# Single Technology Appraisal

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

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Jazz Pharmaceuticals:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. AMMF – The Cholangiocarcinoma Charity – authored by patient expert, Mr Paul Howard

4. **Expert personal perspectives** from:
   a. Professor John Bridgewater – clinical expert, nominated by Jazz Pharmaceuticals
   b. Dr Suzanne Darby – clinical expert nominated by AMMF – The Cholangiocarcinoma Charity
   c. Mr Paul Howard – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity
   d. Mr Andrew Clay – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity

5. **External Assessment Report** prepared by Aberdeen HTA Group

6. **External Assessment Report – factual accuracy check**

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

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

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

## Company evidence submission

**July 2025**

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# Abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 3L | Third-line |
| 5FU | Fluorouracil |
| A&E | Accident and emergency |
| ADA | Anti-drug antibody |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADCP | Antibody-dependent cellular phagocytosis |
| AE | Adverse event |
| AIC | Akaike Information Criterion |
| ALT | Alanine aminotransferase |
| AoV | Ampulla of Vater |
| ASC | Active symptom control |
| ASMR | Annual standardised mortality rate |
| ASR | Annual standardised rate |
| AST | Aspartate aminotransferase |
| BIC | Bayesian Information Criterion |
| BL | Baseline |
| BNF | British National Formulary |
| BONT | Best on-treatment |
| BOR | Best overall response |
| BPI | Brief Pain Index |
| BSA | Body surface area |
| BSC | Best supportive care |
| BSG | British Society for Gastroenterology |
| BTC | Biliary tract cancer |
| CAPOX | Capecitabine and oxaliplatin |
| CBR | Clinical benefit rate |
| CCA | Cholangiocarcinoma |
| CE | Conformité Européenne |
| CEA | Cost-effectiveness analysis |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CisGem | Cisplatin and gemcitabine |
| CNS | Central nervous system |
| cORR | Confirmed objective response rate |
| CR | Complete response |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| dCCA | Distal cholangiocarcinoma |
| DCO | Data cut-off |
| DCR | Disease control rate |
| dMMR | Mismatch repair deficient |
| DOR | Duration of response |
| DPD | Dihydropyrimidine dehydrogenase |
| DSU | Decision support unit |
| EAG | External assessment group |
| EAMS | Early Access to Medicines Scheme |
| EAS | Efficacy analysis set |
| EC | European Commission |
| ECA | External control arm |
| eCCA | Extrahepatic cholangiocarcinoma |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| eMC | Electronic medicines compendium |
| eMIT | Electronic market information tool |
| EORTC | European Organisation For Research And Treatment Of Cancer |
| EPAR | European public assessment report |
| ESCAT | European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets |
| ESMO | European Society for Medical Oncology |
| ESS | Effective sample size |
| EUR | Euro |
| FA | Folinic acid |
| FDA | Food and Drug Administration |
| FGFR | Fibroblast growth factor receptor |
| FISH | Fluorescence in-situ hybridisation |
| FOLFIRI | Folinic acid, fluorouracil, and irinotecan |
| FOLFIRINOX | Folinic acid, fluorouracil, irinotecan, and oxaliplatin |
| FOLFOX | Folinic acid, fluorouracil, and oxaliplatin |
| FOX | Fluorouracil and oxaliplatin |
| GBC | Gallbladder cancer |
| GBP | Great British Pound |
| GemCap | Gemcitabine and capecitabine |
| GemCarbo | Gemcitabine and carboplatin |
| GEMOX | Gemcitabine and oxaliplatin |
| HCRU | Healthcare resource utilisation |
| HER2 | Human epidermal growth factor receptor 2 |
| HER2+ | Human epidermal growth factor receptor 2-positive |
| HIV | Human immunodeficiency virus |
| HPB | Hepato-pancreatic biliary |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| iCCA | Intrahepatic cholangiocarcinoma |
| ICER | Incremental cost-effectiveness ratio |
| ICR | Independent central review |
| IDH1 | Isocitrate dehydrogenase 1 |
| IHC | Immunohistochemistry |
| ILD | Individual level data |
| INV | Investigator assessment |
| IQR | Interquartile range |
| IRR | Infusion-related reaction |
| ISH | In-situ hybridisation |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| IV | Intravenous |
| IVD | In-vitro diagnostic |
| KM | Kaplan-Meier |
| LMER | Linear mixed-effect regression |
| LMM | Linear mixed model |

| | |
|---|---|
| LV | Leucovorin |
| LVEF | Left ventricular ejection fraction |
| LY | Life year |
| LYG | Life year gain |
| MAIC | Matching-adjusted indirect comparison |
| MDT | Multi-disciplinary team |
| MedDRA | Medical dictionary for regulatory activities |
| mFOLFIRI | Modified folinic acid, fluorouracil, and irinotecan |
| mFOLFOX | Modified folinic acid, fluorouracil, and oxaliplatin |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MoM | Method of moments |
| MRI | Magnetic resonance imaging |
| MSI | Microsatellite instability |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NGS | Next-generation sequencing |
| NHB | Net health benefit |
| NICE | National Institute for Health and Care Excellence |
| NR | Not reported |
| NTD | New Taiwan Dollar |
| NTRK | Neurotrophic tropomyosin kinase receptor |
| OR | Odds ratio |
| ORR | Objective response rate |
| OS | Overall survival |
| OWSA | One-way sensitivity analysis |
| PartSA | Partitioned survival analysis |
| PAS | Patient access scheme |
| pCCA | Perihilar cholangiocarcinoma |
| PD | Progressive disease |
| PD1 | Programmed cell death protein 1 |
| PDL1 | Programmed death ligand 1 |
| PF | Progression free |
| PFS | Progression-free survival |
| PHQ | Patient Health Questionnaire-9 |
| PICC | Peripherally-inserted central catheter |
| PIM | Promising Innovative Medicine |
| PLD | Patient level data |
| PR | Partial response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| PSM | Partitioned survival model |
| PSS | Personal social services |
| PSSRU | Personal Social Services Research Unit |
| Q2W | Every 2 weeks |
| Q4W | Every 4 weeks |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RDI | Relative dose intensity |
| RECIST | Response evaluation criteria in solid tumors |
| RWE | Real-world evidence |
| rwOS | Real-world overall survival |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Safety analysis set |
| SD | Stable disease |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SMD | Standardised mean differences |
| SmPC | Summary of product characteristics |
| SMR | Standardised mortality ratio |
| SOC | Standard of care |
| SoC | Standard of care |
| StD | Standard deviation |
| TA | Technology assessment |
| TFL | Tables, figures, and listings |
| ToT | Time on treatment |
| TRAE | Treatment-related adverse event |
| TRSAE | Treatment-related serious adverse event |
| TSD | Technical support document |
| TTD | Time to death |
| UCLH | University College London Hospital |
| USD | United States Dollar |
| VAS | Visual analogue scale |
| WTP | Willingness-to-pay |

# 1 Decision problem, description of the technology and clinical care pathway

## *1.1 Decision problem*

The submission covers the technology's full anticipated UK marketing authorisation for this indication: zanidatamab as [redacted] is indicated for the treatment of [redacted] (1).

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | • Adults with unresectable HER2-postive advanced biliary tract cancer previously treated with at least 1 prior line of systemic therapy | Adults with unresectable HER2-postive (IHC3+) advanced biliary tract cancer previously treated with at least 1 prior line of systemic therapy | The decision problem addressed aligns with the expected marketing authorisation for zanidatamab |
| **Intervention** | • Zanidatamab | As per NICE scope | Not applicable |
| **Comparator(s)** | • Established clinical management without zanidatamab, which may include:<br>– Folinic acid, fluorouracil, and oxaliplatin (FOLFOX)<br>– Best supportive care (including active symptom control) | As per NICE scope | Not applicable |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Response rates (including overall response rates)<br>• Time to treatment discontinuation<br>• Adverse effects of treatment<br>• Health-related quality of life | As per NICE scope | Not applicable |
| **Economic analysis** | • The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>• The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>• Costs will be considered from an NHS and Personal Social Services perspective. | As per NICE scope | Not applicable |

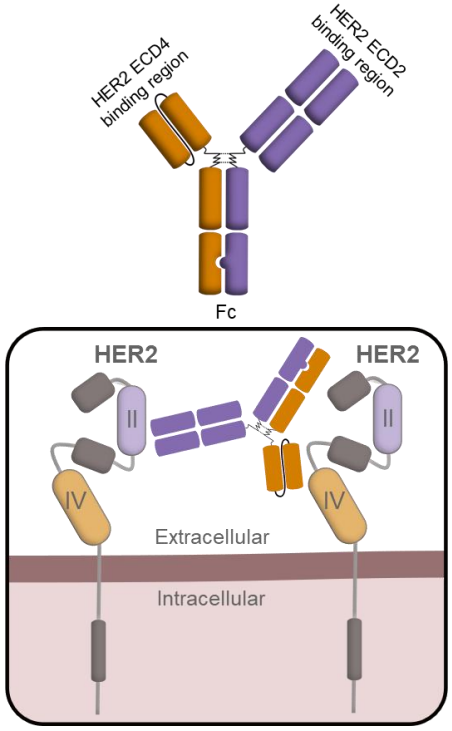
| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.<br>• The availability and cost of biosimilar and generic products should be taken into account | | |

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor 2; NICE, National Institute for Health and Care Excellence.

## 1.2 *Description of the technology being evaluated*

Details of the technology being appraised in the submission are provided in **Table 2**. The draft summary of product characteristics (SmPC) for zanidatamab is provided in Appendix A.

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Zanidatamab (ZIIHERA®) |
| **Mechanism of action** | Zanidatamab is a novel dual HER2-targeted bispecific antibody that simultaneously binds both extracellular domains 2 and 4 on separate HER2 monomers (binding in trans [**Figure 1**]). Binding of zanidatamab to different HER2 molecules results in HER2 clustering and internalisation leading to a reduction of the receptor on the cell surface. Zanidatamab binding to HER2 also induces complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. These multiple anti-cancer mechanisms result in tumour growth inhibition and tumour cell death (see **Figure 7** in Section **1.3.6** for more detail) (1).<br><br>**Figure 1: Unique bispecific binding of zanidatamab to HER2**<br>  <br><br>Abbreviations: ECD, extracellular domain; HER2, human epidermal growth factor receptor 2.<br>Source: Elimova (2025) (2). |
| **Marketing authorisation status** | • US FDA approval: 20th November 2024<br>• CHMP positive opinion: 25th April 2025<br>• EC decision received: 27th June 2025<br>• MHRA marketing authorisation expected: [redacted] |
| **Indications and any restriction(s) as described in the** | Zanidatamab as [redacted] is expected to be indicated for the treatment [redacted] |

<table>
<tr><td>summary of product characteristics (SmPC)</td><td>[redacted] (1). [redacted].</td></tr>
<tr><td>Method of administration and dosage</td><td>Each vial of zanidatamab contains 300 mg powder for concentrate for solution for infusion. After reconstitution, 1 vial of 6 mL solution contains 50 mg/mL of zanidatamab (1).<br>Recommended dose of zanidatamab is 20 mg/kg, administered as an IV infusion every 2 weeks (every 14 days) until disease progression or unacceptable toxicity (1).<br>Zanidatamab infusion durations are summarised in the table below (1).
<table>
<tr><th>Dose</th><th>Infusion duration</th></tr>
<tr><td>1st and 2nd</td><td>120 to 150 minutes</td></tr>
<tr><td>3rd and 4th</td><td>90 minutes, if previous infusions were well-tolerated</td></tr>
<tr><td>Subsequent</td><td>60 minutes, if previous infusions were well-tolerated</td></tr>
</table></td></tr>
<tr><td>Additional tests or investigations</td><td>Patients treated with zanidatamab for 2L BTC should have documented HER2-positive tumour status, defined as a score of 3+ by IHC assessed by a CE-marked IVD medical device. If a CE-marked IVD is not available, the HER2 status should be assessed by an alternate validated test (1).</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Zanidatamab is available as a 2-vial pack, each containing 300 mg powder for concentrate for solution for infusion.<br>List price per pack/vial: [redacted] per 2-vial pack<br>Average cycle cost of treatment at list price: [redacted]†<br>Average cost of course of treatment at list price: [redacted]</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>[redacted]<br>Average cycle cost of treatment at PAS price: [redacted]†<br>Average cost of course of treatment at PAS price: [redacted]</td></tr>
</table>

Abbreviations: 2L, second-line; BTC, biliary tract cancer; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IV, intravenous; PAS, patient access scheme.
†Dose dependent on patient weight, RDI and wastage.
‡Cost per course based on an average over a patient's lifetime, calculated in the cost-effectiveness analysis presented in Section 3 (undiscounted).

## 1.3 Health condition and position of the technology in the treatment pathway

***Summary: Overview of 2L HER2+ BTC and zanidatamab***

- BTC comprises a range of rare, invasive, and aggressive cancers of the biliary system, and includes CCA, GBC, and ampullary cancer (3)
- BTC is typically asymptomatic in early stages, so patients often already have advanced disease at diagnosis, when the disease is typically incurable (4, 5)
- A diagnosis of advanced BTC is devastating for patients and caregivers due to the burden of symptoms and current chemotherapy regimens alongside the poor prognosis, which create a substantial mental health burden, with many experiencing anxiety and distress (4, 6-10)
- UK survival rates for BTC are among the worst for any cancer (6, 11, 12). In England from 2001 to 2018, CCA and GBC had 1-year survival of 25.1% and 27.6%, respectively (6)
- Between 2001 and 2018, the incidence of BTC doubled in England, with a corresponding increase in mortality (6)
- People in England in the most socioeconomically deprived groups have a higher incidence of BTC and higher mortality rates from BTC (6)
- In England, 1L treatment of advanced BTC is CisGem with durvalumab (13-15).
- For patients who survive to reach 2L treatment, those with HER2+ IHC3+ BTC have very limited options, with no targeted therapies available. Current SoC for 2L HER2+ IHC3+ BTC is systemic combination chemotherapy with FOLFOX for those well enough for treatment, or palliative care with ASC (13, 16)
- Real-world data show only 28.4% of UK patients with advanced BTC treated with 1L therapy from 2018 to 2021 went on to receive 2L treatment (17)
- Targeted therapies in 2L BTC are currently recommended in England for patients with FGFR2 fusion/rearrangement (pemigatinib [TA722] and futibatinib [TA1005]) or IDH R132 mutations (ivosidenib [TA948]) (13, 18-20)
- Current combination chemotherapy with FOLFOX is associated with a substantial treatment burden due to severe AEs and only demonstrates a modest survival benefit over ASC (median OS of 6.2 months vs. 5.3 months with ASC) (21)
- Zanidatamab monotherapy is an innovative HER2-targeted therapy and represents a ‘step change’ in the 2L treatment of locally advanced or metastatic HER2+ IHC3+ BTC. If recommended, zanidatamab would replace FOLFOX as the SoC
- Zanidatamab is the first chemotherapy-free 2L targeted treatment for patients with advanced or metastatic HER2+ IHC3+ BTC, with a demonstrated median OS of 18.1 months (21, 22)
- Zanidatamab would also provide a new treatment for HER2+ IHC3+ patients who cannot tolerate FOLFOX and currently receive ASC alone
    - Treatment with zanidatamab negates the need for insertion and maintenance of central venous access devices (e.g. PICC or portacath), which minimises the burden of treatment on patients and hospital staff (1, 23, 24)
- The high unmet need in BTC and innovation of zanidatamab is reflected in the [redacted]
- Zanidatamab is already recommended by ESMO in the 2L for patients with HER2+ IHC3+ BTC (14) with EMA approval received in June 2025
- There are currently no HER2-targeted treatments for patients with advanced HER2+ IHC3+ BTC and patients and their families urgently need effective targeted therapies that offer the chance of longer survival over standard chemotherapy with a more manageable tolerability profile and maintained HRQoL

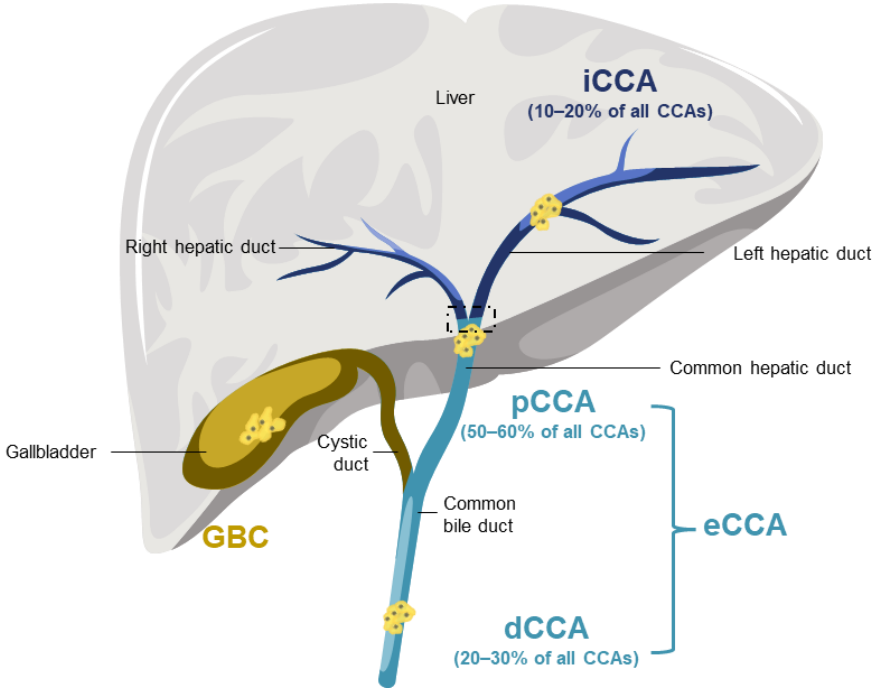

 

### 1.3.1 Disease background: biliary tract cancer

BTC comprises a range of rare, invasive, and aggressive tumours originating from the epithelium of the biliary system (Figure 2), and includes gallbladder cancer (GBC) (arising from the gallbladder or cystic duct), intrahepatic cholangiocarcinoma (iCCA) (arising from the biliary tree within the parenchyma of the liver within the left or right hepatic ducts), extrahepatic cholangiocarcinoma (eCCA) (arising from the bile ducts outside of the liver), and ampullary cancer (arising from the ampulla of Vater, Ampulla of Vater (AoV)) (3, 4, 13, 25-27).

Patients with BTC are typically asymptomatic during the early stages of the disease and, as the disease progresses, may only experience non-specific symptoms such as fatigue, weight loss, and abdominal pain (4). In addition to the aggressive nature of BTC, these factors often lead to patients being diagnosed at advanced stages (11). In the UK, the majority of BTC cases are diagnosed as locally advanced or metastatic (Stage 3 or 4). For cholangiocarcinoma (CCA), only 21% of staged cancers are early stage (Stage 1 or 2), which is less than half the unadjusted proportion for all cancers in England (54%) (11, 12).

**Figure 2: Anatomical locations of BTC subtypes**




Abbreviations: BTC, biliary tract cancer; dCCA, distal cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.
Source: Adapted from Banales (2020) (28).

#### *1.3.1.1 Risk factors*

Although many cases of BTC have no known risk factors (6), patients living with biliary cysts and stones, cirrhosis, and hepatitis B/C, are more at risk of developing

BTC than patients without these conditions (29). Patients who are in the most socioeconomically deprived quintile at the time of diagnosis are associated with a higher incidence of BTC and poorer outcomes (6). However, unlike hepatocellular carcinoma, the most common primary liver cancer globally, the majority of CCA cases are not associated with pre-existing chronic liver disease, alcohol excess, or metabolic syndrome (6). Overall, BTC affects a similar proportion of males and females in England (6).

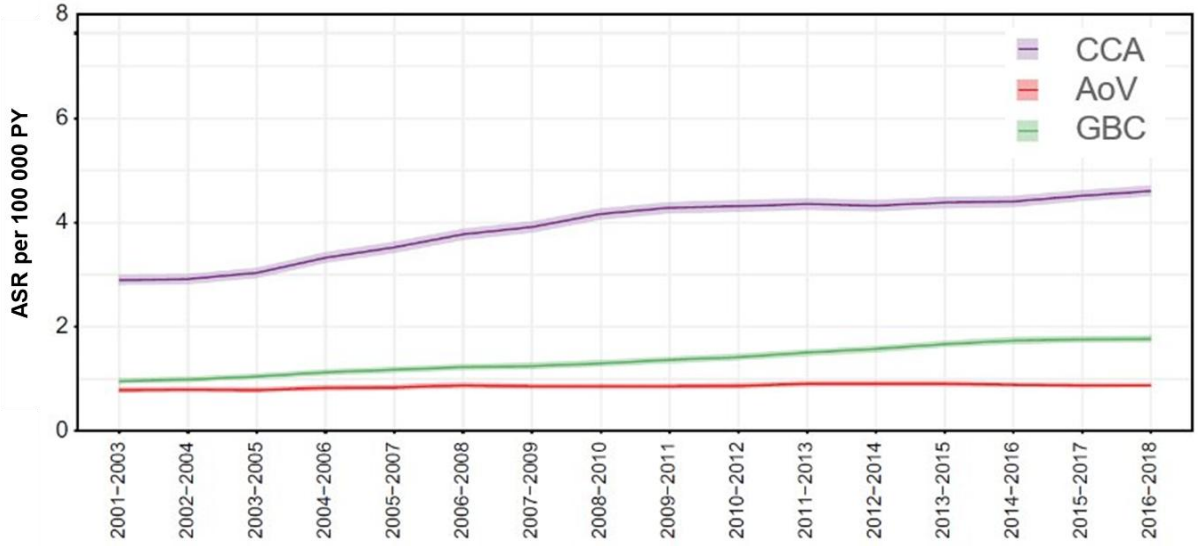
### 1.3.2 Epidemiology in the UK

#### *1.3.2.1 Prevalence/incidence*

BTC is a rare disease (6, 13). In the UK, there are approximately 3,100; 1,100, and 550 new cases of CCA, GBC, and AoV respectively, each year (30, 31). Approximately 79% of patients diagnosed with CCA are diagnosed at an advanced or metastatic stage (11).

In England, incidence of BTC has increased year on year (6); between 2001 and 2018, the incidence of BTC doubled in England, with the number of diagnosed patients with CCA rising from 1,165 to 2,466 and with GBC from 418 to 951 (Figure 3) (6).

**Figure 3: Incidence rate by BTC subtype in England between 2001 and 2018**




Abbreviations: AoV, ampulla of Vater; ASR, age-standardised incidence rate; BTC, biliary tract cancer; CCA, cholangiocarcinoma; GBC, gallbladder cancer.
Source: Tataru (2023) (6).

#### *1.3.2.2 Overall survival and mortality in BTC*

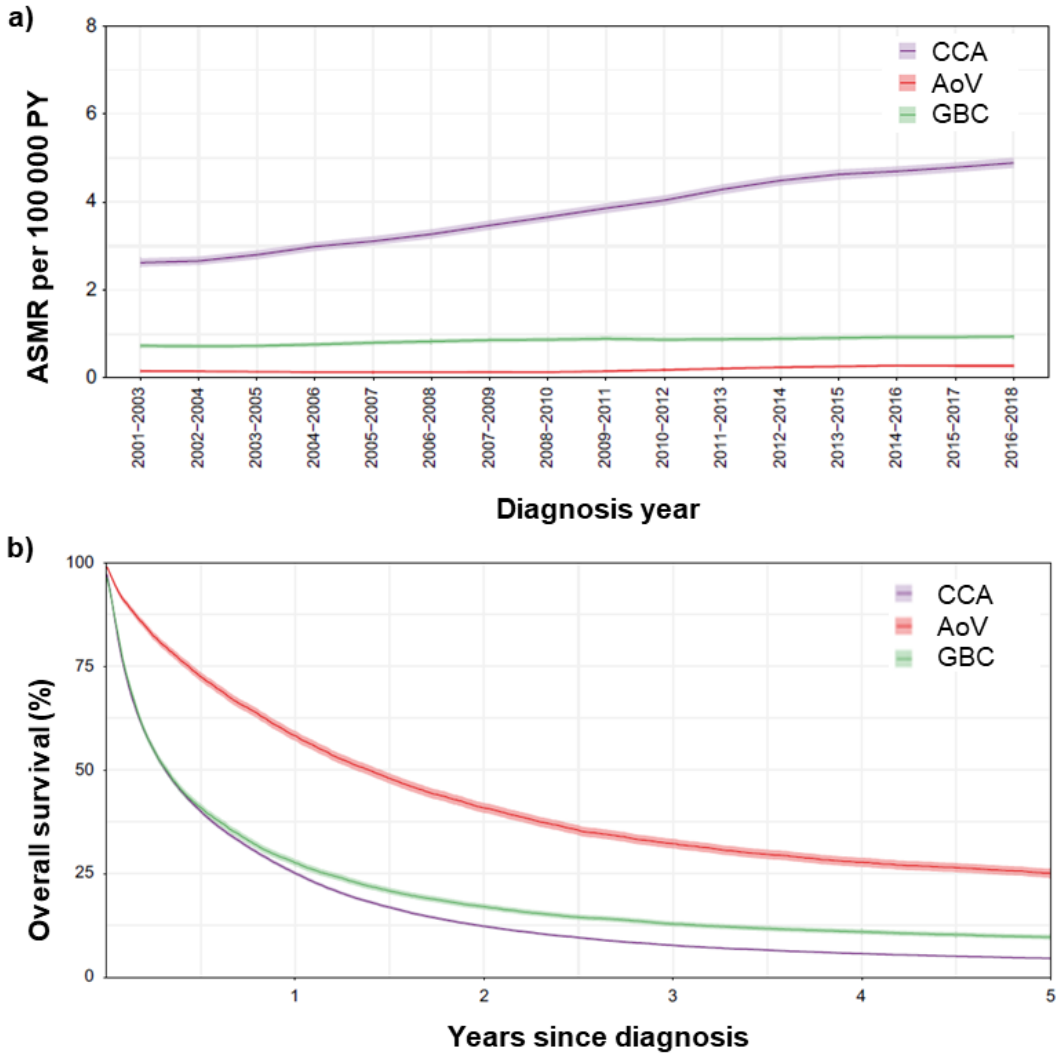
Patients with BTC have a poor prognosis and the majority do not survive beyond 1 year from diagnosis (6). In England between 2001 and 2018, patients with CCA

and GBC had 1-year survival estimates of 25.1% (95% confidence interval [CI]: 24.7, 25.6) and 27.6% (95% CI: 26.8, 28.4), respectively (**Figure 4**) (6).

Mortality rates for BTC also increased from 2001 to 2018, with a similar pattern to incidence (**Figure 4**) (6). At 3 years from diagnosis, the overall survival (OS) estimates for CCA and GBC decreased substantially to 7.7% (95% CI: 7.4, 8.1) and 12.9% (95% CI: 12.3, 13.5), respectively (6).

If patients survive long enough to start systemic therapy, survival rates are poor. In a real-world study of UK patients diagnosed with advanced BTC between 2018 and 2021 who initiated first-line (1L) systemic therapy (n=150), the median OS was 8.8 months from 1L treatment initiation (95% CI: 7.2, 10.6) (17). Similarly, in the UK-based ABC-06 trial, the median OS of patients treated with second-line (2L) folinic acid, fluorouracil, and oxaliplatin (FOLFOX) + active symptom control (ASC) was 6.2 months (21). FOLFOX + ASC only had a modest survival benefit of 0.9 months over palliative care with ASC alone (6.2 months [95% CI 5.4, 7.6] vs 5.3 months [95% CI 4.1, 5.8], respectively) (21).

**Figure 4: Mortality rate and overall survival by BTC subtype in England between 2001 and 2018**




Abbreviations: AoV, ampulla of Vater; ASMR, age-standardised mortality rate; BTC, biliary tract cancer; CCA, cholangiocarcinoma; GBC, gallbladder cancer.
Source: Tataru (2023) (6).

### 1.3.3 Current pathway of care and treatment guidelines

#### *1.3.3.1 Current patient pathway*

##### 1.3.3.1.1 Presentation and diagnosis of BTC

Initially, BTC is typically asymptomatic and patients often present after disease progression with non-specific symptoms such as jaundice, tiredness, and itching (4).

Real-world data in England show 49.6% of patients with CCA and 46.2% with GBC presented through accident and emergency (A&E), with fewer than 15% via the 2-week urgent referral pathway (6). NHS England highlighted GBC and CCA as particularly aggressive cancers that should be diagnosed within 21 days, faster than the 28-day best practice timed pathway standard (32).

This pattern of late diagnosis in BTC is similar to other high mortality cancers (e.g. pancreatic cancer) that are initially asymptomatic or present with non-specific symptoms (33). Emergency presentations of cancers are generally associated with advanced stage disease at diagnosis and poorer outcomes (6, 34). Furthermore, there are often delays from diagnosis until treatment is initiated; in the UK, the median time from advanced BTC diagnosis to treatment in 2018 to 2021 was 4.1 weeks (interquartile range [IQR]: 2.3, 8.3), primarily due to patient choice (17).

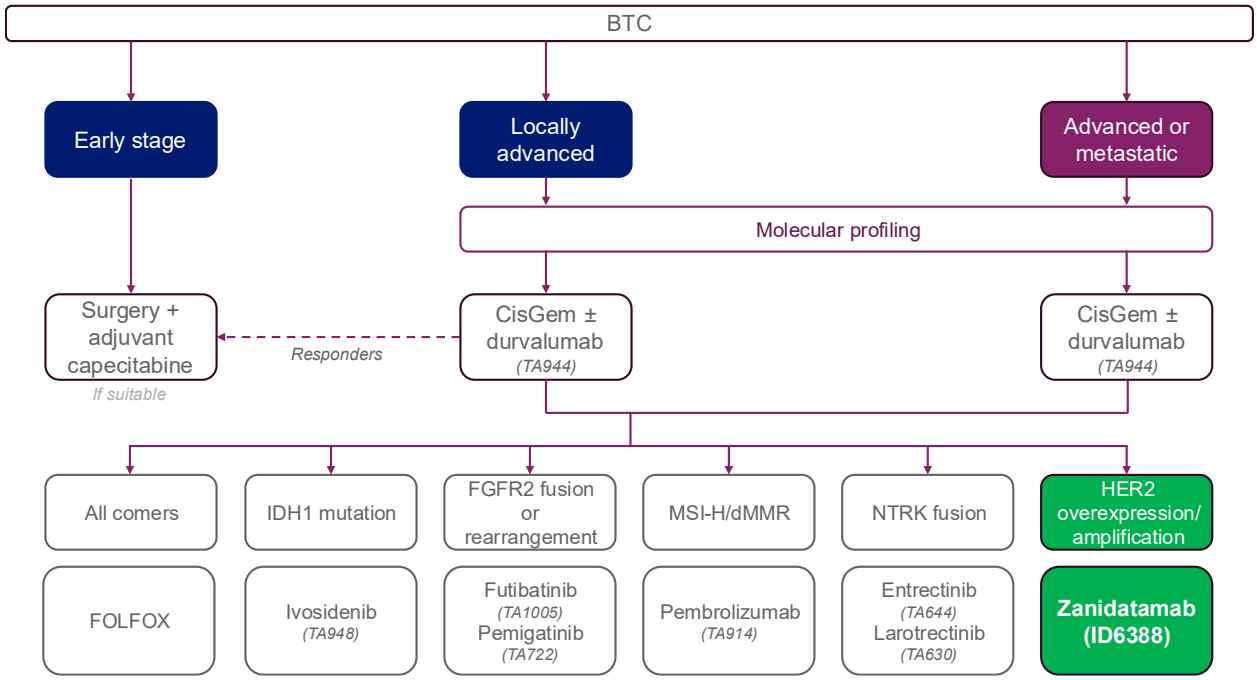
#### 1.3.3.1.2 Provision of care

In England, adults with suspected or confirmed diagnosis of BTC should have assessment, management, and specialist interventions delivered by Specialist hepato-pancreatic biliary (HPB) Cancer Services, which includes management by a specialist multi-disciplinary team (MDT) and a Clinical Nurse Specialist with expertise in HPB cancers (35). However, in clinical practice, this may vary in the NHS (32, 36).

#### 1.3.3.1.3 Treatment of BTC

Figure 5 presents the current treatment pathway for patients with BTC and the proposed place in therapy for zanidatamab.

**Figure 5: Current treatment pathway in BTC and zanidatamab's proposed place in therapy**




Abbreviations: BTC, biliary tract cancer; CisGem, cisplatin and gemcitabine; dMMR, mismatch repair deficient; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; NICE, National Institute for Health and Care Excellence; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; TA, technology appraisal.
Sources: Vogel (2025), relevant NICE TAs (14, 15, 18-20, 37-39).

### *Surgery*

The only curative option for BTC is surgical resection of local disease (14). The majority of patients diagnosed with BTC will be unsuitable for surgery because their cancer is already locally advanced or metastatic (5, 11). Only 21% of patients diagnosed with CCA are considered to have early-stage disease (Stage 1 or 2) (11). In addition, a high proportion of patients who have undergone resection will develop cancer recurrence (40-42).

### *Active symptom control*

Due to the aggressive nature of BTC, many patients are too unwell or do not survive long enough to receive treatment (4, 43); real-world UK data found that approximately 50% of patients with CCA receive no surgery, systemic therapy, or stent insertion for their disease (43). As such, some patients are treated solely palliatively with best supportive care (BSC) and/or ASC which only treats symptoms. In this population, ASC includes interventions such as biliary drainage/stents (surgical intervention to unblock or bypass blockages in the bile duct or small intestine) and/or radiotherapy (44).

### *Pharmacological treatment*

Pharmacological treatment of advanced BTC with systemic or targeted therapies focuses on extending life and reducing symptoms, as described in European Society for Medical Oncology (ESMO) and British Society for Gastroenterology (BSG) guidelines (13, 14) (see **Figure 5**).

1L treatment for advanced BTC typically consists of cisplatin and gemcitabine (CisGem) with durvalumab (13-15). Patients who experience disease progression or unsuitable toxicity after 1L therapies can be offered 2L and third-line (3L) treatment (13, 14, 25).

Currently, 2L treatment of advanced BTC comprises standard combination chemotherapy (FOLFOX) combined with ASC for eligible patients (13, 45). Real-world data of UK patients with BTC requiring 2L treatment (n=44) showed the most common 2L regimens were FOLFOX (n=10; 22.7%), fluorouracil and oxaliplatin (FOX) (n=8; 18.2%) and capecitabine and oxaliplatin (CAPOX) (n=8, 18.2%) (17). However, the proportion of UK patients who live long enough or are fit enough to receive further lines of treatment is low, with only 28.4% and 1.9% of patients receiving 2L and 3L, respectively (17).

### *Burden of 2L chemotherapy*

Combination 2L chemotherapy regimens, such as FOLFOX, can impose a substantial symptomatic burden on patients, caregivers and nursing time (21, 46). Patients must be assessed as fit enough for chemotherapy, due to the heavy treatment burden and severe adverse events (AEs) associated with these regimens

(21). Although FOLFOX is generally considered the current standard of care (SoC) 2L treatment for unresectable locally advanced or metastatic BTC, the burden of treatment is often challenging and/or contraindicated, with only 28.4% of patients receiving subsequent therapy after 1L (17, 21).

Administration of FOLFOX requires aseptic preparation of 3 drugs: folinic acid (FA), fluorouracil (5FU), and oxaliplatin (23). FA and oxaliplatin are administered via infusion through central venous access devices (peripherally-inserted central catheter [PICC], central line, or portacath [availability dependent on centre]). These 'central lines' pose a substantial patient and healthcare burden, are associated with AEs, require invasive procedures to insert and nursing time to maintain (23, 24, 47). Following the 2-hour infusion of FA and oxaliplatin, patients receive 5FU continuously over 46 hours via a portable pump (23). Removal of the pump requires a further hospital attendance or a visit by a chemotherapy nurse (23). In addition, before starting 5FU, patients must be tested for dihydropyrimidine dehydrogenase (DPD) deficiency using a genetic test (23, 48).

#### *1.3.3.2 Advanced BTC: treatment guidelines*

ESMO and BSG guidelines recommend FOLFOX + ASC for 2L treatment of advanced/metastatic BTC after 1L CisGem with durvalumab (13, 14) (**Figure 5**). Early detection (before treatment initiation) of actionable molecular targets is recommended in these guidelines to allow for efficient initiation of treatment with targeted therapies, if eligible (13, 14). Current National Institute for Health and Care Excellence (NICE) guidelines for targeted therapies in the 2L treatment of advanced BTC, supported by ESMO guidelines, recommend the use of pemigatinib (TA722) or futibatinib (TA1005) for patients with advanced CCA with fibroblast growth factor receptor 2 (FGFR2) fusion/rearrangement, and ivosidenib (TA948) for patients with advanced CCA with isocitrate dehydrogenase 1 (IDH1) R132 mutation (18, 19), (20).

No targeted 2L treatments are currently recommended by NICE for patients with HER2+ IHC3+ BTC. However, HER2-targeted therapies, including zanidatamab, are recommended as a 2L treatment by ESMO (14).

#### *1.3.3.3 Molecular profiling in BTC*

ESMO, BSG, and local guidelines all recommend molecular profiling at diagnosis for all patients with BTC (13, 14, 45). Approximately 40 to 60% of BTC tumours have actionable molecular targets suitable for targeted therapy, including IDH1, fibroblast growth factor receptor (FGFR), and neurotrophic tropomyosin kinase receptor (NTRK) mutations (14, 49). **Table 3** presents an overview of the frequency of specific actionable targets in BTC.

**Table 3: Frequency of targetable genetic alterations in BTC**

| Gene | Alteration type | Frequencies in BTC |
|---|---|---|
| IDH1 (19) | Mutation | 1 to 18% |
| FGFR2 (18, 20) | Fusion, mutation | Fusion/rearrangement: <10%<br>Mutation: 2% |
| HER2 (ERBB2/3) | Mutation, amplification | Amplifications: 5 to 10%<br>Mutations: 3 to 5% |
| NTRK1–3 (37, 38) | Fusion | <1% |

Abbreviations: BTC, biliary tract cancer; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1.
Source: Vogel (2025) (14), Rushbrook (2024) (13).

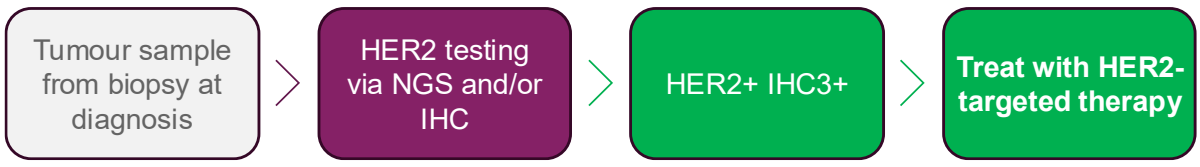
#### 1.3.3.3.1 HER2 status

HER2 overexpression/amplification/mutation (ERBB2 gene) are potential actionable targets in BTC, with approximately 5 to 10% of CCAs, and up to 20% of GBCs suitable for HER2-targeted treatment (3, 25). However, there are currently no HER2-targeted treatments available in England for this population.

HER2 testing at diagnosis and before 1L therapy is recommended by ESMO to allow for targeted treatments in patients with HER2+ IHC3+ BTC, to inform treatment decisions, and to potentially optimise outcomes for patients (14). HER2 overexpression/amplification/mutation can be detected through immunohistochemistry (IHC) testing and/or next-generation sequencing (NGS) (**Figure 6**) (14, 25), which are routine in NHS clinical practice (13, 45, 50).

HER2 testing using NGS and/or IHC at diagnosis can determine if a patient has HER2+ BTC and could be eligible for a HER2-targeted 2L therapy (**Figure 6**). HER2/ERBB2 is now included in the National Genomic Testing Directory's multi-target small variant NGS panel already funded routinely in England to detect IDH1 in CCA (50). In addition, an HER2+ IHC3+ result through IHC testing is required to show if patients are eligible zanidatamab (**Figure 6**). HER2 IHC testing should ideally be done upfront at diagnosis, known as 'reflex' testing, on samples that are already HER2-positive by NGS (36). A clinical study showed that approximately 77.5% of patients with HER2+ BTC were also classified as IHC3+ (22).

**Figure 6: Algorithm to evaluate HER2 IHC3+ status at diagnosis**




Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing.
Sources: Adapted from Dumbrava (2019) (51) and Vogel (2025) (14).

HER2 status has not been proven to be prognostic of patient outcomes in BTC, so it is not expected that the survival of HER2+ patients would differ widely from BTC populations without HER2 amplification, overexpression, or mutation (52). A real-world analysis of 12 US patients with HER2+ BTC treated with 2L chemotherapy identified consistent OS with previously reported OS in 2L BTC regardless of HER2 status (53).

Due to anatomical variation in cancer-inducing molecular alterations, patients with BTC generally do not harbour both 1) an actionable mutation targeted by approved precision medicines and 2) HER2 amplification, overexpression, or mutation (22, 36, 54). In the unlikely situation of a patient with co-existing mutations, concurrent treatment with combined targeted therapies is not expected; instead, the decision on choice of therapy at local MDTs or molecular tumour boards can be aided using guidelines such as the ESMO European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) framework (16).

### 1.3.4 Burden of disease

#### *1.3.4.1 Clinical and humanistic burden*

While early BTC diagnosis offers the potential for curative surgery, most patients are not eligible for surgery, as diagnosis often occurs at an already advanced stage (11, 14). Furthermore, the chance of BTC recurrence following surgery is high, with 56.9% to 86.8% of patients experiencing disease recurrence (40-42).

A diagnosis of advanced BTC is devastating to patients and their families (4), driven by poor prognosis and highly burdensome symptoms and treatment regimens that impact on physical and cognitive functioning, work participation, and emotional wellbeing (4, 7, 10, 55).

BTC has a considerable impact on the quality of life (QoL) of patients. Symptoms of advanced BTC (including fatigue, lack of energy, and abdominal pain) and their management (biliary drainage, radiotherapy, chemotherapy) are highly burdensome and negatively impact daily functioning and QoL (10). The burden of these symptoms extends beyond physical discomfort, resulting in a substantial negative impact on patients' emotional wellbeing, mental health, cognitive functioning, and physical abilities (e.g. difficulty walking) (7, 10, 41). Fatigue is the most commonly reported symptom in patients with CCA, with 67% of patients reporting this symptom as having a considerable or great deal of impact on daily life (55).

The poor prognosis and daily symptoms of BTC create a substantial mental health burden for patients and their families/caregivers, with many experiencing anxiety and distress (7-10). In patients with CCA (n=707), 94% report depression and 34% report moderately severe depression through the Patient Health Questionnaire-9 (PHQ)-9 score (55). In addition, the majority of caregivers of patients with CCA (n=60) report

exhaustion when they go to bed (80%), emotional difficulty (72%), and minimal time for themselves (70%) (55). The main challenges associated with caregiving for patients with CCA are managing the emotional or mental distress of caregiving (83%), pressure of understanding treatment options (60%), and pressure of understanding CCA (55%) (55). Based on depression screening (PHQ-9 score), 10%, 25%, and 38% of caregivers report moderately severe, moderate, and mild depression, respectively (55). Furthermore, almost half (47%) of employed caregivers report a considerable or great deal of impact on employment (55).

The burden of being treated with 2L chemotherapy is substantial, with patients requiring considerable time in hospital or outpatient settings for treatment, insertion and maintenance of a central venous access device (Section **1.3.3.1.3**), and often experiencing severe chemotherapy-related AEs (21, 24, 46, 47). Due to the aggressive nature of BTC, many patients are too unwell to tolerate 2L chemotherapy and have minimal treatment options following 1L treatment (Section **1.3.5**). Availability of chemotherapy-free options, such as zanidatamab for patients with HER2+ IHC3+ BTC, would offer patients a 2L treatment that could improve survival over ASC, without the tolerability burden of chemotherapy (22, 54).

#### *1.3.4.2 Economic and socioeconomic burden*

Although UK-specific economic data for BTC are sparse, studies highlight the healthcare resource utilisation (HCRU) and cost burden of living with this aggressive cancer. Costs associated with treatment and diagnostics (including inpatient hospitalisation and diagnostic imaging) are major contributors to the overall economic burden of BTC globally (56).

A 2024 UK study showed that HCRU for patients with advanced BTC (n=150) included an average of 0.36 A&E visits, 0.44 hospitalisations, and 14.09 office visits per patient per year (17).

The per-patient cost generally increases as patients progress to subsequent lines of therapy, leading to end-of-life costs (56). Patients at the end of life require substantial health care, social care, and social security; the average public expenditure per person in the last year of life in the UK is now estimated to be £33,690, of which £25,460 relates to health and social care (57).

BTC can affect not only older but also younger patients of working age (less than 65 years) (17). In patients with BTC (n=23), approximately 50% reported being unable to work due to the condition (10). In patients with CCA (n=707), 98% reported impact of the disease on their work status (55). Furthermore, almost half (47%) of employed caregivers report a considerable or great deal of impact on their employment (55).

### 1.3.5 Unmet need

Patients with HER2+ IHC3+ BTC have very limited treatment options after 1L therapy with CisGem with durvalumab (14). It is unlikely that these patients would be eligible for other targeted treatments due to the very low frequency of co-expression of actionable mutations (22, 54). Therefore, HER2+ IHC3+ BTC patients are limited to 2L treatment with standard combination chemotherapy with FOLFOX, which has minimal impact on patient survival and is associated with considerable toxicity concerns and poor tolerability (14, 21). Many patients with advanced BTC following 1L treatment are too unwell to undergo chemotherapy; only 28.4% (44 of 155) of UK patients with advanced BTC who had 1L treatment received 2L treatment (17).

In the UK ABC-06 study, patients treated with FOLFOX and ASC showed only a modest improvement in survival, with a median OS improvement of only 0.9 months vs. palliative care with ASC alone (6.2 months [95% CI: 5.4, 7.6] vs. 5.3 months [95% CI: 4.1, 5.8]) (21). In total, 69% of patients receiving FOLFOX in ABC-06 experienced Grade 3 to 5 AEs, including 3 (4%) chemotherapy-related deaths (21).

As such, patients with advanced or metastatic HER2+ IHC3+ BTC urgently need effective 2L targeted therapies with a demonstrated survival benefit over conservative management or standard chemotherapies, with a more manageable tolerability profile, while maintaining their health-related quality of life (HRQoL).

### 1.3.6 Zanidatamab: innovation, mechanism of action and place in treatment pathway

Zanidatamab is an innovative HER2-targeted therapy and represents a ‘step change’ in the 2L treatment of locally advanced or metastatic BTC. If recommended by NICE, zanidatamab will be the first HER2-targeted therapy available to UK patients, whose treatment options are currently limited to systemic chemotherapy with its associated tolerability burden. Zanidatamab has the potential to transform treatment for patients with HER2+ IHC3+ BTC, offering a chemotherapy-free option with improved survival and a more manageable safety profile vs. the current SoC. The high unmet need in BTC and innovation of zanidatamab is reflected in the [redacted]

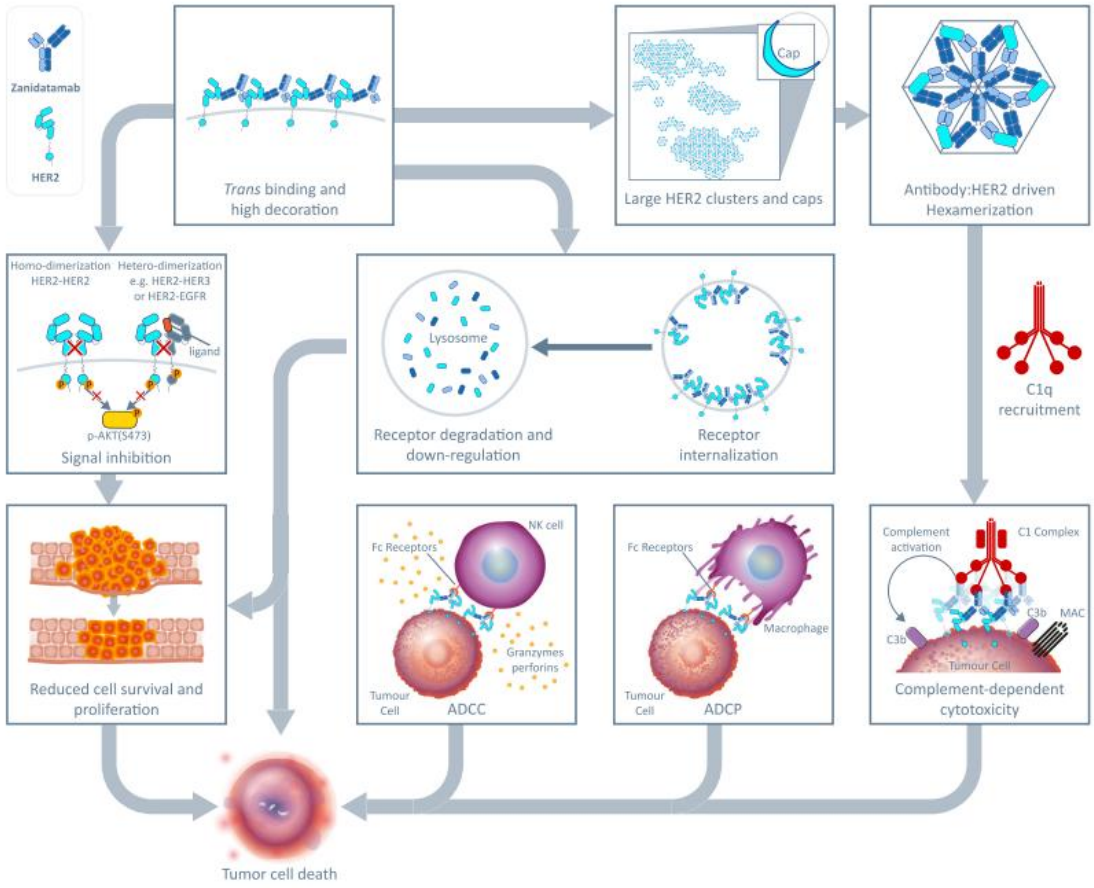
If recommended, zanidatamab will be indicated for [redacted] (1). [redacted]

[redacted] (1).

Zanidatamab has a unique and innovative mode of action (Figure 7): it is a humanised immunoglobulin G isotype 1-like dual bispecific antibody that targets 2 distinct domains of HER2 (58). The unique design and bispecific HER2-binding of zanidatamab results in multiple mechanisms of anti-tumour action (58). Zanidatamab reduces growth signalling, through promoting HER2 cluster formation on the cell surface and internalisation of antibody-bound HER2 molecules. A major driver of zanidatamab's anti-tumour activity is the formation of large cell-surface HER2 clusters that promote complement-dependent cytotoxicity, receptor internalisation, and immune cell recruitment (58). Zanidatamab recruits immune cells and complement molecules to these antibody-HER2 clusters on the cell surface. Recruited immune cells such as natural killer cells and macrophages are then able to kill tumour cells via antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis. Activation of the complement pathway can either directly trigger cellular death or recruit further immune cells (1).

**Figure 7: Mechanism of action of zanidatamab in HER2+ IHC3+ BTC**




Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2-positive; IHC, immunohistochemistry.
Source: Weisser (2023) (58).

Figure 5 presents the proposed positioning of zanidatamab in the UK treatment pathway. If recommended, zanidatamab would provide an additional treatment option for patients with HER2+ IHC3+ BTC, replacing systemic chemotherapy (FOLFOX + ASC). Zanidatamab could also provide a disease-modifying treatment for those patients who are ineligible for or cannot tolerate chemotherapy, who currently only receive ASC alone.

ESMO 2025 guidelines on the management of BTC already recommend zanidatamab in this position of the treatment pathway (14).

Very few patients are expected to require subsequent therapies after 2L treatment in BTC; only 1.9% of 155 UK patients treated between 2018 to 2021 were treated in 3L (17). For these patients, 3L therapy in the existing treatment pathway (after FOLFOX in 2L) is folinic acid, fluorouracil, and irinotecan (FOLFIRI). With the addition of zanidatamab to the treatment pathway, clinical experts noted that FOLFOX would be used in 3L following discontinuation of zanidatamab (36).

No additional service delivery needs are expected with zanidatamab, since molecular profiling with IHC or NGS panels that already includes HER2/ERBB2 should be done at BTC diagnosis, which would identify a patient as HER2-positive before 2L therapy. In order for a patient to be eligible for zanidatamab, a patient must have confirmed HER2+ tumour status defined as a score of 3+ by IHC (1). The biopsy required for this IHC test is recommended by clinical guidelines to be conducted as early as possible at diagnosis. IHC HER2+ testing is already carried out routinely for breast and gastric cancers in the NHS, and is already commonly performed for BTC. Half of the 14 UK clinicians consulted in the Delphi panel stated IHC was undertaken routinely in their clinical practice already. As such, minimal additional service delivery will be needed to assess eligibility for zanidatamab at 2L. In addition, zanidatamab monotherapy will be administered intravenously in outpatient settings already set up to deliver chemotherapy for this patient population. As a single agent delivered intravenously via a peripheral canula, zanidatamab has the potential to reduce pharmacy time, nursing time, infusion time, and maintenance time, when compared with FOLFOX which requires 3 agents delivered via a PICC/portacath as well as an infusion pump over 46 hours, in 14-day cycles.

## *1.4 Equality considerations*

No equality issues associated with zanidatamab are foreseen. However, increased access to targeted therapies, including zanidatamab may reduce health inequalities in UK patient populations with BTC.

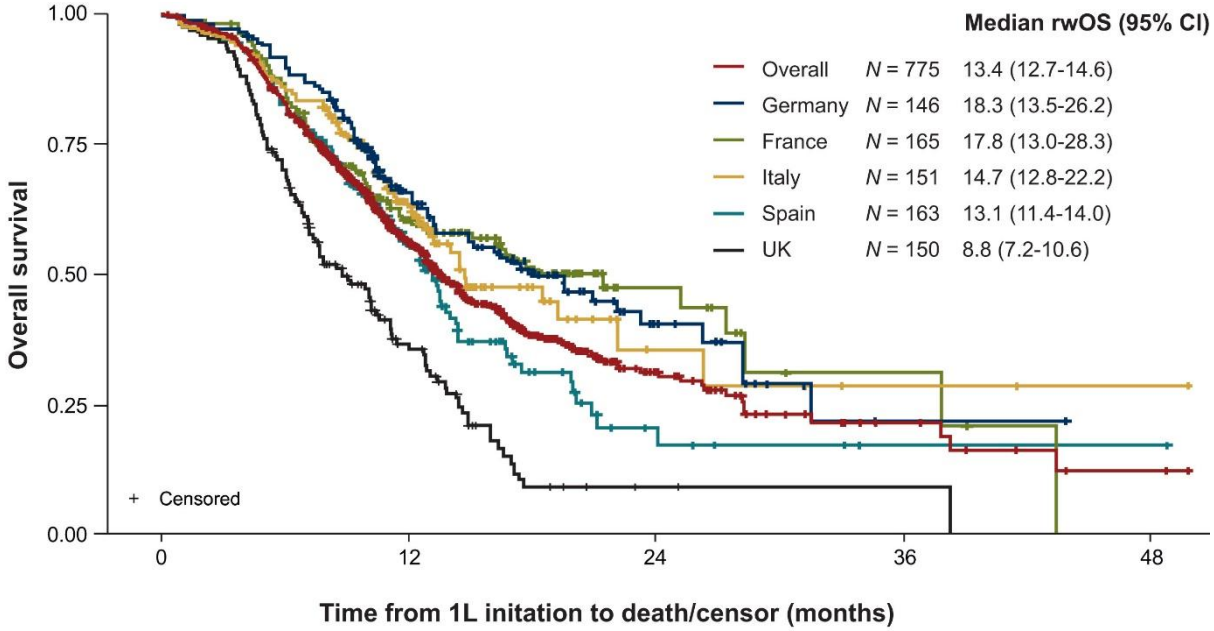
People in England in the most socioeconomically deprived groups have a higher incidence of BTC and higher mortality rates from BTC (6). In 2016 to 2018, the age-standardised mortality rates per 100,000 person-years in the most deprived and least deprived CCA groups were 5.9 (95% CI: 5.6, 6.2) and 4.3 (95% CI: 4.1, 4.5),

respectively, resulting in a “mortality deprivation gap” of 37%. The corresponding differences were 1.4 (95% CI: 1.2, 1.5) and 0.8 (95% CI: 0.7, 0.9) for GBC, and 0.3 (95% CI: 0.2, 0.4) and 0.3 (95% CI: 0.3, 0.4) for AoV cancer (6). In addition, patients with BTC showed substantial regional variation, with the highest incidence and mortality rates in the North of England (6).

Furthermore, considerable disparity is seen in survival between patients treated in the UK compared with other European countries. A real-world study of patients diagnosed with advanced BTC between 2018 and 2021 showed patients in the UK have lower median OS compared with Germany, France, Italy, and Spain (Figure 8), with a statistically significantly difference of 4.6 months overall (17).

**Figure 8: Real-world overall survival of advanced BTC patients diagnosed between 2018 and 2021 (Kaplan-Meier)**




Abbreviations: 1L, first line; BTC, biliary tract cancer; CI, confidence interval; rwOS, real-world overall survival.
Source: Bridgewater (2024) (17).

# 2 Clinical effectiveness

***Summary: zanidatamab clinical effectiveness and safety***

- Efficacy and safety of zanidatamab in patients with HER2+ IHC3+ BTC after 1 or more previous systemic therapies was assessed in the key Phase 2b trial (HERIZON-BTC-01), a Phase 1 trial (ZWI-ZW25-101) (59), and real-world studies in England (60) and France (61):
  - In HERIZON-BTC-01 (a global, multi-centre, single-arm clinical trial, and the largest to date in 2L+ HER2+ BTC), zanidatamab showed meaningful clinical benefit in patients with HER2+ IHC3+ BTC (n=62) and maintained QoL (22, 62):
    - Confirmed ORR in 51.6% of patients
    - Rapid and durable responses, with median DOR of 14.9 months
    - Median OS of 18.1 months and a 12-month OS rate of 65.0%
    - Median PFS of 7.2 months.
    - Modest HRQoL improvement from baseline, particularly in patients with CR or PR
  - Results from ZWI-ZW25-101 (HER2+ IHC3+ BTC, n=14), align with the clinical effectiveness profile seen in HERIZON-BTC-01 (63)
  - Real-world evidence of patients with HER2+ IHC3+ BTC treated with zanidatamab in France and England supports the efficacy seen in clinical trials:
    - England (n=13 evaluable patients): ORR = 54%; DCR = 62% (60)
    - France (n=12 IHC3+): median PFS: 8 months; 1-year estimated OS rate: 90.9% (61)
- In the absence of head-to-head trial data, indirect comparisons show zanidatamab monotherapy has better efficacy vs. relevant comparators (FOLFOX + ASC and ASC alone from ABC-06):
  - Compared through unanchored MAIC (HERIZON-BTC-01 and ABC-06 trials), zanidatamab showed improvements in OS vs. FOLFOX + ASC (weighted HR: [redacted]) or ASC alone (weighted HR: [redacted]) and PFS vs. FOLFOX + ASC (weighted HR: [redacted])
  - A weighted comparison of IHC3+ patients in HERIZON-BTC-01 and an external control arm of IHC3+ patients treated with chemotherapy in the US showed longer median OS (HR: 0.29) and PFS (HR:0.47) with zanidatamab (53)
  - In naive comparisons with the UK ABC-06 trial, zanidatamab shows a substantial survival benefit (OS: 18.1 months) vs. FOLFOX + ASC (OS: 6.2 months) and ASC alone (OS: 5.3 months) (21, 54)
  - Due to methodological uncertainties (as noted in previous TAs) with the MAIC and the external control arm, naive comparison of zanidatamab vs. FOLFOX + ASC and ASC alone is taken forward as the base case approach
- Clinical trial and real-world evidence support a well-tolerated safety profile with zanidatamab, including fewer incidences of severe (Grade 3 to 5) AEs than FOLFOX + ASC (21, 54):
  - In HERIZON-BTC-01, [redacted]% of all patients treated with zanidatamab experienced Grade 3 or 4 TRAEs
  - In ABC-06, patients treated with FOLFOX experienced 38.3% of Grade 3 to 5 TRAEs, with 3 (4%) chemotherapy-related deaths
  - In real-world evidence, patients in England (n=20) treated with zanidatamab experienced only 1 (5%) severe (Grade 3) AE of diarrhoea (60), while patients in France (n=20; all patients [IHC2+ and IHC3+])) reported no severe (Grade 3+) AEs (61)
- Zanidatamab monotherapy provides a much-needed chemotherapy-free HER2-targeted treatment for patients with HER2+ IHC3+ BTC, with substantial improvements in survival compared with FOLFOX + ASC and improved tolerability, whilst maintaining QoL (21, 54). The favourable safety profile of zanidatamab also offers patients not fit enough for chemotherapy a life-extending treatment option

## 2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in August 2023, with updates in September 2024 and March 2025, to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments for advanced or metastatic BTC, in patients who have been previously treated with 1 or more lines of therapy.

An overview of the methodology, including search strategy, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix B.

## 2.2 List of relevant clinical effectiveness evidence

The clinical SLR database searches identified 2 studies reporting on the efficacy and safety of zanidatamab in patients with HER2+ locally advanced or metastatic BTC.

HERIZON-BTC-01 (NCT04466891) was a pivotal Phase 2b open-label, single-arm, multi-centre international study to assess the efficacy and safety of zanidatamab and is considered the key evidence for zanidatamab (22). Data from HERIZON-BTC-01 has been included in the economic model presented in this submission.

The second study, ZWI-ZW25-101 (NCT02892123), was a Phase 1 dose-escalation and expansion study of zanidatamab in HER2-expressing or HER2-amplified solid tumours, including BTC (63). Zanidatamab demonstrated encouraging, durable anti-tumour activity in patients with HER2+ BTC in the Phase 1 study (63), which was largely consistent with the results from the HERIZON-BTC-01 trial (22). However, the study enrolled a small BTC population and was not sufficiently powered to detect significant differences between treatment groups. Therefore, these data are only considered as supportive evidence; key findings from this study are presented in Appendix L.

In addition to the 2 studies identified through database searches in the clinical SLR, Jazz Pharmaceuticals identified 2 further studies that provide supportive evidence for clinical effectiveness and safety; these are real-world studies of patients treated with zanidatamab under compassionate use in England (University College London Hospital [UCLH]) (60) and France (61).

An overview of the studies used to support this submission are presented in **Table 4**.

**Table 4: Clinical effectiveness evidence for zanidatamab in 2L HER2+ BTC**

| Study | HERIZON-BTC-01 | ZWI-ZW25-101 | UCLH real-world evidence study | France real-world study |
|---|---|---|---|---|
| **Study design** | Phase 2b, open-label, single-arm, multi-centre international study | Phase 1, multi-centre, dose-escalation and expansion trial | Retrospective, observational, real-world study | Retrospective, observational, real-world study |
| **Population** | Patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC<br>• Full population: n=87<br>• Cohort 1 (IHC2/3+): n = 80<br>• HER2+ IHC3+: n=62 | Patients with HER2-amplified solid tumours, including BTC<br>• Full population (Part 2): n=86<br>• BTC population (Part 2): n=22<br>• HER2+ IHC3+ BTC: n=14 | Patients with HER2-amplified BTC after 1L treatment with CisGem ± durvalumab<br>• Full population: n=20<br>• 2L+ HER2+ IHC3+: n=NR | Patients with HER2+ BTC previously treated with systemic therapy<br>• Full population: n=20<br>• 2L+ HER2+ IHC3+: n=12 |
| **Intervention(s)** | Zanidatamab | Zanidatamab | Zanidatamab | Zanidatamab |
| **Comparator(s)** | N/A – HERIZON-BTC-01 was a single arm study | N/A – ZWI-ZW25-101 was a single arm study | N/A | N/A |
| **Indicate if study supports application for marketing authorisation** | Yes | Yes | No | No |
| **Indicate if study used in the economic model** | Yes | No – supportive evidence for efficacy and safety only | Yes - real-world patient demographics used in scenario analyses | No – supportive evidence for efficacy and safety only |
| **Rationale if study not used in model** | N/A | HERIZON-BTC-01 was considered more appropriate for inclusion in the model | N/A | HERIZON-BTC-01 was considered more appropriate for inclusion in the model |
| **Reported outcomes specified in the decision problem[†]** | ORR<br>**OS**<br>**PFS**<br>**TTD** | ORR<br>PFS<br>AEs | ORR<br>OS<br>AEs | PFS<br>OS<br>AEs |

| Study | HERIZON-BTC-01 | ZWI-ZW25-101 | UCLH real-world evidence study | France real-world study |
|---|---|---|---|---|
| | **AEs**<br>**HRQoL** | | | |
| **All other reported outcomes** | DOR<br>DCR | CBR<br>DCR | N/A | DCR<br>DOR |
| **Key data sources** | Unpublished data:<br>• CSP (64)<br>• CSR DCO 11th July 2024(54)<br>• IHC3+ subpopulation TFLs DCO 11th July 2024 (62)<br>• SAP (65)<br>Publications:<br>• Harding (2023) (primary publication) DCO 10th October 2022 (22)<br>• Pant (2024) DCO 28th July 2023 (66)<br>• Pant (2024) DCO 10th October 2022 (67) | Unpublished data:<br>• CSR (59)<br>Publication:<br>• Meric-Bernstam (2022) (63) | Publication:<br>• Crespo-Cruz (2025) (60) | Publication:<br>• Smolenschi (2025) (61) |
| **Data included in submission dossier** | Methodology: Section 2.3.1<br>Clinical effectiveness: Section 2.6.1 (IHC3+) and Appendix J (full population and interim DCO)<br>Safety: Section 2.11.1 | Methodology: Appendix L.1<br>Clinical effectiveness: Appendix L.2<br>Safety: Appendix D.1 | Methodology: Section 2.3.2.1<br>Clinical effectiveness: Section 2.6.2.1<br>Safety: Section 2.11.2 | Methodology: Section 2.3.2.2<br>Clinical effectiveness: Section 2.6.2.2<br>Safety: Section 2.11.2 |

Abbreviations: AE, adverse event; BTC, biliary tract cancer; CBR, clinical benefit rate; CSP, clinical study protocol; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; HRQoL, health-related quality of life; IHC, immunohistochemistry; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SAP, statistical analysis plan; TFL, tables, figures, lists; TTD, time to treatment discontinuation; UCLH, University College London Hospitals.
†Outcomes in bold are the outcomes incorporated into the model.

## 2.3 Summary of methodology of the relevant clinical effectiveness evidence

### 2.3.1 HERIZON-BTC-01

#### 2.3.1.1 Summary of trial methodology

An overview of HERIZON-BTC-01 methodology is presented in **Table 5**. Full details are provided from Section **2.3.1.1.1** onwards.

**Table 5: Summary of HERIZON-BTC-01 methodology**

| | |
|---|---|
| **Study reference/ID** | HERIZON-BTC-01 (NCT04466891) |
| **Study design** | Global, multi-centre, single-arm, Phase 2b trial of zanidatamab (20 mg/kg IV Q2W) in patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC (including GBC, iCCA, and eCCA subtypes) with disease progression on previous gemcitabine-based therapy |
| **Location/setting** | Patients were recruited into 32 clinical trial sites in Canada, Chile, China, France, Italy, South Korea, Spain, UK, and USA |
| **Eligibility criteria** | Eligible patients were aged ≥18 years with HER2-amplified BTC confirmed by ISH per central testing, at least 1 measurable target lesion per RECIST v1.1, and an ECOG PS of 0 or 1 (22) |
| **Population and sample size** | • Overall population: n= 87<br>– Cohort 1 (HER2 IHC3+ and 2+ tumours): n=80<br>◊ IHC3+ subpopulation: n=62<br>– Cohort 2 (HER2 IHC1+ or 0 tumours): n=7 |
| **Primary endpoint** | • cORR by RECIST v1.1, assessed by ICR |
| **Secondary endpoint** | • cORR by RECIST v1.1, assessed by INV<br>• DCR by RECIST v1.1, assessed by ICR and INV<br>• DOR by RECIST v1.1, assessed by ICR and INV<br>• Proportion of patients with DOR at least 16 weeks by RECIST v1.1, assessed by ICR and INV<br>• PFS by RECIST v1.1, assessed by ICR and INV<br>• OS<br>• AEs |
| **Exploratory outcomes** | • HRQoL (EQ-5D-5L and BPI-sf) |

Abbreviations: cORR, confirmed objective response rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ICR, independent central review; RECIST, response evaluation criteria in solid tumours.
Sources: Harding (2023) (22); HERIZON-BTC-01 CSR (2025) (54).

##### 2.3.1.1.1 Trial design

HERIZON-BTC-01 was a Phase 2b, open-label, single-arm, multi-centre international study to assess the efficacy and safety of treatment with zanidatamab in

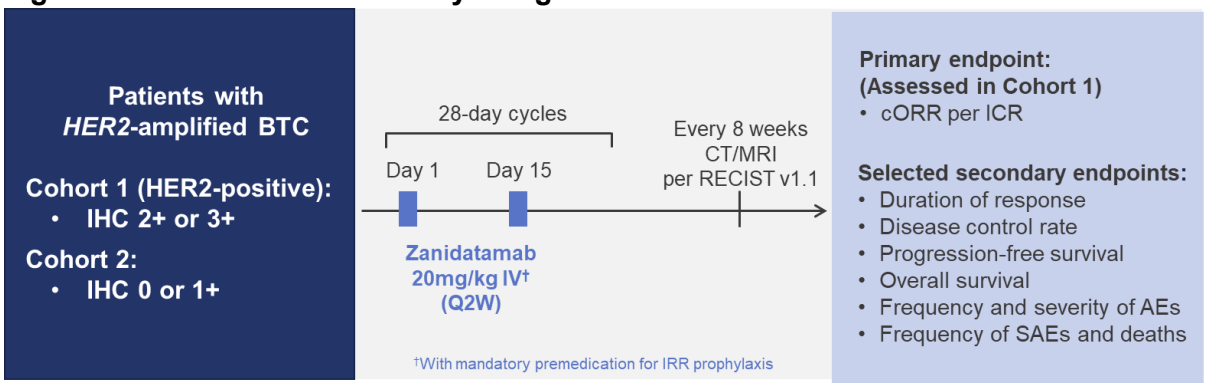
patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC previously treated with 1 or more lines of therapy with disease progression on previous gemcitabine-based therapy (22). HERIZON-BTC-01 is the largest clinical trial to date in 2L+ HER2+ BTC.

New or archival tumour tissue was required from each patient for HER2 amplification and HER2 protein expression testing using in-situ hybridisation (ISH) and IHC assays, respectively. Patients were tested for HER2 status any time after diagnosis of advanced or metastatic disease, but before trial enrolment (54). Patients who had HER2-amplified tumours confirmed by central laboratory ISH were enrolled into prospectively defined cohorts based on HER2 IHC score:

- Cohort 1: patients with HER2-amplification by ISH and HER2 overexpression by IHC, with a score of IHC2+ or IHC3+, defined as HER2+ (n=80)
- Cohort 2: patients with HER2-amplification by ISH and HER2 overexpression by IHC, with a score of IHC0 or IHC1+, defined as HER2- and HER2-low, respectively (n=7)

All patients enrolled in HERIZON-BTC-01 received zanidatamab intravenously at 20 mg/kg every 2 weeks (Q2W) on Days 1 and 15 of each 28-day cycle. The recommended dosage of zanidatamab (20 mg/kg Q2W) was based on results from the dose-expansion part of the Phase 1 trial ZWI-ZW25-101, which investigated zanidatamab in patients with HER2-expressing solid tumours (54) (see Appendix L). Patients continued on zanidatamab treatment until unacceptable toxicity, disease progression, death, loss to follow-up, pregnancy, physician decision, or withdrawal of consent (54). An overview of the trial design is presented in **Figure 9**.

**Figure 9: HERIZON-BTC-01 study design**




Abbreviations: AE, adverse event; BTC, biliary tract cancer; cORR, confirmed objective response rate; CT, computed tomography; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; IRR, infusion-related reaction; IV, intravenous; MRI, magnetic resonance imaging; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event.
Source: Adapted from Harding (2023) (22).

#### 2.3.1.1.2 Study objectives

The primary objective of HERIZON-BTC-01 was to evaluate the anti-tumour activity of zanidatamab monotherapy in patients with advanced or metastatic HER2-amplified BTC previously treated with 1 or more previous lines of therapy (54).

Secondary objectives of the study, relevant to this appraisal, were:

- To further evaluate the anti-tumour activity of zanidatamab monotherapy in patients with advanced or metastatic HER2-amplified BTC
- To evaluate the safety and tolerability of zanidatamab monotherapy in participants with advanced or metastatic HER2-amplified BTC

#### 2.3.1.1.3 Study locations

Patients were recruited at 32 clinical trial sites in Canada, Chile, China, France, Italy, South Korea, Spain, UK, and US (22), including 2 patients from 1 site in the UK.

#### 2.3.1.1.4 Data cut-offs

Three data cut-offs (DCOs) were performed. The primary DCO collected data up to 10th October 2022, with subsequent DCOs (28th July 2023, 11th July 2024) collecting updated results from longer follow-up of the original study participants.

The final DCO (11th July 2024) has been used to inform the economic model and outcomes from this DCO are presented throughout this submission as confidential. As the interim DCO (28th July 2023) was used to inform the European Medicines Agency (EMA) regulatory submission, these results have been presented alongside the final DCO throughout the submission. Full trial results from the interim DCO can also be found in Appendix J.

No further DCOs are planned and the trial results presented from the final DCO are considered final.

#### 2.3.1.1.5 Eligibility criteria

Patients eligible for enrolment in the HERIZON-BTC-01 trial were aged 18 years or older with pathologically confirmed, unresectable, locally advanced or metastatic HER2-amplified GBC, iCCA, or eCCA (22). Patients must have also received at least 1 previous gemcitabine-containing systemic chemotherapy regimen for unresectable, locally advanced or metastatic disease, or were in the neoadjuvant or adjuvant setting with progression or recurrence within 6 months of completion.

Patients were excluded from the trial if they had previously received treatment with HER2-targeting agents; received systemic anticancer therapy within 3 weeks of, or radiotherapy within 2 weeks of the first dose of zanidatamab; had untreated or symptomatic central nervous system (CNS) metastases; or had leptomeningeal disease (54).

Details of key inclusion and exclusion criteria for HERIZON-BTC-01 are presented in Table 6. A full list of inclusion and exclusion criteria are presented in Appendix K.

**Table 6: Eligibility criteria - HERIZON-BTC-01**

| Inclusion | Exclusion |
|---|---|
| • Males and females aged 18 years of age or older†<br>• Histologically or cytologically confirmed BTC, including iCCA, eCCA, and GBC<br>• Locally advanced or metastatic BTC, not eligible for curative resection, transplantation, or ablative therapies<br>• Received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and experience disease progression after or developed intolerance to the most recent prior therapy<br>• At least 1 measurable target lesion by RECIST v1.1<br>• Positive test for HER2 amplification by ISH assay<br>• ECOG PS 0 or 1<br>• Adequate haematologic, liver, cardiac, and kidney function<br>• Negative serum or urine pregnancy test, for relevant participants, within 3 days prior to first dose of zanidatamab | • Patients who had received systemic anticancer therapy or radiotherapy within 3 and 2 weeks, respectively, of the first dose of zanidatamab<br>• Major surgery within 4 weeks of the first dose of zanidatamab<br>• Prior treatment with HER2-targeted agents<br>• Untreated or symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks of the first dose of zanidatamab<br>• Known leptomeningeal disease<br>• Concurrent uncontrolled or active hepatobiliary disorders or untreated or ongoing complications after laparoscopic procedures or stent placement<br>• Prior or concurrent malignancy or treatment with the potential to interfere with the safety or efficacy of the assessment of the investigational regimen<br>• Significant acute infection or chronic infections not stabilised with treatment<br>• Active hepatitis, HIV-1, or HIV-2<br>• Breastfeeding or pregnancy, or patients planning pregnancy<br>• History of life-threatening hypersensitivity to monoclonal antibodies, recombinant proteins, or excipients in the drug formulation of zanidatamab<br>• Treatment with anthracyclines within 90 days of first dose of zanidatamab<br>• Use of systemic corticosteroids within 2 weeks of first dosing<br>• Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies<br>• QTcF greater than 470 ms<br>• History of myocardial infarction or unstable angina within 6 months prior to enrolment<br>• Acute or chronic uncontrolled pancreatitis or Child-Pugh Class C liver disease<br>• Any other factors that could impact safety or compliance with study procedures. |

Abbreviations: eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancerHER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; ISH, in-situ hybridisation; PS, performance status.
Source: Harding (2023) (22); HERIZON-BTC-01 CSR (2025) (54).

#### 2.3.1.1.6 Required, permitted, and disallowed concomitant medications

Concomitant medications that were required, permitted, or disallowed during HERIZON-BTC-01 were as follows:

- ***Required medications:*** All participants received mandatory prophylactic treatment for potential infusion reactions 30 to 60 minutes before each zanidatamab infusion. Pretreatment prophylaxis included corticosteroids (either hydrocortisone 100 mg IV or dexamethasone 10 mg IV or equivalent or per institutional guidelines), antihistamines (diphenhydramine 50 mg orally or IV or per institutional guidelines), and acetaminophen or paracetamol (650 to 1,000 mg orally or per institutional guidelines).
- ***Permitted medications:*** Concomitant medications for supportive therapy, including transfusions and bisphosphonates, and supportive care treatments, including growth factors and colony-stimulating factors, were allowed as required. Corticosteroid treatment (topical, ocular, intra-articular, intranasal, and/or inhalational) was permitted for acute medical conditions, for physiological replacement of systemic corticosteroids, for prophylaxis, and for treatment of non-autoimmune conditions. Routine prophylaxis with non-live vaccines and vaccines for COVID-19 were allowed. For patients who experienced an infusion reaction despite the required prophylaxis, other medication (per investigator or institutional standards), including H2-blockers, could be given in addition to the required medications. All other therapies not specifically listed in the exclusion criteria or prohibited therapy were also permitted.
- ***Disallowed medications:*** Patients were not permitted to receive cancer-related surgery, other investigational therapy, or systemic anti-cancer therapy during the study. Chinese or other herbal medicines, for the treatment of cancer, were also prohibited. Radiation therapy was generally prohibited; however, was permitted under certain circumstances (e.g. palliative radiation therapy to non-target sites) with sponsor approval. Use of alternative supplemental therapies was discouraged.

#### 2.3.1.1.7 Trial endpoints

***Efficacy and safety outcomes***

Table 7 presents the endpoints assessed in HERIZON-BTC-01 and their corresponding definitions. The primary endpoint of the HERIZON-BTC-01 trial was confirmed objective response rate (cORR) as assessed by independent central review (ICR) for Cohort 1. Secondary endpoints included duration of response (DOR) by response evaluation criteria in solid tumours (RECIST) v1.1, proportion of patients with a DOR 16 weeks or greater by RECIST v1.1, disease control rate (DCR) by RECIST v1.1, progression-free survival (PFS) by RECIST v1.1, and OS, all of which were assessed by ICR and investigator assessment (INV). Objective

response rate (ORR) was additionally assessed as a secondary endpoint by INV. All endpoints were also evaluated in Cohort 2 (54).

Safety analyses included frequency and severity of AEs, SAEs, deaths, clinical laboratory abnormalities, and frequency of dose modifications or discontinuation of zanidatamab (54). All AEs were coded to standard 'preferred terms' and system organ classifications using medical dictionary for regulatory activities (MedDRA) v25.0. Severity was graded by study investigators using National Cancer Institute-common terminology criteria for adverse events (NCI-CTCAE) v5.0 (54).

**Table 7: Summary of efficacy and safety endpoints – HERIZON-BTC-01**

| Study endpoint | Definition |
|---|---|
| **Primary endpoint** | |
| cORR | Confirmed objective response was defined as achieving a confirmed BOR of CR or PR per RECIST v1.1 |
| **Secondary endpoints** | |
| ORR by RECIST v1.1 assessed by INV | Objective response was defined as achieving a BOR of CR or PR per RECIST v1.1. |
| DOR by RECIST v1.1 assessed by ICR and INV | DOR was defined as the time from the first confirmed objective response (CR or PR) to documented PD per RECIST v1.1, or death from any cause. Patients who were alive and had not progressed at the time of the analysis were censored at the time of their last tumour assessment that was a CR, PR, SD, or non-CR/non-PD |
| Proportion of patients with a DOR ≥16 weeks by RECIST v1.1, assessed by ICR and INV | The proportion of patients with a DOR (i.e. the time from the first confirmed objective response [CR or PR] to documented PD per RECIST v1.1, or death from any cause) of ≥ 16 weeks |
| DCR by RECIST v1.1 assessed by ICR and INV | Disease control was defined as a BOR of stable disease or confirmed CR or PR per RECIST v1.1. |
| PFS by RECIST v1.1 assessed by ICR and INV | PFS was defined as the time from the first dose of study treatment to the date of documented disease progression (per RECIST v1.1) or death from any cause, whichever occurred first. Patients who were alive and had not progressed at the time of the analysis were censored at the time of their last tumour assessment that was a CR, PR, SD, or non-CR/non-PD. |
| OS | OS was defined as the time from the first dose of study treatment until the date of death from any cause or date last known alive for patients who did not die.<br>Patients alive at the time of analysis were considered as censored on the date the subject was last known to be alive (i.e. date of last contact). |
| **Safety** | |
| Frequency and severity of AEs, SAEs, deaths laboratory abnormalities, and frequency of zanidatamab dose modification or discontinuation | AEs were defined as AEs with an onset during or after receipt of the first dose of zanidatamab and up to and including 30 days after the last dose.<br>SAEs were summarised by preferred term and SOC using counts and percentages. Multiple occurrences of the same SAE within a patient were counted only once for the timeframe under |

| Study endpoint | Definition |
|---|---|
| | consideration. In addition to summary tables, listings of SAEs were produced.<br>A summary of deaths including cause of death was produced showing deaths that occurred ≤30 days after the last dose vs. those that occurred >30 days after the last dose. A listing of all deaths was also provided. |

Abbreviations: BOR, best overall response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; INV, investigator assessment; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumours; SAE, serious adverse event; SOC, standard of care.
Source: HERIZON-BTC-01 CSR (2025) (54).

***Patient-reported outcomes***

HRQoL was assessed using the EQ-5D-5L questionnaire, the Brief Pain Index-short form (BPI-sf), and opioid use.

Key outcomes assessed using the EQ-5D-5L and BPI-sf were as follows:

- Frequency and percentage of reported responses to the 5 dimensions of the EQ-5D-5L
- Patient's self-reported health status on a visual analogue scale (EQ-VAS) and disease-related pain (BPI-sf) at baseline, end of treatment, time of BOR, and best score while on treatment, was summarised using descriptive statistics. Change from baseline for the EQ-VAS and BPI-sf was defined for each patient at each post-baseline time point as the post-baseline score minus the baseline score

#### 2.3.1.1.8 Pre-planned subgroups

Prespecified subgroup analyses for efficacy endpoints included:

- Age (<65 or ≥65 or <75 or ≥75)
- Sex (male or female)
- Race (Asian or non-Asian)
- Geographical region (North America, Asia, or other)
- HER2 IHC score (2+ or 3+)
- Anatomical site (GBC, iCCA, eCCA)
- Number of previous therapies for advanced disease (<2 or ≥2)
- Disease stage at baseline (Stage IIB, III or IV)
- Intolerance to most receive previous treatment (yes or no)
- Baseline ECOG PS (0 or 1)

***Note: As IHC3+ BTC is the population of interest for this submission, all data presented in this section refer to the IHC3+ subpopulation of Cohort 1 from the HERIZON-BTC-01 trial (i.e. patients with HER2+ IHC3+ disease) (1, 54).***

Disease response by disease subtype is presented in Appendix C. No additional subgroup data are presented.

### *2.3.1.2 Baseline characteristics and demographics*

#### 2.3.1.2.1 Full trial population

Baseline (BL) patient characteristics for the full trial population showed no meaningful differences to the population relevant to the proposed marketing authorisation (IHC3+; please see Section 2.3.1.2.2). Characteristics and demographics of the full trial population are presented in Appendix J.1.

#### 2.3.1.2.2 IHC3+ population

Patient characteristics at baseline are summarised in Table 8, characteristics of the full Cohort 1 and the IHC3+ population were similar. The median age was [redacted] years (range: [redacted] years), with [redacted] aged below 65 years. There was a slightly greater proportion of females ([redacted]) and [redacted] of patients were of Asian ethnicity. The majority of patients ([redacted]) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 1.

**Table 8: Characteristics of participants with HER2+ BTC in HERIZON-BTC-01 at baseline (SAS)**

| HERIZON-BTC-01<br>Baseline characteristics | Cohort 1 (IHC2/3+)<br>(n=80) | IHC3+<br>(n=62) |
|---|---|---|
| Age, years<br>Mean (StD)<br>Median (min, max) | <br>62.5 (9.56)<br>64.0 (32, 79) | [redacted] |
| Age category, n (%)<br><65 years<br>≥65 years | <br>41 (51.3)<br>39 (48.8) | [redacted] |
| Sex, n (%)<br>Female<br>Male | <br>45 (56.3)<br>35 (43.8) | [redacted] |
| Race,† n (%)<br>American Indian or Alaska Native<br>Asian<br>White<br>Not reportable‡<br>Unknown | <br>1 (1.3)<br>52 (65.0)<br>23 (28.8)<br>2 (2.5)<br>2 (2.5) | [redacted] |
| Race,† n (%)<br>Asian<br>Non-Asian | <br>52 (65.0)<br>28 (35.0) | [redacted] |

| HERIZON-BTC-01<br>Baseline characteristics | Cohort 1 (IHC2/3+)<br>(n=80) | IHC3+<br>(n=62) |
|---|---|---|
| Geographic region, n (%)<br>North America<br>Asia<br>Other | <br>18 (22.5)<br>50 (62.5)<br>12 (15.0) | [redacted] |
| ECOG PS, n (%)<br>0<br>1 | <br>22 (27.5)<br>58 (72.5) | [redacted] |

Abbreviations: BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; HER2+, human epidermal growth factor receptor 2-positive; IHC, immunohistochemistry; PS, performance status; SAS, safety analysis set.
†Participants could select more than 1 race category.
‡Not reportable: Collection and/or reporting of this information was prohibited by local and/or regional laws and regulations.
Source: EMA EPAR (2025) (68), HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

BL disease characteristics are presented in **Table 9**, characteristics of the full Cohort 1 and the IHC3+ population were similar. Approximately half ([redacted]) of IHC3+ patients in HERIZON-BTC-01 had GBC; [redacted] of these patients had progressed on prior therapy and [redacted] were intolerant to prior therapy.

