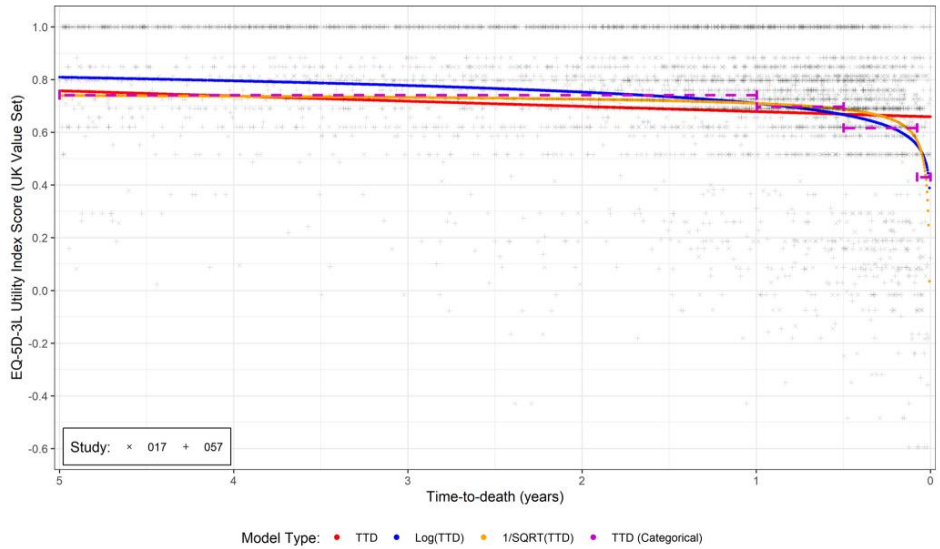
***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Figure 5: EQ-5D-3L utility (UK value set) versus time to death in the pooled CheckMate-017 and CheckMate-057 studies, including preferred model fits



Abbreviations: SQRT, square root TTD, time to death.
Source: Hatswell (2023) (22).

Figure 6 presents the continuous model used in the company's base case versus individual utility observations. In this figure, the continuous time-to-death model does not estimate high utilities close to death but instead shows a sharp decrease in utility from 6 months. This model accurately represents a patient's experience, as confirmed by clinical and patient experts, and the AMMF survey. In the appraisal committee meeting, the clinical experts noted that patients tend to have a fairly stable quality of life (outside of treatment side effects), which then rapidly decreases in the days approaching death.

Therefore, Jazz maintains that the time-to-death continuous model approach best reflects the quality of life of patients with biliary tract cancer and consider the variation in the individual observations not to be of concern. In addition, uncertainty around the continuous model is already

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***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	captured within the cost-effectiveness analyses in probabilistic sensitivity analyses. Jazz hopes that the additional analyses reassure the committee as to the validity of Jazz's preferred approach to the utilities. **Figure 6: HERIZON-BTC-01 utility observations versus time-to-death** 
9. Utility values (disutilities)	In Section 3.11 of the draft guidance, the committee acknowledged several disutilities had been applied in the company's model. The committee also noted the EAG's concerns regarding double counting and disutilities associated with Grade 1 or 2 adverse events. Jazz welcomes the careful consideration of utility data in this appraisal. We also note that the committee acknowledged it was *"plausible that people would have better quality of life when on zanidatamab"* and also acknowledged that *"people who have zanidatamab are typically healthier after progression".*

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	As utility data were only available for zanidatamab from the HERIZON-BTC-01 study, Jazz would like to confirm that the additional disutilities applied were intended to capture important differences in quality of life experienced between patients treated with zanidatamab and patients treated with FOLFOX or active symptom control. The committee acknowledged that it was *"plausible that people would have better quality of life when on zanidatamab"* and also acknowledged that *"people who have zanidatamab are typically healthier after progression".* This is strongly supported by evidence from the AMMF survey responses (quoted above in Comment number 8) and clinical and patient expert testimony at the committee meeting. As such, the disutilities capture relevant differences in quality of life due to: • Specific Grade 3 adverse events (this also accounted for zanidatamab adverse events) • Administration of a PICC line versus a portacath • Treatment-specific disutility to capture other quality of life differences not captured in the above, including, but not limited to: o Administration of portacath versus intravenous administration o Increased frequency of lower grade adverse events o Aftermath of multiple toxicities and lack of effective further treatment options Jazz maintains that only accounting for Grade 3 adverse events and administration via PICC line does not fully capture the quality of life differences between zanidatamab and FOLFOX, as stressed by patient and clinical representatives in committee as well as evidenced in the AMMF survey responses (3, 6). In Section 3.3, the draft guidance states that "*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."* This testimony strongly justifies inclusion of a treatment specific- disutility for FOLFOX in the company base case and contradicts the exclusion by the EAG. However, to alleviate the committees concerns regarding double counting and to reduce any remaining uncertainty, Jazz have revised the company base case to exclude the separate Grade 3 adverse event disutilities and administration disutilities, leaving only the treatment-specific disutility. In the revised base case, it is conservatively assumed that the treatment-specific disutility captures all quality of life differences associated with the different treatment arms (see Appendix 4 for revised base case results). In addition, Jazz have explored the scenarios as requested by the committee, which are presented in Appendix 5. Results of the additional utility scenario analyses show that whichever approach is taken to utilities (see Figure 12 and Figure 13 in Appendix 5), the effect on the incremental cost effectiveness ratio is relatively small. The committee requested the following to explore: *1) "treatment-specific utility values that are fully justified including:* *a. providing adverse event decrements separately to explore face validity of these treatment-specific values*

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***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	b. simplifying the utilities and disutilities to avoid double-counting *c. excluding disutility for grade 1 or 2 adverse events* *2) non-treatment-specific utility values with simplified disutilities to avoid double-counting and excluding disutility for grade 1 or 2 adverse events* 3) *a comparison with utilities used in previous NICE evaluations in this disease area."* Jazz would like to highlight that patient-level data from ABC-06 to inform treatment-specific utility values are not available. Jazz have previously tried to obtain additional data from the ABC-06 study but did not receive any response from the authors. In addition, Jazz are not aware of any health-state utility estimates for FOLFOX and active symptom control in biliary tract cancer that are publicly available. However, Jazz have informed NICE of this during consultation and our suggested approach (described below) was confirmed as acceptable within the timeline. 1. To estimate treatment-specific utility values, the utilities reported in the ABC-06 study publication at baseline and 4 months have been used to calculate progression-free and progressed health state utilities for FOLFOX and active symptom control. This approach assumes that the published baseline utility value represents the progression-free utility value. Using the proportion of patients who are progression-free/alive at 4 months for each treatment, the published 4 month value is used to back-calculate a progressed utility for each treatment arm. Further details of how these have been calculated are presented in Appendix 3. The resulting health-state utility values based on ABC-06 are estimated to be: • FOLFOX: 0.77 progression-free; 0.41 progressed • Active symptom control: 0.75 progression-free; 0.47 progressed Although the utility values show a large decrement between health states, estimates for FOLFOX and active symptom control are appropriate based on the feedback received from patient and clinical representatives. The committee recognised the impact of FOLFOX on quality of life based on the patient testimonies presented during the appraisal meeting. The AMMF online survey reported some of the impacts highlighted by patients regarding their experience with FOLFOX (3, 6): *"The treatments caused side effects and made it impossible for me to function properly and certainly I couldn't go back to work… It felt like being poisoned."*

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	"…my mum felt really well when she started…Chemotherapy was difficult for her, she had minimal quality of life due to side effects …My mum has said repeatedly she could never go through chemotherapy again – it's no life." After progression on FOLFOX, there are very limited treatment options other than systemic chemotherapy, and only if the patient is well enough to tolerate subsequent treatment as such the survival at this point is extremely poor (estimated mean survival of 2.7 months post progression). Therefore, quality of life is expected to decline upon progression with FOLFOX. In the treatment-specific scenario, utilities for zanidatamab are based on the progression-based utilities from HERIZON-BTC-01 (see Company submission, Section 3.4). This scenario does not apply any additional disutilities and assumes that the differences between the health-state utility values between zanidatamab and FOLFOX and active symptom control are inherently captured within the values. 2. Jazz have presented a scenario applying the same health-state utility values (based on HERIZON-BTC-01) and including only the treatment-specific disutility to avoid any concern regarding double counting. As noted previously, only including disutilities for Grade 3 adverse events and administration via PICC line does not fully capture the quality of life differences between zanidatamab and FOLFOX. 3. The utility values used in prior biliary tract cancer appraisals in second line (pemigatinib [TA722]; ivosidenib [TA948]; futibatinib [TA1005]) are redacted and therefore not available to compare to those used for zanidatamab. The health-related quality of life systematic literature review identified a total of 26 studies, the majority of which were obtained from economic evaluations. Among the studies reporting health-state utility values for advanced biliary tract cancer, not all studies used the NICE reference case utility method and non-directly reported utility estimates for FOLFOX and active symptom control or active symptom control alone. A summary of the papers identified in the systematic literature review is presented in Appendix 7. The most relevant studies identified using the correct reference case were McCarthey (2024) reporting health-state EQ-5D utilities from the KEYNOTE-158 study (pembrolizumab) and SMC (2023) for first line durvalumab from the TOPAZ-1 study. These studies were already identified by the company and EAG and were explored in scenario analyses (see EAG report Section 4.2.7) though do not represent appropriate values for FOLFOX and active symptom control. Results are presented in Figure 14 and Figure 15 in Appendix 5, and show that the effect on the incremental cost effectiveness ratio is relatively small regardless of approach. These comprehensive results should reassure the committee of the impact improved quality of life with zanidatamab has on the cost-effectiveness estimates. When taken together with the relevant evidence from patients and carers, these additional analyses should minimise the uncertainty on the interpretation of the utility analysis, especially in the context of a very rare cancer with a high unmet need.

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

10. Relative dose intensity	In Section 3.12 of the draft guidance, *"the committee concluded that the model should include a relative dose intensity of 78% for FOLFOX."* Jazz wishes to highlight that there is no precedent for applying relative dose intensity to FOLFOX in prior biliary tract cancer appraisals (TA722 (14) and TA948 (10)). However, based on the publication sourced by the EAG, the preferred relative dose intensity has been included in the revised company base case (Appendix 4). Jazz have updated the base case to reflect the treatment patterns of FOLFOX due to its substantial toxicity profile, as confirmed by the patient and clinical experts in the committee meeting.
11. Frequency of cardiac monitoring	Jazz are pleased to provide the revised company base case in Appendix 4 reflecting the use of electrocardiogram monitoring rather than echocardiography for FOLFOX, to align with NHS practice. The cost of electrocardiogram used in the updated base case has been sourced from the National Cost Collection 23/24. The cost of £118 (EY51Z - Electrocardiogram Monitoring or Stress Testing - Total HRGs) has been included in the economic model. This cost is aligned with the electrocardiogram cost used in TA948 (ivosidenib) (10) to inform regular electrocardiogram monitoring.
12. Minor issues	As requested, Jazz have incorporated adjustments (IHC3-positive population for adverse events and utility values and exclusion of end-of-life morphine cost) recommended by the EAG and committee into the economic model. Appendix 4 presents the updated company base case incorporating these changes.
13. Severity	Jazz agrees with the conclusions of the EAG report that a severity weight of 1.7 should be applied to all analyses in this appraisal. The revised company base case and new scenario analysis provided at consultation should reassure the committee that in all analyses, the absolute and proportional shortfalls resulted in a severity modifier of 1.7. Jazz also wish to highlight that using a severity modifier of 1.7 would be in line with previous appraisals of targeted therapies of second line biliary tract cancer, including TA948 (ivosidenib) (10).
14. Other factors (Equality)	Section 3.16 included "*some evidence that there are socioeconomic differences in the mortality rates for biliary tract cancer".* Jazz welcomes that the evidence reporting existing health inequalities for those living with biliary tract cancer in the UK has been included in the draft guidance. However, Jazz wish to highlight that the published evidence from the AMMF reports socioeconomic differences in incidence and treatment for biliary tract cancer, as well as mortality (23, 24). Increased access to innovative targeted therapies, including zanidatamab, are likely to reduce health inequalities in UK populations living with biliary tract cancer. To aid committee decision-making and allow consideration of a potential reduction in health inequalities due to adoption of

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***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	zanidatamab, Jazz has performed a simple distributional cost-effectiveness analysis using the University of York's health inequality calculator (25) with assumptions in line with the 2025 NICE support document (see Appendix 6). This is a simplified analysis performed in the time available for consultation using NICE's preferred approach, including: stratification by Index of Multiple Deprivation, equal uptake across groups, no health inequality aversion weight and an equal distribution of health opportunity cost. Even in a small population such as second line HER2-positive biliary tract cancer, results of the equity impact report show zanidatamab compared with FOLFOX has a net health inequality benefit of [redacted] quality-adjusted life years (Appendix 6). When interpreted reasonably in the context of a very rare cancer, this supportive analysis using robust socioeconomic evidence from the AMMF should reassure the committee that innovative treatments such as zanidatamab have the plausible potential to reduce health inequalities in biliary tract cancer, which would be welcomed by a patient community with such a high unmet need. Jazz believes that, in line with the NICE methods guide (section 6.2.38), when considering the relevance of health inequality impacts on the value of the technology, this analysis should allow some flexibility to the range normally considered a cost-effective use of NHS resources.
15. Other factors (Innovation)	Jazz welcome the committee's acknowledgement of zanidatamab as a *"step-change"* in treatment and how highly patients would value zanidatamab. There are no HER2-directed therapies available on the NHS for patients with HER2-positive biliary tract cancer and current second line therapy with FOLFOX is associated with considerable toxicity and only a modest survival benefit (1). The high unmet need in biliary tract cancer and innovation of zanidatamab is also reflected in the [redacted]. Considering the innovation of zanidatamab in this patient population, and in line with the NICE methods guide (section 6.2.33), the committee may be able to make recommendations accepting a higher degree of uncertainty for innovative technologies, and Jazz believe this should be considered in this appraisal.
16. Uncaptured benefits (carer quality of life)	In Section 3.17 of the draft guidance, the committee noted that: *"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"*. Jazz welcome the recognition by the committee of the substantial impact of advanced biliary tract cancer on carers in the draft guidance. Jazz agree that the impact on carers of patients with biliary tract cancer is important and highly relevant to capture in the modelling, particularly given the testimony from the patient experts in the committee meeting and to take account for the strong evidence presented in the AMMF survey that reported the substantial impact of caring for, and caring about, a person with biliary tract cancer incurs on carers, and other family members (3, 6): *"For the first year of her diagnosis I was 'on-call' 24 hours a day to help with day-to-day activities when she felt well, to take her to her appointments when she couldn't walk"*

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	"We moved house shortly after her diagnosis so I could accommodate my mother (and my 90 y/o grandmother) for end-of-life care" In the same survey, carers of people who had been treated with zanidatamab highlighted an extremely positive impact to their quality of life (3, 6): *"My outlook on life has changed, as I can now see/hope for a long-term future. I don't worry so much about my wife becoming incidentally ill as this treatment is not so aggressive on the immune system compared to other treatments"* *"We have been on family trips together and there are many days where we can forget about the cancer. Being able to spend valuable time making memories together like this is the best advantage of this treatment. There were times when we thought [my partner] would never meet [our son], so to be able to have this time together is invaluable".* To aid committee decision-making and to more accurately quantify the positive impact of zanidatamab treatment on carers' quality of life as well as patients, Jazz have used up-to-date methodology to include caregiver utilities in the company base case and provided additional scenarios to fully explore the impact on the cost-effectiveness results. In the revised base case, the 'multiplier approach' cited by Pennington (2026) has been included, which estimates carer quality-adjusted life year gains as a proportion of patient quality-adjusted life year gains using a ratio (26). To estimate the utility benefits of zanidatamab for caregivers in biliary tract cancer, a multiplier of 16% has been assumed, in line with published methods (27). Scenarios are also explored using the Swedish TLV proposed "standard rate" of a carer utility multiplier of 50% (28, 29), and a scenario without carer utilities applied. Appendix 4 presents the revised company base case including caregiver utilities and scenarios are presented in Appendix 5
17. Uncaptured benefits (socioeconomic)	Jazz understands that the remit of NICE and the scope of the appraisal is the NHS and PSS perspective. However, the draft guidance does not reflect the strong patient evidence provided by the AMMF in their submission and the experiences of patients heard at the committee meeting on the uncaptured benefits of zanidatamab treatment on both patient and carer's ability to work and participate in family and social life. In the AMMF survey, 3 in 4 patients (72.4%) and 2 in 3 caregivers (64.7%) reported that biliary tract cancer had a negative impact on productivity at work, with more than half of patients (57.8%) permanently or temporarily stopping work (3). Patients and caregivers reported (3, 6): *"Before my diagnosis, I missed a lot of work and my productivity at work was affected since I was feeling ill. I had to take lots of time off for months to attend appointments to get a diagnosis. After my diagnosis I went on sick leave to focus on my health and treatment"* [Patient]

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	"I had to be signed off work to care for my husband when he was discharged from hospital as I also had two young children to care for. After my husband passed, I had a further six months off work coming to terms with the shock of his diagnosis and loss within a three-week period when he'd otherwise been a relatively fit and healthy 48 year-old father of two." [Caregiver] *"I have needed time off work as after 12 months of supporting a cholangiocarcinoma patient on chemotherapy - I was struggling with work and went down to 60% on returning"* [Caregiver] Patients with biliary tract cancer and their caregivers reported a positive impact in this aspect, when treated with zanidatamab (3, 6): *"I am back at work and feel strong mentally and physically. My quality of life is excellent: people would think there was nothing wrong with me. I have travelled, spent time with my family happily and I am no longer the sick person anyone has to look after. I feel lucky and grateful, optimistic and confident. Had someone told me I would be feeling like this in August 2023 when I was diagnosed, I would have thought that it would be a dream. I am living my dream, without exaggeration."* [Patient] *"I was able to return to work and help them as needed. I'm not being called so frequently… Had my mother not been on [zanidatamab], my grandma would likely have needed 24hr or residential care (likely state funded), and I may have lost or left my job to look [after] my mother."* [Caregiver] Jazz understands that this cannot be taken into account in the modelling quantitatively and as such has not been included, but as a patient-relevant uncaptured benefit and, in light of the strong evidence presented, it is important that this is acknowledged in the final guidance and considered qualitatively as an uncaptured benefit in committee decision-making.
18. Issues of factual inaccuracy	Section 3.1: clarification to be added for factual accuracy (see bold text)- "The committee noted that **for those patients with ampullary cancer,** only ampullary cancer arising from the ampulla of Vater was within the scope of this evaluation."

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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Zanidatamab for treating HER2-positive advanced biliary tract cancer after 1 or more systemic treatments [ID6388]

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***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

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

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

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Appendix 1: Landmark survival analysis

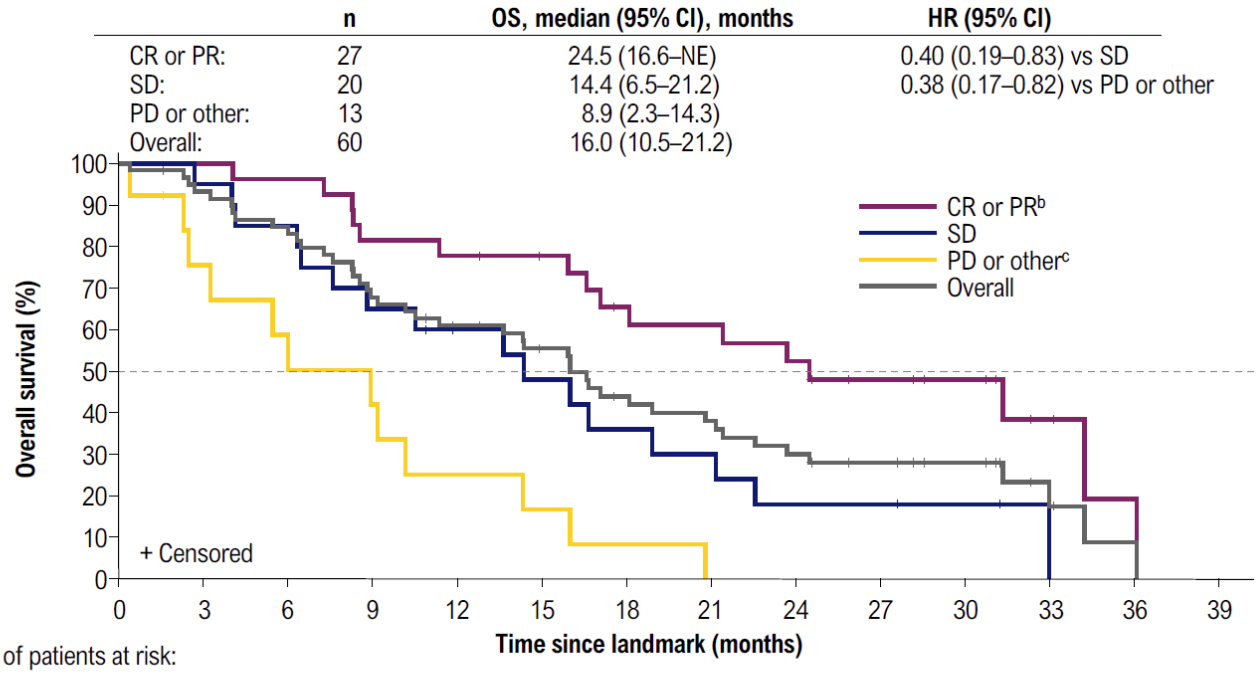
Methods

A post-hoc analysis of HERIZON-BTC-01 including patients with IHC3-positive biliary tract cancer was conducted. Landmark survival models were employed at Week 9 (initial response evaluation) and Week 25 (time point by which all responses occurred). Responders had ≥1 assessment of complete or partial response by the landmark. These results have been reported by Harding (2026) (7).

Results

By the Week 9 landmark, there were 27 responders (3 complete response, 24 partial response) and 20 patients had stable disease, 12 had progressive disease, and 1 did not have an assessment. Post-landmark median overall survival was longer for responders (24.5 month; 95% confidence interval: 16.6, not estimable) and patients with stable disease (14.4 months; 95% confidence interval: 6.5, 21.2) vs all others (8.9 months; 95% confidence interval: 2.3, 14.3) (Figure 7). Hazard ratio was 0.40 (95% confidence interval: 0.19, 0.83) for responders vs. patients with stable disease and 0.38 (95% confidence interval: 0.17, 0.82) for patients with stable disease vs all others (Figure 7).

Figure 7: Overall survival[a] from Week 9 of treatment in responders (complete or partial response)[b], patients with stable disease, or patients with progressed disease/other[c]



Number of patients at risk:														
CR or PR:	27	27	26	22	21	19	15	14	12	9	7	3	1	0
SD:	20	19	17	13	10	8	6	5	3	3	2	0	0	0
PD or other:	13	9	7	5	3	2	1	0	0	0	0	0	0	0
Overall:	60	55	50	40	34	29	22	19	15	12	9	3	1	0

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; OS, overall survival; PD, progressed disease; PR, partial response; SD, stable disease.

[a] Overall survival was estimated using Kaplan-Meier methodology, with confidence intervals based on the Brookmeyer and Crowley method with log-log transformation.

[b] Included patients with confirmed or unconfirmed complete or partial response on or prior to the Week 9 landmark.

[c] Other included 1 patient without a tumour assessment prior to Week 9 who went on to achieve a partial response.

Source: Harding (2026) (7).