**Table 9: Disease characteristics for participants with HER2+ BTC in HERIZON-BTC-01 at baseline (SAS)**

| HERIZON-BTC-01<br>Disease characteristics | Cohort 1 (IHC2/3+)<br>(n=80) | IHC3+<br>(n=62) |
|---|---|---|
| Disease subtype, n (%)<br>GBC<br>iCCA<br>eCCA<br>Perihilar<br>Distal | <br>41 (51.3)<br>23 (28.8)<br>16 (20.0)<br>8 (10.0)<br>8 (10.0) | [redacted] |
| Stage at initial diagnosis, n (%)<br>I<br>II<br>III<br>IV<br>Unknown | <br>2 (2.5)<br>9 (11.3)<br>23 (28.8)<br>44 (55.0)<br>2 (2.5) | [redacted] |
| Stage at study entry,† n (%)<br>IIIA<br>IIIB<br>IV<br>IVB | <br>1 (1.3)<br>8 (10.0)<br>27 (33.8)<br>44 (55.0) | [redacted] |
| Baseline hepatic impairment,‡ n (%)<br>None<br>Mild<br>Moderate<br>Severe | <br>44 (55.0)<br>35 (43.8)<br>1 (1.3)<br>0 | [redacted] |
| Baseline renal impairment,§ n (%)<br>Normal<br>Mild to moderate | <br>27 (33.8)<br>53 (66.3) | [redacted] |

| HERIZON-BTC-01<br>Disease characteristics | Cohort 1 (IHC2/3+)<br>(n=80) | IHC3+<br>(n=62) |
|---|---|---|
| Outcome to most recent prior therapy, n (%)<br>Progressed<br>Intolerant | <br>72 (90.0)<br>8 (10.0) | [redacted] |
| Time from initial diagnosis to metastatic or locally advanced (months)<br>Mean (StD) | <br>4.7 (9.76) | [redacted] |
| Prior history of brain metastases, n (%)<br>Yes<br>No | <br>1 (1.3)<br>79 (98.8) | [redacted] |
| Baseline sum of diameters,‡‡ (mm)<br>Independent central review<br>Median (min, max)<br>Investigator<br>Median (min, max) | <br><br>68.0 (13, 183)<br><br>67.5 (14, 205) | <br><br>[redacted]<br><br>[redacted] |

Abbreviations: BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; SAS, safety analysis set; StD, standard deviation.
†Disease staging varied by disease subtype; categories IV and IVB are mutually exclusive.
‡Per criteria of National Cancer Institute Organ Dysfunction Working Group.
§Baseline renal impairment per the Cockcroft-Gault formula for estimating creatinine clearance and FDA guidance titled: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, September 2020.
¶Based on central laboratory companion diagnostic testing.
††All participants enrolled in the study were ISH+ at screening, based on a central laboratory companion diagnostic test.
‡‡Sum of diameters of target lesions selected for disease response assessment per RECIST v1.1 tumour assessment.
Source: EMA EPAR (2025) (68), HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

Prior anti-cancer therapies at baseline are presented in **Table 10**. All patients received at least 1 gemcitabine-based therapy, as per the inclusion criteria.

**Table 10: Prior anti-cancer therapies at baseline (SAS)**

| HERIZON-BTC-01 | Cohort 1 (IHC2/3+)<br>(n=80) | IHC3+<br>(n=62) |
|---|---|---|
| Prior systemic cancer therapy, n (%)<br>Yes<br>Number of regimens<br>Median (min, max) | <br>80 (100.0)<br><br>1.0 (1, 8) | <br>[redacted]<br><br>[redacted] |
| Prior therapy for metastatic or locally advanced disease,† n (%)<br>Yes<br>Number of regimens‡<br>Median (min, max) | <br>80 (100.0)<br><br>1.0 (1, 7) | <br>[redacted]<br><br>[redacted] |
| Number of regimens‡<br><2<br>≥2 | <br>47 (58.8)<br>33 (41.3) | <br>[redacted] |
| Regimen received§<br>Gemcitabine/oxaliplatin | <br>12 (15.0) | <br>[redacted] |

| HERIZON-BTC-01 | Cohort 1 (IHC2/3+) (n=80) | IHC3+ (n=62) |
|---|---|---|
| Gemcitabine/cisplatin | 61 (76.3) | [redacted] |
| Gemcitabine/fluoropyrimidine | 5 (6.3) | |
| Gemcitabine/other | 2 (2.5) | |
| Gemcitabine monotherapy | 4 (5.0) | |
| Fluoropyrimidine-based¶ | 27 (33.8) | |
| PD1/PDL1 inhibitor | 21 (26.3) | |
| Prior radiotherapy, n (%) | | |
| Yes | 13 (16.3) | [redacted] |
| No | 67 (83.8) | |
| Prior surgeries with curative intent, n (%) | | |
| Yes | 25 (31.3) | [redacted] |
| No | 55 (68.8) | |

Abbreviations: IHC, immunohistochemistry; PD1, programmed cell death protein 1; PDL1, programmed death ligand 1; SAS, safety analysis set.
†Includes gemcitabine-based therapies received in the adjuvant/neoadjuvant setting if progression occurred within 6 months of completion of surgery.
‡Total regimens as designated by the investigator.
§All participants received gemcitabine-based therapy, as per the inclusion criteria. Participants were counted at most under each regimen type received and may be counted in multiple categories.
¶Excludes regimens in combination with gemcitabine.
Source: EMA EPAR (2025) (68), HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

## 2.3.2 Supporting evidence

### *2.3.2.1 UCLH real-world evidence study*

A retrospective observational study based on real-world use of zanidatamab was conducted in 20 patients with HER2+ BTC treated in the medical oncology service at UCLH between 2022 and 2025 (60). All patients had previously received 1L SoC therapy with CisGem with or without durvalumab (60). In total, 70% of patients received zanidatamab as 2L and 30% as 3L (60). Most patients accessed zanidatamab under compassionate use (60).

The endpoints studied were objective response, OS, and AEs (60).

At baseline, 13 of 20 patients (65%) included in the study were female. The mean age at diagnosis was 55 years and mean weight at treatment initiation was 66 kg. Overall, 12 patients (60%) had GBC, 3 patients (15%) had distal cholangiocarcinoma (dCCA), 3 patients (15%) had iCCA, 1 patient (5%) had perihilar cholangiocarcinoma (pCCA), and 1 patient (5%) had ampullary adenocarcinoma. Half (50%) of patients had previous surgery with curative intent, and half (50%) had metastatic or unresectable disease at diagnosis (60).

### *2.3.2.2 Real-world evidence in France*

A national multi-centre retrospective study of patients with BTC treated with zanidatamab in France was conducted as part of a compassionate access

programme (61). All patients had a HER2+ tumour defined as IHC3+ or IHC2+ with fluorescence in-situ hybridisation (FISH) amplification or HER2 amplification detected by NGS. HER2 status was assessed locally in each institution. Data on the patients, disease characteristics, and treatment outcomes were collected from electronical medical files. Patients were followed until death, loss to follow-up, or the DCO (January 2025).Zanidatamab was administered intravenously at 20 mg/kg Q2W. Treatment continued until disease progression according to RECIST v1.1, death, or toxicity.

The primary endpoint of the study was PFS. Secondary endpoints include OS, DCR, response rates, and AEs (61).

The study included 20 patients with metastatic BTC enrolled between 2022 and 2024, of which 12 patients had confirmed HER2+ IHC3+ BTC. Median age at diagnosis was 61.5 years (IQR: 55, 69) and the majority of patients had GBC (60%) (61). Full patient demographics are presented in **Table 11**.

**Table 11: Baseline characteristics for the real-world evidence study in France**

| Baseline characteristics | Full population (n=20) |
|---|---|
| Age, years (IQR) | 61.5 (55, 69) |
| Sex, n (%) | |
| Female | 10 (50.0) |
| Male | 10 (50.0) |
| Disease subtype, n (%) | |
| GBC | 12 (60.0) |
| iCCA | 6 (30.0) |
| eCCA | 2 (10.0) |
| Disease status, n (%) | |
| Localised | 6 (30.0) |
| Metastatic | 14 (70.0) |
| Site of metastases, n (%) | |
| Liver | 15 (75.0) |
| Regional lymph nodes | 15 (75.0) |
| Lung | 11 (55.0) |
| Distant lymph nodes | 7 (35.0) |
| Peritoneal | 7 (35.0) |
| HER2 status, n (%) | |
| IHC3+ | 12 (60.0) |
| IHC2+/FISH amplified | 6 (30.0) |
| NGS HER2 amplified | 2 (10.0) |
| Previous systemic chemotherapy 1L, n (%) | |
| CisGem + durvalumab | 15 (75.0) |
| CisGem | 2 (10.0) |
| FOLFIRINOX | 1 (5.0) |
| GEMOX | 1 (5.0) |
| FOLFOX | 1 (5.0) |

Abbreviations: 1L, first-line; CisGem, cisplatin and gemcitabine; eCCA, extrahepatic cholangiocarcinoma; FISH, fluorescence in-situ hybridisation; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin; GEMOX, gemcitabine and oxaliplatin; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; IQR, interquartile range; NGS, next-generation sequencing.
Source: Smolenschi (2025) (61).

### 2.3.3 Expert elicitation/opinion

#### *2.3.3.1 Delphi study*

A 2-round modified Delphi study was conducted to elicit structured expert insights into clinical decision-making factors on treatment options for patients with HER2+ IHC3+ BTC. Consensus was established from 11 to 14 UK-based BTC clinical experts who had extensive experience in the treatment of BTC.

Clinical experts responded to the Delphi study through an online questionnaire covering the key themes of prognostic factors in 2L BTC outcomes, survival extrapolations in HER2+ BTC, time on treatment assumptions for 2L BTC treatment, treatment effect over time and subsequent treatment options. The majority of questions included in the Delphi study were asked to indicate the responder's agreement using a 5-point Likert scale from "Strongly agree" to "Strongly disagree"; expert consensus was established if 70% or more of responders strongly agreed/agreed or strongly disagreed/disagreed to a statement. Consensus was established after 2 rounds of survey. Additional free text fields were included to obtain any further comments on each topic from the clinical experts.

Insights from the Delphi panel were used to inform the economic model and are included throughout the dossier. The full report is provided as an 'unpublished' reference (69).

#### *2.3.3.2 Clinician interviews*

In addition to the Delphi study, 8 virtual interviews with UK oncologists with expertise in managing patients with BTC, were conducted in February and March 2025 to validate aspects of the submission. Insights from the clinician interviews are included throughout the dossier. The full report is provided in the reference pack (36).

## *2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

### 2.4.1 HERIZON-BTC-01

#### *2.4.1.1 Populations analysed*

Details of the population sets analysed in HERIZON-BTC-01 are presented in **Table 12**.

**Table 12: Population analysis sets in HERIZON-BTC-01**

| Analysis set | Description |
|---|---|
| Screened | All patients who signed the main study informed consent form. |
| Enrolled | All patients who signed the main study informed consent form, were eligible for the trial, and received approval to enrol at the end of screening. |
| Safety | All safety evaluable patients enrolled in Cohort 1 and Cohort 2 (cohorts defined in 2.3.1.1.1).<br>A patient was considered safety evaluable if they received any amount of zanidatamab. |
| Efficacy | Cohort 1 (Primary) – included all response evaluable patients enrolled in Cohort 1. The primary analysis of efficacy was performed using this analysis set.<br>Cohort 2 – included all response evaluable patients enrolled in Cohort 2 |
| Response evaluable | The following Response Evaluable Analysis Sets were evaluated for this study:<br>Cohort 1 - included all response evaluable participants enrolled in Cohort 1<br>Cohort 2 - included all response evaluable participants enrolled in Cohort 2<br>Response evaluable included all patients in the Safety Analysis Set with measurable disease at baseline and at least 1 evaluable post-baseline disease assessment (per RECIST v1.1) or who discontinued study treatment due to death or unequivocal clinical progression.<br>Separately, patients with IHC3+ within Cohort 1 were evaluated to assess the efficacy within this specific subpopulation. |
| Pharmacokinetics | All patients who received any amount of zanidatamab and had at least 1 post-baseline pharmacokinetic assessment. |
| Immunogenicity | All patients who received any amount of zanidatamab and had both baseline ADA and at least 1 post-baseline ADA result available. |

Abbreviations: ADA, anti-drug antibody; IHC, immunohistochemistry; RECIST, response evaluation criteria in solid tumours.
Source: HERIZON-BTC-01 CSR (2025) (54).

#### *2.4.1.2 Hypothesis objective*

The aim of HERIZON-BTC-01 was to evaluate the efficacy and safety of treatment with zanidatamab in patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC with disease progression on previous gemcitabine-based therapy. The study had a single-arm, open-label design and no statistical hypothesis was tested.

#### *2.4.1.3 Statistical analysis*

Statistical analyses were conducted for each endpoint as follows:

- **ORR:** the proportion of participants with an objective response and the corresponding 2-sided, exact Clopper Pearson binomial 95% CI was calculated for the ICR and investigator assessments of disease response
- **BOR:** summarised using counts and percentages for the ICR and investigator assessments

- **DOR, OS, PFS:** estimated using the KM method with corresponding 95% CIs calculated using the Brookmeyer and Crowley method with log-log transformation
- **DCR:** the proportion of participants achieving disease control and the corresponding 2-sided, exact Clopper Pearson binomial 95% CI was estimated for the ICR and investigator assessments

#### *2.4.1.4 Sample size and power calculation*

HERIZON-BTC-01 aimed to enrol approximately 100 participants (75 in Cohort 1 and 25 in Cohort 2). No formal sample size calculations were performed.

The sample size of 75 patients in Cohort 1 was informed by Clopper-Pearson exact binomial 95% CIs. With 75 patients, there was a 92% chance of observing a cORR with lower limit of the 95% CI, excluding a historical response rate of 10% if the true cORR was 25% (22).

Patients with an IHC of 0 or 1+ – defined as having HER2-negative and HER2-low disease, respectively – were enrolled into Cohort 2 (22).Estimates have shown that approximately 25% of screened patients with HER2-amplified BTC would have tumours associated with IHC of 0 or 1+. Cohort 2 therefore aimed to enrol 25 patients. No statistical assumption was tested for this exploratory Cohort 2 (22, 54).

#### *2.4.1.5 Participant flow in HERIZON-BTC-01*

During the enrolment period of 15 September 2020 and 16 March 2022, 847 patients were pre-screened for HER2-amplification; of these, 171 (20%) had HER2-amplified tumours, of which 131 (77%) entered study screening and 87 (66%) were enrolled (22, 54). Cohort 1 (i.e. HER2+ tumours defined as IHC2+/ISH+ or 3+) consisted of 80 patients. Sixty-two (77.5%) patients had a HER2 status of IHC3+.

The median duration of follow-up was 33.4 months (range: 28 to 45) (54). As of the DCO date (11 July 2024), all patients had discontinued treatment with zanidatamab. The most common reason for zanidatamab discontinuation was radiographic progression (n=73; 83.9%) (54).

Figure 10 presents the patient flow following screening in HERIZON-BTC-01.

**Figure 10: Participant flow in HERIZON-BTC-01**

Abbreviations: AE, adverse event; BTC, biliary tract cancer; CNS, central nervous system; EC, exclusion criterion; ECOG PS, Eastern Cooperative Group performance status; HER2, human epidermal growth factor receptor 2; IC, inclusion criteria; QTcF, QT with Fridericia correction.
Source: HERIZON-BTC-01 CSR (2025) (54).

### 2.4.2 Supporting evidence

#### *2.4.2.1 UCLH real-world evidence study*

The primary aim of the real-world study was to explore the clinical results of zanidatamab use in 1 centre in England (UCLH) (60). Data were analysed using Microsoft Excel (60).

#### *2.4.2.2 Real-world evidence in France*

The real-world study was an investigator initiated national multi-centre retrospective study of all patients with refractory metastatic BTC treated with zanidatamab in 5 French centres as part of a compassionate access programme (61). The primary aim of the study was to assess the efficacy and safety of zanidatamab outside of clinical trials (61).

The Kaplan-Meier (KM) method was used to estimate PFS and OS. Descriptive statistics were used for quantitative variables. Univariate and multivariate analyses were performed to explore associations between the variables and PFS and OS. Cox regression was used for categorical and continuous variables and Cox proportional hazards models were applied for unadjusted and adjusted analyses. Due to the small sample size, survival probability differences were evaluated with the Z test. Significance was evaluated at a threshold of $p \leq 0.05$. All statistical analyses were performed using Stata v18.0 (61).

## *2.5 Critical appraisal of the relevant clinical effectiveness evidence*

A detailed summary of quality assessment results for HERIZON-BTC-01, ZWI-ZW25-101, the real-world study of patients in England, and the real-world study of patients in France are provided in Appendix B.4. The overall risk of bias was considered to be low for all studies, except for the real-world study in England which had a higher risk of bias due to the limited reporting inherent to a conference abstract, e.g. in study design, methodology, results, and interpretation.

## *2.6 Clinical effectiveness results of the relevant studies*

### 2.6.1 HERIZON-BTC-01: clinical effectiveness results

The Phase 2b HERIZON-BTC-01 trial is the pivotal trial of the clinical efficacy of zanidatamab in patients with HER2+ unresectable, advanced or metastatic BTC after 1 or more systemic treatments, and is the largest trial in HER2+ BTC to date.

As HER2+ IHC3+ BTC is the population of interest for this submission:

- All data presented in this section refer to the IHC3+ subpopulation of Cohort 1 from the HERIZON-BTC-01 trial (i.e. patients with HER2+ IHC3+ disease), for the final DCO 11th July 2024, unless specified otherwise
- As results from the final DCO are considered confidential, results from the DCO used to inform the regulatory submission (28th July 2023) for the same population are also presented where relevant in this section and in full in Appendix J
- Data for the full trial population are presented in Appendix J

For brevity, the HER2+ IHC3+ BTC subpopulation cohort is referred to as IHC3+ BTC throughout the dossier.

#### *2.6.1.1 Primary endpoint: cORR (RECIST v1.1) per ICR – IHC3+*

The cORR results from the final DCO (11th July 2024) for patients with IHC3+ BTC are summarised in **Table 13**. For the 62 patients evaluated, the cORR was 51.6% (95% CI: 38.6, 64.5), including 29 patients (46.8%) with a best overall response (BOR) of partial response (PR) and 3 patients (4.8%) with a BOR of complete response (CR) per ICR (62).

**Table 13: Primary endpoint – cORR by ICR per RECIST v1.1 (EAS [DCO 11 July 2024])**

| Endpoint | HERIZON-BTC-01<br>IHC3+<br>(n=62) |
|---|---|
| cORR<br>n (%)<br>95% CI | <br>32 (51.6)<br>38.6, 64.5 |
| Confirmed BOR, n (%)<br>CR<br>PR<br>SD<br>PD<br>Not evaluable | <br>3 (4.8)<br>29 (46.8)<br>17 (27.4)<br>13 (21.0)<br>0 |

Abbreviations: BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCO, data cut-off; EAS, efficacy analysis set; IHC, immunohistochemistry; ICR, independent central review; PD, progressed disease; PR, partial response; RECIST, response evaluation criteria in solid tumours; SD, stable disease.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

The cORR results at the interim DCO (28th July 2023), which informed the regulatory submission, were consistent with the final DCO. At the interim DCO, for the 62 patients evaluated, the cORR was 51.6% (95% CI: 38.6, 64.5), including 29 patients (46.8%) with BOR of PR and 3 patients (4.8%) with a BOR of CR per ICR (66, 68).

### *2.6.1.2 Key secondary endpoints – IHC3+*

#### 2.6.1.2.1 Disease response

The DOR and DCR results from the final DCO (11th July 2024) for patients with IHC3+ BTC are summarised in **Table 14**. The median DOR, as assessed by ICR, of the 32 responders was 14.9 months (95% CI: 7.4, 24.0) (62). The number of responders with DOR ≥16 weeks was [redacted] ([redacted]%) and the KM probability estimate at 16 weeks was [redacted]% (95% CI: [redacted], [redacted]) (62).

**Table 14: Secondary endpoints – disease response by ICR per RECIST v1.1 (EAS [DCO 11 July 2024])**

| Endpoint | HERIZON-BTC-01<br>IHC3+ |
|---|---|
| DOR, months<br>n<br>Median (95% CI)<br>Min, max | <br>32<br>14.9 (7.4, 24.0)<br>[redacted] |
| Responders with DOR ≥16 weeks<br>n<br>n (%)<br>95% CI | [redacted] |
| KM DOR estimate at Week 16<br>n<br>Probability (95% CI) | [redacted] |
| First confirmed response, weeks<br>n<br>Median<br>Min, max | [redacted] |
| Percentage of patients responding by, n (%)<br>n<br>Week 9<br>Week 17<br>Week 25<br>Week 33<br>Week 41 | [redacted] |
| DCR<br>n<br>n (%)<br>95% CI | <br>62<br>49 (79.0)<br>66.8, 88.3 |

Abbreviations: CI, confidence interval; DCO, data cut-off; DCR, disease control rate; DOR, duration of response; EAS, efficacy analysis set; ICR, independent central review; KM, Kaplan-Meier; RECIST, response evaluation criteria in solid tumours.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

The DOR results were consistent at the interim DCO (28th July 2023) for patients with IHC3+ BTC (n=62). The median DOR, as assessed by ICR, of the 32 responders was 14.9 months (95% CI: 7.4, 24.0) (68).

#### 2.6.1.2.2 Progression-free survival

The PFS results from the final DCO (11th July 2024) for patients with IHC3+ BTC are summarised in Table 15. A total of [redacted] PFS events occurred, of which [redacted] patients presented with radiographic progression and [redacted] patients died. Of the [redacted] censored patients, [redacted] initiated subsequent cancer therapy, [redacted] withdrew consent, and [redacted] had 2 missed or unevaluable response assessments. The median PFS was 7.2 months (95% CI: 5.4, 9.4) (Figure 11). The 6-month and 12-month PFS rates were [redacted]% (95% CI: [redacted], [redacted]) and [redacted]% (95% CI: [redacted], [redacted]), respectively.

**Table 15: Secondary endpoint – PFS per RECIST v1.1 (EAS [DCO 11 July 2024])**

| Endpoint | HERIZON-BTC-01 IHC3+ (n=62) |
|---|---|
| **ICR** | |
| Total events, n (%)<br>Radiographic progression<br>Death | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median PFS, months (95% CI) | 7.2 (5.4, 9.4) |
| KM PFS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of PFS follow-up, months<br>Median<br>Min, max | [redacted] |
| **INV** | |
| Total events, n (%)<br>Radiographic progression<br>Death | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median PFS, months (95% CI) | [redacted] |
| KM PFS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of PFS follow-up, months<br>Median<br>Min, max | [redacted] |

Abbreviations: CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; KM, Kaplan-Meier; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

**Figure 11: KM plot of PFS – EAS (DCO 11 July 2024)**

Abbreviations: CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; IHC, immunohistochemistry; KM, Kaplan-Meier; PFS, progression-free survival.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).



The PFS results were consistent at the interim DCO (28th July 2023) for the IHC3+ population. Per ICR, the median PFS was 7.2 months (95% CI: 5.4, 9.4) (66).

#### 2.6.1.2.3 Overall survival

The OS results from the final DCO (11th July 2024) for patients with IHC3+ BTC are summarised in **Table 16**. The median OS was 18.1 months (95% CI: 12.2, 22.9) (**Table 16**, **Figure 12**). The 6-month and 12-month OS rates were [redacted]% (95% CI: [redacted], [redacted]) and [redacted]% (95% CI: [redacted], [redacted]), respectively. The median duration of OS follow-up was [redacted] months.

**Table 16: Secondary endpoint – OS per RECIST v1.1 (EAS [DCO 11 July 2024])**

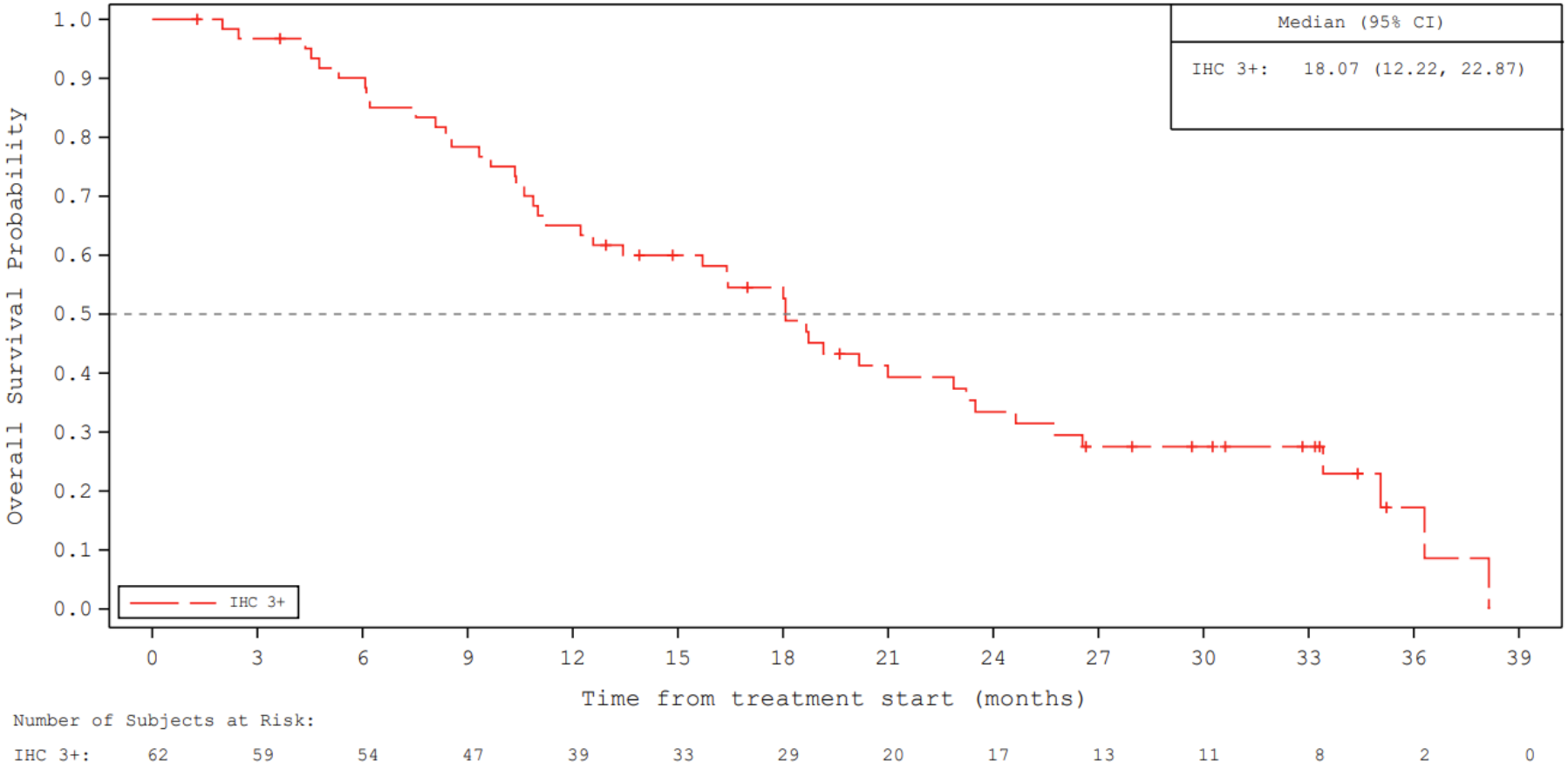
| Endpoint | HERIZON-BTC-01<br>IHC3+<br>(n=62) |
|---|---|
| Total events, n (%) | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median OS, months (95% CI) | 18.1 (12.2, 22.9) |
| KM OS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of OS follow-up, months<br>Median<br>Min, max | [redacted] |

Abbreviations: CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; KM, Kaplan-Meier; OS, overall survival; RECIST, response evaluation criteria in solid tumours.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

The OS from the interim DCO (28th July 2023), which informed the regulatory submission, were consistent with the final DCO. The median OS was 18.1 months (95% CI: 12.2, 22.9) (68). The 6-month and 12-month OS rates were 90.1% (95% CI: 79.2, 95.4) and 65.0% (95% CI: 51.6, 75.6), respectively (66).

**Figure 12: KM plot of OS – EAS (DCO 11 July 2024)**




Abbreviations: CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; IHC, immunohistochemistry; KM, Kaplan-Meier; OS, overall survival.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (62).

### *2.6.1.3 Time to treatment discontinuation – IHC3+*

The duration of treatment results from the final DCO (11th July 2024) for patients with HER2+ IHC3+ BTC are presented in Table 17. The median duration of treatment with zanidatamab in HERIZON-BTC-01 was [redacted] months (Table 17). At the final DCO, [redacted] patients (n=[redacted] had discontinued treatment, with the majority ([redacted]%) discontinuing due to radiographic progression (Table 17).

**Table 17: Duration of treatment with zanidatamab in HERIZON-BTC-01 (SAS [DCO 11 July 2024])**

| Duration of treatment | HERIZON-BTC-01 IHC3+ (n=62) |
|---|---|
| Mean, months (StD) | [redacted] |
| Median, months<br>25th, 75th percentiles<br>Min, max | [redacted] |
| Reason for discontinuation, n (%)<br>All<br>Radiographic progression<br>Clinical progression<br>AE<br>Death<br>Physician decision<br>Study terminated by sponsor | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; SAS, safety analysis set; StD, standard deviation.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

### *2.6.1.4 Patient-reported outcomes*

HRQoL was assessed using the EQ-5D-5L questionnaire, the BPI-sf, and opioid use. EQ-5D-5L and BPI-sf data for the IHC3+ population are described below and data for Cohort 1 are presented in Appendix J.3.1. Opioid use data are provided for Cohort 1 below as these data are not available in the IHC3+ population.

#### 2.6.1.4.1 EQ-5D-5L – IHC3+

The individual dimensions of the EQ-5D-5L questionnaire by disease response in patients with IHC3+ BTC are presented in Appendix J.3.1. Patients who experienced a PR reported the greatest improvement in HRQoL from baseline to best on-treatment (BONT) score across all domains, followed by patients with stable disease (SD) (62). Amongst patients with progressive disease (PD), HRQoL remained stable between baseline and best on-treatment score.

#### 2.6.1.4.2 EQ-5D VAS – IHC3+

Table 18 presents the change in EQ-5D visual analogue scale (VAS) scores from baseline to best on-treatment score. Patients who responded to zanidatamab treatment (i.e. experienced a CR or PR) reported clinically meaningful improvements in EQ-5D VAS (defined as exceeding the minimally important difference of 7 points) from baseline to time of BONT score (62). Amongst patients who experienced SD, improvement of EQ-5D VAS scores was demonstrated; however, this was not considered clinically meaningful. Patients with PD demonstrated no change, with a median change from baseline of [redacted].

**Table 18: Exploratory endpoint – EQ-5D VAS (SAS [DCO 11 July 2024])**

| | CR (n=3) | PR (n=29) | SD (n=17) | PD (n=13) | Total (n=62) |
|---|---|---|---|---|---|
| Baseline<br>VAS score<br>n<br>Mean<br>StD<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BONT†<br>VAS score<br>n<br>Mean<br>StD<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| VAS score change from baseline‡<br>n<br>Mean<br>StD<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BONT, best on-treatment; CR, complete response; DCO, data cut-off; PD, progressive disease; PR, partial response; SAS, safety analysis set; SD, stable disease; StD, standard deviation; VAS, visual analogue scale.
Change from baseline is defined for each subject as the post-baseline value minus the baseline value. Therefore, positive values for change from baseline represent an improvement post-baseline.
†The BONT is the highest post-baseline value observed.
‡Change from baseline is defined for each subject as the post-baseline value minus the baseline value. Therefore, positive values for change from baseline represent an improvement post-baseline.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (62).

#### 2.6.1.4.3 Brief pain index – IHC3+

Patients treated with zanidatamab reported a modest improvement in pain through the BPI-sf. The mean pain score at baseline for all 59 IHC3+ BTC patients surveyed was [redacted] (standard deviation [StD]: [redacted]). The BONT mean pain score for 59 patients who completed the survey was [redacted] (StD: [redacted]) and the mean pain score for 41 patients at the end of treatment was [redacted] (StD: [redacted]) (62).

#### 2.6.1.4.4 Opioid use – Cohort 1

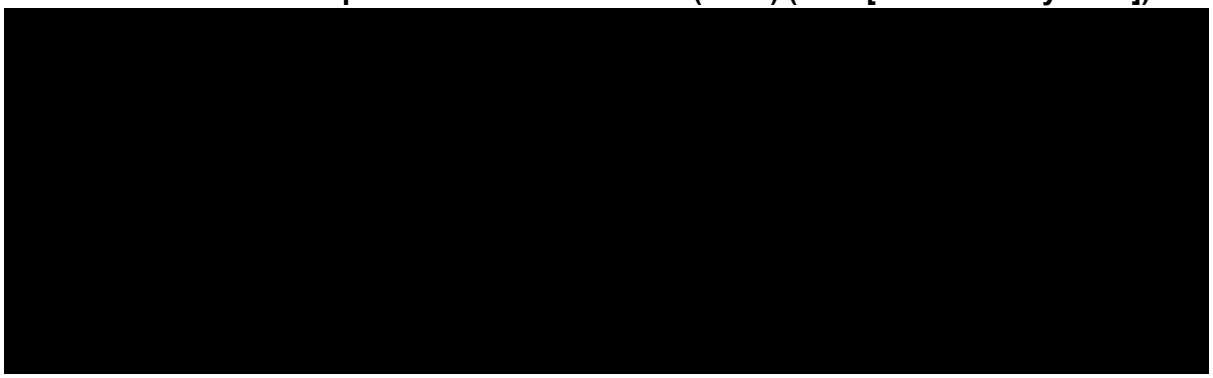
Opioid use for the IHC3+ subpopulation was not reported in HERIZON-BTC-01. However, results for Cohort 1 are presented in Table 19. Approximately one-quarter ([redacted]%) of the 80 patients used opioids at baseline. Patients who experienced a BOR of PD had the highest increase from baseline in opioid use. For overall post-baseline opioid use, [redacted]% of patients with PD had increased use, compared with [redacted]% of patients with BOR of confirmed PR and [redacted]% of patients with BOR of SD (Figure 13) (54). Patients with BOR of confirmed PR or SD were also more likely to have a decrease in opioid use during the trial ([redacted]% and [redacted]% decreased opioid use, respectively) than patients with PD ([redacted]% decreased opioid use) (54).

**Table 19: Summary of opioid use at baseline and overall post-baseline by confirmed BOR by ICR (SAS [DCO 11 July 2024])**

| Time point/category | Confirmed BOR | | | | | |
|---|---|---|---|---|---|---|
| | CR (n=3) | PR (n=30) | SD (n=22) | PD (n=24) | NE (n=1) | Total (n=80) |
| Baseline<br>Used opioids, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Overall post-baseline<br>n<br>Used opioids, n (%)<br>Change from baseline<br>Increased opioids<br>Decreased opioids<br>No change<br>No use | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BOR, best overall response; CR, complete response; DCO, data cut-off; ICR, independent central review; NE, not evaluable; PD, progressive disease; PR, partial response; SAS, safety analysis set; SD, stable disease.
Source: HERIZON-BTC-01 CSR (54).

**Figure 13: Proportion of patients who increased opioid use for disease-related pain from baseline to overall post-baseline – Cohort 1 (n=80) (SAS [DCO: 11 July 2024])**



Abbreviations: BL, baseline; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Opioid use was summarised as the change from baseline over time and in the last 24 hours. Patients who did not report using opioids (last 24 hours) at baseline are also included.
Source: HERIZON-BTC-01 CSR (54).

### 2.6.2 Supporting evidence: efficacy results

#### *2.6.2.1 UCLH real-world evidence study*

In 20 patients treated with zanidatamab in a single centre between 2022 and 2024, the ORR was 54% with a DCR of 62%. Of evaluated patients (n=13), BOR was CR in 2 patients (16%), PR in 5 patients (38%), SD in 1 patient (8%), mixed response in 1 patient (8%) and PD in 4 patients (30%). The median OS had not yet been reached at the time of submission (60).

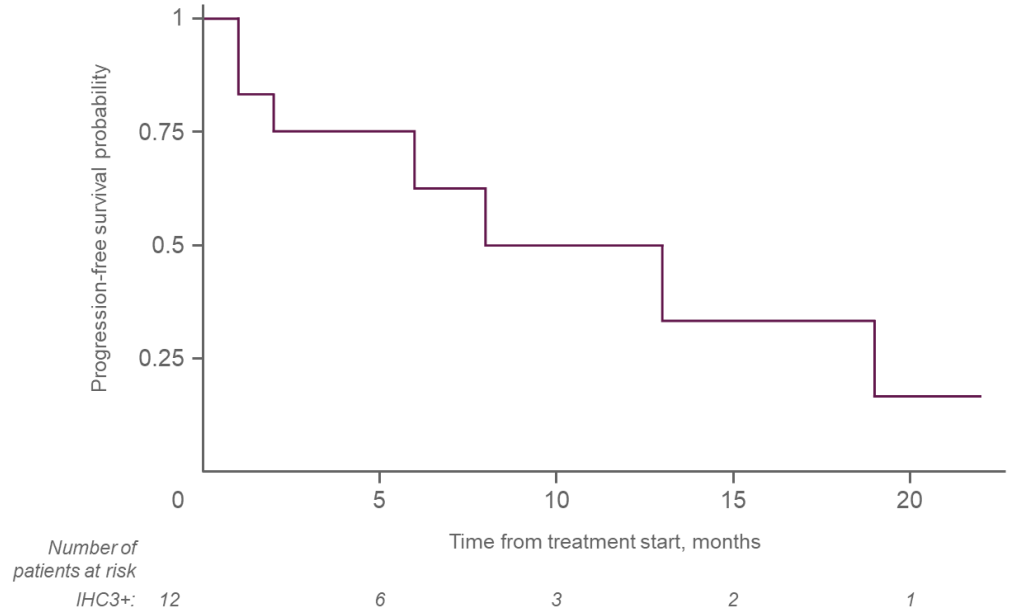
#### *2.6.2.2 Real-world evidence in France*

##### 2.6.2.2.1 Progression-free survival

In patients with IHC3+ BTC treated with zanidatamab (n=12), the median PFS was 8.0 months (95% CI: 1.5, 18.4) (61). The KM plot for patients with IHC3+ BTC is presented in **Figure 14**.

In all patients treated with zanidatamab (IHC2+ and IHC3+, n=20), after a median follow-up of 8.5 months (95% CI: 3.3, 11.8), the median PFS was 6.7 months (95% CI: 1.3, 11.8). Specifically, patients with IHC3+ demonstrated a significantly longer PFS than IHC2+ (8 months vs. 1.4 months, p=0.02)

**Figure 14: KM plot of PFS - real-world evidence study in France (IHC3+)**



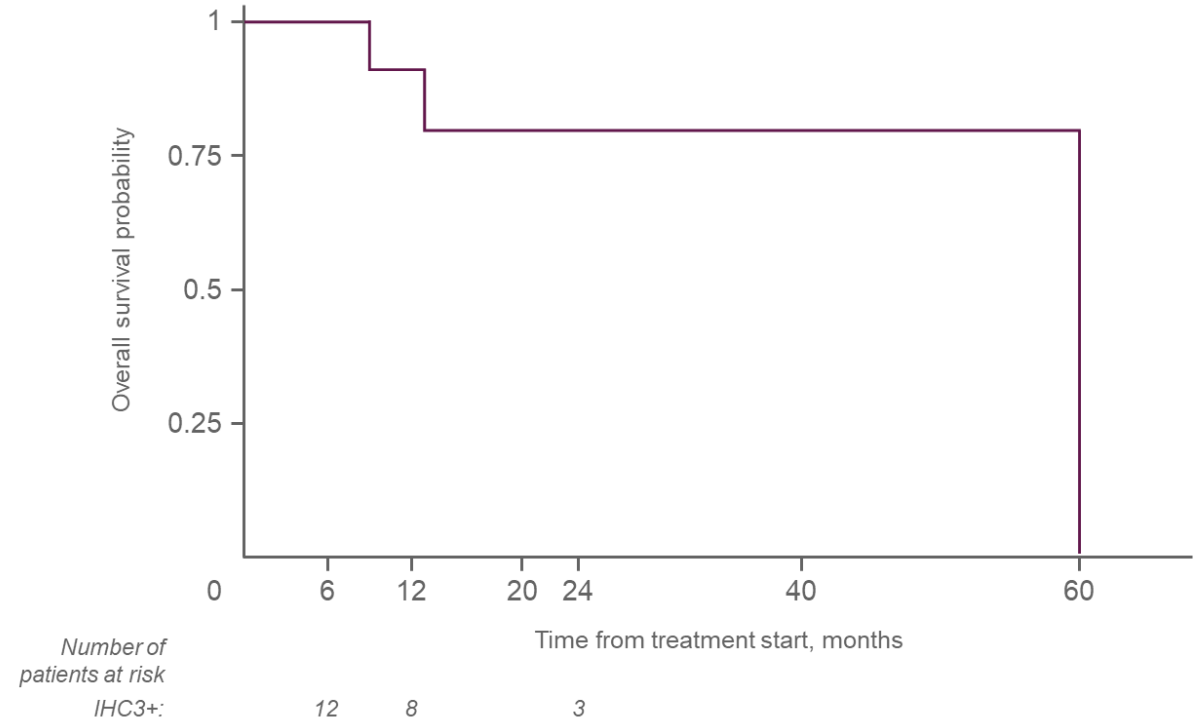

Abbreviations: IHC, immunohistochemistry; KM, Kaplan-Meier; PFS, progression-free survival.
Source: Adapted from Smolenschi (2025) (61).

##### 2.6.2.2.2 Overall survival

For patients with IHC3+ BTC (n=12), the estimated OS rate was 90.9% (95% CI: 50.8, 98.7) at 1 year and 79.6% (95% CI: 39.3, 94.5) at 2 years (**Figure 15**) (61).

For the full population (n=20), the 1-year OS rate was 79.1% (95% CI: 53.2, 91.6). and the 2-year OS rate was 73.0% (95% CI: 46.5, 87.9) (61). No significant difference between IHC3+ and IHC2+ was observed (p=0.39), likely due to the small sample size and limited number of events.

**Figure 15: KM plot of OS - real-world evidence in France (IHC3+)**




Abbreviations: IHC, immunohistochemistry; KM, Kaplan-Meier; OS, overall survival.
Source: Adapted from Smolenschi (2025) (61).

#### 2.6.2.2.3 Disease response

Across the full population (n=20), confirmed PR was observed in 8 (40%) patients, with SD in 5 (25%), and PD in 7 (35%) (61). The DCR was 65% and a median DOR of 7.3 months (95% CI: 2.1, 16.0) was observed (61).

## *2.7 Subsequent treatments used in the relevant studies*

### 2.7.1 HERIZON-BTC-01

An overview of the reported subsequent treatments used for patients with HER2+ IHC3+ BTC in HERIZON-BTC-01 are presented in **Table 20**. Time on subsequent treatment was not captured in this trial.

**Table 20: Summary of the subsequent lines of treatment used in HERIZON-BTC-01 (SAS [DCO 11 July 2024])**

| Subsequent treatment, n (%) | IHC3+ population of HERIZON-BTC-01 (n=62) |
|---|---|
| Fluorouracil; folinic acid; oxaliplatin | [redacted] |
| Calcium folinate; fluorouracil; irinotecan hydrochloride | [redacted] |
| Lenvatinib mesilate | [redacted] |
| Nivolumab | [redacted] |
| Pyrotinib maleate | [redacted] |
| All other non-therapeutic products | [redacted] |
| Fluorouracil | [redacted] |
| Sintilimab | [redacted] |
| Capecitabine | [redacted] |
| Cisplatin | [redacted] |
| Fluorouracil; folinic acid; irinotecan | [redacted] |
| Oxaliplatin | [redacted] |
| Pembrolizumab | [redacted] |
| Trastuzumab | [redacted] |
| Trastuzumab deruxtecan | [redacted] |
| Trastuzumab deruxtecan nxki | [redacted] |
| Camrelizumab | [redacted] |
| Capecitabine; cisplatin | [redacted] |
| Catequentinib | [redacted] |
| Cisplatin; fluorouracil | [redacted] |
| Combinations of antineoplastic agents | [redacted] |
| Gemcitabine hydrochloride | [redacted] |
| Gimeracil; oteracil potassium; tegafur | [redacted] |
| Herbal anticancer remedies | [redacted] |
| Investigational antineoplastic drugs | [redacted] |
| Irinotecan sucrosofate pegylated liposomal | [redacted] |
| Ivosidenib | [redacted] |
| Lenvatinib | [redacted] |
| Ly 3410738 | [redacted] |
| Paclitaxel | [redacted] |
| Paclitaxel nanoparticle albumin-bound | [redacted] |
| Pertuzumab | [redacted] |
| Pertuzumab; trastuzumab | [redacted] |
| Rivoceranib mesylate | [redacted] |

| Subsequent treatment, n (%) | IHC3+ population of HERIZON-BTC-01 (n=62) |
|---|---|
| Tegafur | [redacted] |
| Toripalimab | [redacted] |
| Trastuzumab emtansine | [redacted] |
| Zw 49 | [redacted] |

Abbreviations: DCO, data cut-off; IHC, immunohistochemistry; SAS, safety analysis set.
Source: HERIZON-BTC-01 subsequent treatments (2025) (70).

### 2.7.2 Supporting evidence

Subsequent treatments were not reported in the England (UCLH) or France real-world studies (60, 61).

## *2.8 Subgroup analysis*

### 2.8.1 HERIZON-BTC-01

As IHC3+ BTC is the population of interest for this submission, all efficacy data presented from HERIZON-BTC-01 in the submission refer to the IHC3+ subpopulation of Cohort 1 from the trial (i.e. patients with HER2+ IHC3+ disease). Results by BTC subtype are presented in Appendix C. No additional subgroup data are presented.

### 2.8.2 Supporting evidence

Subgroup analyses were not reported in the England (UCLH) real-world evidence (RWE) study (60). The France real-world study only reported subgroup analyses by IHC status, which has been reported in Section **2.6.2.2** (61).

## *2.9 Meta-analysis*

The clinical trial programme that has evaluated the efficacy and safety of zanidatamab in the population of interest for this appraisal (HERIZON-BTC-01 and ZWI-ZW25-101) consisted of single-arm trials; therefore, a meta-analysis of available evidence is not applicable to this appraisal.

## 2.10 Indirect and mixed treatment comparisons

### *Indirect treatment comparisons: summary*

#### *Overview*

- HERIZON-BTC-01 was a single-arm trial, so comparisons were conducted to indirectly assess the relative effectiveness of zanidatamab compared with FOLFOX + ASC, and ASC alone using the most relevant data from the ABC-06 trial
- Various approaches to comparison were explored, including unanchored MAICs, an external control arm analysis, and naive comparison
- Due to limitations in the MAICs and external control arm analysis, there remains substantial uncertainty with the comparisons. As such, and in line with previous appraisals, a naive comparison was considered most suitable for the cost-effectiveness model

#### *Unanchored MAICs*

- MAICs were conducted to indirectly compare the OS and PFS of zanidatamab vs. FOLFOX + ASC, and ASC alone:
  - Analyses compared the IHC3+ cohort from HERIZON-BTC-01 and the ABC-06 study population, for which HER2 status was not determined
  - As ABC-06 was limited to 2L only vs. 2L+ for HERIZON-BTC-01, the initial sample size for HERIZON-BTC-01 used in the unweighted analysis was smaller than the number of patients in the IHC3+ population ([redacted] vs. 62)
  - ESS after weighting was n=[redacted], likely due to a lower proportion of patients with intrahepatic and locally advanced disease in HERIZON-BTC-01 vs. ABC-06
  - Results of weighted and unweighted comparisons were similar, with unweighted analyses providing similar or more conservative HR estimates:
    - PFS estimates were significantly improved with zanidatamab vs. FOLFOX + ASC (unweighted HR: [redacted]; weighted HR: [redacted];), a [redacted]% improvement in survival without disease progression
    - OS was significantly improved with zanidatamab vs. FOLFOX + ASC (unweighted HR: [redacted]; weighted HR: [redacted]) and ASC alone (unweighted HR: [redacted]; weighted HR: [redacted]): an approximate [redacted]% improvement in survival

#### *External control arm analysis*

- A weighted comparison of IHC3+ patients in HERIZON-BTC-01 and an external control arm of IHC3+ patients treated with chemotherapy in the US showed (53, 71):
  - Longer median OS with zanidatamab vs. chemotherapy (18.1 vs. 3.3 months; HR: 0.29)
  - Longer PFS with zanidatamab vs. chemotherapy (7.3 vs. 2.3; HR: 0.47)

#### *Naive comparisons:*

- A side-by-side comparison of results from HERIZON-BTC-01 and ABC-06 showed PFS by INV was greater for zanidatamab than FOLFOX + ASC, [redacted] months vs. 4.0 months. PFS was not assessed for the ASC only arm of ABC-06
- OS was considerably improved for zanidatamab (18.1 months) vs. FOLFOX + ASC (6.2 months) and ASC alone (5.3 months)

#### *Conclusions:*

- In line with previous appraisals, a naive comparison was considered the most appropriate for use in the cost-effectiveness model, due to considerable uncertainties in the unanchored MAICs and external control arm (18)

ITCs were conducted to assess the relative treatment efficacy of zanidatamab vs. FOLFOX + ASC, and ASC alone. Three approaches were explored, as summarised in Table 21, each of which are discussed further in the below sections.

**Table 21: Overview of ITC approaches**

| | Unanchored MAICs | External control arm analysis | Naive comparison |
|---|---|---|---|
| Endpoints explored | OS<br>PFS | OS<br>PFS | OS<br>PFS |
| Comparator(s) | FOLFOX + ASC<br>ASC alone | Chemotherapy | FOLFOX + ASC<br>ASC alone |
| Source of comparative evidence | ABC-06 (21) | Real-world retrospective data from US Flatiron Health Research Analytic Database (71, 72) | ABC-06 (21) |
| Presentation in the dossier | Section 2.10.2 | Section 2.10.3 | Section 2.10.4 |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

### 2.10.1 Identification of the most relevant clinical studies

As HERIZON-BTC-01 was a single-arm study, an SLR was conducted to identify appropriate studies relevant for the comparators. As described in Section 2.1, 16 studies from 47 publications of patients with HER2 alterations and 190 studies from 408 publications for the BTC population without HER2 alterations met the inclusion criteria for the clinical SLR. From these, 2 studies were identified as relevant to the decision problem to compare zanidatamab with FOLFOX + ASC, and ASC alone: HERIZON-BTC-01 (54) and ABC-06 (21). A summary of these studies is provided in Table 22. The design of HERIZON-BTC-01 is described in detail in Section 2.3.1.1. The trial design and key results of ABC-06 are provided in Appendix N.

**Table 22: Summary of studies used for the ITCs**

| Characteristic | HERIZON-BTC-01 | ABC-06 |
|---|---|---|
| Intervention(s) | Zanidatamab | FOLFOX + ASC, ASC |
| HER2 targeted treatment | Targeted | Non-targeted |
| Data source (reference) | ILD (54) | Published manuscript (21) |
| Study design | Single arm study | RCT (comparative) |
| Enrolment dates | 2020 to 2022 | 2014 to 2018 |

| Characteristic | HERIZON-BTC-01 | ABC-06 |
|---|---|---|
| n | Overall: 87<br>Cohort 1: 80<br>Cohort 2: 7<br>IHC3+: 62 | Overall: 162<br>FOLFOX + ASC: 81<br>ASC: 81 |
| Population | HER2-amplified BTC treated with previous gemcitabine-based therapy. Subgroups: IHC3+ and IHC2+ (Cohort 1), IHC0 IHC1 (Cohort 2), and IHC3+ only | Locally advanced or metastatic BTC with PD to first-line chemotherapy |
| Comparator | - | ASC alone |
| Primary endpoint | ORR | OS (ITT) |
| Secondary endpoint(s) | Disease response by ICR, ORR by BTC anatomical subtype | Safety |
| Median follow-up duration | 33.4 months<br>(range: 28 to 45) | 21.7 months<br>(IQR: 17.2, 30.8) |
| HER2 testing method | IHC score, confirmed by central laboratory ISH | Not performed |

Abbreviations: ASC, active symptom control; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, individual level data; ISH, in-situ hybridisation; ITC, indirect treatment comparison; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; RCT, randomised controlled trial.

In addition to the studies identified through the SLR, Jazz Pharmaceuticals provided an additional study of real-world treatment patterns and clinical outcomes in HER2+ (IHC3+) patients in the US that was used as an external control arm for comparison (53).

### 2.10.2 Unanchored MAICs

Methods of the unanchored MAICs are presented in Appendix B.2.2.1

#### *2.10.2.1 Results*

##### 2.10.2.1.1 Patient characteristics

A side-by-side comparison of patient characteristics at baseline for HERIZON-BTC-01 and ABC-06 are presented in **Table 23**.

**Table 23: Patient characteristics at baseline for HERIZON-BTC-01 (IHC3+ population - DCO 11 July 2024) and ABC-06**

| Characteristic | HERIZON-BTC-01 IHC3+ (n=62) | HERIZON-BTC-01 IHC3+ 2L only patients (n=[redacted]) | ABC-06 (n=162) |
|---|---|---|---|
| Intervention | Zanidatamab | Zanidatamab | FOLFOX + ASC or ASC alone |
| Median age, years (range) | [redacted] | [redacted](NR) | 65 (26 to 84) |
| Race, n (%)<br>White<br>Asian<br>Other | [redacted] | NR<br>NR<br>NR | NR<br>NR<br>NR |
| Ethnicity, n (%)<br>Hispanic/Latino<br>Other | [redacted] | NR<br>NR | NR<br>NR |
| Region, n (%)<br>North America<br>Asia<br>Other | [redacted] | NR<br>[redacted]<br>NR | 0<br>0<br>162 (100) |
| Female, n (%) | [redacted] | [redacted] | 82 (50.6) |
| ECOG PS, n (%)<br>0<br>1<br>2 | [redacted] | [redacted] | 53 (32.7)<br>107 (66.0)<br>0 |
| Previous radiotherapy, n (%) | [redacted] | NR | NR |
| Previous surgery, n (%) | [redacted] | NR | 72 (44.4) |
| Previous lines of therapy, n (%)<br>1<br>2+<br>Median (range) | [redacted] | [redacted] | 162 (100)<br>0<br>1.0 (1 to 1) |
| IHC result, n (%)<br>IHC3+<br>IHC0/1+/2+ | 62 (100)<br>0 | [redacted] | NR<br>NR |
| Disease stage at study entry, n (%)<br>Locally advanced (Stage III)<br>Metastatic (Stage IV) | [redacted] | [redacted] | 29 (17.9)<br>133 (82.1) |
| Tumour site, n (%)<br>GBC<br>iCCA<br>eCCA | [redacted] | NR<br>NR<br>NR | 134 (21.0)<br>72 (44.4)<br>45 (27.8) |
| Albumin levels, n (%)<br><35 g/L<br>≥35 g/L | NR<br>NR | NR<br>NR | 40 (24.7)<br>122 (75.3) |

Abbreviations: 2L, second-line; ASC, active symptom control; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; IV, intravenous; NR, not reported; PS, performance status.
Sources: HERIZON BTC IHC3+ subgroup analysis (2025) (62); Lamarca (2021) (21).

Patient characteristics of the prognostic matching variables for zanidatamab, FOLFOX + ASC, and ASC alone are presented in **Table 24**.

The inclusion criteria of the ABC-06 trial were similar to HERIZON-BTC-01 in some respects; both included patients with locally advanced or metastatic BTC (including CCA and GBC) and ECOG status 0 and 1 who had progressed on previous therapy, including 1 prior (CisGem) chemotherapy. However, the ABC-06 inclusion criteria were more specific in requiring patients to be 2L, as opposed to 2L+ in HERIZON-BTC-01. As a result of this, the HERIZON-BTC-01 data were trimmed to include 2L patients only for FOLFOX and ASC analyses.

ABC-06 did not require a HER2 testing result for inclusion. As such, it was not possible to determine the proportion of patients in ABC-06 who were HER2+ IHC3+, which is a limitation of the matching-adjusted indirect comparison (MAIC), since all patients in the analysis population of HERIZON-BTC-01 were HER2+ IHC3+. Instead, a comparison with real-world patients with HER2+ IHC3+ BTC in an external control arm is provided in Section **2.10.3**.

Median age was comparable between HERIZON-BTC-01 (IHC3+ cohort) and ABC-06 (FOLFOX + ASC and ASC arms) trial populations (**Table 24**). HERIZON-BTC-01 had a slightly higher proportion of females compared with the FOLFOX + ASC arm, but was similar to the ASC arm ([redacted] vs. 47% and 54% in ABC-06). The proportion of patients with ECOG 0 was similar ([redacted] in HERIZON-BTC-01 vs. 31% and 35% in ABC-06). Percentages of patients with intrahepatic disease and metastatic disease at study entry were higher for both arms of the ABC-06 trial compared with HERIZON-BTC-01.

The ABC-06 trial only recruited patients from the UK, whereas HERIZON-BTC-01 recruited mainly from Asia and North America ([redacted]% of the full population were from Europe). However, it was not possible to match Asia region as a variable because the large difference in this measure at baseline between the trials ([redacted] vs. 0%), combined with the already restricted HERIZON-BTC-01 dataset to match previous treatment lines, resulted in the match not converging.

Overall, the HERIZON-BTC-01 sample size reduced by [redacted] from n=[redacted] before matching to an effective sample size (ESS) of n=[redacted]. Although the 2 trial groups had closely matched proportions of patients with ECOG 0, this loss of ESS is likely a result of the HERIZON-BTC-01 intrahepatic site and locally advanced disease proportions being around half those of the ABC-06 population.

**Table 24: Characteristics for HERIZON-BTC-01 (IHC3+ cohort) before and after weighting vs. ABC-06**

| Characteristic | ABC-06 | HERIZON-BTC-01 unweighted | HERIZON-BTC-01 re-weighted | Matched |
|---|---|---|---|---|
| Patients, n | 162 | [redacted] | - | - |
| ESS (% of original sample) | - | - | [redacted] | - |
| ECOG 0, % | 32.7 | [redacted] | [redacted] | ✓ |
| ECOG 0 or 1, % | 98.8 | [redacted] | [redacted] | × |
| Proportion 2L | 100 | [redacted] | [redacted] | ✓ |
| Intrahepatic tumour site, % | 44.4 | [redacted] | [redacted] | ✓ |
| Locally advanced, % | 17.9 | [redacted] | [redacted] | ✓ |
| Asia region, % | 0 | [redacted] | [redacted] | × |
| HER2 IHC3+, % | - | [redacted] | [redacted] | × |
| Median age, years | 65.0 | [redacted] | [redacted] | × |
| Female, % | 50.6 | [redacted] | [redacted] | × |

Abbreviations: 2L, second-line; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
Source: ITC report (2025) (73).

#### 2.10.2.1.2 Survival

PFS and OS curves were only moderately changed after re-weighting HERIZON-BTC-01 to the FOLFOX + ASC and ASC alone arms of ABC-06, which is reflective of the relatively high ESS.

***Progression-free survival***

As PFS for the ASC arm of ABC-06 was not reported, a comparison of PFS between zanidatamab vs. ASC alone could not be made.

For the PFS comparison with FOLFOX + ASC, point estimates in both weighted and unweighted analyses favoured zanidatamab and were statistically significant (**Figure 16** and **Figure 17**). The proportion of patients with PFS is notably higher for zanidatamab, and the Cox regression analyses show a [redacted]% reduction in progression or death compared with FOLFOX + ASC (hazard ratio (HR): [redacted] [95% CI: [redacted], [redacted]]) for unweighted, with similar findings after the MAIC (HR:[redacted] [95% CI: [redacted], [redacted]]) as shown in **Figure 16**.

**Figure 16: Forest plot of Cox proportional hazards models (unweighted and weighted) for PFS for HERIZON-BTC-01 (IHC3+ cohort) vs. FOLFOX + ASC**

Abbreviations: CI, confidence interval; ESS, effective sample size; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; MAIC, match adjusted indirect comparison; PFS, progression-free survival.
Source: ITC report (2025) (73).

**Figure 17: PFS KM curves for zanidatamab in HERIZON-BTC-01 (unweighted and weighted) vs. FOLFOX + ASC in ABC-06**

Shaded areas depict 95% confidence interval.
Abbreviations: CI, confidence interval; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; IHC, immunohistochemistry; KM, Kaplan-Meir; PFS, progression-free survival.
Source: ITC report (2025) (73).

***Overall survival***

For OS, there were statistically significant improvements with zanidatamab in comparison with FOLFOX + ASC and ASC alone in both unweighted and weighted analyses, as depicted in **Figure 18**.

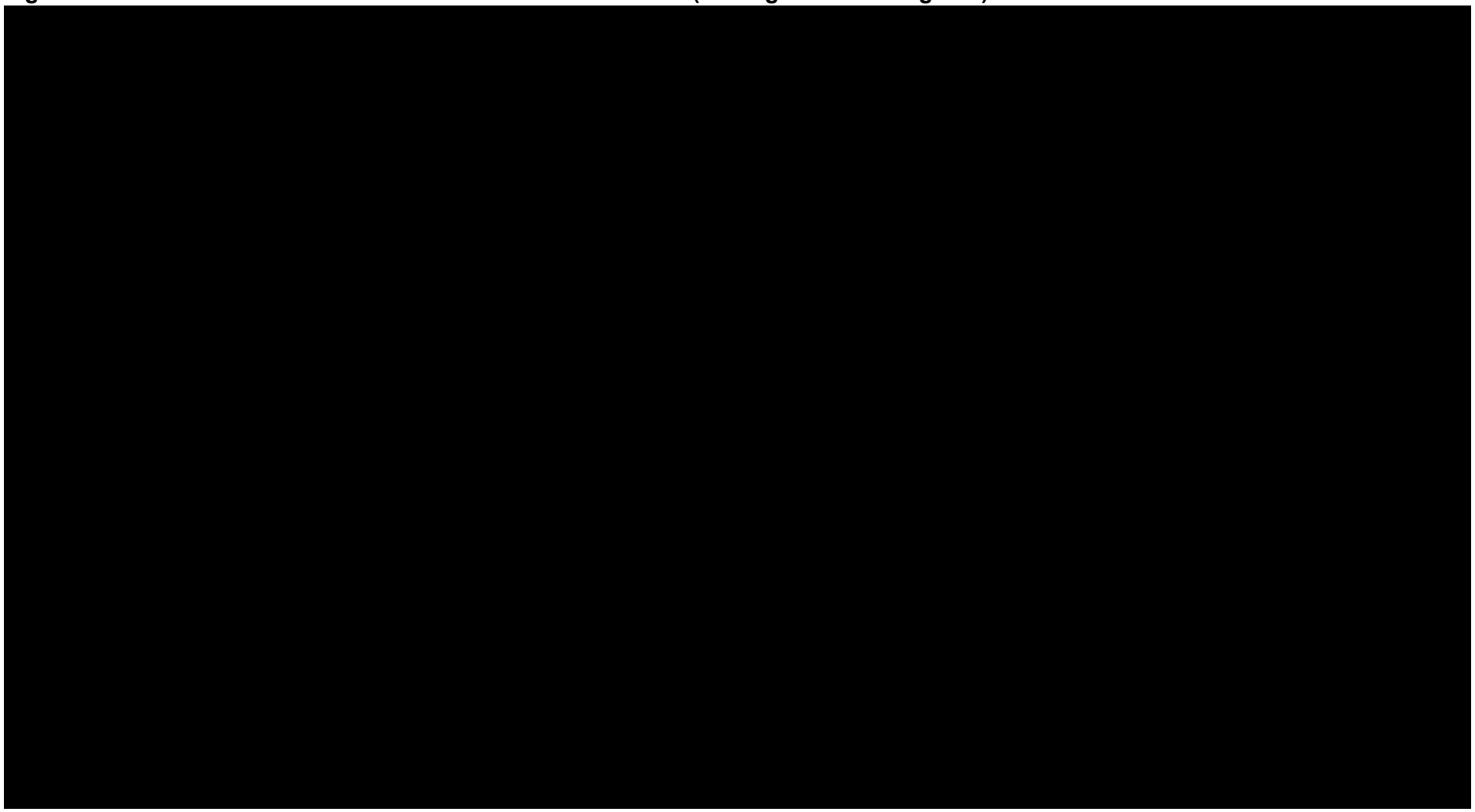
Median OS was considerably longer for zanidatamab vs. FOLFOX + ASC (**Figure 19**). There was also strong statistical evidence from the unweighted and weighted Cox models to support this reduction in mortality. Unweighted analyses showed a HR of [redacted] (95% CI: [redacted]), with a similar outcome seen in the weighted analysis, showing a HR of [redacted] (95% CI: [redacted]).

Median OS was also considerably longer for zanidatamab vs. ASC alone (**Figure 20**). The improvement in OS was observed in the unweighted and weighted Cox regression analysis, with strong statistical support for improvements in OS for zanidatamab. Unweighted analyses showed a HR of [redacted] (95% CI: [redacted]), with a similar outcome seen in the weighted analysis, showing a HR of [redacted] (95% CI: [redacted]) as shown in **Figure 18**.

**Figure 18: Forest plot of Cox proportional hazards models (unweighted and weighted) for OS for HERIZON-BTC-01 (IHC3+ cohort) vs. comparators**

Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, match adjusted indirect comparison; OS, overall survival.
Source: ITC report (2025) (73).

**Figure 19: OS KM curves for zanidatamab in HERIZON-BTC-01 (unweighted and weighted) and FOLFOX + ASC in ABC-06**



Shaded areas depict 95% confidence interval.
Abbreviations: CI, confidence interval; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; IHC, immunohistochemistry; KM, Kaplan-Meier; OS, overall survival.
Source: ITC report (2025) (73).

**Figure 20: Overall survival KM curves for zanidatamab in HERIZON-BTC-01 (unweighted and weighted) and ASC in ABC-06**

Shaded areas depict 95% confidence interval.
Abbreviations: ASC, active symptom control; CI, confidence interval; IHC, immunohistochemistry.
Source: ITC report (2025) (73).

### *2.10.2.2 Uncertainties in the MAIC*

#### 2.10.2.2.1 Uncertainties in matching

Both arms of the ABC-06 trial (the FOLFOX + ASC arm and the ASC only arm) were combined for the MAICs. For the comparison, the unweighted sample size for HERIZON-BTC-01 was significantly reduced as the individual level data (ILD) had to be trimmed to only include 2L patients to match with ABC-06. After trimming, the HERIZON-BTC-01 characteristics differed from ABC-06, with approximately half of patients having locally advanced and intrahepatic disease. These differences were reflected in the fall in ESS after matching. Although the percentage of patients from the Asia region could be inferred (with ABC-06 being run only from UK centres), it was not possible for the Asia region match to converge given the already small patient numbers as a result of trimming. As HER2 testing was not required in ABC-06, it was not possible to match populations based on HER2 status. Since the prognostic impact of HER2 status is not well established, comparison with an external control arm was also conducted (Section **2.10.3**).

A key assumption of the MAICs is that patients from ABC-06 are similar to those in HERIZON-BTC-01. There were some small differences in patient characteristics between HERIZON-BTC-01 and ABC-06, mainly between the key prognostic variables, as well as percentage female and median age. However, it is important that only 'observed' characteristics are recorded. Should there be unobserved differences between patients or important characteristics not planned to be included in the matching process, there may be residual bias in comparisons.

Another limitation is that the MAIC approach reweights the available patient to match the patient population from the comparator study. As such, the estimate of effectiveness is essentially the estimate in the population from the comparator study, not HERIZON-BTC-01. This also means that the zanidatamab results from the MAIC do not match those from the HERIZON-BTC-01 study (due to the reweighting) and therefore do not match the decision problem population.

#### 2.10.2.2.2 Other areas of uncertainty

Beyond the matched characteristics, it should be highlighted that there is uncertainty in BTC as to which characteristics are prognostic. Outcomes are poor across studies, and the relatively small difference reweighting has made in the MAIC highlights that patient characteristics are not particularly prognostic/predictive of outcomes.

A further limitation that applies to cross-study outcomes beyond PFS is that outcomes are confounded by the subsequent treatments received, which may differ between regions. The different levels of post-progression treatment and different types of treatment received will likely impact OS, meaning differences cannot be solely attributed to the initial treatment. As such, comparisons are more akin to

treatment strategies, rather than individual treatments. As noted, this does not apply to PFS comparisons, which are unaffected by subsequent treatments.

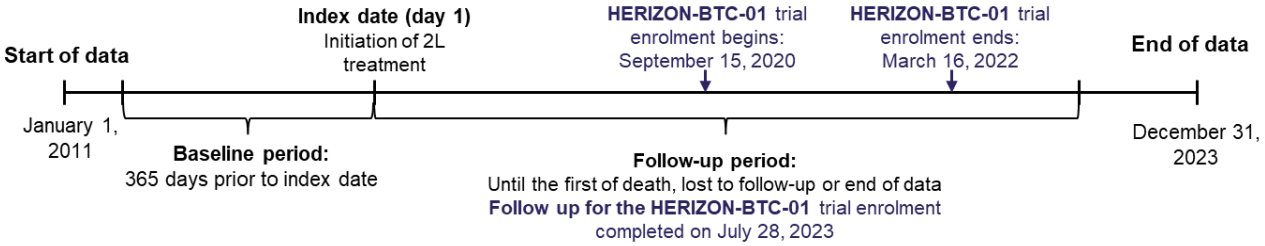
### 2.10.3 External control arm analysis

#### *2.10.3.1 Methods*

A retrospective observational study was conducted using data from the Flatiron Health Research Analytic Database (longitudinal, deidentified, patient-level database derived from electronic health records in the USA), from January 2011 to December 2023 (Figure 21) (71). Patients with HER2-expressing (IHC3+) locally advanced or metastatic BTC who received 2L treatment with 6 months or more of potential follow-up and 2 or more distinct visits were included in the analysis (71). Follow-up began at initiation of 2L treatment until date of last recorded activity, death, or loss to follow-up (71).

Outcomes were assessed from the external control arm against a zanidatamab cohort, which included patients with HER2+ IHC3+ BTC from HERIZON-BTC-01. This analysis was conducted prior to the availability of the final DCO for HERIZON-BTC-01 and therefore uses the previous DCO of 28th July 2023.

**Figure 21: Study schema for the external control arm analysis**




Abbreviations: 2L, second line.
Source: Kim (2025) (71).

#### 2.10.3.1.1 Statistical analysis

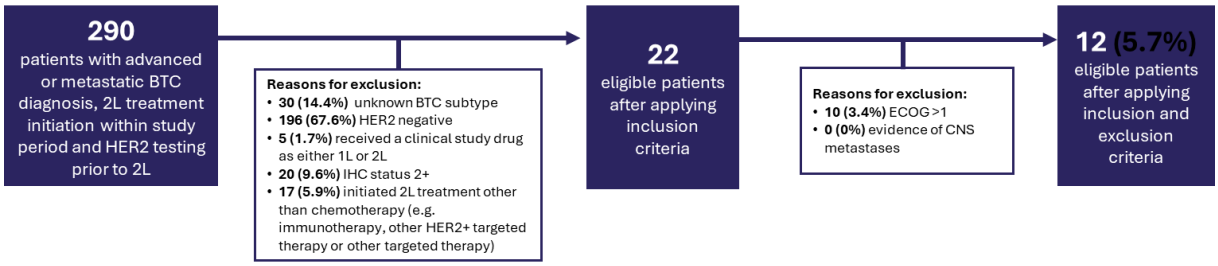
To account for potential imbalance of key prognostic factors at baseline, standardised mortality ratio (SMR) weighting was applied. Covariate balance before and after weighting was assessed using standardised mean differences (SMD). Median survival and HRs were estimated using SMR-weighted KM and Cox proportional hazards regression (71).

#### *2.10.3.2 Results*

#### 2.10.3.2.1 Patient characteristics

Approximately 29,000 patients had a BTC diagnosis in the US Flatiron Database, and 12 with HER2+ IHC3+ BTC were included in the analysis per the inclusion criteria (Figure 22). The mean patient age was 66 years (StD: 8.6) (Table 25) (71).

**Figure 22: Study flow diagram for the external control arm analysis**

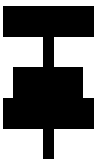
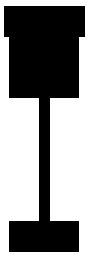



Abbreviations: 1L, first line; 2L, second line; BTC, biliary tract cancer; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2-positive; IHC, immunohistochemistry.
Source: Kim (2025) (71).

Of the 12 patients included, 9 (75.0%) had GBC and 3 (25.0%) had iCCA or eCCA (71). Systemic treatments observed as 2L chemotherapy in the external control arm are presented in **Table 26**: the majority (66.7%) were treated with FOLFOX or FOLFIRI.

Patients in the zanidatamab and external control arm cohorts were well balanced in terms of mean age at 2L initiation and history of chronic liver disease. Both cohorts had greater than 75% of patients with metastatic (Stage III/ IV) disease (**Table 25**) (71). There was a higher proportion of female patients and patients with GBC in the external control arm than in the zanidatamab cohort (71).

**Table 25: Characteristics of patients in HERIZON-BTC-01 and US patients included in the external control arm**

| | HERIZON-BTC-01 HER2+ IHC3+ BTC (n=62) | External control arm HER2+ IHC3+ BTC (n=12) | SMD |
|---|---|---|---|
| Treatment arm | Zanidatamab | External control | - |
| Mean age, years (StD) | 62.7 (9.3) | 66 (8.6) | 0.37 |
| Female, n (%) | 34 (54.8) | 8 (66.7) | 0.24 |
| Race/ethnicity,[†] n (%)<br>Asian<br>Black or African American<br>Hispanic or Latino<br>White<br>Other |  |  |  |
| Disease subtype, n (%)<br>GBC<br>iCCA or eCCA | <br>33 (53.2)<br>29 (46.8) | <br>9 (75.0)<br>3 (25.0) | <br>-0.47 |
| History of chronic liver disease, n (%) | 11 (18.0) | 2 (17.0) | 0.03 |
| Group stage at initial diagnosis,[‡] n (%)<br>Stage I or II<br>Stage III or IV | <br>10 (16.7)<br>50 (83.3) | <br>2 (22.2)<br>7 (77.8) | <br>0.14 |
| ECOG PS,[§] n (%)<br>0<br>1 | <br>20 (32.3)<br>42 (67.7) | <br>4 (40.0)<br>6 (60.0) | <br>-0.16 |
| Comorbidities,[¶] n (%)<br>Diabetes mellitus<br>Chronic kidney disease<br>Peripheral vascular disease<br>Ulcer disease<br>Chronic pulmonary disease<br>Myocardial infarction<br>Congestive heart failure<br>Dementia |  |  |  |

Abbreviations: BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; PS, performance status; SMD, standardised mean difference; StD, standard deviation.
[†]Data were missing for 2 patients in the zanidatamab cohort and 1 patient in the external control arm.
[‡]Data were missing for 2 patients in the zanidatamab cohort and 3 patients in the external control arm.
[§]Data were missing for 2 patients in the external control arm.
[¶]A patient could present with more than 1 comorbidity.
Source: Kim (2025) (53), Jazz Pharmaceuticals (2025) (72).

**Table 26: Overview of 2L chemotherapy used in the external control arm**

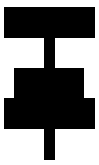
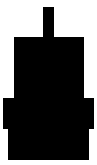
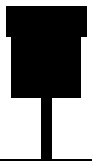
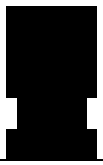
| Systemic chemotherapy treatment, n (%) | External control arm (IHC3+) (n=12) |
|---|---|
| FOLFOX | 6 (50.0) |
| FOLFIRI | 2 (16.7) |
| CisGem | 1 (8.3) |
| 5FU | 1 (8.3) |
| GemCap | 1 (8.3) |
| GemCarbo | 1 (8.3) |

Abbreviations: 2L, second-line; 5FU, fluorouracil; CisGem, cisplatin and gemcitabine; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GemCap, gemcitabine and capecitabine; GemCarbo, gemcitabine and carboplatin; IHC, immunohistochemistry.
Source: Jazz Pharmaceuticals (2025) (72).

### *Patient characteristics after adjustment for baseline confounding*

Patient characteristics after adjustment are presented in **Table 27**.

**Table 27: Characteristics of patients in HERIZON-BTC-01 and US patients included in the external control arm after adjustment for baseline confounding**

| | HERIZON-BTC-01 HER2+ IHC3+ BTC (n=62) | External control arm† HER2+ IHC3+ BTC (n=62) | SMD |
|---|---|---|---|
| Treatment arm | Zanidatamab | External control | - |
| Mean age,‡ years (StD) | 63 (9.3) | 63 (8.1) | 0.07 |
| Female,‡ n (%) | 34 (54.8) | 34 (54.9) | 0.00 |
| Race/ethnicity, n (%)<br>Asian<br>Black or African American<br>Hispanic or Latino<br>White<br>Other |  |  |  |
| Disease subtype,‡ n (%)<br>GBC<br>iCCA or eCCA | <br>33 (53.2)<br>29 (46.8) | <br>31 (50.4)<br>31 (49.6) | 0.06 |
| History of chronic liver disease, n (%) | 11 (18.0) | 7 (11.0) | 0.20 |
| Group stage at initial diagnosis, n (%)<br>Stage I or II<br>Stage III or IV | <br>10 (16.7)<br>50 (83.3) | <br>8 (22.2)<br>28 (77.8) | 0.14 |
| ECOG PS, n (%)<br>0<br>1 | <br>20 (32.3)<br>42 (67.7) | <br>15 (26.8)<br>40 (73.2) | 0.11 |
| Comorbidities,§ n (%)<br>Diabetes mellitus<br>Chronic kidney disease<br>Peripheral vascular disease<br>Ulcer disease<br>Chronic pulmonary disease |  |  |  |

| | HERIZON-BTC-01 HER2+ IHC3+ BTC (n=62) | External control arm† HER2+ IHC3+ BTC (n=62) | SMD |
|---|---|---|---|
| Myocardial infarction<br>Congestive heart failure<br>Dementia | | | |

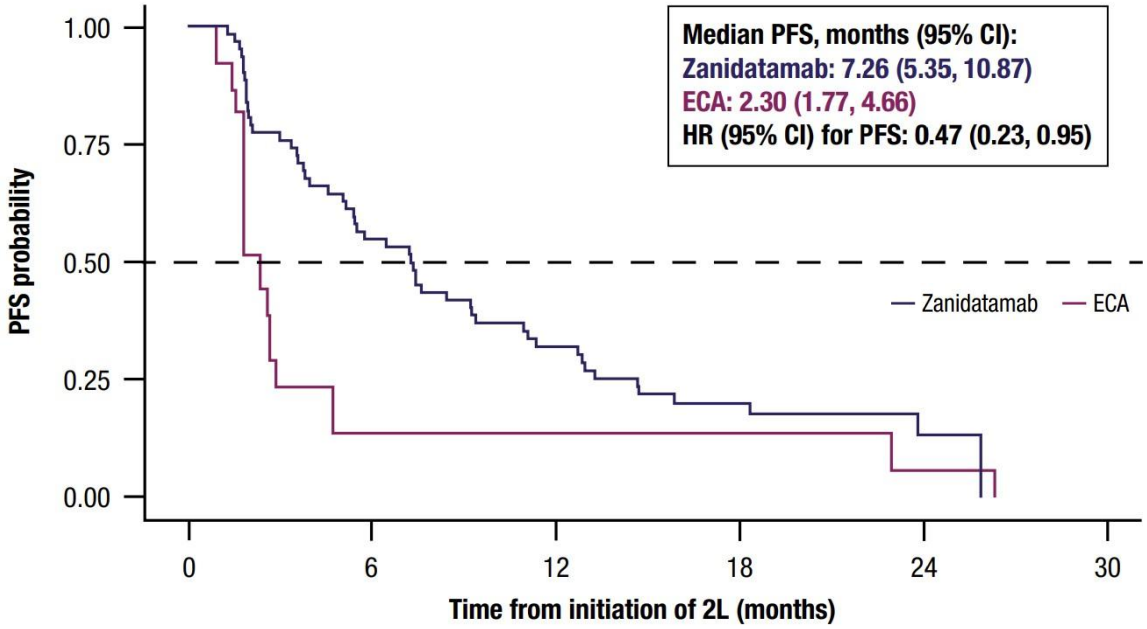
Abbreviations: BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; iCCA, intrahepatic cholangiocarcinoma; PS, performance status; SMD, standardised mean difference; StD, standard deviation.
†Percentages were calculated based on the number of patients with available data for each characteristic.
‡Covariate included in the propensity score model used to generate the SMR weights.
§A patient could present more than 1 comorbidity.
Source: Kim (2025) (53), Jazz Pharmaceuticals (2025) (72).

#### 2.10.3.2.2 Progression-free survival

Results showed median PFS was significantly longer for patients treated with zanidatamab (7.26 months [95% CI: 5.35, 10.87]) vs. patients treated with chemotherapy in the external control arm (2.30 months [95% CI: 1.77, 4.66]) (HR: 0.47 [95% CI: 0.23, 0.95]) (71). The KM plot for PFS is presented in **Figure 23**.

Zanidatamab was associated with a 41% and 18% increased PFS rate after 6 months and 12 months, respectively (71). At 6 months, the PFS rate with zanidatamab was 55% (95% CI: 44, 69) and for the external control arm it was 14% (95% CI: 4, 47) (71). At 12 months, the PFS rate with zanidatamab was 32% (95% CI: 22, 46) compared with 14% (95% CI: 4, 47) in the external control arm (71).

**Figure 23: SMR-weighted KM plot for PFS with zanidatamab and external control arm**



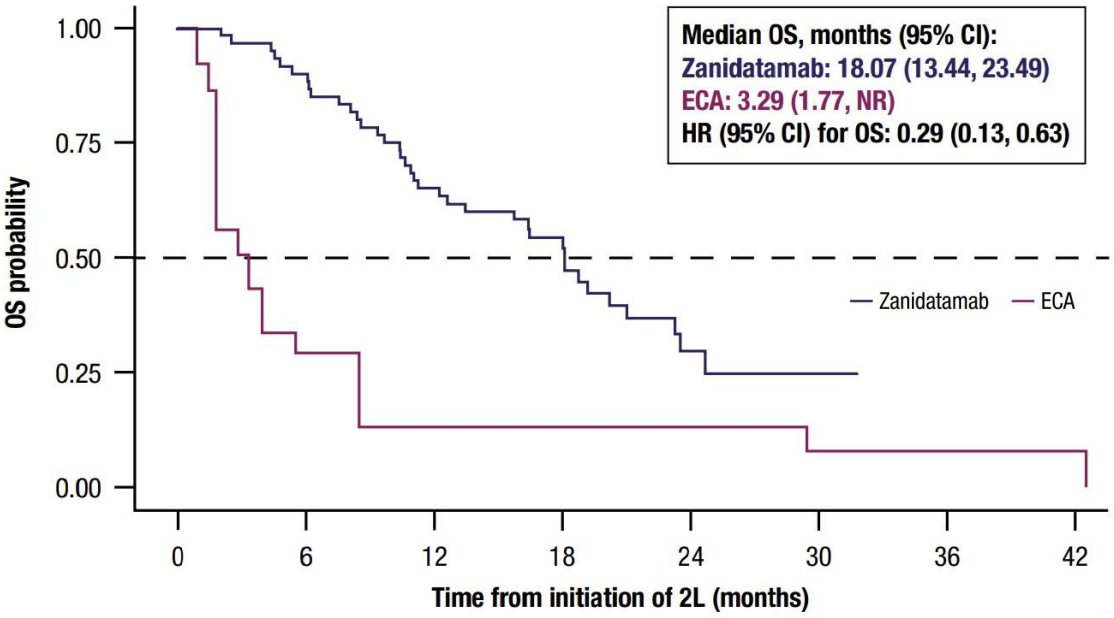

Abbreviations: 2L, second line; CI, confidence interval; ECA, external control arm; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; SMR, standardised mortality ratio.
Source: Kim (2025) (71).

#### 2.10.3.2.3 Overall survival

Results showed median OS was significantly longer for patients treated with zanidatamab (18.07 months [95% CI: 13.44, 23.49]) vs. patients treated with chemotherapy in the external control arm (3.29 months [95% CI: 1.77, not reported (NR)]) (HR: 0.29 [95% CI: 0.13, 0.63]) (71). The KM plot for OS is presented in Figure 24.

Zanidatamab was associated with a 61% and 52% increased OS rate after 6 months and 12 months, respectively (71). At 6 months, the OS rate with zanidatamab was 90% (95% CI: 83, 98) and for the external control arm was 29% (95% CI: 11, 75) (71). At 12 months, the OS rate with zanidatamab was 65% (95% CI: 54, 78) compared with 13% (95% CI: 3, 55) in the external control arm (71).

**Figure 24: SMR-weighted KM plot for OS with zanidatamab and external control arm**




Abbreviations: 2L, second line; CI, confidence interval; ECA, external control arm; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; SMR, standardised mortality ratio.
Source: Kim (2025) (71).

### *2.10.3.3 Uncertainties in the external control arm analysis*

The external control arm analysis provides additional comparative information regarding the survival benefit in an HER2+ IHC3+ BTC population of zanidatamab compared with systemic chemotherapy used in routine practice in the US. However, this analysis has a number of limitations. Firstly, although the Flatiron database is extensive, only 12 patients were eligible for inclusion in the analysis, which limited the ability to implement all the eligibility criteria from the HERIZON-BTC-01 trial to the external control arm cohort (71). The small sample size also limited the ability to adjust for all prognostic factors in the analysis (71). Secondly, the analysis focuses on comparing randomised controlled trial (RCT) evidence with RWE evidence, which

leads to additional uncertainty in the similarity of outcomes reported. Finally, the external control arm considers only patients in the US, where prescribing practices (e.g. in 2L chemotherapies) and patient demographics, including comorbidities, may differ from standard practice in England and Wales. However, given the lack of available comparator data specifically in a population with HER2+ IHC3+ BTC, this analysis provides supportive evidence of the treatment effect of zanidatamab.

### 2.10.4 Naive comparison

Due to the limitations of the MAICs (Section 2.10.2.2) and only moderate differences between the unweighted and weighted analyses, a naive comparison is also presented. For the reasons above, the naive comparison was considered the most appropriate to model the cost-effectiveness of zanidatamab vs. FOLFOX + ASC, and ASC alone. This is in line with TA722 (pemigatinib) appraisal, where the committee acknowledged that because of the rarity of BTC, the data on the comparators from ABC-06 were the best available evidence. Despite the limitations, it concluded that the comparative efficacy and safety data from ABC-06 were the most appropriate evidence for decision making (Section 2.10.5).

Comparisons of efficacy outcomes for zanidatamab from HERIZON-BTC-01 relevant to the economic modelling are presented in Section 2.10.4.1, with full results presented in Section 2.6.1. Efficacy outcomes for FOLFOX + ASC and ASC alone from ABC-06 are also presented in Section 2.10.4.1, with full results presented in Appendix N.

#### *2.10.4.1 Survival (PFS and OS) in HERIZON-BTC-01 and ABC-06*

##### 2.10.4.1.1 Progression-free survival

An overview of the PFS results from HERIZON-BTC-01 and ABC-06 are presented in Table 28.

As presented in Section 2.6.1, the median PFS by ICR of patients with HER2+ IHC3+ BTC treated with zanidatamab in HERIZON-BTC-01 was 7.2 months (95% CI: 5.4, 9.4) (62). The median PFS by INV was [redacted] months (95% CI: [redacted]) (62). The 6-month and 12-month PFS KM rate by ICR were [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]), respectively (62). The 6-month and 12-month PFS KM rate by INV were [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]), respectively (62).

In the FOLFOX + ASC arm of ABC-06, the median PFS was 4.0 months (95% CI: 3.2, 5.0) (21). The 6-month and 12-month PFS rate were 32.1% (95% CI: 22.3, 42.3) and 8.6% (95% CI: 3.8, 16.0), respectively (21). PFS was not reported for the ASC arm (21).

**Table 28: PFS as reported in HERIZON-BTC-01 and ABC-06**

| | HERIZON-BTC-01 | | ABC-06 |
|---|---|---|---|
| Intervention | Zanidatamab | Zanidatamab | FOLFOX + ASC |
| n | 62 | 62 | 81 |
| Assessment | ICR | INV | INV |
| Median PFS, months (95% CI) | 7.2 (5.4, 9.4) | [redacted] | 4.0 (3.2, 5.0) |
| PFS rate, % (95% CI)<br>6-months<br>12-months | [redacted] | [redacted] | <br>32.1 (22.3, 42.3)<br>8.6 (3.8, 16.0) |

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICR, independent central review; INV, investigator assessment; PFS, progression-free survival.
Sources: HERIZON-BTC-01 : IHC3+ subgroup analysis (2025) (62); ABC-06: Lamarca (2021) (21).

#### 2.10.4.1.2 Overall survival

An overview of the OS results from HERIZON-BTC-01 and ABC-06 are presented in **Table 29**.