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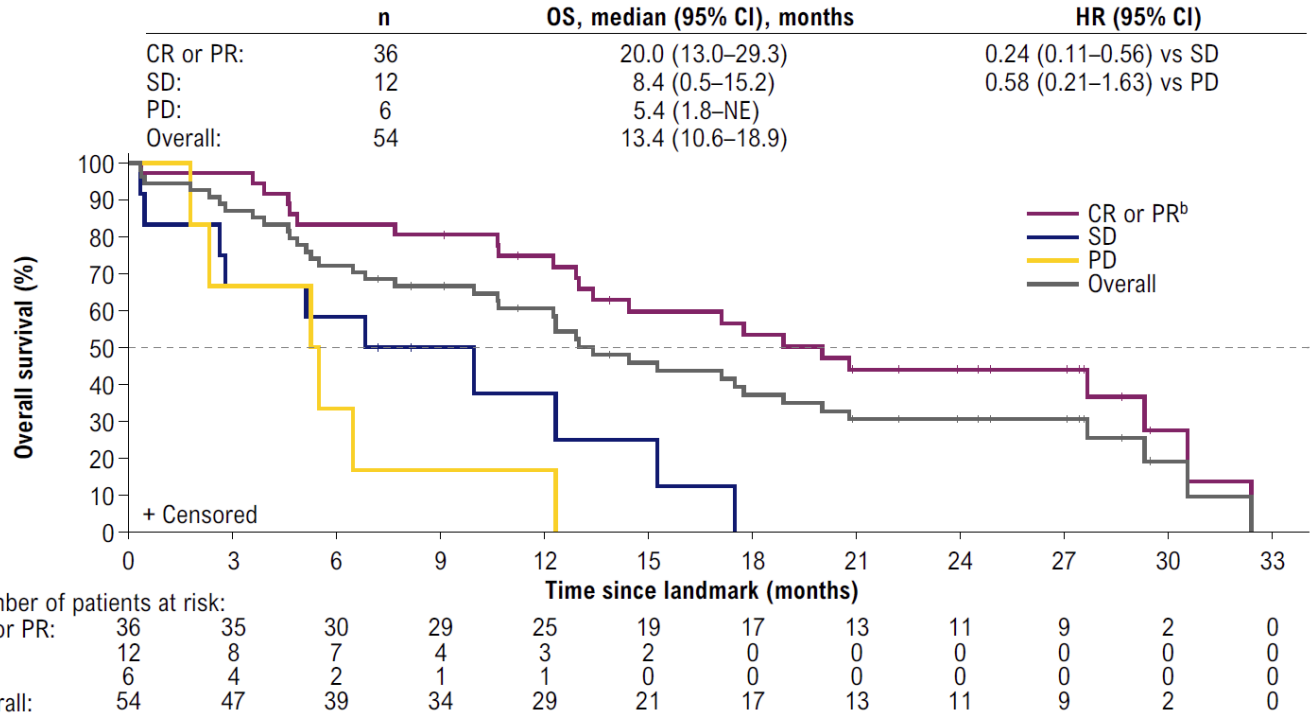
***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Seven (35%) of the 20 patients with stable disease by Week 9 achieved partial response by Week 25. There were 36 responders (3 complete response, 33 partial response), 12 patients with stable disease, and 6 patients with progressed disease by Week 25 (Figure 8). Considering the additional 4 months to landmark, post-landmark median overall survival was consistent with the Week 9 landmark (responders, 20.0 months [95% confidence interval: 13.0, 29.3]; stable disease, 8.4 months [95% confidential interval: 0.5, 15.2]; progressed disease, 5.4 months [95% confidence interval:1.8, not estimable]) (Figure 7 and Figure 8).

Figure 8: Overall survival[a] from Week 25 of treatment in responders (complete or partial response)[b], patients with stable disease, or patients with progressed disease



Number of patients at risk:

CR or PR:	36	35	30	29	25	19	17	13	11	9	2	0
SD:	12	8	7	4	3	2	0	0	0	0	0	0
PD:	6	4	2	1	1	0	0	0	0	0	0	0
Overall:	54	47	39	34	29	21	17	13	11	9	2	0

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; OS, overall survival; PD, progressed disease; PR, partial response; SD, stable disease.
[a] Overall survival was estimated using Kaplan-Meier methodology, with confidence intervals based on the Brookmeyer and Crowley method with log-log transformation.
[b] Included patients with confirmed or unconfirmed complete or partial response on or prior to the Week 25 landmark.
Source: Harding (2026) (7).

In HERIZON-BTC-01, patients who responded to zanidatamab by Week 9 or Week 25 demonstrated prolonged survival compared with all other patients (70% and 79% reduction in the risk of death, respectively). Patients who achieved stable disease by Week 9 or Week 25 had a 62% and 42% reduction in the risk of death, respectively, vs. patients with progressed disease or no evaluation. Patients with stable disease prior to Week 9 demonstrated an encouraging median overall survival of 14.4 months, and 35% achieved a response by Week 25.

Conclusions

In HERIZON-BTC-01, responders to zanidatamab by Week 9 or 25 and patients with stable disease by Week 9 demonstrated improved survival compared with all others (progressed disease and not assessed). These results support a prognostic association between objective response or stable disease with zanidatamab and longer overall survival in biliary tract cancer.

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

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Appendix 2: Subsequent treatment subgroup analysis

Patients and methods

Among the IHC3+ population of HERIZON-BTC-01, 29 were identified as initiating subsequent therapy during overall survival follow-up.

Patients were classified according to their first subsequent treatment type after zanidatamab, either "chemotherapy" or "non-chemotherapy". A 7 day window was used to capture one-off[1] or combination treatments. If both chemotherapy and non-chemotherapy treatments were used within the 7 day window, the subject was preferentially assigned to the chemotherapy group. Table 1 presents the list of next subsequent treatment use and classification for the analysis.

Table 1: First subsequent therapy use after zanidatamab (HERIZON-BTC-01; IHC3+)

	n	N=62 (%)	Treatment group
Patients who received no subsequent treatment	33	53.2	-
Patients who received at least one subsequent treatment	29	46.7	-
First subsequent therapy			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

	n	N=62 (%)	Treatment group
[redacted]	[redacted]	[redacted]	[redacted]

Results

Figure 9 presents the overall survival from the point of receiving subsequent treatment split by treatment group from HERIZON-BTC-01 (IHC3-positive cohort). Of the patients who received subsequent treatment (n=29), 17 (58.6%) received chemotherapy as their next subsequent treatment.

Subjects receiving any subsequent treatment after zanidatamab (n=29), experienced a median overall survival of [redacted] months (95% confidence interval: [redacted]) after starting subsequent treatment. Subjects initiating a chemotherapy regimen first (n=17) experienced a median overall survival of [redacted] months (95% confidence interval: [redacted]) while those initiating a non-chemotherapy regimen first (n=12) experienced a median overall survival of [redacted] months (95% confidence interval: [redacted]). The median values are not too dissimilar, moreover the confidence intervals overlap and the difference between treatment groups was not statistically significant (log-rank test, p=0.11). The unadjusted Cox hazard ratio showed a non-statistically significant difference for chemotherapy vs. non-chemotherapy of [redacted] (95% confidence interval: [redacted]).

Figure 9: Overall survival from point of receiving next subsequent treatment

Abbreviations: CI, confidence interval; NPT, non-protocol treatment.

The analyses demonstrates that there is no evidence to show that patients who received subsequent treatment, and the type of subsequent treatment, impacts the overall survival after treatment with zanidatamab and there was no significant difference between treatment groups.

However, it must be noted that these analyses have limitations. The patient numbers are relatively small resulting in large steps in the Kaplan-Meier when an event occurs. It is also difficult to fully interpret the Cox hazard ratio due to the wide confidence intervals (likely due to the small sample sizes). In addition, there is likely to be bias in the analyses as there is no controlling for confounders. For example, patients who receive subsequent treatments may be more or less ill than those who did not receive subsequent treatment and there may be specific confounders

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

which would determine whether a patient received subsequent treatment, and what kind of subsequent treatment, which may also be prognostic of death.

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Appendix 3: Calculation of treatment-specific utility values from ABC-06

As requested and discussed with NICE, treatment-specific utilities were calculated using the utility data published from the ABC-06 study (30), from 138 UK patients treated with FOLFOX and active symptom control, or active symptom control alone.

Patients treated with FOLFOX and active symptom control (n=73) were estimated to have a baseline utility of 0.77 and a 4 month utility of 0.70 (where 56.7% of patients remain progression-free and 70.4% patients remain alive). Of those who were alive at 4 months, it was calculated that 80.6% were progression-free and 19.4% were progressed. Given that it can be inferred that the reported overall 4 month utility is a calculation of: *% progression-free x progression-free utility + % progressed x progressed utility* the progressed utility value can be back-calculated assuming that the reported baseline utility represents the progression-free health-state utility. The utilities for active symptom control were calculated in the same way. As the proportion of patients treated with active symptom control who were progression-free at 4 months from the ABC-06 study is not known, the proportion was estimated from the modelled efficacy of active symptom control. Table 2 presents the calculations and sources to estimate the treatment-specific health-state utility values for FOLFOX and active symptom control and active symptom control alone. Please note that these utilities were not included in base case, but as a scenario.

Table 2: FOLFOX and active symptom control and active symptom control alone treatment-specific utility calculations

Calculation step	FOLFOX and active symptom control	Active symptom control	Source
(a) Baseline utility	0.77	0.75	ABC-06 (30)
(b) 4 month utility	0.70	0.62	ABC-06 (30)
(c) Proportion progression-free at 4 months	56.7%	35.0%	ABC-06 (1) Calculation from modelled PFS
(d) Proportion alive at 4 months	70.4%	64.8%	ABC-06 (1)
(e) Proportion progressed at 4 months	13.7%	29.7%	Calculation (d-c)
(f) Proportion progression-free and alive at 4 months	80.6%	54.1%	Calculation (c/d)
(g) Proportion progressed and alive at 4 months	19.4%	45.9%	Calculation (f/e)
Progression-free utility	**0.77**	**0.75**	**Assumed same as baseline**
Progressed utility	**0.41**	**0.47**	**Calculation (b- a*f)/g**

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Appendix 4: Revised company base case

Deterministic results

Jazz are pleased to present their revised base case taking into consideration the feedback during the committee meeting, comments within the draft guidance, and committee's preferences. Details of the changes and justifications are provided throughout the consultation document. [redacted]

In summary the revised base case includes the following:

- [redacted]
- 3.5% discounting for costs and quality-adjusted life years
- Applying correction to application of administration disutility
- Extrapolating zanidatamab overall survival using the log-logistic curve
- Extrapolating zanidatamab progression-free survival using the log-logistic curve
- Extrapolating zanidatamab time-on-treatment using the gamma curve
- Using time-to-death utilities with continuous model
- Including treatment specific disutility
- Excluding adverse event disutilities
- Excluding disutility for administration of PICC vs portacath
- Applying a hazard ratio to FOLFOX progression-free survival to estimate time-on-treatment
- Applying 78% relative dose intensity to FOLFOX
- Using total HRG costs for electrocardiogram to inform FOLFOX treatment monitoring
- Using the HERIZON-BTC-01 IHC3-positive population as the source for adverse event rates and utility values
- Excluding the company's end-of-life morphine cost
- Including carer utilities with a 16% multiplier

Revised base case results with patient access scheme demonstrate that treatment with zanidatamab is more costly, but more effective than chemotherapy or active symptom control, associated with deterministic incremental cost-effective ratio of [redacted] versus FOLFOX + active symptom control and [redacted] versus active symptom control alone (Table 3). The revised results still meet the criteria for the severity modifier, resulting in a quality adjusted life year weighting of x1.7, which is reflected in the results.

Zanidatamab is associated with respective life year and quality adjusted life year gains (including the severity modifier and carer utilities) of [redacted] and [redacted] compared to FOLFOX and active symptom control, increasing to life year and quality adjusted life year gains of [redacted] and [redacted] when compared to active symptom control alone, demonstrating the substantial improvement in survival and quality of life with zanidatamab treatment.