As presented in Section **2.6.1**, the median OS of patients with HER2+ IHC3+ BTC treated with zanidatamab in HERIZON-BTC-01 was 18.1 months (95% CI: 12.2, 22.9) (62). The 6-month and 12-month OS KM rates were [redacted]% (95% CI: [redacted]) and [redacted]% (95% CI: [redacted]), respectively (62).

In the FOLFOX + ASC arm of ABC-06, the median OS was 6.2 months (95% CI: 5.4, 7.6 (21). The 6-month and 12-month OS rate were 50.6% (95% CI: 39.3, 60.9) and 25.9% (95% CI: 17.0, 35.8), respectively (21). In the ASC only arm, the median OS was 5.3 months (95% CI: 4.1, 5.8) and the 6-month and 12-month OS rates were 35.5% (95% CI: 25.2, 46.0) and 11.4% (95% CI: 5.6, 19.5), respectively (21).

**Table 29: OS as reported in HERIZON-BTC-01 and ABC-06**

| | HERIZON-BTC-01 | ABC-06 | |
|---|---|---|---|
| Intervention | Zanidatamab | FOLFOX + ASC | ASC |
| n | 62 | 81 | 81 |
| Median OS, months (95% CI) | 18.1 (12.2, 22.9) | 6.2 (5.4, 7.6) | 5.3 (4.1, 5.8) |
| OS rate, % (95% CI)<br>6-months<br>12-months | [redacted] | 50.6 (39.3, 60.9)<br>25.9 (17.0, 35.8) | 35.5 (25.2, 46.0)<br>11.4 (5.6, 19.5) |

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival.
Sources: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62); ABC-06: Lamarca (2021) (21).

### 2.10.5 Indirect treatment comparisons: conclusions

In the absence of head-to-head data to compare zanidatamab with FOLFOX + ASC, and ASC alone, as many approaches as possible were explored to indirectly

compare the best available evidence, including unanchored MAICs, an external control arm analysis, and naive comparisons.

Unanchored MAICs were conducted to indirectly compare the OS and PFS of zanidatamab with FOLFOX + ASC, and ASC alone. Overall, the unanchored MAICs showed a statistically significant improvement in PFS with zanidatamab compared with FOLFOX + ASC (weighted HR: [redacted]), and a statistically significant improvement in OS compared with FOLFOX + ASC (HR: [redacted]) and ASC alone (HR: [redacted]). Unweighted analyses provided similar, or more conservative, HR estimates for OS and PFS compared with MAIC estimates.

A weighted comparison of HER2+ IHC3+ patients in HERIZON-BTC-01 and an external control arm of IHC3+ patients treated with chemotherapy in the US showed significantly longer PFS with zanidatamab (7.3 vs 2.3 months; HR: 0.47) and median OS (18.1 vs 3.3 months; HR: 0.29) with zanidatamab compared with chemotherapy (53).

Due to the uncertainties of the MAICs (Section **2.10.2.2**) and the external control arm analysis (Section **2.10.3.3**), with considerable differences in trial patient population, limited patient numbers, and variation in treatment, a naive comparison was considered the most suitable for the base case in the evaluation of cost-effectiveness (see Section **3**). This approach is also aligned with the approach that was deemed acceptable in TA722 (pemigatinib) (18).

Naive comparisons of zanidatamab with FOLFOX + ASC, and ASC alone show zanidatamab offers a considerable survival benefit for eligible patients. Treatment with zanidatamab in HERIZON-BTC-01 resulted in a median OS of 18.1 months (62), compared with 6.2 months and 5.3 months in the FOLFOX + ASC, and ASC alone arms of the ABC-06 trial, respectively (21). Median PFS per INV was also longer for zanidatamab ([redacted] months) (54) naively compared with FOLFOX + ASC (4.0 months) (PFS was not assessed for ASC alone in ABC-06) (21).

## 2.11 Adverse reactions

***Summary: Overview of zanidatamab safety***

- Zanidatamab is a chemotherapy-free regimen with a manageable and well-tolerated safety profile in BTC, as shown in HERIZON-BTC-01, and supported by the Phase 1 trial and real-world evidence (54, 60, 61, 63)
- In HERIZON-BTC-01, only [redacted] of patients experienced a Grade 3 to 4 TRAE, with no treatment-related deaths (Grade 5 TRAEs) (54)
  - There were few patients with TRSAEs [redacted] and only 2 TRAEs that led to discontinuation (54)
  - The most common TRAEs were diarrhoea, IRRs, and anaemia, which were generally manageable without dose reductions (54)
- Results from the Phase 1 trial were broadly similar, as all TRAEs in the BTC population (n=22) were mild to moderate (Grade 1 or 2) in severity
- In 2 real-world studies, no SAEs were reported in a single-centre study in England (n=20) and no Grade 3+ TRAEs were reported in a compassionate use study in France (n=20) (60, 61)
- MAICs of safety data showed statistically significantly fewer Grade 3+ TRAEs for patients treated with zanidatamab in HERIZON-BTC-01 vs. those treated with FOLFOX + ASC in ABC-06 (OR: [redacted]; p=0.01)
- Compared with FOLFOX + ASC in ABC-06, naive comparison of TRAEs and TRSAEs in HERIZON-BTC-01 by grade and severity shows a favourable tolerability profile for zanidatamab with fewer treatment-related Grade 3 and 4 AEs ([redacted]% vs. 34.6%), [redacted] Grade 5 TRAEs ([redacted] vs. 3 deaths), and fewer TRSAEs ([redacted]% vs 25.9%) (21, 54)
- Patients with HER2+ BTC are currently limited to systemic combination chemotherapy with FOLFOX, which has substantial toxicity concerns and poor tolerability, so zanidatamab offers a potentially more manageable chemotherapy-free treatment option

The safety profile of zanidatamab in BTC has been studied in 2 clinical trials (HERIZON-BTC-01 [Section 2.11.1] and ZWI-ZW25-101 [Appendix D.1]), including 233 patients worldwide and is supported by RWE from England (UCLH, n=20) and France (n=20) [Section 2.11.2]). As head-to-head trials are not available, comparative safety evidence of zanidatamab monotherapy vs. combination chemotherapy with FOLFOX + ASC is provided by naive comparisons and a MAIC of HERIZON-BTC-01 vs. ABC-06 (Section 2.10) (54, 60, 61, 63, 73).

### 2.11.1 HERIZON-BTC-01 – full cohort

The safety results presented in the following sections are for the full HERIZON-BTC-01 safety set (safety analysis set (SAS); n=87; see Section 2.4.1.1 for details). Safety data specifically for the IHC3+ population were not generated, with the exception of treatment exposure, as safety of any medicine is not expected to

vary between populations and greater patient numbers provide more robust evidence for the safety profile of zanidatamab.

AE data were recorded in the HERIZON-BTC-01 trial at all DCOs. In this section, AE data are presented from the final DCO (11th July 2024) at a follow-up of 33.4 months.

#### *2.11.1.1 Treatment exposure*

All 87 patients enrolled in HERIZON-BTC-01 received zanidatamab. In the IHC3+ population, the median duration of treatment was [redacted] months (range: [redacted] to [redacted]) with a median of [redacted] cycles initiated (range: [redacted] to [redacted]). A summary of zanidatamab exposure for the IHC3+ population, as well as the overall trial population, is presented in **Table 30**.

**Table 30: Duration of zanidatamab exposure – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| | IHC3+ (n=62) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|---|
| Duration of treatment,† months<br>Mean (StD)<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of cycles initiated‡<br>Mean (StD)<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] |
| Relative dose intensity,§ %<br>Mean (StD)<br>Median<br>Min, max | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: DCO, data cut-off; IHC, immunohistochemistry; SAS, safety analysis set; StD, standard deviation.
†Duration of zanidatamab treatment is calculated as: minimum of ([treatment end date + 14 days], death date, DCO date, start of new anticancer therapy) = [treatment start date]+1/30.4375.
‡If at least 1 dose of zanidatamab was administered.
§Relative dose intensity (%) = 100% × actual dose intensity (mg/kg/week) / intended dose intensity (mg/kg/week).
Source: HERIZON-BTC-01 CSR (2025) (54); HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62).

Treatment exposure at the interim DCO (28th July 2023) was consistent with the final DCO. For all 87 patients in the study who received zanidatamab, the median duration of treatment was 5.1 months (range: 0.5 to 27.2) and the mean duration of treatment was 7.5 months (StD: 6.93) (68). The median relative dose intensity was 100.0% (range: 67.2, 100.0) and the mean relative dose intensity was 97.6% (StD: 6.17) (68).

#### *2.11.1.2 Adverse events: overview*

The safety results presented in the following sections are for the full HERIZON-BTC-01 SAS. Safety analysis for the IHC3+ population was not conducted as safety of any medicine is not expected to vary between populations and greater patient numbers provide more robust evidence for the safety profile of zanidatamab.

An overview of all AEs reported in HERIZON-BTC-01 is presented in **Table 31**. The majority of patients ([redacted]%) experienced at least 1 AE, defined as any AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment, inclusive, of which [redacted]% were considered as TRAEs, related to zanidatamab by the investigator. Grade 3+ AEs were reported in [redacted]% of patients participating in HERIZON-BTC-01, and [redacted] patients ([redacted]%) experienced at least 1 serious adverse event (SAE). Only [redacted] participants ([redacted]%) had TRSAEs. AEs leading to discontinuation of study treatment were reported in [redacted] patients ([redacted]). Across all patients, [redacted] AEs resulting in death were reported, [redacted] of which were considered related to zanidatamab by the investigator.

**Table 31: Overview of AEs – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| AE, n (%) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any AE† | [redacted] | [redacted] | [redacted] |
| Study drug related | [redacted] | [redacted] | [redacted] |
| Any Grade 3+ AE | [redacted] | [redacted] | [redacted] |
| Study drug related | [redacted] | [redacted] | [redacted] |
| Any SAE | [redacted] | [redacted] | [redacted] |
| Study drug related | [redacted] | [redacted] | [redacted] |
| Any AE resulting in death‡ | [redacted] | [redacted] | [redacted] |
| Study drug related | 0 | [redacted] | [redacted] |
| Any AE resulting in discontinuation | [redacted] | [redacted] | [redacted] |
| Study drug related | 2 (2.5) | [redacted] | [redacted] |
| Any AE resulting in: | | | |
| Infusion interruption | [redacted] | [redacted] | [redacted] |
| Dose delay | [redacted] | [redacted] | [redacted] |
| Dose held (skipped) | [redacted] | [redacted] | [redacted] |
| Dose reduction | [redacted] | [redacted] | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; SAS, safety analysis set.
Study-drug relationship as determined by investigator
†Any AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment, inclusive.
‡Includes death that occurred within the safety reporting period plus deaths >30 days after the final dose of study treatment.
Source: HERIZON-BTC-01 CSR (2025) (54).

A similar AE profile was observed at the interim DCO (28th July 2023). The majority of patients (96.6%) experienced at least 1 AE, inclusive, of which 72.4% were considered as TRAEs, related to zanidatamab by the investigator (66, 68). Grade 3+ AEs were reported in 63.2% of patients participating in HERIZON-BTC-01, and 45 patients (51.7%) experienced at least 1 SAE (66, 68). Only 8 participants (9.2%) had TRSAEs (66). AEs leading to discontinuation of study treatment were reported in 2 patients (2.3%) (66, 68). Across all patients, 3 AEs resulting in death were reported, none of which were considered related to zanidatamab by the investigator (68).

Additional safety outcomes from the interim DCO used to support the regulatory submission are presented in Appendix J.

#### *2.11.1.3 Most common AEs by preferred term*

The most common AEs occurring in HERIZON-BTC-01 were gastrointestinal disorders ([redacted]%), investigations ([redacted]%), infections and infestations ([redacted]%), general disorders and administration site conditions ([redacted]%), metabolism and nutrition disorders ([redacted]%), injury, poisoning and procedural complications ([redacted]%), and blood and lymphatic system disorders ([redacted]%). A summary of AEs occurring in 10% or more of patients is presented in **Table 32**.

**Table 32: AEs occurring in 10% or more of patients by MedDRA preferred term – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| MedDRA preferred term, n (%) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any AE | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] |
| Infusion related reaction | [redacted] | [redacted] | [redacted] |
| Anaemia | [redacted] | [redacted] | [redacted] |
| Abdominal pain | [redacted] | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] | [redacted] |
| Nausea | [redacted] | [redacted] | [redacted] |
| Pyrexia | [redacted] | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] | [redacted] |
| Weight decreased | [redacted] | [redacted] | [redacted] |
| Ejection fraction decreased | [redacted] | [redacted] | [redacted] |
| Fatigue | [redacted] | [redacted] | [redacted] |
| Hypokalaemia | [redacted] | [redacted] | [redacted] |
| Pruritus | [redacted] | [redacted] | [redacted] |
| Blood bilirubin increased | [redacted] | [redacted] | [redacted] |
| Hypertension | [redacted] | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] | [redacted] |
| Blood alkaline phosphatase increased | [redacted] | [redacted] | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; MedDRA, medical dictionary for regulatory activities; SAS. safety analysis set.
Multiple occurrences of an event within a participant are counted only once. Events are presented by decreasing frequency of preferred term in the total column. AEs coded using MedDRA version 25.0.
Source: HERIZON-BTC-01 CSR (2025) (54).

#### 2.11.1.3.1 Most common TRAEs by preferred term

Overall, [redacted] patients ([redacted]%) experienced at least 1 treatment-related adverse event (TRAE). The most common TRAEs (occurring in more than 5% of patients) were: diarrhoea ([redacted]%), infusion-related reaction (IRR) ([redacted]%), ejection fraction decreased ([redacted]%), nausea ([redacted]%), alanine aminotransferase (ALT) increased ([redacted]%), aspartate aminotransferase (AST) increased ([redacted]%), vomiting ([redacted]%), and fatigue ([redacted]%) (Table 33).

**Table 33: TRAEs occurring in 5% or more of patients by MedDRA preferred term – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| MedDRA preferred term, n (%) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any TRAE | [redacted] | [redacted] | [redacted] |
| Diarrhoea | 32 (40.0) | [redacted] | [redacted] |
| Infusion related reaction | 28 (35.0) | [redacted] | [redacted] |
| Ejection fraction decreased | 9 (11.3) | [redacted] | [redacted] |
| Nausea | 8 (10.0) | [redacted] | [redacted] |
| Alanine aminotransferase increased | 6 (7.5) | [redacted] | [redacted] |
| Aspartate aminotransferase increased | 6 (7.5) | [redacted] | [redacted] |
| Vomiting | 6 (7.5) | [redacted] | [redacted] |
| Fatigue | 5 (6.3) | [redacted] | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; MedDRA, medical dictionary for regulatory activities; SAS, safety analysis set; TRAE, treatment-related adverse event.
Multiple occurrences of an event within a participant are counted only once. Events are presented by decreasing frequency of preferred term in the total column. AEs coded using MedDRA version 25.0.
Source: HERIZON-BTC-01 CSR (2025) (54).

### *2.11.1.4 Grade 3+ AEs by preferred term*

A total of [redacted] patients ([redacted]%) treated with zanidatamab experienced Grade 3+ events, of which [redacted] patients ([redacted]%) experienced a highest severity of Grade 3, 5 patients ([redacted]%) experienced Grade 4 events, and 4 patients ([redacted]%) experienced a Grade 5 event (Table 34). The most frequently reported Grade 3+ AEs were anaemia ([redacted]%), diarrhoea ([redacted]%), and hypertension ([redacted]%) (Table 34).

Grade 3+ AEs considered related to zanidatamab by the investigator were reported in [redacted] patients ([redacted]%). The highest severity of TRAE was Grade 3 in [redacted] patients ([redacted]%) and Grade 4 in [redacted] patient ([redacted]%). [redacted] Grade 5 AEs (deaths) were considered related to zanidatamab. Grade 3+ TRAEs occurring in more than 1 patient were diarrhoea ([redacted]%), anaemia ([redacted]%), ejection fraction decrease ([redacted]%), and AST increase ([redacted]%).

**Table 34: Overview of Grade 3+ AEs occurring in 5% or more of patients by preferred term – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| MedDRA preferred term, n (%) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any Grade 3+ AE† | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |
| Anaemia | [redacted] | [redacted] | [redacted] |
| Study drug related | 3 (3.8) | | |
| Diarrhoea | [redacted] | [redacted] | [redacted] |
| Study drug related | 4 (5.0) | | |
| Hypertension | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |
| Alanine aminotransferase increased | [redacted] | [redacted] | [redacted] |
| Study drug related | 1 (1.3) | | |
| Cholangitis | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |
| Hypokalaemia | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |
| Jaundice cholestatic | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |
| Pneumonia | [redacted] | [redacted] | [redacted] |
| Study drug related | | | |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; MedDRA, medical dictionary for regulatory activities.
Relationship to zanidatamab as determined by the investigator.
†Any Grade 3+ AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment, inclusive occurring in 2 or more participants
Source: HERIZON-BTC-01 CSR (2025) (54).

### *2.11.1.5 Serious adverse events*

A total of [redacted] patients ([redacted]%) experienced at least 1 SAE during the HERIZON-BTC-01 trial, defined as: fatal, life-threatening, caused or prolonged an existing hospitalisation, was disabling or incapacitating, caused congenital anomaly or birth defect, or was an important medical event that could have jeopardised the patient and could have required medical or surgical intervention to prevent 1 of the outcomes listed. SAEs occurring in 5% or greater of patients were cholangitis ([redacted]%), jaundice cholestatic ([redacted]%), and pneumonia ([redacted]%) (54).

Only [redacted] patients ([redacted]%) experienced TRSAEs considered by the investigator to be related to zanidatamab: ALT and AST increase ([redacted]), anaemia, diarrhoea, ejection fraction decreased, enteritis, IRR, oral candidiasis, and pneumonitis (all occurring in [redacted] patient each). SAEs occurring in 2% or greater of patients are presented in **Table 35** and TRSAEs are presented in **Table 36**.

**Table 35: SAEs occurring in 2% or more of patients by MedDRA preferred term – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| MedDRA preferred term | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any SAE, n (%) | [redacted] | [redacted] | [redacted] |
| Cholangitis | [redacted] | [redacted] | [redacted] |
| Jaundice cholestatic | [redacted] | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] | [redacted] |
| Biliary obstruction | [redacted] | [redacted] | [redacted] |
| Sepsis | [redacted] | [redacted] | [redacted] |
| Obstruction gastric | [redacted] | [redacted] | [redacted] |
| Alanine aminotransferase increased | [redacted] | [redacted] | [redacted] |
| Asthenia | [redacted] | [redacted] | [redacted] |
| Bacteraemia | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] |
| Haematemesis | [redacted] | [redacted] | [redacted] |
| Jaundice | [redacted] | [redacted] | [redacted] |
| Pleural effusion | [redacted] | [redacted] | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set.
Multiple occurrences of an event within a participant are counted only once. Events are presented by decreasing frequency of preferred term in the total column. AEs coded using MedDRA version 25.0.
Source: HERIZON-BTC-01 CSR (2025) (54).

**Table 36: TRSAEs by MedDRA preferred term – HERIZON-BTC-01 SAS (DCO 11 July 2024)**

| MedDRA preferred term, n (%) | Total (n=87) |
|---|---|
| Any TRSAE | [redacted] |
| Alanine aminotransferase increased | [redacted] |
| Aspartate aminotransferase increased | [redacted] |
| Anaemia | [redacted] |
| Diarrhoea | [redacted] |
| Ejection fraction decreased | [redacted] |
| Enteritis | [redacted] |
| Infusion related reaction | [redacted] |
| Oral candidiasis | [redacted] |
| Pneumonitis | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set.
Multiple occurrences of an event within a participant are counted only once. Events are presented by decreasing frequency of preferred term in the total column. AEs coded using MedDRA version 25.0.
Source: HERIZON-BTC-01 CSR (2025) (54).

#### *2.11.1.6 Adverse events resulting in treatment discontinuation*

[redacted] patients ([redacted]%) experienced AEs that resulted in discontinuation of zanidatamab; [redacted] due to a Grade 3 AE of pneumonitis and [redacted] due to a Grade 2 AE of ejection fraction decreased. [redacted] events were considered by the investigator to be related to zanidatamab treatment.

#### *2.11.1.7 Adverse events of special interest and selected adverse events*

##### 2.11.1.7.1 Infusion-related reactions

Zanidatamab was administered as monotherapy as an IV infusion every 2 weeks. A total of [redacted] patients ([redacted]%) experienced [redacted] events of IRR, [redacted] of which was an SAE ([redacted]%). Nearly all patients with IRR ([redacted]%) had Grade 1 or 2 events (mild or moderate severity) (54). The most frequently reported IRR symptoms included chills ([redacted] patients), pyrexia/fever ([redacted] patients), and elevated blood pressure ([redacted] patients). Only [redacted] patient experienced a Grade 3 IRR, which was resolved with supportive measures and did not preclude zanidatamab treatment (54).

The median time to onset of IRR from infusion start was [redacted] minutes (range: [redacted] to [redacted]) (54). The majority of patients who had IRR (n=[redacted]) experienced an IRR during the first cycle of zanidatamab treatment and most (n=[redacted]%) did not experience recurrent IRRs. All IRRs resolved, with a median time to resolution of [redacted] minutes (range: [redacted] to [redacted]).

##### 2.11.1.7.2 Cardiac events

All cardiac events were clinically asymptomatic and confounded by pre-existing or concurrent conditions (54). Confirmed cardiac events occurred in [redacted] patients ([redacted]%); a total of [redacted] events of ejection fraction decreased were recorded in these patients, [redacted] events each were Grade 2 and Grade 3 (54). For [redacted] patient, the event was considered serious. [redacted] events across [redacted] patients were considered related to zanidatamab by the investigator and were managed as follows: [redacted] patient had no changes to zanidatamab dosing; [redacted] patients had a zanidatamab dose delay; [redacted] patient had their dose of zanidatamab held (skipped); [redacted] patient had zanidatamab discontinued. The median time to first onset was [redacted] (range: [redacted]). [redacted] cardiac events were resolved by the DCO with a median time to resolution of [redacted] (range: [redacted]).

##### 2.11.1.7.3 Diarrhoea

A total of [redacted] patients ([redacted]%) reported [redacted] events of diarrhoea. In total, [redacted] patients ([redacted]%) experienced a total of [redacted] events of diarrhoea considered related to zanidatamab by the investigator. [redacted]patients ([redacted]%) experienced diarrhoea as an SAE, requiring hospitalisation. Among patients who reported diarrhoea, over half ([redacted] patients) experienced only [redacted]event ([redacted]% of overall population), and [redacted] patients had [redacted] or more events ([redacted]% overall). Most patients reported a Grade 1 or Grade 2 event as the highest severity ([redacted] and [redacted] patients, respectively). Grade 3

diarrhoea was reported in [redacted] patients. [redacted] Grade 4 or Grade 5 events were reported. The median time to resolution of diarrhoea was [redacted] (range: [redacted]).

Prophylactic treatment to minimise the impact of diarrhoea on patients made this AE generally manageable; oncologists in the UK noted that diarrhoea AEs may be reduced in clinical practice (36).

#### 2.11.1.7.4 Deaths

[redacted] patients ([redacted]%) died during the safety reporting period (within 30 days of last dose of zanidatamab); [redacted] deaths were considered related to zanidatamab. [redacted] of the deaths were due to disease progression and [redacted] were due to AEs (hepatic failure, haematemesis, and underlying cancer), (54). A total of [redacted] patients ([redacted]%) died more than 30 days after the last dose of zanidatamab; [redacted] ([redacted]%) due to disease progression, [redacted] ([redacted]%) due to AE (multiple organ dysfunction that began during the safety reporting period but death occurred more than 30 days after the last dose), [redacted] ([redacted]%) due to other reasons, and [redacted] ([redacted]%) due to an unknown cause (Table 37) (54). [redacted] patients with an unknown cause of death had discontinued study treatment due to PD. A summary of deaths that occurred in patients that participated in the HERIZON-BTC-01 trial is presented in Table 37.

**Table 37: Summary of deaths (SAS [DCO 11 July 2024])**

| Cause of death | Cohort 1 IHC2/3+ (n=80) | Cohort 2 IHC0/1+ (n=7) | Total (n=87) |
|---|---|---|---|
| Any death, n (%) | [redacted] | [redacted] | [redacted] |
| Within 30 days of last dose<br>Disease progression<br>AE | [redacted] | [redacted] | [redacted] |
| More than 30 days after last dose<br>Disease progression<br>AE<br>Other<br>Unknown‡ | [redacted] | [redacted] | [redacted] |

Abbreviations: AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; SAS, safety analysis set.
† Cause of death was reported as “billiar [sic]septic shock”.
‡ Cause of death was not available at the study centre.
Source: HERIZON-BTC-01 CSR (2025) (54).

### 2.11.2 Supporting safety evidence: additional studies

Additional studies that provided supportive safety data for zanidatamab include the Phase 1 clinical trial ZWI-ZW25-101 (63) and 2 real-world studies in England (UCLH) and France (60, 61).

In the dose expansion phase of the Phase 1 study, ZWI-ZW25-101, patients with HER2+ BTC (n=22) were included and assessed for safety (63). All 22 patients with BTC experienced at least 1 AE, and 15 (68.0%) patients had at least 1 AE considered to be related to zanidatamab. No patients experienced a Grade 3+ TRAE

and one patient experienced an SAE considered to be related to zanidatamab. No zanidatamab-related dose reductions, discontinuations, or deaths occurred in the BTC cohort.

In a real-world study of compassionate use of zanidatamab in patients with HER2+ BTC in UCLH (n=20), the most frequent AEs were infusion reactions (Grade 1 to 2), diarrhoea (1 patient with Grade 3), and vomiting (Grade 2), but no SAEs were observed during the study period (60).

In a similar real-world study conducted in France in patients with HER2+ BTC treated with zanidatamab (n=20), 3 patients (15%) experienced a Grade 2 IRR during the first administration, with favourable outcomes (61). No cardiac toxicities were reported and Grade 1 to 2 diarrhoea was the most frequent AE (40%, n=8) (61). No Grade 3 or 4 TRAEs were observed (61). One patient required dose adjustment for Grade 2 diarrhoea (61).

Further details of supportive studies that report AEs are provided in Appendix D.

### 2.11.3 Indirect treatment comparisons: safety

As HERIZON-BTC-01 was a single-arm trial, indirect treatment comparisons were attempted to assess the relative safety of zanidatamab vs. FOLFOX + ASC and ASC alone.

Unanchored MAICs show an improved safety profile for zanidatamab compared with FOLFOX + ASC, when considering TRAEs. As all AEs in the ASC arm of ABC-06 were considered as treatment-emergent, rather than treatment-related (21), TRAEs for this arm could not be compared.

As there are considerable uncertainties surrounding MAIC analysis of safety, naive comparisons are also presented and were deemed the most appropriate (Section 2.11.3.2) for use in the cost-effectiveness model.

#### *2.11.3.1 Unanchored MAICs*

Unanchored MAICs were attempted to assess the safety profiles of zanidatamab monotherapy vs. combination chemotherapy with FOLFOX + ASC, and palliative care with ASC alone using the most appropriate trial data. As described in Section 2.10.2, the most relevant safety evidence identified for the comparators FOLFOX + ASC, and ASC alone is from the ABC-06 trial (21).The full published safety data from ABC-06 are provided in Appendix N. Full details of the methodology for the ITCs are provided in Appendix B.2.2.1.

Comparisons of safety data are often complex and problematic in cross-study comparisons, due to inconsistent reporting of AEs and length of study follow-up. Therefore, results comparing safety outcomes should be treated with caution.

#### 2.11.3.1.1 Methods

Composite measures of “any TRAE” and “Grade 3+ TRAEs” were generated from the safety data for ABC-06 and HERIZON-BTC-01. These composite measures were used to calculate ORs and 95% CIs to quantify differences in TRAE rates. Analyses were performed both without weights and with the weights from the MAIC incorporated into the regression model. For weighted analyses, robust standard errors were used. All safety analyses were performed on the full HERIZON-BTC-01 population (n=87).

Differences between HERIZON-BTC-01 and ABC-06 relating to safety assessment that may influence safety comparison were identified, as presented in **Table 38**. As ASC is a palliative treatment with no associated TRAEs, only comparison with FOLFOX + ASC was possible in this analysis.

**Table 38: Variation in treatment exposure in HERIZON-BTC-01 and ABC-06**

| | HERIZON-BTC-01 | ABC-06 | |
|---|---|---|---|
| Intervention | Zanidatamab | FOLFOX + ASC | ASC |
| n | 87 | 81 | 81 |
| Median follow-up, months | 33.4 (range: 28 to 45) | 21.7† (IQR: 17.2, 30.8) | 21.7† (IQR: 17.2, 30.8) |
| Treatment duration, months (range) | [redacted] | 2.3† (41 to 111) | 2.3† (41 to 111) |
| Number of cycles received, median | [redacted] (range:[redacted]) | 5 (IQR: 2, 6) | N/A |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IQR, interquartile range; N/A, not applicable.
Sources: HERIZON-BTC-01 CSR (54); Lamarca (2021).
†Values reported for both arms of the trial only.

#### 2.11.3.1.2 Results

Overall, the unanchored MAIC shows an improved tolerability profile for zanidatamab monotherapy compared with a combination chemotherapy regimen of FOLFOX + ASC. Comparisons of TRAEs from HERIZON-BTC-01 and ABC-06 using the MAIC approach are summarised in **Table 39.** The median follow-up for each trial is presented in **Table 38** as this could influence the number of AEs reported. The longer the follow-up duration, the more time there would be for safety events to occur. However, most AEs are expected to occur early in the follow-up, soon after receiving treatment. The duration of AEs was also not reported in ABC-06.

Zanidatamab had fewer TRAEs of any grade compared with FOLFOX + ASC, although the results were not statistically significant (unweighted odds ratio [OR]: [redacted] [95% CI: [redacted], [redacted]], p=[redacted]; weighted OR: [redacted] [95% CI: [redacted], [redacted]], p=[redacted]).

The improved safety profile of zanidatamab compared with chemotherapy with FOLFOX + ASC was more evident for Grade 3+ TRAEs (defined as those that required medical intervention, with or without hospitalisation depending upon clinical sequelae). Results of the MAIC show there were statistically significant reductions in

the incidence of Grade 3+ TRAEs for zanidatamab compared with FOLFOX + ASC (OR: [redacted] [95% CI: [redacted]], p=[redacted]), although the weighted comparison was slightly attenuated, meaning statistical significance was not reached (OR: [redacted] [95% CI: [redacted]], p=[redacted]).

**Table 39. Comparison of TRAEs using data from the full HERIZON-BTC-01 cohort.**

| n (ESS) | HERIZON-BTC-01 events, n (%) | Comparator | Comparator, N | Comparator events, n, (%) | OR (95% CI) | p-value | Weighted OR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| Any TRAE | | | | | | | | |
| 87 (33) | [redacted] | FOLFOX + ASC | 81 | 68 (84) | [redacted] | [redacted] | [redacted] | [redacted] |
| Grade 3+ TRAE | | | | | | | | |
| 87 (33) | [redacted] | FOLFOX + ASC | 81 | 31 (38) | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; CI, confidence interval; ESS, effective sample size; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OR, odds ratio; TRAE, treatment-related adverse event.
Median duration of study follow-up for HERIZON-BTC-01 was 21.9 months. Odds ratios generated using logistic regression as a statistical test to compare adverse event rates. ORs below 1 favour zanidatamab. Weighted ORs incorporate weights from a match-adjusted indirect comparison matching on prognostic factors with robust standard errors for CIs.
Source: ITC report (2025) (73).

### *2.11.3.2 Naive comparisons*

#### 2.11.3.2.1 TRAEs by severity and TRSAEs

The unanchored MAIC did not assess TRAEs by severity grade, or TRSAEs, including chemotherapy-related SAEs, which are described in ABC-06. As serious AEs are most likely to impact on costs and QALYs, a naive comparison of these safety outcomes between HERIZON-BTC-01 and ABC-06 is presented.

Table 40 presents the Grade 3+ TRAEs by severity as reported in HERIZON-BTC-01 and ABC-06 for zanidatamab ([redacted]% overall) and FOLFOX + ASC (34.6% overall), respectively. In ABC-06, the most frequently reported Grade 3+ chemotherapy-related AEs were neutropenia (10 patients [12%]), fatigue/lethargy (9 patients [11%]), and infection (8 patients [10%]). There were 3 chemotherapy-related deaths (1 each due to infection, acute kidney injury, and febrile neutropenia) reported in the FOLFOX + ASC arm (21). In comparison, there were [redacted] deaths related to zanidatamab in HERIZON-BTC-01 (54).

TRSAEs are presented in Table 41. In ABC-06, 29 TRSAEs were reported in 21 patients (25.9%) treated with FOLFOX + ASC. The most frequently reported TRSAEs were vomiting (3 patients [3.7%]), diarrhoea, febrile neutropenia, lung infection, neutropenic sepsis, PICC line infection, and sepsis (all occurring in 2 patients each [2.5%]) (21). In comparison, TRSAEs were reported in [redacted] patients ([redacted]%) treated with zanidatamab in HERIZON-BTC-01 (54).

**Table 40: Overview of Grade 3+ TRAEs by severity in HERIZON-BTC-01 and ABC-06 occurring in 2% or more of patients**

| | HERIZON-BTC-01 Zanidatamab (n=87) | | | ABC-06 FOLFOX + ASC (n=81) | | |
|---|---|---|---|---|---|---|
| **TRAE, n (%)** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 3** | **Grade 4** | **Grade 5** |
| Any TRAE | [redacted] | [redacted] | [redacted] | 23 (28.4) | 5 (6.2) | 3 (3.7) |
| Diarrhoea | [redacted] | [redacted] | [redacted] | 2 (2.5) | 0 | 0 |
| Anaemia | [redacted] | [redacted] | [redacted] | 2 (2.5) | 0 | 0 |
| Ejection fraction decreased | [redacted] | [redacted] | [redacted] | 0 | 0 | 0 |
| AST increased | [redacted] | [redacted] | [redacted] | 0 | 0 | 0 |
| Acute kidney injury | [redacted] | [redacted] | [redacted] | 1 (1.2) | 0 | 1 (1.2) |
| Neutropenia | [redacted] | [redacted] | [redacted] | 8 (9.9) | 2 (2.5) | 0 |
| Fatigue or lethargy | [redacted] | [redacted] | [redacted] | 9 (11.1) | 0 | 0 |
| Infection† | [redacted] | [redacted] | [redacted] | 6 (8.6) | 1 (1.2) | 1 (1.2) |
| Vomiting | [redacted] | [redacted] | [redacted] | 2 (2.5) | 0 | 0 |

| | HERIZON-BTC-01 Zanidatamab (n=87) | | | ABC-06 FOLFOX + ASC (n=81) | | |
|---|---|---|---|---|---|---|
| **TRAE, n (%)** | **Grade 3** | **Grade 4** | **Grade 5** | **Grade 3** | **Grade 4** | **Grade 5** |
| Biliary event‡ | [redacted] | [redacted] | [redacted] | 2 (2.5) | 0 | 0 |
| Hypertension | [redacted] | [redacted] | [redacted] | 2 (2.5) | 0 | 0 |

Abbreviations: ASC, active symptom control; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
†Lung, urinary, fever, or not specified, excluding liver or biliary.
‡Includes liver infection, increase bilirubin or alkaline phosphatase, and hepatitis.
Sources: HERIZON-BTC-01 CSR (54); Lamarca (2021) (21).

**Table 41: Overview of TRSAEs in HERIZON-BTC-01 and ABC-06 occurring in 2% or more of patients**

| TRSAE, n (%) | HERIZON-BTC-01 Zanidatamab (n=87) | ABC-06 FOLFOX + ASC (n=81) |
|---|---|---|
| Any TRSAE | [redacted] | 21 (25.9) |
| Vomiting | [redacted] | 3 (3.7) |
| Diarrhoea | [redacted] | 2 (2.5) |
| Febrile neutropenia | [redacted] | 2 (2.5) |
| Lung infection | [redacted] | 2 (2.5) |
| Neutropenic sepsis | [redacted] | 2 (2.5) |
| PICC line infection | [redacted] | 2 (2.5) |
| Sepsis | [redacted] | 2 (2.5) |

Abbreviations: ASC, active symptom control; PICC, peripherally-inserted central catheter; TRSAE, treatment-related serious adverse event.
Sources: HERIZON-BTC-01 CSR (54); Lamarca (2021) (21).

### 2.11.4 Safety overview

The well tolerated safety profile of a chemotherapy-free zanidatamab regimen in patients with HER2+ BTC is supported by clinical trial data and RWE, including 233 patients worldwide in clinical trials and 40 patients in real-world studies. An improved tolerability profile of zanidatamab monotherapy compared with combination chemotherapy with FOLFOX + ASC is supported by MAICs and naive comparison.

In HERIZON-BTC-01, over a considerable follow-up of [redacted] months, zanidatamab demonstrated a manageable and tolerable safety profile with low rates of Grade 3+ TRAEs ([redacted]% of patients), few TRSAEs ([redacted]%), and only [redacted] TRAEs that led to treatment discontinuation (22, 54). [redacted] deaths related to zanidatamab were reported. Across the HERIZON-BTC-01 population, the most common TRAEs were diarrhoea, IRRs, and anaemia, which were generally manageable and resolved quickly in an outpatient setting without dose reductions (22, 54).

Real-world studies in England and France, and the Phase 1 trial ZWI-ZW25-101, support the safety profile of zanidatamab in BTC. All TRAEs in the BTC population of ZWI-ZW25-101 were mild to moderate (Grade 1 or 2) in severity (63). No Grade 3+ TRAEs were reported in a real-world study of 20 patients in France (61), and no SAEs were reported in a real-world study of 20 English patients (60).

As HERIZON-BTC-01 was a single-arm study, relative risk could not be calculated. Instead, unweighted indirect comparisons support a statistically significant reduction in the incidence of Grade 3+ TRAE incidence with zanidatamab vs. FOLFOX + ASC. Due to the considerable uncertainties associated with the MAIC of safety between HERIZON-BTC-01 and ABC-06, a naive comparison was considered the most appropriate for inclusion in the cost-effectiveness analysis (CEA) (Section 3). Naive comparisons of severe (Grade 3+) TRAEs and TRSAEs showed considerably fewer events for zanidatamab vs. FOLFOX + ASC. Only [redacted] Grade 4 TRAE ([redacted]%) was reported in HERIZON-BTC-01 vs. 5 Grade 4 TRAEs (6.2%) and 3 Grade 5 TRAEs (3.7%) in ABC-06 (21, 54). TRSAEs were reported in [redacted]% of patients in HERIZON-BTC-01 vs. 25.9% of patients in ABC-06 (21, 54).

## *2.12 Ongoing studies*

No ongoing studies for zanidatamab in the indication relevant to this appraisal that will report in the next 12 months were identified in the SLR. The real-world study in England is still ongoing and median OS has not been reached (60).

## *2.13 Interpretation of clinical effectiveness and safety evidence*

### 2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

#### *2.13.1.1 Summary of efficacy evidence*

HERIZON-BTC-01 is the largest study conducted in patients with previously treated HER2+ unresectable, locally advanced, or metastatic BTC (22). Results showed a clinically meaningful survival benefit in patients with HER2+ IHC3+ BTC treated with zanidatamab (n=62). (54). For the primary endpoint, 51.6% of patients achieved cORR, with a median OS of 18.1 months (95% CI: 12.2, 22.9), a 12-month OS rate of [redacted]% (95% CI: [redacted]), and a median PFS of 7.2 months (95% CI: 5.4, 9.4) (54). Zanidatamab demonstrated durable responses, with a median DOR of 14.9 months (95% CI: 7.4, 24.0) and [redacted]% with a response duration of 16 weeks or longer (54).

The efficacy of zanidatamab observed in clinical trials is supported by RWE. In a single-centre study in England (n=13 evaluated), an ORR was observed in 54% of patients (60). In a compassionate use study in France (n=12 IHC3+), median PFS

was 8.0 months (95% CI: 1.5, 18.4), with an estimated 1-year OS rate of 90% (95% CI: 51, 98) (61).

#### *2.13.1.2 Summary of comparative evidence:*

HERIZON-BTC-01 was a single-arm study, so unanchored MAICs, an external control arm analysis, and naive comparisons were attempted to assess the comparative efficacy of zanidatamab vs. FOLFOX + ASC, or ASC alone (21).

Unanchored MAICs of HERIZON-BTC-01 and ABC-06 identified large and statistically robust improvements in OS for zanidatamab vs. both FOLFOX + ASC (weighted HR: [redacted]) and ASC alone (weighted HR: [redacted]) (Section **2.10.2.1**). PFS data were not reported for the ASC arm in ABC-06, but the median PFS for zanidatamab vs. FOLFOX + ASC showed a statistically significant reduction in disease progression with zanidatamab (weighted HR: [redacted]).

To compare HER2+ patient populations, an external control arm analysis compared zanidatamab-treated patients from HERIZON-BTC-01 with an external control arm of HER2+ (IHC3+) BTC patients from the US Flatiron database treated with chemotherapy. Results confirmed a substantial PFS and OS benefit of zanidatamab vs. chemotherapy (PFS HR: 0.47; OS HR: 0.29) specifically in a HER2+ population (Section **2.10.3**).

Naive comparisons were considered the most suitable for the base case in the cost-effectiveness model, due to limitations in the MAICs (Section **2.10.2.2**) and external control arm analysis (Section **2.10.3.3**), which included differences in trial patient populations, limited patient numbers, and variation in treatments. Similar to the MAICs and external control arm, results of the naïve comparison confirmed that zanidatamab showed a substantial survival benefit (Section **2.10.4)**. Treatment with zanidatamab in HERIZON-BTC-01 showed a median OS of 18.1 months (62), naively compared with 6.2 months and 5.3 months in the FOLFOX + ASC and ASC alone arms of the ABC-06 trial, respectively (21).

#### *2.13.1.3 Summary of QoL and safety findings:*

In HERIZON-BTC-01, zanidatamab showed modest improvements in HRQoL over the study period as measured by EQ-5D-5L. Results showed reduced pain, pain interference, and clinically meaningful improvements in EQ-5D VAS scores in responders to treatment from baseline to time of their best-on-treatment score, suggesting zanidatamab may improve HRQoL through disease control (54). Patients who achieved CR, PR, or SD also reported the greatest improvements in pain/BPI with resulting reductions in opioid use (54). In Phase 1 and real-world evidence, QoL was not quantitatively assessed (60, 61, 63).

As a chemotherapy-free regimen, zanidatamab demonstrated a well-tolerated safety profile in HERIZON-BTC-01 (22, 54). Grade 3+ TRAEs were reported in [redacted]% of

patients (n=[redacted]), with only [redacted] patient experiencing a Grade 4 event, and [redacted] deaths were reported (54).

The manageable tolerability profile of zanidatamab observed in clinical trials is supported by Phase 1 results and real-world studies in patients in England (UCLH) and France, which showed similar low levels of TRAEs (59-61, 63).

Unanchored MAICs and naive comparisons of safety data demonstrate the improved tolerability profile of zanidatamab vs. FOLFOX + ASC (Section **2.10**). An unanchored MAIC showed statistically significant reductions in the incidence of Grade 3+ TRAEs for zanidatamab vs. FOLFOX + ASC (p=[redacted]). Naive comparisons of Grade 3/4/5 TRAEs and SAEs also showed an improved tolerability profile for zanidatamab vs. FOLFOX + ASC (21, 62).

#### *2.13.1.4 Conclusions: clinical evidence*

Advanced BTC has a poor prognosis and its diagnosis is devastating for patients and their families (4). In England, patients with HER2+ BTC have no targeted treatment options and those fit enough to reach 2L therapy are limited to combination chemotherapy (FOLFOX + ASC), or palliative care (ASC alone). Zanidatamab 2L monotherapy shows substantial improvements in survival of approximately 1 year compared with FOLFOX + ASC, and ASC alone, and maintains QoL during these valuable additional months. Zanidatamab is a chemotherapy-free regimen with an improved tolerability profile compared with FOLFOX + ASC, with a reduced incidence of Grade 3+ TRAEs and TRSAEs (22, 54). The favourable safety profile of zanidatamab monotherapy may also be suited to patients who would not be well enough for combination chemotherapy and would only receive palliative care with ASC, providing them with a much-needed life-extending treatment option.

### 2.13.2 Strengths and limitations of the clinical evidence base for the technology

The strengths of the clinical evidence base for zanidatamab are as follows:

- HERIZON-BTC-01 is the largest clinical trial to date in this rare cancer population of 2L HER2+ BTC (n=87), conducted across 32 centres in 9 countries (22, 54).
- The primary endpoint (cORR) and secondary endpoints (DOR, DCR, PFS, and OS) of HERIZON-BTC-01, are considered relevant and clinically appropriate endpoints to assess the efficacy of treatments in oncology (18-20).
- HERIZON-BTC-01 reflects the proposed indication and anticipated use of zanidatamab in clinical practice in England and Wales (1, 54). The trial dosing for zanidatamab aligns with that used in clinical practice (22, 54).
- The clinical trial efficacy and safety are also supported by 22 patients with BTC from a Phase 1 trial (63) and real-world experience of 20 patients treated with

zanidatamab in an NHS centre in England (UCLH) and 20 patients treated in France (n=12 IHC3+) (60, 61).

Due to the rarity of BTC, particularly HER2+ IHC3+ in 2L, the totality of the evidence from HERIZON-BTC-01, ZWI-ZW25-101, and real-world studies should be considered in decision-making, and aligns with the level of evidence provided by other treatments in similar patient populations (18, 20).

The limitations of the clinical evidence base are as follows:

- No direct comparative data are available for zanidatamab. HERIZON-BTC-01 was a single-arm study. However, single-arm trials are common for rare cancers with a limited patient pool and acute unmet need, allowing for quicker patient access to new treatments.
- To compare zanidatamab with the SoC for 2L BTC, all alternative sources of comparative evidence were explored, including MAICs, use of an external control arm, and naive comparison. Due to limitations in the MAICs (Section **2.10.2.2**) and the external control arm (Section **2.10.3.3**), a naive comparison between HERIZON-BTC-01 and ABC-06 was considered the most reliable and appropriate for modelling.
- HERIZON-BTC-01 had a high proportion of patients from Asia. However, applicability of the trial to routine clinical practice in England has been confirmed by UK clinicians with extensive experience in BTC through a Delphi study and clinician interviews (36, 69).

# 3 Cost effectiveness

***Summary: cost-effectiveness analysis***

- A 3-health state partitioned survival model simulated patients with locally advanced or metastatic HER2+ IHC3+ BTC previously treated with at least 1 prior line of systemic therapy, in line with the relevant subgroup of the pivotal HERIZON-BTC-01 clinical trial, the final NICE scope, and expected UK licence (14, 22, 54, 74)
- No head-to-head evidence was available for the relevant comparators (FOLFOX + ASC or ASC alone); therefore, an unadjusted side-by-side (naive) comparison informed the comparative efficacy, with a scenario analysis using the results of the MAICs (**Section 2.10**)
- Clinical sources for survival, utilities and AE data in the model included:
  - Survival (OS and PFS) for zanidatamab extrapolated from HERIZON-BTC-01 (54)
  - Survival (OS and PFS) for FOLFOX+ ASC and ASC alone (OS only) from ABC-06 (21)
  - Utilities from EQ-5D data collected in HERIZON-BTC-01 using a TTD approach, which best reflects the natural decline in QoL approaching death. A continuous model was used in the base case; other TTD models, progression-based utilities, and literature sources were explored in scenario analysis
  - Disutilities and costs applied for Grade 3+ AEs, FOLFOX administration with central venous access devices, treatment-specific differences, and general decline with age

***Strengths and limitations***

- Given the rarity of HER2+ IHC3+ BTC, there are limitations regarding patient numbers and comparator evidence. The ABC-06 study does not report patients with HER2+ BTC and only included a 2L population
  - HER2 status is not proven to be prognostic of outcomes in BTC, so survival of patients with HER2+ BTC is not expected to differ widely from HER2-negative BTC
  - Both naive comparisons (base case) and MAICs (scenario) of efficacy data from HERIZON-BTC vs. ABC-06 data are explored in the cost-effectiveness analyses
- When possible, the model inputs are evidence-based, clinically validated and the most appropriate UK data to support decision-making in the context of a rare cancer with a high unmet need
- Comprehensive sensitivity and scenario analyses are explored to test the impact of uncertainties on cost-effectiveness results

***Results***

- Due to the severity of advanced BTC, and the lack of a new 2L treatment for HER2+ patients in decades, zanidatamab meets the criteria for the highest severity weighting, and a QALY weighting of ×1.7 is applied in the analysis
- In the base case, the ICER compared to FOLFOX + ASC was £[redacted] per QALY gained and £[redacted] compared to ASC alone
  - The QALY gain vs. FOLFOX is [redacted], increasing to [redacted] vs. ASC alone, due to increased LYs with zanidatamab while maintaining QoL. In addition, QoL with FOLFOX + ASC is reduced due to increased incidence of severe AEs with chemotherapy. QoL is also reduced with ASC alone due to lack of effective treatment options and disease control
- Sensitivity analyses demonstrate the robustness of cost-effectiveness results, with zanidatamab remaining cost-effective across all modelled scenarios

***Conclusion***

- Results suggest that zanidatamab is a cost-effective treatment compared with FOLFOX + ASC, with ICERs within the range that NICE considers a cost-effective use of NHS resources, especially for rare, severe cancers such as advanced BTC
- Given the rarity and severity of advanced HER2+ IHC3+ BTC, fewer than [redacted] patients are likely to be eligible for zanidatamab, so the budget impact in NHS England will be low

## 3.1 Published cost-effectiveness studies

A systematic review of the literature was conducted to identify published economic evaluations and cost-effectiveness studies of potential relevance to the decision problem addressed in this appraisal. Electronic database searches were conducted in April 2024 with updates performed in September 2024 and March 2025.

The scope of the economic SLR was published economic models and cost-effectiveness studies in patients with advanced or metastatic BTC. A detailed description of the review methods and results are reported in Appendix E. A summary of the identified studies is provided in **Table 42**.

**Table 42: Summary list of published cost-effectiveness studies in 2L advanced/metastatic BTC**

| Study | Summary of model | Patient population | QALYs | Costs (currency, year) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| **Chemotherapy** | | | | | |
| Kamble 2024 (75)<br>Global | • Systematic review of economic burden<br>• Gemcitabine-based chemotherapy most common in 1L BTC (24.0-100.0%)<br>• 5FU-based chemotherapy most common in 2L BTC (12.3-74.3%) | Metastatic and/or unresectable BTC | N/A | N/A | N/A |
| **Pembrolizumab** | | | | | |
| McCarthy 2024 (76)<br>UK | • Cost-effectiveness analysis comparing pembrolizumab with mFOLFOX/mFOLFIRI<br>• Multi-tumour partitioned survival model<br>• Healthcare payers' perspective<br>• Time horizon: lifetime (40 years)<br>• Cycle length: 3 weeks | Previously treated MSI-H/dMMR tumours | • Pembrolizumab: 3.88<br>• SoC: 0.72 | GBP, 2021<br>• Pembrolizumab at list price: 129,469<br>• SoC: 28,221.78 | • 32,085 |
| **Pemigatinib** | | | | | |
| Chueh 2022 (77)<br>Taiwan | • Cost-utility analysis comparing pemigatinib + mFOLFOX with 5FU<br>• Partition survival model<br>• Time horizon: 5 years | Advanced iCCA patients who failed the 1L therapy | • Incremental QALYs:<br>• 0.13 | NTD, not reported<br>• Incremental cost:<br>• 459,697 | • 3,411,098 |

| Study | Summary of model | Patient population | QALYs | Costs (currency, year) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| | • Perspective and cycle length not reported | | | | |
| Chen 2023 (78)<br>Taiwan | • Cost-effectiveness analysis comparing pemigatinib with mFOLFOX or 5FU<br>• Partition survival model<br>• Healthcare payers' perspective<br>• Time horizon: 5 years<br>• Cycle length: 1 month | Advanced iCCA with FGFR2 fusions/rearrangements in whom 1L gemcitabine-based chemotherapy failed | • Pemigatinib: 1.15<br>• mFOLFOX: 0.56<br>• 5FU: 0.47 | NTD, 2022<br>• Pemigatinib: 4,177,572<br>• mFOLFOX: 749,130<br>• 5FU: 524,472 | • Pemigatinib vs mFOLFOX: 5,814,700<br>• Pemigatinib vs 5FU: 5,380,241 |
| Chueh 2023 (79)<br>Taiwan | • Cost-effectiveness analysis comparing pemigatinib + mFOLFOX with 5FU<br>• Partition survival model<br>• Healthcare payers' perspective<br>• Time horizon: 5 years<br>• Cycle length: 1 month | Advanced iCCA with or without FGFR2 fusions/rearrangements in whom 1L gemcitabine-based chemotherapy failed | • New pemigatinib/mFOLFOX treatment regimen: 0.61<br>• Current 5FU treatment: 0.47 | NTD, 2021<br>• New pemigatinib/mFOLFOX treatment regimen: 984,168<br>• Current 5FU treatment: 524,472 | • 3,411,098 |
| Tzanetakos 2023 (80)<br>Greece | • Cost-effectiveness analysis comparing pemigatinib with mFOLFOX + ASC<br>• Partition survival model<br>• Healthcare payers' perspective<br>• Time horizon: lifetime<br>• Cycle length not reported | Advanced iCCA with FGFR2 fusion/rearrangements who have progressed on at least one line or prior systemic therapy | • Pemigatinib: 1.63<br>• ASC: 0.41<br>• mFOLFOX + ASC: 0.44 | EUR, 2022<br>• Cost per patient:<br>• Pemigatinib: 85,534<br>• ASC: 1,010<br>• mFOLFOX + ASC: 2,537 | • ASC: 69,345<br>• mFOLFOX + ASC: 69,928 |

| Study | Summary of model | Patient population | QALYs | Costs (currency, year) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| **Ivosidenib** | | | | | |
| Chen 2023 (81)<br>Taiwan | • Cost-effectiveness analysis comparing ivosidenib with mFOLFOX or 5FU<br>• Partition survival model<br>• Healthcare payers' perspective<br>• Time horizon: 10 years<br>• Cycle length: 4 weeks | Previously treated adult IDH1-mutant advanced iCCA | • Ivosidenib: 0.92<br>• mFOLFOX: 0.53<br>• 5FU/LV: 0.47 | NTD, 2022<br>• Ivosidenib: 4,368,907<br>• mFOLFOX: 599,085<br>• 5FU/LV: 466,176<br>•USD, 2022:<br>• Ivosidenib: 146,558<br>• mFOLFOX: 20,097<br>• 5FU/LV: 15,638 | •NTD:<br>• Ivosidenib vs mFOLFOX: 9,670,485<br>• Ivosidenib vs 5FU/LV: 8,664,634<br>• US:<br>• Ivosidenib vs mFOLFOX: 324,404<br>• Ivosidenib vs 5FU/LV: 290,662 |

Abbreviations: 1L, first-line; 2L, second-line; 5FU, fluorouracil; ASC, active symptom control; BTC, biliary tract cancer; CAD, Canadian dollar; CisGem, cisplatin and gemcitabine; dMMR, deficient mismatch repair; EUR, Euro; FGFR2, fibroblast growth factor receptor 2; GBP, Great Britain pound; iCCA, intrahepatic cholangiocarcinoma; ICER, incremental cost-effectiveness ratio; IDH1, isocitrate dehydrogenase 1; JPY, Japanese yen; LV, leucovorin; mFOLFIRI, modified folinic acid, fluorouracil, and irinotecan; mFOLFOX, modified folinic acid, fluorouracil, and oxaliplatin; MSI-H, microsatellite instability-high; N/A, not applicable; NR, not reported; NTD, New Taiwan dollar; QALM, quality-adjusted life months; QALYs, quality-adjusted life years; SoC, standard of care; USD, United States dollar.

## 3.2 Economic analysis

The SLR did not identify any published economic evaluations considering zanidatamab for the treatment of locally advanced or metastatic HER2+ IHC3+ BTC. Therefore, a de novo economic model was developed to assess the cost-effectiveness of zanidatamab against relevant treatment options within NHS England. The key features of this model are described in the subsections below.

### 3.2.1 Patient population

The population considered in the CEA is patients with locally advanced or metastatic HER2+ IHC3+ BTC previously treated with at least 1 prior line of systemic therapy. This is in line with the sub population of patients in the pivotal HERIZON-BTC-01 clinical trial and expected licence in the UK (22, 54, 74).

### 3.2.2 Model structure

The de novo cost-effectiveness model was developed in Microsoft Excel® using an area under the curve, partitioned survival analysis (PartSA) structure. The model structure is made up of 3 health states: progression free (or pre-progression), progressed disease (or post-progression), and death. It adopts a cohort-level structure in which time is captured as discrete cycles.

A progression-based model structure was chosen as it is reflective of the natural history of BTC, a PD, which in turn allows lifetime cost and health outcomes to be accurately estimated. In addition, this structure is in line with the secondary outcomes in the pivotal HERIZON-BTC-01 trial (PFS and OS) and consistent with those used in previous appraisals in BTC: TA722 for pemigatinib (18), TA948 for ivosidenib (19), and TA1005 for futibatinib (20).

The model structure and permitted flow of patients is shown in **Figure 25**. All patients begin in the ‘progression-free’ health state and receive treatment with either zanidatamab or the comparator (i.e. FOLFOX + ASC, or ASC alone), and within this health state, patients can remain per model cycle, or are at risk of disease progression or death. Patients in the ‘progressed disease’ health state either remain in this health state per model cycle or are also at risk of transitioning to ‘death’, which is an absorbing state.

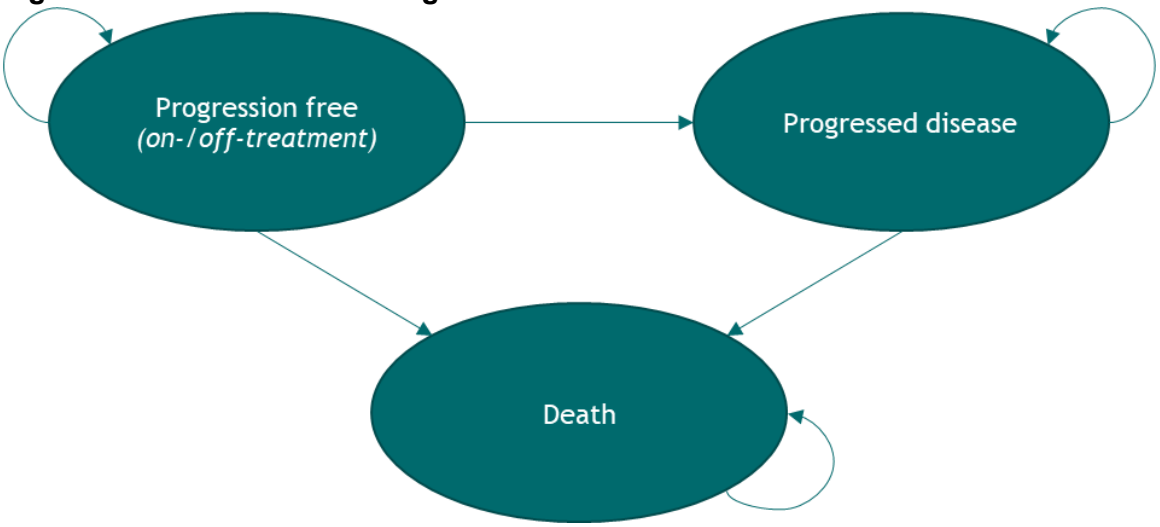
The occupancy of the ‘progression-free’ state is calculated as the area underneath the PFS curve, while the ‘progressed disease’ state is calculated as the area between the OS curve and the PFS curve. The proportion of patients in each health state at any time point (per cycle) is therefore calculated as follows:

- Progression-free = PFS
- Progressed disease = OS – PFS
- Death = 1 – OS

A time on treatment (ToT) curve is used to calculate the proportion of patients within the 'progression-free' health state who are on treatment and is used for the calculation of drug costs.

**Figure 25: Model structure diagram**




### *3.2.2.1 Model settings*

The perspective of the economic evaluation is that of the NHS and personal social services (PSS) in England for costs, and direct health effects for patients, in line with the NICE reference case (82). As per the NICE reference case, all health effects were measured in QALYs. In line with the Treasury Green Book for future health and life benefits and ongoing industry discussions, an annual 1.5% discount rate is used for QALYs and costs.

The base case adopts a lifetime horizon. As the analysis is for advanced or metastatic BTC, it is assumed that 30 years is sufficient to constitute a lifetime horizon as all patients have died by this point.

A cycle length of 1 week is used to adequately capture and reflect changes in health, yet short enough to capture the dosing schedules of zanidatamab and comparators. Given the short cycle length, the application of a half cycle correction is not considered necessary to account for uncertainty in the timing of transitions within the cycle period.

Table 43 summarises the key features of the economic analysis within this evaluation (with justification for choices made); and compares these features with the prior NICE appraisals in BTC. It should be noted that the prior appraisals are not specifically for previously treated advanced HER2+ BTC, but are targeted therapies for other BTC gene mutations.

**Table 43: Features of the economic analysis**

| Factor | Previous NICE evaluations in 2L BTC | | | Current evaluation | |
|---|---|---|---|---|---|
| | TA722 (pemigatinib) | TA948 (ivosidenib) | TA1005 (futibatinib) | Chosen values | Justification |
| Perspective | NHS and PSS | NHS and PSS | NHS and PSS | NHS and PSS | Consistent with the NICE reference case |
| Model type | PartSA | PartSA | PartSA | PartSA | Partitions survival into pre- and post-progressed health states, allowing costs and health outcomes to be estimated accurately and transparently |
| Time horizon | Lifetime, 40 years | Lifetime, 20 years | Lifetime, 40 years | Lifetime, 30 years | Lifetime horizon chosen to capture relevant differences in costs and outcomes between treatments, in line with the NICE reference case. 30 years is considered sufficient for representing a lifetime horizon in the modelled patient population, as all patients have died by this time point |
| Cycle Length | 1 week | 1 week | 21 days | 1 week | 1-week considered short enough to adequately capture meaningful changes in health status |
| Half-cycle correction | No | No | Yes | No | Not considered necessary due to the short cycle length |
| Annual time preference discount rate | 3.50% for costs and QALYs | 3.50% for costs and QALYs | 3.50% for costs and QALYs | 1.5% for costs and QALYs | In line with Green Book and ongoing industry discussions |
| Source of utilities | EORTC QLC C30 mapped to EQ5D utilities. FIGHT-202 PLD analysis | EQ-5D-5L (ClarIDHy trial) mapped to EQ-5D-3L (Hernández Alava et al. mapping function) | EQ-5D-3L from FOENIX-CCA2 | EQ-5D-5L (HERIZON-BTC-01) mapped to EQ-5D-3L (Hernández Alava et al. mapping function) | Consistent with NICE reference case |

| Factor | Previous NICE evaluations in 2L BTC | | | Current evaluation | |
|---|---|---|---|---|---|
| | **TA722 (pemigatinib)** | **TA948 (ivosidenib)** | **TA1005 (futibatinib)** | **Chosen values** | **Justification** |
| Source of costs | eMC<br>NHS reference costs 2017/2018 | eMIT<br>National Cost Collection 20/21<br>BNF<br>PSSRU | BNF<br>eMIT<br>National Cost Collection 21/22 | BNF<br>PSSRU<br>eMIT<br>National Cost Collection 23/24 | Consistent with NICE reference case |
| Outcomes | QALYs, life years, costs, incremental results | QALYs, life years, costs, incremental results | QALYs, life years, costs, incremental results | QALYs, life years, costs, incremental results | Consistent with NICE reference case |

Abbreviations: 2L, second-line; BNF, British National Formulary; BTC, biliary tract cancer; eMC, Electronics Medicines Compendium; EORTC, European Organisation For Research And Treatment Of Cancer; NICE, National Institute for Health and Care Excellence; PartSA, partitioned survival analysis; PSS, personal social services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-years.

### 3.2.3 Intervention technology and comparators

The intervention modelled in the analysis is zanidatamab, administered at a dose of 20 mg/kg on days 1 and 15 of each 28-day cycle. Treatment is administered as an IV infusion until disease progression or unacceptable toxicity as per the expected SmPC and dose received in the pivotal HERIZON-BTC-01 trial (1, 22, 54). Dose adjustments and modifications have been included as per the HERIZON-BTC-01 trial.

As described in Section 1.3, 2L treatment options for patients with BTC are very limited. No HER2-targeted therapies are currently reimbursed for patients with previously treated HER2+ BTC. Current 2L treatments of advanced BTC involve combination chemotherapy regimens, mainly FOLFOX + ASC; however, due to the aggressive nature of BTC, some patients are treated solely with ASC.

In TA722 (pemigatinib for BTC with FGFR2 fusion/rearrangement), and TA948 (ivosidenib for BTC with IDH1 mutation), clinical experts confirmed that after 1 previous line of treatment, patients would usually be treated in the UK NHS with FOLFOX + ASC, or ASC alone (if no targeted gene alterations present) (18, 19). In this assessment, the majority of clinicians consulted in the Delphi Panel agreed that FOLFOX was routinely used to treat unresectable BTC in the 2L setting (69). Therefore, in line with the final scope issued by NICE and clinical opinion, FOLFOX + ASC and ASC alone are included as comparators in the economic analysis. Patients receiving FOLFOX will also receive concomitant ASC, which includes (but is not limited to) anti-emetics, analgesia, steroids, stents, and other treatments for biliary-related complications and cancer-related symptom management (21).

## *3.3 Clinical parameters and variables*

Clinical data informing the zanidatamab, FOLFOX + ASC, and ASC arms of the model base case are summarised in Table 44 and described in further detail throughout this Section.

**Table 44: Summary of clinical data sources used in the model base case**

| Component | Application within the model | Source(s) for zanidatamab | Source(s) for FOLFOX + ASC | Source(s) for ASC alone |
|---|---|---|---|---|
| Baseline characteristics | Used to estimate age- and sex-matched general population mortality and utility values, and used in weight-based dosing calculations | HERIZON-BTC-01 (IHC3+ population - not treatment specific) | | |
| OS | Parametric survival curves to estimate lifetime OS outcomes and determine health state occupancy | HERIZON-BTC-01 (IHC3+ population) | ABC-06 (naive comparison) | ABC-06 (naive comparison) |

| Component | Application within the model | Source(s) for zanidatamab | Source(s) for FOLFOX + ASC | Source(s) for ASC alone |
|---|---|---|---|---|
| PFS | Parametric survival curves to estimate lifetime PFS outcomes and determine health state occupancy | HERIZON-BTC-01 (IHC3+ population) | ABC-06 (naive comparison) | Assumed based on OS HR from MAIC |
| ToT | Parametric survival curves to estimate lifetime ToT outcomes and capture costs | HERIZON-BTC-01 (IHC3+ population) | Estimated HR from median PFS and ToT reported in ABC-06 | N/A |
| AEs | Inform the proportion of patients who incur treatment-related AE management costs and utility decrements | HERIZON-BTC-01 (Cohort 1 population) | ABC-06 | N/A |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; IHC, immunohistochemistry; MAIC, matching-adjusted indirect comparison; N/A, not applicable; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62); Lamarca (2021) (21).

### 3.3.1 Baseline patient characteristics

BL patient characteristics of the cohort entering the model were aligned with the population in the HERIZON-BTC-01 study (**Table 45**). Mean age and the proportion of female patients are based on the IHC3+ population to align with the decision problem population. These were used in the model to calculate age- and sex-matched general population mortality rates and estimate corresponding HRQoL.

As there were only 2 patients from the UK included in HERIZON-BTC-01, height and weight data were taken from UK-specific sources. Crespo-Cruz (2025) conducted a retrospective observational study evaluating the use of zanidatamab in 20 patients in England (60). The mean weight of these patients at treatment initiation was 66 kg. The Health Survey for England 2022 reports the mean height of adult patients to be 169.09 cm (83). Body surface area (BSA) was then calculated from the height and weight data using the Mosteller method (84). These were used in the calculation of drug acquisition costs for treatments reliant on weight- or BSA-based dosing (discussed further in Section **3.5.1**).

Alternative height and weight data using the intention to treat (ITT) overall HERIZON-BTC-01 population are tested in scenario analyses (Section **3.10.3**).

**Table 45: Baseline patient characteristics used in the model base case – HERIZON-BTC-01**

| Characteristic | Mean | Standard deviation | Source |
|---|---|---|---|
| Age, years | [redacted] | [redacted] | HERIZON-BTC-01 IHC3+ subgroup analysis (2025) (62). |
| Female, % | [redacted] | [redacted] | |
| Height, cm | [redacted] | [redacted] | HSE (2022) (83) |
| Weight, kg | [redacted] | [redacted] | Crespo-Cruz (2025) (60) |
| BSA, m | [redacted] | [redacted] | Calculated from the Mosteller method (84) |

Abbreviations: BSA, body surface area; HSE, health survey for England; NR, not reported.

### 3.3.2 Clinical effectiveness

#### *3.3.2.1 Survival analysis approach*

Efficacy data from the pivotal HERIZON-BTC-01 trial were used to inform OS, PFS, and ToT in the model using the IHC3+ population (n=62), from the final HERIZON-BTC-01 DCO (11th July 2024). The trial is discussed in detail in Section 2.6, and the survival data are shown in Section 2.6.1.2.

As there were no head-to-head data to compare zanidatamab with FOLFOX + ASC and ASC alone, efficacy data for the comparators are informed by the ABC-06 trial (21). The UK-based ABC-06 trial that compared FOLFOX+ASC and ASC alone (21) was considered the most appropriate source of comparator evidence by NICE for pemigatinib in TA722 (18), and for futibatinib in TA1005 (20). ITCs were attempted and incorporated within the economic model, including unanchored MAIC and naive comparisons (see Section 2.10). Given the limitations of the MAIC, naive comparisons were chosen to inform the base case with the MAIC analyses tested in scenario analysis.

Section 2.10 describes the MAIC conducted between the HERIZON-BTC-01 study and the ABC-06 study, where the zanidatamab population was adjusted to match the ABC-06 study population. A key limitation of the indirect treatment comparison (ITC) was that the ABC-06 trial was a broader population than HER2+ and includes only 2L patients. The ABC-06 population were patients with histologically or cytologically verified locally advanced or metastatic BTC (including CCA, GBC, and AoV) progressing after 1L CisGem chemotherapy. HER2+ status was not reported in the ABC-06 trial; therefore, the proportion of patients who overlap with the decision problem is unknown. However, HER2 status is not proven to be prognostic of patient outcomes in BTC (52) therefore the lack of HER2 information within the ABC-06 trial is not expected to substantially affect results (see Section 1.3). In order to construct the MAIC, zanidatamab data needed to be selected to only include the 2L patients to

match the ABC-06 study, which reduced the sample size by [redacted]% from n=62 to n=[redacted] (see Section 2.10).

According to the preference of the committee in the TA722 (pemigatinib) appraisal (18), it was more appropriate to fit independent curves to each treatment arm, instead of applying the assumption of proportional hazards to non-proportional hazard models. As such, a similar approach using the unadjusted outcomes of the HERIZON-BTC-01 IHC3+ population and the ABC-06 trial were used to inform the survival projections without adjustment for zanidatamab and FOLFOX + ASC and ASC, respectively. This naive comparison approach also preserves zanidatamab data to be consistent with the decision problem and licensed indication population, given the MAIC survival outcomes are for a different patient population (i.e. 2L only and not IHC3+ HER2+ specific).

The scenario using the MAIC-adjusted data for zanidatamab (see Section 3.10.3) is described in more detail within Appendix O.

To inform the model, partitioned survival models (PSMs) were fitted to OS, PFS, and ToT data, where available, using the exponential, generalised gamma, Gompertz, log-logistic, log-normal, Weibull, and gamma distributions. The selection of the most appropriate distribution has been made in accordance with the NICE decision support unit (DSU) technical support document (TSD) 14 (85). The visual inspection of extrapolated survival, alongside Akaike and Bayesian information criteria (AIC, BIC) were used to determine the most appropriate model to characterise the observed KM data. Then, clinical validation was sought using structured expert elicitation in line with NICE methodology outlined in TSD26 (86). A Delphi panel of 11 to 14 UK experts was used to help interpret OS and PFS estimates and determine clinical plausibility of long-term outcomes, to help select the most appropriate parametric curve to inform the base case distribution (69). Description of the approach and rationale to inform the base case for OS, PFS, and ToT are discussed in turn throughout this section.

#### *3.3.2.2 Overall survival*

##### 3.3.2.2.1 Zanidatamab

As discussed in Section 3.3.2.1, PSMs were fitted to the unadjusted KM OS curve from the IHC3+ population (n=62), using the final HERIZON-BTC-01 DCO (11th July 2024).

AIC and BIC scores can be used to determine the relative fit of alternative PSMs to the observed data. Table 46 presents the AIC and BIC scores for the extrapolated OS for zanidatamab. Gamma and log-normal are statistically the best fitting curves according to AIC and BIC, respectively. Figure 26 presents the model fits for zanidatamab over a 10-year time horizon. All curves appeared to fit the data well (with the exception of exponential).

The majority of clinical experts from the Delphi panel agreed that the expected survival rate of zanidatamab at 6 months and 12 months would be at least 70% and 60%, respectively (69). There was also consensus that the expected OS would be at least 25% at 36 months and less than 10% at 60 months. [redacted] by the clinical experts at 6, 12 and 60 months (see **Table 47**), though when asked to provide a specific expected survival rate the majority of clinicals estimated between 45 to 65% at 1 year and around 10% at 5-years. The exponential curve [redacted], however this had the poorest fit to the data (**Table 47**). The log-logistic curve [redacted] and also has a good fit to the data and second best statistical fit. As such, log-logistic was chosen to inform the base-case OS curve for zanidatamab. The exponential distribution was explored in scenario analysis [redacted] (see Section **3.10.3**).

**Table 46: Statistical goodness-of-fit scores – OS – HERIZON-BTC-01**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 378.30 | 380.40 |
| Generalised gamma | 370.80 | 377.20 |
| Gompertz | 373.60 | 377.90 |
| Log-logistic | 369.90 | 374.20 |
| Log-normal | 369.30 | 373.50 |
| Weibull | 370.10 | 374.40 |
| Gamma | 369.20 | 373.50 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

**Figure 26: Parametric curve fits - OS – HERIZON-BTC-01**

Abbreviations: KM, Kaplan-Meier; OS, overall survival.
Source: HERIZON-BTC-01 (54).

**Table 47: Landmark analysis – OS – HERIZON-BTC-01**

| Distribution | Landmark survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60 months |
| Exponential | [redacted] | [redacted] | [redacted] | [redacted] |
| Generalised gamma | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | [redacted] | [redacted] | [redacted] | [redacted] |
| Log-logistic | [redacted] | [redacted] | [redacted] | [redacted] |
| Log-normal | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | [redacted] | [redacted] | [redacted] | [redacted] |
| Gamma | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: OS, overall survival.

#### 3.3.2.2.2 FOLFOX + ASC

Published OS data from the ABC-06 study were used to inform OS extrapolations for FOLFOX + ASC. KM data were digitised from the published trial (21) and pseudo patient-level data were then created using the Guyot algorithm (87). PSMs were then fitted to the pseudo patient-level data and included in the model.

Table 48 presents the AIC and BIC scores for the extrapolated OS for FOLFOX + ASC which shows that log-normal was statistically the best fitting curve. Figure 27 presents the model fits for FOLFOX over a 10-year time horizon. All curves fit the data well and show little discrepancy in OS projections.

Clinical consensus was reached at the Delphi panel that estimated survival rates with FOLFOX + ASC of at least 50%, at least 25%, and less than 5% at 6, 12 and 36 months respectively (69). The majority of curves met this criteria at 6 months and 36 months (see Table 49). When asked to provide specific estimates at 12-months, clinicians' estimates ranged from 5% to 30%, which aligns with all the OS estimates from the curves at 12-months. In the TA722 (pemigatinib) appraisal, clinical experts estimated that for FOLFOX+ASC, the expected survival at 3 years would be approximately 3%. At 5 years, while the probability of survival would be very low it was more likely to be slightly higher than the 0.1% (18). Log-normal best reflects this criteria at 3 and 5 years estimating 2.4% and 0.5%, respectively.

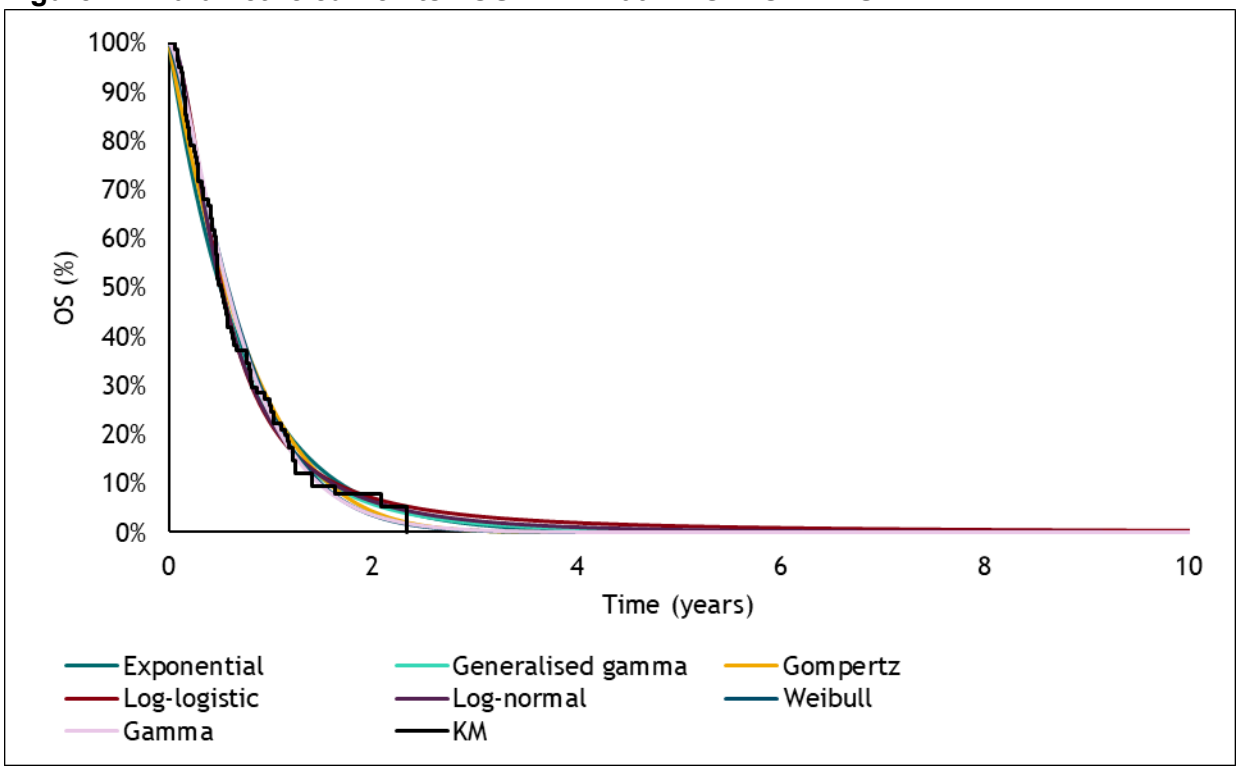
Given that log-normal was statistically the best fitting, visually fits the data well and is more in line with structured expert elicitation, this curve was chosen for the base-case for FOLFOX + ASC OS. Exponential, and generalised gamma were explored in scenario analysis (see Section 3.10.3) as these also had plausible estimates at 5-years.

**Table 48: Statistical goodness-of-fit scores – OS – ABC-06 – FOLFOX + ASC**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 483.89 | 486.28 |
| Generalised gamma | 475.95 | 483.13 |
| Gompertz | 484.22 | 489.01 |
| Log-logistic | 476.27 | 481.06 |
| Log-normal | 474.10 | 478.89 |
| Weibull | 479.52 | 484.31 |
| Gamma | 477.34 | 482.13 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

**Figure 27: Parametric curve fits - OS – ABC-06 – FOLFOX + ASC**




Abbreviations: ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival.
Source: Digitised from ABC-06 (21).

**Table 49: Landmark estimates – OS – ABC-06 – FOLFOX + ASC**

| Distribution | Landmark survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Exponential | 50.5% | 25.5% | 1.7% | 0.1% |
| Generalised gamma | 52.0% | 22.8% | 1.9% | 0.3% |
| Gompertz | 53.8% | 26.3% | 0.4% | 0.0% |
| Log-logistic | 52.1% | 22.3% | 3.4% | 1.3% |
| Log-normal | 51.2% | 22.8% | 2.4% | 0.5% |
| Weibull | 56.4% | 25.1% | 0.4% | 0.0% |
| Gamma | 56.2% | 24.2% | 0.5% | 0.0% |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival.

#### 3.3.2.2.3 ASC

As with the FOLFOX arm, OS data from the ABC-06 study (21) was used to inform OS extrapolations for ASC using digitised KM data and creating patient-level data using the Guyot algorithm (87).

Table 50 presents the AIC and BIC scores for the extrapolated OS for ASC. Log-logistic was statistically the best fitting curve according to both AIC and BIC.

Although several of the PSMs have relatively close AIC/BIC statistics to the best fitting curve, some curves have much higher AIC/BIC statistics (e.g. the exponential, Weibull and Gompertz curves), which could infer a poorer fit for ASC. **Figure 28** presents the model fits for ASC over a 10-year time horizon. Exponential, Gompertz, Weibull and gamma visually fit the data poorly as they are unable to capture the plateau at around 1 year leaving generalised gamma, log-logistic and log-normal and potential options.

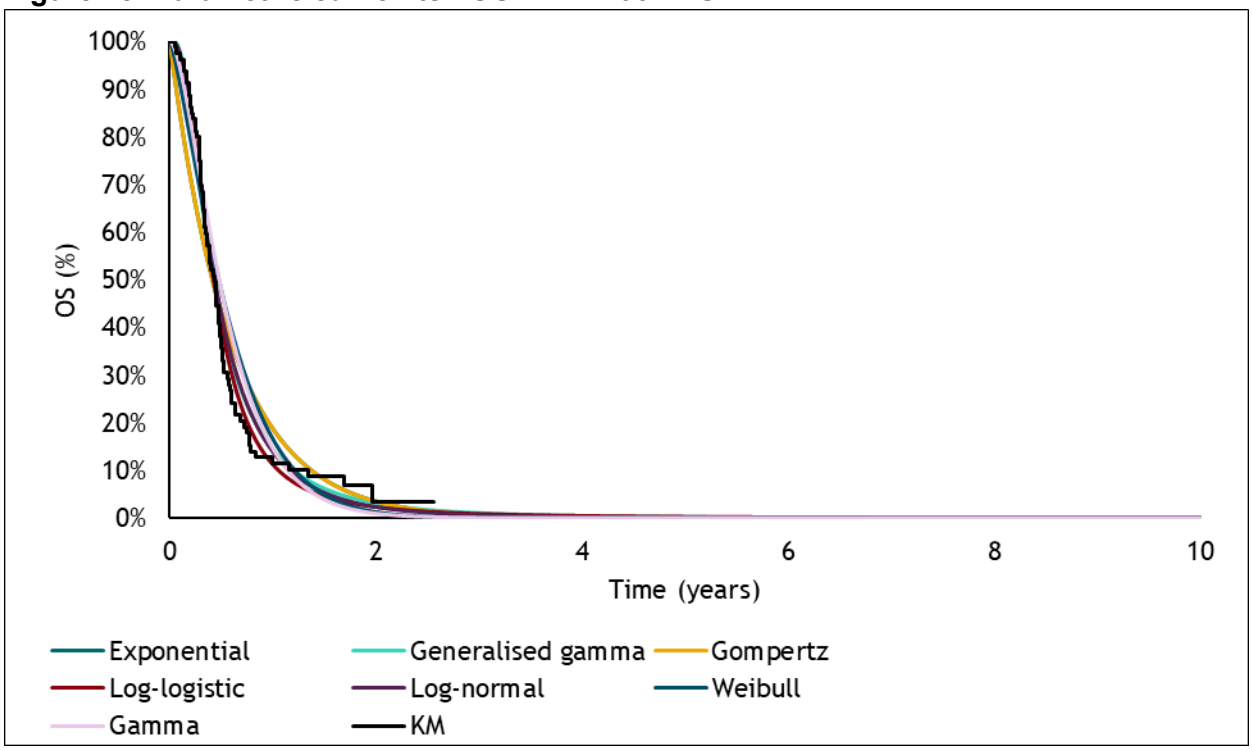
At the Delphi panel, there was consensus agreement that ASC would have poorer OS than FOLFOX+ASC (69). All curves projected lower OS than FOLFOX+ASC (**Table 51**). Given the plausibility of the log-logistic curve, best statistical fit and that it is one of the curves that visually fit the data well, this was chosen as the base-case for ASC OS. Generalised gamma projected a higher estimate at 3 years compared to the other curves and exponential, Weibull, Gompertz and gamma had visibly poor fits to the data therefore only log-normal was tested in scenario analysis as an alternative plausible curve (see Section **3.10.3**).

**Table 50: Statistical goodness-of-fit scores – OS – ABC-06 - ASC**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 441.50 | 443.90 |
| Generalised gamma | 417.20 | 424.40 |
| Gompertz | 443.50 | 448.30 |
| Log-logistic | 410.90 | 415.70 |
| Log-normal | 416.10 | 420.90 |
| Weibull | 435.90 | 440.70 |
| Gamma | 429.20 | 434.00 |

Abbreviations: AIC, Akaike information criterion; ASC, active symptom control; BIC, Bayesian information criterion; OS, overall survival.

**Figure 28: Parametric curve fits - OS – ABC-06 - ASC**




Abbreviations: ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival.
Source: Digitised from ABC-06 (21).

**Table 51: Landmark estimates – OS – ABC-06 –ASC**

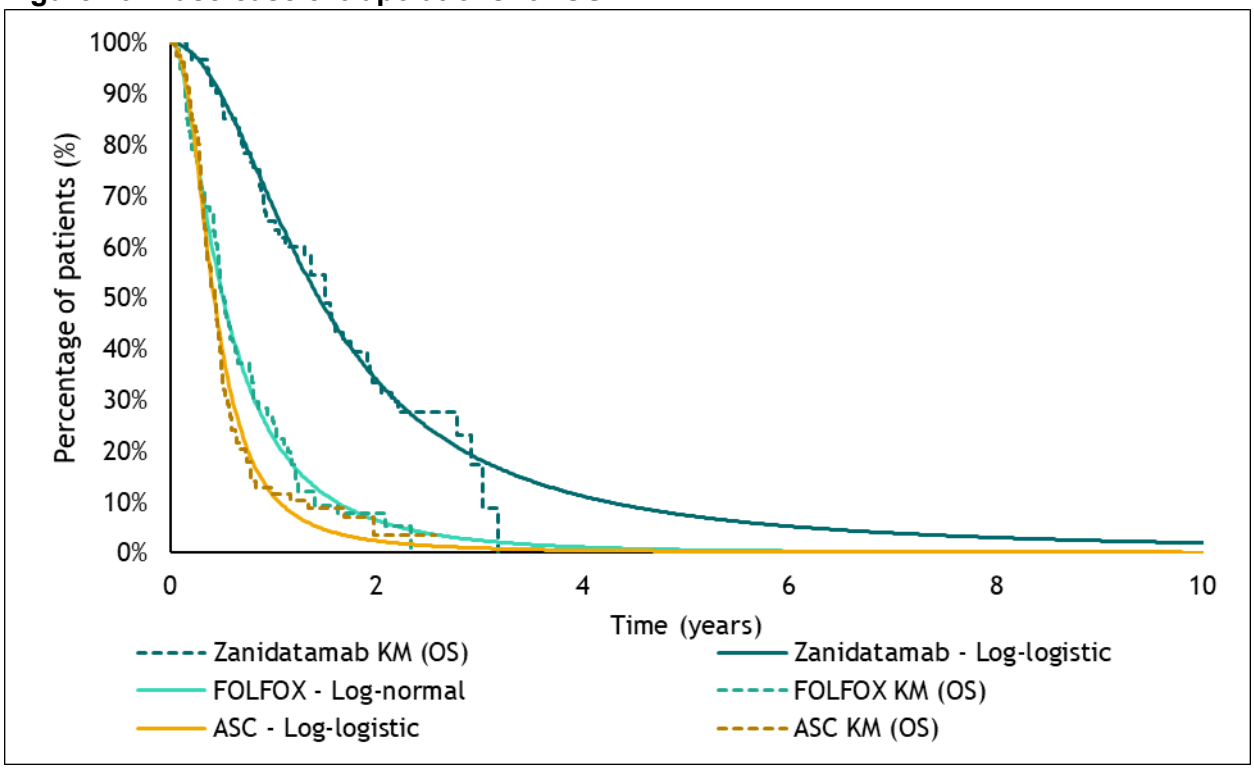
| Distribution | Landmark survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Exponential | 43.4% | 3.6% | 0.7% | 0.0% |
| Generalised gamma | 41.9% | 3.1% | 1.1% | 0.2% |
| Gompertz | 43.4% | 3.5% | 0.7% | 0.0% |
| Log-logistic | 40.5% | 2.3% | 0.9% | 0.3% |
| Log-normal | 43.1% | 2.3% | 0.6% | 0.1% |
| Weibull | 48.0% | 1.3% | 0.1% | 0.0% |
| Gamma | 48.1% | 1.0% | 0.1% | 0.0% |

Abbreviations: OS, overall survival.

#### 3.3.2.2.4 Summary of base case extrapolations

Figure 29 provides a summary of the base-case extrapolation for OS applied within the model for each treatment arm. Validation of the base case curves are presented in Section 3.13.

**Figure 29: Base-case extrapolations for OS**




Abbreviations: ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival.
Source: HERIZON-BTC-01 (54); digitised from ABC-06 (21).

### *3.3.2.3 Progression-free survival*

#### 3.3.2.3.1 Zanidatamab

As per OS and discussed in Section 3.3.2.1, PSMs were fitted to the unadjusted PFS from the IHC3+ population (n=62), using the final HERIZON-BTC-01 DCO (11th July 2024). Radiological progression was INV in the ABC-06 trial, therefore, to align with this assessment, the INV PFS from HERIZON-BTC-01 was used for the base case. A scenario using ICR-based PFS is also presented.

Table 52 presents the AIC and BIC scores for the extrapolated PFS for zanidatamab. Generalised gamma and log-normal are statistically the best fitting curves according to AIC and BIC, respectively. However, the majority fit statistics are relatively close to one another (within 10 points). Figure 30 presents the model fits for zanidatamab over a 10-year time horizon. All curves appeared to fit the data well (with the exception of exponential).

The majority of clinicians at the Delphi panel estimated the PFS to be between 50 to 55% at 6 months, 30 to 35% at 12 months, and at least 15% at 36 months (69). Most of the curves project [redacted] at 6 months compared to clinical opinion, and [redacted] at 12 and 36 months (Table 53). Generalised gamma, Gompertz and log-logistic [redacted]

[redacted]. Generalised gamma has the best statistical fit however if selected, [redacted]. As such, the next statistically best fitting curve (log-logistic) was chosen to inform the base case PFS curve for zanidatamab.

Generalised gamma and Gompertz are tested in scenario analysis [redacted] (see Section 3.10.3).

**Table 52: Statistical goodness-of-fit scores – PFS – HERIZON-BTC-01**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 382.40 | 384.50 |
| Generalised gamma | 372.00 | 378.30 |
| Gompertz | 382.60 | 386.90 |
| Log-logistic | 375.90 | 380.10 |
| Log-normal | 373.60 | 377.80 |
| Weibull | 384.30 | 388.60 |
| Gamma | 383.80 | 388.10 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

**Figure 30: Parametric curve fits - PFS – HERIZON-BTC-01**

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.
Source: HERIZON-BTC-01 (54).

**Table 53: Landmark estimates – PFS – HERIZON-BTC-01**

| Distribution | Landmark progression-free survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Exponential | [redacted] | [redacted] | [redacted] | [redacted] |
| Generalised gamma | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | [redacted] | [redacted] | [redacted] | [redacted] |
| Log-logistic | [redacted] | [redacted] | [redacted] | [redacted] |
| Log-normal | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | [redacted] | [redacted] | [redacted] | [redacted] |
| Gamma | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: PFS, progression-free survival.

#### 3.3.2.3.2 FOLFOX+ ASC

PFS data as determined by INV from the ABC-06 study was used to inform PFS extrapolations for FOLFOX + ASC. As with OS, KM data were digitised from the published trial (21) and pseudo patient-level data were then created using the Guyot algorithm (87). PSMs were then fitted to the pseudo patient-level data and included in the model.

Table 54 presents the AIC and BIC scores for the extrapolated PFS for FOLFOX + ASC. Generalised gamma was statistically the best fitting curve according to AIC and BIC, closely followed by log-normal and log-logistic. Figure 31 presents the model fits for FOLFOX + ASC over a 10-year time horizon. All curves fit the data reasonably well, with the exception of exponential and Gompertz, which overestimates PFS from around 1 year.

The majority of clinicians at the Delphi study agreed that the estimated PFS of FOLFOX+ASC would be between 20 to 30% at 6 months, and between 5 to 10% at 12 months (69). All clinical experts agreed that PFS at 3 years would be less than 5%. All curves projected higher estimates than clinical opinion at 6 months, driven by the observed data in the ABC-06 study (Table 55). Log-normal, log-logistic and gamma projected the most plausible estimates at 1-year according to structured clinical opinion. Given that log-normal was statistically the best fitting out of the more plausible options, and gives a good visual fit to the data, this was chosen as the base case for FOLFOX + ASC PFS. Log-logistic and gamma were tested in scenario analysis (see Section 3.10.3).

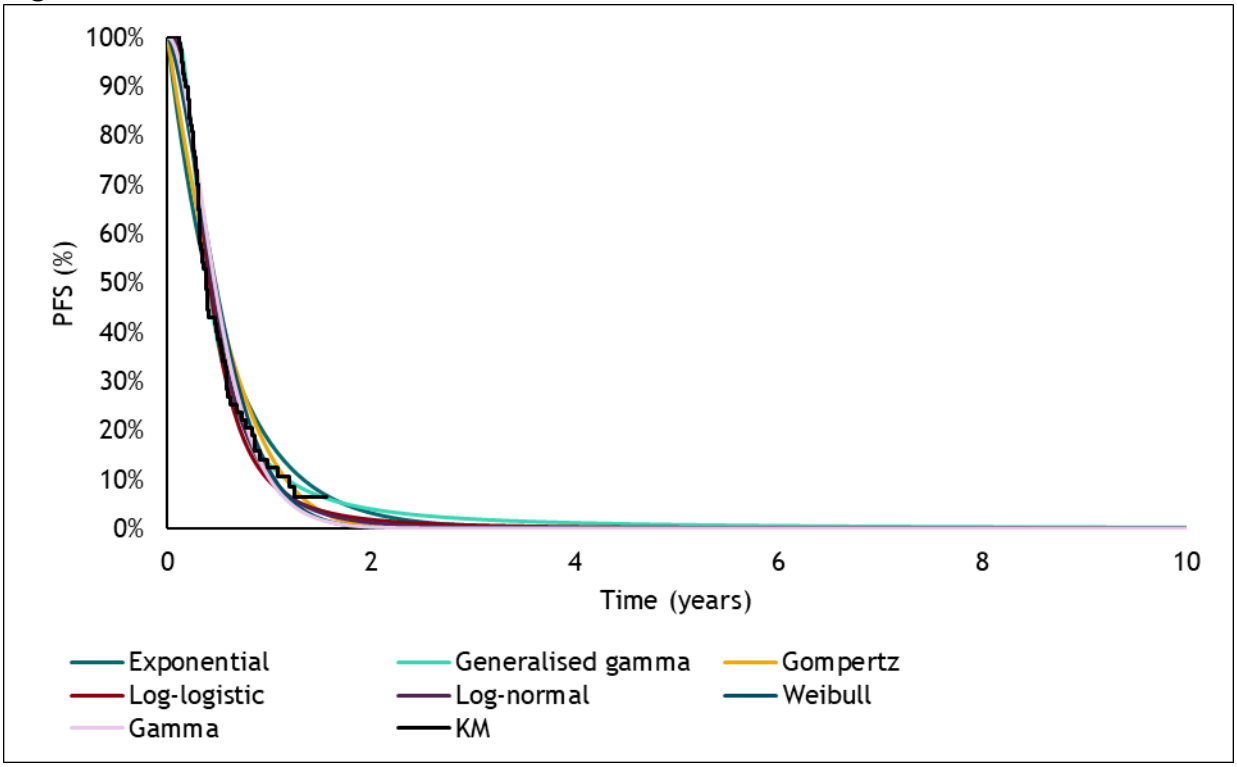
**Table 54: Statistical goodness-of-fit scores – PFS – ABC-06 – FOLFOX + ASC**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 389.71 | 392.11 |
| Generalised gamma | 354.09 | 361.27 |
| Gompertz | 388.67 | 393.46 |

| Distribution | AIC | BIC |
|---|---|---|
| Log-logistic | 358.79 | 363.58 |
| Log-normal | 357.75 | 362.53 |
| Weibull | 376.21 | 381.00 |
| Gamma | 368.95 | 373.74 |

Abbreviations: AIC, Akaike information criterion; ASC, active symptom control; BIC, Bayesian information criterion; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

**Figure 31: Parametric curve fits - PFS – ABC-06 – FOLFOX + ASC**




Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, progression-free survival.
Source: Digitised from ABC-06 (21).

**Table 55: Landmark estimates – PFS – ABC-06 – FOLFOX + ASC**

| Distribution | Landmark progression-free survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Exponential | 42.2% | 17.8% | 0.6% | 0.0% |
| Generalised gamma | 37.4% | 13.1% | 1.9% | 0.2% |
| Gompertz | 45.3% | 15.5% | 0.0% | 0.0% |
| Log-logistic | 38.4% | 9.7% | 0.7% | 0.0% |
| Log-normal | 41.3% | 10.8% | 0.2% | 0.0% |

| Distribution | Landmark progression-free survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Weibull | 47.0% | 12.0% | 0.0% | 0.0% |
| Gamma | 45.7% | 10.3% | 0.0% | 0.0% |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

#### 3.3.2.3.3 ASC alone

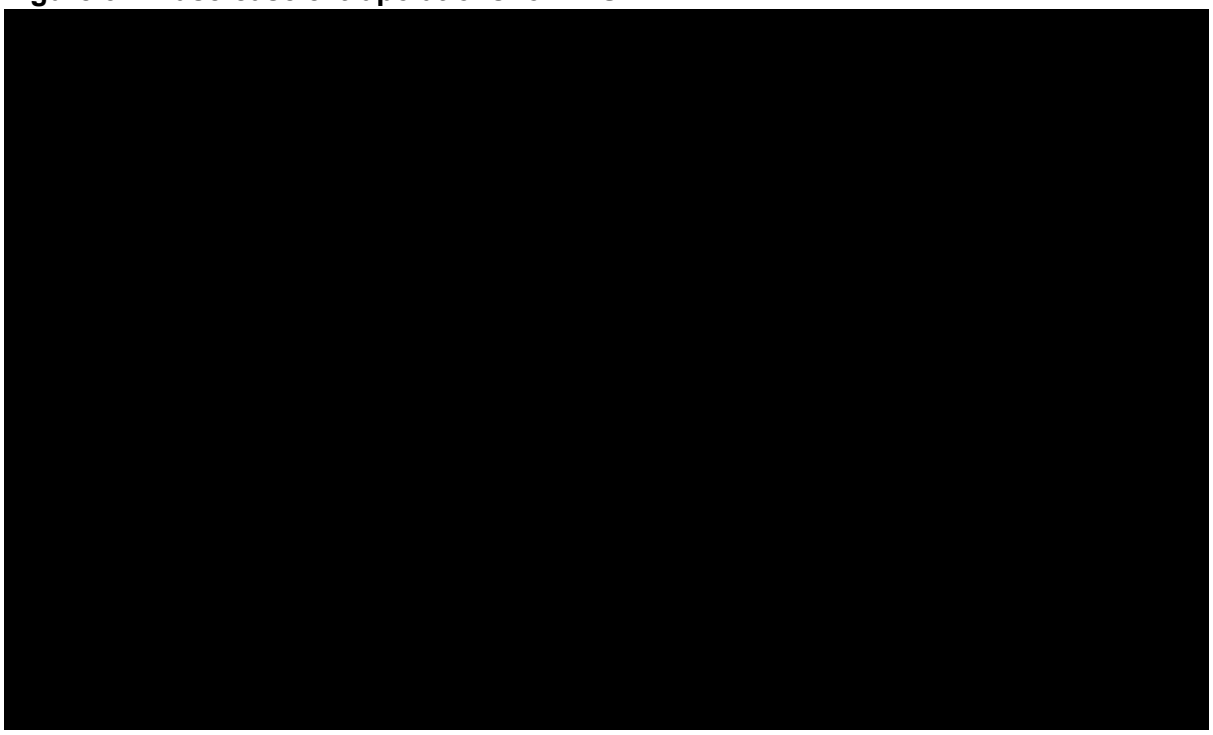
In the ABC-06 study, patients assigned to ASC alone did not have regular radiological tumour evaluation. Therefore, in the absence of PFS data reported for ASC, the OS HR derived from the MAIC is used to estimate the PFS.

The OS HR ([redacted]) between zanidatamab and ASC was assumed to be a proxy for the PFS treatment benefit and the inverse is applied to zanidatamab's PFS curve. Although this relies on a proportional hazards assumption, and it assumes that the HR derived for the ABC-06 population can be transferred to the HERIZON-BTC-01 population, there is a lack of alternative options. In TA722, the company estimated ASC PFS assuming that it was the same as FOLFOX PFS (18). However, this assumption is likely to overestimate ASC PFS given that the OS benefit of FOLFOX + ASC versus ASC alone in ABC-06 would translate to a PFS benefit. This was supported structured expert opinion at the Delphi panel which agreed that PFS has a strong correlation relationship with predicting OS and that patients receiving ASC alone would have poorer PFS than those on FOLFOX + ASC (69).

#### 3.3.2.3.4 Summary of base case

Figure 32 provides a summary of the base-case extrapolation for PFS applied within the model for each treatment arm. Validation of the base case curves are presented in Section 3.13.

**Figure 32: Base-case extrapolations for PFS**



Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, progression-free survival.
Source: HERIZON-BTC-01 (54); Digitised from ABC-06 (21).

#### *3.3.2.4 Time on treatment*

##### 3.3.2.4.1 Zanidatamab

Patient-level ToT data from the IHC3+ population from HERIZON-BTC-01 was used to determine the drug and administration costs associated with zanidatamab. A summary of the ToT data from HERIZON-BTC-01 is provided below in **Figure 33**.

**Figure 33: HERIZON-BTC-01 IHC3+ ToT Kaplan-Meier**

Abbreviations: CI, confidence interval; ToT, time on treatment.
Source: HERIZON-BTC-01 (54).

Table 56 presents the AIC and BIC scores for the extrapolated ToT for zanidatamab. Log-normal is statistically the best fitting curves according to AIC and BIC, respectively. However, the other distributions fit statistics are relatively close to one another (within 10 points). Figure 34 presents the model fits for zanidatamab over a 10-year time horizon which shows all the curves fit the data reasonably well until around 20 months where most patients are starting to discontinue treatment (69).

In the HERIZON-BTC-01 study, all patients had discontinued treatment, the majority of which was due to progression ( ). Therefore, the gamma curve was selected to inform the model base case for zanidatamab as this gave the most pessimistic long-term outcomes in line with the observed data (Table 57). Gompertz and Weibull were also explored in scenario analyses (see Section 3.10.3).

**Table 56: Statistical goodness-of-fit scores – ToT – HERIZON-BTC-0 1**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 416.70 | 418.80 |
| Generalised gamma | 415.60 | 422.00 |
| Gompertz | 417.70 | 421.90 |
| Log-logistic | 417.10 | 421.40 |
| Log-normal | 414.40 | 418.60 |
| Weibull | 416.40 | 420.70 |
| Gamma | 415.50 | 419.80 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.

**Figure 34: Parametric curve fits - ToT – HERIZON-BTC-01**

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment.
Source: HERIZON-BTC-01 (54).

**Table 57: Landmark estimates – ToT – HERIZON-BTC-01**

| Distribution | Landmark progression-free survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Exponential | [redacted] | [redacted] | [redacted] | [redacted] |
| Generalised gamma | [redacted] | [redacted] | [redacted] | [redacted] |
| Gompertz | [redacted] | [redacted] | [redacted] | [redacted] |
| Log-logistic | [redacted] | [redacted] | [redacted] | [redacted] |

| Distribution | Landmark progression-free survival | | | |
|---|---|---|---|---|
| | 6 months | 12 months | 36 months | 60-months |
| Log-normal | [redacted] | [redacted] | [redacted] | [redacted] |
| Weibull | [redacted] | [redacted] | [redacted] | [redacted] |
| Gamma | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ToT, time on treatment.

#### 3.3.2.4.2 FOLFOX + ASC

In ABC-06, ToT KM data were not reported for FOLFOX + ASC; therefore, parametric survival models could not be explored. Instead, 2 options to estimate ToT for the comparator are included in the model:

- Approach 1: Assumes ToT is equivalent to PFS.
- Approach 2: Estimates a HR based on the reported median PFS for the FOLFOX arm (4.0 months) and reported median number of treatment cycles (5 cycles = 2.3 months based on a 14-day treatment cycle) from the ABC-06 study. The resulting relative difference estimates a HR of 0.575 which is then applied to the FOLFOX + ASC PFS curve.

Due to the lack of reported ToT data for FOLFOX, clinical experts at the Delphi panel were asked their views on using PFS as proxy (69). Consensus was reached on the use of PFS as a substitute for ToT. They further noted that ToT is commonly based on treatment progression, and as a result would unlikely cause the overestimation of treatment costs. As such, the first approach assuming the same as PFS is used in the base case. The second approach, using the estimated HR, is explored as a scenario analysis (see Section **3.10.3**).

FOLFOX is administered Q2W for a maximum of 12 cycles (24 weeks) in both ToT approaches, in line with the SmPC (88-90).

#### 3.3.2.4.3 ASC

ASC ToT curves are not considered within the analysis, as no treatment acquisition or administration costs are applied in the ASC arm of the model.

#### 3.3.2.4.4 Summary of base case

**Figure 35** provides a summary of the base-case extrapolation for ToT applied within the model for each treatment arm. Validation of the base case curves are presented in Section **3.13**.

**Figure 35: Base-case extrapolations for ToT**

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; ToT, time-on-treatment.
Source: HERIZON-BTC-01 (54).

### 3.3.3 Safety

Treatment-related Grade 3+ AEs that occurred in 2% or more patients from HERIZON-BTC-01 and ABC-06 are included in the CEA. This is in line with similar analyses, as Grade 3+ TRAEs are those that are likely to impact on costs and QALYs. Cohort 1 (HER2+, n=80) from HERIZON-BTC-01 was used to inform the zanidatamab AEs, to ensure any safety events were captured in a broader population of patients treated with zanidatamab.

There is a substantial treatment burden for patients undergoing combination chemotherapy, with patients requiring considerable time in hospital for severe AEs (see Section **1.3.4**). In the ABC-06 study, 10 patients discontinued FOLFOX treatment early due to intolerable toxicity, and Grade 3 to 5 AEs were reported in 56 (69%) of patients, including 3 chemotherapy-related deaths (21). In HERIZON-BTC-01, 2 patients discontinued zanidatamab due to toxicity. Only [redacted] of Cohort 1 patients reported a Grade 3 or 4 AE with no Grade 5 TRAE reported (see Section **2.11**).

To reflect the severity of TRAEs associated with different grades appropriately, costs have been included by grade of AE. Further details of the costs used for AEs are

described in Section 3.5.3. As only TRAEs are considered, no AEs are assumed for ASC. Table 58 presents the AEs included in the economic model for each treatment.

**Table 58: Grade 3+ TRAEs occurring in 2% or more patients**

| AE | Zanidatamab (n=80) | | | FOLFOX + ASC (n=81) | | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 5 | Grade 3 | Grade 4 | Grade 5 |
| Acute kidney injury | - | - | - | 1 (1.2%) | 0 (0.0%) | 1 (1.2%) |
| Anaemia | 3 (3.8%) | 0 (0.0%) | 0 (0.0%) | 2 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Aspartate aminotransferase increased | 1 (1.3%) | 1 (1.3%) | 0 (0.0%) | - | - | - |
| Biliary event | | | | 2 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Diarrhoea | 4 (5.0%) | 0 (0.0%) | 0 (0.0%) | 2 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Ejection fraction decreased | 3 (3.8%) | 0 (0.0%) | 0 (0.0%) | - | - | - |
| Fatigue | - | - | - | 9 (11.1%) | 0 (0.0%) | 0 (0.0%) |
| Febrile neutropenia | - | - | - | 0 (0.0%) | 1 (1.2%) | 1 (1.2%) |
| Hypertension | - | - | - | 2 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Infection | - | - | - | 6 (7.4%) | 1 (1.2%) | 1 (1.2%) |
| Neutropenia | - | - | - | 8 (9.9%) | 2 (2.5%) | 0 (0%) |
| Vomiting | - | - | - | 2 (2.5%) | 0 (0.0%) | 0 (0.0%) |
| Source | HERIZON-BTC-01 (54, 62) | | | ABC-06 (21) | | |

Abbreviations: AE, adverse event; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; TRAE, treatment-related adverse event.

## *3.4 Measurement and valuation of health effects*

### 3.4.1 Health-related quality-of-life data from clinical trials

In the HERIZON-BTC-01 trial, the EQ-5D-5L questionnaire was administered to patients to measure HRQoL, while the BPI-sf was used to measure pain relating to disease. Both questionnaires were given at baseline and then every 8 weeks, as well as within 7 days of the end of treatment.

### 3.4.2 Mapping of utility values

In line with NICE guidance, the EQ-5D-5L responses were ‘crosswalked’ to EQ-5D-3L values using the algorithm developed by Hernandez (2023) (91).

Two methods to estimate the utility values were taken forward into the economic model. The first approach estimates utility values based on progression status to align with the health-states of the PartSA. The second approach estimates utilities

based on different time to death (TTD) health states. These are described in turn below.

#### *3.4.2.1 Progression health-state utility estimation*

Table 59 provides summary statistics from HERIZON-BTC-01 for UK utility values at screening, pre-progression, post-progression, and overall. To utilise more patients and data, the full population of Cohort 1 (IHC2+/IHC3+) was used for the analysis. All 80 patients provided a total of 448 utility values, with the mean utility observed for pre- and post-progression being [redacted] and [redacted], respectively.

**Table 59: Summary statistics by INV progression status - UK utility (Cohort 1)**

| Variable | N† | n‡ | Mean | StD | Min | Lower Quartile | Median | Upper Quartile | Max |
|---|---|---|---|---|---|---|---|---|---|
| Overall | [redacted] | | | | | | | | |
| Screening | [redacted] | | | | | | | | |
| Pre-progression | [redacted] | | | | | | | | |
| Post-progression | [redacted] | | | | | | | | |

Abbreviations: INV, investigator assessment; StD, standard deviation.
†Number of patients.
‡Number of utility values.

The majority of patients (76 out of 80) had a value for 'screening' utility from the 4-week period prior to treatment. These utility values at screening are different to 'post-baseline' values, since it is assumed a patient cannot progress prior to beginning treatment.

Linear mixed model (LMM) regressions were fitted to the utility data to support the interpretation of changes in utility according to progression status (by INV). The use of LMM enables dependencies within the data (i.e. correlated repeated measurements within patients) to be accounted for when demonstrating the overall mean pattern of change over time. A simple model was run using only a binary explanatory variable for progression, including screening utilities as a random effect, in addition to repeated measurements per patient.

The UK-based utility coefficients derived from the progression model are presented in Table 60. The resulting health-state utilities are presented in Table 61.

**Table 60: LMM regression output – UK-based utility (Cohort 1)**

| Parameter | Coefficient | 95% CI | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | <0.001 |

| Parameter | Coefficient | 95% CI | p-value |
|---|---|---|---|
| Progressed† | [redacted] | [redacted] | <0.001 |

Abbreviations: CI, confidence interval; LMM, linear mixed model.
†Progression assessed by investigator.

**Table 61: Resulting health state utilities from the LMM (Cohort 1)**

| Parameter | Model 1 (progression-based) |
|---|---|
| PF | [redacted] |
| PD | [redacted] |

Abbreviations: LMM, linear mixed model; PD, progressive disease; PF, progression free.
†Calculated applying both the 'off treatment' and 'progression' coefficient.

These utility values are similar to those reported from other clinical trials in previously treated BTC (76) (Section 3.4.3).

#### *3.4.2.2 Time-to-death utility estimates*

As an alternative to the progression-based health-state utility approach, a TTD utility approach was also implemented using the HERIZON-BTC-01 trial data. The TTD utility approach attempts to define patient QoL upon their 'time to death'. QoL is expected to decline the closer a patient gets to death, which can be considered more appropriate than a progression-based approach which has a static value associated with the non-progressed and progressed states. The TTD approach has been used and preferred by NICE in previous advanced oncology technology appraisals including TA997 (92), TA983 (93) and others, as it may better capture the deterioration in QoL as patients approach death than the progression-based utilities (94). There were a limited number of utility assessments for people with progressed cancer in HERIZON-BTC-01. So, health state utilities from the trial data may only reflect QoL close to the time of cancer progression, rather than the entirety of the remaining time living with progressed cancer.

The conducted analysis used 2 methods to estimate patients' TTD utility: creating groups for specific ranges of TTD, and using TTD (or a transformed version of it) as a continuous explanatory variable. The feasibility of conducting the TTD analysis are detailed in the report provided in Appendix P. The report also contains a full description of the methods used to deal with assumptions around censoring, the systematic selection of a 'shortlist' of best-fitting TTD groupings, and testing of a range of capping points for the continuous models. The 'capping points' are calculated via a process in which the maximum TTD duration is limited to a certain value (or 'cap') prior to estimating the continuous models, in order to prioritise data fitting in the months closest to death. Therefore, any patients with TTD greater than the cap were assumed to have TTD at the cap. The results presented below and

included within the economic model are based on the final selected grouping and continuous model cap.

The final TTD groupings chosen were less than 84 days, between 84 and 195 days, and over 196 days from death. The summary statistics of the final TTD groupings are presented in **Table 62**.

**Table 62: Summary statistics of final TTD groupings**

| Group, days from death | n pts. | n obs. | Mean Utility (StD) | Min value | 25th percentile | 50th percentile | 75th percentile | Max value |
|---|---|---|---|---|---|---|---|---|
| <84 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 84-195 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥196 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: obs., observations; pts., patients; StD, standard deviation; TTD, time to death.
†All patients with censored survival placed in this group.

Regressions were run to estimate the utility in each TTD grouping to account for multiple observations per patient. Linear mixed-effect regressions (LMERs) were used, where utility was estimated based on the fixed effect of grouping, with a random intercept by subject to account for between patient differences.

The LMER coefficients are presented for the final selected TTD groupings in **Table 63**. The regression is presented in two different formats with the intercept either excluded or included. With the intercept included, the intercept represents the estimate for the group furthest from death, with the coefficients for the other groups showing the decrement associated with each compared to the intercept. With the intercept excluded, each coefficient shows the absolute utility of each group estimated by the model. The p-values presented for the models including intercept represent the difference from the constant. Note that p-values are excluded for the intercept excluded results because the p-values would be for the coefficient differing from zero and thus not meaningful.

**Table 63: LMER of final TTD groups (decrements and group values)**

| Parameter | Intercept with decrements (95% CI) | Group utility values |
|---|---|---|
| Intercept (≥196 days) | [redacted] | [redacted] |
| 84-195 days | [redacted] | [redacted] |
| <84 days | [redacted] | [redacted] |

Abbreviations: CI, confidence interval; LMER, liner mixed-effect regression; TTD, time to death.

In addition to the LMERs for group models, continuous models were explored. Five models were fitted to the data with utility explained by the linear, log, inverse square root, inverse exponent, and square of TTD days. Details of these models are provided in the report in Appendix P. As mentioned previously, a range of capping points to the data were tested based on goodness-of-fit of the resulting models (the details for which are explained in Appendix P). Ultimately, the value of 252 days was selected as the final cap as it was judged to balance the best fitting 'cap values' across goodness of fit measures and models. This was applied to the final continuous models used for the economic model.

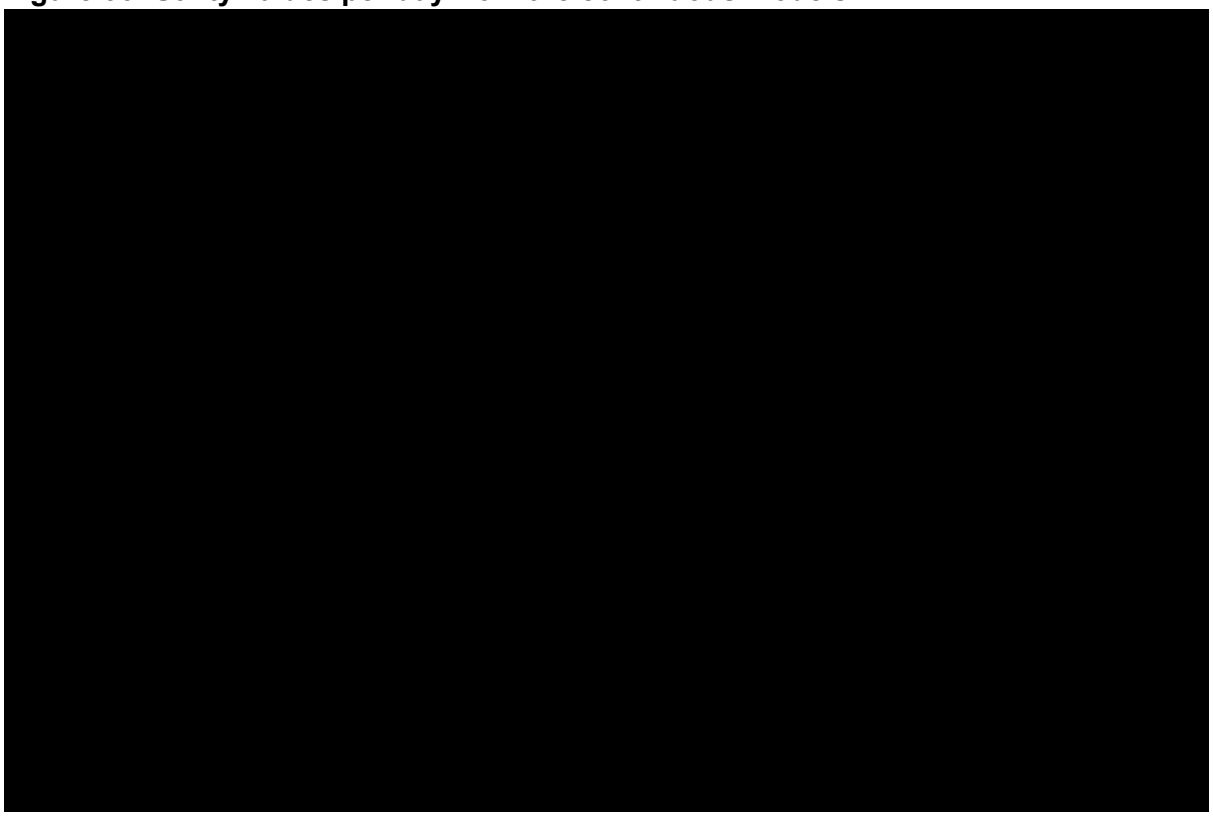
Results for the continuous models are presented in **Table 64** with a comparison of model fit by AIC. Model coefficients are included in the table though they are not easily interpretable given the transformations of the TTD days variable. The equations used are provided for context. **Figure 36** presents the resulting utility values from the 5 TTD continuous models.

**Table 64: Continuous TTD models fits – UK utility**

| Parameter | TTD days | Log TTD days | Inverse square root TTD days | Inverse exponent TTD days | Square TTD days |
|---|---|---|---|---|---|
| Intercept (α) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Coefficient (β) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Equation for utility | $\alpha + \beta * TTD$ | $\alpha + \beta * \ln(TTD)$ | $\alpha + \frac{\beta}{\sqrt{TTD}}$ | $\alpha + \beta * scaled(TTD)$ | $\alpha + \beta * TTD^2$ |
| AIC | -397.7 | -398.3 | -397.8 | -396.8 | -397.1 |

Abbreviations: AIC, Akaike information criterion; TTD, time to death.
TTD capped at 252 days.

**Figure 36: Utility values per day from the continuous models**



Abbreviations: exp, exponential; sqrt, square root; TTD, time-to-death.

The inverse square root was the best fitting according to the AIC, though model fit statistics were similar across the 5 models. The TTD(days), TTD, and Inverse exponential (TTD) models result in little difference across the per time-to-death days suggesting QoL only slightly declines the closer death occurs. The log(TTD) and inverse squareroot(TTD) models decrease as time-to-death comes closer which is more in line with expectations.

### 3.4.3 Health-related quality-of-life studies

Systematic database searches for other relevant HRQoL data using SLR was conducted from January 2014 to 12 April 2024 and further updated in September 2024 and March 2025. A total of 26 studies were included in the full text review. Further details of the SLR can be found in Appendix F.

The majority of the 26 studies reporting utilities in BTC were obtained from economic evaluations. Fourteen of the studies were from Asian countries (China, Taiwan, Japan or Thailand). The 6 studies from the UK were health technology assessment (HTA) submissions for NICE or Scottish Medicines Consortium (SMC). Little information was available to identify which QoL instrument was used to measure utility values. In addition, other critical information regarding population characteristics, disease area, and country of origin were often unavailable, introducing limitations in comparing reported utilities between studies.

Only 1 of the studies identified was based on a HER2+ BTC population and reported VAS utilities. The 6 UK studies were not directly applicable for the decision problem as they were either in 1L BTC (TA944/SMC2582 – durvalumab (15)) or a different mutation (TA722 – pemigatinib [FGFR2] (18); TA1005 – futibatinib [FGFR2] (20); TA948 – ivosidenib [IDH1 R132] (19); TA914 – pembrolizumab [microsatellite instability high (MSI-H)/ mismatch repair deficient (dMMR)] (39)). Most of the appraisals redacted the utility outputs used within the cost-effectiveness models with the exception of 1L durvalumab. The 1L durvalumab model used the EQ-5D-5L utilities from the TOPAZ-1 trial mapped to EQ-5D-3L (0.797 for the PFS health state and 0.679 for the PD health state).

The only other study identified from the SLR which used EQ-5D utility values was the Tsukiyama (2016) study (95). This study published the cost-effectiveness of CisGem versus gemcitabine in 1L advanced BTC in Japan. The utility values were based on EQ-5D values from the CEA registry (96).

McCarthy (2024) (76) published the CEA of 2L pembrolizumab for previously treated MSI-H/dMMR solid tumours including advanced BTC. The utility values used for the advanced BTC subgroup were derived from the EQ-5D-3L utility values for the BTC subgroup in the KEYNOTE-158 trial using the UK value set (0.80 for the PFS health state and 0.70 for the PD health state).

McCarthy (2024) was taken forward to explore as a scenario to inform health-state utilities, because this was a UK specific economic analysis and reported previously accepted utility values for an advanced previously treated BTC population; however, the populations differ in terms of oncogenic mutations.

### 3.4.4 Impact of adverse reactions on utility

The impact of Grade 3+ TRAEs in 2% or more of the trial population on HRQoL was included in the cost-effectiveness model. Disutility values were identified from published literature accepted in prior appraisals in BTC or similar disease areas. Due to the lack of availability of granular disutility by AE severity, the AEs for Grades 3 to 5 were grouped for the calculation of treatment specific AE disutility.

The impact of AEs on patient utility was applied as a one-off quality-adjusted life year (QALY) loss in the first model cycle and based on the expected duration of each AE (the data for which were sourced from the HERIZON-BTC-01 study). When an AE duration could not be estimated from HERIZON-BTC-01, the duration was assumed to be the mean of the available duration estimates from the trial. Given the different safety profiles of zanidatamab and chemotherapy, and that the AEs associated with FOLFOX treatment are generally more severe and likely to require longer hospital stays, grouping the disutilities at the same level of severity and assuming the same duration as per zanidatamab in HERIZON-BTC-01 is a conservative assumption,

and is likely to underestimate the disutility of the AEs for FOLFOX compared with zanidatamab.

**Table 65: Disutilities and durations for Grade 3+ TRAEs**

| AE | Disutility | Duration, days | Source for disutility | Source for duration |
|---|---|---|---|---|
| Acute kidney injury | -0.053 | [redacted] | Sullivan (2006) (97) | Average of HERIZON-BTC-01 AEs |
| Anaemia | -0.085 | [redacted] | TA439 (98) | HERIZON-BTC-01 |
| Aspartate aminotransferase increased | 0.000 | [redacted] | TA722 (18) | HERIZON-BTC-01 |
| Biliary event | -0.085 | [redacted] | TA722 (18) | HERIZON-BTC-01 |
| Diarrhoea | -0.103 | [redacted] | Lloyd (2006) (99) | HERIZON-BTC-01 |
| Ejection fraction decreased | -0.019 | [redacted] | Sullivan (2006) (97) | HERIZON-BTC-01 |
| Fatigue | -0.085 | [redacted] | TA722 (18) | Average of HERIZON-BTC-01 AEs |
| Febrile neutropenia | -0.150 | [redacted] | Lloyd (2006) (99) | Average of HERIZON-BTC-01 AEs |
| Hypertension | -0.036 | [redacted] | Sullivan (2006) (97) | HERIZON-BTC-01 |
| Infection | -0.218 | [redacted] | Stein (2018) (100) | Assumed same as anaemia (TA722) |
| Neutropenia | -0.061 | [redacted] | TA439 (98) | Average of HERIZON-BTC-01 AEs |
| Vomiting | -0.048 | [redacted] | Nafees (2008) | HERIZON-BTC-01 |

Abbreviations: AE, adverse event; TRAE, treatment-related adverse event.

The total disutility per treatment arm is provided in **Table 66**. As expected given the higher incidence of TRAEs, the total disutility is higher for the FOLFOX arm than the zanidatamab arm; however, as discussed, this could still be an underestimation based on the reported safety profiles.

**Table 66: On treatment disutilities applied for Grade 3+ TRAEs**

| Treatment arm | Disutility applied |
|---|---|
| Zanidatamab | 0.000668 |
| FOLFOX | 0.003081 |

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

### 3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

#### *3.4.5.1 Health-state utility values*

In the base case, utilities derived from the HERIZON-BTC-01 trial have been used directly to inform health-state utility values. Given that a patient's QoL can be determined by the closer they are to death, the TTD approach has been used in the base case. The continuous TTD model which had the best statistical fit was chosen to inform the base case (i.e. the inverse square root). Although the fit statistics were similar across the models, some of the models looked more plausible.

The alternative TTD models and progression-based model are explored in scenario analyses (see Section **3.10.3**).

As only 2 UK patients were included in HERIZON-BTC-01, there is some uncertainty in the utility values from the trial. As such, previously accepted utility values in 2L BTC from McCarthy (2024) are also explored as a scenario analysis (76) (see Section **3.4.3**)

#### *3.4.5.2 Treatment-specific disutility*

As there are no comparative utilities for FOLFOX + ASC, or ASC alone compared to zanidatamab, data from the literature have been used to calculate a treatment-specific disutility to account for the reduced QoL experienced by patients being treated with combination chemotherapy with FOLFOX + ASC, or palliative care with ASC alone.

The treatment-specific disutility is included separately to the disutility associated with Grade 3+ AEs, as it covers the other aspects of the QoL differences and therefore not double counted. As a combination chemotherapy regimen with a high incidence of AEs and requirement for a central line for administration, patients who are treated with FOLFOX + ASC are likely to have worse QoL compared with those treated with zanidatamab monotherapy. The toxicity of FOLFOX and associated impact may not be fully captured within Grade 3+ AEs i.e. more frequent Grade 1 or 2 AEs can impact QoL more than few Grade 3 or 4 AEs. In addition, patients who are treated with palliative care alone without active pharmacotherapy using ASC are likely to experience disease-related impacts to QoL due to lack of disease control. As such, the model includes a further disutility for the FOLFOX + ASC and ASC treatment arms.

The treatment specific disutilities were calculated using the utility data published from the ABC-06 study (101), from 138 UK patients treated with FOLFOX + ASC, or ASC alone. Patients treated with FOLFOX + ASC (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). The utility reduction from baseline to 4-months was calculated as 90.9%. The equivalent utilities from the HERIZON-BTC-01 were calculated with a baseline utility of [redacted] and '4-month' utility of [redacted] using the progression-free and progressed utility values estimated from the regression model, and weighted based on the same proportion of patients being progression-free as FOLFOX + ASC at 4 months. The equivalent FOLFOX + ASC utility in HERIZON-BTC-01 was calculated using the reduction from baseline on the baseline HERIZON-BTC-01 value (i.e. [redacted] x 90.9% = [redacted]). The decrement for FOLFOX was then estimated to be the difference between the '4-month equivalent' utility values; [redacted] – [redacted] = [redacted].

The decrement for ASC was calculated in the same way. As it is not known from the ABC-06 study the proportion of patients treated with ASC who were progression-free at 4 months, the proportion was estimated from the modelled efficacy of ASC. The decrement for ASC was estimated to be [redacted].

These decrements were applied to the per cycle TTD utility values estimated from HERIZON-BTC-01 and used to inform the FOLFOX and ASC health state utility values. **Table 67** presents the calculations and sources to estimate the decrement for FOLFOX and ASC.

**Table 67: FOLFOX + ASC and ASC utility decrement calculations**

| Calculation step | Utility Value | Source |
|---|---|---|
| (a) HERIZON-BTC-01 baseline utility | [redacted] | HERIZON-BTC-01 (54) |
| *FOLFOX disutility* | | |
| (b) FOLFOX baseline utility | 0.77 | ABC-06 (101) |
| (c) FOLFOX 4-month utility | 0.70 | ABC-06 (101) |
| (d) FOLFOX % progression-free at 4 months | 56.7% | ABC-06 (21) |
| (e) FOLFOX reduction from baseline | 90.9% | Calculation (c/b) |
| (f) Equivalent FOLFOX utility at 4 months in HERIZON-BTC-01 | [redacted] | Calculation (a*e) |
| (g) Equivalent zanidatamab utility to FOLFOX at 4 months | [redacted] | Calculation (d*[redacted] + (1-d)*[redacted] |
| **FOLFOX + ASC decrement** | [redacted] | **Calculation (g-f)** |
| *ASC disutility* | | |
| (h) ASC baseline utility | 0.75 | ABC-06 (101) |
| (i) ASC 4-month utility | 0.62 | ABC-06 (101) |
| (j) ASC % progression-free at 4 months | 35.0% | Calculation from modelled PFS |
| (k) ASC reduction from baseline | 82.7% | Calculation (i/h) |

| Calculation step | Utility Value | Source |
|---|---|---|
| (l) Equivalent ASC utility at 4 months in HERIZON-BTC-01 | [redacted] | Calculation (a*k) |
| (m) Equivalent zanidatamab utility to ASC at 4 months | [redacted] | Calculation (j*[redacted] + (1-j)*[redacted] |
| **ASC decrement** | [redacted] | **Calculation (m-l)** |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

#### *3.4.5.3 Age-related disutility*

Age-related utility decrements have been included in the model to account for the decline in QoL associated with ageing in line with NICE DSU guidance.

The recent DSU report on estimating general population utility values recommends using the Health Survey for England 2014 dataset which is a direct observation of EQ-5D-3L published by Hernandez-Alava (2022) (102). The study used a series of Adjusted Limited Dependent Variable Mixture Models to calculate the expected EQ-5D-3L utility values for males and females.

The resulting expected utility value inputs are included in the economic model, and are multiplied by the modelled distribution of males and females alive over time to create age and sex-matched general population utility values.

#### *3.4.5.4 Administration disutility for central venous access devices*

Zanidatamab is a monotherapy administered as a single peripheral IV infusion Q2W using a canula. As discussed in Section **3.5.1.2**, FOLFOX is a combination chemotherapy regimen of 3 drugs administered in a 14 day cycle. Two of the chemotherapy drugs (folinic acid and oxaliplatin) are administered sequentially using a long-term implanted central venous access device (usually a PICC or portacath). These devices are implanted for the entire duration of the chemotherapy, which impose an additional QoL burden for patients and require invasive procedures for implantation, maintenance, and removal (23, 24, 47). The remaining chemotherapy drug (5FU) is administered continuously over 48 hrs via an IV pump, which is kept in place for 48 hours and then removed by a healthcare professional.

As such, a disutility for administration of FOLFOX has been included in the economic model. This value has been taken from a CEA of 3 types of central venous access devices (Hickman lines, portacath, and PICC) in routine clinical practice from a UK perspective (24). The health utility difference between portacath vs PICC was reported to be -0.013. This additional disutility is included only for the assumed proportion of patients having a portacath device over a PICC line whilst on FOLFOX treatment in the model (50% PICC/50% portacath). The disutility for those patients having a PICC with FOLFOX vs an IV infusion with zanidatamab is considered to be

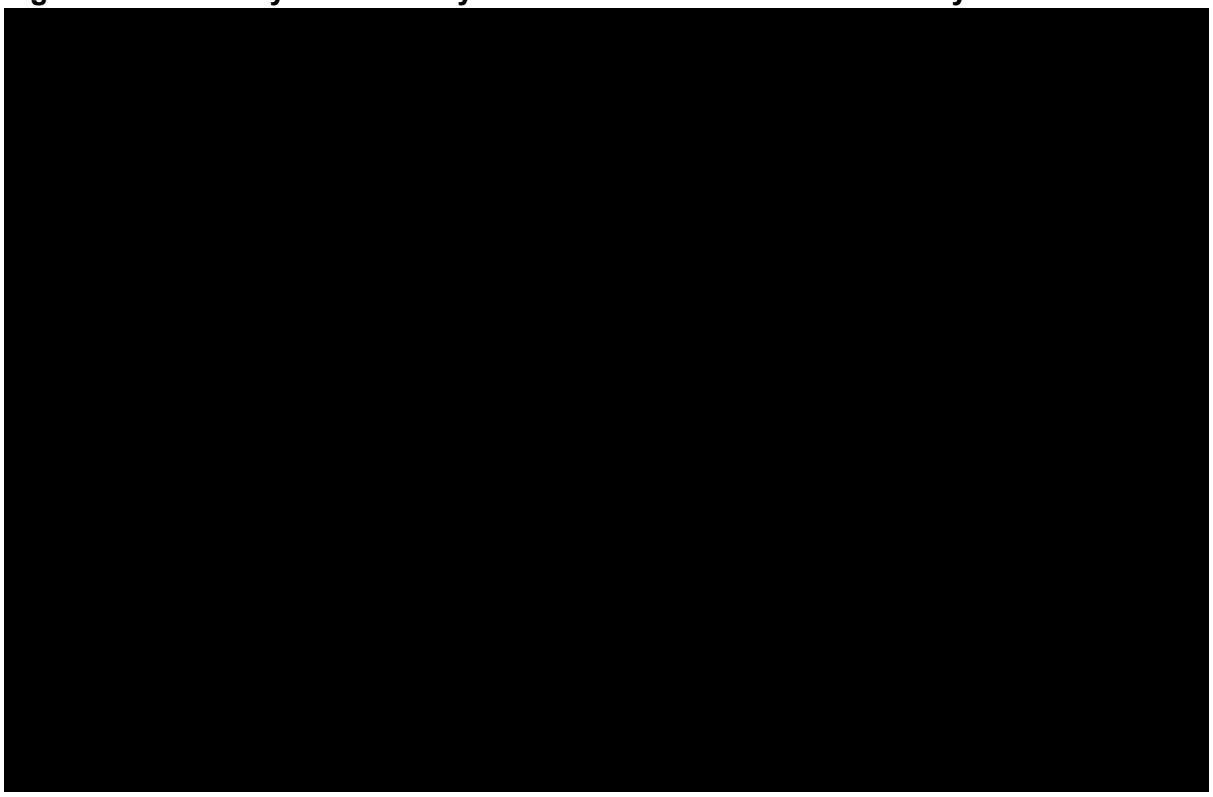

 

already accounted for in the treatment-specific disutility described in Section 3.4.5.2. The proportion of patients having a portacath vs. a PICC were supported by the UK clinician interviews (36).

### *3.4.5.5 Summary of base case utility values*

A summary of the base case utility values per TTD day is presented in Figure 37 and other treatment-specific disutilities included in the model are presented in Table 68.

**Figure 37: Summary of TTD utility values for cost-effectiveness analysis base case**



Abbreviations: TTD, time-to-death

**Table 68: Summary of disutility values for cost-effectiveness analysis base case**

| State | Utility value | Reference in submission (section and page number) | Justification |
|---|---|---|---|
| Treatment specific disutility:<br>FOLFOX + ASC<br>ASC | [redacted] | Section 3.4.5.2, page 139 | To account for differences between treatments not captured in the other disutilities such as frequent grade 1/2 adverse reactions or lack of treatment options |
| Disutility for administration of FOLFOX using a portacath | -0.013 | Section 3.4.5.4, page 141 | To account for the impact of invasive administration using a central line on QoL |

| State | Utility value | Reference in submission (section and page number) | Justification |
|---|---|---|---|
| Grade 3+ AE disutilities<br>Zanidatamab<br>FOLFOX + ASC | <br>-0.000668<br>-0.003081 | Section 3.4.4, page 137 | To account for the impact of TRAE on QoL |

Abbreviations: AE, adverse event; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; QoL, quality of life; TRAE, treatment-related adverse event.

## *3.5 Cost and healthcare resource use identification, measurement and valuation*

An economic SLR was undertaken to identify cost and resource use studies for 2L HER2+ BTC. Full details of the SLR methods, identified studies and results are presented in Appendix G.

### 3.5.1 Intervention and comparators' costs and resource use

#### *3.5.1.1 Drug acquisition costs*

The drug unit costs in the model were sourced from the drugs and pharmaceutical electronic market information tool (eMIT) (103) or the British National Formulary (BNF) (104) and are presented in **Table 69**. There is a proposed confidential simple discount patient access scheme (PAS) for zanidatamab resulting in [redacted]

Patients receiving palliative care with ASC alone may receive biliary drainage using stents, antibiotics, analgesia, steroids, and antiemetics (21). The costs for these interventions are not explicitly included in the model, as these are expected to be the same on all treatment arms and therefore will not impact the modelled outcomes.

**Table 69: Unit drug costs**

| Drug | Vial Size | Pack size (number of vials) | Unit cost, £ | Source |
|---|---|---|---|---|
| Zanidatamab | 300 mg | 2 | [redacted] | Jazz Pharmaceuticals |
| Oxaliplatin | 50 mg | 1 | 6.48 | eMIT 2025 (103) |
| | 100 mg | 1 | 14.27 | |
| | 200 mg | 1 | 11.31 | |
| Fluorouridine (5FU) | 500 mg | 1 | 3.26 | eMIT 2025 (103) |
| | 1000 mg | 1 | 3.20 | |

| Drug | Vial Size | Pack size (number of vials) | Unit cost, £ | Source |
|---|---|---|---|---|
| | 2500 mg | 1 | 4.62 | |
| | 5000 mg | 1 | 6.27 | |
| Folinic acid (leucovorin) | 50 mg | 1 | 20.00 | BNF 2025 (104) |
| | 100 mg | 1 | 37.50 | |
| | 300 mg | 1 | 100.00 | |
| | 350 mg | 1 | 161.15 | |

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

The dosing schedule for zanidatamab was taken from HERIZON-BTC-01, which is in line with the proposed licence and SmPC in the UK (1, 22, 54). Zanidatamab is administered at a dose of 20 mg/kg on days 1 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

The dose for FOLFOX was taken from the ABC-06 study, which is also in line with the respective SmPCs, administered Q2W over 2 days for a maximum of 12 cycles. Oxaliplatin is administered at a dose of 85 mg/m, concurrently with FA 350 mg IV (21, 90). 5FU is administered at a dose of 400 mg/m$^2$ by bolus injection on day 1, and 2,400 mg/m$^2$ as continuous infusion starting day 1 and finishing on day 2 (21).

To account for dose reductions, missed doses and treatment interruptions, an relative dose intensity (RDI) was included in the base case. In HERIZON-BTC-01 dose modifications and dose delays of zanidatamab were allowed for certain treatment-related AEs (64). Therefore, the RDI of [redacted] from HERIZON-BTC-01 was used for zanidatamab, calculated as the actual dose received divided by the intended dose of drug. In the ABC-06 study, a maximum of 2 dose reductions were allowed per drug; level 1 represented a 20% reduction and level 2 represented a 50% reduction. If level 2 was not tolerated then the drug was discontinued (21). Starting doses could also be adjusted based on a patient's age and creatinine levels. The resulting RDI was not reported in the ABC-06 study, therefore an assumption was made where the RDI was the same as zanidatamab (i.e. [redacted] for all study drugs).

Drug wastage was calculated through the 'method of moments' (MoM) approach to calculate the average number of vials that would be required per 1 administration of treatment (105). The MoM approach first derives a log-normal distribution for the average patient's weight based on the mean (StD) measured at baseline from HERIZON-BTC-01. The log-normal distribution is then used to predict the proportion of patients requiring each number of vials to administer the required dose. This

method assumes that patients only receive whole vials (i.e. no vial sharing), and thus accounts for drug wastage.

Table 70 presents the dosing schedules, dose intensity and final cost per treatment cycle including wastage.

**Table 70: Dosing schedule and cost per treatment cycle**

| Treatment | | Dose | RDI | Cost per treatment cycle,† £ | Source |
|---|---|---|---|---|---|
| Zanidatamab | | 20 mg/kg day 1 and day 15 Q4W | [redacted] | [redacted] | HERIZON-BTC-01 (22) |
| FOLFOX | Oxaliplatin | 85 mg/m$^2$ Q2W | [redacted] | [redacted] | ABC-06 (21) |
| | 5FU (bolus) | 400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | 5FU (continuous) | 2,400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | Folinic acid | 350 mg Q2W | [redacted] | [redacted] | |

Abbreviations: 5FU, fluorouracil; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PAS, patient access scheme; Q2W, every 2 weeks; Q4W, every 4 weeks; RDI, relative dose intensity.
† Includes RDI and PAS and assuming average UK patient.

#### *3.5.1.2 Administration costs*

Zanidatamab is administered by simple IV infusion using a peripherally inserted cannula. The cost of administration is taken from the National Cost Collection 23/24 dataset represented by the delivery of simple parenteral chemotherapy at first attendance (SB12Z) (106).

For FOLFOX, folinic acid and oxaliplatin are both administered via complex infusion through central venous access devices (PICC, central line, or portacath). These can pose a substantial burden for patients and require invasive procedures to insert (see Section 1.3.3.1.3). For the first administration of FOLFOX, the additional costs of implantation and removal of PICC and portacath and its associated complications are included. These costs are taken from Heggie (2024) who looked at the cost-effectiveness of Hickman, PICC, and portacath within the UK NHS (24). The total cost and complications of PICC and portacath reported was £1,545 and £1,722 per patient, which are then uplifted from 2017/18 costs using the inflation indices from the Personal Social Services Research Unit (PSSRU) report 2023 (107). Portacaths are more cost-effective to the NHS, but are not used in all services according to UK clinical experts (36); therefore, in the model it is assumed that 50% of patients have a PICC line and 50% have a Portacath device.

After the first cycle, the cost of combination chemotherapy infusion for FOLFOX is represented by the delivery of complex chemotherapy, including prolonged infusion treatment, at first attendance from the National Cost Collection 23/24 (SB14Z) (106).

As 5FU is administered continuously over a 46-hour period, an additional cost of £157.13 per visit is applied for patients returning to hospital to have their portable pump removed by a nurse.

The administration costs are presented in **Table 71**.

**Table 71: Administration costs**

| Treatment | | Administration | Cost type | Unit cost, £ | Source/description |
|---|---|---|---|---|---|
| Zanidatamab | | 120-150 minutes intravenous infusion in cycle 1 decreased to 90 mins if well tolerated | Simple IV – per administration | 133.39 | National Cost Collection 23/24: Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z) (106) |
| FOLFOX | 5FU (bolus) | 5-10 min bolus (day 1) | Complex IV – per administration† | 337.16 | National Cost Collection 23/24: Deliver complex chemotherapy, including prolonged infusional treatment, at First Attendance (SB14Z) (106) |
| | 5FU (continuous) | 46-hours continuous intravenous infusion (day 1-2) | Oncology nurse for removal – per treatment cycle | 157.13 | National Cost Collection 23/24: 370 Medical oncology services – Non-consultant led - Non-admitted face-to-face (WF01A) (106) |
| | Oxaliplatin/ folinic acid | 2 hours intravenous infusion concurrently (day 1) | PICC or Portacath insertion costs and complications – one-off cost | 1,631.83 (PICC) 1,932.61 (Portacath) | Heggie (2024) uplifted to 2023 costs from PSSRU 2023 (24, 107) |

Abbreviations: 5FU, fluorouracil; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IV, intravenous; PICC, peripherally-inserted central catheter; PSSRU, Personal Social Services Research Unit.
†Also covers the cost of oxaliplatin and folinic acid IV infusions

### *3.5.1.3 Pre-medication drug costs*

To prevent infusion-related reactions, some treatments require prophylaxis treatment before administration.

In the HERIZON-BTC-01 trial, all patients received mandatory treatment for potential IRRs 30 to 60 minutes before the start of each zanidatamab infusion. This included pre-treatment with corticosteroids, antihistamines and paracetamol (22, 64).

In ABC-06, antiemetic pre-medication was also suggested for patients receiving FOLFOX (subject to local protocols). This included dexamethasone and ondansetron hydrochloride (bolus injections on day 1 followed by oral on days 2 and 3) with metoclopramide hydrochloride on days 1 to 7 of the treatment cycle.

As such, the model includes the costs of pre-medications which are applied to each dose per treatment cycle. A summary of the pre-medication costs, and dosing by treatment arm is provided in **Table 72**.

**Table 72: Pre-medication costs**

| Treatment | Pre-medication | Pack Size | Unit cost, £ | Dose | Cost per dose, £ |
|---|---|---|---|---|---|
| Zanidatamab | Corticosteroids (hydrocortisone) | 30 x 20 mg | 1.60 | 100 mg IV | 0.27 |
| | Antihistamines (Cinnarizine) | 84 x 15 mg | 4.05 | 50 mg orally | 0.16 |
| | Paracetamol | 24 x 500 mg | 1.22 | 1000 mg orally | 0.10 |
| FOLFOX | Dexamethasone sodium phosphate | 10 x 3.3 mg | 3.08 | 8 mg IV (day 1) | 0.75 |
| | Ondansetron hydrochloride (IV) | 5 x 8 mg | 3.06 | 8 mg IV (day 1) | 0.61 |
| | Ondansetron hydrochloride (oral) | 10 x 8 mg | 0.67 | 8 mg oral twice a day on days 2 and 3 | 0.27 |
| | Dexamethasone | 50 x 2 mg | 2.38 | 4 mg oral twice a day on days 2 and 3 | 0.38 |
| | Metoclopramide hydrochloride | 28 x 10 mg | 0.43 | 10-20 mg three times a day on days 1-7 | 0.16 |

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IV, intravenous.
Source: eMIT (103); HERIZON-BTC-01 (54); Lamarca (2021) (21).

### 3.5.2 Health-state unit costs and resource use

#### *3.5.2.1 Health-state costs*

HCRU estimates were sourced from prior appraisals for pemigatinib (TA722 - CCA with FGFR2 alterations) (18) and ivosidenib (TA948 - CCA with IDH1 mutations) (19). TA722 based resource use on ESMO guidelines for BTC follow-up and clinical expert opinion. Based on the clinical opinion received in TA722, computed tomography (CT) scans were assumed to be performed once every 12 months following progression. In addition, the cost of daily pain medication was also captured in the progressed disease state.

The ESMO and BSG guidelines state that there is no universal follow-up schedule; however, it may consist of 3 to 6 monthly visits for the first 2 years and 6 to 12 monthly visits for up to 5 years including a combination of clinical examination, laboratory investigations, tumour markers, and CT scans (13, 25). These are aligned with the resource use and frequencies within the TA948 submission which assumes 3-monthly clinical examinations and blood tests in both the progression-free and progressed state (19). TA948 also aligned the frequencies for CT scans post-progression and daily morphine with the frequencies assumed in TA722.

The health-state resource use frequencies used in the model base case are presented in **Table 73**.

**Table 73: Health-state resource use frequencies**

| Resource use | Progression-free | Progressed | Source |
|---|---|---|---|
| Oncologist | Every 3 months | Every 3 months | TA722 (18)<br>TA948 (19)<br>ESMO 2023 (25) |
| Complete blood count test | Every 3 months | Every 3 months | |
| CT scan | Every 3 months | Once every 12 months | |
| Morphine | - | 1mg daily | |

Abbreviations: CT, computed tomography.

**Table 74** presents unit costs for HCRU items, which were sourced from the National Cost Collection (2023/24) (106) and the BNF (for morphine sulphate) (108). The resulting HCRU costs per 7-day model cycle are £24.84 and £54.45 in the progression-free and progressed disease health states, respectively.

**Table 74: Health-state resource use unit costs**

| Resource item | Unit cost, £ | Source |
|---|---|---|
| Oncologist | 192.95 | National Cost Collection 23/24: Medical oncology - Outpatient attendances. WF01A (Consultant led) (106) |

| Resource item | Unit cost, £ | Source |
|---|---|---|
| Complete blood count test | 8.04 | National Cost Collection 23/24: Haematology - 370 - medical oncology (106) |
| CT scan | 123.03 | National Cost Collection 23/24: Computerised Tomography Scan of Three Areas, with Contrast - Total HRGs (106) |
| Morphine | 5.24 | BNF 2025 - Morphine Sulfate (1mg/1ml) - Torbay Pharmaceuticals (108) |

Abbreviations: BNF, British National Formulary; CT, computed tomography.

#### *3.5.2.2 Special warning monitoring*

Zanidatamab, folinic acid, oxaliplatin, and 5FU require additional monitoring for 'special warnings' associated with their labels.

For zanidatamab, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of treatment by echocardiogram or multigated acquisition scan at regular intervals during treatment. As such, the cost of LVEF monitoring has been included for the patients treated with zanidatamab (1). In TA862 (trastuzumab-deruxtecan for HER2+ breast cancer), the company included a cost for LVEF follow-up based on £130 every 3 months, as suggested by the external assessment group (EAG) for TA458 (109, 110). Therefore, this cost has also been assumed, uplifted to 2023/2024 costs and applied every 3 months to those on treatment.

Other monitoring is advised for patients treated with zanidatamab, this includes monitoring for symptoms of pneumonitis, IRRs and a pregnancy test. These are assumed to be carried out during the administration visit and therefore no extra costs are applied.

There are several special warnings for oxaliplatin, the key ones requiring additional monitoring are for neurological symptoms, renal impairment and QT prolongation (90).

- A neurological exam should be performed before each administration and periodically after. It is assumed that this would take place at the administration visit and not require additional resource.
- Renal impairment should be closely monitored for adverse reactions. It is assumed that this is done during the regular disease monitoring visits (see **Table 73**).
- QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. A cost of an echocardiology is therefore applied before and after each dose of oxaliplatin.

5FU requires additional monitoring for haematological effects, cardiotoxicity and tumour lysis syndrome (89).

- Treatment of 5FU is usually followed by leukopenia with the lowest white blood count between the 7th and 14th day of the first course of treatment. This is usually back to normal levels by the 30th day. As such, daily monitoring of platelet and white blood count is recommended. Based on this, it is assumed that daily monitoring of bloods is only required in the first 30 days after the first course applied as an upfront cost in the first cycle.
- Cardiac function should be regularly monitored during treatment due to the association of cardiotoxicity with 5FU. It is assumed that the echocardiology test is covered by the one conducted prior to oxaliplatin use.
- Patients with tumour lysis syndrome should be closely monitored. It is assumed that these are covered by the disease monitoring visits (see **Table 73**).

FA in combination with 5FU recommends full blood counts prior to each treatment, weekly during the first 2 courses, and at the time of anticipated white blood cell nadir in all courses thereafter. This is assumed to be covered by the daily bloods for 30 days after the first course of 5FU.

- Electrolytes and liver function tests are also recommended prior to each treatment for the first 3 courses, and prior to every other course thereafter (88).

A summary of the additional monitoring costs and frequencies for FOLFOX are presented in **Table 75**.

**Table 75: Special warning monitoring**

| Treatment | Resource | Frequency | Unit cost | Frequency source | Cost source |
|---|---|---|---|---|---|
| Zanidatamab | LVEF follow-up | Every 3-months | £154.09 | TA458 | TA458 (109) PSSRU 2024 (107) |
| FOLFOX | Echocardiology | Before and after each administration | £115.56 | Oxaliplatin SmPC Fluorouracil SmPC | National Cost Collection 23/24: Simple Echocardiogram, 19 years and over - Total HRGs (106) |
| | Complete blood count | Daily for the 30 days after the first course | £8.04 | Fluorouracil SmPC | National Cost Collection 23/24: Haematology - 370 - medical oncology (106) |
| | Liver function test | Prior each treatment for first three cycles, then every other | £8.04 | Leucovorin SmPC | National Cost Collection 23/24: Haematology - |

| Treatment | Resource | Frequency | Unit cost | Frequency source | Cost source |
|---|---|---|---|---|---|
| | | course thereafter (7 out of the 12 cycles) | | | 370 - medical oncology (106) |

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; LVEF, left ventricular ejection fraction; SmPC, summary of product characteristics.

### 3.5.3 Adverse reaction unit costs and resource use

The unit costs for the management of AEs were sourced from the National Cost Collection 23/24 (106). Different 'CC' scores from the costing codes were used to differentiate the costs of managing Grade 3, 4, and 5 AEs, with higher CC scores assumed to be representative of higher-grade AEs. **Table 76** summarises the costs associated with each grade of each AE.

The unit cost of each AE is applied to the incidence rate within each treatment (as outlined in Section **3.3.3** **Table 58**). The total weighted cost per treatment arm was calculated and applied as a one-off cost within the first cycle of the economic model.

**Table 76: Adverse event unit costs in the economic model**

| AE | Grade 3 | Grade 4 | Grade 5 | National Cost Collection Code |
|---|---|---|---|---|
| Acute kidney injury | £5,007.04 | £6,324.44 | £8,070.52 | NEI LS - Acute Kidney Injury with Interventions - LA07k; LA07J; LA07H (106) |
| Anaemia | £2,491.26 | £2,935.07 | £3,380.10 | NEI LS - Iron Deficiency Anaemia - SA04K; SA04J; SA04H (106) |
| Aspartate aminotransferase increased | £0.00 | £0.00 | £0.00 | Watchful waiting – no cost assumed as per TA722 (18) |
| Biliary event | £7,430.87 | £10,342.74 | £17,435.41 | NEI LS - YG02Z - Percutaneous Insertion of Multiple Stents, into Hepatic or Bile Ducts - YG04B; YG04A; YG02Z (106) |
| Diarrhoea | £3,735.08 | £4,337.53 | £5,216.82 | NEI LS - Nutritional Disorders without Interventions - FD04E; FD04D; FD04C (106) |
| Ejection fraction decreased | £2,849.56 | £2,956.56 | £3,430.62 | NEI LS - Heart Failure or Shock - EB03E; EB03D; EB03C (106) |
| Fatigue | £2,491.26 | £2,935.07 | £3,380.10 | NEI LS - Iron Deficiency Anaemia - SA04K; SA04J; SA04H (106) |
| Febrile neutropenia | £3,729.32 | £4,255.51 | £6,288.05 | NEI LS - Agranulocytosis - SA35C; SA35B; SA35A (106) |
| Hypertension | £221.48 | £221.48 | £221.48 | WF01A consultant led follow up visit - medical oncology (service code 370) (106) |

| AE | Grade 3 | Grade 4 | Grade 5 | National Cost Collection Code |
|---|---|---|---|---|
| Infection | £7,909.81 | £9,979.90 | £11,829.77 | NEI LS - Sepsis with multiple interventions - WJ06C; WJ06B; WJ06A (106) (18) |
| Neutropenia | £3,729.32 | £4,255.51 | £6,288.05 | NEI LS - Agranulocytosis - SA35C; SA35B; SA35A (106) |
| Vomiting | £3,735.08 | £4,337.53 | £5,216.82 | NEI LS - Nutritional Disorders without Interventions - FD04E; FD04D; FD04C (106) |

Abbreviations: AE, adverse event.

### 3.5.4 Miscellaneous unit costs and resource use

#### *3.5.4.1 IHC3+ testing cost for zanidatamab*

NGS panel testing and/or IHC testing at diagnosis can determine if a patient has HER2+ BTC. NGS panel testing for common mutations (including IDH1, FGFR2, NTRK and HER2) is already done routinely in the NHS for patients diagnosed with BTC to determine the appropriateness of later lines of therapy, as HER2/ERBB2 is included in the National Genomic Testing Directory small panel for CCA (see Section 1.3.3.3). In order for a patient to be eligible for zanidatamab, a patient must have confirmed HER2+ tumour status defined as a score of 3+ by IHC (1). The biopsy required for this IHC test is recommended by clinical guidelines to be conducted as early as possible at diagnosis. IHC HER2+ testing is already carried out routinely for breast and gastric cancers in the NHS, and is already commonly performed for BTC. Half of 14 UK clinicians consulted in the Delphi panel stated it was undertaken routinely in their clinical practice already. As such, no additional cost would be incurred for HER2+ patients to assess their eligibility for zanidatamab at 2L. However, as it is still not routine in all practices, the cost of IHC testing has been included in the model base case. Its exclusion is tested in scenario analysis (Section 3.10.3).

The total IHC testing cost is calculated using the expected incidence rate of IHC3+ in patients with HER2+ BTC and the unit cost per IHC test. The expected cost of identifying a patient with IHC3+ is the expected cost per patient tested multiplied by: 1/the expected incidence of IHC3+ disease. This value is then applied to the zanidatamab arm as a one-off lump sum in the first model cycle. **Table 77** provides a summary of the inputs used to calculate the total IHC testing cost.

**Table 77: IHC testing costs**

| | Input | Source |
|---|---|---|
| (a) IHC test cost | £40.00 uplifted to £47.41 | NHS 2017, uplifted to 2023/24 costs using PSSRU 2024 inflation indices (107, 111) |
| (b) IHC3+ incidence | 77.5% | HERIZON-BTC-01 (22) |
| Total IHC test cost | £61.18 | Calculation a*(1/b) |

Abbreviations: IHC, immunohistochemistry; PSSRU, Personal Social Services Research Unit.

#### *3.5.4.2 DPYD testing for FOLFOX*

Before 5FU is started, all patients treated with this chemotherapy in the UK NHS must also have a one-off DPYD genetic test to determine if dose reductions are needed due to DPD deficiency (23, 48). Fluoropyrimidines (like 5FU) are antimetabolite chemotherapies which have a narrow therapeutic window between minimum effective and maximum tolerated doses. Variants in the DPYD gene have been associated with reduced enzyme activity (which plays a key role in fluoropyrimidine drugs) which can lead to an increased risk of severe or fatal toxicity in patients receiving these treatments (48).

Therefore, the cost of a DPYD test for patients treated with FOLFOX is included in the model base case. A cost of £100 is included in the model as an upfront cost for all FOLFOX + ASC patients (112, 113).

#### *3.5.4.3 Subsequent treatments*

Clinical experts stated that very few patients would receive subsequent treatment after progressing on 2L treatment but a small number (approximately 20 to 25%) may receive some form of treatment if they are fit and well enough (69).

The clinicians stated that without access to HER2-targeted treatments, patients would most likely receive FOLFIRI after FOLFOX treatment. If zanidatamab were the 2L treatment, then patients would be offered FOLFOX at their 3L treatment (69). In the ABC-06 trial which is UK based, 13% of patients received subsequent treatment; 3% in the form of phase 1 treatments, and 10% received subsequent chemotherapy (21).

Subsequent treatment mix in the model base case is from UK clinical opinion. It is assumed that 25% of patients receive subsequent therapy after progression on zanidatamab or FOLFOX treatment. Note that this is likely to be an overstatement based on the data from ABC-06, where 13% of the total patients received a subsequent line of treatment. In the base case, if patients are already receiving only ASC, then it is assumed that they would not be fit enough for further treatment and do not receive subsequent treatment costs. After FOLFOX, all patients receiving subsequent treatment are assumed to receive FOLFIRI, whereas those receiving

subsequent treatment after zanidatamab are assumed to receive FOLFOX. The subsequent treatment costs for FOLFOX and FOLFIRI are presented in **Table 78**.

A scenario is explored which uses the distributions of subsequent treatments as per the trial data (HERIZON-BTC-01 and ABC-06). This scenario is described further in Appendix Q.

**Table 78: Subsequent treatment costs**

| Subsequent treatment | | Dose | Duration, months | Total cost, £ | Source |
|---|---|---|---|---|---|
| FOLFOX | Oxaliplatin | 85 mg/m2 Q2W | 3.91 | 2,994.13 | Lamarca (2021) (21) |
| | 5FU | 400 mg/m2 Q2W | | 26.28 | |
| | 5FU | 46-hour continuous 2,400 mg/m2 IV infusion Q2W | | 1,419.42 | |
| | Leucovorin (FA) | 350 mg Q2W | | 1,352.12 | |
| FOLFIRI | Irinotecan | 180 mg/m2 Q2W | 1.38 | 1,115.81 | Caparica (2019) (114) |
| | 5FU | 400 mg/m2 Q2W | | 18.19 | |
| | 5FU | 48- hour continuous 2,400 mg/m2 IV infusion | | 489.59 | |
| | Leucovorin (FA) | 200 mg/m2 Q2W | | 580.44 | |

Abbreviations: 5FU, fluorouracil; FA, folinic acid; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; Q2W, every 2 weeks.

#### *3.5.4.4 End-of-life*

A one-off terminal care cost was applied in the economic model which was assumed to account for the costs of supporting patients in a palliative (end-of-life) setting, immediately before death. The same cost is applied to all treatment arms, to the proportion of patients who enter the death health state in each cycle.

The end-of-life cost was taken from a recent report from Cummins (2025) (57). Marie Curie commissioned Nuffield Trust and the Health Economic Unit to estimate the range of public expenditure that supports the care of people in their last year of life in the UK. The report states a mean cost per person among three health sectors in England (health care, social care and social security). The total end of life health

care and social care cost was reported as £24,920.00 which has been uplifted to 2023/204 costs to £25,779.74.

## *3.6 Severity*

HER2+ BTC is a rare cancer, and patients have a poor prognosis as the majority do not survive beyond 1-year from diagnosis (6). Patients with advanced BTC have considerably lower QoL compared to those without BTC and the impact of diagnosis can have devastating consequences to patients and their families, driven by the poor prognosis and highly burdensome symptoms (4, 7, 10). There is a clear unmet need for patients with HER2+ advanced or metastatic BTC who urgently need effective 2L targeted therapies.

In line with the NICE 2022 methods guide (82), the absolute and proportional QALY shortfall associated with current SoC in patients with advanced HER2+ BTC who have previously been treated compared with the general population was calculated. These estimates were obtained using the R-Shiny tool developed by Schneider (2021) (115). The published QALY shortfall tool provides 5 methods for estimating population quality-adjusted life expectancy. The reference case uses the ONS with an EQ-5D-3L value set and Health Survey for England data from 2014 (91, 116, 117). Further descriptions of the methods can be found within the published tool (115).

A summary of the characteristics used to estimate lifetime QALYs without disease in the population are informed by the patient baseline characteristics (see Section **3.2.1**) and are presented in **Table 79**.

**Table 79: Summary features of QALY shortfall analysis**

| Factor | Value | Reference to section in submission |
|---|---|---|
| Sex distribution, female % | 55% | Section 3.2.1 |
| Starting age | 62 years | |

Abbreviations: QALY, quality-adjusted life year.

The utility values from the economic model for the comparators are based on TTD days per model cycle (see Section **3.4.5.5**, **Figure 37**).

The total remaining discounted QALYs for patients treated with the comparators were taken from the cost-effectiveness model results (and input into the QALY shortfall tool to two decimal places). Using the patient characteristics and the reference case QALY shortfall method, the estimated total QALYs for the general population (without the disease) is 14.75. The absolute and proportional QALY shortfalls for patients treated with both comparators meet the threshold of a QALY weight of 1.7 (**Table 80**). This is also consistent with the severity modifier accepted

in the TA948 ivosidenib submission which also compared to FOLFOX + ASC, and ASC alone as SoC.

**Table 80: Summary of QALY shortfall analysis**

| Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | QALY shortfall |
|---|---|---|
| 14.75 | FOLFOX: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY: x1.7 |
| | ASC: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY: x1.7 |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; QALY, quality-adjusted life year.

## *3.7 Uncertainty*

BTC is a rare cancer, and HER2+ BTC is exceptionally rare, accounting for 5 to 10% of CCAs and up to 20% of GBC (3, 25). Due to the rarity of the disease, no direct evidence of the efficacy of zanidatamab compared to UK SoC were available and limited comparator data was available with the correct mutation. This is demonstrated in the ABC-06 study which did not report mutation-specific BTC data (21) but supportive evidence in this submission is provided by the external control arm study, which only included patients with HER2+ IHC3+ BTC (71).

Nevertheless, efficacy, safety and utility data are available from a large single arm trial in the relevant population for zanidatamab, which shows a clinically meaningful benefit in patients treated with 1 or more lines of therapy (see Section **2.6**). This is also supported by 2 investigator-led real-world studies of patients treated with zanidatamab in clinical practice (60, 61). Multiple approaches to assess comparative efficacy have been attempted, which all demonstrate a substantial survival benefit of zanidatamab compared to FOLFOX + ASC and ASC alone when compared naively, using a MAIC or using a real-world external control arm analysis.

The model base case has been informed by structured expert elicitation, as well as external validation and exploration of uncertainty through the use of alternative comparative approaches. Extensive sensitivity analyses have also been performed to test the structural and parameter uncertainty with a summary of components and approaches tested. More conservative assumptions continue to demonstrate the clinical and cost-effectiveness of zanidatamab versus FOLFOX + ASC and ASC alone.

## 3.8 Summary of base-case analysis inputs and assumptions

### 3.8.1 Summary of base-case analysis inputs

A summary of inputs from the base case analysis are presented in Table 81.

**Table 81: Summary of variables applied in the economic model**

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| **Model settings** | | | |
| Time horizon (years) | 30 | Varied in scenario analysis | Section 3.2.2.1 |
| Model cycle length (weeks) | 1 | Not varied | |
| Annual discount rate: Costs | 1.5% | Varied in scenario analysis | |
| Annual discount rate: QALYs | 1.5% | Varied in scenario analysis | |
| **Patient characteristics** | | | |
| Age (mean, years) | [redacted] | Not varied | Section 3.3.1 |
| Proportion female (%) | [redacted] | Not varied | |
| Height (mean, cm) | [redacted] | Not varied | |
| BSA (m) | [redacted] | Not varied | |
| Weight (mean, kg) | [redacted] | Not varied | |
| **Drug costs** | | | |
| RDI: Zanidatamab | [redacted] | [redacted] (Normal) | Section 3.5.1.1 |
| Zanidatamab (300 mg) | £[redacted] | Not varied | |
| Oxaliplatin (50 mg) | £6.48 | 6.3 - 6.66 (Normal) | |
| Oxaliplatin (100 mg) | £14.27 | 13.95 - 14.59 (Normal) | |
| Oxaliplatin (200 mg) | £11.31 | 10.99 - 11.63 (Normal) | |
| 5FU (500 mg) | 3.26 | 3.25 - 3.27 (Normal) | |
| 5FU (1000 mg) | £3.20 | 3.18 - 3.21 (Normal) | |
| 5FU (2500 mg) | £4.62 | 4.6 - 4.65 (Normal) | |
| 5FU (5000 mg) | £6.27 | 6.24 - 6.29 (Normal) | |
| Leucovorin (50 mg) | £20.00 | 16.08 - 23.92 (Normal) | |
| Leucovorin (100 mg) | £37.50 | 30.15 - 44.85 (Normal) | |
| Leucovorin (300 mg) | £100.00 | 80.4 - 119.6 (Normal) | |
| Leucovorin (350 mg) | £161.15 | 129.57 - 192.73 (Normal) | |
| **Administration costs** | | | |
| Oral | £240.44 | 193.32 - 287.57 (Normal) | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Simple IV | £133.39 | 107.24 - 159.53 (Normal) | Section 3.5.1.2 |
| Complex (pro-longed) | £337.16 | 271.08 - 403.24 (Normal) | |
| Nurse | £157.13 | 126.34 - 187.93 (Normal) | |
| PICC insertion and complication costs | £1,701.32 | 1367.87 - 2034.78 (Normal) | |
| Portacath insertion and complications costs | £2,014.91 | 1619.99 - 2409.82 (Normal) | |
| Proportion receiving PICC vs Portacath device | 50% | 40% - 60% (Beta) | |
| **IHC3+ testing costs** | | | |
| Incidence of IHC3+ in HER2+ BTC | 77.5% | 61% - 91% (Beta) | Section 3.5.4.1 |
| Current proportion of patients tested | 0.0% | 0% - 0% (Beta) | |
| New proportion of patients tested | 100.0% | 100% - 100% (Beta) | |
| Proportion receiving NHS genetic testing | 0.0% | 0% - 0% (Beta) | |
| NHS genetic testing cost | £37.69 | 30.30 – 45.07 (Normal) | |
| Proportion receiving IHC/ISH test | 100.0% | 100% - 100% (Beta) | |
| IHC/ISH test cost | £47.41 | 38.12 – 56.71 (Normal) | |
| Proportion receiving Next Generation Sequencing | 0.0% | 0% - 0% (Beta) | |
| Next Generation Sequencing cost | £0.00 | 0.00 – 0.00 (Normal) | |
| **DPYD testing cost** | | | |
| Cost per test | £100.00 | 80.40 – 119.60 (Normal) | Section 3.5.4.2 |
| **Pre-medication costs** | | | |
| Corticosteroids (hydrocortisone) (20 mg) | £1.60 | 1.56 - 1.64 (Normal) | Section 3.5.1.1 |
| Antihistamines (Cinnarizine) (15 mg) | £4.05 | 4.04 - 4.05 (Normal) | |
| Paracetamol (500 mg) | £1.22 | 1.22 - 1.23 (Normal) | |
| Dexamethasone (IV) (3.3 mg) | £3.08 | 3.07 - 3.1 (Normal) | |
| Dexamethasone (oral) (2 mg) | £2.38 | 2.37 - 2.38 (Normal) | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Ondansetron hydrochloride (IV) (8 mg) | £3.06 | 3.03 - 3.09 (Normal) | |
| Ondansetron hydrochloride (oral) (8 mg) | £0.67 | 0.67 - 0.68 (Normal) | |
| Metoclopramide hydrochloride (10 mg) | £0.43 | 0.43 - 0.43 (Normal) | |
| **Healthcare resource use costs** | | | |
| Oncologist | £192.95 | 155.13 - 230.77 (Normal) | Section 3.5.2.1 |
| Complete blood count test | £8.04 | 6.47 - 9.62 (Normal) | |
| CT scan | £123.03 | 98.92 - 147.14 (Normal) | |
| Morphine (1mg) | £5.24 | 4.21 - 6.27 (Normal) | |
| MRI scan | £202.40 | 162.73 - 242.07 (Normal) | |
| Echocardiography | £115.56 | 92.91 - 138.2 (Normal) | |
| Liver function test | £8.04 | 6.47 - 9.62 (Normal) | |
| **Healthcare resource use frequency** | | | |
| PF: Oncologist | 4.00 | 3.22 - 4.78 (Normal) | Section 3.5.2.1 |
| PF: Complete blood count test | 4.00 | 3.22 - 4.78 (Normal) | |
| PF: CT scan | 4.00 | 3.22 - 4.78 (Normal) | |
| PF: Morphine (1 mg) | 0.00 | 0 - 0 (Normal) | |
| PD: Oncologist | 4.00 | 3.22 - 4.78 (Normal) | |
| PD: Complete blood count test | 4.00 | 3.22 - 4.78 (Normal) | |
| PD: CT scan | 1.00 | 0.8 - 1.2 (Normal) | |
| PD: Morphine (1 mg) | 365.25 | 293.66 - 436.84 (Normal) | |
| **Special monitoring** | | | |
| QT interval monitoring: Echocardiography | 2.00 | 1.61 - 2.39 (Normal) | Section 3.5.2.2 |
| Haematological monitoring: Complete blood count test | 30.00 | 24.12 - 35.88 (Normal) | |
| Liver function test frequency | 0.58 | 0.47 - 0.7 (Normal) | |
| **Adverse event costs** | | | |
| ***Grade 3*** | | | |
| Acute kidney injury | £5,007.04 | 4025.68 - 5988.4 (Normal) | Section 3.5.3 |
| Anaemia | £2,491.26 | 2002.99 - 2979.54 (Normal) | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Aspartate aminotransferase increased | 0.00 | 0 - 0 (Normal) | |
| Biliary event | £7,430.87 | 5974.44 - 8887.29 (Normal) | |
| Diarrhoea | £3,735.08 | 3003.01 - 4467.14 (Normal) | |
| Ejection fraction decreased | £2,849.56 | 2291.06 - 3408.06 (Normal) | |
| Fatigue | £2,491.26 | 2002.99 - 2979.54 (Normal) | |
| Hypertension | 221.48 | 178.07 - 264.88 (Normal) | |
| Infection | £7,909.81 | 6359.51 - 9460.1 (Normal) | |
| Neutropenia | £3,729.32 | 2998.39 - 4460.26 (Normal) | |
| Vomiting | £3,735.08 | 3003.01 - 4467.14 (Normal) | |
| ***Grade 4*** | | | |
| Aspartate aminotransferase increased | 0.00 | 0 - 0 (Normal) | Section 3.5.3 |
| Febrile neutropenia | £4,255.51 | 3421.44 - 5089.57 (Normal) | |
| Infection | £9,979.90 | 8023.88 - 11935.92 (Normal) | |
| Neutropenia | £4,255.51 | 3421.44 - 5089.57 (Normal) | |
| ***Grade 5*** | | | |
| Acute kidney injury | £8,070.52 | 6488.73 - 9652.32 (Normal) | Section 3.5.3 |
| Febrile neutropenia | £6,288.05 | 5055.62 - 7520.49 (Normal) | |
| Infection | £11,829.77 | 9511.17 - 14148.36 (Normal) | |
| **Adverse event frequency** | | | |
| Anaemia Grade 3 frequency: Zanidatamab | [redacted] | [redacted] | Section 3.3.3 |
| Aspartate aminotransferase increased Grade 3 frequency: Zanidatamab | [redacted] | [redacted] | |
| Diarrhoea Grade 3 frequency: Zanidatamab | [redacted] | [redacted] | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Ejection fraction decreased Grade 3 frequency: Zanidatamab | [redacted] | [redacted] | |
| Aspartate aminotransferase increased Grade 4 frequency: Zanidatamab | [redacted] | [redacted] | |
| Acute kidney injury Grade 3 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Anaemia Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Biliary event Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Diarrhoea Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Fatigue Grade 3 frequency: FOLFOX | 11.11% | 0.05 - 0.19 (Beta) | |
| Hypertension Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Infection Grade 3 frequency: FOLFOX | 7.41% | 0.03 - 0.14 (Beta) | |
| Neutropenia Grade 3 frequency: FOLFOX | 9.88% | 0.04 - 0.17 (Beta) | |
| Vomiting Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Febrile neutropenia Grade 4 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Infection Grade 4 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Neutropenia Grade 4 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Acute kidney injury Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Febrile neutropenia Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Infection Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Acute kidney injury Grade 3 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Anaemia Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Biliary event Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Diarrhoea Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Fatigue Grade 3 frequency: FOLFOX | 11.11% | 0.05 - 0.19 (Beta) | |
| Hypertension Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Infection Grade 3 frequency: FOLFOX | 7.41% | 0.03 - 0.14 (Beta) | |
| Neutropenia Grade 3 frequency: FOLFOX | 9.88% | 0.04 - 0.17 (Beta) | |
| Vomiting Grade 3 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Febrile neutropenia Grade 4 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Infection Grade 4 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Neutropenia Grade 4 frequency: FOLFOX | 2.47% | 0.00 - 0.07 (Beta) | |
| Acute kidney injury Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Febrile neutropenia Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| Infection Grade 5 frequency: FOLFOX | 1.23% | 0.00 - 0.05 (Beta) | |
| **Adverse event disutility** | | | |
| Acute kidney injury | -0.05 | -0.05 - -0.05 (Beta) | Section 3.4.4 |
| Anaemia | -0.09 | 0.00 - -0.65 (Beta) | |
| Aspartate aminotransferase increased | 0.00 | 0.00 – 0.00 (Beta) | |
| Biliary event | -0.09 | 0.00 - -0.65 (Beta) | |
| Diarrhoea | -0.10 | -0.08 - -0.12 (Beta) | |
| Ejection fraction decreased | -0.02 | -0.02 - -0.02 (Beta) | |
| Fatigue | -0.09 | 0.00 - -0.65 (Beta) | |
| Febrile neutropenia | -0.15 | -0.12 - -0.18 (Beta) | |
| Hypertension | -0.04 | -0.03 - -0.04 (Beta) | |
| Infection | -0.22 | -0.18 - -0.26 (Beta) | |
| Neutropenia | -0.06 | -0.05 - -0.07 (Beta) | |
| Vomiting | -0.05 | -0.02 - -0.08 (Beta) | |
| **Adverse event duration (days)** | | | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Acute kidney injury | [redacted] | [redacted] | Section 3.4.4 |
| Anaemia | [redacted] | [redacted] | |
| Aspartate aminotransferase increased | [redacted] | [redacted] | |
| Biliary event | [redacted] | [redacted] | |
| Diarrhoea | [redacted] | [redacted] | |
| Ejection fraction decreased | [redacted] | [redacted] | |
| Fatigue | [redacted] | [redacted] | |
| Febrile neutropenia | [redacted] | [redacted] | |
| Hypertension | [redacted] | [redacted] | |
| Infection | [redacted] | [redacted] | |
| Neutropenia | [redacted] | [redacted] | |
| Vomiting | [redacted] | [redacted] | |
| **Subsequent treatments** | | | |
| Irinotecan unit cost | 8.99 | 8.76 – 9.21 (Normal) | Section 3.5.4.3 |
| Zanidatamab % receiving FOLFOX | 100% | Varied in scenario analysis | |
| FOLFOX + ASC % receiving FOLFIRI | 100% | Varied in scenario analysis | |
| Proportion receiving subsequent treatment | 25% | 0.20 – 0.30 (Beta) | |
| **Terminal care cost** | | | |
| Terminal care | £24,920.00 | 23000.52 – 26839.48 (Normal) | Section 3.5.4.4 |
| **Utility values** | | | |
| TTD utilities | - | Multivariate normal | Section 3.4.2.2 |
| ASC disutility | [redacted] | [redacted] (Beta) | Section 3.4.5.2 |
| FOLFOX disutility | [redacted] | [redacted] (Beta) | |

| Variable | Value | Measurement of uncertainty and distribution: confidence interval (distribution) | Reference to section in submission |
|---|---|---|---|
| Portacath disutility | -0.013 | -0.01 - -0.02 (Beta) | Section 3.4.5.4 |
| **FOLFOX treatment duration (months)** | | | |
| Median treatment duration | 2.30 | 1.85 - 2.75 (Normal) | Section 3.3.2.4 |
| Median PFS | 4.00 | 3.22 - 4.78 (Normal) | |
| **Efficacy** | | | |
| Zanidatamab OS | Log-logistic | Multivariate normal | Section 3.3.2 |
| Zanidatamab PFS | Log-logistic | Multivariate normal | |
| Zanidatamab ToT | Gamma | Multivariate normal | |
| FOLFOX + ASC OS | Log-normal | Multivariate normal | |
| FOLFOX + ASC PFS | Log-normal | Multivariate normal | |
| ASC OS | Log-logistic | Multivariate normal | |
| HR – Zanidatamab vs ASC OS | [redacted] | [redacted] (Log-normal) | |

Abbreviations: 5FU, fluorouracil; ASC, active symptom control; BSA, body surface area; BTC, biliary tract cancer; CT, computed tomography; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PICC, peripherally-inserted central catheter; ToT, time on treatment; TTD, time to death.