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

Draft guidance comments form

***Consultation on the draft guidance document – deadline for comments: 5pm** on **Tuesday 3 February 2026**. Please submit via NICE Docs.*

Table 3: Revised base-case results (with patient access scheme)

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7 severity modifier and carer multiplier)	ICER versus zanidatamab, £/QALY
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICER, incremental cost-effectiveness ratio; LYG, life year gain.

Probabilistic results

Mean results from the probabilistic sensitivity analysis including patient access scheme are presented in Table 4 and the cost-effectiveness planes versus FOLFOX and active symptom control are presented in Figure 10 and Figure 11 respectively. The probabilistic results are consistent with those observed in the revised deterministic analysis.

Table 4: Mean PSA results (including patient access scheme)

Technologies	Total			Incremental			ICER, £/QALY
	Costs, £	LYG	QALYs	Costs, £	LYG	QALYs (x1.7 severity modifier and carer multiplier)	
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICER, incremental cost-effectiveness ratio; LYG, life year gain; PSA, probabilistic sensitivity analysis.

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

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Figure 10: Pairwise cost-effectiveness plane (including patient access scheme) - zanidatamab versus FOLFOX and active symptom control

Abbreviations: FOLFOX, folinic acid, fluorouracil and oxaliplatin; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

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Figure 11: Pairwise cost-effectiveness plane (including patient access scheme) - zanidatamab versus active symptom control

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

The cost-effectiveness acceptability curves are presented in Figure 12 for zanidatamab versus FOLFOX and Figure 13 versus active symptom control. At a willingness-to-pay threshold of £30,000, the probability that zanidatamab is cost-effective compared to FOLFOX and active symptom control is [redacted]% and [redacted]% compared to active symptom control alone.

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

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Figure 12: Cost-effectiveness acceptability curve (including patient access scheme) – zanidatamab versus FOLFOX and active symptom control

Abbreviations: FOLFOX, folinic acid, fluorouracil and oxaliplatin; WTP, willingness-to-pay.

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

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Figure 13: Cost-effectiveness acceptability curve (including patient access scheme) – zanidatamab versus active symptom control

Abbreviations: ASC, active symptom control; PAS, patient access scheme; WTP, willingness-to-pay.

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

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Appendix 5: Scenario analysis

Jazz have explored scenarios around the revised base case inline with the committee's requests regarding exploring alternative utility analyses. These include:

- Treatment specific progression-based utilities
- Non-treatment specific utilities with simple disutility
- Carer utility multiplier based on TLV (50%)
- Not applying carer utilities

Results of the scenario analyses are presented in Table 5 for both comparators and tornado plots presented in Figure 14 and Figure 15. Results of the additional scenario analyses show that whichever approach is taken to utilities, the effect on the incremental cost effectiveness ratio is relatively small. All results meet the 1.7 severity modifier

Table 5: Scenario analysis results (including patient access scheme)

Topic	Base case	Scenario	ICER (zanidatamab versus comparator), £	
			FOLFOX	ASC
Base case			[redacted]	[redacted]
Progression-based utilities	TTD continuous Treatment specific disutility	Progression-based treatment specific utilities: Zanidatamab: HERIZON-BTC-01 FOLFOX+ASC/ASC: ABC-06 No disutilities applied	[redacted]	[redacted]
		Progression-based non-treatment specific utilities: HERIZON-BTC-01 Treatment specific disutility	[redacted]	[redacted]
Carer utilities	Multiplier approach (16%)	Multiplier approach (50%)	[redacted]	[redacted]
		Not applied	[redacted]	[redacted]

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICER, incremental cost-effectiveness ratio; TTD, time to death.

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

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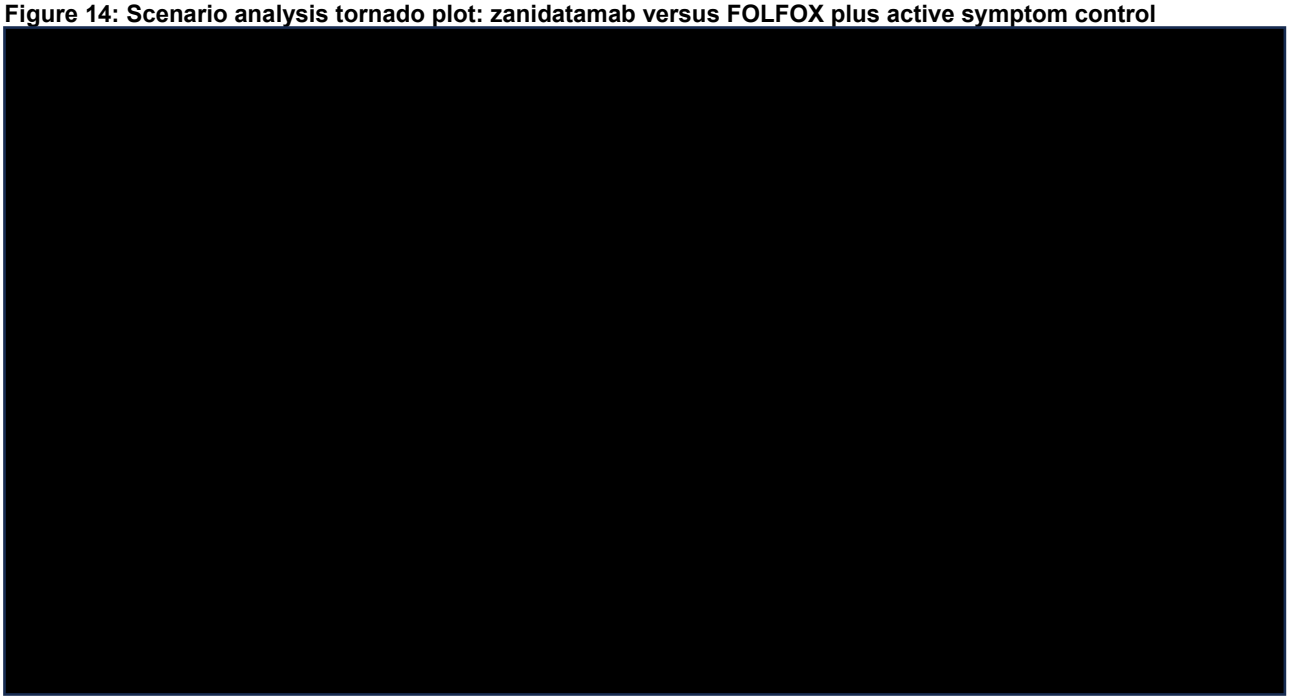
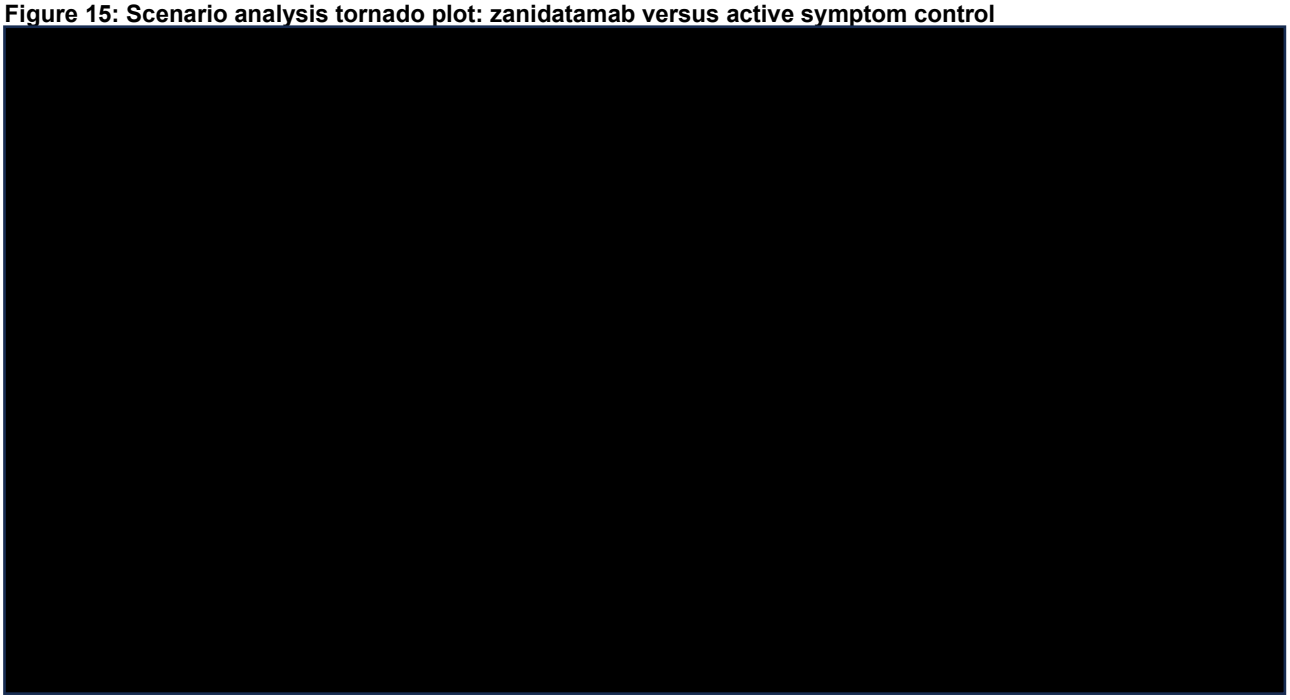
Figure 14: Scenario analysis tornado plot: zanidatamab versus FOLFOX plus active symptom control



Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICER, incremental cost-effectiveness ratio.

Figure 15: Scenario analysis tornado plot: zanidatamab versus active symptom control



Abbreviations: ICER, incremental cost-effectiveness ratio.

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

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Appendix 6: Health inequality report

This report was generated by entering user-defined assumptions into a health inequality impact calculator (https://shiny.york.ac.uk/dceasimple) produced by the University of York (25). The University of York offers no guarantees of any kind for the results produced.

The following analysis compares **Zanidatamab** against **Chemotherapy**.

Table 6: Main model results

Net health inequality benefit	[redacted] quality-adjusted life years (QALYs)
Incremental cost-effectiveness ratio	[redacted]/QALY
Equity-weighted incremental cost-effectiveness ratio	[redacted]/QALY
Incremental cost-effectiveness ratio change	£0 (0%)
Threshold weight	x1.00
Incremental net health benefit	[redacted]QALYs
Equity-weighted incremental net health benefit	[redacted]QALYs
Decision threshold	£30,000
Marginal productivity	£30,000
Atkinson parameter	0

Abbreviations: QALY, quality-adjusted life year.

Table 7: Distributional results

	IMD1	IMD2	IMD3	IMD4	IMD5	Total
Share of eligible population	24%	19%	19%	19%	17%	100%
Uptake	100%	100%	100%	100%	100%	
Inc. QALY/recipient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Share of opportunity costs	20%	20%	20%	20%	20%	100%
Recipients (in 1,000s)	0.012	0.01	0.01	0.01	0.009	0.051
Recipients (share)	24%	19%	19%	19%	17%	100%
Gross health benefit (QALYs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunity costs (QALYs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net health benefit (QALYs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IMD, Index of Multiple Deprivation; QALY, quality-adjusted life year.

Inputs

This section summarises the user-defined assumptions used to create the results and plots.

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

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Table 8: Input parameters

Variable	Value
Intervention name	Zanidatamab
Comparator name	Chemotherapy
Incremental QALYs	[redacted]
Incremental cost, £	[redacted]
Intervention type	Disease population
Intervention disease category (ICD-10)	C22
Age range	64; 80
Eligible population	50
Uptake in IMD1 (most deprived), %	100
Uptake in IMD2, %	100
Uptake in IMD3, %	100
Uptake in IMD4, %	100
Uptake in IMD5 (least deprived), %	100
Effectiveness in IMD1 (most deprived)	1.000
Effectiveness in IMD2	1.000
Effectiveness in IMD3	1.000
Effectiveness in IMD4	1.000
Effectiveness in IMD5 (least deprived)	1.000
Share of eligible population IMD1 (most deprived)	0.240
Share of eligible population IMD2	0.190
Share of eligible population IMD3	0.190
Share of eligible population IMD4	0.190
Share of eligible population IMD5 (least deprived)	0.170
Health opportunity cost distribution	flat
Marginal productivity	30,000
Atkinson inequality aversion value	0.000
Decision threshold, £	30,000

Abbreviations: IMD, Index of Multiple Deprivation; QALY, quality-adjusted life year.

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

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Consultation on the draft guidance document – deadline for comments: 5pm *on* ***Tuesday 3 February 2026****. Please submit via NICE Docs.*

Distributional health impact

[redacted]

[redacted]

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

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[redacted]

[redacted]

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

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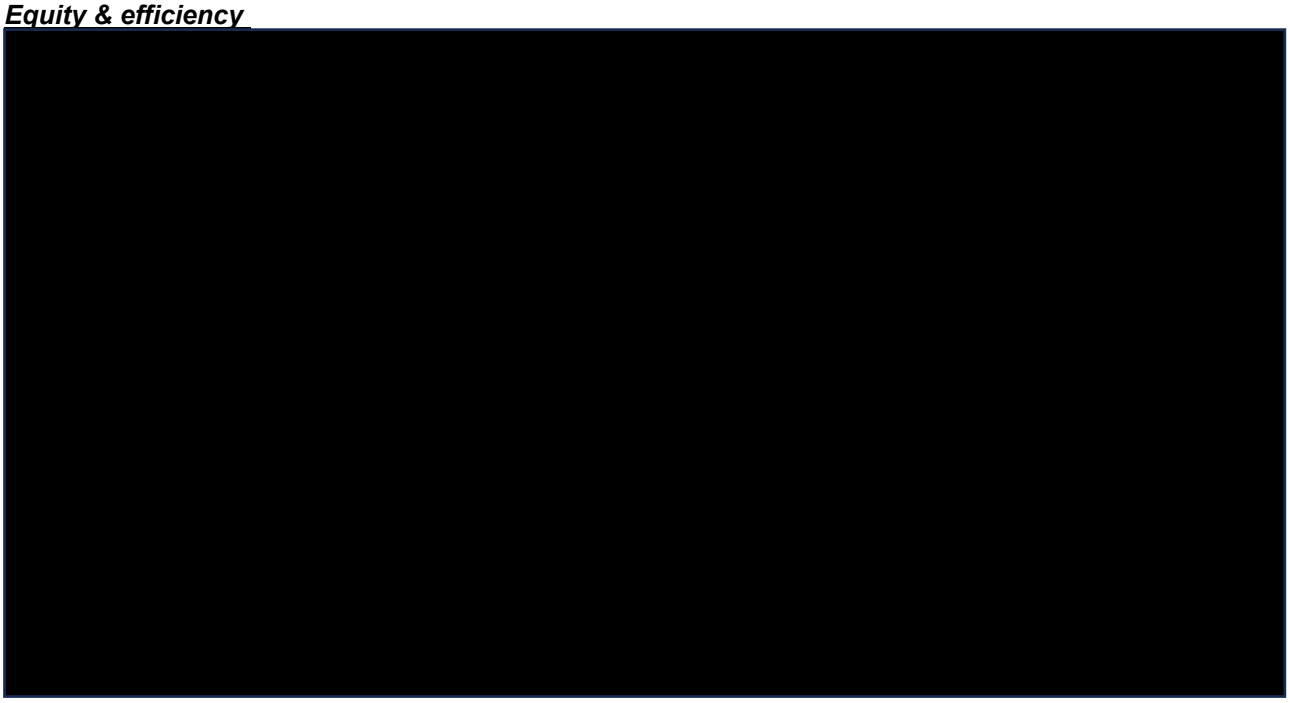
Equity & efficiency



Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

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

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Appendix 7: Health-related quality of life studies identified in the systematic literature review

Table 9: Utility data by disease stage

Study name	Patient population	Treatment line	Treatments	Utility (range) in progression-free disease	Utility (range) in post-progression disease	Utility method	Source of utility values
Zheng 2023 (31)	Advanced BTC	2L	Durvalumab plus Gemcitabine and Cisplatin vs Gemcitabine and Cisplatin	0.76 (0.61–0.91)	0.68 (0.54–0.82)	NR	Zhao (2022) (32)
Kashiwa 2023 (33)	Unresectable or recurrent BTC	1L	Gemcitabine/ pazopanib therapy in Greek patients	0.55 (0.7–1.3)	0.541 (0.7–1.3)	NR	Sgouros (2020) (34)
Wasan 2023 (35)	HER2+ locally advanced, unresectable or metastatic BTC	NR	HERIZON-BTC-01	0.4 to 0.88 (CR: 0.4, n=1; PR: 0.8, n=21; SD: 0.88, n=21)	0.8 (NR)	Median VAS	HERIZON-BTC-01 (8)
Zhu 2023 (36)	Unresectable, locally advanced or metastatic BTC	2L	Atezolizumab plus bevacizumab, sorafenib	0.76 (0.608–0.912)	0.68 (0.544–0.816)	NR	Zhao (2022) (32)
Tsukiyama 2016 (37)	Advanced BTC	NR	Gemcitabine alone in combination with cisplatin	0.69 (NR)	0.71 (NR)	EQ-5D	The CEA Registry (38)
Zhao 2023 (39)	Advanced BTC	NR	Durvalumab plus Gemcitabine and Cisplatin vs Gemcitabine and Cisplatin	0.9 (0.675–1.125)	0.4 (0.3–0.5)	NR	Cillo (2015) (40)
Liu 2024 (41)	Unresectable, locally advanced or metastatic BTC	1L	Dose-adjusted sorafenib vs BSC	0.76	0.68	NR	TA474 (formerly TA189) (42)
Kashiwa 2024 (43)	Advanced BTC	1L	Gemcitabine alone in combination with cisplatin	0.690 (70–130%)	0.710 (70–130%)	NR	The CEA Registry (38)
Luo 2024 (44)	Advanced BTC	1L	Sunitinib vs interferon OR interferon alfa vs temsirolimus	0.79 (0.60–0.80)	0.69 (0.45–0.72)	NR	Remák (2007) (45)

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

Draft guidance comments form

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Study name	Patient population	Treatment line	Treatments	Utility (range) in progression-free disease	Utility (range) in post-progression disease	Utility method	Source of utility values
NICE 2024 (11)	Unresectable, locally, advanced or metastatic BTC	NR	Durvalumab plus Gemcitabine and Cisplatin vs Gemcitabine and Cisplatin	Redacted	Redacted	EQ-5D	TOPAZ-1 (46)
SMC 2023 (47)	Unresectable, locally, advanced or metastatic BTC	NR	Durvalumab plus Gemcitabine and Cisplatin vs Gemcitabine and Cisplatin	0.797 (0.787–0.807)	0.679 (0.638–0.720)	NR	TOPAZ-1 (46)
Chen 2023 (48)	Advanced iCCA	NR	Sorafenib TA474	0.76 (0.57–0.95)	0.68 (0.51–0.85)	NR	TA474 (42)
Chen 2024a (49)	Advanced iCCA	NR	Pemigatinib, Sorafenib TA474 & ABC-06 & NIFTY (5-FU)	0.76 (0.57–0.95)	0.68 (0.51–0.85)	NR	TA474 (42) Chueh (2023) (50) Chen (2023) (48)
Chen 2024b (51)	Advanced or metastatic MSI-H cancers	41% had received 1L	KEYNOTE-158&164, Trastuzumab vs single agent chemo, Cetuximab, Cetuximab Plus Irinotecan, and Panitumumab, Pembrolizumab vs fluoropyrimidine, oxaliplatin, and irinotecan	0.77	0.67	NR	KEYNOTE-158 (52)
Chen 2024c (53)	Unresectable GBC	1L	Oxaliplatin and gemcitabine vs fluorouracil and folinic acid	0.77	0.64	NR	Roth (2012) (54)
McCarthy 2024 (55)	Advanced CCA	41% had received 1L	KEYNOTE-158 & 164, Pembrolizumab vs fluoropyrimidine, oxaliplatin	0.71	0.65	EQ-5D-3L	KEYNOTE-158 (56)

Abbreviations: 1L, first line; 2L, second line; 5-FU, fluorouracil; BTC, biliary tract cancer; BSC, best supportive care; CCA, cholangiocarcinoma; CR, complete response; GBC, gallbladder cancer; HER2+, human epidermal growth factor receptor 2-positive; iCCA, intrahepatic cholangiocarcinoma; MSI-H, microsatellite instability-high; NR, not reported; PR, partial response; SD, stable disease; SLR, systematic literature review; VAS, visual analogue scale.

NICE National Institute for Health and Care Excellence

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

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

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Jazz Pharmaceuticals - £25,000 - March 2025 (ceased)** Support for AMMF's 2025 European Conference **Jazz Pharmaceuticals - £10,000 – May 2025 (ceased)** Support for translating patient education materials for AMMF's European website **Jazz Pharmaceuticals - £10,000 – July 2025 (ceased)** Support for AMMF's 2025 Patient and Carers Webinars
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Paul Howard

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The draft recommendation explains that the committee made their decision, in part at least, because zanidatamab has not been directly compared in a clinical trial with the usual treatment (i.e. FOLFOX chemotherapy with active symptom control (ASC) or ASC only). It is unreasonable to require a multi-arm clinical trial that directly compares zanidatamab with current second-line treatments for HER2-positive advanced biliary tract cancer patients due to the small numbers of this patient cohort. Biliary tract cancers including cholangiocarcinoma, gallbladder cancer, and ampullary cancer are relatively uncommon – the age-standardised incidence rate in England in 2016-2018 were 4.6, 1.8, and 0.9 per 100,000 person-years respectively. According to information about the condition provided in the draft recommendation, HER2 gene faults are present in about 5% to 10% of cholangiocarcinomas, and up to 20% of gallbladder cancers. In addition, biliary tract cancers are commonly diagnosed at advanced stages when treatment options are limited. A significant proportion of patients do not receive any cancer-specific treatment – data published by NHS England's National Disease Registration Service show that fewer than one-in-three (32.4%) people diagnosed with cholangiocarcinoma during 2013-2022 received one or more available treatments for their cancer. Due to the small numbers receiving treatment in this patient population, a multi-arm clinical trial will be extremely challenging. As such, it should be reasonable to make indirect comparisons with other clinical trials (i.e. ABC06). With rare cancers, there will be a degree of uncertainty about how much new therapies may improve health-related quality of life compared with usual treatment. However, zanidatamab has provided significant improvements in quality of life and extended survival for participants in the clinical trial and several patients whose case studies we shared in our evidence submission. This treatment can give patients and their families hope, despite having a diagnosis of a cancer with few treatment options.
2	On page 17 of the draft recommendation, the committee concluded that progression-based utility values were more appropriate than the time-to-death approach proposed by the company. Whilst we lack robust evidence about patient utility at end of life, AMMF has heard regular anecdotal evidence that patients tend to have relatively stable utility throughout their disease, until a rapid deterioration at end of life. We have heard from family members and caregivers, how their loved ones with cholangiocarcinoma suddenly decline and "drop off a cliff". *"I lost my beautiful sister five months after she was diagnosed with cholangiocarcinoma, when she was just 37 years old. It all happened so fast. There are no words to describe it. It was so sudden. So unexpected."* **– Sister of a cholangiocarcinoma patient** *"I felt cheated that he had this cancer no one had heard of. In the space of three weeks, I went from telling my sons that [my husband] was ill, to telling them he had gone."* **– Wife of a cholangiocarcinoma patient** ***"****My 58-year-old mum died from this. She had no symptoms until the final three weeks."* – **Daughter of a cholangiocarcinoma patient**