### 3.8.2 Assumptions

Table 82 presents a summary of key modelling assumptions.

**Table 82: Summary of key modelling assumptions**

| Topic | Key assumption | Justification |
|---|---|---|
| Cycle length | 1 week is appropriate | Assumed to be sufficiently short enough to represent the frequency of clinical events and interventions and is aligned with the administration of the multiple treatments included within the model (treatment cycles in weeks). |
| Time horizon | A lifetime time horizon of 30 years is appropriate | 30 years reflects the maximum lifetime of patients based on a starting age of 62.5 years. The impact of varying time horizon on the results was tested in sensitivity analysis. |
| Comparators | ASC costs not included as they are assumed to apply to all treatments | Costs for ASC procedures are not explicitly included in the model, as they would be expected to be the same on all treatment arms and therefore not impact the modelled outcomes. |
| | RDI = [redacted] for comparators missing values | The assumptions ensure that all treatments have a dose intensity value. |

| Topic | Key assumption | Justification |
|---|---|---|
| Efficacy | It is assumed that a naive comparison is more appropriate | No direct (head-to-head) evidence are available comparing zanidatamab with FOLFOX or ASC.<br>Due to limitations of the ITC relating to HER2 status and treatment line, the naive approach was considered more informative. |
| Adverse events | Cohort 1 was used to inform the zanidatamab AEs from HERIZON-BTC-01 | This utilises the most data and it is unlikely that AEs would differ by IHC2+ or 3+ status. |
| Disutilities | Disutilities for AEs are assumed the same between Grade 3 – 4 AEs and durations are assumed the same between zanidatamab and FOLFOX + ASC | Due to lack of evidence. This is a conservative assumption, and is likely to underestimate the disutility of the AEs for FOLFOX compared with zanidatamab based on the more severe safety profile of FOLFOX + ASC in comparison. |
| Survival curves | ASC PFS HR is assumed to be the same HR as OS from the MAIC. | PFS for ASC was not reported in the ABC-06 trial therefore assumptions were required to estimate the PFS. |
| | ToT data for FOLFOX was assumed the same as PFS. | ToT KM data for FOLFOX was not reported therefore alternative approaches were considered. Structured expert elicitation determined that the use of PFS as proxy was appropriate. |
| | Identification of the most appropriate survival curves describing OS, PFS and ToT | Extensive analyses have been undertaken to identify appropriate survival curves describing the efficacy of each treatment, with reference to the guidance from the NICE DSU. However, to address the uncertainty around these parameters, scenario analyses have been conducted by applying alternative assumptions around extrapolations. Clinical validation was also sought to ensure extrapolations were clinically plausible using structured expert elicitation in line with TSD26 via a Delphi panel (86). |
| Utility | Utility values are informed by HERIZON-BTC-01 cohort 1 data | These values were derived from the appropriate patient population and utilises more patient data than subgrouping by IHC3+. EQ-5D-3L is the preferred utility measure as per NICE reference case. |
| | TTD utility approach was used for the base case | The TTD approach has been extensively used and accepted by NICE in previous technology appraisals like TA997 (92), TA983 (93), and many others, as it may better capture the deterioration in QoL as patients approach death than the progression-based utilities (94). |
| | Health-state utility values for FOLFOX and ASC were | Patients treated with FOLFOX or just have ASC alone are likely to have worse QoL. The toxicity of FOLFOX and associated |

| Topic | Key assumption | Justification |
|---|---|---|
| | assumed to be lower than zanidatamab | impact isn't always captured within Grade 3+ AEs i.e. more frequent Grade 1 or 2 AEs can impact QoL more than few Grade 3 AEs. Patients not on active treatment are likely to progress faster due to lack of disease control. |
| | AE disutility duration for FOLFOX was assumed to be the same as zanidatamab from HERIZON-BTC-01 | Data for AE durations for FOLFOX were not reported. Due to the higher severity of AEs for FOLFOX versus zanidatamab it is likely that the durations will be longer for FOLFOX patients, therefore this assumption is conservative. |

Abbreviations: AE, adverse event; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; IHC, immunohistochemistry; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.

## *3.9 Base-case results*

### 3.9.1 Base-case incremental cost-effectiveness analysis results

Base case results with PAS demonstrate that targeted treatment with zanidatamab is more costly, but more effective than chemotherapy or ASC, associated with deterministic ICERs of £[redacted] versus FOLFOX + ASC and £[redacted] versus ASC.

The base case deterministic results (with and without PAS discount for zanidatamab) are presented in **Table 83** and **Table 84** with net health benefit (NHB) results provided in **Table 85** (at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained). It should be noted that the population considered meets the criteria for the severity modifier, resulting in a QALY weighting of x1.7, which is reflected in the results.

Zanidatamab is associated with respective life year (LY) and QALY gains (including the severity modifier) of [redacted] and [redacted] compared to FOLFOX + ASC, increasing to LY and QALY gains of [redacted] and [redacted] when compared to ASC alone, demonstrating a substantial improvement in survival with zanidatamab treatment. The majority of the QALY gain with zanidatamab is due to patients living significantly longer on targeted treatment compared with combination chemotherapy with FOLFOX + ASC or palliative care with ASC alone, accompanied by reduced treatment-specific disutility from the improved tolerability profile of zanidatamab versus FOLFOX.

At a WTP of £30,000/QALY with the severity modifier also applied, the NHB is greater than 0 versus FOLFOX + ASC thus indicating zanidatamab increases the

overall population health whilst remaining cost-effective compared to current treatment options.

**Table 83: Base-case results (without PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs (x1.7 severity modifier) | 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.

**Table 84: Base-case results (with PAS)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs (x1.7 severity modifier) | 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.

**Table 85: Net health benefit (with PAS)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs (x1.7 severity modifier) | NHB at £20,000 | NHB at £30,000 |
|---|---|---|---|---|---|---|
| Zanidatamab | [redacted] | [redacted] | | | | |
| FOLFOX + ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; NHB, net health benefit; PAS, patient access scheme.

## *3.10 Exploring uncertainty*

### 3.10.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through a probabilistic sensitivity analysis (PSA). In PSA, all parameters are simultaneously varied from an assigned distribution and random inputs are drawn. Results were sampled across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty (assessed by visual inspection of convergence plots in the submitted cost-effectiveness model).

Mean results from the PSA including PAS are presented in **Table 86** and the cost-effectiveness planes versus FOLFOX and ASC are presented in **Figure 38** and **Figure 39** respectively. The probabilistic results are consistent with those observed in the deterministic analysis, and with the PAS are below the threshold that NICE considers a cost-effective use of NHS resources.

**Table 86: Mean PSA results (including PAS)**

| Technologies | Total | | | Incremental | | | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs (x1.7 severity modifier) | |
| 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; PAS, patient access scheme; PSA, probabilistic sensitivity analysis.

**Figure 38: Pairwise cost-effectiveness plane (including PAS) - zanidatamab versus FOLFOX + ASC**

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

**Figure 39: Pairwise cost-effectiveness plane (including PAS) - zanidatamab versus ASC**

Abbreviations: ASC, active symptom control; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

The cost-effectiveness acceptability curves are presented in **Figure 40** for zanidatamab versus FOLFOX and **Figure 41** versus ASC. At a WTP threshold of £30,000, the probability that zanidatamab is cost-effective compared to FOLFOX + ASC is [redacted]% and [redacted]% compared to ASC.

**Figure 40: Cost-effectiveness acceptability curve (including PAS) – zanidatamab versus FOLFOX + ASC**

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PAS, patient access scheme; WTP, willingness-to-pay.

**Figure 41: Cost-effectiveness acceptability curve (including PAS) – zanidatamab versus ASC**

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

### 3.10.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, holding all other parameters constant. Inputs were set to their upper and lower limits, while all other parameters were maintained at their base case setting. If the variance of a parameter was not available, a simplified assumption was made assuming that the standard error was 10% of the mean values. Correlated inputs with joint uncertainty, such as parametric survival models that are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

**Table 87** and **Figure 42** present the ICERs and tornado plots of the 10 parameters that had the largest influence on the incremental cost-effectiveness ratio (ICER) comparing zanidatamab to FOLFOX and those comparing zanidatamab to ASC are shown in **Table 88** and **Figure 43** respectively. Overall, all parameters varied had little impact on the ICERs; the parameters which had the largest impact for FOLFOX + ASC were the inputs for administration, time on treatment and RDI. Similar inputs had the largest impact for the ICER compared to ASC, with the addition of the treatment specific disutility.

**Table 87: OWSA results (including PAS) – zanidatamab versus FOLFOX + ASC**

| Parameter | ICER at lower bound (£) | ICER at upper bound (£) |
|---|---|---|
| RDI: Zanidatamab - Zanidatamab | [redacted] | [redacted] |
| PORT disutility | [redacted] | [redacted] |
| Administration cost: Proportion receiving PICC vs PORT device | [redacted] | [redacted] |
| Administration cost: Simple IV | [redacted] | [redacted] |
| Administration cost: Complex (pro-longed) | [redacted] | [redacted] |
| Infection Grade 3 frequency: FOLFOX | [redacted] | [redacted] |
| FOLFOX disutility | [redacted] | [redacted] |
| HCRU cost: Echocardiography | [redacted] | [redacted] |
| QT interval monitoring: Echocardiography | [redacted] | [redacted] |
| Infection Grade 5 frequency: FOLFOX | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HCRU, healthcare resource utilisation; ICER, incremental cost-effectiveness ratio; IV, intravenous; OWSA, one-way sensitivity analysis; PICC, peripherally-inserted central catheter.

**Figure 42: Tornado plot showing OWSA results on the ICER (including PAS) – zanidatamab versus FOLFOX + ASC**

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HCRU, health care resource use; ICER, incremental cost-effectiveness ratio; IV, intravenous; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PFS, progression-free survival; PORT, portacath; RDI, relative dose intensity; ToT, time on treatment.

**Table 88: OWSA results (including PAS) – zanidatamab versus ASC**

| Parameter | ICER at lower bound (£) | ICER at upper bound (£) |
|---|---|---|
| RDI: Zanidatamab - Zanidatamab | [redacted] | [redacted] |
| ASC disutility | [redacted] | [redacted] |
| Administration cost: Simple IV | [redacted] | [redacted] |
| Proportion receiving subsequent trt - Zanidatamab | [redacted] | [redacted] |
| HCRU cost: Morphine (1mg) | [redacted] | [redacted] |
| HCRU frequency (PD): Morphine (1mg) | [redacted] | [redacted] |
| HCRU cost: Oncologist | [redacted] | [redacted] |
| HR - PFS (INV) vs ASC | [redacted] | [redacted] |
| Diarrhoea Grade 3 frequency: Zanidatamab | [redacted] | [redacted] |
| Administration cost: Complex (pro-longed) | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; HCRU, healthcare resource utilisation; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INV, investigator assessment; IV, intravenous; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; trt, treatment.

**Figure 43: Tornado plot showing OWSA results on the ICER (including PAS) – zanidatamab versus ASC**

Abbreviations: ASC, active symptom control; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

### 3.10.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. Results of the scenario analyses are presented in **Table 89** for both comparators. When compared to FOLFOX + ASC, the majority of scenarios remained cost-effective within the range that NICE considers a cost-effective use of NHS resources. Exceptions included the use of alternative utility values, different OS curves and using matched data to inform zanidatamab's efficacy. The results of the scenarios had a small impact on the ICER compared to ASC alone. The key scenarios which had the largest impact was the use of different OS curves and use of the literature to inform utilities.

**Table 89: Scenario analysis results (including PAS)**

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | | Justification/plausibility of scenario |
|---|---|---|---|---|---|
| | | | FOLFOX | ASC | |
| **Base case** | | | [redacted] | [redacted] | N/A |
| Time horizon | 30 years | 20 years | [redacted] | [redacted] | To explore alternative time horizons. As the reference case is a lifetime horizon, up to 40 years may be plausible for patients with BTC. 40 years was used in TA722 and TA1005, and 20 years in TA948. |
| | | 40 years | [redacted] | [redacted] | |
| Discount rates | 1.5% for costs and QALYs | 3.5% | [redacted] | [redacted] | To explore the impact of using non-Green Book discount rates. |
| RDI | Included | Excluded | [redacted] | [redacted] | To explore impact if full dose of treatments are taken in clinical practice |
| IHC3+ testing | Included | Excluded | [redacted] | [redacted] | To explore impact of excluding IHC3+ testing cost; this scenario was specified in the NICE scope. Given IHC HER2 testing is already routine for patients with BTC in ~50% of NHS centres, patients are already being tested without zanidatamab, so excluding IHC3 testing costs could be justified and this scenario is clinically plausible. |
| Subsequent treatment source | UK clinical opinion | Trial data | [redacted] | [redacted] | To explore the distributions as per the clinical trials (HERIZON-BTC-01 and ABC-06). Given not all subsequent treatments are available in the UK, as subsequent treatments received in HERIZON-BTC-01 included trial medications and are unlikely to align with NHS practice, so these scenarios may not be clinically plausible. |
| Utility approach | | Progression-based | [redacted] | [redacted] | |

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | | Justification/plausibility of scenario |
|---|---|---|---|---|---|
| | | | FOLFOX | ASC | |
| | TTD – continuous (inverse square root) | TTD – continuous (TTD days) | [redacted] | [redacted] | To explore alternative utility approaches using the trial data and alternative values from the literature |
| | | TTD – continuous (log TTD) | [redacted] | [redacted] | |
| | | TTD – continuous (inverse exponential) | [redacted] | [redacted] | |
| | | TTD – continuous (TTD) | [redacted] | [redacted] | |
| | | TTD groupings | [redacted] | [redacted] | |
| | | McCarthy (2024) | [redacted] | [redacted] | |
| Age-adjusted disutilities | Included | Excluded | [redacted] | [redacted] | To explore the impact of excluding age-related disutility. |
| Treatment-related disutility | Included | Excluded | [redacted] | [redacted] | To explore the impact of excluding treatment-specific disutility. Given the well described impact on patient and carer QoL of combination chemotherapy with FOLFOX and the impact of having a PICC line which is included in this disutility, a FOLFOX-related disutility that is based on utility measures from a UK trial is clinically plausible, so this scenario may not be justifiable. |
| Zanidatamab OS curve | Log-logistic | Exponential | [redacted] | [redacted] | Exponential curve aligned closely with clinical opinion using structured expert elicitation so deemed the most clinically plausible. |

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | | Justification/plausibility of scenario |
|---|---|---|---|---|---|
| | | | FOLFOX | ASC | |
| Zanidatamab PFS curve | Log-logistic | Generalised gamma | [redacted] | [redacted] | Generalised gamma and Gompertz aligned the best with clinical opinion at 6, 12 and 36 months. |
| | | Gompertz | [redacted] | [redacted] | |
| Zanidatamab ToT curve | Gamma | Gompertz | [redacted] | [redacted] | Gompertz and Weibull had good fit to the data and were the most pessimistic curves which aligned with the observed data. |
| | | Weibull | [redacted] | [redacted] | |
| FOLFOX + ASC OS curve | Log-normal | Exponential | [redacted] | [redacted] | Exponential and generalised gamma had plausible estimates at 5-years according to structured clinical opinion |
| | | Generalised gamma | [redacted] | [redacted] | |
| FOLFOX + ASC PFS curve | Log-normal | Log-logistic | [redacted] | [redacted] | Log-logistic and gamma had plausible estimates at 1-year according to structured clinical opinion |
| | | Gamma | [redacted] | [redacted] | |
| FOLFOX + ASC ToT approach | Equal to PFS | Median ToT and PFS HR | [redacted] | [redacted] | No ToT data available for FOLFOX + ASC therefore alternative scenarios were developed to explore the impact. |
| ASC OS curve | Log-logistic | Log-normal | [redacted] | [redacted] | Log-normal was an alternative curve which visually fit the data well |
| PFS definition for zanidatamab | INV | ICR | [redacted] | [redacted] | To explore the impact of using the alternative PFS definition |
| Efficacy approach | Naive comparison | MAIC | [redacted] | [redacted] | No head-to-head comparison of zanidatamab and comparators therefore an ITC was explored |

Abbreviations: ASC, active symptom control; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.

## 3.11 Subgroup analysis

There are no subgroups considered within the CEA.

## 3.12 Benefits not captured in the QALY calculation

BTC is a devastating disease which not only affects patients but also has a huge impact on their families and carers, due to its poor prognosis and burdensome symptoms that impact on physical and cognitive functioning, work participation, and emotional wellbeing (4, 7, 10, 55). The majority of caregivers of patients with CCA report exhaustion, emotional difficulty, and minimal time for themselves (55). Carers face tough challenges such as managing the emotional or mental distress of caregiving and the pressure of understanding treatment options with 73% reporting some form of depression (55). This can also have a knock-on effect on carers who are also employed (55). Due to lack of robust carer QoL data, carer QALYs were not explicitly included in the model, so any effect of increased patient survival/QoL with zanidatamab as a chemotherapy-free treatment on the health and wellbeing of carers or other family members is not accounted for in the cost-effectiveness results but is unlikely to have an impact.

Around 22% of BTC patients are of working age, therefore not only does BTC impact the QoL of the patient and their carers, but can have a substantial economic impact by impacting their work status, which is not captured within the EQ-5D questionnaire (17, 55). No productivity costs are included in the model for patients (or carers), so any effect of zanidatamab's increased patient survival and impact on QoL as a chemotherapy-free treatment on the ability to work of patients (or carers) is not accounted for in the cost-effectiveness results.

BTC is associated with a greater incidence and worse survival for patients who are in the most socioeconomically deprived quintile at the time of diagnosis (6). Results split by socioeconomic group are not available, so a distributional CEA was not possible to show the impact of zanidatamab in deprived populations. However, given the disparity on outcomes in CCA regionally in England (6), the adoption of zanidatamab has the potential to reduce health inequalities experienced by patients with BTC who live in poorer communities.

There are a lack of targeted treatment options for patients with HER2+ BTC, with patients limited to standard 2L chemotherapies such as FOLFOX which have minimal impact on patient survival and are associated with considerable toxicity, poor tolerability, and are highly burdensome (14, 21). In HERIZON-BTC-01, zanidatamab demonstrated a clinically meaningful survival benefit in patients with HER2+ IHC3+ BTC treated with 1 or more previous lines of therapy, which is supported by RWE. In the comparative efficacy analyses, zanidatamab showed substantial benefit in PFS and OS comparison to FOLFOX + ASC and ASC alone.

The availability of zanidatamab, if approved, will also offer a life-extending treatment option for patients with advanced HER2+ BTC who are too unwell for burdensome treatment with chemotherapy and are limited to ASC.

## *3.13 Validation*

### 3.13.1 Validation of cost-effectiveness analysis

The cost-effectiveness model was quality assured by a senior health economist not involved in the model building who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The model was also subject to stress testing, using extreme scenarios to test for technical modelling errors and plausibility of results.

### 3.13.2 Expert validation of the cost-effectiveness analysis

As described in Section **2.3.3.1**, a 2-round Delphi study was conducted with 11 to 14 UK-based BTC clinical experts. Insights from the Delphi study were used to inform the economic analysis in terms of survival estimates, treatment comparators and subsequent therapies. A description of the Delphi study is provided in Section **2.3.3.1** and the full report is provided as a reference.

In addition to the Delphi study, virtual interviews were conducted with 8 UK clinical oncologists (see Section **2.3.3.2**). Insights from the clinical interviews were used to inform the economic analyses and included throughout this dossier. The full report is provided as a reference.

### 3.13.3 Validation of model outcomes

Internal and external validation of the CEA demonstrated that modelled OS and PFS estimates closely reflected observed outcomes and outcomes reported in the published literature (see Appendix H and Appendix R).

## *3.14 Interpretation and conclusions of economic evidence*

### 3.14.1 Summary of the cost-effectiveness evidence

The de novo model uses a 3-health state PSM that simulates patients with locally advanced or metastatic HER2+ IHC3+ BTC previously treated with at least 1 prior line of systemic therapy, and is considered to accurately reflect the disease progression of BTC. The cost-effectiveness analyses show that zanidatamab is a cost-effective treatment compared to current SoC for patients with previously treated locally advanced or metastatic HER2+ IHC3+ BTC.

Treatment options are limited for HER2+ BTC in 2L+ with only combination chemotherapy with FOLFOX available for patients who are well enough, which can

be associated with burdensome administration using a central venous access device and severe toxicity. As such, there is an unmet need for an effective HER2-targeted treatment option that is more tolerated by patients. Zanidatamab is a novel dual HER2-targeted bispecific antibody that represents a 'step change' in the 2L+ treatment of locally advanced or metastatic BTC, providing a targeted, chemotherapy-free option without the need for a central line for administration.

The HERIZON-BTC-01 trial demonstrates the clinical efficacy and favourable safety profile of zanidatamab and provides the survival, utility and AE data for the zanidatamab arm of the model. No head-to-head clinical data were available for the relevant comparators (FOLFOX + ASC or ASC alone); therefore, a naive comparison using the UK-based ABC-06 study informed the comparative efficacy in the base case, with a scenario analysis explored using the results of the MAIC. The results show a substantial OS benefit of over 11 months for zanidatamab when compared with FOLFOX + ASC and ASC alone in both the naive comparison and MAIC. Improved PFS of over 2 months was also shown for zanidatamab compared with FOLFOX + ASC in both scenarios (ASC PFS was not reported in ABC-06). These results were supported by analyses of an external control arm of HER2+ IHC3+ BTC patients treated with chemotherapy, which also demonstrated a longer median OS for zanidatamab. The trials also showed superior safety results for zanidatamab, with less severe AEs reported for those in the zanidatamab arm of the HERIZON-BTC-01 trial than those in the ABC-06 trial.

### 3.14.2 Strengths and limitations

BTC is a rare cancer with approximately 4,750 new cases each year in the UK, 79% of which are diagnosed at an advanced or metastatic stage. HER2 overexpression/amplification/mutation is only found in approximately 15% of BTC cases, and of these, approximately 77.5% are classified as IHC3+. Given the rarity of patients with HER2+ IHC3+ BTC, the limited number of trial patients and lack of direct comparator data there are some uncertainties of the cost-effectiveness. However, the methods and data used within the analyses are evidence-based or have been clinically validated, are in line with previous assessments for 2L targeted therapies, and are believed to be the most robust available for the UK setting to support decision making, in the context of a rare cancer with a high unmet need.

The ABC-06 study was identified as the best available evidence for the comparators as the study assessed FOLFOX + ASC versus ASC alone in UK patients; however, the main limitation of the comparisons is the differences in populations, specifically in the lack of information in regard to the number of patients with HER2+ BTC in the ABC-06 trial. Nevertheless, HER2 status has not been proven to be prognostic of patient outcomes in BTC, so survival of patients with HER2+ BTC is not expected to differ widely from non-HER2+ BTC populations.

To construct the MAIC, the zanidatamab population was reduced by 33% to align with the ABC-06 trial 2L only population, increasing the uncertainty. As such, due to these limitations, the naive approach was considered more appropriate for the base case with the MAIC tested in scenario analysis.

Independent parametric survival models were used to extrapolate OS and PFS HERIZON-BTC-01 study for zanidatamab and the ABC-06 study for FOLFOX + ASC and ASC. This approach avoids the need to rely on the proportional hazard assumption. The choice of base case curves was carefully considered based on structured expert elicitation according to NICE methodology to ensure the long-term estimates were plausible. The ABC-06 study reported robust results for both comparators; however, there were gaps in the available evidence, which necessitated assumptions. PFS for ASC alone was not published and ToT data for FOLFOX + ASC was not available. The estimation of PFS for ASC and ToT for FOLFOX + ASC was constructed through the best available evidence and alternative approaches tested in scenario analysis.

The model also includes comprehensive sensitivity and scenario analysis to explore the impact of parametric and methodological uncertainties on cost-effectiveness results.

### 3.14.3 Summary of cost-effectiveness results

Due to the severity of advanced BTC that has progressed on previous therapies, and the lack of a targeted therapy for patients with HER2+ disease, zanidatamab meets the criteria for the highest severity weighting; as such, a QALY weighting of ×1.7 is applied in the CEA.

In the base case, with-PAS ICERs compared to FOLFOX + ASC were £[redacted] per QALY gained and £[redacted] compared to ASC, suggesting that versus active treatment, zanidatamab is within the range that NICE considers a cost-effective use of NHS resources. The QALY gain vs. FOLFOX is [redacted], increasing to [redacted] vs. ASC alone. These substantial QALY gains at the end of life are due to increased LYs and improved QoL with zanidatamab, being a HER2-targeted and chemotherapy-free treatment without the need for a central venous access device for infusion. With FOLFOX + ASC, QoL is reduced due to increased incidence of severe AEs with combination chemotherapy. QoL is also reduced with ASC alone due to lack of effective treatment options and disease control. Sensitivity analyses demonstrate the robustness of cost-effectiveness results. Zanidatamab remains cost-effective across most modelled scenarios at the £30,000/QALY threshold.

### 3.14.4 Conclusions

In summary, results suggest that zanidatamab is a cost-effective 2L treatment compared with FOLFOX + ASC for patients with previously treated locally advanced

or metastatic HER2+ IHC3+ BTC. In most modelled scenarios, ICERs were within the range that NICE considers a cost-effective use of NHS resources, especially when assessing rare, severe cancers with a high unmet need, such as advanced BTC.

HER2-targeted monotherapy with zanidatamab is more costly, but more effective than FOLFOX + ASC, or ASC alone; as a result of substantial survival gains of over 11 months and improvement in overall QoL with zanidatamab due to its favourable tolerability profile as a chemotherapy-free, targeted treatment.

Given the rarity and severity of advanced HER2+ IHC3+ BTC, fewer than [redacted] patients are likely to be eligible for zanidatamab, so the budget impact in NHS England will be low.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

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

# Summary of Information for Patients (SIP)

**July 2025**

| Template version | Date amended | Changes since previous version |
|---|---|---|
| 2.0 | Dec 2023 | Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness. |

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID6388_Zanidatamab _SIP_Final_22July2025 [noCON]** | **1.0** | **No** | **22nd July 2025** |

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

### SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

| |
|---|
| Generic name: Zanidatamab<br>Brand name: ZIIHERA® |

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

If recommended by NICE, zanidatamab will be used to treat adults with biliary tract cancer (a cancer of the structures that store, transport, and release bile; including bile duct cancer, gallbladder cancer, and ampullary cancer), when:

- A sample of the tumour (taken during a biopsy) has been tested, using a technique called immunohistochemistry (IHC) or other accepted test, and found to have the highest level of a protein called human epidermal growth factor receptor 2 on its surface (known as HER2-positive), shown by a score of 3+ (known as 'IHC3+'), and
- The cancer cannot be removed by surgery and has spread into nearby tissues or lymph nodes (locally advanced) or to other parts of the body (metastatic disease), and
- The cancer has returned or worsened after at least 1 previous course of anti-cancer medicine (typically chemotherapy with cisplatin and gemcitabine in combination with durvalumab immunotherapy).

Zanidatamab is a type of medicine that is known as a 'targeted treatment', which means that it has been designed to recognise and attach to the HER2 protein on the cancer cells, which may slow or stop the cancer cells from growing and/or may kill them.

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

UK marketing authorisation (official UK approval for a medicine to be made available for patients) from the UK Medicines and Healthcare Product Regulatory Agency for zanidatamab in this condition and patient population is pending approval.

Zanidatamab was approved for use in the United States by the US Food and Drug Administration (FDA) in November 2024 and by the European Medicines Agency (EMA) on 27th June 2025.

Please refer to Section 1.2 of the main submission document for more information.

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Disclosures are presented in the table below.

| Entity | Year | Type of support | Activity |
|---|---|---|---|
| AMMF | 2023 | Financial - £25,000 | Hybrid European Conference sponsorship |
| AMMF | 2024 | Financial - £25,000 | Hybrid European Conference sponsorship |
| AMMF | 2024 | Financial - £25,000 | Project grant – Patient Pathway Mapping |
| AMMF | 2024 | Financial - £10,000 | Project grant – Patient Educational Materials Translations |
| AMMF | 2024 | Financial - £10,000 | Pharmaceutical Forum sponsorship |
| AMMF | 2025 | Financial - £25,000 | Hybrid European Conference sponsorship |

AMMF is the UK's only cholangiocarcinoma (bile duct cancer) charity.

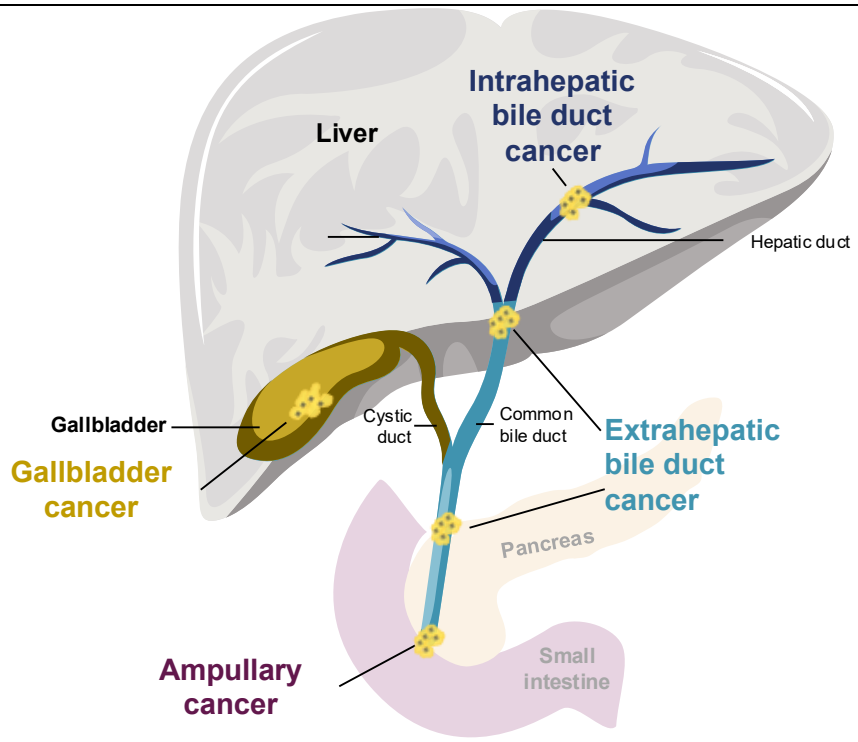
## SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Biliary tract cancer comprises a range of rare, invasive, and deadly cancers that include gallbladder cancer, bile duct cancer (also known as cholangiocarcinoma), and ampullary cancer (see figure below) (1-6).




Sources: Adapted from Banales (2020) (7) and Hennedige (2014) (8).

Biliary tract cancer is a rare cancer (6, 9). In the UK, there are approximately 3,100 new cases of bile duct cancer, 1,100 new cases of gallbladder cancer, and 550 cases of ampullary cancer each year (10, 11). In England, the number of diagnosed cases and deaths from biliary tract cancer is rising (9). Unfortunately, most patients (79%) are only diagnosed with biliary tract cancer when the cancer has already spread to other parts of the body and the disease has become incurable (known as advanced biliary tract cancer) (12, 13).

One of the reasons for a late diagnosis is that symptoms of advanced biliary tract cancer are often vague, such as yellowing of the skin (jaundice), weight loss, sickness, fever, tiredness, lack of energy, and pain in the stomach area, which can be debilitating and substantially reduce a patient's ability to continue normal daily activities (2). Biliary tract cancer has been shown to considerably impact patients' quality of life (14, 15). In addition to symptoms caused by the cancer, patients and their families/caregivers generally experience a poor quality of life following diagnosis, with up to 94% of patients experiencing depression, anxiety, and/or distress (14-16). The patient experience with advanced biliary tract cancer is described in further detail in 2d.

Hearing that the cancer is so advanced and thus incurable has a devastating impact on patients and their families/caregivers (12). Survival rates for biliary tract cancer in the UK are among the worst for any cancer, with only around 1 in 10 patients expected to be alive 3 years after their diagnosis (2, 9). The average survival of patients with biliary tract cancer who receive treatment in the UK is considerably worse than in other European countries (UK average survival of 8.8 months; Spain, Italy, France, and Germany: average survival of 13.4 months) (17).

The current treatment regimens for biliary tract cancer can be time consuming and exhausting, which negatively impact patients' lives and those of their families/carers. This is due to frequent and serious side effects, in addition to how they are administered through devices inserted into a central vein, which requires regular hospital visits for

administration, maintenance, and pump removal (18), which is described in further detail in 2c.

### 2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients with biliary tract cancer that hasn't spread to other parts of the body typically show no symptoms or have only mild and general symptoms, such as jaundice, tiredness, and itching (2, 19). Symptoms generally worsen as the cancer spreads, but these symptoms can be vague and are often not clearly related to the disease, which causes biliary tract cancer to be commonly diagnosed at a late and advanced stage (12, 13).

A number of tests can initially establish if a patient has biliary tract cancer, including: blood tests, scans (e.g. ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]), biopsy, or physical examination) (10).

To be eligible for treatment with zanidatamab, patients must have already been diagnosed with advanced biliary tract cancer and have been treated with at least 1 previous therapy and their tumour be tested as HER2-positive, as described in 1b.

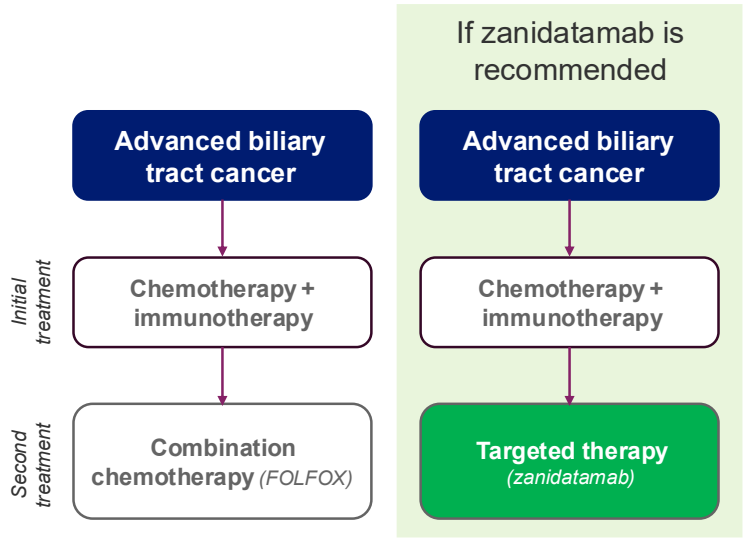
To be eligible for treatment with zanidatamab, additional testing is required to determine if a tumour has a high level of HER2 protein (IHC3+) (as described in 1b). British and European clinical guidelines recommend that this testing is done at diagnosis to avoid treatment delays (3, 6, 20).

### 2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The figure below presents an overview of how patients with HER2-positive biliary tract cancer are treated in the UK currently and shows where patients would be considered for zanidatamab, if it were to be recommended by NICE (20).




Abbreviations: FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IHC, immunochemistry.
Source: Vogel et al (2025) (20).

**Early stage cancer:** When biliary tract cancer is diagnosed at an early stage, before the cancer has spread, treatment usually involves surgery to remove and hopefully cure the cancer, and if required, chemotherapy (capecitabine) to remove any further cancer cells and stop them growing back (6, 20). Zanidatamab will not be used to treat early stage cancer.

**Advanced stage cancer:** Patients with advanced biliary tract cancer could be considered for zanidatamab. For patients whose cancer has already spread to other parts of the body and cannot be removed by surgery, patients are typically offered a first treatment, which is usually combination chemotherapy (cisplatin and gemcitabine) with immunotherapy (durvalumab) (6, 20). If the cancer does not respond or stops responding to this initial treatment and the cancer continues to grow (progression), patients will stop receiving the first treatment and, if they are well enough, may try a second treatment option.

Typically, the second treatment option offered currently to patients in the UK with advanced biliary tract cancer is combination chemotherapy with 3 drugs known as FOLFOX (folinic acid, fluorouracil, and oxaliplatin) (6, 20). This treatment is associated with 1 month longer survival over palliative care with 'active symptom control' (described in the paragraph below), but has considerable side effects (18).

While undergoing any treatments for advanced biliary tract cancer, or in patients who are too unwell to undergo a new course of therapy, any symptoms that occur can also be treated to relieve pain and discomfort (e.g. surgical insertion of stents to unblock and drain bile ducts due to a blockage). These palliative treatments, known as 'active symptom control,' can include invasive surgical procedures and do not treat the cancer itself, but aim to improve a patient's quality of life in their remaining months.

**Targeted treatments:** Some biliary tract cancers have specific genetic changes in their cells that make them different to normal cells ('mutations'). Innovative drugs, called targeted treatments, work specifically in biliary tract cancers that have genetic changes to reduce or stop cancer cells from spreading (21). Some targeted treatments are already available in England; for example, some biliary tract cancers have an 'IDH1 mutation' that can be targeted with ivosidenib, others will have an 'FGFR2 mutation' that can be targeted with pemigatinib or futibatinib.

For advanced biliary tract cancers that are tested to be HER2-positive (IHC3+), zanidatamab could provide a targeted treatment option that works by recognising and attaching to HER2 proteins on the cancer cells, causing the cancer cells to die or their growth to slow down or stop.

The number of people in England who will be eligible to have zanidatamab will be low, around 40 patients. Of all patients diagnosed with biliary tract cancer in the UK (approximately 4,750), around 79% will be locally advanced or metastatic (12). Of these, around 38% will be able to be treated with a first therapy (22), and then approximately 28% are well enough to receive a second therapy (17). Only around 15% of these patients will have HER2-positive disease (6), of which approximately 77.5% will be IHC3+ (20, 23).

If recommended, zanidatamab will be the first HER2-targeted therapy available on the NHS for patients with advanced HER2-positive (IHC3+) biliary tract cancer. Zanidatamab is expected to be used as a second treatment instead of combination chemotherapy with FOLFOX in eligible patients (see green box in the figure above).

### 2d) Patient-based evidence (PBE) about living with the condition

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A diagnosis of advanced biliary tract cancer is devastating for both patients and their families (2) because of the poor likelihood of survival, the burdensome symptoms that negatively impact patients' lives, and the intensive chemotherapy treatment plans that can affect physical and mental functioning, ability to work, and emotional wellbeing (2, 14-16).

Given that most patients are diagnosed when their cancer is already at an advanced stage, the impact on patient quality of life and wellbeing is substantial (12, 14, 15). Symptoms of advanced biliary tract cancer (including jaundice, weight loss, sickness, fever, tiredness, lack of energy, and stomach pain) and their treatment (symptom control, radiotherapy, chemotherapy) are difficult to cope with, and negatively affect daily functioning and quality of life (14, 19). Of 23 patients with biliary tract cancer interviewed in 1 study, everyone (100%) reported lack of energy both from their cancer and their chemotherapy treatment (14). One patient reported the stomach pain associated with biliary tract cancer as the worst pain they'd ever had, with an inability to move because of it (14). More than half of patients interviewed in this study reported additional symptoms such as difficulty eating, bloating, diarrhoea, feeling sick (nausea), insomnia, fever or chills, and muscle loss, highlighting the major difficulties this disease brings to patients' lives (14). The burden of symptoms extends beyond physical discomfort, resulting in a substantial negative impact on patients' emotional wellbeing, mental health, ability to think (cognitive functioning), and physical abilities (e.g. difficulty walking) (14, 15, 24).

The poor outlook and daily symptoms of biliary tract cancer can also have a considerable impact on the mental health of both patients and their families/caregivers, with many experiencing anxiety and distress (14, 15, 25, 26). Approximately 3 in 10 patients with bile duct cancer reported having the highest level of depression, and 9 in 10 patients reported

some form of depression (ranging from mild to severe) (16). In addition, the majority of caregivers of patients with bile duct cancer reported major difficulties in carrying out their daily activities (16). Around half of carers report having their jobs impacted as a result of a family member having this cancer, with as much as 38% of their time being dedicated to caring for their family member (16).

Current treatment with FOLFOX chemotherapy can also impose a substantial burden on patients and their families, with patients often experiencing multiple, and in many cases severe, side effects of this treatment. Patients need to spend hours in hospital or outpatient settings for infusions every 2 weeks, in addition to further appointments for insertion, maintenance, and removal of central line/pumps, which are required for chemotherapy infusions (18, 27-29). Due to the aggressive nature of biliary tract cancer, many patients are too unwell to tolerate the burden of multiple rounds of chemotherapy (17). However, patients currently only have the option for additional chemotherapy as a second treatment, if they are not eligible for treatment with targeted therapies.

## SECTION 3: The treatment

### 3a) How does the new treatment work?

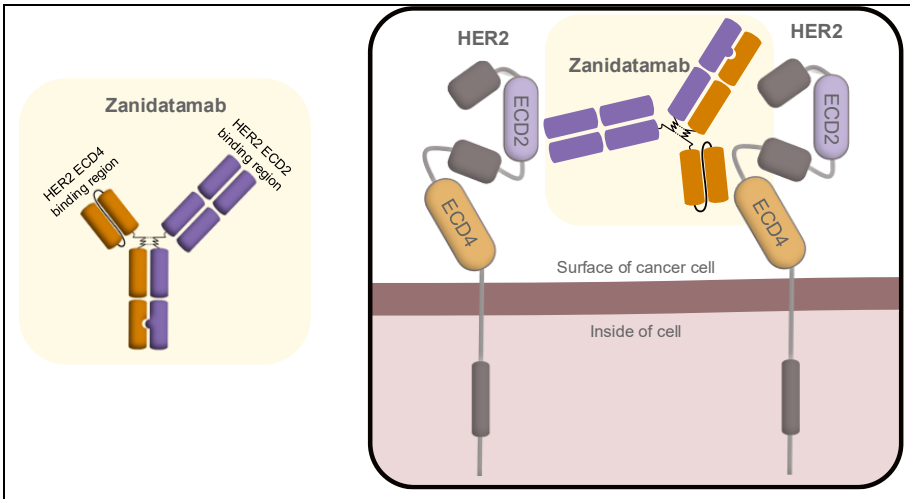
What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Zanidatamab is known as a HER2-targeted therapy, which means that it has been designed specifically to attach to cells that have a protein called HER2 on their surface. As described in 1b, HER2 is found in large amounts on the surface of some cancer cells, where it stimulates their growth. When zanidatamab attaches to HER2 on cancer cells, it may slow or stop the cells from growing and/or may kill them. Zanidatamab is a type of medicine called a bispecific antibody (see figure below). An antibody is a large protein that recognises and attaches to another specific protein on a cell's surface, such as HER2. Bispecific means it attaches to 2 different parts of the HER2 receptor (see figure below). Patients will be eligible for zanidatamab if they have biliary tract cancer that has been tested as HER2-positive (IHC3+) (see 1b and 2b for more information)




Abbreviations: ECD, extracellular domain; HER2, human epidermal growth factor receptor 2.
Source: Adapted from Elimova (2025) (30).

If recommended by NICE, zanidatamab will be the first HER2-targeted treatment available to treat advanced biliary tract cancer, providing a new chemotherapy-free option for patients who are well enough to try a second treatment. Zanidatamab is likely to help patients live longer than standard chemotherapy with FOLFOX, with fewer and less serious side effects (18, 23).

2c describes how zanidatamab would fit into a patient's treatment plan. If recommended, zanidatamab would provide an alternative treatment option for patients with HER2-positive advanced biliary tract cancer, as a targeted alternative to combination chemotherapy with FOLFOX. In addition, some patients may only receive procedures or medicines to treat their symptoms (active symptom control) because chemotherapy isn't suitable for them, or they can't tolerate the side effects. For these patients, if they are well enough for a second treatment, zanidatamab could also provide a potentially life-extending treatment as an additional option to palliative care with active symptom control.

The draft Summary of Product Characteristics (SmPC) is available in the reference pack provided to NICE.

### 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

No, zanidatamab is intended to be used on its own as a 'monotherapy'.

### 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

To be treated with zanidatamab, a patient will have to attend an outpatient clinic once every 14 days and be given zanidatamab by a drip into a vein. The amount each patient receives depends on their body weight; for each kilogram of body weight, the patient will receive 20 mg of zanidatamab. For the first 2 visits, the infusion will take 120 to 150 minutes; however, this can be reduced to 90 minutes for the third and fourth visits and to 60 minutes for following visits, if previous infusions were well tolerated (31). The number of infusions will depend on how the patient responds to treatment and how well they tolerate the treatment (31).

Zanidatamab is a single medicine injected into a vein using an intravenous drip and unlike chemotherapy, does not need a central line (e.g. PICC, portacath, or Hickman lines) or intravenous pump. As such, zanidatamab could reduce the treatment burden on patients and the number of hospital staff needed to deliver treatment when compared with chemotherapy (23, 32).

The existing treatment for eligible patients is combination chemotherapy with FOLFOX (6, 20). Administration of FOLFOX is more time-consuming and complex than zanidatamab, requiring 3 separate medicines: folinic acid, fluorouracil, and oxaliplatin (32). Treatment with folinic acid and oxaliplatin requires the patient to have a long plastic tube (central line/PICC line/portacath) inserted into a vein through an invasive hospital procedure that remains in place throughout the course of treatment, which could last for several months (18, 32). These tubes also require regular maintenance and 'flushing' by nurses as they can get blocked and are associated with infection (28, 29). Following treatment with folinic acid and oxaliplatin, patients will be given a small continuous pump to administer the fluorouracil, which takes 46 hours; the pump has to be disconnected either at hospital or by a home visit from a nurse (32). In addition, before starting fluorouracil, patients must be tested to determine if they lack an enzyme called dihydropyrimidine dehydrogenase, as low levels of this enzyme could incur severe side effects from the chemotherapy (32).

### 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The efficacy and safety of zanidatamab in advanced biliary tract cancer has been tested in 2 clinical trials involving patients worldwide, and is supported by further efficacy and safety results from 2 real-world studies in hospitals in England and France:

- The key Phase 2b trial (HERIZON-BTC-01) (23) (clinical trial)
- A Phase 1 trial (ZWI-ZW25-101) (33) (clinical trial)
- A real-world study at University College Hospital London in England (34)
- A real-world study in France (23, 33-35)

### HERIZON-BTC-01

HERIZON-BTC-01 is the main source of clinical efficacy evidence for zanidatamab. This was a global clinical trial assessing the efficacy and safety of zanidatamab in adults with advanced (locally advanced or metastatic) HER2-positive biliary tract cancer who had been treated with at least 1 previous medicine. All patients treated in this clinical trial were treated with zanidatamab, as biliary tract cancer is a rare disease and the number of patients globally with HER2-positive disease is very low. Trials in which all patients receive the same treatment, like in HERIZON-BTC-01, are called 'single-arm' trials. Single-arm trials are common for rare diseases where there are a limited number of eligible patients and they are underserved by currently available treatments, allowing for quicker patient access to new treatments. In total, 62 patients had HER2-positive biliary tract cancer with IHC3+. This clinical trial has finished. Further information is available from the publications and website below:

- Harding (2023) (23) (Plain language summary available here)
- Pant (2024) (36)
- Clinical trials website (NCT04466891)

### ZWI-ZW25-101

Prior to the HERIZON-BTC-01 trial, a first-in-human trial was conducted (ZWI-ZW25-101), which evaluated the safety and efficacy of zanidatamab in a number of cancers, including biliary tract cancer. A total of 22 patients with biliary tract cancer were included in this trial, of which 14 had HER2-positive biliary tract cancer with IHC3+. This trial has finished. Further information is available below:

- Meric-Bernstam (2022) (33)
- Clinical trials website (NCT02892123)

### Real-world evidence

The clinical trial results are also supported by recent 'real-world' results (published 2025) of patients treated with zanidatamab outside of clinical trials in real-life hospital settings through an early access programme in France and a compassionate use programme in England (34, 35). In the study in France, 12 patients had HER2-positive biliary tract cancer with IHC3+ (35). For the study in England, a total of 20 patients were included; however, the IHC status was not known for all patients (34).

### Comparing zanidatamab with current treatments

To assess how the outcomes of patients who are treated with zanidatamab may compare with patients who receive current treatment with chemotherapy (FOLFOX), results from the clinical trial with zanidatamab (HERIZON-BTC-01) were compared with results from another clinical trial (ABC-06). The ABC-06 trial assessed the efficacy and safety of FOLFOX and active symptom control compared with active symptom control alone in the UK. Patients in this trial had advanced biliary tract cancer that had been treated with 1 previous therapy. This trial is finished; further information is available below:

- Lamarca (2021) (18)
- Clinical trials website (NCT01926236)

### 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

## HERIZON-BTC-01 (patients with HER2-positive IHC3+ biliary tract cancer)

The HERIZON-BTC-01 trial ran until 11th July 2024. Efficacy results from the final date of data collection are considered confidential in nature and are presented in Section 2.6 of the main submission. Results from the previous data collection date (28th July 2023) are publicly available and are presented below.

- More than half of the 62 patients (51.6%) treated with zanidatamab had a reduction in the size of their tumour (36). Half of patients lived for 18 months after starting treatment with zanidatamab, and lived without their cancer spreading for 7.2 months (36). In addition, patients whose cancer shrunk with zanidatamab treatment had, on average (median), 14.9 months before their cancer worsened (36).

In contrast, after 1 year of treatment with FOLFOX in the ABC-06 trial, only 26% of patients were still alive. On average, half of patients lived for only 6.2 months, and lived without their cancer spreading for 4.0 months (18).

## Real-world evidence

Real-world evidence supports the results seen in the zanidatamab clinical trial:

- In 20 patients treated with zanidatamab at 1 hospital in England, 54% had a reduction in size of their tumour (34).
- In 12 patients treated with zanidatamab in France, after 1 year of treatment, 63% of patients with HER2-positive biliary tract cancer with IHC3+ were still alive; the average (median) time before the cancer spread in these patients was 8 months (35).

### 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

As well as the positive impact zanidatamab has on controlling the progression of the cancer and keeping patients alive longer than currently available chemotherapy options (see 3e for more information), it may also improve or maintain patient quality of life (37).

The HERIZON-BTC-01 trial ran until 11th July 2024. Quality of life results from the final date of data collection are considered confidential in nature and are presented in Section 2.6 of the main submission. Results from the first data collection date (10th October 2022) that are publicly available are presented below.

- Treatment with zanidatamab led to reduced pain, less pain interference, and meaningful improvements in overall quality of life measured using a questionnaire where patients self-rate their health from the worst to the best health they can imagine (EQ-5D visual analogue score) (37).
- Patients whose tumour(s) shrunk or remained the same size during treatment (complete or partial responders) reported the most improvements in pain, with these patients requiring less painkillers (opioids) than patients whose cancer had spread (37).

### 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Zanidatamab treatment was generally tolerated by patients, with fewer and less serious side effects than has been seen when patients are treated with FOLFOX (18, 23).

The HERIZON-BTC-01 trial ran until 11th July 2024. Safety results from the final date of data collection are considered confidential in nature and are presented in Section 2.11 of the main submission. Results from the previous data collection date (28th July 2023) that are publicly available are presented below.

- Approximately 3 in 4 patients experienced a side effect due to treatment with zanidatamab (36), but fewer than 1 in 10 patients experienced a serious side effect caused by treatment with zanidatamab in HERIZON-BTC-01 (36). No patients died as a direct result of treatment with zanidatamab (36).
- The most common side effects from zanidatamab treatment in HERIZON-BTC-01 were diarrhoea, reactions related to infusion of the medicine, reduction in the amount of blood pumped by the heart in each beat, and feeling sick (nausea) (36). Side effects related to zanidatamab were generally manageable without the need for hospitalisation and without reducing the dose of zanidatamab (23, 36).

In contrast, in ABC-06, approximately 8 out of 10 patients experienced side effects caused by treatment with FOLFOX, while 38% (31 patients) experienced severe and 4% (3 patients) died due to FOLFOX treatment (18).

The safety results of zanidatamab that were seen in HERIZON-BTC-01 are supported by the ZWI-ZW25-101 clinical trial and real-world evidence in England and France, all of which reported no severe side effects caused by zanidatamab (33-35).

### 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Sadly, advanced biliary tract cancer is incurable, so receiving a diagnosis of this disease is devastating for patients, their families, and caregivers (2). Currently, in England, patients with advanced HER2-positive biliary tract cancer whose first treatment has not worked only have a limited number of second options: receiving combination chemotherapy (FOLFOX) and/or palliative treatments to manage their symptoms (active symptom control).

Zanidatamab is a new type of chemotherapy-free medicine that specifically targets HER2 on the cancer cells and, if recommended by NICE, will be the first HER2-targeted therapy available on the NHS specifically for patients with advanced HER2-positive (IHC3+) biliary tract cancer. Based on the clinical trial results discussed above for HERIZON-BTC-01 and ABC-06, zanidatamab is expected to help patients live approximately 1 year longer than with FOLFOX, while maintaining or improving patient quality of life during these valuable additional months.

Zanidatamab is associated with fewer and less severe side effects than FOLFOX, which is beneficial to patients and those who care for them (18, 36). Also, patients who are too unwell to undergo chemotherapy with FOLFOX, who currently have no further treatment options, may be able to have zanidatamab, providing them with a targeted medicine instead of only symptom management that does not treat the cancer itself.

Finally, zanidatamab is a ‘monotherapy’ consisting of 1 medicine, which will be administered once every 14 days via a drip, without the need for additional visits in between. As described in 3c, this is likely to offer a much simpler treatment approach than FOLFOX, without the need for invasive procedures to insert a tube into the vein, or extra healthcare visits to look after the PICC line/portacath and pump that is needed for administration of FOLFOX.

### 3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

As with many anti-cancer drugs, most patients treated with zanidatamab in the HERIZON-BTC-01 trial experienced some type of side effect related to treatment (23, 36); however, patients experienced fewer and less severe side effects than patients treated with combination chemotherapy with FOLFOX in ABC-06 (18).

To be treated with zanidatamab, patients will require hospital attendance every 14 days for the medicine to be administered by a drip into the vein (intravenous infusion); however,

no additional visits in between treatments are required, in contrast to FOLFOX treatment, which is much more time-consuming and complex, as described in 3c and 3h.

### 3i) Value and economic considerations

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

## How the model reflects the condition

- To predict or 'model' the value of zanidatamab over a patient's lifetime when compared with other treatments, a mathematical tool known as a 'cost-effectiveness model' was produced. Cost-effectiveness models compare treatments in terms of cost, as well as their effect on both length and quality of life.
- The cost-effectiveness model assesses differences in cost of treatment, length of life, and quality of life between people treated with zanidatamab, combination chemotherapy with FOLFOX, or active symptom control. The results of the model are presented as an overall value called the cost per quality-adjusted life year (QALY); 1 QALY is equal to 1 year of life in perfect health.
- The model aims to simulate the journey of a person with advanced biliary tract cancer by modelling different stages of the disease called 'health states'. The health states that this model uses are:
  - 'Progression-free' (the cancer is not getting worse)
  - 'Progressed disease' (the cancer is getting worse)
  - 'Death' (the person has died).
- In the model, a hypothetical group of patients stay in a health state and as the cancer gets worse, move to the next health state over time. All patients start in the 'progression-free' health state when they receive their first treatment with zanidatamab, FOLFOX, or active symptom control.
- The model works by simulating how patients move between the health states when given different treatments; the more effective the treatment, the more time patients will spend in each of the 'Progression-free' or 'Progressed disease' health states before dying, and thus have a longer life expectancy. Patients accrue different costs to the NHS and social care system depending on which health state they are in.

- The model uses survival curves (graphs based on clinical data from the trials) to estimate how many patients are still alive at each point in time, and how many patients stay progression free.

### Clinical trial outcomes used in the model

- The HERIZON-BTC-01 clinical trial studied the efficacy (looking at the overall survival and the time until the disease progressed), as well as the quality of life for patients receiving zanidatamab and the side effects associated with treatment. All of these efficacy, quality of life, and side effect data for HER2-positive IHC3+ patients from the trial were included in the model. The model uses efficacy data from the final data collection date of HERIZON-BTC-01, which is considered confidential in nature and is presented in Section 2.6 of the main dossier.
- The ABC-06 UK-based clinical trial studied the efficacy, quality of life and side effects for patients receiving FOLFOX and active symptom control, or active symptom control only, and these data are included in the model for FOLFOX and active symptom control. In the ABC-06 study, patients treated with FOLFOX and active symptom control lived without their disease progressing for 4.0 months and lived for an average of 6.2 months overall.
- As the trials ran for a limited time period, the model includes estimates of what would have happened to patients if they had continued their treatment beyond the time period of the trial, to predict efficacy outcomes over a total of 30 years. Statistical prediction models were used to estimate future survival based on the data available from the trial results, which is a common approach when estimating cost-effectiveness of cancer treatments. The predictions selected were based on how well they could replicate the trial data, and how realistic the predictions were over the long term, based on advice from doctors with expertise in biliary tract cancer working in the UK.

### Modelling how much a treatment extends life

- Model results show treatment with zanidatamab helps patients live longer than those treated with FOLFOX and active symptom control by delaying cancer progression.
- The model predicts how these differences would affect patient survival over the long term, up to 30 years.

### Modelling how much a treatment impacts quality of life

- Quality of life data in the model were based on results of a questionnaire (the EQ-5D-5L) collected during the HERIZON-BTC-01 trial. How a patient's quality of life is affected by the disease is captured in the model by taking into account the natural decline in quality of life as a patient is near to death, with patients who live longer (e.g. due to treatment with zanidatamab) experiencing a slower decline in quality of life and hence having a better quality of life for longer than patients who do not live as long.
- The model also considers how treatment side effects and how the medicine is administered via a central line (PICC/portacath) may negatively affect patient quality of life. Data from the HERIZON-BTC-01 for zanidatamab, and ABC-06 trial for FOLFOX and active symptom control informed the types and severity of side effects experienced on these treatments, and how many patients experienced each side effect. As patients treated with zanidatamab experienced fewer and less severe side effects compared with FOLFOX, the model shows less of an impact on quality of life with zanidatamab compared with combination chemotherapy with FOLFOX.

## Modelling how the costs of treatment differ with the introduction of zanidatamab

- Healthcare costs to the NHS and social care that are likely to be different with zanidatamab compared with FOLFOX or active symptom control are included in the model:
  - Administration of zanidatamab does not require insertion, maintenance, or removal of central line/PICC line/portacath whereas FOLFOX does (see 3c for more detail), resulting in lower associated costs for zanidatamab
  - FOLFOX requires a continuous fluorouracil pump for 46 hours and removal of the pump (as described in 3c), which needs additional hospital attendance or nurse visits, leading to higher associated costs with FOLFOX
  - Patients experience fewer and less severe side effects with zanidatamab compared with FOLFOX resulting in fewer healthcare costs treating the side effects and less time in hospital, leading to lower costs for zanidatamab
  - Costs of the medicines and any medication required before or at the time of administration of treatment with zanidatamab or FOLFOX to reduce or prevent side effects leading to higher medication costs for zanidatamab but lower costs for medications required to reduce or prevent side effects.
- Other healthcare and social care costs included in the model are also captured, including:
  - Monitoring requirements for each medicine
  - Treatments received after zanidatamab/FOLFOX/active symptom control
  - Any costs associated with care at a patient's end of life.

## Uncertainty

- Due to the rarity of biliary tract cancer, there is no evidence that directly compares the efficacy of zanidatamab with FOLFOX and active symptom control from the same trial; as such, when comparing these treatments in the model, differences in the separate trial populations may lead to uncertainty.
  - Two additional 'indirect' comparisons of the trial results were undertaken where only patients from each trial that had the most similar characteristics were included, or results were compared to patients treated in the real-world; however, these comparisons had many limitations and were not used in the model.
- The model was informed by expert opinion from UK doctors with expertise in biliary tract cancer and externally checked to reassure that the results were as realistic as possible where there was uncertainty in the data. In addition, a large number of alternate versions of the model were tested in 'scenario analyses', where certain factors are changed to establish which have the biggest effect on the results.

## Health economic model conclusions

- Zanidatamab is more costly, but more effective than combination chemotherapy with FOLFOX or active symptom control, as it is likely to make people live longer and stop their cancer from worsening while maintaining or improving their quality of life.
- The cost-effectiveness results are considered commercially confidential and are presented in Section 3.9 of the main submission.

## Additional factors

- When assessing the cost-effectiveness of new medicines, it is important to factor in how severe the disease is. NICE uses a 'severity modifier', which is a rule that gives

treatments for more severe diseases a greater weighting than those to treat less severe diseases. As such the health benefits of treatments for severe diseases are valued more highly by NICE than those diseases that are less severe (38).

- Advanced HER2-positive biliary tract cancer has a very substantial impact on a patient's quality and length of life. Current second treatment options for patients who are well enough to receive them are FOLFOX and active symptom control, which only help patients live for around 6 months and are associated with side effects. The severity of this cancer and the low chances of survival and poor quality of life for patients with the current treatment options means that for this submission, zanidatamab for advanced HER2-positive biliary tract cancer qualifies for the highest possible severity modifier weighting of 1.7×. This means that the difference in QALYs between zanidatamab and FOLFOX or active symptom control estimated by the model are then multiplied by 1.7, making it more likely that it can be judged as cost-effective by NICE.
- There are other potential benefits of zanidatamab compared with FOLFOX and active symptom control that are not taken into account in the modelling results, such as: reduced burden and improved quality of life of caregivers and other family members; impact on patient and caregiver ability to work and stay in work for longer; impact on patient and caregiver ability to participate in social activities; and improving the current health inequalities experienced by patients with biliary tract cancer who live in poorer communities.

## 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Zanidatamab is a type of medicine known as a targeted therapy. Zanidatamab is a medicine that recognises and attaches to HER2, which is found in large amounts on the surface of some cancer cells where it stimulates their growth. When zanidatamab attaches to the HER2 receptor on cancer cells, it may slow or stop the cancer cells from growing and/or may kill them.

Zanidatamab represents a 'step change' in the treatment of advanced HER2-positive (IHC3+) biliary tract cancer due to the potential for patients to live substantially longer than those treated with currently available treatment (see 3e), with fewer and less severe side effects than chemotherapy. If recommended by NICE, zanidatamab will be the first HER2-targeted chemotherapy-free medicine available for this patient population, whose treatment options are currently limited to combination chemotherapy with FOLFOX, or active symptom control only.

Unlike people who have advanced biliary tract cancer with other genetic changes (such as IDH1 or FGFR2 mutations) who can already be offered a targeted therapy, people with HER2-positive biliary tract cancer are currently underserved; they are only offered the same standard combination chemotherapy that has not changed in decades, and this treatment is not targeted to work specifically against their particular type of cancer mutation. This means their chances of survival are very poor, as well as having to endure the side effects of chemotherapy.

### 3k) Equalities

| Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.<br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here |
|---|
| No equality issues associated with the use of zanidatamab have been identified or are foreseen.<br><br>However, if patients with advanced biliary tract cancer can be treated with targeted therapies (including zanidatamab), this may help to reduce the health inequalities that are experienced in England by people with biliary tract cancer living in poorer communities or in certain parts of the country. This is because biliary tract cancer is more common, and survival is lowest in patients who live in poorer English communities (9). Data show people in the most socioeconomically deprived groups at the time of diagnosis have a 37% higher chance of death than those who are not in deprived groups (9). In addition, a person's chance of survival also depends on where they live in the country. Data from patients with biliary tract cancer in England show substantial regional variation, with more cases and a greater likelihood of death for those living in the North of England compared with the rest of the country (9).<br><br>Finally, real-world data from 2018 to 2021 has shown that people with advanced biliary tract cancer in the UK do not live as long as those in other European countries. Patients in the UK who are treated for advanced biliary tract cancer have an average life expectancy that is 4.6 months shorter than those in Europe; this disparity is substantial when patients with advanced biliary tract cancer are expected to survive for less than a year overall (17). |

## **SECTION 4:** Further information, glossary and references

### 4a) Further information

| Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.<br>Where possible, please provide open access materials or provide copies that patients can access. |
|---|
| Further information on biliary tract cancer:<br>• https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer<br>• https://www.cancerresearchuk.org/about-cancer/gallbladder-cancer<br>• https://www.cancerresearchuk.org/about-cancer/ampullary-cancer<br>• https://www.nhs.uk/conditions/bile-duct-cancer/<br>• https://www.nhs.uk/conditions/gallbladder-cancer/<br>• https://ammf.org.uk/wp-content/uploads/2024/01/AMMF-Rethink-Liver-Cancer-White-Paper-Jan-20242023-DIGITAL.pdf<br>• https://ammf.org.uk/wp-content/uploads/2024/04/About-AMMF-Leaflet-2023-White-Cover.pdf<br>• https://ammf.org.uk/wp-content/uploads/2020/02/EN-Biliary-Tract-Cancer-Guide-for-Patients.pdf<br>Further information on zanidatamab: |

- https://www.ema.europa.eu/en/medicines/human/EPAR/ziihera
- https://www.tandfonline.com/doi/epdf/10.1080/14796694.2024.2368952

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

## 4b) Glossary of terms

**Active symptom control:** Treatments to address symptoms which are impacting a patient's health or life, e.g. surgery to remove a blockage in the bile ducts to allow drainage.

**Bispecific antibody:** A protein that has been designed to target and attach to 2 specific protein targets on a cell.

**Biliary tract cancer:** A range of rare, invasive, and aggressive cancers that occur in the gallbladder, the ampulla and bile ducts (cholangiocarcinoma).

**Central venous access device (also called a central line):** A device which is inserted to allow administration of chemotherapy (e.g. FOLFOX). Examples include peripherally-inserted central catheter (PICC), portacath, or Hickman lines.

**FOLFOX:** A combination chemotherapy of folinic acid, fluorouracil, and oxaliplatin, used to treat patients with advanced biliary tract cancer who have previously been treated with, typically, standard chemotherapy (cisplatin and gemcitabine) and immunotherapy.

**HER2-positive:** A subset of cancers that test positive for overexpression or amplification of human epidermal growth factor receptor 2, which are suitable for HER2-targeted therapies.

**Immunohistochemistry:** A diagnostic test conducted on a biopsy sample to determine if a cancer is HER2-positive.

**Locally advanced disease:** the cancer has spread into nearby tissues or lymph nodes.

**Metastatic disease:** The cancer has spread to other organs in the body.

**Mutation:** Specific genetic changes in cells that make them different to normal cells.

**QALY:** One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale).

**Targeted therapy:** A treatment that can target known changes (e.g. biliary tract cancer with IDH1 mutation can be treated with ivosidenib) on cancer cells to stop or slow the spread of the cancer.

## 4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text: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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

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

## Clarification questions

**August 2025**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6388 zanidatamab EAG Clarification letter v1.0_responses_FINAL_29August2025_[CON] | 1.0 | Yes | 29th August 2025 |

# Section A: Clarification on effectiveness data

## *Systematic literature review methods*

**A1. Appendix B, Section B.1.2:**

Please clarify the number of reviewers performing data extraction of the included studies and whether they worked independently.

For the clinical systematic literature review (SLR), data were extracted by 1 reviewer and all extractions were verified against the original sources by a second independent reviewer.

**A2. Appendix B, Section B.4:**

Please clarify the number of reviewers conducting risk of bias assessments for the included studies and whether the reviewers worked independently.

For the clinical SLR, risk of bias assessments were performed by 1 reviewer and checked against the original sources by a second independent reviewer.

**A3. Company submission, Sections 2.2 and 2.10:**

For each zanidatamab study and each source of evidence used in Section 2.10 please clarify whether you have access to individual patient data (IPD) or published data only.

IPD were available for HERIZON-BTC-01 (see Table 22 of company submission) and the external control arm (ECA) analysis (Section 2.10.3). Only published data were available for ABC-06 (Sections 2.10.4 and 2.10.6).

**A4. PRIORITY. Company submission, Section 2.10:**

The zanidatamab data used in the economic model were primarily derived from the subset of HERIZON-BTC-01 who were BTC HER2+ IHC3+ (n=62) with some analyses further limited to the second line population (n=[redacted]). To increase the number of participants contributing to the analyses, did you also consider including the HER2+ IHC3+ participants from ZWI-ZW25-101 or the French real-world evidence study? If so, please provide full details of any additional analyses performed using these data sources.

The total number of patients with HER2+ IHC3+ BTC receiving zanidatamab at the licensed dosage was 14 in Part 2 of the Phase 1 ZWI-ZW25-101 study (1, 2) and 12 in the France real-world evidence (RWE) study (3). While inclusion of these patients would expand the data pool for the economic model, using data from a small number of patients from different studies risks introducing additional uncertainty due to between-study heterogeneity. This is particularly the case for RWE, such as the study conducted in France, where clinical practices and treatment patterns may differ from the UK. In addition, the Phase 1 study included 5 patients previously treated with HER2-targeted therapies not currently available in the UK, while this was an exclusion criterion in HERIZON-BTC-01. The median number of any prior therapy in the Phase 1 trial was 4 (range: 1 to 11), further limiting the ability to match the population to the ABC-06 trial. Therefore, while the Phase 1 and RWE data support the efficacy and safety of zanidatamab, the pivotal, label-enabling HERIZON-BTC-01 trial was considered to provide the most relevant and robust data for the economic analyses.

**A5. PRIORITY. Company submission, Section B.1.3.4:**

The ABC-06 study, which was non-targeted and did not report HER2+ status, was used as a comparator alongside the HERIZON-BTC-01 IHC3+ data, despite the literature review identifying eligible targeted comparator studies. For each of the non-zanidatamab studies in Table 5 (Appendix B.1.3.4), please provide the main reasons why it was not selected as a source of comparator data. While we are aware that brief reasons are already available in an Excel file, we are seeking a more comprehensive rationale for the exclusion of each study. We understand that one reason for selecting ABC-06 was its inclusion in a previous NICE appraisal; however, for this question, we are specifically interested in reasons unrelated to the prior use in NICE submissions.

Further details on reasons for exclusion of each identified non-zanidatamab study from the clinical SLR are presented in the Appendix of these responses. All of the excluded studies described irrelevant comparators not available in the UK (e.g. trastuzumab deruxtecan, pertuzumab) that could not inform comparison of zanidatamab with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and/or FOLFOX + active symptom control (ASC) as defined in the scope for this appraisal.

Jazz Pharmaceuticals consider the use of the ABC-06 study to be the best available evidence to inform the comparative evidence for a number of reasons:

- ABC-06 is the pivotal UK RCT of treatments in second-line (2L) biliary tract cancer (BTC), with good reporting of outcomes, a sizeable cohort for the rarity of the disease, and relevant comparators representative of treatment patterns in the UK (4-7).

- Comparing HERIZON-BTC-01 to a randomised controlled Phase 3 study containing only UK patients provides a more robust analysis than comparing to international RWE, as there are more similarities in the collection of outcome data between the two trials, including their structured, prospective data collection, standardised outcome measures, and centralised assessments.

- ABC-06 has been used in prior appraisals of targeted treatments in 2L BTC for comparative data where it was recognised as the most appropriate comparative data source (TA722 – pemigatinib "the comparative efficacy and safety data from ABC-06 were the most appropriate evidence for decision making" (8); TA948 – ivosidenib "it concluded that the ITC and subgroup results were sufficient for decision making" (9)).

**A6. PRIORITY. Company submission, Section 2.10:**

As previously stated, the primary zanidatamab data used in the economic model were derived from the subset of HERIZON-BTC-01 who were HER2+ IHC3+ (Cohort 1), but the study used as a comparator (ABC-06) included a wider range of BTC patients. Did you consider incorporating the non-IHC3+ data from 1 or more of the following studies in this analysis: HERIZON BTC-01, ZWI-ZW25-101, the UCLH real-world evidence study or the French real-world evidence study? If yes, please provide full details of any additional analyses conducted.

Non-IHC3+ BTC is not expected to be included in the UK marketing authorisation for zanidatamab (and was not included in the FDA or EMA labels), and Jazz Pharmaceuticals are not seeking reimbursement in this population. Therefore, non-IHC3+ efficacy data for zanidatamab were not included in the economic model. The

ABC-06 comparator efficacy data in the model were for a non-IHC3+ population and aligns with the approach taken in TA722 and TA948 as FGFR2 and IDH status in the ABC-06 trial was also not reported, but represented the best available evidence for the comparators, as noted in our response to A5.

The expected UK indication for zanidatamab is as follows:

Zanidatamab as [redacted] is indicated for the treatment [redacted] (10).

[redacted].

**A7. Company submission, Section 2.10.3.1.1:**

Please provide additional information on the methodology used to conduct the external control arm analysis.

Jazz Pharmaceuticals note this question has since been disregarded by the EAG; however, the final unpublished and confidential version of the ECA analysis report has become available since submission and is provided in the reference pack.

# Section B: Clarification on cost-effectiveness data

## *Economic model settings*

**B1. Company Submission, Section 3.2.2.1, P109:**

The company's economic model applies a discount rate of 1.5% per annum for both costs and QALYs. However, according to the current NICE methods guide (Section 4.5), a discount rate of 3.5% should be used in the base case analysis, with 1.5% reserved for scenario analyses. The EAG does not consider the criteria outlined in Section 4.5.3 of the NICE methods guide to be met for this appraisal. Please update the economic model and all cost-effectiveness analyses to use a discount rate of 3.5% per annum for costs and QALYs.

The UK Government, NICE and industry agree that there is an evidence-based case for reducing the discount rate, in line with Treasury Green Book for future health and life benefits (11). The Life Sciences Sector Plan Action 26 states that changes through NICE's modular updates "can be considered where they are evidence based, financially sustainable, and represent value to the taxpayer" (12). Through the Voluntary Scheme for Branded Medicines Pricing, Access, and Growth (VPAG) expedited review, it was confirmed that changing the discount rate to 1.5% for costs and benefits satisfies these criteria. It is anticipated that at the time of the first committee for zanidatamab, the discount rate will have changed to 1.5% and as such, has been maintained in the company base case to aid decision-making.

In addition, the company maintains that zanidatamab fulfils all the criteria for HST instead of STA, and disagrees with NICE's HST checklist for zanidatamab that criterion 1 (the condition is very rare) and criterion 4 (there are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options) are not met. In support of this, NHS England's budget impact assessment for this appraisal concluded that only [redacted] people in England would be eligible for zanidatamab. Furthermore, the [redacted].

Despite not meeting NICE's HST criteria, due to the very low patient numbers and the high unmet need for a life-extending and well tolerated targeted therapy for patients with advanced BTC, we hope that the committee can apply greater flexibility in its decision-making around the non-reference case discount rate and acceptability of zanidatamab as an effective use of NHS resources, as well as the degree of certainty around the value for money, in line with 6.2.34 of the new NICE 2025 manual. For completeness, the deterministic results of the company base case using the 3.5% discount are presented in Table 1.

**Table 1: Deterministic results (with PAS) – 3.5% discount**

| Technologies | Total | | | Incremental | | | ICER versus zanidatamab, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| 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.

Mean results from the probabilistic sensitivity analysis (PSA) are presented in Table 2 and the cost-effectiveness planes versus FOLFOX and ASC are presented in Figure 1 and Figure 2 respectively. The probabilistic results are consistent with the deterministic results.

**Table 2: Mean PSA results (including PAS) – 3.5% discount**

| Technologies | Total | | | Incremental | | | ICER, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| 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; PAS, patient access scheme; PSA, probabilistic sensitivity analysis.

### Figure 1: Pairwise cost-effectiveness plane (including PAS) - zanidatamab versus FOLFOX + ASC – 3.5% discount

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

### Figure 2: Pairwise cost-effectiveness plane (including PAS) - zanidatamab versus ASC – 3.5% discount

Abbreviations: ASC, active symptom control; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

The cost-effectiveness acceptability curves are presented in Figure 3 for zanidatamab versus FOLFOX and Figure 4 versus ASC. At a willingness-to-pay (WTP) threshold of £30,000, the probability that zanidatamab is cost-effective compared to FOLFOX + ASC is [redacted] and [redacted] compared to ASC.

**Figure 3: Cost-effectiveness acceptability curve (including PAS) – zanidatamab versus FOLFOX + ASC – 3.5% discount**

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PAS, patient access scheme; WTP, willingness-to-pay.

**Figure 4: Cost-effectiveness acceptability curve (including PAS) – zanidatamab versus ASC – 3.5% discount**

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

Table 3 and Figure 5 present the incremental cost-effectiveness ratios (ICERs) and tornado plots of the 10 parameters that had the largest influence on the ICER comparing zanidatamab to FOLFOX and those comparing zanidatamab to ASC are shown in Table 4 and Figure 6 respectively.

**Table 3: OWSA results (including PAS) – zanidatamab versus FOLFOX + ASC – 3.5% discount**

| Parameter | ICER at lower bound, £ | ICER at upper bound, £ |
|---|---|---|
| PORT disutility | [redacted] | [redacted] |
| RDI: Zanidatamab - Zanidatamab | [redacted] | [redacted] |
| Administration cost: Proportion receiving PICC vs PORT device | [redacted] | [redacted] |
| Administration cost: Simple IV | [redacted] | [redacted] |
| Administration cost: Complex (pro-longed) | [redacted] | [redacted] |
| Infection Grade 3 frequency: FOLFOX | [redacted] | [redacted] |
| FOLFOX disutility | [redacted] | [redacted] |
| HCRU cost: Echocardiography | [redacted] | [redacted] |
| QT interval monitoring: Echocardiography | [redacted] | [redacted] |
| Infection Grade 5 frequency: FOLFOX | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HCRU, healthcare resource utilisation; ICER, incremental cost-effectiveness ratio; IV, intravenous; OWSA, one-way sensitivity analysis; PICC, peripherally-inserted central catheter.

**Figure 5: Tornado plot showing OWSA results on the ICER (including PAS) – zanidatamab versus FOLFOX + ASC – 3.5% discount**


[redacted]

Abbreviations: ASC, active symptom control; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HCRU, health care resource use; ICER, incremental cost-effectiveness ratio; IV, intravenous; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PFS, progression-free survival; PORT, portacath; RDI, relative dose intensity; ToT, time on treatment.

**Table 4: OWSA results (including PAS) – zanidatamab versus ASC – 3.5% discount**

| Parameter | ICER at lower bound, £ | ICER at upper bound, £ |
|---|---|---|
| RDI: Zanidatamab - Zanidatamab | [redacted] | [redacted] |
| ASC disutility | [redacted] | [redacted] |
| Administration cost: Simple IV | [redacted] | [redacted] |
| Proportion receiving subsequent trt - Zanidatamab | [redacted] | [redacted] |
| HCRU cost: Morphine (1 mg) | [redacted] | [redacted] |
| HCRU frequency (PD): Morphine (1 mg) | [redacted] | [redacted] |
| HR - PFS (INV) vs ASC | [redacted] | [redacted] |
| HCRU cost: Oncologist | [redacted] | [redacted] |
| Diarrhoea Grade 3 frequency: Zanidatamab | [redacted] | [redacted] |
| Administration cost: Complex (pro-longed) | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; HCRU, healthcare resource utilisation; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INV, investigator assessment; IV, intravenous; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; trt, treatment.

**Figure 6: Tornado plot showing OWSA results on the ICER (including PAS) – zanidatamab versus ASC – 3.5% discount**

Abbreviations: ASC, active symptom control; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

Results of the scenario analyses are presented in Table 5 for both comparators.

Justification for each scenario are presented in Table 89 of the company submission.

**Table 5: Scenario analysis results (including PAS) – 3.5% discount**

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| **Base case** | | | [redacted] | [redacted] |
| Time horizon | 30 years | 20 years | [redacted] | [redacted] |
| | | 40 years | [redacted] | [redacted] |
| Discount rates | 1.5% for costs and QALYs | 3.5% | [redacted] | [redacted] |
| RDI | Included | Excluded | [redacted] | [redacted] |
| IHC3+ testing | Included | Excluded | [redacted] | [redacted] |
| Subsequent treatment source | UK clinical opinion | Trial data | [redacted] | [redacted] |
| Utility approach | TTD – continuous (inverse square root) | Progression-based | [redacted] | [redacted] |
| | | TTD – continuous (TTD days) | [redacted] | [redacted] |
| | | TTD – continuous (log TTD) | [redacted] | [redacted] |
| | | TTD – continuous (inverse exponential) | [redacted] | [redacted] |
| | | TTD – continuous (TTD) | [redacted] | [redacted] |
| | | TTD groupings | [redacted] | [redacted] |
| | | McCarthy (2024) | [redacted] | [redacted] |
| Age-adjusted disutilities | Included | Excluded | [redacted] | [redacted] |
| Treatment-related disutility | Included | Excluded | [redacted] | [redacted] |
| Zanidatamab OS curve | Log-logistic | Exponential | [redacted] | [redacted] |
| Zanidatamab PFS curve | Log-logistic | Generalised gamma | [redacted] | [redacted] |
| | | Gompertz | [redacted] | [redacted] |
| Zanidatamab ToT curve | Gamma | Gompertz | [redacted] | [redacted] |
| | | Weibull | [redacted] | [redacted] |
| FOLFOX + ASC OS curve | Log-normal | Exponential | [redacted] | [redacted] |
| | | Generalised gamma | [redacted] | [redacted] |
| FOLFOX + ASC PFS curve | Log-normal | Log-logistic | [redacted] | [redacted] |
| | | Gamma | [redacted] | [redacted] |

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| FOLFOX + ASC ToT approach | Equal to PFS | Median ToT and PFS HR | [redacted] | [redacted] |
| ASC OS curve | Log-logistic | Log-normal | [redacted] | [redacted] |
| PFS definition for zanidatamab | INV | ICR | [redacted] | [redacted] |
| Efficacy approach | Naive comparison | MAIC | [redacted] | [redacted] |

Abbreviations: ASC, active symptom control; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.

## *Clinical effectiveness parameters used in the economic model*

**B2. PRIORITY. Appendix O, P178-182:**

Appendix O describes the fitting of MAIC-adjusted overall and progression-free survival curves. To allow a better understanding of the advantages and disadvantages of different approaches for informing the OS and PFS extrapolations in the economic model, where feasible, please provide further evidence assessing whether the proportional hazards (PH) assumption is likely to hold. If the available evidence suggests that the PH assumption may be reasonable for the comparison of zanidatamab versus FOLFOX, please include a scenario analysis applying a HR estimated from the MAIC.

To assess whether the proportional hazard assumption may hold between zanidatamab from HERIZON-BTC-01 and FOLFOX from ABC-06, a log-cumulative hazard plot (LCHP) was produced for both overall survival (OS) and progression-free survival (PFS) endpoints.