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

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3	The utility models considered by the committee assume that patients receiving zanidatamab will experience disease progression. However, following the publication of the draft recommendation, AMMF has received testimony from a patient who currently has no sign of disease following treatment with zanidatamab: *"I was first diagnosed in Feb 2023 after symptoms of jaundice, pain, and weight loss led to surgery. The histology confirmed a diagnosis of CCA. I was given a 6-month course of capecitabine and given the all clear after this. Unfortunately, I had recurrence in August 2024 and started on Gem/Cis/Durva chemotherapy/immunotherapy regime in October. I was also on the ABC10 trial, and they found I have a HER2 amplification mutation, so I was suitable for zanidatamab. In Jan 2025 I started on zanidatamab only. While on chemotherapy and immunotherapy the cancer was stable, however zanidatamab continued to shrink the tumour until Sep 2025 when a CT scan showed complete remission."* **– cholangiocarcinoma patient** This testimony, along with some of the other remarkable responses to zanidatamab treatment reported to AMMF by patients and their loved ones, indicates that an accurate model should account not only for treatment until progression and death, but also the possibility of response leading to re-staging and potentially curative surgery, and even complete response (i.e. no signs of disease).
4	On page 18 of the draft recommendation, it is noted that disutility associated with grade 1 or 2 adverse events is not usually included in models because a consistent quality-of-life reduction from these events is not supported by evidence. We have heard testimony from patients about how side effects and adverse events from treatment including fatigue, hair loss, and changes to appetite and sleep have a profound impact on them and their loved ones. Patients have remarked upon the significant difference in quality of life when treated with zanidatamab compared to chemotherapy, due to the better side effect profile. *"The side effects on [Gem/Cis/Durva] were dire: I suffered constant nausea and sickness, and debilitating fatigue. My hair thinned and I had no energy. The steroids made it impossible to sleep, and I struggled with my appetite. It was impossible to live my previous life. I hated looking like this in front of my children and although it sounds wrong, I struggled with guilt over the suffering I could see I was bringing them. My husband was depressed, anxious, and frightened all the time and tried to hide it. It made me feel like I had brought this all down on my family and for a long while I found little comfort anywhere. On zanidatamab I was cooking, hiking, having a social life and living in a totally unremarkable and yet precious way: just ordinary and normal. The difference between taking zanidatamab and the other drugs is essentially the difference between medicine and poison: whilst zanidatamab had no noticeable side effects, the other drugs feel like they are killing you slowly. My life went back to normal for a good period on zanidatamab and I went on holidays with my family and was no longer being looked after by everyone, an uncomfortable and upsetting experience for everyone."* **– cholangiocarcinoma patient** ***"****I started taking zanidatamab in April 2024 and my last treatment was the beginning of November 2025. Unfortunately, by November my cancer was once more progressing and it was decided to stop the zanidatamab. In December 2025 I started regorafenib through my husband's private healthcare from work. Taking this kind of drug after zanidatamab was like being hit by a truck. My weight has gone into free fall, and I feel nauseous all the*

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments: 5pm on **Tuesday 3 February 2026**. Please submit via NICE Docs.

	time. I have sores in my mouth and nose, on my arms, and the fatigue is very hard. My voice is now very high pitched and hoarse. I have terrible constipation and food has become a challenge every day." **– cholangiocarcinoma patient** *"While on chemotherapy and immunotherapy I felt constantly tired and just getting through the days. I also had to move back in with my parents as I was unable to safely live alone and cook etc. Now on zanidatamab, I'm back to my own place living independently. Able to play cricket again and live my normal productive life."* **– cholangiocarcinoma patient**
5	We welcome the committee's conclusion on page 22 of the draft recommendation that there were uncaptured positive benefits of zanidatamab for caregivers. AMMF has heard testimony from several patients treated with zanidatamab who were able to return to employment or caregiving for others and based on those, we believe that this should also be considered an uncaptured benefit. *"From our experience, [my partner] has fewer side effects than the Gem/Cis/Durva treatment. The infusion time is quicker, which is also better. He has more energy, and our lives are far more 'normal' since he started the zanidatamab treatment. [My partner] has also been able to go back to work part-time."* **– Partner of a cholangiocarcinoma patient** *"I was a teacher and Head of Department and overnight I felt I had lost that life forever. I couldn't consider working in that state of health on the other chemo treatments, but on zanidatamab I resumed walking into work with literally no sign that anything was wrong with me. My energy levels were normal, and I resumed yoga, swimming, and hiking. I decided to return to work part time and found that it suited me. It was a great feeling being able to be the person I was, back at work, a dream really. I love my job. Having cancer has halved my wages, but at least zanidatamab opened the door for me to be able to return to work. I think about those with jobs who don't have sick pay and part-time opportunities and shudder to think how they have to struggle financially on top of the existential crisis in which they find themselves."* **– cholangiocarcinoma patient** *"While on chemotherapy and immunotherapy I was unable to work and regularly admitted to hospital with issues such as cholangitis. I started zanidatamab in January and by April I was back to working full time. I now work full time and have done since September 2025. My schedule is 8-8 Monday, 8-5 Tuesday-Friday for 2 weeks, then week 3 (when treatment is) I work Monday and Wednesday only. With Tuesday off for clinic, Thursday off for treatment, and the Friday off for a recovery day. I'm back at work 8-8 the Monday after treatment. Something unachievable when on chemo."* **– cholangiocarcinoma patient**

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

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6	On page 23, the draft recommendation indicates uncertainty with the ICER over whether subsequent treatments, which may not be available in the NHS, affected overall survival in HERIZON-BTC-01. On page 10, it suggests that the only subsequent treatment for patients receiving zanidatamab in the NHS is FOLFOX. If zanidatamab is adopted for use by the NHS, FOLFOX with active symptom control (ASC) would be considered the standard of care third-line therapy for this patient population. However, some patients may access a wider range of subsequent treatments through private healthcare, clinical trials or NHS targeted therapies for newly emerged genetic alterations in their tumours. Due to the well-tolerated side effect profile and efficacy of zanidatamab, patients who receive the treatment and experience progression of their disease may be more likely to receive subsequent life-extending therapies than patients who receive FOLFOX + ASC or ASC alone. This was indicated by the clinical experts during the first committee meeting and is recorded on page 18.
7	Following the publication of the draft recommendation, AMMF received statements from some cholangiocarcinoma patients who had received zanidatamab treatment. We have shared them here to highlight how important they consider this treatment option to be: *"When you get a diagnosis of bile duct cancer you find out pretty quickly that you are one of the unlucky ones: whilst other cancers have so much money spent on developing new drugs and therefore survival rates for several cancers are just seeming to improve year on year, you discover that few drugs are ever dedicated to your cancer and that your treatment options are limited. This limitation might not look much on paper but for those of us with lives and families we long to stay with, it means more tragedy, more loss, and sadness for the children I will leave behind, and the husband left alone, because without new drugs like these, there's really very little to hope for. When I went on zanidatamab, I truly felt that at last I had a chance to have life instead of the terrible prognosis I struggled to accept. I felt well on the drug and my cancer, instead of threatening my life every day, was shrinking remarkably and leaving me to simply live; not a lot to ask for really. Please let people like me have this option: anyone offered it has few if any real alternatives and this drug offers real hope. This is a relatively rare cancer: please don't close down this option."* – **cholangiocarcinoma patient** ***"****Zanidatimab has enabled me to go from a death sentence, at best a few years left, to now having hope I can live the life I want to, contribute to society through work - which I love - and spend time with friends and family, which is the most important thing in life. I'm concerned that not approving this treatment for NHS patients will add to the inequalities in cholangiocarcinoma care we are already seeing – with people who are able to access clinical trials or have private healthcare benefiting from new life-extending treatments; and those that can't go on a trial or afford to pay for insurance, not surviving. We are losing too many people to this cancer every year. It has an appalling survival rate that hasn't improved for decades. But that can and will change if all NHS patients are given access to all available treatment options."*** **– cholangiocarcinoma patient**

Insert extra rows as needed

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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Draft guidance comments form

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

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

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Payment for advisory boards and preceptorship programme from Jazz 2024-5 £8,700 2025-6 £450
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	John Bridgewater

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Are the summaries of clinical and resource savings reasonable interpretations of the evidence?** As a whole yes. I find it difficult to ascribe any certainty with respect to predicting long-term survival curves as zanidatumab has not been given to patient's more than 5 years ago and as such any prediction is a guess. I would however describe any benefit in survival to zanidatumab

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

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	rather than subsequent therapies because the survival benefit from the latter are extremely poor. Many patients given the option of FOLFOX chemotherapy following an effective toxicity free targeted therapy simply do not take it.
2	**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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The benefit from zanidatumab for similar to that of other targeted therapies for biliary tract cancer already approved by NICE. It would be fundamentally unfair if this benefit was not granted to patients with HER2 amplification.
3	**Has all of the relevant evidence been taken into account?** There is been no mention of the expanded access program report we presented at ENSCCA in May 2025. I attach the abstract. Unveiling the secrets of real-world use of Zanidatamab in an English biliary tract cancer cohort. Marina I. Crespo-Cruz, MD, MSc1, Morteza Jalali, MD, PhD2, and John Bridgewater MD, PhD1,3. 1. University College London Hospitals (UCLH), London, UK. 2. Jazz Oncology, Jazz Pharmaceuticals, London, UK. 3. University College London (UCL) Cancer Institute, London, UK. Background and Aims: Biliary tract cancer (BTC) is a rare, aggressive cancer, with few treatment options and poor survival. Molecular profiling has become a cornerstone of BTC patient management to personalize treatments and optimize outcomes. The HER2 tyrosine kinase receptor is overexpressed in up to 20% of extrahepatic BTCs and several inhibitors have been tested in clinical studies with encouraging results. Zanidatamab is a dual HER2-directed bispecific antibody which has previously shown promising activity with a manageable safety profile in BTCs progressing on standard-of-care therapies. It is accessible in the context of clinical trials and compassionate use in some settings. We aimed to explore the clinical results of Zanidatamab use in our centre. Methods: We conducted a retrospective observational study based on real-world data (RWD), to evaluate the use of Zanidatamab in 20 patients treated in the medical oncology service at UCLH between 2022 and 2025. Most patients have accessed Zanidatamab under compassionate use. We analysed the data using Microsoft Excel. No change in patient care was made and data was anonymised, such that individual patient consent was not required. Results: 20 patients were included in our study. 65% of patients were female and 35% were male. Mean age at diagnosis was 55 and mean weight on treatment initiation was 66kg. 12 patients (60%) had cancers of gallbladder origin, 3 patients (15%) were distal cholangiocarcinomas, 3

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

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	patients (15%) were intrahepatic and 1 patient had a hilar cholangiocarcinoma. The remaining patient had an ampullary adenocarcinoma. 50% of patients had undergone surgery for localised BTC and 50% had a metastatic or unresectable debut. The most frequent sites of metastatic disease were the liver, lymph nodes, lungs and peritoneum. All patients received first line standard of care Cisplatin, Gemcitabine +/- Durvalumab. 70% received Zanidatamab as a second line treatment and 20% as third line. 2 patients are awaiting start and 1 deteriorated before treatment initiation. The mean number of administered cycles has been 8 and 8 patients are still receiving Zanidatamab. We observed objective responses in 60% of evaluated patients, mixed responses in 15% and 25% of patients progressed on first evaluation. 4 patients have not had restaging yet and 1 patient has had a complete response. The most frequent side effects were infusion reactions, diarrhoea and vomiting. We observed no serious adverse events. The median overall survival has not yet been reached. Conclusion: Zanidatamab has promising efficacy with a manageable safety profile in patients with HER2-amplified biliary tract cancers in the real-world population setting. Zanidatamab continues to be investigated in ongoing studies as a treatment option in HER2-positive cancers.
4	**Are the recommendations sound and a suitable basis for guidance to the NHS?** I do not agree with the outcome. Zanidatumab is a step change in terms of treatment and should be available for patients with this extremely poorly served cancer.
5	Zanidatumab is an effective toxicity pretreatment that changes the lives of patient's with advanced biliary tract cancer very much for the better. It should be approved and made available.