The LCHP for OS is presented in Figure 7. The LCHP shows that the curves converge around 10 months but then are reasonably parallel thereafter. The Therneau and Grambsch's non proportionality test has a p-value of 0.5273 (failing to

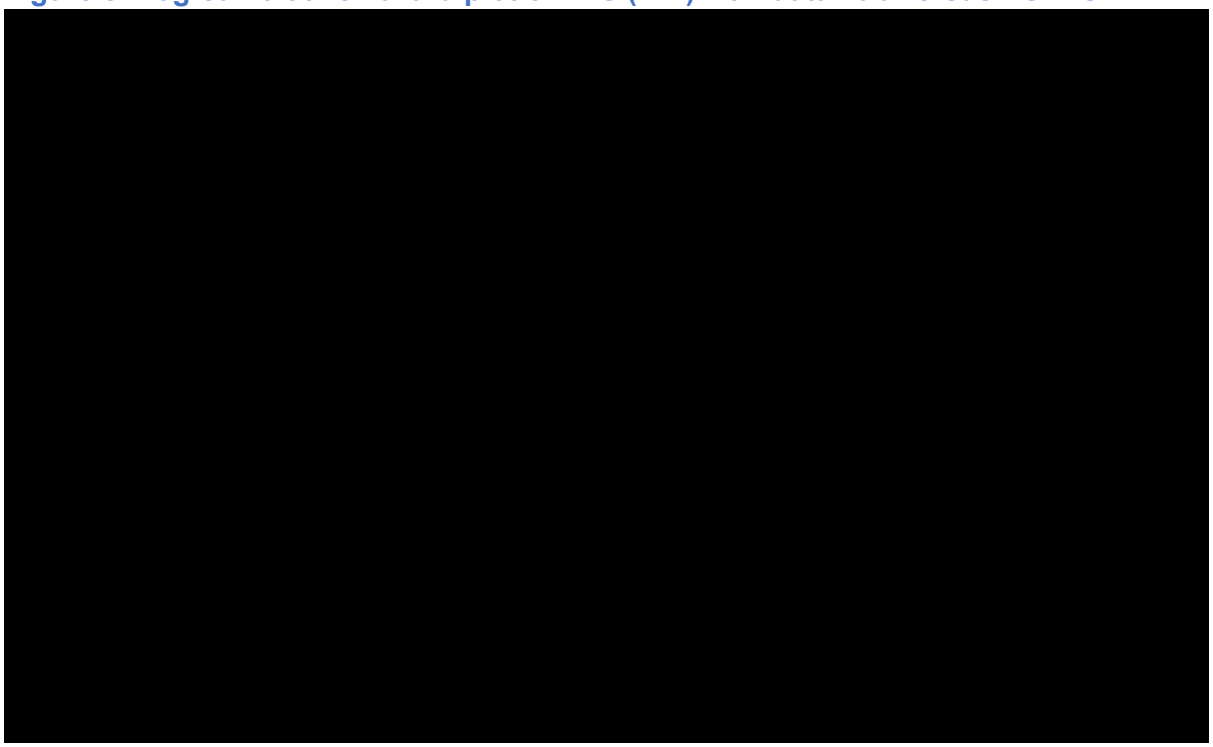
reject the null hypothesis that PH holds at the 5% significance level). As such, it may be reasonable to assume that PH holds for OS between zanidatamab and FOLFOX.

**Figure 7: Log-cumulative hazard plot of OS: zanidatamab versus FOLFOX**

Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival

The LCHP for PFS by investigator assessment (INV) is presented in Figure 8. The LCHP shows that the curves are not parallel over time, clearly crossing at around 3 months. This is further supported by the Therneau and Grambsch's test of non-proportionality that rejects the null hypothesis (p-value 0.0229). As such, the PH assumption does not hold for PFS between zanidatamab and FOLFOX.

**Figure 8: Log-cumulative hazard plot of PFS (INV): zanidatamab versus FOLFOX**



Abbreviations: FOLFOX, folinic acid, fluorouracil, and oxaliplatin; INV, investigator; PFS, progression-free survival

Given that the PH assumption does not hold for PFS, it was not appropriate to present a scenario using the hazard ratio (HR) produced from the matching-adjusted indirect comparison (MAIC). Further to this, there are also several reasons why the HRs were not utilised in the economic model. Firstly, as both FOLFOX and ASC were from the same trial, it was possible to conduct the matched analysis on the entire ABC-06 population and therefore the MAIC weights do not differ by comparator. As such, the weighted zanidatamab data remains the same when comparing to both FOLFOX and ASC; therefore, it is possible to avoid the need to rely on the PH assumption by applying parametric survival curves to the matched data when using the indirect treatment comparison (ITC) approach in the model. As shown above, the PH assumption does not hold for 1 of the key endpoints.

Another limitation of applying the HR approach is that it does not allow different curves (and hence different hazards) to be explored between the treatment arms. Zanidatamab is a HER2-targeted treatment, whilst FOLFOX is a combination of chemotherapy drugs for systemic treatment; therefore, due to the different mechanism of actions, it is clinically plausible that the hazard profiles are likely to differ between treatment arms.

Moreover, the curve fitting process (outlined in Section 3.3.2 of the company submission) determined that the log-logistic curves were the most appropriate curves to inform zanidatamab OS and PFS in the base case, which are non-proportional hazard models. As such, it would not be appropriate to apply a HR to a non-proportional hazard model if this can be avoided with an alternative approach. This was also the preference of the committee in the TA722 (pemigatinib) appraisal, where in order to extrapolate the ABC-06 trial data, the committee concluded that it was more appropriate to fit independent curves to each arm instead of applying the assumption of proportional hazards to non-proportional hazard models (8).

**B3. Section 3.3.2.1, P114:**

The EAG note that an external control arm analysis has been undertaken to inform clinical-effectiveness data, but that these data do not appear to have been incorporated into the economic modelling. Please provide a full justification for the decision not to include the external control arm in the economic modelling. The EAG appreciate there are limitations with all methods explored, but some further explanation as to why the external control arm approach was deemed less appropriate would be useful. Should the company wish to reconsider the use of the external control arm approach in the economic modelling, please update the economic model accordingly.

The ECA analysis was conducted to allow a head-to-head comparison of zanidatamab and standard of care using real-world data from a HER2+ IHC3+ population. This was attempted as comparative efficacy in the target populations was seen as an evidence gap in previous appraisals for targeted therapies in BTC. However, there are a number of limitations with the ECA analyses that were considered for the economic model, these are detailed in Section 2.10.3.3 of the company submission and summarised below:

- Patient numbers were limited in the control arm, only 12 patients were eligible for inclusion, which reduced the ability to implement all eligibility criteria from the HERIZON-BTC-01 trial. In addition, the small sample size also limited the ability to adjust for all prognostic factors in the analyses.

- The analyses compared a randomised controlled trial (RCT) with evidence from real-world patients, which may have different ways of collecting outcomes or different definitions. Given that the FOLFOX results in the ECA showed poorer efficacy than that of the ABC-06 trial, using the clinical trial may provide more conservative estimates.

- The ECA utilised the Flatiron database and therefore only considers US patients, which are likely to have different prescribing practices to UK clinical practice. As such the ECA also included patients treated with folinic acid, fluorouracil, and oxaliplatin (FOLFIRI) and capecitabine and oxaliplatin (CAPOX), not just FOLFOX, which is the relevant comparator included at scoping for this appraisal and was used in ABC-06.

Based on all the reasons above, it was deemed more appropriate to use the ABC-06 study to inform comparative efficacy within the economic model, as this was a UK based study with a  sizeable cohort for the rarity of the disease, that included patients treated in UK clinical practice with the correct comparators for this appraisal, and accepted as comparative efficacy in prior appraisals of BTC 2L targeted therapies.

For completeness, the ECA analyses has been implemented in the model as a scenario as requested. The ECA has been included within the amended cost-effectiveness model delivered with these responses. The results of the comparison to the ECA are presented in Table 6. Details of the inclusion of this comparator within the model are provided in the Appendix.

**Table 6: Deterministic results (with PAS) – ECA**

| Technologies | Total | | | Incremental | | | ICER versus zanidatamab, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| Zanidatamab | [redacted] | [redacted] | [redacted] | | | | |
| ECA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: ECA, external control arm; ICER, incremental cost-effectiveness ratio; LYG, life year gain.

**B4. PRIORITY. Section 3.3.2.1, P114:**

The EAG note that it may be possible to conduct an external control analysis using FOLFOX data collected and reported in the systemic anti-cancer therapy (SACT) dataset. The SACT dataset may provide a more appropriate data source for an external control analysis because it may allow better matching of participants to the IHC3+ population used in the HERIZON-BTC-01 zanidatamab study. Could the company please investigate the feasibility of accessing SACT data for this appraisal? If feasible, please update the external control analysis using these data and integrate the results into the economic model.

The company appreciate the EAG's suggestion to use SACT data to provide a data source for the comparators. As discussed and resolved at the clarification call on Tuesday 19 August, this was previously considered by Jazz Pharmaceuticals; however, due to the lack of routine HER2 IHC testing for BTC in the UK (as described by clinical experts (4)), small patient numbers given the rarity of HER2+ IHC3+ BTC in 2L setting and the proportion of patients who are well enough to be treated with FOLFOX, and the time and resources needed to access such an analysis, this was not considered feasible. Furthermore, timelines for data collection did not align with the timelines of the appraisal process and would not have been available in time for submission.

Further RWE sources have also been investigated. Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), in collaboration with Association pour l'étude des Cancers et Affections des voies Biliaires (ACABi) and Besançon University Hospital, conducted the ACABi PRONOBIL multicentre cohort study to identify prognostic and predictive markers in patients with BTC. Among the patients in this database, only 3 were identified as IHC3+. Separately, the ENSCCA Registry, endorsed by the European Network for the Study of Cholangiocarcinoma (ENSCCA), is a large multicentre observational study of patients with histologically or cytologically confirmed cholangiocarcinoma. No patients in this registry had IHC test results recorded. A similar study conducted in the UK would likely produce similar results and yield far too few patients for use.

Therefore, as HER2 IHC testing is not currently routine in clinical practice in the UK (4), using SACT data would likely result in either a very low patient number, (with the

same limitations as the US ECA analysis conducted) or a wider cohort of patients with HER2 status unknown (with the same limitations as the ITC vs. ABC-06).

As discussed in response to A5, ABC-06 is considered the best available evidence to inform the comparative evidence for the appraisal. The only currently available 2L treatment for patients with HER2+ IHC3+ BTC, as confirmed by clinical experts in the UK and previous appraisals, is systemic therapy with FOLFOX or palliative treatment with ASC. Therefore, the comparative evidence presented is considered the most robust available within this population for the previously noted reasons:

- ABC-06 is the pivotal UK RCT of treatments in 2L BTC, with good reporting of outcomes, a sizeable cohort for the rarity of the disease, and relevant comparators representative of treatment patterns in the UK (4-7).
- Comparing HERIZON-BTC-01 to a randomised controlled Phase 3 study containing only UK patients provides a more robust analysis than comparing to international RWE, as there are more similarities in the collection of outcome data between the two trials, including their structured, prospective data collection, standardised outcome measures, and centralised assessments.
- ABC-06 has been used in prior appraisals of targeted treatments in 2L BTC for comparative data where it was recognised as the most appropriate comparative data source (TA722 – pemigatinib “the comparative efficacy and safety data from ABC-06 were the most appropriate evidence for decision making” (8); TA948 – ivosidenib “it concluded that the ITC and subgroup results were sufficient for decision making” (9)).

**B5. Company submission, Section 3.3, P132 (Table 58):**

Please clarify whether blank cells within the adverse event table mean that the named events were not measured, or whether the event count was 0. Please comment on any potential biases that may arise from the approach used to collect AE data.

All treatment-related treatment-emergent adverse events (TEAEs) included in this table were based on investigator assessment. The method of collation and reporting

of TEAEs was consistent across the study and conducted in accordance with the study protocol requirements. Therefore, the observed differences reflect true study findings, rather than differences in data capture for the HERIZON-BTC-01 study. It is important to note the entries for ABC-06 trial for FOLFOX is based on only the published data as IPD was not available; therefore, there could be reporting bias against zanidatamab.

- "0" indicates that the treatment-related TEAEs were observed only at a lower severity (e.g. Grade 2), with no treatment related TEAEs reported at the higher grades (e.g. Grade 3, 4, or 5).
- "–" (blank cell) indicates that no treatment related TEAEs were observed at Grade 3+ in the study.

**B6. Company submission, Section 3.3, P132 (Table 58):**

The adverse event rates used in the economic model are derived from the full cohort 1 of the HERIZON-BTC study, rather than from the IHC3+ subgroup. Please comment on the potential magnitude of any bias this may introduce into the cost-effectiveness results.

The justification for using the full Cohort 1 adverse events (AEs) for the economic model is to utilise more available safety data for zanidatamab (n=80 versus n=62). There is no clinical justification why AEs would differ between HER2+ subgroups; therefore, using a broader population was considered appropriate with no expected bias. We validated this with a UK clinical expert[*] with experience of treating patients with advanced BTC in the NHS with targeted therapies, including zanidatamab. The clinical expert stated that there would be no clinical reason for a difference in the zanidatamab safety profile for patients with different levels of HER2 expression, and that the safety data can be interpreted for the whole cohort. Regulatory submissions for zanidatamab in this patient population similarly utilise a wider cohort of patients from HERIZON-BTC-01, which is detailed in the summary of product characteristics (10, 13).

[*] Professor John Bridgewater, Consultant Medical Oncologist UCLH, manages approximately 200 to 250 patients with BTC in the UK NHS annually and leads the UK's National Cancer Research Institute (NCRI) Study Group for upper gastrointestinal malignancy.

For completeness, the AEs for the IHC3+ subgroup of HERIZON-BTC-01 have been incorporated into the economic model as a scenario (see 'Controls' sheet cell J88). Table 7 presents the AEs included for the IHC3+ subgroup.

**Table 7: Grade 3+ TRAEs (IHC3+ subgroup)**

| AE | Zanidatamab (n=62) | | |
|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 5 |
| Anaemia | [redacted] | [redacted] | [redacted] |
| Aspartate aminotransferase increased | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] |
| Ejection fraction decreased | [redacted] | [redacted] | [redacted] |
| Source | HERIZON-BTC-01 (14, 15) | | |

Abbreviations: AE, adverse event; TRAE, treatment-related adverse event.

Results using the IHC3+ subgroup are presented in Table 8.

**Table 8: Deterministic results (with PAS) – IHC3+ AE subgroup**

| Technologies | Total | | | Incremental | | | ICER versus zanidatamab, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| Zanidatamab | [redacted] | [redacted] | [redacted] | | | | |
| FOLFOX + ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

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

## *Health state utility values*

**B7. PRIORITY. Company submission, Section 3.4.2.1:**

Please clarify why all analyses of utility data have been conducted using the full population of the HERIZON-BTC-01 study, rather than using the IHC3+ sub-group. Please provide the following information:

- A detailed clinical justification, informed by consultation with clinical experts, explaining the extent to which the full Cohort 1 population is generalisable to the IHC3+ subgroup in terms of utility parameters for the economic model.

- A complete set of utility analyses derived from the IHC3+ subgroup, using both the health state and time-to-death approaches. If these data are not currently available, please clarify whether they could be obtained for analysis.

- If data for the IHC3+ subgroup are available, please include functionality within the economic model to allow the use of either data set for the estimation of utilities.

The justification for using the full dataset from Cohort 1 from HERIZON-BTC-01 for the utility analyses, rather than the subgroup of IHC3+ patients is to utilise more data (n=80 versus n=62 overall, which reduces to n=64 versus n=49 post-progression). This was deemed appropriate as the majority of patients within Cohort 1 are IHC3+ (n=62) versus IHC2+ (n=18); therefore, the data mostly represents the IHC3+ patients. Clinical experts confirmed that the main impact on patients' quality of life (QoL) is disease control (i.e. response) as this is more likely to reduce the disease burden and pain (4). The complete response (CR) and objective response rate (ORR) per investigator assessment for patients in Cohort 1 was [redacted] and [redacted], compared to [redacted] and [redacted] in the IHC3+ subgroup, respectively. The majority of responders were within the IHC3+ group, this would suggest that the QoL would be improved in the IHC3+ subgroup in comparison to Cohort 1.

We validated this approach with a UK clinical expert† who stated that as zanidatamab works better in patients with HER2+ IHC3+ BTC, it may be appropriate to use this cohort for treatment-related utility analysis in accordance with the label, as quality of life is certainly based on treatment effect. As the treatment benefit is greater for the IHC3+ cohort, any treatment-related utility benefit is likely to be greater in IHC3+ than IHC2+.

† Professor John Bridgewater, Consultant Medical Oncologist UCLH, manages approximately 200 to 250 patients with BTC in the UK NHS annually and leads the UK's National Cancer Research Institute (NCRI) Study Group for upper gastrointestinal malignancy.

As it is plausible the QoL in patients with HER2+ IHC3+ BTC may differ from other subtypes, the utility analysis from HERIZON-BTC-01 using the IHC3+ subgroup is presented below for completeness. The same methods described in Section 3.4 of the company submission have been used for the analysis. Table 9 provides summary statistics from HERIZON-BTC-01 for UK utility values at screening, pre-progression, post-progression, and overall for the IHC3+ subgroup. All 62 patients provided a total of 398 utility values, with the mean utility observed for pre- and post-progression being [redacted] and [redacted], respectively.

**Table 9: Summary statistics by INV progression status - UK utility (IHC3+ subgroup)**

| Variable | N† | n‡ | Mean | StD | Min | Lower Quartile | Median | Upper Quartile | Max |
|---|---|---|---|---|---|---|---|---|---|
| Overall | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Screening | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pre-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Post-progression | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: INV, investigator assessment; StD, standard deviation.
†Number of patients.
‡Number of utility values.

The UK-based utility coefficients derived from the linear mixed model (LMM) progression model are presented in Table 10. The resulting health-state utilities are presented in Table 11.

**Table 10: LMM regression output – UK-based utility (IHC3+ subgroup)**

| Parameter | Coefficient | 95% CI | p-value |
|---|---|---|---|
| Intercept | [redacted] | [redacted] | <0.001 |
| Progressed† | [redacted] | [redacted] | <0.001 |

Abbreviations: CI, confidence interval; LMM, linear mixed model.
†Progression assessed by investigator.

**Table 11: Resulting health state utilities from the LMM (IHC3+ subgroup)**

| Parameter | Model 1 (progression-based) |
|---|---|
| PF | [redacted] |
| PD | [redacted] |

Abbreviations: LMM, linear mixed model; PD, progressive disease; PF, progression free.

The time-to-death (TTD) groupings of less than 84 days, between 84 and 195 days, and over 196 days from death summary statistics are presented in Table 12.

**Table 12: Summary statistics of TTD groupings (IHC3+ subgroup)**

| Group, days from death | n pts. | n obs. | Mean Utility (StD) | Min value | 25th percentile | 50th percentile | 75th percentile | Max value |
|---|---|---|---|---|---|---|---|---|
| <84 | | | | | | | | |
| 84-195 | | | | | | | | |
| ≥196 | | | | | | | | |

Abbreviations: obs., observations; pts., patients; StD, standard deviation; TTD, time to death.
†All patients with censored survival placed in this group.

The linear mixed-effect regression (LMER) coefficients are presented for the TTD groupings in Table 13.

**Table 13: LMER of final TTD groups (decrements and group values) – IHC3+ subgroup**

| Parameter | Intercept with decrements (95% CI) | Group utility values |
|---|---|---|
| Intercept (≥196 days) | | |
| 84-195 days | | |
| <84 days | | |

Abbreviations: CI, confidence interval; LMER, liner mixed-effect regression; TTD, time to death.

Results for the continuous TTD models are presented in Table 14 with a comparison of model fit by Akaike information criterion (AIC). Model coefficients are included in the table though they are not easily interpretable given the transformations of the TTD days variable. The equations used are provided for context. Figure 9 presents the resulting utility values from the 5 TTD continuous models.

**Table 14: Continuous TTD models fits – UK utility (IHC3+ subgroup)**

| Parameter | TTD days | Log TTD days | Inverse square root TTD days | Inverse exponent TTD days | Square TTD days |
|---|---|---|---|---|---|
| Intercept (α) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Coefficient (β) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Equation for utility | $\alpha + \beta * TTD$ | $\alpha + \beta * \ln(TTD)$ | $\alpha + \frac{\beta}{\sqrt{TTD}}$ | $\alpha + \beta * scaled(TTD)$ | $\alpha + \beta * TTD^2$ |
| AIC | -341.2 | -341.1 | -340.8 | -343.5 | -341.8 |

Abbreviations: AIC, Akaike information criterion; TTD, time to death.
TTD capped at 252 days.

**Figure 9: Utility values per day from the continuous models (IHC3+ subgroup)**

Abbreviations: exp, exponential; sqrt, square root; TTD, time-to-death.

The inverse square root was the best fitting according to the AIC, though model fit statistics were similar across the 5 models. The TTD(days), TTD, and Inverse exponential (TTD) models result in little difference across the per time-to-death days suggesting QoL only slightly declines the closer death occurs. The log(TTD) and inverse squareroot(TTD) models decrease as time-to-death comes closer which is more in line with expectations.

As requested, the IHC3+ utility subgroup data has been incorporated into the economic model as an option (see 'Controls' sheet cell J89). Results using the IHC3+ subgroup are presented in Table 15. In line with the company base case, the continuous TTD model which had the best statistical fit was chosen to inform this scenario (i.e. the inverse square root).

**Table 15: Deterministic results (with PAS) – IHC3+ utility subgroup**

| Technologies | Total | | | Incremental | | | ICER versus zanidatamab, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| 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; IHC, immunohistochemistry; LYG, life year gain; PAS, patient access scheme.

**B8. PRIORITY. Company submission, Section 3.4.5.2, P.140:**

The company's economic model applies treatment-specific utility decrements for the FOLFOX and FOLFOX + ASC treatment arms. These decrements are applied in both the progression-free and progressed disease states. Please provide a detailed clinical justification - supported by additional clinical evidence where available – for the use of different utility values across treatment arms (within health state). Please also clarify why the treatment-specific disutilities are expected to persist into the progressed state for patients who received FOLFOX, despite treatment being discontinued at that point.

Combination chemotherapy with FOLFOX is associated with a high toxicity burden that is unlikely to be fully captured by Grade 3+ AEs. For example, frequent Grade 1 or 2 AEs could potentially impact patient QoL more negatively than fewer AEs of a higher grade. Patients receiving FOLFOX are also on treatment for a short period with a low expected response rate (ORR 5% [n=4/81]) (6). Clinical experts interviewed highlighted how patient QoL is mainly determined by level of disease control and effectiveness of treatment; i.e. lower disease control would equate to lower QoL due to the disease burden and pain experienced (4). As such, it is

expected that patients receiving zanidatamab are expected to experience higher QoL compared with those treated with FOLFOX due to greater disease control, with an expected ORR of [redacted] (Cohort 1 by INV) (15). Further, improved QoL is likely to last through progression, because the decline in QoL associated with progression (or TTD) will be relative to the patient's baseline.

We validated this concept with a UK clinical expert‡ who confirmed that patient QoL is highly correlated with treatment effect. In support of the inclusion of treatment-specific utility and disutility values, the expert emphasised that the most important determinant of patient QoL is whether the treatment is effective or not. There is strong supportive clinical trial evidence with chemotherapy to show that if an anti-cancer treatment is effective, it has a positive impact on patient QoL. In ABC-06, patient-reported QoL is better with FOLFOX than with ASC even with the toxicity of chemotherapy, because it is more effective; this is true of other cancer trials, e.g. oesophageal cancer. If you have a treatment that is more effective, with much better response rates, such as with zanidatamab, you would expect the treatment to have an overwhelming impact on patient QoL, as effectiveness of treatment is the largest factor on utility gain or loss. As such, you would expect patients treated with zanidatamab to have a better QoL than those treated with FOLFOX or ASC. The clinical expert agreed that better QoL with zanidatamab is likely to last through to the progressed state, because decline in QoL related to progression will start from a higher level with zanidatamab than those whose disease is less well controlled with FOLFOX or ASC, who will have a lower QoL before progression/whilst on treatment. For these reasons, there will almost certainly be a utility benefit beyond progression; however, it is very difficult to estimate how long a treatment's QoL benefit would last beyond progression and it is almost impossible to determine as it is multifactorial. The clinical expert also confirmed that is very difficult to measure QoL post-progression as very few people are willing to complete QoL questionnaires after this point, as their QoL declines so rapidly after progression.

The company's base case applies TTD utilities instead of progression-based utilities to better reflect the rapid decline in QoL experienced as a patient approaches death.

‡ Professor John Bridgewater, Consultant Medical Oncologist UCLH, manages approximately 200 to 250 patients with BTC in the UK NHS annually and leads the UK's National Cancer Research Institute (NCRI) Study Group for upper gastrointestinal malignancy.

However, it is important that the same rationale is applied using this approach, as patients treated with zanidatamab are likely to have a better QoL whilst on treatment and therefore better disease control, so that the rate of QoL decline is the same between treatment arms but the starting point is from a higher level for patients treated with zanidatamab compared to patients treated with FOLFOX or ASC.

## *Costs*

**B9. PRIORITY. Company submission, Section 3.5.1.1, P145:**

The Relative Dose Intensity (RDI) for FOLFOX is assumed to be equal to that of zanidatamab ([redacted]%). Please provide a detailed justification for assuming the same RDI applies to both FOLFOX and zanidatamab. Please include any clinical or empirical evidence supporting this assumption. The FOLFOX is associated with substantial adverse events, and it might be assumed that FOLFOX would have a lower RDI compared to zanidatamab. Please comment on the validity of this assumption and, if appropriate, provide some scenario analyses exploring a lower RDI for FOLFOX.

The justification for applying the same RDI to both FOLFOX and zanidatamab was due to the lack of data available to use to support a specific RDI for FOLFOX in BTC. This assumption is in line with previous HTAs in 2L BTC. which did not assume any difference in RDI for FOLFOX (TA722 (8) and TA948 (9)). As such, Jazz Pharmaceuticals believe the use of the RDI obtained from the HERIZON-BTC-01 trial ([redacted]%) to be most relevant to this appraisal, or to not be considered at all (assuming 100% RDI), in line with precedent from other appraisals.

However, in response to this request, we have explored scenarios in the model using alternative RDI for FOLFOX. Suibhne (2012) (16) was a retrospective study in Ireland exploring the RDI of 'FOLFOX 6' patients of differing BMI treated for colorectal cancer (all stages). The study found that the average RDI for FOLFOX was 64.78% for patients with normal BMI and a scenario was explored using this value. Results with this RDI used in the model (see 'Controls' sheet cell J90) are presented below in Table 16.

We validated this approach with a UK clinical expert[§] who stated that for patients with advanced BTC receiving 2L FOLFOX, accurate RDI data from ABC-06 were not available. However, it is likely to be similar to the colorectal data and that it is a reasonable assumption, although the prognosis for patients with advanced BTC is worse than patients with colorectal cancer. The expert stated that FOLFOX has significant toxicities (mainly neuropathy and fatigue), so dose reductions for those cumulative toxicities would be expected, which would be of a similar incidence in the colorectal cancer cohort. Given that there is no evidence-based value for a RDI for FOLFOX in 2L BTC, the company maintains it is most appropriate and reasonable to use an RDI in line with zanidatamab ([redacted]) or should be excluded in the modelling (ie. 100%), in line with previous appraisals of targeted therapies.

**Table 16: Deterministic results (with PAS) – FOLFOX RDI at 64.78%**

| Technologies | Total | | | Incremental | | | ICER versus zanidatamab, £/QALY |
|---|---|---|---|---|---|---|---|
| | Costs, £ | LYG | QALYs | Costs, £ | LYG | QALYs (x1.7 severity modifier) | |
| 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.

**B10. Company submission, Section 3.5.2, P149-152:**

The economic model includes separate resource use and costs for special monitoring requirements and routine monitoring of patients. Please confirm with clinical experts that it is appropriate to assume that the special monitoring resource use requirements are in addition to routine monitoring. Please clarify whether there is a risk of double-counting resource use requirements and, if appropriate, provide alternative scenario analyses.

Routine monitoring represents disease-specific monitoring for BTC based on a patient's health state (progression-free or progressed) that is not treatment related,

[§] Professor John Bridgewater, Consultant Medical Oncologist UCLH, manages approximately 200 to 250 patients with BTC in the UK NHS annually and leads the UK's National Cancer Research Institute (NCRI) Study Group for upper gastrointestinal malignancy.

and hence the same frequency regardless of treatment arm. Special warnings specific to each treatment, as outlined in the respective summary of product characteristics, are additional monitoring requirements added per treatment. These costs are also only applied to patients on treatment and not accounted for when they discontinue.

As described in Section 3.5.2.2 in the company submission, for zanidatamab, left ventricular ejection fraction (LVEF) should be assessed prior to initiation of treatment and at regular intervals. These costs are not already captured within routine monitoring and therefore inclusion of this is not double counting.

As a combination chemotherapy treatment, there are several tests required for FOLFOX outside of those captured within routine monitoring for advanced BTC. An echocardiogram is required before and after each administration to monitor for any AEs on cardiac function and QT intervals. A liver function test is also recommended prior to each dose of treatment for the first 3 cycles then every other cycle thereafter. These are not already captured within routine monitoring, so inclusion of these tests is not double counting. For fluorouracil, treatment can be followed by leukopenia; therefore, daily monitoring of platelet and white blood count is recommended. As this is usually back to normal levels after the 30$^{th}$ day, the model assumed daily blood tests for the first 30 days after the first administration. Complete blood counts are captured within routine monitoring but are assumed to take place every 3 months; therefore, additional blood tests for the first 30 days are not already captured and inclusion of these are not double counting.

We validated this approach with a UK clinical expert[**] who stated that the only additional monitoring for zanidatamab over and above ASC is an echocardiogram every 3 months, and the duration of monitoring due to the difference in time on treatment. The monitoring of patients on FOLFOX is different to patients on ASC due to the additional monitoring requirements of being on chemotherapy, which includes clinical review, blood tests and scans. Patients managed with ASC would not have regular scans, but the patient would be seen in clinic. The clinical expert also

[**] Professor John Bridgewater, Consultant Medical Oncologist UCLH, manages approximately 200 to 250 patients with BTC in the UK NHS annually and leads the UK's National Cancer Research Institute (NCRI) Study Group for upper gastrointestinal malignancy.

confirmed that echocardiograms are used in the vast majority of UK clinical practice and multigated acquisition (MUGA) scans are not used.

**B11. PRIORITY. Company submission, Section 2.7.1, P60 (Table 20) and economic model subsequent treatment costs:**

The distribution of subsequent treatments from the HERIZON-BTC-01 (IHC3+ subgroup) does not fully align with the distribution applied in column G of the costs tab in the economic model. This may be due to the use of different data cuts in the report (July 2024) and the economic model (November 2024). Please clarify:

- which distribution is the most appropriate for consideration in the economic model.
- whether the most up-to-date available data are reported throughout the submission (including the clinical effectiveness and cost-effectiveness sections of the submission).
- If required, please update all analyses in the clinical and cost-effectiveness sections using the most recent available data cut.

The subsequent treatment distribution in column G of the costs tab in the economic model are correct and are using the final data cut of HERIZON-BTC-01 (data cut off [DCO] July 2024). The reference in the model (cell G244) should be amended to 'HERIZON-BTC-01 (Jul24 DCO)'. The distribution does not fully align with the distribution presented in Table 20 of the company submission as further steps were taken in order to produce a list of treatments for the economic model. These steps are detailed in Appendix Q and described below.

To establish a list of treatments to consider in the CEM, the most common subsequent therapies used in the HERIZON-BTC-01 trial (with n>2) or those considered applicable to UK practice were extracted. The remainder of the subsequent treatments were then re-categorised and assigned to 1 of the included subsequent therapies (based on similar mechanism of action or expected treatment cost). This approach was taken in order to reduce the number of subsequent therapies to be costed for in the cost-effectiveness model (CEM), whilst also maintaining the total number of treatments received with little impact to the expected

total cost. The full list of subsequent treatments from HERIZON BTC-01 and their re-categorisation is presented in Table 71 of Appendix Q. For example, there was only 1 instance of paclitaxel (shown in Table 20 of the company submission); however, for the economic model this was re-categorised as 'capecitabine' given this was a more frequent chemotherapy option in the trial (shown in Table 71 of Appendix Q).

## Section C: Textual clarification and additional points

### *HERIZON-BTC-01 CSR*

**C1. HERIZON-BTC-01 CSR:**

Please provide a version of the HERIZON-BTC-01 CSR with active links to the tables listed in Section 14.

A zipped folder containing the linked CSR and all associated appendices, tables, and figures is provided. Please download the entire zipped folder to the same source ensure links to all the associated documents work (if any problems with any of the hyperlinks please contact us).

**C2. Company submission, Section 3.5.1, P.146.**

There is a minor discrepancy between the PICC and Portacath costs reported in Table 71 of the company submission (PICC= £1,631.83; Portacath = £1,932.61) and the values included in the economic model, costs tab (PICC= £1,701.32; Portacath = £2,014.91). Please clarify which set of values is correct and should be used in the economic model.

Jazz Pharmaceuticals can confirm that the values included in the economic model are correct (PICC= £1,701.32; Portacath = £2,014.91). The values reported in Table 71 of the company submission had not been updated following the publication of latest inflation indices (PSSRU 2024). The inflation indices reference in Table 71 should also be updated to state 'Heggie (2024) uplifted to 2023 costs from PSSRU 2024'. Please note that the actual reference provided is correct (i.e. referring to PSSRU 2024).

**C3. Company submission, Section 3.4.4, P.139. Table 65**

The EAG were unable to locate the Nafees (2008) study in the reference pack. Could the company please provide this reference / paper for completeness?

A PDF of Nafees 2008 has been provided with these responses and the full reference details are as follows:

Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84.

## References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2. Meric-Bernstam F, Beeram M, Hamilton E, Oh DY, Hanna DL, Kang YK, et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. Lancet Oncol. 2022;23(12):1558-70.
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4. Jazz Pharmaceuticals. (Unpublished) Clinician interview transcripts. 2025.
5. Jazz Pharmaceuticals. (Unpublished) FOLFOX or investigational HER2-targeted product (zanidatamab) for biliary tract cancer (BTC): Delphi Panel Survey 2025.
6. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701.
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10. Jazz Pharmaceuticals. (Unpublished) Draft UK MHRA Summary of Product Characteristics. Ziihera (zanidatamab). 2025.
11. HM Treasury. The Green Book. 2024. Available from: https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-government/the-green-book-2020. Accessed on: 20th August 2025
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14. Jazz Pharmaceuticals. (Unpublished) A Phase 2b, Open-label, Single-arm Study of Zanidatamab (ZW25) Monotherapy in Participants with Advanced or Metastatic HER2-amplified Biliary Tract Cancers (HERIZON-BTC-01). Clinical Study Report - Final. 2025.

15. Jazz Pharmaceuticals. (Unpublished) HERIZON-BTC-01 IHC3+ Cohort 1 Subgroup Analysis - Tables, Listings, and Figures. DCO 11th July 2024. 2025.
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# Appendix

## *A5*

**Table 17: Reasons for exclusion of non-zanidatamab studies identified in clinical SLR**

| # | Study | Citation | Reason for exclusion |
|---|---|---|---|
| 1 | HERIZON-BTC-01 | Jazz Pharmaceuticals (Unpublished). A Phase 2b, Open-label, Single-arm Study of Zanidatamab (ZW25) Monotherapy in Participants with Advanced or Metastatic HER2-amplified Biliary Tract Cancers *(HERIZON-BTC-01 clinical study report)* | NA – included zanidatamab study |
| 2 | | Harding et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol. 2023;24(7):772-82. | NA – included zanidatamab study |
| 3 | | Pant et al. Results from the pivotal phase (Ph) 2b HERIZON-BTC-01 study: Zanidatamab in previously-treated HER2-amplified biliary tract cancer (BTC). J Clin Oncol. 2023;41(16). | NA – included zanidatamab study |
| 4 | | Wasan et al. 101P - Quality of life (QoL) outcomes in patients (pts) with zanidatamab (zani)-treated HER2-positive (HER2+) biliary tract cancer (BTC) in the phase IIb HERIZON-BTC-01 study. Ann Oncol. 2023;34(2):S219. | NA – included zanidatamab study |
| 5 | | Pant et al. A phase IIb, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers. J Clin Oncol. 2021:39(3):TPS352. | NA – included zanidatamab study |
| 6 | | Harding et al. HERIZON-BTC-01 study group. A plain language summary of the results from the phase 2b HERIZON-BTC-01 study of zanidatamab in participants with HER2-amplified biliary tract cancer. Future Oncol. 2024;20(31):2319-29. | NA – included zanidatamab study |
| 7 | | Pant et al. Zanidatamab (zani) in previously treated HER2+ biliary tract cancer (BTC): Impact on patient-reported pain outcomes in the phase 2b HERIZON-BTC-01 study. J Clin Oncol. 2024;42(3). | NA – included zanidatamab study |
| 8 | | Sun et al. Zanidatamab (ZW25; Zani) in patients (pts) with previously treated advanced human epidermal growth factor receptor 2 (HER2)-amplified biliary tract cancer (BTC): Asia subgroup analysis of the phase IIb HERIZON-BTC-01 study. Ann Oncol. 2023;34:S1522–33. | NA – included zanidatamab study |
| 9 | | Pant et al. Results from the pivotal phase (Ph) 2b HERIZON-BTC-01 study: Zanidatamab in previously treated HER2-amplified biliary tract cancer (BTC). 2023;41(16):4008. | NA – included zanidatamab study |
| 10 | | A Study of ZW25 (Zanidatamab) in subjects with advanced or metastatic HER2-amplified biliary tract cancers (HERIZON-BTC-01). Available at: https://clinicaltrials.gov/study/NCT04466891?cond=biliary%20tract%20cancer&aggFilters=results:with&rank=3 | NA – included zanidatamab study |

| # | Study | Citation | Reason for exclusion |
|---|---|---|---|
| 11 | | Oh et al. Asia subgroup overall survival and long-term follow-up results of the phase IIb HERIZON-BTC-01 study: Zanidatamab in previously treated human epidermal growth factor receptor 2 (HER2)-amplified biliary tract cancer (BTC). Ann Oncol. 2025;35:S1453. | NA – included zanidatamab study |
| 12 | Zanidatamab | Meric-Bernstam et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. Lancet Oncol. 2022;23(12):1558-70. | NA – included zanidatamab study |
| 13 | | Meric-Bernstam et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): results from a phase I study. J Clin Oncol. 2021;39:299. | NA – included zanidatamab study |
| 14 | Zanidatamab | Crespo-Cruz. Unveiling the secrets of real-world use of zanidatamab in an English biliary tract cancer cohort. Presented at Precision BTC Network meeting; 22–23 May; Mallorca, Spain; 2025. | NA – included zanidatamab study |
| 15 | Zanidatamab | Smolenschi et al. Real-world efficacy of zanidatamab in patients with HER2 positive advanced biliary tract cancers. Eur J Cancer. 2025;3;222:115432. | NA – included zanidatamab study |
| 16 | SUMMIT | Harding et al. Antitumour activity of neratinib in patients with HER2-mutant advanced biliary tract cancers. Nat Commun. 2023;6;14(1):630. | Irrelevant comparator (neratinib) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. These trials were all single-arm so could not provide other relevant comparator data. |
| 17 | | Harding et al. Targeting HER2 mutation–positive advanced biliary tract cancers with neratinib: Final results from the phase 2 SUMMIT basket trial. J Clin Oncol. 2022;40:4079. | |
| 18 | | Harding et al. Targeting HER2 (ERBB2) mutation-positive advanced biliary tract cancers with neratinib: Results from the phase II SUMMIT 'basket' trial. Clin Oncol. 2021;39:320. | |
| 19 | | Harding et al. Treating HER2-mutant advanced biliary tract cancer with neratinib: benefits of HER2-directed targeted therapy in the phase 2 SUMMIT 'basket' trial. Ann Oncol. 2019;30:iv127. | |
| 20 | HERB | Ohba et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing unresectable or recurrent biliary tract cancer (BTC): An investigator-initiated multicenter phase 2 study (HERB trial). J Clin Oncol. 2022;40:4006. | Irrelevant comparator (trastuzumab deruxtecan) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. These trials were all single-arm so could not provide other relevant comparator data. |
| 21 | | Ohba et al. Multicenter phase II trial of trastuzumab deruxtecan for HER2-positive unresectable or recurrent biliary tract cancer: HERB trial. Future Oncol. 2022;18(19):2351-60. | |
| 22 | | Ohba et al. Multicenter phase II study of trastuzumab deruxtecan (DS-8201) for HER2-positive unresectable or recurrent biliary tract cancer: HERB trial. J Clin Oncol. 2020;38:TPS4654. | |
| 23 | | Ohba et sl. Trastuzumab deruxtecan in human epidermal growth factor receptor 2-expressing biliary tract cancer (HERB; NCCH1805): a multicenter, single-arm, Phase II trial. J Clin Oncol. 2024;42(27):3207–7. | |
| 24 | KCSG-HB19-14 | Lee et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). Lancet Gastroenterol Hepatol. 2023;8(1):56-65. | Irrelevant comparator (trastuzumab) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. These trials were all single- |
| 25 | | Lee et al. Trastuzumab plus FOLFOX for gemcitabine/cisplatin refractory HER2-positive biliary tract cancer: A multi-institutional phase II trial of the Korean Cancer Study Group (KCSG-HB19-14). J Clin Oncol. 2022;40(16). | |

| # | Study | Citation | Reason for exclusion |
|---|---|---|---|
| | | | arm so could not provide other relevant comparator data. |
| 26 | DESTINY-PanTumor02 (DP-02) | Meric-Bernstam et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 Phase II trial. J Clin Oncol. 2024;42(1):47-58. | Irrelevant comparator (trastuzumab deruxtecan) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 27 | | Meric-Bernstam et al. LBA34 Trastuzumab deruxtecan (T-DXd) for pretreated patients (pts) with HER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 (DP-02) study. Ann Oncol. 2023;34:S1273-4. | |
| 28 | | Meric-Bernstam et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results. J Clin Oncol. 2023;41(17_suppl):LBA3000. | |
| 29 | | Makker et al. 148P DESTINY-PanTumor02 study of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: Exploratory biomarker analyses of HER2 expression and gene amplification in tissue and plasma. Ann Oncol. 2023;34:S239-40. | |
| 30 | | Li et al. 654O Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with solid tumors harboring specific HER2-activating mutations (HER2m): Primary results from the international phase II DESTINY-PanTumor01 (DPT-01) study. Ann Oncol. 2023;34:S459-60. | |
| 31 | | A Study of T-DXd for the Treatment of Solid Tumors Harboring HER2 Activating Mutations (DPT01). ClinicalTrials.gov, NCT04639219. | |
| 32 | | Oaknin et al. Efficacy of trastuzumab deruxtecan in HER2-expressing solid tumors by enrollment HER2 IHC status: post hoc analysis of DESTINY-PanTumor02. Adv Ther. 2024;41(11):4125–39. | |
| 33 | NR | Piha-Paul et al. A first-in-human phase I study of TAS0728, an oral covalent binding inhibitor of HER2, in patients with advanced solid tumors with HER2 or HER3 aberrations. Invest New Drugs. 2021;39(5):1324-1334. | Irrelevant comparator, - not included in the scope of the SLR or the appraisal as it is not approved. This was a single-arm trial so could not provide other relevant comparator data. |
| 34 | SGNTUC-019 | Yoshiaki et al. Tucatinib and trastuzumab for previously treated HER2-positive metastatic biliary tract cancer (SGNTUC-019): A phase 2 basket study. J Clin Oncol. 2023;41(16_suppl):4007. | Irrelevant comparator (tucatinib and trastuzumab) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 35 | | Nakamura et al. Tucatinib and trastuzumab for previously treated human epidermal growth factor receptor 2-positive metastatic biliary tract cancer (SGNTUC-019): a Phase II basket study. J Clin Oncol. 2023;41(36):5569–78. | |
| 36 | | Bekaii-Saab et al. P-74 SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations: Biliary tract cancer cohort (trial in progress). Ann Oncol. 2022; 33:S273-4. | |
| 37 | | Bekaii-Saab et al. P-37 SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations: Biliary tract cancer cohort (trial in progress). Ann Oncol. 2021; 32:S108-9. | |

| # | Study | Citation | Reason for exclusion |
|---|---|---|---|
| 38 | NR | Li et al. Safety and efficacy of pyrotinib in patients with NSCLC and other advanced solid tumors with activating HER2 alterations: A phase I basket trial. J Clin Oncol. 2020;38(15_suppl):3510. | Irrelevant comparator - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 39 | NR | Patel et al. 313 A phase 1 evaluation of tebotelimab, a bispecific PD-1 X lag-3 dart® molecule, in combination with margetuximab in patients with advanced HER2+ neoplasms. J Immunother Cancer 2020;8(Suppl 3):A1–A559 | Irrelevant comparator - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 40 | MyPathway | Javle et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2021;22(9):1290-300. | Irrelevant comparator (pertuzumab and trastuzumab) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 41 | | Meric-Bernstam et al., MyPathway HER2 basket study: Pertuzumab (P) + trastuzumab (H) treatment of a large, tissue-agnostic cohort of patients with HER2-positive advanced solid tumors. J Clin Oncol. 2021;39:3004. | |
| 42 | | Javle et al. Pertuzumab + trastuzumab for HER2-positive metastatic biliary cancer: Preliminary data from MyPathway. J Clin Oncol. 2017;35:402. | |
| 43 | NR | Yao et al. The HER2-targeting ADC SHR-A1811 in HER2 expressing/mutated advanced non-breast solid tumors (STs): Results from the global phase I study. Ann Oncol. 2023;34;S461-2. | Irrelevant comparator - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm phase I trial so could not provide other relevant comparator data. |
| 44 | | Yao et al. Abstract CT175: Safety, tolerability, pharmacokinetics, and antitumor activity of SHR-A1811 in HER2-expressing/mutated advanced solid tumors: a global phase 1, multi-center, first-in-human study. Cancer Res. 2023;83(8_Supplement):CT175. | |
| 45 | | Yao et al. Safety, efficacy, and pharmacokinetics of SHR-A1811, a human epidermal growth factor receptor 2-directed antibody-drug conjugate, in human epidermal growth factor receptor 2-expressing or mutated advanced solid tumors: a global Phase I trial. J Clin Oncol. 2024;42(29):3453–65. | |
| 46 | TAPUR | Cannon et al. Pertuzumab plus trastuzumab (P+T) in patients (pts) with biliary tract cancer (BTC) with ERBB2/3 amplification (amp), overexpression (oe), or mutation (mut): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. J Clin Oncol. 2023;41:546. | Irrelevant comparator (pertuzumab and trastuzumab) - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm basket trial so could not provide other relevant comparator data. |
| 47 | | Cannon et al. Pertuzumab plus trastuzumab in patients with biliary tract cancer with ERBB2/3 alterations: results from the targeted agent and profiling utilization registry study. J Clin Oncol. 2024;42(27):3228–37. | |

| # | Study | Citation | Reason for exclusion |
|---|---|---|---|
| 48 | NR | Feng et al. Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell. 2018;9(10):838–47. | Irrelevant comparator - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm phase I trial so could not provide other relevant comparator data. |
| 49 | NR | Gong et al. Safety and efficacy of IBI354 (anti-HER2 ADC) in patients (pts) with advanced gastrointestinal (GI) cancers: Results from a phase I study. Ann Oncol. 2024;35:S467–8. | Irrelevant comparator - not included in the scope of the SLR or the appraisal as it is not available in the UK for BTC. This was a single-arm phase I trial so could not provide other relevant comparator data. |

Abbreviations: NA, not applicable; NR, not reported; SLR, systematic literature review.

## *B3*

### ECA – overall survival

KM data from the ECA study were digitised from the report and pseudo patient-level data were then created using the Guyot algorithm (17). Partitioned survival models (PSMs) were then fitted to the pseudo patient-level data and included in the model.

Table 18 presents the AIC and BIC scores for the extrapolated OS for ECA which shows that generalised gamma was statistically the best fitting curve. Figure 10 presents the model fits for ECA over a 10-year time horizon. Only a few of the curves fit the data well, likely due to the small patient numbers creating large steps in the Kaplan-Meier (KM) data, particularly towards the tail.

**Table 18: Statistical goodness-of-fit scores – OS – ECA**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 78.41 | 78.89 |
| Generalised gamma | 74.55 | 76.01 |
| Gompertz | 78.45 | 79.42 |
| Log-logistic | 75.92 | 76.89 |
| Log-normal | 75.54 | 76.51 |
| Weibull | 79.12 | 80.09 |
| Gamma | 79.81 | 80.78 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ECA, external control arm; OS, overall survival.

**Figure 10: Parametric curve fits - OS – ECA**

Abbreviations: ECA, external control arm; KM, Kaplan-Meier; OS, overall survival.

### ECA – progression-free survival

As with OS, KM data were digitised from the ECA report and pseudo patient-level data were then created using the Guyot algorithm (17). PSMs were then fitted to the pseudo patient-level data and included in the model.

Table 19 presents the AIC and BIC scores for the extrapolated PFS for the ECA. Generalised gamma was statistically the best fitting curve according to AIC and BIC, closely followed by log-normal and log-logistic. Figure 11 presents the model fits for ECA over a 10-year time horizon. The majority of curves struggle to fit the observed data due to the shape of the KM likely due to small patient numbers creating large steps.

**Table 19: Statistical goodness-of-fit scores – PFS – ECA**

| Distribution | AIC | BIC |
|---|---|---|
| Exponential | 68.57 | 69.05 |
| Generalised gamma | 61.01 | 62.46 |
| Gompertz | 68.54 | 69.51 |
| Log-logistic | 63.99 | 64.96 |
| Log-normal | 64.77 | 65.74 |
| Weibull | 69.80 | 70.77 |
| Gamma | 70.40 | 71.37 |

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ECA, external control arm; PFS, progression-free survival.

**Figure 11: Parametric curve fits - PFS – ECA**

Abbreviations: ECA, external control arm; KM, Kaplan-Meier; PFS, progression-free survival.

## ECA – Time on treatment

The same approach used to estimate the treatment duration for FOLFOX+ASC has been used for the ECA arm. For the base case, it is assumed that the proportion of patients on treatment is the same as those who are progression-free. An alternative option is available where a HR was estimated based on the reported median PFS for the ECA arm ( months) and reported median treatment duration ( months).

The resulting relative difference estimates a HR of [redacted][1], which is then applied to the ECA PFS curve.

### ECA - Treatment costs

The ECA includes treatments for FOLFOX (n=[redacted]), FOLFIRI (n=[redacted]), fluorouracil (n=[redacted]), gemcitabine + cisplatin (n=[redacted]), gemcitabine + carboplatin (n=[redacted]), gemcitabine + capecitabine (n=[redacted]). For simplicity, the gemcitabine chemotherapies have been combined and costed as the gemcitabine + cisplatin combination.

Unit costs for the treatments not presented in the Company submission are presented in Table 20.

**Table 20: Unit drug costs - ECA**

| Drug | Vial Size | Pack size (number of vials) | Unit cost, £ | Source |
|---|---|---|---|---|
| Irinotecan | 100 mg | 1 | 8.99 | eMIT 2025 (18) |
| Gemcitabine | 200 mg | 1 | 4.44 | |
| Cisplatin | 100 mg | 1 | 37.74 | |

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

Table 21 presents the dosing schedules, dose intensity and final cost per treatment cycle including wastage for treatments within the ECA.

**Table 21: Dosing schedule and cost per treatment cycle - ECA**

| Treatment (distribution) | | Dose | RDI | Cost per treatment cycle,† £ | Source |
|---|---|---|---|---|---|
| FOLFOX (50%) | Oxaliplatin | 85 mg/m$^2$ Q2W | [redacted] | [redacted] | ABC-06 (6) |
| | 5FU (bolus) | 400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | 5FU (continuous) | 2,400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | Folinic acid | 350 mg Q2W | [redacted] | [redacted] | |
| FOLFIRI (25%) | Irinotecan | 180 mg/m$^2$ Q2W | [redacted] | [redacted] | Caparica et al. (2019) (19) |
| | 5FU (bouls) | 400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | 5FU (continuous) | 2,400 mg/m$^2$ Q2W | [redacted] | [redacted] | |
| | Folinic acid | 200 mg Q2W | [redacted] | [redacted] | |
| Gemcitabine + cisplatin (25%) | Gemcitabine | 1,000 mg/m$^2$ Q2W | [redacted] | [redacted] | Ioka et al. (2022) (20) |
| | Cisplatin | 25 mg/m$^2$ Q2W | [redacted] | [redacted] | |

Abbreviations: 5FU, fluorouracil; ECA, external control arm; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; Q2W, every 2 weeks; Q4W, every 4 weeks; RDI, relative dose intensity.
† Includes RDI and wastage

The administration costs for each regimen in the ECA are presented in Table 22.

**Table 22: Administration costs - ECA**

| Treatment | | Administration | Cost type | Unit cost, £ | Source/description |
|---|---|---|---|---|---|
| FOLFOX | 5FU (bolus) | 5-10 min bolus (day 1) | Complex IV – per administration† | 337.16 | National Cost Collection 23/24: Deliver complex chemotherapy, including prolonged infusional treatment, at First Attendance (SB14Z) (21) |
| | Oxaliplatin/ folinic acid | 2 hours intravenous infusion concurrently (day 1) | | | |
| | 5FU (continuous) | 46-hours continuous intravenous infusion (day 1-2) | Oncology nurse for removal – per treatment cycle | 157.13 | National Cost Collection 23/24: 370 Medical oncology services – Non-consultant led - Non-admitted face-to-face (WF01A) (21) |
| | | | PICC or Portacath insertion costs and | 1,631.83 (PICC) 1,932.61 (Portacath) | Heggie (2024) uplifted to 2023 costs from PSSRU 2023 (22, 23) |

| Treatment | | Administration | Cost type | Unit cost, £ | Source/description |
|---|---|---|---|---|---|
| | | | complications – one-off cost | | |
| FOLFIRI | 5FU (bolus) | 5-10 min bolus (day 1) | Complex IV – per administration† | 337.16 | National Cost Collection 23/24: Deliver complex chemotherapy, including prolonged infusional treatment, at First Attendance (SB14Z) (21) |
| | Irinotecan/ folinic acid | 30 – 90 minute intravenous infusion concurrently (day 1) | | | |
| | 5FU (continuous) | 46-hours continuous intravenous infusion (day 1-2) | Oncology nurse for removal – per treatment cycle | 157.13 | National Cost Collection 23/24: 370 Medical oncology services – Non-consultant led - Non-admitted face-to-face (WF01A) (21) |
| | | | PICC or Portacath insertion costs and complications – one-off cost | 1,631.83 (PICC) 1,932.61 (Portacath) | Heggie (2024) uplifted to 2023 costs from PSSRU 2023 (22, 23) |
| Gemcitabine + cisplatin | Gemcitabine/ cisplatin | 30 minute infusion (day 1 and 8) | Simple IV – per administration | 133.39 | National Cost Collection 23/24: Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z) (21) |

Abbreviations: 5FU, fluorouracil; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IV, intravenous; PICC, peripherally-inserted central catheter; PSSRU, Personal Social Services Research Unit.
†Also covers the cost of oxaliplatin/irinotecan and folinic acid IV infusions

### ECA – utilities

The same utilities used in the company base case are used for the ECA arm i.e. continuous TTD utilities (see Company submission Section 3.4.5.1). It is assumed that ECA has the same AE disutility and treatment disutility as FOLFOX + ASC (see Company submission Section 3.4.4 and Section 3.4.5.2). PICC and portacath administration disutilities are also applied for the FOLFOX and FOLFIRI treatments (see Company submission Section 3.4.5.4).

### ECA – other cost inputs

It is unclear whether the AEs reported for ECA are Grade 3+ and these are not split by severity. Therefore, it has been assumed that AE proportions and costs are the same as FOLFOX (see Company submission 3.5.3).

Health-state monitoring, pre-medication, special monitoring, subsequent treatments and end-of-life costs for the ECA are also assumed the same as FOLFOX.

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

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

# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

## About you

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| **1.Your name** | Paul Howard |
| **2. Name of organisation** | AMMF – The Cholangiocarcinoma Charity |
| **3. Job title or position** | Head of Policy & Research |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | AMMF is a charity, registered with the Charity Commission for England and Wales; Registration No. 1198095. AMMF was founded in 2002, as the world's first charity dedicated solely to cholangiocarcinoma (bile duct cancer). Today, AMMF remains the UK's only cholangiocarcinoma charity, now working nationally and across Europe, as well as actively contributing globally.<br><br>AMMF provides information and support to those who need it, campaigns to raise awareness of this devastating disease, and encourages and supports specialised research teams in their work towards better diagnostic techniques and treatments.<br><br>The charity is funded by donations from members of the public, and a small proportion of industry funding is received as sponsorship for specific projects, such as the annual AMMF European Cholangiocarcinoma Conference.<br><br>AMMF is not a membership organisation. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]** | AMMF has received funding from several pharmaceutical companies in the last 12 months. Each grant is outlined below:<br>• **September 2024 - £25,000 – Jazz Pharma**<br>Support to map patient pathways and develop a Patient Charter.<br>• **November 2024 - £5,000 – AstraZeneca**<br>Support for AMMF's European website.<br>• **November 2024 - £5,000 – AstraZeneca**<br>Support to deliver a patient education webinar about molecular profiling.<br>• **January 2025 - £24,993 – Taiho**<br>Support for AMMF's European Conference 2025.<br>• **February 2025 - £14,993 – Servier** |

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| **If so, please state the name of the company, amount, and purpose of funding.** | Support to map patient pathways and develop a Patient Charter.<br>• **March 2025 - £25,000 – Jazz Pharma**<br>Support for AMMF's European Conference 2025.<br>• **April 2025 - £24,993 – Servier**<br>Support for AMMF's European Conference 2025.<br>• **May 2025 - £45,000 – AstraZeneca**<br>Support for AMMF's European Conference 2025.<br>• **May 2025 - £10,000 – AstraZeneca**<br>Support for Hepatobiliary Nurse Study Day<br>• **May 2025 - £5,000 - Boehringer Ingelheim**<br>Support for AMMF's European Conference 2025.<br>• **May 2025 - £10,000 – Jazz Pharma**<br>Support for translating patient education materials for AMMF's European website |
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | Using social media, and with the help of healthcare professionals involved in the HERIZON-BTC-01 clinical trial, I was able to connect with several patients who have experience of zanidatamab therapy. Some of these patients and their partners/caregivers completed short questionnaires based on the questions within this template. Several of the quotations within this submission are taken from responses to those questionnaires.<br><br>AMMF also conducted an online survey from 27th June to 20th July 2025 to collect experiences and opinions from patients and their partners/caregivers/family. The survey received a total of 80 responses (34 patients and 36 caregivers/family). Several of the quotations within this submission are taken from responses to this survey.<br><br>Additionally, we referenced several published papers about cholangiocarcinoma. Links have been included for these references throughout the submission. |

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| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | **Symptoms**<br>Cholangiocarcinoma (CCA) causes few symptoms in its early stages. Any early symptoms that do present tend to be quite vague and non-specific. Possible symptoms include nausea, loss of appetite, abdominal discomfort, tiredness, feeling generally unwell, weight loss and high temperatures.<br><br>*"A lot of time was wasted in the first 2 months as my local GP just kept telling me I had pulled a muscle or got indigestion."* **– A cholangiocarcinoma patient**<br><br>Symptoms that are more specific, such as jaundice, typically do not present until more advanced stages when a tumour blocks the flow of bile from the liver to the intestine. Jaundice can cause yellowing of the sclera and skin (although this may be less obvious in people with darker skin tones), dark urine, pale stools and itchy skin.<br><br>Some patients may not experience significant symptoms caused by cholangiocarcinoma, but side-effects of treatments are common, and these can severely impact quality of life.<br><br>*"I have just completed 8 cycles of Cis/Gem/Durv treatment, and all my symptoms were experienced during treatment (not before). The only symptom I had experienced for several years previously was bloating."* **– A cholangiocarcinoma patient**<br><br>A survey conducted by AMMF found that fatigue/tiredness and abdominal pain/discomfort were the most reported symptoms, experienced by almost three-in-four (72.5%) patients. Fatigue/tiredness most reported as having the biggest impact on day-to-day life (43.5%) followed by pain/discomfort (32.3%).<br><br>To help relieve symptoms of jaundice, many patients will have a stent inserted to hold the bile duct open and restore flow. Unfortunately, these stents can get blocked due to a build-up of thick bile or the tumour growing through it. A blocked stent may lead to a biliary tract infection (cholangitis), which can rapidly become serious and may lead to biliary sepsis. Symptoms of a blocked stent/infection include high temperature/fever, jaundice, and chills/shivering. If these symptoms develop, patients may urgently require antibiotics, and the stent may need to be replaced.<br><br>*"Physically the cancer itself presented me with no problems but having to have biliary stents has been painful, potentially risky and periodically this makes me very sick requiring hospital stays."* **– A cholangiocarcinoma patient**<br><br>The lack of specific symptoms at earlier stages, together with a poor awareness at primary care level, frequently results in CCA being diagnosed late. |

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| | **Survival**<br>Most patients receive their diagnosis when the cancer is in advanced stages, when it is inoperable and thus a terminal diagnosis.<br><br>Statistics provided by the National Cancer Registration and Analysis Service (NCRAS) revealed that in England between 2017 and 2019, 1-year survival was under 30%. In England between 2014 and 2016, 5-year survival was 5%.[1]<br><br>For many patients this diagnosis and the prognosis can be truly shocking, and they find it very difficult to assimilate the details. Patients struggle to accept that available treatment options are so limited, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left.<br><br>For the small proportion of CCA patients who can receive potentially curative surgery, the majority will develop recurrent disease. A large study by Hyder *et al* found the median recurrence-free survival of 301 patients who had resection for intrahepatic CCA was only 20 months, with 53.5% developing a recurrence during the median follow-up duration of 31 months.[2]<br><br>**Employment**<br>Our survey revealed that 72.4% of patients "completely" or "somewhat" agree that their productivity at work was adversely affected by their diagnosis. More than one-in-three (35.9%) patients who responded to our survey had permanently stopped working following their diagnosis and a further 21.9% had temporarily stopped working.<br><br>*"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"* **– A cholangiocarcinoma patient**<br><br>**Partners/Family/Caregivers**<br>For loved ones and carers, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one and ask for advice on clinical trials and treatment options that are not available through the health service.<br><br>*"It is a terrible position to be in to watch someone you love so much face such a devastating illness as well as her facing the prospect of early death. I felt frightened and stressed every day. I felt anxious and powerless to improve her situation and watching her suffer was unbearable."* ***– Husband of a cholangiocarcinoma patient*** |

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| | Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms with what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'.<br><br>*"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."* **– Wife of a cholangiocarcinoma patient**<br><br>Employment and work productivity of carers is commonly affected because of responsibilities associated with caregiving. Many caregivers report having to make adjustments at their workplace, such as taking time off or reducing their contracted hours. Our online survey found that almost two-in-three (64.7%) caregivers "completely" or "somewhat" agreed that their productivity at work had been adversely affected.<br><br>*"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, to attend ED with her. I lived 2 hours away, was working as a hospital doctor and had a 1-year-old at the time. We moved house shortly after her diagnosis so I could accommodate my mother (and my 90 y/o grandmother) for end-of-life care. I feel I have been personal doctor at home as well as for work – 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."* **– Daughter of a cholangiocarcinoma patient**<br><br>[1] *Cancer Research UK - https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival (accessed 18/07/25)*<br>[2] *Recurrence after operative management of intrahepatic cholangiocarcinoma - https://doi.org/10.1016/j.surg.2012.12.005* |

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| **7. What do patients or carers think of current treatments and care available on the NHS?** | Currently a surgical resection or transplantation (for a small proportion of selected patients) are the only potentially curative treatment options for patients diagnosed with CCA. However, patients are typically diagnosed too late for surgery to be viable. An analysis of cholangiocarcinoma patient records in England from 2014-2017 found that only 12.4% received potentially curative surgery.[1]<br><br>*"They told me surgery was my only chance of survival, but it might already be too late."* **– A cholangiocarcinoma patient**<br><br>Most people diagnosed with CCA are inoperable and have no potentially curative treatment options, leaving only a very limited selection of systemic therapies aimed at extending life. In England, between 2014-2017, over half (50.5%) of patients received no cancer-specific treatment at all.[1] In advanced disease, CCA patients who do not receive systemic therapy have a very short life expectancy, typically 3-4 months.[2]<br><br>The current standard first-line treatment for those with inoperable CCA is a combination of the chemotherapies gemcitabine and cisplatin (GemCis) with the immunotherapy, durvalumab.<br><br>*"[Durvalumab] has helped hold my cancer back. It gave us more birthdays, more time around the dinner table, more ordinary moments that now feel extraordinary."* **– A cholangiocarcinoma patient**<br><br>*"I went onto a treatment of chemotherapy combined with immunotherapy. The treatments caused side effects and made it impossible for me to function properly and certainly I couldn't go back to work in my job as a secondary school English teacher and Head of Department. It felt like being poisoned. This treatment was effective for a fairly short time before it failed, and the immunotherapy didn't work at all."* **– A cholangiocarcinoma patient**<br><br>For people with whom first-line therapy is no longer controlling their disease, second-line therapy is either a targeted therapy (for those with targetable mutations) or a systemic therapy such as the combination chemotherapy FOLFOX which has a modest benefit on survival and can be poorly tolerated. Undergoing chemotherapy, which might or might not extend their life for a few months, is often at the expense of quality of life, and that of their families.<br><br>*"Starting palliative chemotherapy was difficult since you know it's not going to be curative (although you hope this cancer might be especially sensitive) and you are told it may prolong your life only by a few months. Making this decision was particularly challenging, since my mum felt really well when she started – and you know how dreadful the side-effects of chemo are. Chemotherapy was difficult for her, she had minimal quality of life due to side effects while she was taking it* |

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| | *and although she had shrinkage of the tumour, the question was whether there was really any point since there was no-where to go after the 8 rounds, except perhaps more of the same. My mum has said repeatedly she could never go through chemotherapy again – it's no life. She had several admissions with pain and sepsis, blood transfusions for anaemia, and finally neutropenic sepsis during cycle 7."* **– Daughter of a cholangiocarcinoma patient**<br><br>There is significant regional variance in the treatment of CCA. Analysis of patient treatment data from 2014-2017 in England found that the percentage of patients who received potentially curative surgery ranged from 8.8% to 16.2% across Cancer Alliances. Similarly, the percentage of patients in receipt of systemic therapy ranged from 12.4% to 29.4%.[1]<br><br>*"I believe if you go to the right hospital, you will get the right treatment at the right time. Unfortunately, you go to your nearest hospital, and we found in our case they had no specialist team and the whole system takes too long from diagnosis to any treatment. My wife was made more ill in the NHS. Where she is now, her treatment has been what you would hope for."* **– Husband of a cholangiocarcinoma patient**<br><br>Our survey found that more than one-in-three (36.2%) CCA patients sought a second opinion about their diagnosis and/or treatment options.<br><br>*"My care was very poor at the start, if I hadn't pushed myself for 2nd opinions, I wouldn't be here today."* **– A cholangiocarcinoma patient**<br><br>[1] *Cohort study to assess geographical variation in cholangiocarcinoma treatment in England* - http://dx.doi.org/10.4251/wjgo.v15.i12.2077<br>[2] *British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma* - *https://gut.bmj.com/content/73/1/16* |

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| **8. Is there an unmet need for patients with this condition?** | The most significant unmet need for CCA patients is earlier and faster diagnosis. Analysis of CCA patients in England from 2006-2017 found that the most common route to diagnosis was emergency presentation (49.6%)[1]. Only 55% of CCA patients had records with complete staging, of which 79% received a stage 3 or 4 tumour diagnosis.[1]<br><br>In our online survey, almost one-in-three (30%) reported that it took them over three months to receive a diagnosis of CCA from the time they first felt unwell and sought medical advice. A potential contributing factor is the rate of initial misdiagnosis. Almost one-in-three (31.4%) respondents indicated that they were initially misdiagnosed before later being diagnosed with CCA. If more CCA patients could be diagnosed at earlier stages, it could have a significant positive impact on their outcome.<br><br>*"Doctor thought it was gastroenteritis and sent off stool tests about one month before she went yellow"* **– Family member of a cholangiocarcinoma patient**<br><br>In addition, advancements in treatment for CCA have been very slow, with few new therapies introduced in recent decades. During this time, the improvement in survival rates for people diagnosed with CCA has fallen significantly behind improvement in survival for many other cancers. Currently in the NHS, although there are approved therapies targeting FGFR2 and IDH1 in the second line, the only approved second-line treatment option for HER-2 positive patients with advanced CCA is the combination chemotherapy FOLFOX, which has a modest benefit on survival and can be poorly tolerated. These patients need access to more effective therapies, which are better tolerated (with fewer side effects), and will improve survival. CCA patients want to be able to live longer, with a better quality of life following their diagnosis.<br><br>Some CCA patients report difficulty in accessing molecular profiling tests to see whether they may be eligible for a targeted therapy. In our online survey, 17.6% of patients reported that molecular profiling tests had not been carried out, with a further 11.8% of respondents who were unsure whether it had been done. It is essential that all CCA patients have molecular profiling tests to identify whether they have a targetable gene fault, such as being HER2-positive. Without molecular profiling tests being carried out, some CCA patients miss out on their optimal treatment.<br><br>For the small proportion of patients who have successful curative surgery, improved adjuvant therapies are needed to help reduce the significant risk of recurrence.<br><br>[1] *Regional variation in routes to diagnosis of cholangiocarcinoma in England from 2006 to 2017 - http://dx.doi.org/10.3748/wjg.v29.i24.3825* |

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| **9. What do patients or carers think are the advantages of the technology?** | Patients and carers look to new technologies and therapies with the hope they will offer extended survival over the current standards of care that might be offered. Although zanidatamab is not curative, for them the treatment is something they know could be effective in extending survival, especially when their first-line therapy is no longer working for them.<br><br>*"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 and has completely gone from my lungs and lymph nodes where it had spread to. I am able to live a normal life and no longer feel completely defined by my cancer."* **– A cholangiocarcinoma patient treated with zanidatamab**<br><br>*"My mother has had 4 years of good quality life due to [zanidatamab]. She regained her independence and is currently caring for my 95 y/o grandmother. We are still dealing with medical problems as they arise, since her disease is progressing, but she has had some time to recover from her year on chemo, visit family and move closer to me. I was able to return to work and help them as needed. I'm not being called so frequently, so am able to maintain my job at 80% LTFT and look after my family. 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 my mother."* - **Daughter of a cholangiocarcinoma patient treated with zanidatamab**<br><br>*"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."* **– Husband of a cholangiocarcinoma patient treated with zanidatamab**<br><br>*"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 new 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."* **– Partner of a cholangiocarcinoma patient treated with zanidatamab**<br><br>Zanidatamab presents an alternative second-line treatment option for CCA patients who have a HER2 mutation - approximately 17.4% of extrahepatic CCA and 4.8% of intrahepatic CCA patients[1]. Zanidatamab can potentially offer a realistic improvement for a group of patients for whom there is so little in terms of effective treatments. This additional therapy, which offers the chance for some people diagnosed with CCA to have a little more time with their loved ones, is incredibly important after receiving the shock of diagnosis and a dismal prognosis. |

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| | *"[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. 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."* **– *A cholangiocarcinoma patient treated with zandidatamab***<br><br>*"[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. It is almost unbelievable just how different our lives are now she is on this treatment. She experiences little or no side effects."* **– Husband of a cholangiocarcinoma patient treated with zanidatamab**<br><br>It is reported that the side-effect profile for zanidatamab is favourable compared with chemotherapy, which can be poorly tolerated by CCA patients.<br><br>*"From our experience, [my partner] has less 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. [He] has also been able to go back to work part-time."* **– Partner of a cholangiocarcinoma patient treated with zanidatamab**<br><br>*"I feel the advantage for this treatment is that there are a lot fewer side effects compared to chemotherapy alternatives, I don't feel as tired and I'm able to continue doing exercise. 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)."* **– A cholangiocarcinoma patient treated with zanidatamab**<br><br>[1]*New Horizons for Precision Medicine in Biliary Tract Cancers* - https://doi.org/10.1158/2159-8290.CD-17-0245 |

## Disadvantages of the technology

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| **10. What do patients or carers think are the disadvantages of the technology?** | The patients and caregivers we have spoken to did not see any significant disadvantages with this treatment when compared with alternative options. Some patients described the time required for the treatment administration and some side effects, but they consider these minor inconveniences.<br><br>*"There are no disadvantages that come to mind. I do have to go and get blood tests every two weeks and I have treatment which takes up most of an afternoon every two weeks. The infusion is only an hour, but the waiting around takes the time. This is a small thing to have to do for the rewards. I don't like having a port but really, that's nothing: I am alive."* **– A cholangiocarcinoma patient treated with zanidatamab**<br><br>*"Currently, the only disadvantage is the distance [my partner] has to travel for treatment. It would be great if the treatment was available locally."* **– Partner of a cholangiocarcinoma patient treated with zanidatamab**<br><br>*"Very mild diarrhoea for a few days and a feeling of bloating immediately after treatment. The disadvantages are negligible in comparison to the benefits."* **– A cholangiocarcinoma patient treated with zanidatamab**<br><br>Patients and carers did express concern about continued access to the treatment, particularly as it is not currently available through the NHS.<br><br>*"It is not available on the NHS, and I worry about possible supply issues."* **– Husband of a cholangiocarcinoma patient** |

## Patient population

| | |
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| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | This treatment is only suitable for a sub-group of CCA patients – those who are HER2-positive. This means that their cancer cells must make extra copies of the HER2 gene (HER2 amplification) and they must have higher-than-normal HER2 protein amounts.<br><br>Most CCA patients will have different gene faults, only some of which currently have targeted treatments.<br><br>It is essential that all CCA patients have molecular profiling tests to identify whether they have a targetable gene fault, such as being HER2-positive. Without molecular profiling tests being carried out, some CCA patients could miss out on their optimal treatment. Within their guidelines for the diagnosis and management of cholangiocarcinoma, the British Society for Gastroenterology (BSG) recommendation 41 states, ***"CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise."*** Therefore, ideally, a CCA patient should have molecular profiling completed at diagnosis to identify the optimal treatment options and minimise any delays in initiating therapy. |

## Equality

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| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | None that I am aware of. |

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| **13. Are there any other issues that you would like the committee to consider?** | Whilst the incidence of CCA is rising in England, in 2016-2018 the age-standardised incidence rate was 4.6 per 100,000 person years.[1] The sub-group of CCA patients who are HER2-positive is much smaller; approximately 17.4% of extrahepatic CCA and 4.8% of intrahepatic CCA patients.[2] The small number of people for whom zanidatamab may be a suitable treatment needs to be considered when assessing evidence and developing a recommendation.<br><br>Currently, CCA patients who are HER2-positive have no approved targeted therapies. Zanidatamab addresses this unmet need and can provide significant improvements in quality of life and give extra time with loved ones, as demonstrated by the case studies within this submission.<br><br>[1] *Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation* - https://doi.org/10.1016/j.jhepr.2023.100983<br>[2] *New Horizons for Precision Medicine in Biliary Tract Cancers* - https://doi.org/10.1158/2159-8290.CD-17-0245 |

## Key messages

| | |
|---|---|
| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • Cholangiocarcinoma typically presents with few symptoms in the early stages and those that are present tend to be vague and non-specific. This contributes to the disease commonly being diagnosed at late stages, when it is advanced and usually inoperable.<br>• Surgical resection or liver transplantation are currently the only potentially curative treatments for cholangiocarcinoma, but these are not viable for most patients. Even in patients who have successful surgery, recurrence of the cancer is common.<br>• For most cholangiocarcinoma patients the only treatment options include chemotherapy, aimed at extending life. This is often accompanied by significant side effects which negatively impact quality of life for patients and their family.<br>• The introduction of the targeted therapy, zanidatamab, presents an alternative treatment option for some CCA patients who have advanced disease that is no longer being controlled by first-line therapy. This option has a favourable impact on survival and improved tolerability when compared with second-line chemotherapy.<br>• It is vital that all CCA patients receive molecular profiling tests at the earliest opportunity to ensure they are matched with the optimal treatment with minimal delays. |

Thank you for your time.

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**Single Technology Appraisal**

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

**Clinical expert statement**

## Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Thursday 20 November 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

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# Part 1: Treating HER2-positive advanced biliary tract cancer and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | John Bridgewater |
| **2. Name of organisation** | UCL |
| **3. Job title or position** | Prof |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with HER2-positive advanced biliary tract cancer?<br>☒ A specialist in the clinical evidence base for HER2-positive advanced biliary tract cancer or zanidatamab?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☒ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. What is the main aim of treatment for HER2-positive advanced biliary tract cancer?** | The primary aims of treatment for HER2-positive advanced biliary tract cancer is to prolong life with an improved quality of life. |

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| (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | I consider a significant clinical benefit to be stabilisation of tumour growth at worst and improvement of the patient's symptoms. The data for Zanidatumab suggests that approaching 50% of patients will shrinkage of the tumour by more 50% in size, commonly correlating with an improvement in symptoms. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in HER2-positive advanced biliary tract cancer?** | The outlook for the HER2-positive advanced biliary tract cancer patients following progression first-line therapy is poor with a median survival of less than 6 months if receiving standard of care second-line FOLFOX chemotherapy. Modest benefit in survival of just over 1 month compared to best supportive care must be balanced against the significant impact of chemotherapy toxicity. As such the options are poor and many patients do not have second-line FOLFOX as a consequence.<br><br>An effective second-line option is urgently required. |
| **11. How is HER2-positive advanced biliary tract cancer currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | The standard of care options for patients who are HER2 positive or negative is second-line FOLFOX chemotherapy based on the ABC06 study.<br><br>The current ESMO guideline suggests the use of second-line trastuzumab and pertuzumab for HER2-positive advanced biliary tract cancer although this is not reimbursed in any European country.<br><br>The pathway of care is poorly-defined with respect to 2 issues:<br><br>1 HER2 testing is not reimbursed or commonly offered by histopathology despite being currently available and relatively cheap. Any approval of HER2 targeted therapy would have to be accompanied by mandatory testing at the time of diagnosis either at a local level or at the delegated cellular pathology genomic Centre (CPGC). |

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| | 2 the uptake of previously approved targeted therapies at second-line treatment for biliary tract cancer such as pemigatinib and ivosidenib has been poor, with less than third of potentially treatable patients receiving targeted therapy. As such there is a significant educational gap that requires improvement in order to best implement any approved targeted therapy.<br><br>If improved, patients with HER2-positive advanced biliary tract cancer would receive Zanidatumab either instead of or in sequence with FOLFOX, a significant change. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)<br>• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | Introduction of Zanidatumab would require a 3 weekly intravenous infusion above and beyond current standard of care. The treatment is safe and well tolerated and would not significantly impact on resource above and beyond that already described.<br><br>The avoidable toxicities include cardiac impairment requiring 3 monthly surveillance with ejection fraction measurement. |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | I would expect the technology to significantly increase survival and quality of life compared to current standard of care. |

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| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | The treatment is effective for HER2 3+ patients only, the data for HER2 2+ being significantly less impressive. There are otherwise no discriminating criteria. |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | The technology should be easy to introduce although clearly an extra resource implication. In general this resource would be limited to the requirement for daycare administration. There are no significant toxicities requiring hospital admission or supervision following treatment. |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | The patient will require standard of care imaging as they would have done if Zanidatumab had not been given. It would be exceptional that standard of care CT scanning would not be able to monitor the efficacy of treatment. |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | My personal experience with Zanidatumab is that quality of life is significantly improved and significantly better than it patients were treated with standard of care second-line FOLFOX. In this respect patient testimony rather than quality of life instruments will contribute significantly to the perceived benefit of this treatment. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Zanidatumab would significantly improve survival and quality of life for these extremely needy patients above and beyond the current standard of care treatment with chemotherapy. |

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| • Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | I would agree that it is a step change in treatment with respect to the potential benefits. |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | There are no significant toxicities and the toxicities are significantly better than those experienced from treatment with standard care FOLFOX chemotherapy. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | This treatment could be extrapolated to UK practice without significant difficulty. The most significant outcomes would be an improvement in survival and quality of life. I am not aware of any further adverse reactions not identified in clinical trials to date. |
| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | There have not been any randomised data comparing Zanidatumab to standard of care although there are currently 2 studies, one in first-line in combination with chemotherapy, and a second study comparing Zanidatumab to continuation of standard of care therapy (SAFIR-ABC10). These studies will provide further evidence for the degree of efficacy although the data will not be available for 2 to 3 years. |
| **22. How do data on real-world experience compare with the trial data?** | Real world data have been presented (Crespo-Cruz, ENSCCA May 2025) and suggest a similar outcome to the trial data. |
| **23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this** | I know no significant inequalities. |

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| **treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why.<br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

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## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Zanidatimab is a novel targeted therapy for HER2 +ve biliary tract cancer patients.

It is effective with modest toxicities when compared to standard care second-line FOLFOX chemotherapy.

Survival and quality of life are significantly improved for the majority of patients.

Resource implications (a 3 weekly infusion) with ejection fraction monitoring are modest and deliverable.

A change of practice with respect to HER2 immunohistochemistry and education about targeted therapy would be needed.

Thank you for your time.

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**Single Technology Appraisal**

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

**Clinical expert statement**

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Tuesday 25 November 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

# Part 1: Treating HER2-positive advanced biliary tract cancer and current treatment options

**Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality**

| | |
|---|---|
| **1. Your name** | Dr Suzanne Darby |
| **2. Name of organisation** | Sheffield Teaching Hospitals NHS Foundation Trust |
| **3. Job title or position** | Consultant Medical Oncologist |
| **4. Are you (please tick all that apply)** | ☐ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with HER2-positive advanced biliary tract cancer?<br>☐ A specialist in the clinical evidence base for HER2-positive advanced biliary tract cancer or zanidatamab?<br>☐ Other (please specify): |
| **5. Do you wish to agree with your nominating organisation's submission?**<br>(We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ Yes, I agree with it<br>☐ No, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☒ Other (they did not submit one, I do not know if they submitted one etc.) |
| **6. If you wrote the organisation submission and/or do not have anything to add, tick here.**<br>(If you tick this box, the rest of this form will be deleted after submission) | ☐ Yes |
| **7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |
| **8. What is the main aim of treatment for HER2-positive advanced biliary tract cancer?** | To improve survival (progression-free and/or overall survival) whilst maintaining/improving quality of life for patients. |

| | |
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| (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability) | |
| **9. What do you consider a clinically significant treatment response?**<br>(For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount) | Maintaining stable disease or achieving partial or complete radiological responses, or reducing symptom burden for patients. |
| **10. In your view, is there an unmet need for patients and healthcare professionals in HER2-positive advanced biliary tract cancer?** | Yes. In that advanced biliary tract cancer (ABC) patients often have actionable mutations (such as HER2) and targeting these may improve survival by using targeted therapies which are often effective and less toxic than alternative chemotherapeutic strategies. |
| **11. How is HER2-positive advanced biliary tract cancer currently treated in the NHS?**<br>• Are any clinical guidelines used in the treatment of the condition, and if so, which?<br>• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)<br>• What impact would the technology have on the current pathway of care? | Standard therapy for HER2 positive ABC cancers would currently be the same as for non-HER2 positive ABC cancers in that no HER2 targeted therapy is currently available via the NHS outside of a clinical trial. This would involve first line chemo-immunotherapy and second/subsequent line chemotherapy options.<br>I am aware of some clinicians being able to access compassionate funding for HER2 targeted therapies but this is not standard or routine.<br>I would anticipate that having availability for zanidatamab routinely would create a more equitable scenario where eligible patients would be able to access this. |
| **12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?**<br>• How does healthcare resource use differ between the technology and current care?<br>• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) | Zanidatamab would create an additional option for treatment. In the second line setting currently patients would receive chemotherapy. This is a non-targeted option with limited benefit.<br>I would expect that this would be used by specialist oncologists.<br>Much of the infrastructure in terms of facilities and equipment are in place. Resources for testing within pathology will be needed. However, it may be worthwhile considering the increased workload on staff with increased treatment options and increased patient survival. Investment in staffing would be useful. |

| | |
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| • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) | |
| **13. Do you expect the technology to provide clinically meaningful benefits compared with current care?**<br>• Do you expect the technology to increase length of life more than current care?<br>• Do you expect the technology to increase health-related quality of life more than current care? | Yes. |
| **14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | No. |
| **15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?**<br>(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) | This will be easier to prepare, dispense, deliver and monitor than current 2nd line treatment options. |
| **16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | Not obviously |
| **17. Do you consider that the use of the technology will result in any substantial health-related benefits that** | Much easier to receive as a patient. For example, current standard 2nd line treatment involves having a PICC (or other central) line inserted and treatment delivered over around 50 hours. Zanidatamab is delivered over a short period of time via a peripheral cannula. Zanidatamab is also given less frequently. This |

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| **are unlikely to be included in the quality-adjusted life year (QALY) calculation?**<br>• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care | involves fewer hospital attendances for patients over a set period of time, less invasive procedures and less time spent in hospital. |
| **18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?**<br>• Is the technology a 'step-change' in the management of the condition?<br>• Does the use of the technology address any particular unmet need of the patient population? | There is a shift for many cancers in targeting molecular changes which has resulted in some impressive responses in patients with significant improvements in survival. Targeted treatments are usually much better tolerated than non-targeted therapies (usually chemotherapy). There are already well-established therapies available for ABC with other targetable mutations (for example IDH1, FGFR2) which are well-established in clinical practice and this offers a further option for eligible patients. |
| **19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Zanidatamab is generally well-tolerated and side effects can usually be managed. Overall its toxicity is less than chemotherapy alternatives. Quality of life is therefore likely to be better. IN addition with increased efficacy we would expect QoL to be maintained for longer from disease perspective. |
| **20. Do the clinical trials on the technology reflect current UK clinical practice?**<br>• If not, how could the results be extrapolated to the UK setting?<br>• What, in your view, are the most important outcomes, and were they measured in the trials?<br>• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?<br>• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | Yes<br><br>Significant improved survival in patients with measurable targetable mutation. |

| | |
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| **21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | no |
| **22. How do data on real-world experience compare with the trial data?** | Limited real world data given drug is not currently in routine use in the UK. |
| **23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.<br>Please state if you think this evaluation could<br>• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation<br>• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population<br>• lead to recommendations that have an adverse impact on disabled people.<br>Please consider whether these issues are different from issues with current care and why. | No |

| | |
|---|---|
| More information on how NICE deals with equalities issues can be found in the NICE equality scheme.<br>Find more general information about the Equality Act and equalities issues here. | |

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## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Zanidatamab addresses an unmet need in advanced biliary tract cancers (ABC)

Zanidatamb offers a less toxic and more effective treatment options for ABC patients than currently available.

Zanidatamab gives an option for ABC patients that is easier to prepare, deliver and receive

There is standard testing available within NHS services that can identify patients eligible for zanidatamb

Survival can be very significantly prolonged with this technology in eligible patients

Thank you for your time.