Insert extra rows as needed

Checklist for submitting comments

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	n/a
Conflict	n/a
Comments on the DG:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

The outcomes overall for biliary tract cancer patients in the UK remain poor overall (as per the recent AMMF White Paper), although new treatments such as upfront immunotherapy have improved this in recent years. Second line treatment with FOLFOX only increases overall survival by 6 weeks compared to best supportive care (as per ABC-06), so better options for second line treatment are sorely needed. Pemigatinib, the first licensed FGFR2 fusion inhibitor was licensed in second line treatment in biliary tract cancer based on the results of a phase II study which did not show as positive a results as the results of HERIZON-BTC-01 for zanidatamab; so I am unclear as to why one would be licenced and the other not considering that they are aiming to treat a similar population (biomarker positive second line biliary tract cancer patients) and have similar levels of evidence.

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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Gallbladder cancer is more common in female patients, and IHC 3+ HER2 positive biliary tract cancers are more likely to be gallbladder cancers (20%). Not having a targeted treatment option available for these patients will fail to improve outcomes for these patients, and will disproportionately affect female biliary tract cancer patients.

Has all of the relevant evidence been taken into account?

There is new evidence soon to be published formally on an analysis of the results of the BILCAP phase III clinical trial which indicates that patients with ERBB2 amplification (HER2 positive tumours) in fact have worse outcomes

(without anti-HER2 targeted treatment) than non-amplified tumours, which is in line with results from other tumour types such as breast cancer.

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

I think that the outcomes for patients receiving FOLFOX as second line treatment for biliary tract cancer are particularly poor, with a 6 week overall survival benefit as per ABC-06. Zanidatamab, in the selected IHC 3+ patient subgroup has been shown to be both safe and effective in these patients. The overall cost will be limited as this patient group is not particularly large, but there is a very large potential benefit to these patients compared to current standard of care if they receive zanidatamab.

Zanidatamab for treating HER2-positive advanced biliary tract cancer after one or more systemic treatments [ID6388]

EAG critique of company ACD response (February 2026)

Produced by Aberdeen HTA Group

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Date completed **V2.0 February 26th, 2026**

Contains [redacted]

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR176697.

Overview and summary

This document provides the EAG's critique of the additional information submitted by the company in response to the ACD. Critique follows the order of which issues were addressed in the company's ACD response and focuses more detailed critique on areas of residual disagreement between company and committee (or EAG) preferred assumptions from ACM1. Our critique concludes with cost-effectiveness analyses showing the company implemented changes post ACM1, committee and EAG preferred assumptions for ACM2 as well as some additional scenario analyses describing the impact of remaining uncertainties on the ICER. Commercial in confidence prices for comparators and subsequent treatments do not apply for ACM2 as none of the subsequent treatments included in the committee preferred base case have commercial in confidence arrangements in place.

Version 2.0 of this critique updates version 1 by:

A) Updating the reported ICER for zanidatamab vs. ASC (Table 3, EAG scenario 10) to correct an error in the company's model for the calculation of ASC progressed disease utility. The correction applies only to the ASC arm, and when progression-based utilities are used in the model.

B) Updating EAG scenarios in Table 3 to include the latest available eMIT prices, according to the most recently available NICE price tracker.

C) Providing additional scenario analyses exploring alternative health state utilities requested by the lead team at the pre-meeting brief (applied at the end of Table 5), described in the Utility values (disutility) section below.

Clinical effectiveness evidence:

In their response the company emphasised the survival benefits of zanidatamab in the available single-arm and real-world studies and reiterated that the totally of evidence from these studies should be considered, given the relative rarity and poor prognosis of this type of cancer. A patient survey conducted in 2025 by the AMMF cholangiocarcinoma charity also suggested benefits for patients taking zanidatamab. The company also estimates that only around 50 patients per year in England would be eligible for treatment with zanidatamab. An

additional long-term survival analysis of the HERIZON-BTC-01 study was presented which, although based on small numbers, suggested [redacted].

There is no significant change in the position of the EAG. It agrees that the available evidence indicates that zanidatamab is highly likely to be associated with improved survival in this population, but currently the evidence for its comparative effectiveness against other treatments is more limited, leading to uncertainty about the parameters used in the cost-effectiveness modelling. The EAG agrees with the company that the overall clinical effectiveness evidence needs to be interpreted in the context that this is a rare form of cancer with no evidence from large-scale randomised trials or meta-analyses.

Generalisability of the trials (previous PD-1 use):

To address the concern that most participants in HERIZON-BTC-01 did not receive PD-1 or PD-L1 inhibitor treatment in line with current NHS practice, a subgroup analysis was conducted suggesting no major differences in survival by previous PD-1 status. It was also noted that the French real-world study included 15 out of 20 patients with durvalumab and systemic chemotherapy.

The EAG agrees that the presented subgroup analysis indicates [redacted] *for those with and without prior PD-L1 use but notes that this appears to be based on a small number of participants receiving PD-L1 (n=16).*

Generalisability of the trials (subsequent treatments):

NICE's guidance notes that some people had a range of subsequent treatments that would not be offered in the NHS, which could potentially inflate the survival benefit of zanidatamab. The company states that most (33/62) participants in HERIZON-BTC-01 had no subsequent treatment, and that 17 of the remaining 29 participants received systemic chemotherapy, aligning with NHS practice. Only four received PD-1 or PD-L1 inhibitors and three received a subsequent HER2-directed therapy. An additional subgroup analysis conducted by the company showed no evidence of survival difference for those receiving chemotherapy and non-chemotherapy treatments.

The EAG agrees that most HERIZON-BTC-01 participants received standard therapies that would be available in an NHS setting. It also notes that, although there was no evidence of differences between these groups, the subgroup analysis presented was based on small numbers of participants.

Indirect treatment comparisons:

Although the company did not present significant new evidence, it highlighted that many different approaches were used to help reduce uncertainty in the indirect comparison estimates. These included the matching-adjusted indirect comparison (MAIC) and the external control arm analysis using the Flatiron database.

The EAG agrees that the naïve comparison with the ABC-06 study remains the best approach to derive OS and PFS extrapolations for the cost-effectiveness modelling, as long as these results are interpreted cautiously due to the potential sources of uncertainty and bias. The EAG was less comfortable with the other indirect comparison methods undertaken as there was limited justification for the assumptions of the MAIC analysis and the external control arm analysis was based on very small numbers. However, it also notes that they provided generally similar results.

Survival analysis extrapolations:

The company revised base case analysis continues to prefer the use of a Log Logistic (LL) curve for OS and PFS. The EAG report raised a concern that the LL curve for OS leads to a small proportion of the treated cohort being alive over an extended period. This adds uncertainty because longer-term outcomes are unknown. Furthermore, when preparing the EAG report, the EAG's clinical expert explained that whilst not impossible, extrapolation curves predicting extended long-term survival generally lacked face validity, based on current knowledge and treatment expectations for zanidatamab. The EAG therefore preferred the use of an extrapolation curve for OS that tended to zero more quickly over time but still retained some potential for longer-term survival, albeit at a lower proportion than preferred by the company. This suggested a Log Normal (LN) curve might be appropriate for Zanidatamab

OS. The committee preferred a more conservative assumption for OS in the ACD, using a Gamma curve.

The EAG note that the committee preferred the gamma curve for OS does tend to zero more quickly. However, the EAG also accepts the company's concerns that, without the company's capping of survival curves, the PFS and OS curves would cross under the committee's preferred assumptions. The EAG are of the view that the use of a Gamma OS curve without adjusting or updating the PFS curve, lead to a conservative assumption about the overall benefit profile of zanidatamab compared to FOLFOX. The EAG retains our preference for the use of the LN curve for zanidatamab OS, but provide analyses using both the conservative, committee preferred (gamma) and optimistic, company preferred LL curve as scenario analyses. The EAG also provides a scenario where the gamma curve is applied to OS, PFS, and ToT for illustration. Whilst internally consistent for zanidatamab, this approach would likely also underestimate the magnitude of incremental benefit for zanidatamab relative to FOLFOX.

Zanidatamab Time on treatment:

The company revised base case maintains the original company submission preference to apply a Gamma curve for modelling zanidatamab ToT.

The EAG maintains our preferred base case assumptions, which are to apply a LN curve for zanidatamab ToT, aligned with committee preferred assumptions from the ACD. The EAG report, Section 4.2.5 provides a detailed justification of the preferred assumptions for Zanidatamab time on treatment. The company preferred approach, using the Gamma ToT curve, alongside the LL PFS curve, leading to a very small proportion of the progression free cohort remaining on treatment over time. In the EAG's view this lacks face validity, particularly given the favourable adverse event profile of zanidatamab, clinical expert opinion sought by the EAG that people would remain on treatment whilst beneficial, and lack of required treatment discontinuation rules. The EAG has not been presented with any evidence to suggest that patients who are progression free would discontinue treatment at an increasing rate over time. The only scenario in which the EAG would consider a gamma curve to be potentially appropriate for ToT for zanidatamab would be if committee also

preferred a gamma curve for both OS and PFS. Such a scenario would minimise the extent to which the proportion progression free and on treatment increases substantially over time.

Utility values (Suitability of the time-to-death modelling approach):

The company and EAG / committee's preferences remain misaligned with regard to the most appropriate approach to utility estimation. The company has reiterated the preference to use a time-to-death utility approach rather than the EAG preferred progression-based utility approach.

Section 4.2.7 provides a more detailed summary of the advantages and disadvantages of both the progression based and time-to-death approaches, with the EAG's preference for progression-based utilities driven by 1) concern about differences in the time from progression to death between the different treatment arms, meaning that time-to-death utility decrements have a greater impact in the PFS state for FOLFOX than in zanidatamab; 2) The time-to-death utilities lack face validity in the IHC3+ population with higher utility closer to death when looking at the raw utility data by time to death over 3 time periods; 3) Applying the progression based utility approach ensures consistency between the approach taken to model costs and QALYs. The EAG does not consider any additional information to have been provided in the ACD response that would change our preference for the use of progression-based utilities in the economic model.

Utility values (disutility):

The EAG appreciates the company has acknowledged the likelihood of double counting arising from inclusion of adverse event disutility, administration disutility and treatment specific disutility and address this concern by excluding adverse event grade 3+ and administration disutility in its base case because they may be counted in the treatment specific disutility applied in the model.

The EAG consider the company's revised approach to be reasonable, and acknowledge that this reduces the risk of double counting treatment specific disutilities. The EAG note that the committee requested scenarios exploring the impact of treatment specific disutilities applied in the PFS state only. This scenario does not appear to have been explored by the company in

response to clarification. The EAG have provided this scenario analysis for the committee's information, using the progression-based utility approach. The EAG also provides a scenario with an alternative approach, where treatment specific utilities are removed but port and adverse event disutilities are applied. This provides a range of plausible options for the ICER to avoid the potential for double counting for committee's consideration.

The company also explored an additional scenario analysis in response to the ACD applying treatment specific disutilities derived from the ABC-06 study for FOLFOX. The company uses utility values reported at baseline and four months from ABC-06 study publication to estimate utility for the progression free and progressed health states.

The EAG is however concerned that the approach taken using ABC-06 data introduces additional uncertainty by assuming that baseline utility is equal to progression free utility. The EAG view is that the approach take is more uncertain than using HERIZON study utilities because it is unclear whether the assumption that baseline utility is equal to PFS utility is accurate. For example, one would expect people remaining progression free on treatment might have better QoL than baseline, but on the other hand adverse effects might reduce QoL. The net impact, magnitude and direction of bias generated by these uncertainties is unclear. The EAG therefore prefers to use the HERIZON study data.