## Your privacy

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NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

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

## Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

## Information on completing this form

In part 1 we are asking you about living with HER2-positive advanced biliary tract cancer or caring for a patient with HER2-positive advanced biliary tract cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

### Help with completing this form

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NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 20 November 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

**Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

Patient expert statement

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

# Part 1: Living with this condition or caring for a patient with HER2-positive advanced biliary tract cancer

**Table 1 About you, HER2-positive advanced biliary tract cancer, current treatments and equality**

| | |
|---|---|
| **1. Your name** | Paul Howard |
| **2. Are you (please tick all that apply)** | ☐ A patient with HER2-positive advanced biliary tract cancer?<br>☐ A patient with experience of the treatment being evaluated?<br>☐ A carer of a patient with HER2-positive advanced biliary tract cancer?<br>☒ A patient organisation employee or volunteer?<br>☐ Other (please specify): |
| **3. Name of your nominating organisation** | AMMF – The Cholangiocarcinoma Charity |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☒ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☐ I am drawing from personal experience<br>☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am drawing on the |

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| | experiences of people diagnosed with advanced biliary tract cancer, in particular cholangiocarcinoma (CCA; bile duct cancer), and their loved ones. My knowledge of their experiences is gathered from conducting online surveys, reading posts in AMMF's online discussion forums, and speaking directly with patients and their families.<br>☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with HER2-positive advanced biliary tract cancer?**<br>**If you are a carer (for someone with HER2-positive advanced biliary tract cancer) please share your experience of caring for them** | N/A |
| **7a. What do you think of the current treatments and care available for HER2-positive advanced biliary tract cancer on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | Most people diagnosed with a biliary tract cancer are inoperable and therefore have no potentially curative treatment options available to them. Patients with advanced cholangiocarcinoma who do not receive treatment have a very short life expectancy, typically 3-4 months.<br><br>The treatment options for advanced biliary tract cancers are limited but can extend survival. Some patients and their loved ones reported positive outcomes in AMMF's online surveys:<br>• *"It worked - if it hadn't reduced my tumours I would not be here today."*<br>• *"Despite all the unpleasantness experienced, chemo got rid of some of his tumours and bought us time to go on a trial. The trial gave us even more time for which we are eternally grateful."* |

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| | • *"I have been on some combination of gem/cis/durva for nearly 3 years. It has been effective with manageable side effects."*<br><br>However, patients often experience side effects and adverse events due to their treatment which can have a significant impact on their quality of life. I have outlined more detail about this in Question 8, about the disadvantages of current NHS treatments.<br><br>Whilst some patients with advanced biliary tract cancers have tumours with faults in IDH1 or FGFR2 genes that can be treated with life-extending targeted therapies through the NHS, there is currently no targeted therapy for HER2-positive tumours available through the NHS. The standard of care second-line treatment for patients with advanced HER2-positive tumours is the combination chemotherapy FOLFOX, which has a worse side effect profile and lower treatment efficacy than targeted therapies.<br><br>In AMMF's online surveys, patients and their caregivers reported a mixture of experiences about their care. Several reported positive experiences with their healthcare teams:<br>• *"Nursing staff were on the whole brilliant, alert to symptom changes and supportive of her and her needs with doctors."*<br>• *"Excellent support and very quick responsive service from my health team."*<br>However, several reported negative aspects of their treatment and care such as the need for regular visits to the hospital, poor communication, and delays:<br>• *"She received her first 5 chemo and immuno sessions as a hospital inpatient, it was never clear what time she would get her treatment."*<br>• *"Lack of information, we are constantly chasing the hospital up."*<br>• *"The treatment itself was fine but there were often mix ups and inconsistencies as to how blood test results had been filed which meant* |

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| | *more blood tests had to be carried out on the day of treatment and on one occasion where I had a late appointment I had to go home and go back the next day."*<br>Several respondents commented that their healthcare team had insufficient knowledge about cholangiocarcinoma:<br>• *"A lot of the staff at our local hospital had zero knowledge on this cancer."*<br>• *"My local cancer hospital does not have the knowledge and expertise of treatment other than chemo."*<br>• *"Original consultant did not have enough experience."*<br>• *"Unhappy with knowledge base of local oncologist."*<br>• *"I can tell the nurses/doctors in the local hospital care, but it just does not feel specialised enough to deal with this cancer and there seems to be a lack of options, therefore we sought a second opinion, and this opened our eyes to alternative treatment options."*<br><br>My understanding of current treatments and care is informed by experiences and opinions of patients and their family members who have contributed to AMMF's online surveys. |
| **8. If there are disadvantages for patients of current NHS treatments for HER2-positive advanced biliary tract cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | Patients with advanced biliary tract cancers who receive the standard treatments available for their cancer (chemotherapies; immunotherapy) often experience side effects and adverse events due to their treatment which can have a significant impact on their quality of life. In AMMF's online surveys, more than 70% of patients 'completely' or 'somewhat' agreed that the side effects of treatment had a negative impact on their quality of life. In addition, two-in-three patients reported that receiving treatment negatively impacted parts of their life such as employment, hobbies and relationships.<br>• *"Initially I was exhausted for a week after treatment, with chronic stomach pains caused by steroids and anti-sickness drugs."* |

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| | • *"I had Gem/Cis. The actual treatment was ok. However, during treatment I developed sepsis twice and spent a lot of time in the ICU."*<br>• *"FOLFOX gave me neuropathy. Other chemos made me generally sick and tired."*<br>• *"The chemotherapy took a huge toll on my body, and I was hospitalised on 3 separate occasions."*<br>• *"I went onto a treatment of chemotherapy combined with immunotherapy. The treatments caused side effects and made it impossible for me to function properly and certainly I couldn't go back to work in my job as a secondary school English teacher and Head of Department. It felt like being poisoned. This treatment was effective for a fairly short time before it failed, and the immunotherapy didn't work at all."*<br>• *"My mum has said repeatedly she could never go through chemotherapy again – it's no life. She had several admissions with pain and sepsis, blood transfusions for anaemia, and finally neutropenic sepsis during cycle 7."*<br><br>Some patients and caregivers reported challenges around attending the hospital for their treatments:<br>• *"A very long travel for chemo and bloods weekly."*<br>• *"I drove [my wife] to her appointments when she underwent traditional chemotherapy: it was a necessity since she was made weak and ill through the treatment and was unable to get herself there on public transport."* |
| **9a. If there are advantages of zanidatamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?** | Although zanidatamab is not curative, it can be effective in extending survival when first-line therapy is no longer working. It is reported than zanidatamab is more effective in improving survival than the current second-line standard of care; the combination chemotherapy FOLFOX. |

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| **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does zanidatamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | Several patients with HER2-positive advanced cholangiocarcinoma who were treated with zanidatamab and their caregivers shared how effective the treatment was for them:<br>• "*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… My cancer is continuing to shrink in size and has completely gone from my lungs and lymph nodes where it had spread to. I am able to live a normal life and no longer feel completely defined by my cancer."*<br>• *"My mother has had 4 years of good quality life due to [zanidatamab]."*<br>• "*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 new 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."*<br>• *"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)."*<br><br>The patients and caregivers with experience of zanidatamab reported a much more favourable side-effect profile for the treatment compared with chemotherapy and immunotherapy. This helps address the significant side effects of current treatment options and reduces the negative impact on quality of life:<br>• *"[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. I have travelled, spent time with my family happily and I am no longer the sick person anyone has to look after."* |

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| | • "*I have hardly any side effects compared to other treatments and feel better and better each day.*"<br>• "*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.*"<br>• "*[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. It is almost unbelievable just how different our lives are now she is on this treatment. She experiences little or no side effects.*"<br>• *"From our experience, [my partner] has less side effects than the Gem/Cis/Durva treatment."*<br>• *"I feel the advantage for this treatment is that there are a lot fewer side effects compared to chemotherapy alternatives, I don't feel as tired and I'm able to continue doing exercise."*<br><br>One caregiver reported that the treatment administration for zanidatamab was an advantage over current treatment:<br>• *"The infusion time is quicker which is also better."*<br><br>Zanidatamab not only provides the hope of extended survival for patients and their families, but also an improved quality of life compared with other current treatments due to the reduction in side effects. |
| **10. If there are disadvantages of zanidatamab over current treatments on the NHS please describe these.**<br>For example, are there any risks with zanidatamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why | The patients and caregivers we have spoken to did not report any significant disadvantages with this treatment when compared with current treatments on the NHS.<br>• *"There are no disadvantages to this treatment. There are only good things that have come from [my wife] having this treatment."* |

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| | One patient reported some inconvenience attending hospital for blood tests and treatment, but felt the benefits of the treatment outweigh the disadvantages:<br>• *"I do have to go and get blood tests every two weeks and I have treatment which takes up most of an afternoon every two weeks. The infusion is only an hour, but the waiting around takes the time. This is a small thing to have to do for the rewards. I don't like having a port but really, that's nothing: I am alive."*<br><br>Patients and caregivers reported some side effects from zanidatamab, but that these were less severe than those experienced on other current NHS treatments:<br>• *"There are still side effects such as fatigue, but it is manageable."*<br>• "Very mild diarrhoea for a few days and a feeling of bloating immediately after treatment. The disadvantages are negligible in comparison to the benefits." |
| **11. Are there any groups of patients who might benefit more from zanidatamab or any who may benefit less? If so, please describe them and explain why**<br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | Only patients with HER2-positive advanced biliary tract cancers will benefit from this therapy.<br><br>I am not aware of any groups of patients with HER2-positive advanced biliary tract cancers who might benefit more or less from zanidatamab. |
| **12. Are there any potential equality issues that should be taken into account when considering HER2-positive advanced biliary tract cancer and zanidatamab? Please explain if you think any groups of people with this condition are particularly disadvantage**<br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil | An analysis of 8,853 cholangiocarcinoma patient records in England from between 2014-2017 (link) revealed that patients who were more socioeconomically deprived were associated with a lower probability of receiving surgery and systemic therapy. No targeted therapies were available for this patient group during the observed period.<br>It is vital that action is taken to identify and address barriers to accessing treatment for socioeconomically deprived biliary tract cancer patients so that they are not disadvantaged in accessing zanidatamab. |

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| partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | *"I hope that every single person diagnosed with bile duct cancer gets the blood test/ biopsy to check for mutations so that anyone with the HER2 mutation can have this drug. Thank you to those who developed it and thank you to those who let me have it. Words cannot express my gratitude."* ***– A cholangiocarcinoma patient treated with zanidatamab*** |
| **13. Are there any other issues that you would like the committee to consider?** | Biliary tract cancers are aggressive and therefore time is of the essence to initiate treatment. For advanced biliary tract cancer patients to have the best chance of benefitting from zanidatamab, molecular profiling tests to identify HER2-positive tumours must be completed with minimal delay.<br><br>*"If made available, [zanidatamab] cannot take too long to organise – patients rapidly deteriorate with cholangiocarcinoma, and any treatment delay will contribute to mortality."* **- Daughter of a cholangiocarcinoma patient treated with zanidatamab**<br><br>Currently in the NHS, molecular profiling tests are not carried out until after a patient has progressed on first-line therapy (GEM/CIS/DURVA). Due to the time taken to conduct these tests, this may result in a delay in initiating targeted therapy for treatable gene faults. Within their guidelines for the diagnosis and management of cholangiocarcinoma, the British Society for Gastroenterology (BSG) recommendation 41 states, ***"CCA should be subjected to molecular profiling at the earliest opportunity, and results and treatment options should be reviewed by clinicians with appropriate expertise."*** Therefore, ideally, a CCA patient should have molecular profiling completed at diagnosis to identify any treatable gene faults, such as HER2 amplification, to minimise any delays in initiating optimal therapy. |

## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Cholangiocarcinoma is an aggressive and difficult to treat cancer, with a five-year survival rate of only 5%.
- Current treatment options for advanced biliary tract cancers are limited and have modest survival benefits.
- Current treatments commonly have significant side effects and adverse events associated with them, resulting in negative impacts to quality of life for patients.
- Zanidatamab offers improved survival compared with current treatments and has a favourable side effect profile which means that patients and their loved ones can potentially benefit from extended survival and improved quality of life.
- Due to the aggressiveness of cholangiocarcinoma, delays in initiating zanidatamab should be avoided by conducting molecular profiling tests at the earliest opportunity.

Thank you for your time.

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

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Patient expert statement

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

# Part 1: Living with this condition or caring for a patient with HER2-positive advanced biliary tract cancer

**Table 1 About you, HER2-positive advanced biliary tract cancer, current treatments and equality**

| | |
|---|---|
| **1. Your name** | Andrew Clay |
| **2. Are you (please tick all that apply)** | ☐ A patient with HER2-positive advanced biliary tract cancer?<br>☐ A patient with experience of the treatment being evaluated?<br>☐ A carer of a patient with HER2-positive advanced biliary tract cancer?<br>☐ A patient organisation employee or volunteer?<br>☒ Other (please specify): A patient who also volunteers. |
| **3. Name of your nominating organisation** | AMMF |
| **4. Has your nominating organisation provided a submission? (please tick all options that apply)** | ☐ No (please review all the questions and provide answers when possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |
| **5. How did you gather the information included in your statement? (please tick all that apply)** | ☐ I am drawing from personal experience<br>☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Directly from |

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|---|---|
| | patients globally who have participated in trials for zanidatamab and from survey responses submitted to AMMF online surveys.<br>☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **6. What is your experience of living with HER2-positive advanced biliary tract cancer?**<br>**If you are a carer (for someone with HER2-positive advanced biliary tract cancer) please share your experience of caring for them** | I do not have direct experience of living with HER2-positive advanced biliary tract cancer but as a patient with advanced biliary tract cancer since January 2018. I had Whipple surgery in June 2018, followed by a course of Capecitabine for 6 months. The disease progressed to Stage 4 and I received a prognosis of 2-4 months. I then took a course of Gem/Cis for another 6 months before enrolling in an immunotherapy trial (M7824) in November 2019. Although I was only on the trial for 4 months due to the drug impacting my kidneys, it was the last treatment I needed, and I have been in remission since March 2020.<br>I am familiar with a range of targeted treatments for Cholangiocarcinoma. I am a moderator and active participant for the AMMF Facebook forums, and I am also a member of similar forums in the USA and Australia. |
| **7a. What do you think of the current treatments and care available for HER2-positive advanced biliary tract cancer on the NHS?**<br>**7b. How do your views on these current treatments compare to those of other people that you may be aware of?** | a. As far as I am aware, there are currently no specific treatments for HER2-positive advanced biliary tract cancer on the NHS and the treatment is in line with the standard treatment for biliary tract cancers, namely Gemcitabine, Cisplatin and Durvalumbab and/or Capecitabine as well as surgery and possibly radiotherapy.<br>b. Once these treatments have been exhausted, zanidatamab provides an extra treatment that may suppress the advancement of the cancer by more than a year, for patients with HER2-positive that respond to the treatment, that they would otherwise not have. |

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| **8. If there are disadvantages for patients of current NHS treatments for HER2-positive advanced biliary tract cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these** | The side effects for current treatments (Gem/Cis/Durva) include a buildup of toxicity from the chemotherapy making it increasingly difficult to tolerate over time and the effectiveness wears off between 5-7 months. |
| **9a. If there are advantages of zanidatamab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?**<br>**9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**<br>**9c. Does zanidatamab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these** | a. Once current treatments have been exhausted, zanidatamab may suppress the progression of cancer for over 12 months. As biliary tract cancers are so aggressive, this additional time is incredibly valuable to a patient with HER2-positive. Zanidatamab is considered to be better tolerated than Gem/Cis/Durva allowing patients generally a better quality of life as it avoids the cumulative toxicity of chemotherapy and the side effects are more predictable and manageable.<br>b. The timeline that zanidatamab is effective is much longer than the effectiveness of standard treatment and this can be taken after the standard care has been exhausted. The value to be able to extend treatment by another 12 or more months cannot be overstated. These cancers are very aggressive and for patients to have the additional time with their loved ones and more time for potentially other breakthrough treatments to be developed provides a great deal of hope to patients.<br>c. As above. |
| **10. If there are disadvantages of zanidatamab over current treatments on the NHS please describe these.**<br>For example, are there any risks with zanidatamab? If you are concerned about any potential side effects you have heard about, please describe them and explain why | Overall, zanidatamab is better tolerated than current treatments and compliments current treatment for HER2-positive patients who respond to it.<br>Potential side effects for zanidatamab are more predictable and therefore easier to manage. |
| **11. Are there any groups of patients who might benefit more from zanidatamab or any who may benefit less? If so, please describe them and explain why** | Not that I am aware of. |

| | |
|---|---|
| Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | |
| **12. Are there any potential equality issues that should be taken into account when considering HER2-positive advanced biliary tract cancer and zanidatamab? Please explain if you think any groups of people with this condition are particularly disadvantage**<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br>Find more general information about the Equality Act and equalities issues here. | Not that I am aware of. |
| **13. Are there any other issues that you would like the committee to consider?** | No. |

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## Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is currently no treatment specifically for HER2-positive advanced biliary tract cancer patients
- Zanidatamab may suppress progression for these patients up to 15 months (median duration of response)
- Zanidatamab is better tolerated than current treatments thus improving the quality of life post standard treatment.
- Side effects are more predictable and therefore easier to manage
- Click or tap here to enter text.

Thank you for your time.

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

**Produced by** Aberdeen HTA Group


**Authors**

Neil W Scott[1]
Mekazin Tsehaye[2]
Moira Cruickshank[3]
Paul Manson[3]
Adnan Shauka[4]
Miriam Brazzelli[3]
Dwayne Boyers[2]

1 Biostatistics and Health Data Science, Foresterhill, Aberdeen, UK
2 Health Economics Research Unit, University of Aberdeen, UK
3 Aberdeen Centre for Evaluation, Foresterhill, Aberdeen, UK
4 NHS Grampian, Aberdeen, UK

**Correspondence to** Dwayne Boyers
Health Economics Research Unit, University of Aberdeen
2nd Floor, Health Sciences Building, Foresterhill
Aberdeen, AB25 2ZD
d.boyers@abdn.ac.uk


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**Declared competing interests of the authors**

No competing interests to disclose.

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**Rider on responsibility for report**

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contribution of authors**

MC reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; NS checked and critiqued the statistical analyses presented in the company submission; MT and DB reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; PM checked and critiqued the company's search strategies; AS provided clinical guidance and comments on the draft report. DB and MB coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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## List of abbreviations

| Abbreviation | Definition |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 3L | Third-line |
| 5FU | Fluorouracil |
| A&E | Accident and emergency |
| ADA | Anti-drug antibody |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADCP | Antibody-dependent cellular phagocytosis |
| AE | Adverse event |
| AIC | Akaike Information Criterion |
| ALT | Alanine aminotransferase |
| AoV | Ampulla of Vater |
| ASC | Active symptom control |
| ASMR | Annual standardised mortality rate |
| ASR | Annual standardised rate |
| AST | Aspartate aminotransferase |
| BIC | Bayesian Information Criterion |
| BL | Baseline |
| BNF | British National Formulary |
| BONT | Best on-treatment |
| BOR | Best overall response |
| BPI | Brief Pain Index |
| BSA | Body surface area |
| BSC | Best supportive care |
| BSG | British Society for Gastroenterology |
| BTC | Biliary tract cancer |
| CAPOX | Capecitabine and oxaliplatin |
| CBR | Clinical benefit rate |
| CCA | Cholangiocarcinoma |
| CE | Conformité Européenne |
| CEA | Cost-effectiveness analysis |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CisGem | Cisplatin and gemcitabine |
| CNS | Central nervous system |
| cORR | Confirmed objective response rate |
| CR | Complete response |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| dCCA | Distal cholangiocarcinoma |
| DCO | Data cut-off |
| DCR | Disease control rate |
| dMMR | Mismatch repair deficient |
| DOR | Duration of response |
| DPD | Dihydropyrimidine dehydrogenase |
| DSU | Decision support unit |
| EAG | External assessment group |
| EAMS | Early Access to Medicines Scheme |
| EAS | Efficacy analysis set |
| EC | European Commission |
| ECA | External control arm |
| eCCA | Extrahepatic cholangiocarcinoma |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| eMC | Electronic medicines compendium |
| eMIT | Electronic market information tool |
| EORTC | European Organisation For Research And Treatment Of Cancer |
| EPAR | European public assessment report |
| ESCAT | European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets |
| ESMO | European Society for Medical Oncology |
| ESS | Effective sample size |
| EUR | Euro |
| FA | Folinic acid |
| FDA | Food and Drug Administration |
| FGFR | Fibroblast growth factor receptor |
| FISH | Fluorescence in-situ hybridisation |
| FOLFIRI | Folinic acid, fluorouracil, and irinotecan |

| | |
|---|---|
| FOLFIRINOX | Folinic acid, fluorouracil, irinotecan, and oxaliplatin |
| FOLFOX | Folinic acid, fluorouracil, and oxaliplatin |
| FOX | Fluorouracil and oxaliplatin |
| GBC | Gallbladder cancer |
| GBP | Great British Pound |
| GemCap | Gemcitabine and capecitabine |
| GemCarbo | Gemcitabine and carboplatin |
| GEMOX | Gemcitabine and oxaliplatin |
| HCRU | Healthcare resource utilisation |
| HER2 | Human epidermal growth factor receptor 2 |
| HER2+ | Human epidermal growth factor receptor 2-positive |
| HIV | Human immunodeficiency virus |
| HPB | Hepato-pancreatic biliary |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HTA | Health technology assessment |
| iCCA | Intrahepatic cholangiocarcinoma |
| ICER | Incremental cost-effectiveness ratio |
| ICR | Independent central review |
| IDH1 | Isocitrate dehydrogenase 1 |
| IHC | Immunohistochemistry |
| ILD | Individual level data |
| INV | Investigator assessment |
| IQR | Interquartile range |
| IRR | Infusion-related reaction |
| ISH | In-situ hybridisation |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| IV | Intravenous |
| IVD | In-vitro diagnostic |
| KM | Kaplan-Meier |
| LMER | Linear mixed-effect regression |
| LMM | Linear mixed model |
| LV | Leucovorin |
| LVEF | Left ventricular ejection fraction |
| LY | Life year |
| LYG | Life year gain |
| MAIC | Matching-adjusted indirect comparison |
| MDT | Multi-disciplinary team |
| MedDRA | Medical dictionary for regulatory activities |
| mFOLFIRI | Modified folinic acid, fluorouracil, and irinotecan |
| mFOLFOX | Modified folinic acid, fluorouracil, and oxaliplatin |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MoM | Method of moments |
| MRI | Magnetic resonance imaging |
| MSI | Microsatellite instability |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NGS | Next-generation sequencing |
| NHB | Net health benefit |
| NICE | National Institute for Health and Care Excellence |
| NR | Not reported |
| NTD | New Taiwan Dollar |
| NTRK | Neurotrophic tropomyosin kinase receptor |
| OR | Odds ratio |
| ORR | Objective response rate |
| OS | Overall survival |
| OWSA | One-way sensitivity analysis |
| PartSA | Partitioned survival analysis |
| PAS | Patient access scheme |
| pCCA | Perihilar cholangiocarcinoma |
| PD | Progressive disease |
| PD1 | Programmed cell death protein 1 |
| PDL1 | Programmed death ligand 1 |
| PF | Progression free |
| PFS | Progression-free survival |
| PHQ | Patient Health Questionnaire-9 |
| PICC | Peripherally-inserted central catheter |
| PIM | Promising Innovative Medicine |
| PLD | Patient level data |
| PR | Partial response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| PSM | Partitioned survival model |
| PSS | Personal social services |
| PSSRU | Personal Social Services Research Unit |

| | |
|---|---|
| Q2W | Every 2 weeks |
| Q4W | Every 4 weeks |
| QALY | Quality-adjusted life year |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RDI | Relative dose intensity |
| RECIST | Response evaluation criteria in solid tumors |
| RWE | Real-world evidence |
| rwOS | Real-world overall survival |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Safety analysis set |
| SD | Stable disease |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SMD | Standardised mean differences |
| SmPC | Summary of product characteristics |
| SMR | Standardised mortality ratio |
| SOC | Standard of care |
| SoC | Standard of care |
| StD | Standard deviation |
| TA | Technology assessment |
| TFL | Tables, figures, and listings |
| ToT | Time on treatment |
| TRAE | Treatment-related adverse event |
| TRSAE | Treatment-related serious adverse event |
| TSD | Technical support document |
| TTD | Time to death |
| UCLH | University College London Hospital |
| USD | United States Dollar |
| VAS | Visual analogue scale |
| WTP | Willingness-to-pay |

# External assessment group report executive summary

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

## 1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues is in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

## 1.1 Overview of the EAG's key issues

**Table 1 Summary of key issues**

| ID 6388 | Summary of issue | Report sections |
|---|---|---|
| 1 | **Robustness of clinical effectiveness evidence**<br>Clinical effectiveness analyses were limited by small sample sizes and the company's preferred indirect comparison could be affected by bias as analyses not adjusted for clinically relevant confounders. | 3.4, 3.5, 3.6 |
| 2 | **Treatment acquisition costs for zanidatamab and FOLFOX**<br>The combination of time on treatment and relative dose intensity assumptions for zanidatamab and FOLFOX may lead to an under-estimate of the incremental treatment acquisition costs for zanidatamab. | 4.2.6 & 4.2.8 |
| 3 | **Utility estimation approach**<br>The use of a TTD approach may underestimate utilities, especially in the PFS state for the FOLFOX arm. Application of additional disutility for adverse events, treatment administration, and treatment specific disutilities more broadly risks double counting for the FOLFOX and ASC arms of the model. | 4.2.7 |
| 4 | **Frequency of echocardiography monitoring for FOLFOX**<br>There is uncertainty regarding the most appropriate monitoring frequency in UK clinical practice. | 4.2.8 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are

- The company prefers to use a 1.5% discount, but the EAG prefers a 3.5% discount rate in line with the current version of the NICE methods guide at the time of submitted the EAG report.

- The company prefers to use a log logistic OS curve for zanidatamab whereas the EAG prefers a LN curve

- The company prefers a gamma curve for zanidatamab time on treatment whereas the EAG prefers a LN curve

- The company prefers to estimate utilities based on a time to death (TTD) approach whereas the EAG prefers to apply fixed HSUVs to each health state (progression free and progressed disease)

- The company prefers to apply a treatment specific disutility for FOLFOX and for ASC where as the EAG does not.

- The company assumes that the RDI for FOLFOX and zanidatamab are equal whereas the EAG prefers to assume treatment specific RDIs to reflect likely differences in toxicity across the different treatments.

- The company prefers to assume that echocardiography is required for FOLFOX patients before and after each treatment administration whereas the EAG prefers to assume one echocardiography at treatment initiation.

## 1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the duration of life, by extending overall survival

- Increasing the amount of time spent in a progression free health state with higher quality of life.

Overall, the technology is modelled to affect costs by:

- Increasing treatment acquisition costs for zanidatamab, with treatment incurred over a longer time period than for FOLFOX

The modelling assumptions that have the greatest effect on the ICER are:

- Time on treatment and relative dose intensity for zanidatamab and FOLFOX
- The approach to calculate HSUVs in the economic model.

### 1.3 The decision problem: summary of the EAG's key issues

The main deviation from the NICE final scope relates to the population being amended to align with the anticipated licensed indication. The EAG considers the company's approach to be appropriate.

### 1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The company's primary evidence for the clinical effectiveness of zanidatamab for HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy is based on the HERIZON-BTC-01 trial. As no head-to-head evidence was identified, the company conducted an indirect comparison to compare the effectiveness of zanidatamab with two arms of the ABC-06 trial: FOLFOX (folinic acid, fluorouracil, and oxaliplatin) plus ASC (active symptom control) and ASC alone. Available sample sizes were small and, as there were methodological challenges in using matched adjusted methods, a naïve (unadjusted) approach was used as the primary analysis method. Given the potential for bias, the EAG suggests a cautious interpretation of any cost-effectiveness modelling using these results.

**Issue 1 Robustness of clinical effectiveness evidence**

| | |
|---|---|
| **Report section** | 3.4, 3.5, 3.6 |
| **Description of issue and why the EAG has identified it as important** | Clinical effectiveness analyses were limited by small sample sizes, and the company's preferred indirect comparison could be affected by bias as analyses were not adjusted for clinically relevant confounders. This introduces uncertainty to the results of the cost-effectiveness analyses using these estimates. |
| **What alternative approach has the EAG suggested?** | This is a rare cancer, and there is a lack of robust evidence comparing zanidatamab with other comparators. |
| **What is the expected effect on the cost-effectiveness estimates?** | Not known |
| **What additional evidence or analyses might help to resolve this key issue?** | The company could explore combining zanidatamab datasets to increase the sample size, although this is currently challenging due to the diversity in patient populations. They could also explore alternative sources of control data that allow adjusted analysis approaches. |

## 1.5 The cost-effectiveness evidence: summary of the EAG's key issues

### Issue 2 Treatment acquisition costs for zanidatamab and FOLFOX

| | |
|---|---|
| **Report section** | 4.2.6 & 4.2.8 |
| **Description of issue and why the EAG has identified it as important** | The company base case analysis assumes that FOLFOX patients are treated until progression or until the end of the treatment regiment, whichever comes first, whereas a decreasing proportion of the progression free cohort remain on treatment with zanidatamab over time. It is also assumed that the RDI is equal for both treatments. |
| **What alternative approach has the EAG suggested?** | The EAG prefers a LN compared to a Gamma treatment discontinuation curve for zanidatamab and prefers application of treatment specific RDIs to reflect the likely differences in tolerability across economic model arms. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG preferred assumptions lead to an increase in the incremental treatment acquisition costs for zanidatamab compared to FOLFOX and therefore lead to an increase in the base case ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG considers there to be sufficient data available for zanidatamab time on treatment and RDI but note a lack of comparative published data for FOLFOX. Further clinical expert opinion regarding the FOLFOX ToT and RDI parameters would be beneficial. |

**Issue 3 Application of health state utility values in the economic model**

| | |
|---|---|
| **Report section** | 4.2.7 |
| **Description of issue and why the EAG has identified it as important** | The company applies a time-to-death (TTD) utility approach to all arms, with additional treatment specific disutilities for FOLFOX and ASC, treatment administration disutilities for FOLFOX and adverse event disutilities for all treatments. The TTD approach, derived from the HERIZON-BTC-01 zanidatamab study, may overestimate the utility decrements in the FOLFOX arm of the model because the modelled progressed disease duration in FOLFOX is substantially shorter than for zanidatamab.<br>Application of multiple disutilities risks double counting utility decrements in the FOLFOX arm. |
| **What alternative approach has the EAG suggested?** | The EAG prefers to apply utilities by progression status as opposed to the TTD approach. The implications of the company TTD approach may lead to greater QALY decrements being applied in the PFS state of the FOLFOX arm than in the zanidatamab arm. The implied assumption that TTD utilities are independent of progression status may lead to uncertainty in cost-effectiveness results and the EAG considers the progression-based utility approach to be less uncertain.<br>The EAG also prefers to remove the treatment specific disutilities but retain treatment administration disutilities to reduce the risk of double counting utility decrements. |
| **What is the expected effect on the cost-effectiveness estimates?** | The impact of the EAG preferred assumptions is a reduction in the incremental QALYs and therefore an increase in the ICER for zanidatamab vs. comparators. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG are not aware of any other studies or published literature that could address this uncertainty. |

**Issue 4 Special monitoring requirements for FOLFOX**

| | |
|---|---|
| **Report section** | 4.2.8 |
| **Description of issue and why the EAG has identified it as important** | The company assume that echocardiography would be required before and after each treatment administration, but the EAG cannot find any clinical expert or published evidence to support this level of resource use. |
| **What alternative approach has the EAG suggested?** | Based on clinical expert opinion, the EAG prefers to assume one echocardiography at the start of treatment to assess risk. |
| **What is the expected effect on the cost-effectiveness estimates?** | The company assumes that more echocardiography is required for FOLFOX compared to zanidatamab. The EAG preferred approach would increase the ICER by leading to increased incremental costs for zanidatamab vs. comparators. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG would welcome further engagement and advice from a range of UK clinical experts regarding the frequency of echocardiography monitoring for patients receiving FOLFOX in UK clinical practice. |

## 1.6 Summary of EAG's preferred assumptions and resulting ICER

The impact of the EAG's preferred assumptions on the ICER for zanidatamab vs. FOLFOX is outlined in Table 2 below.

**Table 2 Summary of EAG's preferred assumptions and ICER**

| | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|
| **Company preferred base case analysis** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 1 Applying 3.5 % Discount rate to costs and QALYs** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 2 Using Log Normal OS curves for zanidatamab** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 3 using Log normal for ToT curve for zanidatamab** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 4 Applying ratio of median TTD / PFS to ToT curve for FOLFOX** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 5 Using HERIZON-BTC-01 (IHC3+ sub-population) Adverse event population source** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 6 Adjusting FOLFOX administration disutility by cycle length in the TTD approach** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 7 Using HERIZON-BTC-01 (IHC3+ sub population) data source for health state utility** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 8 using Progression base health state values for utility estimation** | | | |
| Zanidatamab | | | |

| | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 9 excluding treatment specific disutility** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 10 Appling 78% FOLFOX RDI based on RWE study** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 11 Applying 1 echocardiography before the initiation of treatment** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **Scenario 12 Morphine usage excluded in the Progressed disease health state** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-12 combined) - deterministic** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | | [redacted] |
| ASC | [redacted] | | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-12 combined) - probabilistic** | | | |
| Zanidatamab | | | |
| FOLFOX | [redacted] | | [redacted] |
| ASC | [redacted] | | [redacted] |

Modelling errors identified and corrected by the EAG are described in Section 4.2.8 and in Chapter 5. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.1 and 6.2 of the EAG report.

# 2 INTRODUCTION AND BACKGROUND

## *2.1 Introduction*

The relevant health condition for the submission received from Jazz Pharmaceuticals is unresectable locally advanced or metastatic human epidermal factor receptor 2 (HER2)-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy. The company's description of the health condition in terms of prevalence, symptoms and complications appears accurate and in line with the decision problem. The relevant intervention for this submission is zanidatamab (brand name: Ziihera).

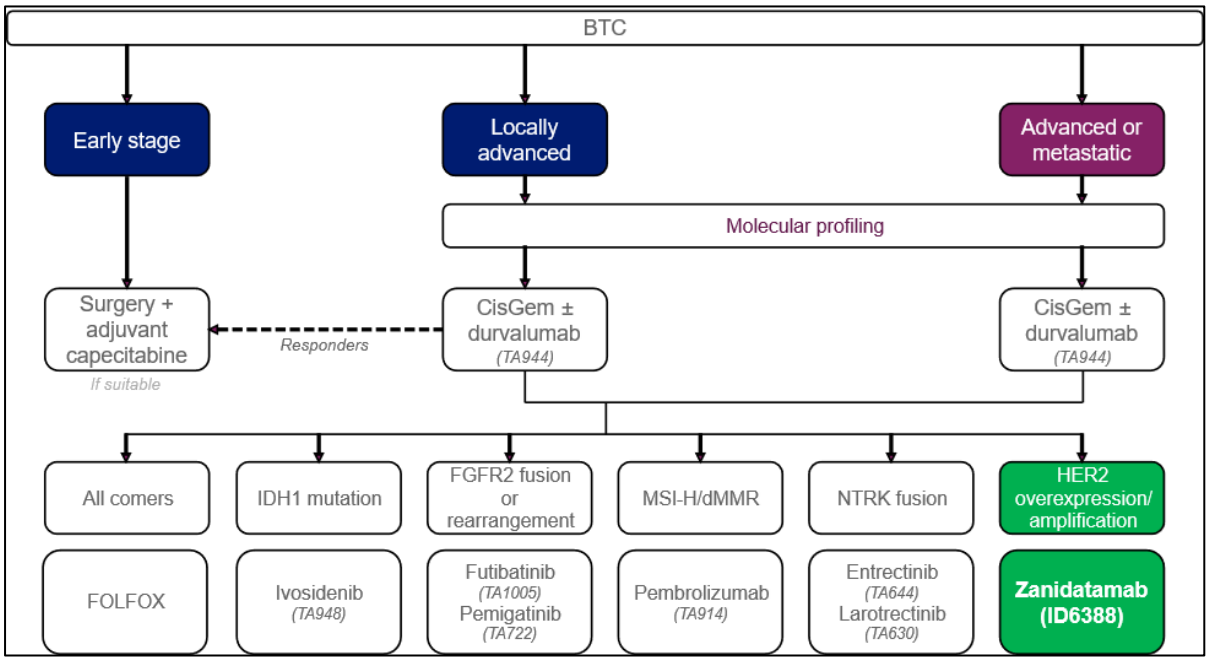
## *2.2 Background*

The company's submission (CS) describes biliary tract cancer (BTC) as a heterogenous group of rare, aggressive tumours, originating in the gallbladder or cystic duct (gallbladder cancer; GBC) or the biliary tree (cholangiocarcinoma; CCA).[1-5] CCA can affect both the intrahepatic (iCCA) and extrahepatic (eCCA) bile ducts or the junction of the hepatic ducts (hilar CCA). Ampullary cancer is the rarest BTC and develops where the bile ducts from the liver and pancreas meet as they enter the small intestine.[2, 5]

Patients with BTC are often asymptomatic, especially in the early stages, and any symptoms that do develop can be non-specific, for example, nausea, fatigue, loss of appetite, abdominal pain and unexplained weight loss. In combination with the aggressive nature of BTC, the disease is often advanced when diagnosed,[2] with emergency presentation being the most common means of diagnosis.[3, 6] Symptoms at more advanced stages include jaundice, light coloured stools and darkening of the urine, although these can vary by BTC subtype.[2]
BTC accounts for < 1% of all cancers.[5] In the UK each year, around 3,100 people are diagnosed with CCA, around 1,100 with GBC and around 550 with ampullary cancer.[7, 8] Between 2001 and 2018, 50,871 BTCs were diagnosed in England with 63.4% being CCA, 23.1% GBC and 13.5% ampullary cancer. More GBC were diagnosed in women (71.1%), while CCA and ampullary cancer were more equally distributed between women and men.[6] During this period, there were 40,215 deaths from BTC (78.1% due to CCA, 18.1% GBC and 3.9% ampullary cancer). Mortality due to CCA or ampullary cancer more than doubled during this period and increased by 70% for GBC.[6] It has been reported that 95% of CCA patients die within 5 years of diagnosis.[9]

The causes of BTC are poorly understood and there are no obvious risk factors for many patients. However, some risk factors have been identified, namely gallbladder cysts and stones, cirrhosis and hepatitis B and C viruses.[9] In addition, age-standardised incidence rates of CCA and GBC in England between 2010 and 2018 were higher over time in the most deprived socioeconomic deprivation quintile as compared to the least deprived group.[6]

The CS cites European Society for Medical Oncology (ESMO) and British Society for Gastroenterology (BSG) guidelines for treatment of advanced BTC.[10, 11] Guidelines recommend molecular profiling at diagnosis to identify suitable molecular targets for targeted therapy.[10-12] Around 40% of BTC tumours have a targetable molecular alteration, including HER2 overexpression, which is recognised as a predictive biomarker and promising target in 5-10% of CCAs and 20% of GBC.[4] The CS states that no HER2-targeted treatments are available for this population at present. The current treatment pathway for patients with BTC and the proposed place in therapy for zanidatamab is presented in Figure 5 of the CS, reproduced as Figure 1 below.




**Abbreviations:** BTC, biliary tract cancer; CisGem, cisplatin and gemcitabine; dMMR, mismatch repair deficient; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; NICE, National Institute for Health and Care Excellence; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; TA, technology appraisal.
Sources: Vogel (2025),[11] relevant NICE TAs[13-19]

**Figure 1 Current treatment pathway in BTC and zanidatamab's proposed place in therapy [reproduced from Figure 5 of the CS]**

*The EAG's clinical expert agrees with the company's current treatment pathway and proposed positioning of zanidatamab.*

### *2.3 Critique of company's definition of decision problem*

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of the adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

**Table 3 Summary of the company's decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| **Population** | Adults with unresectable HER2-postive advanced biliary tract cancer previously treated with at least 1 prior line of systemic therapy | Adults with unresectable HER2-postive (IHC3+) advanced biliary tract cancer previously treated with at least 1 prior line of systemic therapy | The decision problem addressed aligns with the expected marketing authorisation for zanidatamab | The EAG are satisfied that the population is appropriate. |
| **Intervention** | Zanidatamab | As per NICE scope | Not applicable | The intervention described in the CS matches that described in the NICE final scope |
| **Comparator(s)** | • Established clinical management without zanidatamab, which may include:<br>– Folinic acid, fluorouracil, and oxaliplatin (FOLFOX)<br>– Best supportive care (including active symptom control) | As per NICE scope | Not applicable | The EAG's clinical expert considers that the comparators addressed in the CS are appropriate |
| **Outcomes** | • Overall survival<br>• Progression-free survival<br>• Response rates (including overall response rates)<br>• Time to treatment discontinuation<br>• Adverse effects of treatment<br>• Health-related quality of life | As per NICE scope | Not applicable | The EAG's clinical expert is satisfied that the outcomes addressed in the CS are appropriate to the decision problem |
| **Economic analysis** | • The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost | As per NICE scope | Not applicable | The EAG are satisfied that the submission mostly adheres to the NICE reference case. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | per quality-adjusted life year.<br>• The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>• Costs will be considered from an NHS and Personal Social Services perspective.<br>• The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.<br>The availability and cost of biosimilar and generic products should be taken into account | | | However, the EAG considers the appropriate discount rate for this submission to be 3.5% per annum, rather than 1.5% per annum as specified in the company submission and response to clarification queries. |
| **Subgroups** | If evidence allows, results by type of biliary tract cancer | No additional subgroups will be considered | The level of unmet need in 2L HER2+ BTC is very high and restricting zanidatamab to a BTC subgroup risks denying these patients an effective treatment option. Currently, the only 2L treatment for people with HER2+ BTC is FOLFOX, which is associated with a low disease response, poor survival, toxicity, and poor tolerability. The lack of effective and tolerable treatment options has a devastating impact on the lives of people with BTC and their families/caregivers | Analyses for ten prespecified subgroups are available in the clinical study report (CSR), but these are not presented for the IHC3+ subgroup. The EAG notes that the available sample sizes for subgroup analyses were low and corresponding subgroup analyses could not be conducted for the comparator study |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| **Special considerations including issues related to equity or equality** | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. | As per the draft scope. | Increased access to targeted therapies, including zanidatamab if recommended, may reduce health inequalities, as real-world evidence from patients with BTC in England showed a higher incidence of BTC and poorer treatment outcomes in socio-economically deprived populations compared with other areas of England | The EAG is satisfied with the company's approach |

**Abbreviations:** BTC, biliary tract cancer; EAG, external assessment group; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HER2, human epidermal growth factor receptor 2; IHC, Immunohistochemistry score

# 3 CLINICAL EFFECTIVENESS

## *3.1 Critique of the methods of review(s)*

Full details of the methods used by the company to identify and select the clinical evidence relevant to this appraisal are reported in Appendix B of the CS. The EAG's appraisal of the company's systematic literature review (SLR) methodology is summarised in Table 4.

**Table 4 EAG's appraisal of the literature review methods presented in the CS**

| Review process EAG | EAG response | Comments |
|---|---|---|
| Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies? | YES | The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix B of the CS. Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected. |
| Were appropriate bibliographic databases/sources searched? | YES | Sources included Embase, MEDLINE, and CENTRAL for primary research. Relevant conference proceedings, and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches. Full details are provided in Appendix B of the CS. |
| Were eligibility criteria consistent with the decision problem outlined in the NICE final scope? | YES | The eligibility criteria outlined in Section 2.3.1.1.5 of the CS are consistent with the decision problem outlined in the NICE final scope |
| Was study selection conducted by two or more reviewers independently? | YES | For the original SLR and the two updates, title/abstract screening and full-text screening were |

| Review process EAG | EAG response | Comments |
|---|---|---|
| | | conducted by two independent reviewers |
| Was data extraction conducted by two or more reviewers independently? | NO | Data were extracted by one reviewer and verified against the original sources by a second independent reviewer. The EAG is satisfied with the company's approach |
| Were appropriate criteria used to assess the risk of bias of identified studies? | YES | The company used ROBINS-I to assess risk of bias in HERIZON-BTC-01. ROBINS-I is primarily designed to assess comparative non-randomised studies and, thus, includes items not relevant to HERIZON-BTC-01. Overall, the EAG is satisfied with the company's use of ROBINS-I |
| Was the risk of bias assessment conducted by two or more reviewers independently? | YES | Risk of bias assessments were performed by one reviewer and checked against the original sources by a second independent reviewer. The EAG considers the company's approach to be acceptable |
| Was identified evidence synthesised using appropriate methods? | YES | Based on the available data, the company used appropriate methods. The methods used to select the zanidatamab and comparator datasets used in the analyses was not always completely transparent, however. |

The EAG conducted a quality assessment of the methods used by the company for the SLR of clinical evidence based on the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 5.

**Table 5 Quality assessment of the company's systematic literature review of clinical effectiveness evidence**

| CRD quality item | Yes/No/Unclear |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question? | Yes |
| 2. Is there evidence of a substantial effort to search for all of the relevant research? | Yes |
| 3. Is the validity of included studies adequately assessed? | Yes |
| 4. Are sufficient details of the individual studies presented? | Yes |
| 5. Are the primary studies summarised appropriately? | Yes |

### *3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The key clinical effectiveness evidence is presented in Section 2 of the CS. The company's main source of evidence for zanidatamab is HERIZON-BTC-01, an open-label, international, multicenter, single-arm, phase 2b trial of the efficacy and safety of zanidatamab in adults with HER2-amplified, unresectable, locally advanced or metastatic BTC with disease progression on previous gemcitabine-based therapy. *The EAG has no major concerns about the design and conduct of this trial.*

The company identified three further studies: one Phase 1 trial (ZWI-ZW25-101; Meric-Bernstam 2022)[20] and two observational, real-world studies conducted in the UK (Crespo-Cruz 2025)[21] and France (Smolenschi 2025).[22] The company also included data from the US Flatiron Health Research Analytic Database in the external control arm analysis.[23, 24]

The company presents details of HERIZON-BTC-01, ZWI-ZW25-101, the UCLH real-world study and the France real-world study in Table 4 of the CS, adapted with the inclusion of the US Flatiron study as Table 6 below.

The study design of HERIZON-BTC-01 is presented in Figure 9, Section 2.3.1.1.1 of the CS. All patients received 20mg/kg zanidatamab intravenously every two weeks until unacceptable toxicity, disease progression, death, loss to follow-up, pregnancy, physician decision or withdrawal of consent. Eligibility criteria for HERIZON-BTC-

01 are presented in Table 6 of the CS. *The EAG's clinical expert has no concerns about the eligibility criteria of HERIZON-BTC-01.*

The company performed quality assessment on HERIZON-BTC-01 and ZWI-ZW25-101 using the original version of the ROBINS-I tool.[25] The EAG notes ROBINS-I is designed to assess non-randomised comparative studies and that the two trials are indeed non-randomised but are not comparative. Thus, ROBINS-I includes items which are not relevant to these trials. *Overall, the EAG agrees with the company's assessment of low risk of bias for HERIZON-BTC-01.*

**Table 6 Clinical effectiveness evidence for zanidatamab in 2L HER2+ BTC [adapted from Table 4 of the CS]**

| Study | HERIZON-BTC-01 | ZWI-ZW25-101 | UCLH real-world evidence study | France real-world study | US Flatiron Health Research Analytic Database |
|---|---|---|---|---|---|
| **Study design** | Phase 2b, open-label, single-arm, multi-centre international study | Phase 1, multi-centre, dose-escalation and expansion trial | Retrospective, observational, real-world study | Retrospective, observational, real-world study | Retrospective, observational, real-world study |
| **Population** | Patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC<br>Full population: n=87<br>Cohort 1 (IHC2/3+): n = 80<br>HER2+ IHC3+: n=62<br>2L+ HER2+ IHC3+ BTC: n=36 | Patients with HER2-amplified solid tumours, including BTC<br>Full population (Part 2): n=86<br>BTC population (Part 2): n=22<br>HER2+ IHC3+ BTC: n=14 | Patients with HER2-amplified BTC after 1L treatment with CisGem ± durvalumab<br>Full population: n=20<br>2L+ HER2+ IHC3+: n=NR | Patients with HER2+ BTC previously treated with systemic therapy<br>Full population: n=20<br>2L+ HER2+ IHC3+: n=12 | Patients with HER2+ IHC3+ locally advanced or metastatic BTC who received 2L treatment<br>Full population: n= 29,000<br>2L+ HER2+ IHC3+ BTC: n=12 |
| **Intervention(s)** | Zanidatamab | Zanidatamab | Zanidatamab | Zanidatamab | Chemotherapy |
| **Indicate if study supports application for marketing authorisation** | Yes | Yes | No | No | No |
| **Indicate if study used in the economic model** | Yes | No – supportive evidence for efficacy and safety only | Yes - real-world patient demographics used in scenario analyses | No – supportive evidence for efficacy and safety only | No |
| **Reported outcomes specified in the decision problem**[†] | ORR<br>**OS**<br>**PFS**<br>**TTD**<br>**AEs** | ORR<br>PFS<br>AEs | ORR<br>OS<br>AEs | PFS<br>OS<br>AEs | OS |

| Study | HERIZON-BTC-01 | ZWI-ZW25-101 | UCLH real-world evidence study | France real-world study | US Flatiron Health Research Analytic Database |
|---|---|---|---|---|---|
| | **HRQoL** | | | | |
| **All other reported outcomes** | DOR<br>DCR | CBR<br>DCR | N/A | DCR<br>DOR | N/A |
| **Key data sources** | Unpublished data:<br>CSP[26]<br>CSR DCO 11th July 2024[27]<br>IHC3+ subpopulation TFLs DCO 11th July 2024[28]<br>SAP[29]<br>Publications:<br>Harding (2023)[30] (primary publication) DCO 10th October 2022<br>Pant (2024)[31] DCO 28th July 2023<br>Pant (2024)[32] DCO 10th October 2022 | Unpublished data:<br>CSR[27]<br>Publication:<br>Meric-Bernstam (2022)[20] | Publication:<br>Crespo-Cruz (2025)[21] | Publication:<br>Smolenschi (2025) [22] | Unpublished data:<br>External control analysis[24]<br>Publication: Kim 2025[23] |

Abbreviations: AE, adverse event; BTC, biliary tract cancer; CBR, clinical benefit rate; CSP, clinical study protocol; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; HRQoL, health-related quality of life; IHC, immunohistochemistry; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SAP, statistical analysis plan; TFL, tables, figures, lists; TTD, time to treatment discontinuation; UCLH, University College London Hospitals.
[†]Outcomes in bold are the outcomes incorporated into the model.

### 3.2.1 Studies of interest identified

*HERIZON-BTC-01*

Participant flow through the trial is presented in Figure 10 of the CS. A summary of the trial methodology is presented in Table 5 of the CS, reproduced as Table 7.

**Table 7 Summary of HERIZON-BTC-01 methodology [reproduced from Table 5 of the CS]**

| | |
|---|---|
| **Study reference/ID** | HERIZON-BTC-01 (NCT04466891) |
| **Study design** | Global, multi-centre, single-arm, Phase 2b trial of zanidatamab (20 mg/kg IV Q2W) for HER2-amplified, unresectable, locally advanced, or metastatic BTC (including GBC, iCCA, and eCCA subtypes) with disease progression on previous gemcitabine-based therapy |
| **Location/setting** | Patients were recruited into 32 clinical trial sites in Canada, Chile, China, France, Italy, South Korea, Spain, UK, and USA |
| **Eligibility criteria** | Eligible patients were aged ≥18 years with HER2-amplified BTC confirmed by ISH per central testing, at least 1 measurable target lesion per RECIST v1.1, and an ECOG PS of 0 or 1 [30] |
| **Population and sample size** | • Overall population: n= 87<br>– Cohort 1 (HER2 IHC3+ and 2+ tumours): n=80; IHC3+ subpopulation: n=62<br>– Cohort 2 (HER2 IHC1+ or 0 tumours): n=7 |
| **Primary endpoint** | • cORR by RECIST v1.1, assessed by ICR |
| **Secondary endpoint** | • cORR by RECIST v1.1, assessed by INV<br>• DCR by RECIST v1.1, assessed by ICR and INV<br>• DOR by RECIST v1.1, assessed by ICR and INV<br>• Proportion of patients with DOR at least 16 weeks by RECIST v1.1, assessed by ICR and INV<br>• PFS by RECIST v1.1, assessed by ICR and INV<br>• OS<br>• AEs |
| **Exploratory outcomes** | • HRQoL (EQ-5D-5L and BPI-sf) |

**Abbreviations:** cORR, confirmed objective response rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ICR, independent central review; RECIST, response evaluation criteria in solid tumours.
**Sources:** Harding (2023)[30]; HERIZON-BTC-01 CSR (2025).[27]

Among the total of 80 participants recruited across 32 sites, two patients from one site were recruited in the UK. Two cohorts were recruited with Cohort 1 being the focus of the CS, in particular the 62 HER2+ IHC3+ participants and the [redacted] HER2+ IHC3+ second line (2L) participants.

Three data cut-offs (DCO) were conducted:

- 10-10-2022: the primary DCO
- 28-07-2023: used to inform EMA regulatory submission
- 11-07-2024: the basis of the company's submission (CS) and used to inform the economic model

Baseline characteristics and disease characteristics of HERIZON-BTC-101 participants are reported in Tables 8 and 9 of the CS, adapted as Table 8 below. In addition, baseline data for the [redacted] IHC3+ 2L only participants are also presented in Table 8 for completeness, as they are utilised in the company's matching-adjusted indirect comparison (MAIC). Characteristics were similar across the complete cohort 1, the IHC3+ participants and the IHC3+ 2L only participants. *The EAG's clinical expert is satisfied that the HERIZON-BTC-01 participants are typical of those seen in clinical practice in terms of demographic and disease characteristics.*

**Table 8 Baseline characteristics and disease characteristics of participants in HERIZON-BTC-01 [adapted from Tables 8, 9 and 23 of the CS]**

| HERIZON-BTC-01 | Cohort 1 (IHC2/3+) (n=80) | IHC3+ (n=62) | IHC3+ 2L only (n=[redacted]) |
|---|---|---|---|
| **Baseline characteristics** | | | |
| **Age, years**<br>Mean (StD)<br>Median (min, max) | <br>62.5 (9.56)<br>64.0 (32, 79) | [redacted] | <br>NR<br>[redacted] |
| **Age category, n (%)**<br><65 years<br>≥65 years | <br>41 (51.3)<br>39 (48.8) | <br>[redacted] | <br>NR<br>NR |
| **Sex, n (%)**<br>Female<br>Male | <br>45 (56.3)<br>35 (43.8) | <br>[redacted] | <br>[redacted] |
| **Race,[†] n (%)**<br>American Indian or Alaska Native | 1 (1.3) | [redacted] | NR |

| HERIZON-BTC-01 | Cohort 1 (IHC2/3+) (n=80) | IHC3+ (n=62) | IHC3+ 2L only (n=[redacted]) |
|---|---|---|---|
| Asian | 52 (65.0) | [redacted] | NR |
| White | 23 (28.8) | | NR |
| Not reportable‡ | 2 (2.5) | | NR |
| Unknown | 2 (2.5) | | NR |
| **Race,† n (%)** | | | |
| Asian | 52 (65.0) | [redacted] | NR |
| Non-Asian | 28 (35.0) | | NR |
| **Geographic region, n (%)** | | | |
| North America | 18 (22.5) | [redacted] | NR |
| Asia | 50 (62.5) | | [redacted] |
| Other | 12 (15.0) | | NR |
| **ECOG PS, n (%)** | | | |
| 0 | 22 (27.5) | [redacted] | [redacted] |
| 1 | 58 (72.5) | | |
| **Disease characteristics** | | | |
| **Disease subtype, n (%)** | | | |
| GBC | 41 (51.3) | [redacted] | NR |
| iCCA | 23 (28.8) | | NR |
| eCCA | 16 (20.0) | | NR |
| Perihilar | 8 (10.0) | [redacted] | NR |
| Distal | 8 (10.0) | | NR |
| **Stage at initial diagnosis, n (%)** | | | |
| I | 2 (2.5) | [redacted] | NR |
| II | 9 (11.3) | | NR |
| III | 23 (28.8) | | NR |
| IV | 44 (55.0) | | NR |
| Unknown | 2 (2.5) | | NR |
| **Stage at study entry,[a] n (%)** | | | |
| IIIA | 1 (1.3) | [redacted] | |
| IIIB | 8 (10.0) | | NR |
| IV | 27 (33.8) | | NR |
| IVB | 44 (55.0) | | NR |
| | | | NR |
| **Baseline hepatic impairment,[b] n (%)** | | | |
| None | 44 (55.0) | [redacted] | NR |
| Mild | 35 (43.8) | | NR |
| Moderate | 1 (1.3) | | NR |
| Severe | 0 | | NR |
| **Baseline renal impairment,§ n (%)** | | | |
| Normal | 27 (33.8) | [redacted] | NR |
| Mild to moderate | 53 (66.3) | | NR |

| HERIZON-BTC-01 | Cohort 1 (IHC2/3+) (n=80) | IHC3+ (n=62) | IHC3+ 2L only (n=[redacted]) |
|---|---|---|---|
| **Outcome to most recent prior therapy, n (%)** | | | |
| Progressed | 72 (90.0) | [redacted] | NR |
| Intolerant | 8 (10.0) | | NR |
| **Time from initial diagnosis to metastatic or locally advanced (months)** | | | |
| Mean (StD) | 4.7 (9.76) | [redacted] | NR |
| **Prior history of brain metastases, n (%)** | | | |
| Yes | 1 (1.3) | [redacted] | NR |
| No | 79 (98.8) | | NR |
| **Baseline sum of diameters,‡‡ (mm)** | | | |
| Independent central review Median (min, max) | 68.0 (13, 183) | [redacted] | |
| Investigator Median (min, max) | 67.5 (14, 205) | [redacted] | NR<br>NR |
| **Previous radiotherapy, n (%)** | 13 (16.3) | [redacted] | NR |
| **Previous surgery, n (%)** | 25 (31.3) | [redacted] | NR |
| **Previous lines of therapy, n (%)** | | | |
| 1 | 47 (58.8) | [redacted] | [redacted] |
| 2+ | 33 (41.3) | | |
| Median (range) | NR | | |
| **IHC result, n (%)** | | | |
| IHC3+ | NR | 62 (100) | [redacted] |
| IHC0/1+/2+ | NR | 0 | |
| **Disease stage at study entry, n (%)** | | | |
| Locally advanced (Stage III) | 9 (11.3) | [redacted] | [redacted] |
| Metastatic (Stage IV) | 71 (88.8) | | |
| **Tumour site, n (%)** | | | |
| GBC | [redacted] | [redacted] | NR |
| iCCA | | | NR |
| eCCA | | | NR |
| **Albumin levels, n (%)** | | | |
| <35 g/L | NR | [redacted] | NR |
| ≥35 g/L | NR | | NR |

**Abbreviations:** BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; HER2+, human epidermal growth factor receptor 2-positive; IHC, immunohistochemistry; PS, performance status; SAS, safety analysis set.
[†]Participants could select more than 1 race category.
[‡]Not reportable: Collection and/or reporting of this information was prohibited by local and/or regional laws and regulations.
[a]Disease staging varied by disease subtype; categories IV and IVB are mutually exclusive.
[b]Per criteria of National Cancer Institute Organ Dysfunction Working Group.
[§]Baseline renal impairment per the Cockcroft-Gault formula for estimating creatinine clearance and FDA guidance titled: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling, September 2020.
[¶]Based on central laboratory companion diagnostic testing.
[††]All participants enrolled in the study were ISH+ at screening, based on a central laboratory companion diagnostic test.
[‡‡]Sum of diameters of target lesions selected for disease response assessment per RECIST v1.1 tumour assessment.
Source: EMA EPAR (2025),[33] HERIZON-BTC-01 IHC3+ subgroup analysis (2025).[28]

### 3.2.2 Primary and secondary efficacy endpoints

Definitions of HERIZON-BTC-01 endpoints are reported in Table 7 of the CS. The primary endpoint of HERIZON-BCT-01 was confirmed objective response rate (cORR) by RECIST v1.1 assessed by independent central review. The CS presented outcome data for patients with IHC3+ disease assessed at the final DCO 11-07-24. This endpoint was not incorporated into the economic model.

*Primary endpoint: cORR*

Results of cORR are summarised in Table 13 of the CS, reproduced as Table 9.

**Table 9 Primary endpoint – cORR by ICR per RECIST v1.1 (EAS [DCO 11 July 2024]) [reproduced from Table 13 of the CS]**

| Endpoint | HERIZON-BTC-01 IHC3+ (n=62) |
|---|---|
| cORR<br>n (%)<br>95% CI | [redacted] |
| Confirmed Best Overall Response (BOR), n (%)<br>CR<br>PR<br>SD<br>PD<br>Not evaluable | [redacted] |

**Abbreviations:** CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCO, data cut-off; EAS, efficacy analysis set; IHC, immunohistochemistry; ICR, independent central review; PD, progressed disease; PR, partial response; RECIST, response evaluation criteria in solid tumours; SD, stable disease.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025).[28]

*Secondary endpoints incorporated into the economic model*

- **Progression free survival** (PFS): The company presents PFS results by both independent and investigator assessment as Table 15 of the CS, reproduced as Table 10 below. The company states that these PFS results are consistent with the interim DCO (28-07-23) results when the median PFS was 7.2 months (95%CI 5.4, 9.4).

**Table 10 Secondary endpoint – PFS per RECIST v1.1 (EAS [DCO 11 July 2024]) [reproduced from Table 15 of the CS]**

| Endpoint | HERIZON-BTC-01 IHC3+ (n=62) |
|---|---|
| **ICR** | |
| Total events, n (%)<br>Radiographic progression<br>Death | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median PFS, months (95% CI) | 7.2 (5.4, 9.4) |
| KM PFS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of PFS follow-up, months<br>Median<br>Min, max | [redacted] |
| **INV** | |
| Total events, n (%)<br>Radiographic progression<br>Death | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median PFS, months (95% CI) | [redacted] |
| KM PFS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of PFS follow-up, months<br>Median<br>Min, max | [redacted] |

**Abbreviations:** CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; KM, Kaplan-Meier; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours.
**Source:** HERIZON-BTC-01 IHC3+ subgroup analysis (2025).[28]

The Kaplan-Meier plot of PFS is presented as Figure 11 of the CS.

- **Overall survival** (OS): Results for OS are presented in Table 16 of the CS, reproduced as Table 11. The CS reports that these results are consistent with results from the interim DCO (28-07-23), with median OS being 18.1 months (95%CI 12.2, 22.9) and 6- and 12-month OS rates of 90.1% (95%CI 79.2, 95.4) and 65.0% (95%CI 51.6, 75.6), respectively.

**Table 11 Secondary endpoint – OS per RECIST v1.1 (EAS [DCO 11 July 2024]) [reproduced from Table 16 of the CS]**

| Endpoint | HERIZON-BTC-01 IHC3+ (n=62) |
|---|---|
| Total events, n (%) | [redacted] |
| Censored patients, n (%) | [redacted] |
| Median OS, months (95% CI) | 18.1 (12.2, 22.9) |
| KM OS probabilities, % (95% CI)<br>3 months<br>6 months<br>9 months<br>12 months | [redacted] |
| Duration of OS follow-up, months<br>Median<br>Min, max | [redacted] |

Abbreviations: CI, confidence interval; DCO, data cut-off; EAS, efficacy analysis set; KM, Kaplan-Meier; OS, overall survival; RECIST, response evaluation criteria in solid tumours.
Source: HERIZON-BTC-01 IHC3+ subgroup analysis (2025).[28]

The Kaplan-Meier plot of OS is presented as Figure 12 of the CS.

- **Time to treatment discontinuation** (TTD): The company presents results for TTD in Table 17 of the CS. Mean (SD) duration of treatment was [redacted] ([redacted]) months (median: [redacted] months) and [redacted]% ([redacted]) discontinued due to radiographic progression.

- **Health-related quality of life** (HRQoL):
  - EQ-5D-5L: The company reported the individual dimensions of the EQ-5D-5L (Mobility, self-care, usual activities, pain/discomfort, anxiety/depression) in terms of disease response (CR [n=[redacted]], PR [n=[redacted]], SD [n=[redacted]] or PD n=[redacted]) for the

IHC3+patients in Table 54, Appendix J of the CS. Improvements from baseline to best-on-treatment (BONT) scores were evident in all dimensions for all disease response categories with the exception of PD (where there were improvements in mobility, pain/discomfort and anxiety/depression).

- EQ-5D VAS: Change in scores from baseline to BONT for IHC3+ patients are reported in Table 18 of the CS in the same disease response categories as above, with the greatest improvements being in patients experiencing CR, followed by PR. These improvements are described in the CS as "*clinically meaningful*", by exceeding the minimally important difference of seven points. The improvement in patients experiencing SD was not clinically meaningful and those experiencing PD showed a decrease in mean score.
- Brief pain index: for IHC3+ participants (n=59), the CS reported a modest improvement in pain of [redacted]points (SD [redacted]).
- Opioid use: Reported for the entire Cohort 1 only in Table 19 of the CS. The highest increase in opioid use from baseline was reported by those patients experiencing PD.

### 3.2.3 Subgroup analyses

The CS presents subgroup analysis of cORR by disease subtype (Appendix C). There was no significant differences in response by subtype.

### 3.2.4 Adverse events

*HERIZON-BTC-01*

The CS reports safety data for the safety analysis set (SAS) of HERIZON-BTC-01, defined as "*all safety evaluable patients enrolled in Cohort 1 and Cohort 2… A patient was considered safety evaluable if they received any amount of zanidatamab*". The company explained that "*Safety analysis for the IHC3+ population was not conducted as safety of any medicine is not expected to vary between populations and greater patient numbers provide more robust evidence for the safety profile of zanidatamab*". The EAG is satisfied with the company's approach.

Median duration of treatment in the IHC3+ group was [redacted]months (range [redacted], [redacted]) with a median of [redacted] cycles initiated (range [redacted], [redacted]). Mean duration of treatment in the IHC3+ group was [redacted]months (SD [redacted]) with mean [redacted](SD [redacted]) cycles initiated.

An overall summary of treatment-emergent adverse events in HERIZON-BTC-01 is presented in Table 31 of the CS, reproduced as Table 12 below. The company stated that the safety profile at the interim DCO (28-07-23) was similar to the final DCO.

**Table 12 Overview of AEs – HERIZON-BTC-01 SAS (DCO 11 July 2024) [reproduced from Table 31 of the CS]**

| AE, n (%) | Cohort 1 (IHC2+/3+) (n=80) | Cohort 2 (IHC0/1+) (n=7) | Total (n=87) |
|---|---|---|---|
| Any AE[†]<br>Study drug related | [redacted] | [redacted] | [redacted] |
| Any Grade 3+ AE<br>Study drug related | [redacted] | [redacted] | [redacted] |
| Any SAE<br>Study drug related | [redacted] | [redacted] | [redacted] |
| Any AE resulting in death[‡]<br>Study drug related | [redacted] | [redacted] | [redacted] |
| Any AE resulting in discontinuation<br>Study drug related | [redacted] | [redacted] | [redacted] |
| Any AE resulting in:<br>Infusion interruption<br>Dose delay<br>Dose held (skipped)<br>Dose reduction | [redacted] | [redacted] | [redacted] |

**Abbreviations:** AE, adverse event; DCO, data cut-off; IHC, immunohistochemistry; SAS, safety analysis set.
Study-drug relationship as determined by investigator
[†]Any AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment, inclusive.
[‡]Includes death that occurred within the safety reporting period plus deaths >30 days after the final dose of study treatment.
**Source:** HERIZON-BTC-01 CSR (2025).[27]

The most common AEs by preferred term were gastrointestinal disorders ([redacted]), investigation ([redacted]), infections and infestations ([redacted]), general disorders and administration site conditions ([redacted]), metabolism and nutrition disorders ([redacted]), injury, poisoning and procedural complications ([redacted]) and blood and lymphatic system disorders ([redacted]). Adverse events occurring in at least 10% of HERIZON-BTC-01 patients by MedDRA preferred term are presented in Table 32 of the CS. At least 20% of patients experienced diarrhoea ([redacted]), IRR ([redacted]) and anaemia ([redacted]).

**Treatment-related AEs (TRAEs)** were experienced by [redacted] of patients. TRAEs occurring in at least 5% of participants are reported in Table 33 of the CS; those occurring in at least

10% of participants were diarrhoea ( infusion-related reaction ( , and ejection fraction decreased ( ).

**Grade 3 and higher AEs** occurring in at least 5% of patients are presented in Table 34 of the CS. Grade 3+ AEs were experienced by of patients, with experiencing the highest severity of Grade 3, Grade 4 and Grade 5. The most commonly reported Grade 3+ AEs were anaemia ( ; considered related to study drug), diarrhoea ( ; considered related to study drug) and hypertension ( considered related to study drug). Grade 3+ TRAEs occurring in more than one patient were diarrhoea ( %), anaemia ( %), ejection fraction decrease ( %) and AST increase ( %).

**Serious AEs** (SAEs) occurring in at least 2% of patients are presented in Table 35 of the CS. Serious AEs were experienced by of patients with those occurring in at least 5% being cholangitis ( ), jaundice cholestatic ( ) and pneumonia ( ). Treatment-related SAEs (Table 36 of the CS) were experienced by of patients: ALT and AST increase ( ), anaemia, diarrhoea, ejection fraction decrease, enteritis, infusion-related reaction, oral candiasis and pneumonitis ( ).

**Deaths** are summarised in Table 37 of the CS. Overall, of participants died, within 30 days of the last dose of zanidatamab ( deaths due to disease progression and due to AEs: hepatic failure, haematemesis and underlying cancer). In terms of deaths more than 30 days after the last dose of zanidatamab, a total of patients died, with due to disease progression, due to an AE (multiple organ dysfunction that began during the safety reporting period) and due to other reasons. ) patients died due to an unknown cause, of whom had discontinued zanidatamab due to progressive disease.

**Adverse events resulting in discontinuation of treatment** were experienced by ( ) of patients; Grade 3 pneumonitis and Grade 2 decreased ejection fraction event. These were considered treatment-related by the investigator.

**Adverse events of special interest** are reported in Section 2.11.1.7 of the CS and summarised in Table 37 of the CSR, adapted as Table 13 below.

**Table 13 Adverse events of special interest [adapted from Table 37 of the CSR]**

| AESI/Select AE | Cohort 1 (n=80) | Cohort 2 (n=7) | Total (n=87) |
|---|---|---|---|
| Infusion-related reactions | [redacted] | [redacted] | [redacted] |
| Potential cardiac events | [redacted] | [redacted] | [redacted] |
| Confirmed cardiac events | [redacted] | [redacted] | [redacted] |
| Pneumonitis | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] |

- **Infusion-related reactions (IRR):** [redacted] patients experienced [redacted] IRRs of which [redacted] was a SAE. Most IRRs ([redacted]) were of mild or moderate severity (Grade 1 or 2) with [redacted] patient experiencing a Grade 3 IRR. Most patients ([redacted]) with an IRR experienced the IRR during the first cycle of zanidatamab treatment and [redacted] did not experience recurrent IRRs.
- **Cardiac events:** There were [redacted] confirmed ejection fraction decreased events in [redacted] patients, of which [redacted] patient's event was considered serious. These events were all confounded by pre-existing and concurrent medical conditions including atrial fibrillation, history of hypertension or baseline elevated blood pressure, coronary heart disease and/or concurrent chemoport infection with gastrointestinal haemorrhage. [redacted] cardiac events in [redacted] patients were considered related to the study drug by the investigator.
- **Diarrhoea:** [redacted] events were reported in [redacted] of patients. Of these, [redacted] events in [redacted] of patients were considered related to the study drug by the investigator. Diarrhoea was experienced as an SAE requiring hospitalisation in [redacted] patients. Most patients' experience of diarrhoea [redacted] was as Grade 1 or Grade 2 events, with [redacted] reporting Grade 3 events.

Section 2.11.2 and Appendix D of the CS reports supporting safety evidence in the form of a Phase 1 trial (ZWI-ZW25-101)[20] and two real-world studies (in England[21] and France,[22] respectively).

*Overall, the EAG's clinical expert is of the opinion that the AEs reported in the HERIZON-BTC-01 trial are as expected from clinical use of zanidatamab in these patients and has no concerns.*

### *3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

The company employed indirect treatment comparison (ITC) methods to estimate the relative efficacy of zanidatamab compared with FOLFOX + ASC and ASC alone, given that no head-to-head evidence was identified. The SLR identified two relevant studies: HERIZON-BTC-01 and ABC-06.[34] A summary of the two studies is presented in Table 22 of the CS, reproduced as Table 14 below.

**Table 14 Summary of studies used for the ITCs [reproduced from Table 22 of the CS]**

| Characteristic | HERIZON-BTC-01 | ABC-06 |
|---|---|---|
| Intervention(s) | Zanidatamab | FOLFOX + ASC, ASC |
| HER2 targeted treatment | Targeted | Non-targeted |
| Data source (reference) | ILD[27] | Published manuscript[34] |
| Study design | Single arm study | RCT (comparative) |
| Enrolment dates | 2020 to 2022 | 2014 to 2018 |
| n | Overall: 87<br>Cohort 1: 80<br>Cohort 2: 7<br>IHC3+: 62 | Overall: 162<br>FOLFOX + ASC: 81<br>ASC: 81 |
| Population | HER2-amplified BTC treated with previous gemcitabine-based therapy. Subgroups: IHC3+ and IHC2+ (Cohort 1), IHC0 IHC1 (Cohort 2), and IHC3+ only | Locally advanced or metastatic BTC with PD to first-line chemotherapy |
| Comparator | - | ASC alone |
| Primary endpoint | ORR | OS (ITT) |
| Secondary endpoint(s) | Disease response by ICR, ORR by BTC anatomical subtype | Safety |
| Median follow-up duration | [redacted] months<br>(range: [redacted] to [redacted]) | 21.7 months<br>(IQR: 17.2, 30.8) |
| HER2 testing method | IHC score, confirmed by central laboratory ISH | Not performed |

**Abbreviations:** ASC, active symptom control; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, individual level data; ISH, in-situ hybridisation; ITC, indirect treatment comparison; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; RCT, randomised controlled trial.

ABC-06 was a UK-based, multicentre, open-label Phase 3 RCT to investigate whether patients with advanced biliary tract cancer would benefit from the addition of 2L FOLFOX to ASC, following progression to previous 1L treatment with cisplatin and gemcitabine. It included 162 participants who were randomised to receive either FOLFOX plus active

symptom control (ASC) or ASC alone. The population differed from HERIZON-BTC-01 in that the IHC status of participants was not recorded, and it only included second-line (2L) patients. The EAG agrees with the company's assessment that ABC-06 is at high risk of bias, specifically, the trial is not masked, and the pertinent outcomes are subjective. However, for the purposes of this appraisal the randomised groups are treated as observational evidence in the comparison with zanidatamab.

### *3.4 Critique of the indirect comparison and/or multiple treatment comparison*

No randomised controlled trials comparing zanidatamab to other comparators were identified, so the evidence for the effectiveness of zanidatamab came from single-arm studies only, and it was not possible to conduct any head-to-head meta-analyses against other comparators.

Three sets of indirect treatment comparisons (ITC) were undertaken by the company to compare the effectiveness of zanidatamab against relevant comparators. In the following sections, we will first consider the choice of zanidatamab data in these analyses followed by the choice of comparator data. We will then describe the three ITC methodologies in the order they were presented by the company.

Table 15 (adapted from Table 21 of the CS) provides an overview of the three analyses undertaken.

**Table 15: Overview of ITC approaches [adapted from Table 21 of the CS]**

| | Unanchored MAICs | External control arm analysis | Naive comparison |
|---|---|---|---|
| Endpoints explored | OS<br>PFS | OS<br>PFS | OS<br>PFS |
| Source of zanidatamab data and subgroup considered | HERIZON-BTC-01<br>IHC3+ and 2L | HERIZON-BTC-01 | HERIZON-BTC-01<br>IHC3+ |
| Comparator(s) | FOLFOX + ASC<br>ASC alone | Chemotherapy | FOLFOX + ASC<br>ASC alone |
| Source of comparative evidence | ABC-06 | Real-world retrospective data from US Flatiron Health Research Analytic Database | ABC-06 |

Abbreviations: 2L: second line; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC: immunohistochemistry; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

### 3.4.1 Choice of zanidatamab data

The company used data from the HERIZON-BTC-01 study in all three ITC analyses. The other zanidatamab studies identified by the company (ZWI-ZW25-101 and the English and French real-world studies) did not contribute to the cost-effectiveness analyses, except that the English real-world study[21] was used to derive the mean weight at treatment initiation for the economic model base case. Additionally, a US real-world dataset was used for the external control arm analysis.[23]

Table 7 in section 3.2 above provides summary information about the number of participants in the available zanidatamab studies. All studies were small and without a comparator arm. HERIZON-BTC-01 included n=87 BTC patients, of whom n=62 were IHC3+, n-=18 were IHC2 and n=7 were IHC0 or IHC1. Of the n=62 with IHC3+, n=[redacted] were considered second line (2L) patients. ZWI-ZW25-101 included n=86 patients, of whom only n=22 had BTC. Of these, n=14 were IHC3+ and n=8 IHC0-2. The English real-world study (UCLH) included n=20 patients but the IHC status of these was not recorded. The French real-world study included n=20 patients, of whom n=12 were IHC3+. The Flatiron Heath Research Analytic Database (a US real-world database including electronic health records from 2011 to 2023) included around 29,000 patients with BTC, but only 12 were recorded as IHC3+.

It can be seen that the number of participants known to be BTC IHC3+ in these studies was small. HERIZON-BTC-01 included the largest number of IHC3+ participants (n=62) and was the only study to include participants who were confirmed to be both BTC IHC3+ and 2L, but there were only [redacted] people in this category.

The EAG asked whether the company had considered supplementing the HERIZON-BTC-01 data with data from other zanidatamab studies. The company responded that there were small numbers of IHC3+ participants in these studies and that it would add additional uncertainty due to between-study heterogeneity.

The EAG also asked if they considered using non-IHC3+ data from the other zanidatamab studies. They argued that non-IHC3+ BTC is not expected to be included in the UK marketing authorisation for zanidatamab.

*Although the EAG accepts the company's reasons for restricting the analyses to IHC3+ data from HERIZON-BTC-01, it raises concerns over the similarity of the comparator population that had no such restriction. However, the EAG's clinical adviser broadly agrees with the company's approach.*

*The EAG is also concerned that the restriction to 2L participants was applied to one analysis, but not another, and the justification for this inconsistency was not clear. In general, these restrictions lead to a very small number of individuals contributing to the analyses, but none of the additional studies that could have contributed data included more than 14 IHC3+ participants and the clinical characteristics of these populations varied. Therefore, the company's decision to use only HERIZON-BTC-01 data seems reasonable.*

### 3.4.2 Choice of comparator data

The company conducted a systematic literature review to identify studies relevant to this appraisal. The review was restricted to 2L BTC participants previously treated with at least one line of therapy. After updated searches, 18 studies were identified that involved participants with HER2 alterations – four zanidatamab studies with the rest involving other treatments (Table 5, Appendix B.1.3.4). However, the company chose instead to use a

different study (ABC-06) to provide comparator data. This had been used as a source of comparator evidence in at least two previous NICE appraisals.

In the original CS, the rationale for selecting the ABC-06 study as a comparator over other identified studies was not provided. The EAG, therefore, asked why none of the studies identified in the literature review were used. These included treatments such as: neratinib, trastuzumab deruxtecan, trastuzumab, tucatinib and trastuzumab, pyrotinib, tebotelimab, pertuzumab and trastuzumab, SHR-A1811, chimeric antigen receptor modified T cells and IBI354 (anti-HER2 ADC). The company responded that these studies involved "irrelevant" comparators that were not available in the UK. They also highlighted that ABC-06 is a randomised Phase 3 study conducted exclusively in the UK, making it more robust than using real-world evidence. In addition, ABC-06 had been used in previous appraisals of targeted treatments in 2L BTC.

*The EAG agrees that NICE's scope specifies FOLFOX as a comparator, but any established clinical management may also be considered. A further concern is that the IHC status of ABC-06 participants is not known. This means that, when restricting the zanidatamab sample to IHC3+ only, the two populations may not be clinically comparable. The EAG also noted that the company restricted one set of analyses (MAIC) to IHC3+ and 2L, but the primary analyses used in the economic model (naïve comparison) also included participants who were not 2L. However, the EAG's clinical adviser agreed that the company's choice of comparator evidence was reasonable. Unlike FOLFOX, the other comparators identified were not generally used in UK clinical practice, and the alternative studies included small number of participants with BTC. He also advised that the comparison of the IHC3+ population with a population with unknown IHC status was unlikely to be a major concern.*

### 3.4.3 Unanchored MAIC

The first of the three analyses presented by the company was unanchored matched adjusted indirect comparisons (MAIC). This compared zanidatamab data from HERIZON-BTC-01 with data from the two arms (FOLFOX + ASC, ASC alone) of the ABC-06 trial.

The EAG agrees that this is a situation where the use of an unanchored MAIC could be potentially beneficial. An anchored MAIC approach was not possible because of the lack of a connected network comparing zanidatamab versus other comparators, so an unanchored

MAIC can use zanidatamab data that has been adjusted to match published comparator data from another source (ABC-06 in this case).

In this analysis zanidatamab data were "trimmed" to the n=[redacted] who were IHC3+ and 2L, which is a very small number for this kind of adjusted analysis. Although the ABC-06 population were all 2L participants, their IHC status was not known.

In the MAIC analysis adjustment appears to have been made for tumour site, stage of disease and ECOG stage only. 2L vs 3L status would have been used as an adjustment variable, but as HERIZON-BTC-01 was trimmed to just 2L participants, both studies consist of 2L participants only. A second model attempted to adjust for geographic region, but this model failed to converge because HERIZON-BTC-01 contained mostly participants from North America and Asia and ABC-06 included those from the UK. A third model adjusting additionally for age and gender had similar results to the main analysis.

The EAG reviewed the company's MAIC methodology using the criteria in the NICE DSU TSD18.[35]

1. Submissions should provide evidence that population adjustment is likely to produce less biased estimates than using standard methods (here, a naïve comparison). The EAG's clinical adviser agrees that the variables adjusted for are sensible. The company demonstrated that there were some differences in the two populations, e.g., tumour site, but most covariates appeared to have a similar distribution in the two studies. It was also not possible to adjust for region/ethnicity, IHC status or number of previous lines of therapy, either because this information was not available for ABC-06 or because all participants in ABC-06 belonged to just one category.
2. Submissions using unanchored population adjustment must provide evidence on the likely extent of error from unaccounted covariates, in relation to the observed relative treatment effect. The EAG considers that the CS does not make the impact of not adjusting for covariates, such as IHC or 2L status, sufficiently clear.
3. In an unanchored indirect comparison, population adjustment methods should adjust for <u>all</u> effect modifiers and prognostic variables, but data restrictions meant that matching could only be performed on four of these characteristics. The company's clinical experts originally identified 27 variables for OS and 22 variables for PFS as being important prognostic variables for this analysis.[36]

4. It was also unclear whether analyses used the usual linear prediction scale for this outcome (log hazard ratio).
5. The target population for the analyses is the population of the ABC-06 trial, which differs from the population of the HERIZON-BTC-01 study and may differ from clinical practice, although the ABC-06 was conducted in a UK setting.
6. The effective sample size (ESS) of the MAIC analyses reduced from [redacted] to [redacted] after matching. Simulation studies have shown that analyses based on ESS below 30 may not be reliable.[37]
7. Although Kaplan Meier plots showed no evidence of survival curves crossing, the proportional hazards assumption was not formally assessed within the CS.

In the CS, the company recognises that there were multiple uncertainties in the conduct of the MAIC, including the matching process, prediction of outcome and confounding by subsequent treatment received. For this reason, they treat the MAIC analyses as supporting evidence only.

*The EAG agrees with this assessment. The analyses were based on a trimmed sample, included only one of the identified zanidatamab studies and it was not possible to adjust for all relevant predictors of survival, which is an assumption of this type of analysis.*

*For both PFS and OS, results for the MAIC analyses were similar to corresponding unweighted analyses. Despite this, the EAG suggests caution in the interpretation of the HRs obtained from these analyses.*

### 3.4.4 External control arm analysis

The second approach presented by the company was referred to as an "external control arm analysis". Further information on this analysis was provided in a report written by Target RWE.[38] This compared the zanidatamab data from HERIZON-BTC-01 and routine data from a large US patient-level database derived from electronic health records. Various analyses were conducted, but the primary analysis included only 12 eligible participants IHC3+ were eligible for inclusion and compared with 62 IHC3+ participants from HERIZON-BTC-01. Analyses used a propensity score model approach that used standard mortality ratio weighting to reweight the US data to be representative of the HERIZON-BTC-01 population.

*Results indicated improved survival in the zanidatamab cohort. However, the report acknowledged various limitations with these analyses, including small sample size, confounding bias caused by being unable to adjust for all clinically relevant covariates. The control data also is from a US population where prescribing practices differ to those in the UK.*

*This analysis uses similar methodology to the previous MAIC analysis but also has similar limitations. The company, therefore, presents this as supportive evidence only and the EAG agrees with this assessment.*

### 3.4.5 Naïve comparison

The third approach used by the company was a naïve comparison of the zanidatamab data from HERIZON-BTC-01 with the FOLFOX + ASC and ASC only arms of the ABC-06 trial.

This analysis used the IHC3+ subpopulation (n=62) of the zanidatamab study and did not restrict to 2L participants. This differed from the approach used in the MAIC analyses. As previously stated, the comparator study (ABC-06) only included 2L participants.

The company compared published data for ABC-06 on median survival and survival rates at 6 and 12 months with IPD from the HERIZON-BTC-01 study. This information was available for both arms for OS but only for the FOLFOX + ASC arm for PFS.

The results indicated that zanidatamab participants had longer median PFS and OS than FOLFOX +ASC participants and that median OS was also longer for zanidatamab versus ASC only. Survival rates at 6 and 12 months were also better for zanidatamab.

Given the uncertainties with the previous two approaches, the naïve comparison was used as the primary analysis method to provide estimates for economic modelling. However, there are also concerns about using a difference in median survival as an effect size. Unlike means, medians can be sensitive to relatively small changes in the data, especially for smaller sample sizes, and this might lead to biased effect sizes.
Different effect sizes might also have been obtained if the company had excluded non-2L participants, as in the MAIC analyses.

This is a non-randomised comparison without any adjustment for potential confounders, so the result may be subject to bias of unknown magnitude, particularly if the two populations differ for key clinical characteristics. Although some characteristics were similar, there were differences in geographical region, previous treatments and tumour site, and the IHC status of the ABC-06 participants was not known. There could also be differences in unmeasured characteristics.

*Despite these concerns, the EAG's clinical adviser agrees that the decision to compare these studies was reasonable given the lack of alternative data sources. The EAG advises caution, however, when using the results of the naïve comparison for decision making within the economic model. Median differences from an unadjusted observational comparison cannot be considered a particularly reliable effect size for the difference between zanidatamab and other comparators (ASC, FOLFOX + ASC), especially when sample sizes are small.*

### 3.4.6 Conclusions: indirect comparison

All three analyses demonstrated that zanidatamab provided survival benefits over other comparators. Despite uncertainties about the methodology, the EAG believes that it is highly unlikely that zanidatamab is less effective than either FOLFOX + ASC or ASC alone and agrees that the analyses conducted for this submission were reasonable given the limited data available.

However, there remains uncertainty about the magnitude of the effects which were used in the cost-effectiveness analyses. The main concerns include:

- Analyses were based on small numbers of participants and there are wide confidence intervals around these estimates.
- The choice of data source for both zanidatamab and the comparator lacked transparency.
- There was inconsistency between analyses in whether non-2L zanidatamab data were included.
- The company was unable to demonstrate that the assumptions of the MAIC analyses were met and relegated this to supporting evidence only.
- The primary effect size used by the company was based on a naïve comparison that was unadjusted and may be prone to bias.

### *3.5 Additional work on clinical effectiveness undertaken by the EAG*

None

### *3.6 Conclusions of the clinical effectiveness section*

The evidence for this technology came from a small number of single-arm studies, the largest of which (HERIZON-BTC-01) included just 87 participants with BTC and only [redacted] who were classed as both 2L and IHC3+. The EAG has no major concerns about the conduct of this study.

To compare the effect of zanidatamab against other comparators, the company used ABC-06, an RCT of ASC + FOLFOX versus ASC alone. Although the EAG did not find the choice of comparator study particularly transparent, the alternative sources of comparator evidence appear to be small single-arm studies, and most did not assess treatments licensed in the UK, whereas FOLFOX is an established treatment and included as a comparator in NICE's scope.

Due to differences in the populations of HERIZON-BTC-01 and ABC-06, analyses adjusted for important clinical characteristics would be recommended, but the MAIC analyses conducted by the company were limited by the fact that the assumptions were not fully met. This led to the choice of an unadjusted (naïve) analysis as the main source of evidence for the cost-effectiveness modelling. Both adjusted and unadjusted analyses suggested a survival benefit of zanidatamab over the comparator treatments.