Minor coding error for treatment administration disutility for ASC when applying progression-based utilities

The EAG identified a coding error in the application of treatment administration disutilities for progressed disease in the ASC arm of the model. In the company submitted model post ACD, cell AE11 on the PF-ASC tab (calculation of progressed disease utility) incorrectly referenced progression free utility, rather than progressed disease utility. Applying this correction leads to a small reduction in the ICER for zanidatamab vs. ASC when using progression-based utilities in the model. The correction does not impact on ICERs vs. FOLFOX, or on scenarios where time to death utilities are applied.

Relative dose intensity:

In response to the ACD, the company have now aligned with the EAG and committee's preference to apply a lower relative dose intensity of 78% to FOLFOX.

The original EAG report preferred to apply the RDI to both treatment administration and treatment acquisition costs, whereas the company prefers to apply this only to the treatment acquisition costs for FOLFOX in the model. The EAG preference to apply the RDI to both treatment acquisition costs (i.e. dose adjustments) as well as treatment administration (missed administration) only has a minor impact on the ICER.

Frequency and cost of cardiac monitoring for FOLFOX:

The original company submission included the costs of echocardiography, before and after each treatment administration for FOLFOX in the model. Clinical experts at ACM1 explained that electrocardiography (ECG), rather than echocardiography, would be used and that the costs should be substantially lower for ECG, particularly when provided during a chemotherapy administration appointment, without the need for a dedicated diagnostic appointment. The company's revised base case includes the updated cost of ECG, applied before and after each administration, using a unit cost of £117.99, based on a weighted average of all attendances (inpatient, outpatient, day case, directly accessed) for HRG code EY51Z

The EAG, company and committee are now all aligned in preferring the use of ECG rather than echocardiography monitoring for FOLFOX patients. However, the company and EAG remain in disagreement on two issues:

1) *As noted in the ACD, it is likely that ECGs would be accessed directly during FOLFOX treatment appointments and would not require dedicated hospital appointments. The EAG therefore considers the cost of £117.99 used in the company's revised base case to be an overestimate of the costs incurred for the use of ECG to monitor cardiac function in FOLFOX patients. The EAG prefers to apply a unit cost per ECG of £54.00, based on directly accessed services, using HRG code EY51Z.*

2) *The EAG note that the company have retained their preference to apply the costs of ECG before and after every treatment administration. The EAG retains the original position that cardiac monitoring would usually only take place in UK clinical practice, at most, twice over a course of treatment, with one at treatment initiation*

and a later ECG if indicated. The EAG therefore prefers to apply 2 directly accessed ECG costs for FOLFOX patients in total, per course of treatment, as opposed to 2 ECGs per treatment administration preferred in the company updated base case. The EAG's understanding is that the committee preferences from ACM1 are aligned with the EAG preferred base case.

3) *When evaluating the updated model settings from the company, the EAG noted a minor formula error was identified on the patient flow tab for FOLFOX, where the formula required updating to reference ECG instead of the older reference to echocardiography. Whilst the impact on the company preferred base case is minor, it is important to update the formula functionality to ensure that the EAG preferred unit costs and ECG frequencies are correctly captured in the model.*

Carer QoL:

In response to the NICE ACD, stating that there are likely to be uncaptured benefits of zanidatamab in terms of carer spillover effects, the company have updated their preferred base case to include a carer QALY multiplier, applied to incremental patient QALY gains (without the severity weighting) predicted by the economic model for zanidatamab vs. comparators. The multiplier was assumed to be 1.16 for the base case analysis, that is a 16% increase for incremental QALYs, and it was assumed that the multiplier would apply to one affected carer. The 16% multiplier was obtained from a study cited by Pennington 2026 that estimates the spillover impact on utility for patients living with long-term meningitis complications (Al Janabi, 2015). Scenario analyses explored the impact of removing the multiplier and increasing it to a 50% increase in incremental QALYs.

Given the additional modelled life-year gains achieved through treatment with zanidatamab, and the patient utility benefit of delaying progression, it is reasonable to assume that there would be additional spillover utility benefits for carers and families. This is demonstrated within the company's response to ACD through quotations from patients / family, through the testimony provided at the NICE ACM1, and in submissions received ahead of ACM2 from patient organisations. The 0.16 multiplier from Al Janabi, 2015, used in the company revised base case, was based on a regression model using EQ-5D-5L responses from 901 close family members of someone with long-term after-effects of meningitis. The spillover co-

efficient was robust to alternative regression models but analyses showed that the magnitude of the spillover effect was sensitive to whether the carer was a partner, spouse, child etc. The same study also found a 0.041 annual QALY decrement for close family members. Whilst this study shows clear evidence of positive spillover effects from patient utility gains to patient utility gains, it is not clear how transferable a spillover-effect from long-term meningitis survival is to a cohort of patients with advanced BTC or whether this would apply equally across modelled health states. The approach proposed by Pennington 2026, quoted in the company response, also considers life years gained, and patient utility by model health state and would provide a more granular assessment of QoL impacts on carers. Whilst the EAG agrees that a carer disutility is likely to be appropriate for consideration, the evidence is unclear as to what the most appropriate magnitude of utility impact would be in the current patient population. It was not feasible for the EAG to conduct a systematic review of all carer utility studies of relevance to this assessment in preparation for this critique, but the EAG are unaware of any studies in a relevant population that could be used to populate the model for carer utility impacts. For these reasons, the EAG prefers to exclude carer disutilities from the base case cost-effectiveness analysis, but to instead acknowledge that this is an uncaptured benefit, that is difficult to quantify accurately given the available information.

Severity weighting:

The company and EAG remain aligned in considering a 1.7 severity weighting to be appropriate for this appraisal. None of the additional scenarios or evidence provided by the company or other stakeholders in response to the ACD would change that conclusion.

Impact of company and EAG preferred assumptions on the ICER for ACM2

Table 1 below illustrates the impact of changes implemented by the company in response to the ACD, applied to the company's original base case analysis. The company have implemented committee preferred preferences regarding:

1) Applying a 3.5% discount rate to costs and QALYs.
2) Applying the EAG preferred formula correction the to the application of administration disutility for FOLFOX, applies only to comparison vs. ASC.

3) Removing PORT and AE disutility, whilst retaining treatment specific disutility for FOLFOX and ASC.
4) Removing morphine costs already included in end-of-life costs.
5) Updating costs of monitoring cardiac function for FOLFOX patients to assign costs of ECG rather than echocardiography (See above for EAG critique of approach taken and unit costs applied)
6) FOLFOX RDI = 78% (See above for EAG preference to apply to treatment administration and acquisition costs)
7) Apply a HR, calculated from median TOT / median PFS to estimate treatment acquisition costs for FOLFOX.
8) Use the IHC 3+ dataset for health state utility values and AE data in the model.

The EAG are broadly satisfied that the amendments made to the model are transparent, clearly implemented and that the results match the analyses described by the company in their response to ACD. The EAG are also satisfied that the revised economic model can be used to replicate earlier company and EAG preferred analyses. Whilst the EAG agrees that all the implemented changes are appropriate and aligned with committee preferences, the EAG and company preferred implementation of the scenarios differs for the FOLFOX RDI and cardiac function monitoring costs. These points have been critiqued in the relevant sections above.

Table 1 Impact of company revisions between ACM1 and ACM2 on the ICER

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zani vs. comparator); £/QALY
Company preferred base case (ACM1)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 1 post ACM1 (Applying correction to application of administration disutility)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 2 post ACM1 (Remove port and AE disutility)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 3 post ACM1 (Remove Morphine cost)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 4 post ACM1 (Company preferred update to ECG costs)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zani vs. comparator); £/QALY
Company revision 5 post ACM1 (Include caregiver disutility)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 6 Set FOLFOX RDI = 78% (EAG preferred base case, applied to treatment acquisition costs only							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 7 Applying a hazard ratio to FOLFOX progression-free survival to estimate time-on-treatment							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revision 8 Use IHC3+ subgroup for utilities and AE population							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revised base case analysis for ACM2 (Scenarios 1 to 8 combined)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM, appraisal committee meeting; ECG, electrocardiography; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; RDI, relative dose intensity.

Summary of remaining areas of disagreement between company and EAG preferences for ACM2:

Table 2 below summarises the company and EAG preferred assumptions for ACM2 against the NICE committee recommendations from ACM1, and EAG preferred preferences across the key remaining issues of disagreement for ACM2. Table 3 illustrates the impact of adopting the EAG / committee preferred assumptions, applied to the updated company revised base case analysis.

Table 2 Summary of company and EAG preferred assumptions for ACM2

Key issue	Committee ACD preference	Company assumption for ACM2	EAG assumption for ACM2
Areas of company and EAG disagreement in application of preferred changes			
Frequency of cardiac function monitoring (ECG)	Up to a maximum of twice per treatment course	Twice per treatment administration	Twice per course of treatment.
Unit cost of ECG	Explore directly accessed services	Weighted average of all settings (outpatient, day case etc).	Directly accessed services.
FOLFOX RDI	78%, but not specified whether to treatment acquisition, administration or both	78% applied to treatment acquisition costs only	78% applied to treatment acquisition and administration costs.
Areas of company and EAG disagreement			
Carer QoL impacts included?	Consider qualitatively	0.16 multiplier, based on spillover effects from long-term meningitis complications, applied to incremental QALY	Remove multiplier due to uncertainty in magnitude and transferability across settings but include as an

Key issue	Committee ACD preference	Company assumption for ACM2	EAG assumption for ACM2
		gains across all health states.	important uncaptured benefit.
OS curve for zanidatamab	Gamma	Log Logistic	Log Normal
Zanidatamab Time on Treatment	Log Normal	Gamma	Log Normal
Utility approach	Progression based	Time-to-death	Progression based
Unit costs	As per company submission	Updated eMIT prices	Updated eMIT prices as per latest available NICE price tracker.

Abbreviations: ACD, appraisal consultation document; ACM, appraisal committee meeting; ECG, electrocardiography; QALY, quality adjusted life years; RDI, relative dose intensity.

Table 3 Impact of EAG preferred scenarios for ACM2 (applied to company revised base case analysis)

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
Company preferred base case (ACM2).							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Frequency of cardiac monitoring for FOLFOX – twice over the course of treatment).							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (FOLFOX cardiac monitoring unit cost = £54.00, directly accessed diagnostic service for ECG).							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (FOLFOX RDI applied to treatment administration as well as treatment acquisition costs).							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Carer QoL removed)							

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Applying Log normal curve for zanidatamab OS extrapolation – EAG preferred OS curve)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 6 (Applying Gamma curve for zanidatamab OS extrapolation – Committee preferred OS curve)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 7 (Applying Log Normal curve for zanidatamab PFS extrapolation – Committee preferred PFS curve)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 8 (Log normal for Zanidatamab Time on Treatment)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
EAG scenario 9 (Apply progression based instead of time-to-death utility approach)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 10 (Apply eMIT prices as per NICE price tracker)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Committee preferred assumptions from ACM1 (Scenario 1,2,4 and 6-10)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred assumptions for ACM2 (Scenarios 1-5; 8-10 combined)							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM, appraisal committee meeting; ECG, electrocardiography; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years; RDI, relative dose intensity.

Table 4 EAG preferred deterministic and probabilistic analysis for ACM2

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
EAG preferred deterministic for ACM2							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred probabilistic for ACM2							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 EAG preferred scatter plot on the cost-effectiveness plane (Zanidatamab vs. FOLFOX)

Figure 2 EAG preferred cost-effectiveness acceptability curve.

Table 5 Additional scenarios applied to EAG preferred base case for ACM2.

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
EAG preferred deterministic for ACM2							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Apply McCarthy et al. utilities							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Apply treatment specific utility only in the progression free health state							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Remove treatment specific disutility, but apply port and adverse event disutilities							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs (x1.7)	ICER (Zanidatamab vs. comparator); £/QALY
Scenario 4: Number of IHC tests increased, assuming 50% of HER2 patients don't receive routine testing in UK clinical practice.							
Zanidatamab	[redacted]	[redacted]	[redacted]				
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]