*The EAG agrees that these analyses are reasonable, given the limited sources of data, but has concerns about the robustness of this evidence and advises that the derived effect size estimates may not be reliable, recommending cautious interpretation of any models that used them.*

*We would also like to highlight alternative approaches to evidence synthesis that could perhaps be undertaken to increase the certainty of the results obtained. The main limitation is the lack of zanidatamab data, particularly for the IHC3+ subgroup for which the company seeks marketing authorisation. Waiting for large, randomised studies to become available may not be realistic given this is a relatively rare condition. Alternatively, HERIZON-BTC-01*

*data could be supplemented with data from other studies, but most include fewer than 25 BTC patients and these studies have diverse patient populations.*

*The other area of uncertainty comes from the source of control data. If using data from ABC-06, the EAG observed that this publication includes a data sharing agreement - this might allow the use of fully patient-level analyses rather than analyses using published data, although the EAG understands that the company requested data but received no response from the authors.*

*The attempt to use US routine data did not yield particularly useful results, but other real-world datasets could potentially be used. In particular, in the indirect treatment comparison report there is reference to possible analyses using a European dataset. Even if there is a lack of specific data that are both IHC3+ and 2L, a compromise may need to be taken to expand the scope to include other groups.*

# 4 COST EFFECTIVENESS

## *4.1 EAG comment on company's review of cost-effectiveness evidence*

The company conducted a systematic review of economic evaluation models and other cost-effectiveness studies in patients with advanced or metastatic BTC. Full methodology for the systematic review of economic evaluations is provided in Appendix E of the company submission. Seven studies were identified and are summarised in Table 42 of the company submission. Briefly, there were four studies of pemigatinib in two countries (Taiwan and Greece) and one study each for chemotherapy, pembrolizumab and ivosidenib. The pembrolizumab study was the only UK study. The model was a partitioned survival model comparing pembrolizumab vs. mFOLFOX / mFOLFIRI over a 40-year time horizon in a patient population with previously treated MSI-H/dMMR tumours. The ICER was £32,085 at list price for pembrolizumab.[39] The systematic review did not identify any studies evaluating the cost-effectiveness of zanidatamab. However, the company have identified three relevant previous NICE technology appraisals for pemigatinib (TA722),[13] ivosidenib (TA948)[15] and futibatinib (TA1005)[16] for second line BTC treatment.

*The EAG are satisfied that the company have undertaken a thorough review of the published economic evidence of relevance to this appraisal. The EAG notes that whilst all previous appraisals are of targeted therapies for BTC gene mutations other than HER2+, and are thus not direct comparators, the modelling assumptions and comparator assessment (FOLFOX) may be informative for the current assessment of zanidatamab for 2L HER2+ BTC.*

## *4.2 Summary and critique of the company's submitted economic evaluation by the EAG*

### 4.2.1 NICE reference case checklist

Table 16 describes the EAG's assessment of the company submission against the NICE reference case.

**Table 16 NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | Aligned with the NICE reference case. |
| Perspective on costs | NHS and PSS | Aligned with the NICE reference case. |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | Aligned with the NICE reference case. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Aligned with the NICE reference case. |
| Synthesis of evidence on health effects | Based on systematic review | **Some concerns.** Base case economic modelling based on naïve comparison of HERIZON-BTC-01 and ABC-06 study. Alternative approaches (MAIC and external control) explored in scenario analyses. Uncertainty surrounding magnitude of incremental benefit due to methodological limitations with all approaches available to and explored by the company. |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | Aligned with the NICE reference case. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | Aligned with the NICE reference case. |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Aligned with the NICE reference case. |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Aligned with the NICE reference case. |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Aligned with the NICE reference case. Some concerns about administration costs for FOLFOX, explored in Section 4.2.8. |

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Company prefers to use a 1.5% discount rate for costs and health effects. EAG prefers 3.5% as this aligns with the current version of the NICE reference case. |

**Abbreviations**: PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

### 4.2.2 Model structure

The company use a partitioned survival analysis (PartSA) model, developed using Microsoft Excel, with estimated areas under the curve for the proportion of the cohort who are progression free, have progressed disease or have died because of HER2-positive advanced biliary tract cancer after 1 or more systemic treatments. The company's economic model structure is described in Figure 25 of the company submission. Health state occupancy is determined by independently modelled progression-free survival (PFS) and overall survival (OS) curves for each treatment. Zanidatamab OS and PFS curves are derived from the HERIZON-BTC-01 study, with FOLFOX + ASC and ASC curves derived from the ABC-06 study. This essentially represents a naïve comparison between the treatment options in terms of OS and PFS. Treatment discontinuation curves are then fitted to KM treatment discontinuation data from the HERIZON-BTC-01 study to estimate the proportion of the progression free cohort who incur zanidatamab treatment costs in each weekly cycle of the model. For FOLFOX, it is assumed that 100% of patients remain on treatment whilst progression free. All treatments are assumed to be discontinued at the point of progression (or maximum treatment duration) in the model, with those who have progressed disease incurring treatment acquisition costs that are based on UK clinical expert opinion

*The EAG is satisfied that a PartSA model is appropriate for decision making because 1) the positioning of these technologies is quite late in the treatment pathway and 2) the EAG notes that a PartSA has previously been used in several similar NICE appraisals for BTC, namely pemigatinib (TA722),[13] ivosidenib (TA948),[15] and futibatinib (TA1005).[16] Whilst the EAG are generally satisfied with the model structure, there are several uncertainties with regards to population of the model parameters that should be considered for decision making. These are considered in the sections that follow.*

### 4.2.3 Population

The modelled population for the economic model is stated in the company submission (Section 3.2.1) as patients with locally advanced or metastatic HER2+ IHC3+ BTC previously treated with at least 1 prior line of systemic therapy.

*The EAG notes that the stated modelled population is aligned with the anticipated marketing authorisation, and the EAG's clinical expert is satisfied that this represents the cohort of patients who would most likely receive zanidatamab treatment if available in UK NHS clinical practice. The EAG notes that the population described in the marketing authorisation is narrower than that of the full cohort of patients in the HERIZON-BTC-01 study. Cohort 1 of the HERIZON-BTC-01 study (N=80 participants) also included some participants with IHC2+ BTC (N=18). There is some inconsistency between the cohort definition used to define several model parameters. For example, OS and PFS KM data used in the company base case naïve comparison of treatment benefits are obtained from the IHC3+ sub-population (N=62), but utilities are derived from cohort 1 of the BTC-01 study (N=80). In addition to the inclusion of patients beyond the marketing authorisation, the decision to include IHC2+ participants for some modelling parameters but not others could have important clinical implications for the model estimates, particularly of utilities. The EAG's clinical expert explained that higher IHC scores are usually associated with more rapidly evolving BTC than lower scores. Conversely, IHC3+ might be considered less problematic to treat than those with an IHC score of 2. The EAG generally prefers the use of data from a sub-population of the trial cohort with IHC3+ for populating the economic model to maintain consistency with the marketing authorisation (and hence the population most likely to receive treatment in UK clinical practice). It also helps ensure consistency between the dataset used to inform treatment effect sizes and utilities. The EAG does not consider the inclusion of an additional 18 respondents for the estimation of HSUVs to adequately compensate for the limitations of departing from the population as defined in the marketing authorisation.*
*The impact on specific economic modelling parameters is critiqued in Sections 4.2.6 (treatment effectiveness) and 4.2.7 (utilities).*

Baseline model cohort characteristics of age and sex are based on the IHC3+ subpopulation of the HERIZON-BTC-01 study. These characteristics are used to calculate adjusted mortality and general population utility norms for application in the model. The average weight used for the economic model was 66kg, based on reported weight at baseline amongst

a retrospective observational study of N=20 patients receiving zanidatamab in England.[21] Average weight was used to enable calculation of treatment acquisition costs for drugs requiring weight-based dosing, including zanidatamab. This source of weight data was not varied in scenario analyses conducted by the company, but the relevant data are included within the economic model. The company's justification for using the retrospective data rather than the HERIZON-BTC-01 study data was that only n=2 patients were from the UK.

*The EAG note that the company's decision to apply a weight of 66.00kg, rather than the higher weight of 66.88kg from the HERIZON-BTC-01 (IHC 3+) sub-population could create an uncertainty by potentially under-estimating the treatment acquisition costs (i.e. by assuming a lower overall dosage per patient) relative to the modelled treatment benefits (derived from the trial cohort). However, the EAG's clinical expert has clarified that the overall total dose at the patient level is unlikely to be a major treatment effect modifier and that delivery of treatment at an average weight more likely to be seen in clinical practice in the UK is more appropriate. On balance, the EAG considers the company's base case source of patient weight data to be plausible but explores a scenario analysis using the ITT average weight for completeness. The impact of choice of data source for weight-based dosing only has a minor impact on the ICER.*

### 4.2.4 Interventions and comparators

***Intervention:***

The intervention considered within the scope of this evaluation, and incorporated within the economic model is zanidatamab, with a dose of 20 mg/kg administered twice per 28-day cycle (days 1 and 15).

*The EAG are satisfied that the modelled zanidatamab intervention aligns with the marketing authorisation, use in the HERIZON-BTC-01 clinical trial, and aligns with the expected use of the drug in terms of dosage and frequency if it becomes available in UK clinical practice.*

***Comparators:***

The company's model includes two alternative comparators, FOLFOX chemotherapy plus ASC and ASC alone.

*The EAG's clinical advisor is of the opinion that both comparators are relevant to the assessment. Whilst FOLFOX would be considered for some patients, others would not be sufficiently fit to manage the toxicity of FOLFOX and may choose for ASC alone. The EAG therefore considers both FOLFOX + ASC and ASC alone as relevant comparators for this appraisal. Given that FOLFOX+ASC, and ASC are not direct comparators for each other (i.e. they would be used in different patients depending on their fitness to receive treatment), the EAG considers it appropriate to rely primarily on pairwise comparisons, rather than fully incremental cost-effectiveness analyses for decision making.*

### 4.2.5 Perspective, time horizon and discounting

***Perspective***

The cost-effectiveness model reports incremental cost per QALY gained, with costs assessed according to an NHS and Personal Social Services (PSS) perspective.

*The EAG are satisfied that the analysis perspective is appropriate and aligned with the NICE scope. The EAG notes that whilst there may be a carer burden associated with caring for people with BTC, carer disutilities were not included in this assessment. The EAG are satisfied with the company's approach and note that the perspective is consistent with previous NICE appraisals of 2L treatments for BTC.*

***Time horizon***

The cost-effectiveness analysis model uses a 30-year time horizon, with 1-week cycle lengths and no half cycle correction.

*The EAG's clinical expert notes that survival outcomes at 2L HER2+ BTC are poor and that a 30-year time horizon is appropriate for the economic model, as all patients, regardless of treatment arm, would be anticipated to have died after 30 years. Previous NICE appraisals have adopted time-horizons between 20 and 40 years. Within the company's base case economic model, less than 0.2% of either cohort remain alive at year 30 for any of the explored OS extrapolation curves across treatment arms. The EAG is satisfied that any biases are minimal and any further extension of the time horizon beyond 30 years would not materially impact on the ICER.*

*The EAG considers a 1-week cycle length to be reasonable and are satisfied that half-cycle corrections are not necessary given the short duration of the model cycle.*

***Discounting:***

The company use a discounting rate of 1.5% per annum for both costs and QALYs. The original company submission justified the approach on the grounds that a 1.5% rate was in line with the latest version of the treasury Green Book and ongoing industry discussions with NICE. In response to EAG clarification question B1, the company provided further details regarding those industry discussions, noting that the industry anticipates that by the time of the first committee meeting for zanidatamab, that a 1.5% discount rate will become part of the NICE reference case. The company also justify a 1.5% discount on the grounds that the assessment fits more closely with the HST rather than STA process (i.e. that BTC is a very rare condition with only [redacted] people in England considered eligible, and that there are no other acceptable treatment options available. In line with Section 6.2.34 of the new NICE methods document for 2025, the company considers that a 1.5% discount rate is appropriate. Discounting is applied as a continual discount rate applied in each model cycle, with the time factor for the discounting calculation calculated as the proportion of a year in each model cycle. For example, model cycle 26, the discounting time period applied is 0.5 (i.e. 26/52).

*The EAG notes that, at the time of company submission and at the time of the EAG report, the relevant version of the NICE methods guide continues to recommend a 3.5% discount rate for reference case analyses. Until such time as confirmation of a 1.5% discount rate is confirmed, the EAG prefers to adopt the 3.5% discount rate for both costs and QALYs. The EAG acknowledge the company's argument about the rarity of the disease and the limited treatment options available. However, given that a decision has already been made to proceed through the STA process, the EAG considers the 3.5% discount rate to be the most appropriate for decision making. To that end, all analyses reported in the EAG report relate to the 3.5% discount rate unless stated otherwise.*

*The EAG are satisfied that the discounting approach described in the company submission is correctly applied in the economic model. The EAG explores the potential impact of discounting by fixed years as an alternative to the continual approach adopted in the company base case and noted that the impact on the ICER was minimal. The EAG is satisfied that the company's use of a continual discounting approach is appropriate.*

### 4.2.6 Treatment effectiveness and extrapolation

***Summary of data sources for OS, PFS and ToT***

The company base case analysis applies a naïve comparison for OS and PFS in the economic model. For zanidatamab, independent parametric curves are fitted to KM data from the HERIZON-BTC-01 (IHC3+ subpopulation) for both OS and PFS. For FOLFOX+ASC independent parametric curves are fitted to the KM data from the ABC-06 study. For ASC alone, OS curves are fitted using the KM data from the ASC arm of ABC-06, but PFS data were not available. The PFS for ASC was based on an assumed HR for OS, derived from the MAIC. TOT data were based on independent survival curves fitted to KM data from the HERIZON-BTC-01 (IHC3+ population) for zanidatamab. FOLFOX ToT was based on PFS in the base case with a scenario exploring an estimated HR between median PFS and ToT as reported in the ABC-06 study.[34]

*The EAG are satisfied that the company's decisions regarding the most appropriate sources of data are appropriate, given the limited data available. All approaches to estimate relative treatment effects are associated with substantial limitations around heterogeneity in patient populations and small sample sizes further add to these uncertainties. The specific limitations of each approach explored by the company are discussed in greater detail in Section 3.4 above. Whilst none of the approaches are ideal, in this scenario the EAG considers the company's base case approach to be reasonable, given the options available. A naïve comparison avoids the requirement to impose a fixed hazard ratio across the duration of the modelling time frame. This is advantageous because for this appraisal, the preferred baseline curve is unlikely to be compliant with PH assumptions. It would not have been appropriate to apply a fixed HR to the full duration of a non-PH extrapolation curve for OS or PFS. Furthermore, it would not have been possible for the company, given the data available to estimate a more flexible time-dependent HR for application in the model.*

*The company's preferred naïve comparison approach is consistent with the committee preferred assumptions for TA722 which also adopted a naïve comparison approach.[13] However, the EAG are aware that the base case assumptions for TA948, which compared ivosidenib with FOLFOX, using the ABC-06 study, applied a fixed HR over the duration of extrapolation, with the preferred HR derived from a Bucher ITC.[15] The lack of a similar approach across appraisals is likely a reflection of the considerable uncertainty and advantages/limitations with all of the available methods.*

*On balance, despite being highly susceptible to bias associated with heterogeneous patient populations, the EAG accepts the company's base case approach of adopting a naïve comparison and explores the impact of uncertainty by applying effect sizes from the MAIC and external control arm as scenario analyses. The EAG are of the view that the range of plausible ICERs across both the MAIC and the naïve comparison should inform a range of plausible ICERs for decision making.*

***General approach to selecting parametric survival curves for the naïve comparison***

The company have explored a range of different parametric survival curves to fit the respective OS and PFS KM curves from the HERIZON-BTC-01 (IHC3+ subpopulation) and ABC-06 study. Exponential, generalised gamma, gompertz, log-logistic, log-normal, weibull and gamma curves were all considered. The most appropriate distribution was selected based on visual inspection, statistical fit (AIC/BIC) and assessment of clinical validation of modelled projections against landmark survival proportions at 6, 12, 36 and 60 months. Clinical plausibility of extrapolation curves was determined by a delphi panel of 11-14 UK based clinical experts. Full details of the process are provided by the company in supporting documentation.

*The EAG is satisfied that the company's overall methodology for curve selection is appropriate and aligned with TSD 14. The EAG believes that the methodology for clinical validation of selected curves is robust, comprehensive and aligned with recommendations set out in NICE TSD 26.*

***Overall survival curves***

For zanidatamab, the exponential curve appeared to have a poor visual and statistical fit (AIC / BIC) when compared to alternative options for OS. This was despite the exponential having the closest landmark estimates of survival to those predicted by the clinical experts. However, given the poor statistical and visual fit to the KM data, the company have chosen the next closest curve to the landmark estimates provided by clinicians, the log-logistic. The LL curve also had a good statistical and visual fit to the data.

*The EAG finds that there is very little difference between the statistical and visual fits amongst all the curves except for the exponential curve, which the EAG agrees is not*

*appropriate. The impact of different curve selection becomes more pronounced at later landmark timepoints, with zanidatamab OS ranging from [redacted] (Gompertz) to [redacted] (log-logistic) at 60 months follow up. The EAG notes that whilst the log-logistic curve provides clinically plausible estimates of OS, these estimates were based on expectations rather than reported data and so are subject to uncertainty. The EAG points out that a small proportion of the cohort remain alive over the full model duration (about [redacted] in the zanidatamab arm when the log-logistic curve is applied. Although this small proportion is unlikely to be plausible, it could bias results in favour of zanidatamab. The EAG notes that log-normal and gamma curves provided a negligibly better statistical fit and provide longer-term survival landmarks that are more modest ([redacted] and [redacted] respectively at 60 months).*

*The EAG's clinical expert opinion is that few patients would remain alive beyond 5 years and therefore the Gamma curve could be considered a plausible alternative that tends to 0 more quickly and avoids a small proportion remaining alive over the full duration of the model time horizon. Gamma is also a PH-compliant curve, and it may be more appropriate to apply HRs from the MAIC to a gamma than to a LL in scenario analyses. However, applying the gamma curve to zanidatamab OS would imply OS and PFS curves may cross beyond 5 years, which is not plausible and would unfairly bias against zanidatamab. On balance, the EAG considers a log-normal curve to offer a plausible alternative to the company's preferred log-logistic curve, which slightly reduces the proportion alive over the full model time horizon, whilst also maintaining a good match to the landmark estimates anticipated by the company's clinical expert advice.*

For FOLFOX, KM data were digitised and pseudo-patient-level data were created using the Guyot algorithm. The same range of curves was fitted to the pseudo KM output. The company chose the log-normal curve because it provided the best visual and statistical fit to the data while reflecting all relevant expected clinical landmarks.

*The EAG agrees that the log-normal curve is the most appropriate option for FOLFOX OS extrapolation.*

For ASC, a log-logistic curve was chosen because it fits the data well, gives clinically plausible estimates and was the best statistical fit to the data.

*The EAG agrees that the log-logistic curve is appropriate for ASC extrapolation.*

*In summary, for overall survival, the EAG considers the company's approach to curve selection to be reasonable but prefers the use of a log-normal rather than log-logistic curve extrapolation of zanidatamab OS. The company and EAG preferred OS curves are summarised in Figure 2 below. As the landmarks from LN and LL are very close to each other over the first 5 years, the figure below is enhanced beyond 5 years to show the differences between company and EAG preferred curves. The impact of applying the EAG preferred curve in an approximately [redacted] increase in the ICER.*

**Figure 2 Company and EAG preferred overall survival curves**

***Progression free survival***

The company base their PFS extrapolations on investigator assessed rather than IRC assessed progression because this aligns with the approach taken to estimate PFS in the ABC-06 study.

*The EAG agree that it is appropriate to align the definition of progression across the two studies and further note that treatment decisions in UK clinical practice are more likely to be based in INV assessment than IRC. Given that HERIZON-BTC-01 is not a randomised study, the impact of any bias reduction associated with IRC is likely to be minimal and outweighed by the advantages of maintaining a consistent definition across modelled arms.*

For zanidatamab, all curves appear to fit the data equally well in terms of visual fit (except exponential). Generalised gamma is the best fitting curve in terms of statistical fit, but exceeds the estimated OS curve after 5 years when the log-logistic is selected for OS. The company therefore chose the log logistic curve for zanidatamab PFS because it gives reasonable statistical fit, is clinically plausible and maintains face validity when compared to the company preferred OS curve.

*The EAG considers the company's approach to be reasonable and is satisfied that log-logistic is appropriate for zanidatamab PFS. The EAG also notes that selecting a generalised gamma curve for PFS would also violate the face validity of the EAG's scenario analysis for OS using the gamma curve.*

For FOLFOX, generalised gamma, log-logistic and log-normal are all plausible curves. The company select a log-normal because it was the best fit amongst plausible curves.

*The EAG consider the company's approach to be appropriate. The company and EAG preferred PFS curves are aligned and reproduced in Figure 3 below.*

**Figure 3 Company and EAG preferred PFS curves (Reproduced from Figure 32 of the company submission)**

***Time on treatment***

For zanidatamab, time on treatment was estimated in a similar manner to that for PFS and OS. All explored curves fit the data reasonably well. The company prefer the gamma curve because it predicts the lowest proportion on treatment over time (e.g. [redacted] at 5 years). This aligns with the HERIZON-BTC-01 study data, where all patients had discontinued treatment, the majority of which was due to progression ([redacted]), by the end of the study.

*The EAG finds the company's rationale for choosing the curve with the lowest proportion on treatment to be unclear. The justification appears to rest on referencing the proportion of discontinuations in the trial due to progression. However, a more appropriate test of face validity would be to compare the proportion of the PF cohort remaining on treatment at given time points. Considering the company's preferred curves for PFS, which the EAG agrees are appropriate, applying the company's preferred zanidatamab curve would suggest a decreasing proportion of patients who are progression free and alive would remain on treatment. The EAG further notes that without artificially capping the time-on-treatment (ToT) curve to match PFS, the gamma curve for ToT results in curves that substantially cross the selected PFS curve over the first year of extrapolation. Whilst this is true for the majority of survival curves, the proportion exceeding the PFS curve without capping is substantially higher for the Gamma curve than for most others. The proportion progression free and alive who are on treatment in the company base case model then decreases rapidly from [redacted] at 1 year to [redacted] at 2 years and [redacted] at 5 years. The EAG's clinical expert notes that if a patient has responded to treatment, is progression free at 1 year, and has not already discontinued due to adverse events, they are highly likely to remain on the effective treatment until progression. This would suggest that the company's zanidatamab ToT curves lack face validity. The EAG notes that a log-normal curve is the best fitting curve statistically and provides a good visual fit to the data. The EAG considers the LN to be a more appropriate distribution for ToT that provides better longer-term face validity in terms of the proportion of the progression free cohort that remain on treatment. The EAG preferred LN curve for ToT [redacted] and predicts that [redacted] of the progression free cohort remain on treatment at 1, 2 and 5 years respectively. Even under the EAG preferred approach, the treatment acquisition costs for zanidatamab may be underestimated, relative to FOLFOX, because the preferred modelling assumption in the company base case for FOLFOX is that the cohort receives the costs of a full course of treatment up until the point of progression. FOLFOX costs are not adjusted by a ToT curve, whereas zanidatamab costs are, and this may generate a bias in favour of*

*zanidatamab treatment acquisition costs in the model. The EAG's preferred base case analysis is to use the LN curve for ToT for zanidatamab. To align with the approach taken for FOLFOX, a scenario analysis is explored where zanidatamab treatment acquisition costs are applied until progression. The EAG and company preferred curves are compared in terms of the proportion of the progression free cohort remaining on treatment over time in Figure 4. An enhanced graphical representation of the company preferred gamma and EAG preferred LN curves are compared in Figure 5.*

**Figure 4 Comparison of company and EAG preferred ToT curves impact on the proportion of the progression free cohort remaining on treatment over time**

**Figure 5 Comparison of company and EAG preferred zanidatamab ToT curves**

### 4.2.7 Health related quality of life

***Health-related quality of life data sources***

The company conducted a SLR between 2014 and 2025 and 26 studies were included in the full text review. 14 of these studies were from Asian countries and 6 studies were from UK HTA agencies (NICE and SMC). Only one study in the specified population was identified which reports VAS rating. Most of the UK studies were deemed irrelevant for the decision problem as they related to non HER2 gene mutations or were for first line treatments. For previous NICE appraisals, most of the relevant utility data are confidential in nature, have been redacted from published reports and were not available to the company or the EAG for this assessment. The only study with nonredacted utility values were from the durvalumab assessment which reported utilities of 0.79 and 0.679 for PFS and PD health states respectively.[19]

One UK cost-effectiveness analysis, McCarthy (2024),[39] previously accepted as a source of utility values for the advanced BTC population,[14] reported utilities for the BTC subgroup in the KEYNOTE-158 trial using the UK value set. The study estimated a utility value of 0.80 for the progression-free survival (PFS) health state and 0.70 for the progressed disease (PD) health state. The company used these values to inform scenario analyses.

HRQoL data used in the company's model are based on EQ-5D-5L data collected in HERIZON-BTC-01 trial. Within the study, the questionnaire was administered at baseline, every 8 weeks and 7 days before the end of the treatment. Utility values from HERIZON-BTC-01 trial were calculated by cross walking EQ-5D-5L responses to the EQ 5D-3L value set using the NICE DSU recommended mapping function. To increase sample size, the company use the full Cohort 1 instead of the licensed sub-population of interest (IHC3+). The health-state specific utility values were also appropriately adjusted for age and gender.

*The EAG agrees with the company's rationale to use EQ-5D data collected within the HERIZON study to populate the economic model but was unclear as to why the full BTC-01 cohort 1 (N=80) was used instead of the subpopulation with IHC3+ (N=62). The company clarified that the main reason was that the additional sample helped to reduce uncertainty and improve face validity of the utility estimates. Whilst the EAG acknowledges the sample size is small, there is a risk that including IHC2+ patients, where BTC is more slowly progressing but potentially more difficult to treat may not accurately reflect the QoL of patients in the IHC3+ sub-population, for which zanidatamab is licensed. In response to clarification, the company provided full utility data for the IHC3+ specific sub-population and the EAG prefers to use these data for estimating utilities in the economic model.*

*Health related utility value estimation approach*

The company considered two approaches to estimate utilities for the economic model: A) utilities derived based on disease progression status; and B) based on a range of approaches used to explore utilities based on a Time to Death (TTD) approach where the utility drops substantially in the immediate time prior to death. The time to death approach has been used in the company base case while the progression base has been explored in scenario analyses.

<u>Progression based health-state utility</u>

Linear mixed effects regression models (LMMs) were fitted to the observed data to assess changes in utility scores according to disease progression status, as determined by the investigator. A simple model was specified with a binary explanatory variable indicating progression status. To account for within-subject correlation due to repeated measurements, a random effect for each patient was included. Additionally, screening utility values were included as a random effect to adjust for baseline variability across patients. The utility

values derived from the HERIZON-BTC-01 study, and alternative utility values for scenario analyses are detailed in Table 17.

**Table 17 Summary of alternative health state utility values for the economic model using progression-based approach**

| Parameter | Company preferred, HERIZON-BTC-01 study (N=80) | EAG preferred HERIZON-BTC-01 study, IHC 3+ sub-population (N=62) | Durvalumab, TA944[19] (N=806) | McCarthy et al,[39] TA 914[14] (N=Not reported) Cholangiocarcinoma |
|---|---|---|---|---|
| PF | [redacted] | [redacted] | 0.797 | 0.805 |
| PD | [redacted] | [redacted] | 0.679 | 0.702 |

**Abbreviations:** PD, progressed disease; PF, progression free

Time-to-death utility estimates

In the company preferred base case analysis, utility values were estimated based on proximity to death. The company suggested that using a time-to-death (TTD) approach to model health-related quality of life (HRQoL) better captures the decline in quality of life as patients near death, compared with progression-based utility estimates. This approach was considered appropriate because the HERIZON-BTC-01 study included a limited number of utility assessments for people with progressed disease. As a result, the health state utilities derived from the trial may reflect quality of life only around the time of progression, rather than throughout the full period patients live with progressed disease.

The company used two methods to estimate patients' time-to-death (TTD) utility. The base case analysis used TTD (days) as a continuous explanatory variable, with an Inverse square root function. Scenario analyses explored grouping patients into three utility categories based on specific intervals of time to death in days.

For the base case analysis, the company explored several different functions, including TTD days, Log TTD days, Inverse exponent TTD days, Square TTD days and Inverse square root TTD days. Inverse square root was selected as the preferred function because it has the lowest AIC of all approaches considered, and its predictions provide good face validity with

utility values decreasing overall, with an increasing rate of decrease the lower the remaining days to death. The EAG agrees that the inverse square root is the most appropriate model if adopting a TTD approach for utility estimation. HERIZON-BTC-01 (N=80) and the IHC3+ subgroup estimated utility functions are compared in Table 18.

**Table 18: Comparison of preferred TTD continuous utility model using company and EAG preferred data from the HERIZON-BTC-01 study**

| **Parameter** | **Inverse square root TTD days HERIZON-BTC-01 study (Company preferred) *** | **Inverse square root TTD days HERIZON-BTC-01, IHC 3+ sub population (EAG preferred) *** |
|---|---|---|
| Intercept (α) | [redacted] | [redacted] |
| Coefficient (β) | [redacted] | [redacted] |
| Equation for utility | $\alpha + \frac{\beta}{\sqrt{TTD}}$ | $\alpha + \frac{\beta}{\sqrt{TTD}}$ |
| AIC | -397.8 | -340.8 |

**Abbreviations:** AIC, Akaike information criterion; TTD, time to death.
*TTD capped at 252 days.

The second approach explored by the company involved assigning a fixed utility value based on grouping of days. The time-to-death (TTD) categories used in the scenario analysis were less than 84 days, between 84 and 195 days, and more than 196 days before death. To estimate utility values for each TTD group while accounting for multiple observations per patient, linear mixed-effects regressions (LMERs) were conducted. In these models, utility was estimated using the TTD group as a fixed effect, with a random intercept for each patient to account for variability between individuals. Grouped utilities, based on the company preferred utility data set (HERIZON-BTC-01) and EAG preferred dataset (HERIZON-BTC-01, IHC3+ subgroup), provided by the company in response to clarification queries are compared in Table 19 below.

**Table 19: Comparison of TTD utilities using the group-based approach in the company and EAG preferred datasets**

| Group (days from death) | Company preferred BTC-01 cohort 1 | | | | EAG preferred BTC-01, IHC3+ sub-population | | | |
|---|---|---|---|---|---|---|---|---|
| | n pts | n obs. | Mean Utility (SD) | Mean Modelled utility value | n pts | n obs | Mean Utility (SD) | Mean Modelled utility value |
| <84 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| 84-195 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥196 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations**: obs., observations; pts., patients; SD, standard deviation; TTD, time to death.
[†]All patients with censored survival placed in this group.

*The EAG notes that both the Time-to-Death (TTD) and health state-based utilities approaches are associated with advantages and disadvantages. In general, the TTD approach overcomes a key limitation of the progression-based approach, which assumes that utilities remain constant within a health state, usually the progressed health state, over time. This potentially leads to an overestimation of utility values in the progressed disease state, where utility measures are often collected shortly after the point of progression and may not yet fully capture all QoL implications of progressed disease.*

*However, the EAG are of the view that the key advantage of the TTD approach can be best realised when the duration of time within the progressed disease state across all treatment arms is sufficiently long so that the majority of QALY decrements from the approach are accrued within the progressed disease state. The TTD approach essentially assumes that TTD utility decrements are independent of progression status. When the duration of progressed disease is substantially different across groups (model arms), the implication is that the QALY decrements may have a greater impact on QALYs accrued in the progression free state in one arm of the model than another. The EAG are of the view that this adds*

*uncertainty to the QALYs modelled under the TTD approach and may offset some of the advantages of the approach described above. For the company preferred base case model, median time in the progressed disease state is zanidatamab ([redacted] days), FOLFOX (28 days) and ASC (77 days). Given that the TTD model applies utility decrements for up to 256 days prior to death, regardless of health state, this means that the TTD approach has a greater impact on QALYs accrued in the PFS state in the FOLFOX arm, compared to the zanidatamab arm. Whilst the TTD modelling approach itself is not biased, the implication of using TTD data modelled from one source (zanidatamab, where progressed disease is substantially longer) to a treatment where progressed disease duration is substantially shorter (FOLFOX) generates uncertainty regarding the appropriateness of applying the TTD approach in the FOLFOX arm.*

*Furthermore, the EAG notes that the utility values submitted in the company clarification response lack face the validity to support a TTD approach, particularly the grouped approach. The EAG observes that the utility values for the IHC3+ subgroup (EAG preferred dataset) are higher in the group that are less than 84 days from death compared to those between 84-195 days from death group (see Table 19 above). The company note in their clarification response that the lack of face validity is likely due to small numbers reporting utility data <84 days to death and the EAG considers this a reasonable explanation. Whilst this explains the values obtained, it casts some doubt on the validity of applying a TTD approach in the economic model.*

*Finally, the EAG notes that costs (and treatments) in the economic model are driven by progression status. Given that utilities are likely to be driven by the underlying treatments provided, the EAG prefers to take a consistent approach to the way in which costs and utilities are applied in the model. For these reasons, despite acknowledging that there can be advantages of the TTD approach, in this case, the EAG prefers the use of progression-based utilities in its base case analysis.*

*Treatment-specific disutility*

The CS did not find a comparative utilities study to estimate incremental utility benefit between treatments included in the model. However, the company argued that treatment-specific utilities are justified, partially due to the higher rate of grade 1 and 2 AEs in

FOLFOX and ASC, which are not captured in AE disutilities applied in the model, administration disutility associated with use of a PICC line (not captured in the administration disutility), and also due to the lack of disease control in ASC. The disutility calculation is based on baseline and 4 months utility data from the ABC-06 study applied to the HERIZON-BTC-01 population. Details of the calculation approach used to estimate utility decrements is in table 20

**Table 20: FOLFOX + ASC and ASC utility decrement calculations**

| Calculation step | Utility Value | Source |
|---|---|---|
| (a) HERIZON-BTC-01 baseline utility | [redacted] | HERIZON-BTC-01 [40] |
| *FOLFOX disutility* | | |
| (b) FOLFOX baseline utility | 0.77 | ABC-06 [41] |
| (c) FOLFOX 4-month utility | 0.70 | ABC-06 [41] |
| (d) FOLFOX % progression-free at 4 months | 56.7% | ABC-06 [42] |
| (e) FOLFOX reduction from baseline | 90.9% | Calculation (c/b) |
| (f) Equivalent FOLFOX utility at 4 months in HERIZON-BTC-01 | [redacted] | Calculation (a*e) |
| (g) Equivalent zanidatamab utility to FOLFOX at 4 months | [redacted] | Calculation (d*[redacted] + (1-d)*[redacted] |
| **FOLFOX + ASC decrement** | [redacted] | **Calculation (g-f)** |
| *ASC disutility* | | |
| (h) ASC baseline utility | 0.75 | ABC-06 [41] |
| (i) ASC 4-month utility | 0.62 | ABC-06 [41] |
| (j) ASC % progression-free at 4 months | 35.0% | Calculation from modelled PFS |
| (k) ASC reduction from baseline | 82.7% | Calculation (i/h) |
| (l) Equivalent ASC utility at 4 months in HERIZON-BTC-01 | [redacted] | Calculation (a*k) |
| (m) Equivalent zanidatamab utility to ASC at 4 months | [redacted] | Calculation (j*[redacted] + (1-j)*[redacted] |
| **ASC decrement** | [redacted] | **Calculation (m-l)** |

**Abbreviations:** ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

*The EAG are concerned that applying treatment-specific disutility, and the calculation approach taken is subject to limitations, is associated with substantial uncertainty and is not sufficiently supported by the evidence provided in the company submission. First, the company's rationale is based on a higher incidence of grade 1 and 2 adverse events (AEs) in*

*FOLFOX and ASC. The assumption that Grade 1 and 2 AEs translate into a measurable and consistent reduction in quality of life is not adequately substantiated. Grade 1 and 2 AEs are typically mild to moderate, and their actual impact on utility values remains uncertain. Secondly, the estimated disutility is based on studies HERIZON-BTC-01 and ABC-06, and a naïve comparison between the two studies in terms of HSUVs is subject to the same limitations as the comparison of treatment effect due to heterogeneous patient population characteristics and study design. Given the uncertainty of the naïve comparison for treatment effects, which the EAG accepts as the only available evidence, applying additional decrements based on utilities further compounds that uncertainty without any strong evidence of a treatment effect within a health state. The EAG notes that the company's preferred approach applies treatment-specific disutility even during the progressed disease health state after treatment has stopped. There is no evidence to support a continued treatment effect of zanidatamab beyond treatment cessation, and so applying treatment-specific disutility in the progressed state likely generates a bias in favour of zanidatamab. Finally, the EAG are concerned that applying treatment specific disutility, administration disutility (specific to FOLFOX) and adverse event disutility runs the risk of double counting some of the utility decrements when applied together in the economic model. The EAG prefers to not include treatment specific disutilities in the economic model.*

*Adverse event utility decrements*

The company economic model included the negative impact of Grade 3+ TRAEs (≥2% of participants) on HRQoL, using disutility values from prior BTC-related appraisals or similar disease areas. AEs of Grades 3-5 were assigned the same disutility value, due to limited severity-specific data. The company applied AE-related utility losses as a one-time QALY reduction in the first model cycle, based on AE durations from the HERIZON-BTC-01 study. Where HERIZON-BTC-01data were unavailable, average durations from the trial were used. The disutility and duration data for each AE are assumed to be equivalent across treatment arms. The company notes that their approach may be conservative because AEs associated with FOLFOX treatment are likely to be more severe and require longer inpatient stays than zanidatamab and that likely underestimates the impact of AEs for FOLFOX.

*The EAG considers it appropriate to include adverse event disutility and accepts that the company's approach is reasonable.*

*Administration disutility*

The economic model accounted for the disutility associated with FOLFOX administration to account for the impact on QoL of the requirement for an implanted central venous access device, such as a PICC line or Portacath. These devices require an invasive procedure for insertion, ongoing maintenance, and eventual removal, all of which can negatively impact patients' QoL. To reflect this burden, the company applied a utility decrement for the proportion of FOLFOX administered via a Portacath of -0.013.

*The EAG notes that when applied to the TTD utility approach, the disutility of administration was applied as a full decrement in each cycle, but not adjusted for the cycle duration, as in the progression-based utility approach. The EAG considers this to be an error in the application of the disutility in the economic model and has aligned the calculation approach with that of the progression-based utilities. Given the concerns raised above, the EAG does not consider it appropriate to apply disutilities for treatment administration, adverse events, and treatment specific. However, the approach taken to estimate the disutility associated with treatment administration is reasonable and plausible, given the additional QoL decrement associated with having a line inserted and maintained over time on treatment. The EAG therefore accepts that the application of treatment administration disutility for FOLFOX is reasonable, particularly given that the HSUVs from the HERIZON-BTC-01 study will not capture this aspect of quality of life. The company and EAG's preferred approach to inclusion of utilities in the model is compared in Table 21, along with additional scenario analyses to explore the impact of each of these components on the ICER.*

**Table 21 Summary of EAG scenario analyses to explore uncertainty surrounding utility in the economic model.**

| | Company base case | Company scenario | EAG base case | EAG scenario 1 | EAG scenario 2 |
|---|---|---|---|---|---|
| Progression based | | ✓ | ✓ | ✓ | ✓ |
| TTD continuous | ✓ | | | | |
| TTD category | | | | | |
| Tx specific disutility (FOLFOX, ASC) | ✓ | ✓ | | ✓ | |
| AE disutility | ✓ | ✓ | ✓ | ✓ | ✓ |

| | | | | | |
|---|---|---|---|---|---|
| Administration disutility for porthacath (FOLFOX) | ✓ | ✓ | ✓ | | |

### 4.2.8 Resources and costs

The CS included the following costs in the model: drug acquisition costs, drug administration costs, pre-medication drug costs, health-state costs, special warning monitoring, costs associated with grade ≥ 3 treatment-related adverse events (AEs), IHC3+ testing cost for zanidatamab, DPYD testing for FOLFOX, subsequent treatments, and end-of-life care costs. Resource use unit costs were valued using NHS reference costs 2023/24, Personal Social Services Research Unit (PSSRU) 2024. The drug unit costs were sourced eMIT for secondary care prescribing and from the BNF where eMIT prices were not available or for primary care prescribing.

*Drug acquisition costs*

The company has proposed a PAS which takes the form of a simple price discount of [redacted] of the list price; including this discount results in a cost per 2 x 300 mg vials of [redacted]. As described in the HERIZON-BTC-01 dosing schedule and in line with the proposed license and UK SmPC, zanidatamab is given at a dose of 20 mg/kg on days 1 and 15 of every 28-day cycle, continuing until the disease progresses or the patient experiences unacceptable toxicity and discontinues treatment.

The dosing schedule for FOLFOX was taken from ABC-06 study and it is in line with the respective SmPCs. No drug acquisition costs were applied for ASC. The detail about unit cost of drug is presented in section 3.5.1.1, Table 69 of the company submission.

Relative dose intensity (RDI) as reflected in HERIZON-BTC-01 was applied to the drug acquisition cost to account for dose reductions, missed doses and treatment interruptions due to AEs. RDI of [redacted]% from HERIZON-BTC-01 was incorporated into the model per cycle of administration with the assumption that RDI is similar in both arms.

The CS model accounts for drug wastage using the 'method of moments' (MoM) approach to determine the average number of vials needed per treatment administration. This method uses a log-normal distribution of patient weights to predict vial requirements, assuming no vial sharing.

*The EAG considers the treatment acquisition costs for zanidatamab to have been underestimated with respect to the proportion of the progression free cohort assumed to be on treatment, especially after 1 year in the model. A detailed critique of the ToT curves to derive zanidatamab treatment acquisition costs is provided in Section 4.2.6 above.*

*The EAG notes that the company has assumed the same Relative Dose Intensity (RDI) for both arms of the economic model based on the results of the HERIZON-BTC-01 single-arm study. The EAG requested clarification from the company on why the same RDI was used, especially considering that FOLFOX has a higher incidence of treatment-related adverse events. In response to clarification queries, the company noted a lack of published RDI information for FOLFOX as the reason for assuming equivalence to zanidatamab. The company provides scenario analysis based on a RDI for FOLFOX obtained from a retrospective colorectal cancer study.* [34] *The EAG also provides scenario analysis based on a real-world study of FOLFOX for patients with advanced biliary tract cancer, based on 57 patients treated with FOLFOX.*[43] *The EAG notes that limited information is available on RDI definitions from both studies. To avoid introducing unnecessary bias against zanidatamab, the EAG has applied the higher values in the model. Park et al. provides slightly more detail on the calculation approach for RDI. A comparison of the company and EAG preferred RDI assumptions is presented in Table 22.*

**Table 22 Company and EAG preferred Relative dose intensity assumptions**

| Treatment | | Company preferred RDI (base case) | Company RDI (scenario) | Source | EAG preferred RDI | Source |
|---|---|---|---|---|---|---|
| Zanidatamab | | [redacted] | [redacted] | HERIZON-BTC-01[30] | [redacted] | HERIZON-BTC-01[30] |
| FOLFOX | Oxaliplatin | [redacted] | 64.78% | Base case assume = zanidatamab (HERIZON-BTC-01); scenario from Lamarca 2021[34] | 78 % | SJ Park, K Shin et al.[43] |
| | 5FU (bolus) | [redacted] | 64.78% | | 78 % | |
| | 5FU (continuous) | [redacted] | 64.78% | | 78 % | |
| | Folinic acid | [redacted] | 64.78% | | 78 % | |

**Abbreviations:** 5FU, fluorouracil; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; RDI, relative dose intensity.

*Treatment administration Costs*

The CS considered zanidatamab administered through a simple IV infusion through a peripherally inserted cannula assumed to be delivered by simple parenteral chemotherapy at first attendance. However, FOLFOX is administered through complex infusion using central venous access devices. Thus, the CS includes an additional cost of installing access devices and with its complication cost and has been applied in the first cycle of the model of FOLFOX arm. An additional cost of £147.38 per visit was applied for patients returning to the hospital to have their infusion removed by a nurse. An overview of drug administration costs for both arms is provided in Table 71 of the company submission.

*The EAG is satisfied that treatment administration costs are broadly aligned with UK clinical practice but notes that RDIs are applied only to treatment acquisition costs and not to administration in the economic model. This implies that RDI refers solely to adjustments of dose strength rather than missed doses or missed treatment visits. The company description of the zanidatamab RDI notes that it includes dose interruptions and missed doses. For FOLFOX, the EAG was unable to source the original article suggested by the company for scenario analyses (Lamarca et al). However, the EAG preferred RDI source (Park et al.) defines RDI as the ratio of the actual chemotherapy dose delivered to the planned dose over a*

*specified time, expressed as a percentage. This would suggest that both dose adjustments and administration numbers contribute to the total dose over a period of time, and so should be applied to both treatment acquisition and administration costs. Therefore, the EAG prefers to apply the RDI to both treatment acquisition and administration costs.*

*Pre-medication drug costs*

The inclusion of pre-medication drugs in the model was based on findings from the HORIZON-BTC-01 trial, where potential infusion-related reactions were managed with pre-treatment 30 to 60 minutes before zanidatamab treatments. While in FOLFOX treatments, pre-medication from the ABC-06 study involved the administration of antiemetic pre-medication. A summary of the pre-medication costs and dosing by treatment arm is provided in Table 72 of the CS.

*The EAG is satisfied that the premedication included aligns with the premedication used in HORIZON-BTC-01 trial and ABC-06.*

*Health-state costs*

The company's economic model assumes comparable resource use for both the progression-free and post-progression health states (see CS, Table 73). In both states, it assumes patients will have contact with an oncologist and undergo a complete blood count test every three months. Additionally, the model includes four CT scans per year in the progression-free state and one CT scan per year in the progressed disease state. For the progressed disease state, the company also assumes daily morphine use.

*The EAG is satisfied with the company's state health costs. However, it is considered that daily morphine use would likely be included as part of end-of-life care costs and has been excluded from the EAG preferred approach. The impact on the ICER is minimal.*

*Special warning monitoring resource use*

The company submission provides information on special monitoring requirements resource use for zanidatamab and FOLFOX as outlined in Table 23.

**Table 23 Special monitoring resource use for zanidatamab and FOLFOX**

| Treatment | Resource | Frequency | Frequency source |
|---|---|---|---|
| Zanidatamab | LVEF follow-up | Every 3-months | TA458[44] |
| FOLFOX | Echocardiology | Before and after each administration | Oxaliplatin SmPC<br>Fluorouracil SmPC |
| | Complete blood count | Daily for the 30 days after the first course | Fluorouracil SmPC |
| | Liver function test | Prior each treatment for first three cycles, then every other course thereafter (7 out of the 12 cycles) | Leucovorin SmPC |

**Abbreviations:** FOLFOX, folinic acid, fluorouracil, and oxaliplatin; LVEF, left ventricular ejection fraction; SmPC, summary of product characteristics.

*The EAG has reviewed the special warning recommendations from the respective SmPCs of each drug and confirms the requirement for a complete blood count and liver function test for FOLFOX, and LVEF follow-up for zanidatamab. However, there is uncertainty surrounding the most appropriate frequency of echocardiography for the FOLFOX arm of the model. The SmPC for oxaliplatin states that "The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin." The SmPC for 5FU states: "Cardiac function should be regularly monitored during treatment with fluorouracil." These statements, would suggest more frequent monitoring, aligned with the company's preferred assumptions. However, the EAG are concerned that the modelled frequency, whilst aligned with the respective SmPC, might not accurately reflect the use of echocardiography for FOLFOX treated patients in UK clinical practice. The EAG concerns are based on the clinical expert opinion sought by both the company and the EAG. Two company clinical experts noted that echocardiography is not routinely used for FOLFOX in UK clinical practice. Interviewee 6 responded* [redacted] *and interviewee 1 mentioned* [redacted]

[redacted][45] *Remaining interviewees did not provide any direct evidence for echocardiography frequency for FOLFOX. The EAG clinical expert also confirms that echocardiography will not be done unless there are significant problems with cardiac function, and that many of those with significant problems would not be treated with FOLFOX. Having considered the company and EAG clinical expert views, the EAG preferred base case approach is to use echocardiography prior to treatment initiation in the FOLFOX treatment arm. In addition to the clinical expert advice sought, the EAG were unable to find any practice guidance documents for FOLFOX at the NHS trust level where routine use of echocardiography was mentioned. The EAG and company preferred monitoring resource use assumptions for echocardiography are summarised in Table 24.*

**Table 24 Alternative assumptions about the frequency of cardiac function test using echocardiography in the FOLFOX treatment arm**

| Scenario | Description | explanation |
|---|---|---|
| Company base case | Before and after each administration (Q2W) | Where echocardiography takes place before and after each administration of FOLFOX in line with the SmPC for oxaliplatin and 5-FU. |
| EAG base case | Once, prior to treatment initiation | Where echocardiography takes place pretreatment to check cardiac history as outlined in Northern Cancer Alliance[46] and supported by company and EAG clinical expert opinion. |
| Scenario 1 | every 3 months | Monitoring every 3 months: the same frequency with Zanidatamab arm |
| Scenario 2 | No Echocardiography | |

*Subsequent treatment costs*

The proportion of patients receiving subsequent therapies and the mix of subsequent therapies received was based on UK clinical opinion. Distribution of subsequent treatment based on data from HERIZON-BTC-01 and ABC-06 study has been explored in the company scenario analysis.

*The EAG is satisfied that using UK clinical opinions to determine the mix of subsequent treatment is more appropriate for decision making than using trial-based data. The EAG appreciates that the company has explored the trial-based treatment mix in its scenario analyses.*

*Adverse reaction unit costs and resource use*

The model assumes that all Grade 3+ adverse events (AEs) included in the economic analysis are managed through hospital admissions (see CS, Table 76). The company specifically assumes non-elective long-stay admissions and applies different Complications and Comorbidities (CC) scores to the different AEs grade, with the assumption that more severe AEs correspond to higher CC categories.

*The EAG does not consider all AEs require non-elective long-stay admissions, and these are likely to overestimate the costs of treating adverse events, especially Grade 3, that could feasibly be managed through short admissions to hospital. Whilst the exact management approach for the modelled adverse events is unknown, the EAG considers the costs included in the company submission to be the maximum possible costs of managing these events. The EAG notes, however, that the costs of AEs are not a major driver of cost-effectiveness results, but explores applying a 50% reduction in the unit costs of adverse events in scenario analysis to illustrate the impact on the ICER.*

*End-of-life costs*

The CS included end-of-life costs based on a report from Cummins (2025), which outlines the costs associated with supporting individuals in their last year of life in the UK.[47] The reported total cost for end-of-life healthcare and social care was £24,920, which has been adjusted for 2023/24, increasing the figure to £25,779.74. End of life costs were applied to all patients upon entering the death state in the model.

*The EAG notes that the end-of-life costs are higher than in previous cancer-related appraisals and in similar disease end-of-life cost evaluations. However, the EAG believes this has an insignificant impact on the ICER.*

# 5 COST EFFECTIVENESS RESULTS

## *5.1 Company's cost effectiveness results*

The base case results are presented in section 3.9 of the company submission. The company preferred base case ICER includes a simple PAS price discount of [redacted] of the list price; including this discount results in a cost per 2 x 300 mg vials of [redacted]. Application of the PAS price reduces the company preferred ICERs to £[redacted] per QALY gained compared to FOLFOX + ASC and £[redacted] compared to ASC alone. Confidential discounted prices are available for some treatments considered as subsequent therapies. Across a wide range of scenario analyses explored by the company in the main submission, the ICERs vs. FOLFOX + ASC range from [redacted] to [redacted] per QALY gained and vs. ASC alone range from [redacted] to [redacted].

*The EAG notes that the company reported scenario analyses all adopt a 1.5% discount rate for costs and QALYs. As noted in Section 4.5 the EAG does not consider a discount rate of 1.5% to be aligned with the NICE reference case and therefore considers a 3.5% discount rate to be more appropriate for both costs and QALYs. To avoid unnecessary replication of multiple tables of scenario analyses in the EAG report, all ICERs reported in Chapters 5 apply a 3.5% discount rate unless otherwise stated. For readers wishing to see the full set of analyses with a 1.5% discount rate, these can be found in Section 3.9 of the CS and throughout the clarification response document.*

## *5.2 Company's sensitivity analyses*

The full range of company scenario analyses explored in the company submission with a 3.5% discount rate applied, can be found in Table 25. The implication of moving from a 1.5% to 3.5% discount rate is a small increase in the ICER.

**Table 25 Company submission scenario analysis results (including PAS) – 3.5% discount (reproduced from Table 5 of the company response to clarification queries)**

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| Base case | | | [redacted] | [redacted] |
| Time horizon | 30 years | 20 years | [redacted] | [redacted] |
| | | 40 years | [redacted] | [redacted] |
| Discount rates | 3.5% for costs and QALYs | 1.5% | [redacted] | [redacted] |
| RDI | Included | Excluded | [redacted] | [redacted] |
| IHC3+ testing | Included | Excluded | [redacted] | [redacted] |
| Subsequent treatment source | UK clinical opinion | Trial data | [redacted] | [redacted] |
| Utility approach | TTD – continuous (inverse square root) | Progression-based | [redacted] | [redacted] |
| | | TTD – continuous (TTD days) | [redacted] | [redacted] |
| | | TTD – continuous (log TTD) | [redacted] | [redacted] |
| | | TTD – continuous (inverse exponential) | [redacted] | [redacted] |
| | | TTD – continuous (TTD) | [redacted] | [redacted] |
| | | TTD groupings | [redacted] | [redacted] |
| | | McCarthy (2024) | [redacted] | [redacted] |
| Age-adjusted disutilities | Included | Excluded | [redacted] | [redacted] |
| Treatment-related disutility | Included | Excluded | [redacted] | [redacted] |
| Zanidatamab OS curve | Log-logistic | Exponential | [redacted] | [redacted] |
| Zanidatamab PFS curve | Log-logistic | Generalised gamma | [redacted] | [redacted] |
| | | Gompertz | [redacted] | [redacted] |
| Zanidatamab ToT curve | Gamma | Gompertz | [redacted] | [redacted] |
| | | Weibull | [redacted] | [redacted] |
| FOLFOX + ASC OS curve | Log-normal | Exponential | [redacted] | [redacted] |
| | | Generalised gamma | [redacted] | [redacted] |
| FOLFOX + ASC PFS curve | Log-normal | Log-logistic | [redacted] | [redacted] |
| | | Gamma | [redacted] | [redacted] |

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| FOLFOX + ASC ToT approach | Equal to PFS | Median ToT and PFS HR | [redacted] | [redacted] |
| ASC OS curve | Log-logistic | Log-normal | [redacted] | [redacted] |
| PFS definition for zanidatamab | INV | ICR | [redacted] | [redacted] |
| Efficacy approach | Naive comparison | MAIC | [redacted] | [redacted] |

**Abbreviations:** ASC, active symptom control; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment; TTD, time to death.

The company did not reproduce all of the additional scenario analyses provided at clarification response using the EAG's preferred 3.5% discounting rate. These are reproduced by the EAG in Table 26 below.

**Table 26 Company clarification response scenario analysis results (including PAS) – 3.5% discount (Adapted from Tables, 8, 15, 16 of the company response to clarification queries)**

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| **Base case** | | | [redacted] | [redacted] |
| AEs source | Full Cohort 1 | IHC3+ subgroup | [redacted] | [redacted] |
| Utility source | Full Cohort 1 | IHC3+ subgroup | [redacted] | [redacted] |
| FOLFOX RDI | [redacted] | 64.78% | [redacted] | [redacted] |

Company preferred deterministic and probabilistic analyses are compared in Table 27 and 28 below. Scatter plots of probabilistic results on the cost-effectiveness plane and CEACs are reported for each pairwise comparison in figures 6-9.

**Table 27 Company preferred deterministic scenario analyses (3.5% discount)**

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Table 28 Company preferred probabilistic scenario analyses (3.5% discount)**

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted]

**Figure 6 Company preferred scatter plot of cost-effectiveness plane zanidatamab vs FOLFOX (3.5% discount)**

**Figure 7 Company preferred scatter plot of cost-effectiveness plane zanidatamab vs ASC (3.5% discount)**

**Figure 8 Company preferred cost-effectiveness acceptability curve zanidatamab vs FOLFOX (3.5% discount)**

**Figure 9 Company preferred cost-effectiveness acceptability curve zanidatamab vs ASC (3.5% discount)**

### *5.3 Model validation and face validity check*

The company quality assurance approach is described in Section 3.13. The model was scrutinised by a senior health economist not involved in its development and stress testing was conducted by applying extreme scenarios and inspecting corresponding outputs. Clinical experts validated the model outputs in a 2-round Delphi panel with 11-14 UK clinical experts experienced in treating BTC. Validation of model OS and PFS outputs against published literature showed outputs in line with anticipated expectations. Further details of validation are provided in Appendices H and R of the company submission.

*The EAG notes that the company's quality assurance and validation process appear to be comprehensive. The EAG has further assessed the model outputs using the checklist by Tappenden and colleagues and conducted several additional face validity checks. The results of the black-box checks are reported in Table 29. No major issues were identified through black-box checks. Through cell-by-cell inspection of utility traces in the FOLFOX arm of the model, the EAG noticed an inconsistency in the way in which treatment administration disutilities were applied between the progression based and TTD utilities. Application of the disutility on the TTD utility trace did not adjust for the duration of the cycle length. The EAG considers this to be a typographical error within the formula and has provided a correction as detailed in Section 4.2.7 above and applied to EAG analyses in Section 6.*

**Table 29 Model validation and face validity check**

| Model component | Model test | Unequivocal criterion for verification | Issues identified |
|---|---|---|---|
| Clinical trajectory | Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events) | All treatments produce equal estimates of total LYGs and total QALYs | No issue found |
| | Sum expected health state populations at any model time-point (state transition models) | Total probability equals 1.0 | No issue found |
| QALY estimation | Set all health utility for living states parameters to 1.0 | QALY gains equal LYGs | No issue found |
| | Set QALY discount rate to 0 | Discounted QALYs = undiscounted QALYs for all treatments | No issue found |
| | Set QALY discount rate equal to very large number | QALY gain after time 0 tend towards zero | No issue found |
| Cost estimation | Set intervention costs to 0 | ICER is reduced* | No issue found |
| | Increase intervention cost | ICER is increased* | No issue found |
| | Set cost discount rate to 0 | Discounted costs = undiscounted costs for all treatments | No issue found |
| | Set cost discount rate equal to very large number | Costs after time 0 tend towards zero | No issue found |
| Input parameters | Produce n samples of model parameter m | Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.) | No issue found |

| Model component | Model test | Unequivocal criterion for verification | Issues identified |
|---|---|---|---|
| General | Set all treatment-specific parameters equal for all treatment groups | Costs and QALYs equal for all treatments | No issue found |
| | Amend value of each individual model parameter* | ICER is changed | No issue found |
| | Switch all treatment-specific parameter values* | QALYs and costs for each option should be switched | No issue found |
| ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function | | | |

# 6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

## *6.1 Exploratory and sensitivity analyses undertaken by the EAG*

Full justification for all EAG conducted scenarios is incorporated into table 30 and 31 below.

## *6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG*

The results of EAG conducted analyses are provided in Table 32 and 33.

**Table 30 Description and justification of EAG's preferred scenario analyses**

| Scenario number | Parameter or assumption | Company base case | EAG base case | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 1 | Discount rate for costs and QALYs | 1.5% | 3.5% | The EAG's approach is aligned with the current version of the NICE reference case as of the date of EAG report submission | 4.2.5 |
| 2 | OS curves for zanidatamab | Log logistic | Log Normal | The log-normal curve leads to more realistic long-term OS predictions over the totality of the modelled time horizon whilst maintaining a good statistical and visual fit to the KM data and aligning with company sought clinical expert opinion. | 4.2.6 |
| 3 | ToT curve for zanidatamab | Gamma | Log-normal | The log-normal curve leads to a more plausible proportion of the progression free cohort remaining on zanidatamab treatment over time. | 4.2.6 |
| 4 | ToT curve for FOLFOX | Treat to progression | Apply ratio of median TTD / PFS | The scenario analysis implemented in the company economic model provides a more realistic scenario whereby treatment discontinuation of FOLFOX is allowed for reasons other than progression (e.g. adverse events). This aligns with evidence in the company | 4.2.6 |

| Scenario number | Parameter or assumption | Company base case | EAG base case | Justification | Section of EAG report |
|---|---|---|---|---|---|
| | | | | submission that FOLFOX is a difficult treatment for patients to sustain and is aligned with clinical expert opinion sought by the EAG. | |
| 5 | Adverse event population source | HERIZON-BTC-01 cohort | HERIZON-BTC-01 (IHC3+ sub-population) | Using data from the IHC3+ sub- population is more appropriate as it aligns more closely with the marketing authorisation for zanidatamab. | 4.2.6 |
| 6 | Approach to calculating administration dis-utility for TTD approach | Apply full annual disutility per cycle | Adjust disutility by cycle length | EAG approach is more methodologically robust | 4.2.7 |
| 7 | Data source for health state utility values | HERIZON-BTC-01 cohort | HERIZON-BTC-01 (IHC3+ sub population) | The EAG's clinical expert notes that there are important differences between IHC2 and IHC3+ in terms of speed of disease progression and difficulty to treat. Therefore, it is less biased to use data from the sub-population that is most aligned with the marketing authorisation and scope for the assessment | 4.2.7 |

| Scenario number | Parameter or assumption | Company base case | EAG base case | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 8 | Utility estimation approach | Time to death, continuous function, inverse square root TTD days | Progression based health state utility values | 1) TTD utilities lack an element of face validity when observing the raw utility data for grouped utilities, which casts some doubt on the robustness of a TTD approach.<br><br>2) The TTD approach implies a reduction in utility applied in the PFS state for the FOLFOX arm, but not for the zanidatamab arm of the model.<br><br>3) The EAG prefers to align the methodology for applying costs and utilities within the economic model. | 4.2.7 |
| 9 | Treatment specific disutility | Included | Excluded | The EAG considers the application of treatment specific disutilities is likely to double-count the impact of treatment administration and adverse event disutilities already included in the economic model. The calculation approach also has several limitations. | 4.2.7 |

| Scenario number | Parameter or assumption | Company base case | EAG base case | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 10 | FOLFOX RDI | Assumed equal to zanidatamab (RDI = [redacted] | Assume equal to RWE study of FOLFOX (RDI = 78%) | As per evidence raised in the company submission, company clinical expert advice, and EAG expert advice, it is unlikely that FOLFOX and zanidatamab would be expected to have the same RDI due to concerns about treatment tolerability. | 4.2.8 |
| 11 | Special monitoring costs, echocardiography frequency for FOLFOX | Before and after each administration | Once to inform a risk assessment at treatment initiation | The company's preferred echocardiography frequency, based on the SmPCs, is substantially higher than information provided by the company's and EAG's clinical experts. The EAG were not able to find any evidence supporting the company preferred frequency of echocardiography for FOLFOX in UK clinical practice (e.g. from trust-level treatment guidance documents).[46] | 4.2.8 |
| 12 | Morphine costs | Included | Excluded | EAG prefers to exclude because morphine costs are likely already captured in end-of-life bundle costs. | 4.2.8 |
| **13** | **EAG preferred base case analysis** | **--** | **--** | **Scenarios 1-12 combined.** | |

**Abbreviations:** FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; IHC, Immunohistochemistry (score); PFS, progression free survival; RDI, relative dose intensity; TA, technology appraisal; TTD, time to death.

**Table 31 Description and justification of key scenario analyses applied to the EAG preferred base case**

| Scenario number | Parameter or assumption | Company base case | Scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| A | Patient characteristics data source for weight | UK real-world evidence study | HERIZON-BTC-01 study | Company approach reasonable for base case analysis, EAG alternative explored in scenario analyses using data from company economic model. | 4.2.3 & 4.2.8 |
| B | Methodological approach to applying OS and PFS relative treatment effects | Naïve comparisons | MAIC | Whilst the proportional hazards assumption appears to be violated, the MAIC at least attempts to control for heterogeneity across studies | 3.4 & 4.2.6 |
| C | Zanidatamab time on treatment | Gamma curve | Treat to progression | Applies a similar methodology to that used for FOLFOX time on treatment curves. | 4.2.6 |
| D | Progression based health state | HERIZON-BTC-01 cohort | McCarthy et al. | Alternative source aligned with the NICE reference case, applied in TA914 | 4.2.7 |

| Scenario number | Parameter or assumption | Company base case | Scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| | utility value source | | | | |
| E | RDI | Applied to treatment acquisition costs only | Applied to treatment acquisition and administration costs | There is uncertainty about whether the RDI in company and EAG sourced RWE studies applied only to treatment dosages or to both dosages and the number of administrations. | 4.2.8 |
| F | Special monitoring costs, echocardiography frequency for FOLFOX | Before and after each administration | A) Assumed start of treatment and once every three months (3 in total)<br><br>B) None | Scenario analysis aligns the approach with that of zanidatamab requirement of echocardiography. | 4.2.8 |

**Abbreviations:** FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS, progression free survival; RWE, real world evidence; TA, technology appraisal

**Table 32 EAG's preferred scenarios and base case analysis (applied individually)**

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| **Company preferred base case analysis** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 1 Applying 3.5% Discount rate to costs and QALYs** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 2 Using Log Normal OS curves for zanidatamab** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 3 using Log normal for ToT curve for zanidatamab** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 4 Applying ratio of median TTD / PFS to ToT curve for FOLFOX** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 5 Using HERIZON-BTC-01 (IHC3+ sub-population) Adverse event population source** | | | | | |

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 6 Adjusting FOLFOX administration disutility by cycle length in the TTD approach** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 7 Using HERIZON-BTC-01 (IHC3+ sub population) data source for health state utility** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 8 using Progression base health state values for utility estimation** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 9 excluding treatment specific disutility** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 10 Appling 78% FOLFOX RDI based on RWE study** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 11 Applying 1 echocardiography before the initiation of treatment** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario 12 Morphine usage excluded in the Progressed disease health state** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-12 combined) - deterministic** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-12 combined) - probabilistic** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Figure 10 EAG preferred scatter plot of cost-effectiveness plane zanidatamab vs FOLFOX**

**Figure 11 EAG preferred scatter plot of cost-effectiveness plane zanidatamab vs ASC**

**Figure 12 EAG preferred cost-effectiveness acceptability curve zanidatamab vs FOLFOX**

**Figure 13 EAG preferred cost-effectiveness acceptability curve Zanidatamab vs ASC**

**Table 33 EAG scenario analyses applied to the EAG preferred base case**

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| **EAG preferred base case analysis** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario A. Using HERIZON-BTC-01 study for Weight** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario B. Using MAIC approach to OS and PFS relative treatment effects** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario C. Applying treatment to progression for Zanidatamab time on treatment** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario D. Using literature as source for health state utility (McCarthy et al.)** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | Costs (£) | QALYs | Incremental Costs (£) | Incremental QALYs (x1.7) | ICER (£/QALY) x1.7 |
|---|---|---|---|---|---|
| **Scenario E. Applying RDI to administration cost treatment acquisition and administration costs** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Scenario F. Using Echocardiography at the start of each treatment and every 3 months (3 in total)** | | | | | |
| Zanidatamab | [redacted] | [redacted] | | | |
| FOLFOX | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ASC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

### *6.3 Severity weighting*

All of the company analyses apply a severity weighting of 1.7 to incremental QALYs in the economic model. The company's preferred base case analysis adopts an age and sex distribution as defined by the HERIZON-BTC-01 (IHC3+) subgroup with utilities based on the company preferred continuous TTD approach. The absolute and proportional QALY shortfall is calculated as [redacted] and [redacted] with FOLFOX + ASC as the current standard of care, and [redacted] and [redacted] with ASC alone considered standard of care.

*The EAG are satisfied that the approach taken to QALY shortfall calculation is appropriate and that a QALY weighting of x1.7 is appropriate for the company base case set of assumptions. The EAG are also satisfied that the 1.7 weighting is consistent across all scenario analyses presented by the company in the original company submission and response to clarification queries. The EAG are also satisfied that a 1.7 severity modifier is appropriate under the EAG preferred base case analysis. Proportional and absolute QALY shortfalls under the company and EAG preferred base case analyses are described in Table 34 below.*

**Table 34 Summary of QALY shortfall analysis for company and EAG preferred base case analyses**

| | Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | QALY shortfall |
|---|---|---|---|
| Company base Case | 14.75 | FOLFOX: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY: x1.7 |
| | | ASC: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY: x1.7 |
| EAG base case | | FOLFOX: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY:1.7 |
| | | ASC: [redacted] | Absolute: [redacted]<br>Proportional: [redacted]<br>QALY:x1.7 |

**Abbreviations:** ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; QALY, quality-adjusted life year.

### *6.4 Conclusions of the cost effectiveness section*

The company submission has compared the clinical and cost-effectiveness of zanidatamab vs. FOLFOX + ASC and vs. ASC alone. The company have presented a partitioned survival model. Conclusions regarding cost-effectiveness should be interpreted within the context of uncertainty regarding the estimated incremental clinical benefit, which is subject to uncertainties due to a lack of data and comparable studies to enable a robust assessment of OS and PFS outcomes for zanidatamab vs. comparators. Uncertainties surrounding the magnitude of modelled treatment benefit, the approach taken to model health state utility values and assumptions about the treatment acquisition costs for zanidatamab and FOLFOX, based on assumptions about time on treatment are the main drivers of cost-effectiveness results. Regardless of the assumptions applied, the EAG are satisfied that a x1.7 QALY severity weighting is appropriate for this assessment.

# 7 References

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**Single Technology Appraisal**

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

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 6 October 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

**Issue 1 Time-to-death utilities**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 1.5, Page xxiii:**<br>*"The TTD approach may overestimate the utility benefit of zanidatamab by applying utility reductions in the PFS state for FOLFOX but not for zanidatamab."* | The company suggests the EAG remove this statement as it is factually inaccurate in how the TTD approach is implemented. | The company's time-to-death approach models utility values based on a patient's time period before death and is unrelated to their progression status. As such, comparing the timing of the decrement versus the progression health-states is inaccurate. | The EAG accepts that the approaches are applied in the same way across arms. However, the implication of using data from the HERIZON-BTC-01 zanidatamab study to inform TTD utilities in the FOLFOX arm of the model is that a greater utility decrement is applied to QALYs accrued in the PFS state for FOLFOX compared to zanidatamab.<br>The company preferred TTD approach assumes that utility decrements are independent of progression status and the EAG are concerned that this might over-estimate the QALY gains for zanidatamab because the modelled duration of survival within the progressed state is substantially longer for |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | | zanidatamab compared to FOLFOX.<br>The text has been updated to improve clarity. |
| **Section 1.5, Page xxiii:**<br>*"The EAG prefers to apply utilities by progression status to avoid bias, especially within the PFS state,…"* | The company believes this to be a misleading statement to suggest that the time-to-death approach is biased. The company suggests the removal of 'to avoid bias'. | The company's time-to-death approach models utility values based on a patient's time period before death and is unrelated to their progression status.<br>The company uses time-to-death as their base case as it more accurately captures differences in quality-of-life compared to the progression-based approach. As the EAG points out, the progression approach *"assumes that utilities remain constant within a health state over time. This potentially leads to an overestimation of utility values in the progressed disease state, where utility measures are often collected shortly after the point of progression and may not yet* | See response to comment above. The text in the report is reworded more carefully to acknowledge that the method applied is not biased, but that the implications of applying the method may lead to greater QALY decrements being applied in the PFS state of the FOLFOX arm than in the zanidatamab arm. The assumption that TTD utilities are independent of progression status may lead to uncertainty in cost-effectiveness results and the EAG considers the progression-based utility approach to be less uncertain. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | *fully capture all QoL implications of progressed disease."*<br><br>Plotting the time-to-death utilities from the HERIZON-BTC-01 trial (see TTD utility report, Figure 1, CS Appendix P) shows that there is a trend of stable utility further from death, followed by a reduction in utility particularly in the 6-month period closest to death. This trend is expected based on the theory of TTD utility analysis and suggested that such an approach was feasible. The TTD approach has also been used and preferred by NICE in previous advanced oncology technology appraisals including TA997 (1) and TA983 (2) .<br><br>As such, it is misleading to suggest that the TTD approach is biased in comparison to the progression-based approach. | |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.7, Page 55:**<br>*"However, the validity and key advantages of the TTD approach rely on there being sufficient duration of time within the progressed disease state across all treatment arms to model the gradual decline following progression and capturing a steeper decline close to death."* | The company request the EAG either remove this statement or provide a reference to where this information is reported. | The time-to-death approach models utility values based on a patient's time period before death therefore any duration of time before death is appropriately captured.<br>As the continuous models are used in the company's base case over the 'grouping' approach, this allows for flexibility in the time periods before death, rather than using the same utility value for fixed time periods like the progression-approach. As such, the company believe the EAG's statement to be factually incorrect. | The EAG can confirm that the concerns raised in this section do not relate to the validity of the methodological approach. Rather, the EAG is describing its views of the implications of applying the approach across treatment arms with very different durations of progressed disease survival and that the pattern of TTD utility decrements in one treatment arm (zanidatamab) might not necessarily reflect the pattern observed in the FOLFOX comparator.<br>The text is updated to improve clarity and appropriately note where statements are the opinion of the EAG. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.7, Page55/56:**<br>*"Given that the TTD model applies utility decrements for up to 256 days prior to death, regardless of health state, this means that no decrements are applied in the PF state of the zanidatamab arm, but decrements are applied for the full duration of time in the PF state of the FOLFOX arm. This creates a bias in favour of zanidatamab in the economic model, particularly in the PF state."* | The company request the EAG remove this statement. | It is incorrect to suggest that there is no decrement applied in the zanidatamab PF state as patients are continuously dying throughout the model time horizon which will be ultimately captured by the time-to-death utility approach, with the appropriate decrements applied across both the PF and PD states.<br>It is also incorrect to suggest that this is bias, given that this is an artefact of fewer patients dying compared to FOLFOX, therefore there will be higher decrements applied to this treatment arm as more patients are closer to death. | Please see response above. The EAG accept that the TTD approach can impact utilities at any point in the model, independent of progression status. The text has been updated to avoid any misunderstanding of this point and to provide further clarification of the EAG's reasoning for its preferred approach. |

**Issue 2 Time on treatment**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.6, Page 49:**<br>*"The company prefer the gamma curve and the EAG notes that the gamma curve provides one of the lowest estimated proportions on treatment at 5 years ([redacted]* | *"The company prefer the gamma curve as this aligns with the trial data by projecting the lowest projections of ToT (given all patients had discontinued treatment). The EAG notes that the gamma curve provides estimated proportions on treatment at 5 years ([redacted]* | The omission of the company's justification for choice of base case curve misrepresents why the gamma curve was chosen. | Not a factual inaccuracy, however text is updated to improve clarity and to acknowledge the company's rationale for choosing the Gamma curve. |
| **Section 4.2.6, Page 49:**<br>*"The EAG further notes that without artificially capping the time-on-treatment (ToT) curve to match PFS, the gamma curve for ToT results in curves that cross the selected PFS curve over the first year of extrapolation."* | *"The EAG further notes that without artificially capping the time-on-treatment (ToT) curve to match PFS, the majority of survival curves for ToT results in curves that cross the selected PFS curve over the first year of extrapolation due to the crossing of the Kaplan-Meier data from the HERIZON-BTC-01 trial."* | To avoid misrepresentation that the gamma curve is the only issue.<br>This is an issue with most curves given that the Kaplan-Meier data cross. Therefore, this is not an issue specific to the company's base case curve gamma. | Not a factual inaccuracy. However, the text is updated to acknowledge that most ToT curves would cross the PFS curve without capping, but that this issue is more pronounced for the Gamma curve compared to several others. |
| **Section 4.2.6, Page 50:**<br>*"These estimates may still be an under-estimation,…"* | The company request the EAG remove this statement. | It is incorrect to suggest that the ToT percentages are underestimates as these are based on the actual data for | The statement is re-worded to more clearly state that the EAG's preferred ToT approach may still |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | zanidatamab observed in the HERIZON-BTC-01 trial, and request that the statement is removed to reflect this. | underestimate the relative treatment acquisition costs for zanidatamab compared to FOLFOX because of differences in the treatment acquisition cost calculation approach across model arms. The company preferred assumption for FOLFOX is that patients receive the full course of treatment up until the point of progression. FOLFOX costs are not adjusted by a ToT curve, where as zanidatamab costs are, and this may generate a bias in overestimating the relative treatment acquisition costs for zanidatamab compared to FOLFOX. |

**Issue 3 Special warning recommendations**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.8, Page 64:**<br>"*The EAG has reviewed the special warning recommendations from the respective SmPCs of each drug and confirms the requirement for a complete blood count and liver function test for FOLFOX, and LVEF follow-up for zanidatamab. However, the EAG considers the company's base case to overestimate the resource use related to echocardiography for FOLFOX."* | "*The EAG has reviewed the special warning recommendations from the respective SmPCs of each drug and confirms the requirement for a complete blood count and liver function test for FOLFOX, and LVEF follow-up for zanidatamab.*<br>*The SmPC for FOLFOX also states that cardiac function should be closely monitored before and after administration."* | The statement by the EAG is misaligned with the statement in the SmPC for FOLFOX regarding cardiac function. The SmPC clearly states monitoring before and after administration; we request that the EAG revise their interpretation of the echocardiography frequency as it is factually incorrect and misaligned with the other frequencies from the SmPC.<br>The SmPC for oxaliplatin clearly states that *"The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin."*<br>And the SmPC for 5FU states: *"Cardiac function should be regularly monitored during treatment with fluorouracil."* | The EAG thank the company for pointing out this omission from the text in the EAG report. The text has now been updated to more completely reflect the recommendations from the oxaliplatin and FOLFOX SmPCs regarding QT interval and cardiac function monitoring.<br>However, the EAG preferred base case analysis remains unchanged because the approach more closely aligns with the use of echocardiography for FOLFOX in routine UK clinical practice.<br>Whilst the EAG does not dispute the SmPC guidance, it is important to |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | | note that, according to the balance of information available from both the company's and EAG's clinical experts, routine echocardiography does not appear to be commonly performed in routine UK clinical practice.<br><br>Furthermore, the EAG were unable to identify any clear treatment guidance documents at the NHS trust level to confirm the company preferred frequency of echocardiography for FOLFOX in UK clinical practice.<br><br>This remains an area of uncertainty that would benefit from further clinical expert opinion. |
| **Section 4.2.8, Page 65, Table 24:**<br><br>*"Where echocardiography takes place before and after* | *"Where echocardiography takes place before and after each administration of FOLFOX in line* | To accurately represent why the company chose this as the base case frequency. | Text amended as requested. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| *each administration of FOLFOX"* | *with the SmPC for oxaliplatin and 5-FU."* | | |
| **Section 6.2, Page 80, Table 30:**<br>*"The company's approach to the frequency of echocardiography is an overestimate compared to information provided by the company's clinical experts, the EAG's clinical expert, and a lack of information on echocardiography in several NHS trust FOLFOX treatment guidance documents."* | *"The company's approach to the frequency of echocardiography based on the SmPC's is different compared to information provided by the company's clinical experts, the EAG's clinical expert."* | It is incorrect to state that there is lack of information regarding echocardiography for FOLFOX given it is clearly stated within the SmPC. We ask that the EAG consider updating the text to reflect this. | Text updated to provide additional clarification and to make explicit reference to the SmPCs as the source of the company's preferred assumptions. |

**Issue 4 Missing baseline characteristic data for Cohort 1 (IHC2/3+) of HERIZON-BTC-01**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Table 8, Page 17:**<br>Several baseline characteristics for Cohort 1 | Addition of Cohort 1 (IHC2/3+) data to complete table in the EAG report | It is factually incorrect to state that these data are not reported as they are provided in Table 10 (previous radiotherapy, previous | Table 8 has been updated with the requested data |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| (IHC2/3+) of HERIZON-BTC-01 are listed as ‘not reported’. | and removal of ’NR’ where applicable. | surgery, and previous lines of therapy) of the company submission and Table 8 (tumour site and disease stage) of the EAG report. They should be included to provide an overall understanding of the population demographics for HERIZON-BTC-01. | |

**Issue 5 Incorrect data point reported for patient deaths in HERIZON-BTC-01**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 3.2.4, Page 23:**<br>The report states that [redacted] of patients died due to an unknown cause; the percentage should be [redacted]%. | [redacted]) *patients died due to an unknown cause,* [redacted] *of whom had discontinued zanidatamab due to progressive disease.* | Data point correction. | The percentage has been amended as requested |

**Issue 6 Need for distinction between full population and Cohort 1 of HERIZON-BTC-01**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.3, Page 40:**<br>*"The HERIZON-BTC-01 study (N=80 participants) also included some participants with IHC2+ BTC (N=18)."*<br><br>*"For example, OS and PFS KM data used in the company base case naive comparison of treatment benefits are obtained from the IHC3+ sub-population (N=62), but utilities are derived from the full BTC-01 study (N=80)."*<br>**Section 4.2.7, Page 52:**<br>*"…why the full BTC-01 cohort (N=80) was used instead of the subpopulation with IHC3+ (N=62)."* | *"Cohort 1 of the HERIZON-BTC-01 study (N=80 participants) also included some participants with IHC2+ BTC (N=18)."*<br><br>*"For example, OS and PFS KM data used in the company base case naive comparison of treatment benefits are obtained from the IHC3+ sub-population (N=62), but utilities are derived from cohort 1 of the BTC-01 study (N=80)."*<br><br>*"…why the BTC-01 cohort 1 (N=80) was used instead of the subpopulation with IHC3+ (N=62)."* | Cohort 1 should be distinguished from the full trial population. HERIZON-BTC-01 is split into two cohorts. Cohort 1 are patients with HER2+ IHC2+ and 3+ tumours (N=80) and is not the full population within the trial. Cohort 2 includes HER2 IHC1+ or 0 tumours (N=7). | Text amended as requested. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.7, Page 55, Table 19:**<br>*"Company preferred BTC-01 cohort"* | *"Company preferred BTC-01 cohort 1"* | | |

**Issue 7 Incorrect statement about missing Grade 1 and 2 AE data**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.7, Page 57:**<br>Report states that Grade 1 and 2 AE rates were not reported. | *"First, the company's rationale is based on a higher incidence of grade 1 and 2 adverse events (AEs) in FOLFOX and ASC. The assumption that Grade 1 and 2 AEs translate into a measurable and consistent reduction in quality of life is not adequately substantiated. Grade 1 and 2 AEs are typically mild to moderate, and their actual impact on utility values remains uncertain."* | The rates of Grade 1 and 2 AEs can be inferred from the company submission (Section 2.11.1 for HERIZON-BTC-01 and Appendix N.3.2 for ABC-06) and it is factually inaccurate to state these data were not reported. | Text amended as requested. |

**Issue 8 Incorrect reporting of company's scenario analyses**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 5.2, Page 68, Table 25:**<br>The EAG's table reporting the company's scenarios using the 3.5% was taken from the clarification response Table 5.<br>The company's automated scenario analyses reverts back to the 1.5% discount as this is still set as the 'base case' therefore results below scenario 3 are still using the 1.5% discount rate. | The company have corrected Table 5 of the company's response to clarification questions (and subsequently the EAG's Table 25) in Table 1 at the end of this document. | Apologies for this error. We have corrected the discount rate applied for each scenario. | The EAG thank the company for pointing out this issue and for providing a corrected results table. The EAG report has now been updated accordingly. |

**Issue 9 Non-reporting of Grade 3+ TRAEs**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 3.2.4, Page 23:**<br>The report details AEs, TRAEs, and Grade 3+ AEs but omits Grade 3+ TRAEs. | Include Grade 3+ TRAEs, as reported in Section 2.11.1.4 of the CS. The company requests this statement is removed. | Factually inaccurate as Grade 3+ TRAEs are used in the model and therefore should be included. | Details of Grade 3+ TRAEs have been added to Section 3.2.4 |

**Incorrect marking**

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| Section 3.2.1, page 14 (3 iterations)<br>Section 3.4.1, page 28–29 (2 iterations)<br>Section 3.4.3, page 31–32 (2 iterations)<br>Section 3.6, page 35 (1 iteration) | Missing CIC marking for number of patients in 2L IHC3+ group | ***Section 3.2.1:***<br>*"Two cohorts were recruited with Cohort 1 being the focus of the CS, in particular the 62 HER2+ IHC3+ participants and the [redacted] HER2+ IHC3+ second line (2L) participants."*<br>*"In addition, baseline data for the [redacted] IHC3+ 2L only participants are also presented in Table 8 for completeness, as they are utilised in the* | Additional highlighting added |

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| | | *company's matching-adjusted indirect comparison (MAIC)."*<br><br>*In Table 8, 4th column: "IHC3+ 2L only ([redacted])."*<br><br>***Section 3.4.1:***<br><br>*"Of the n=62 with IHC3+, [redacted] were considered second line (2L) patients."*<br><br>*"HERIZON-BTC-01 included the largest number of IHC3+ participants (n=62) and was the only study to include participants who were confirmed to be both BTC IHC3+ and 2L, but there were only [redacted] people in this category."*<br><br>***Section 3.4.3:***<br><br>*"In this analysis zanidatamab data were "trimmed" to the [redacted] who were ICH3+ and 2L, which is a very small number for this kind of adjusted analysis."*<br><br>*"The effective sample size (ESS) of the MAIC analyses* | |

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| | | *reduced from [redacted] after matching."*<br>***Section 3.6:***<br>*"The evidence for this technology came from a small number of single-arm studies, the largest of which (HERIZON-BTC-01) included just 87 participants with BTC and only [redacted] who were classed as both 2L and IHC3+."* | |
| Section 3.2.2, page 19/20 | CIC marking applied to OS data from earlier DCO, which do not need to be confidential | *The CS reports that these results are consistent with results from the interim DCO (28-07-23), with median OS being 18.1 months (95%CI 12.2, 22.9) and 6- and 12-month OS rates of 90.1% (95%CI 79.2, 95.4) and 65.0% (96%CI 51.6, 75.6), respectively.*<br>Please note that the final confidence interval is labelled | Highlighting removed and typo corrected |

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| | | as ‘96%CI’ which should be amended to ‘95% CI’. | |
| Section 4.2.6, page 46 | Missing CIC marking for reporting of survival landmarks from the company’s OS curves | *“The impact of different curve selection becomes more pronounced at later landmark timepoints, with zanidatamab OS ranging from [redacted] (Gompertz) to [redacted] (log-logistic) at 60 months follow up.”*<br><br>*“The EAG points out that a small proportion of the cohort remain alive over the full model duration (about [redacted] in the zanidatamab arm when the log-logistic curve is applied.”*<br><br>*“The EAG notes that log-normal and gamma curves provided a negligibly better statistical fit and provide longer-term survival landmarks that are more modest ([redacted] and [redacted] respectively at 60 months ).”* | Confidential marking updated as requested. |
| Section 4.2.6, page 47 | Missing CIC marking for results | *“The impact of applying the EAG preferred curve in an* | Confidential marking updated as requested. |

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| | | *approximately [redacted] increase in the ICER."* | |
| Section 4.2.7, page 52 | Published patient numbers from HERIZON-BTC-01 are incorrectly marked as CIC | *"The EAG agrees with the company's rationale to use EQ-5D data collected within the HERIZON study to populate the economic model but was unclear as to why the full BTC-01 cohort (N=80) was used instead of the subpopulation with IHC3+ (N=62)."* | Confidential marking removed as requested. |
| Section 4.2.7, page 55 | Missing CIC marking for time in progressed disease state in company model | *"For the company preferred base case model, median time in the progressed disease state is zanidatamab ([redacted] days), FOLFOX (28 days) and ASC (77 days)."* | Confidential marking updated as requested. |

*Table 1: Company submission scenario analysis results (including PAS) – 3.5% discount (reproduced from Table 5 of the company response to clarification queries)*

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| Base case | | | [redacted] | [redacted] |
| Time horizon | 30 years | 20 years | [redacted] | [redacted] |
| | | 40 years | [redacted] | [redacted] |
| Discount rates | 3.5% for costs and QALYs | 1.5% | [redacted] | [redacted] |
| RDI | Included | Excluded | [redacted] | [redacted] |
| IHC3+ testing | Included | Excluded | [redacted] | [redacted] |
| Subsequent treatment source | UK clinical opinion | Trial data | [redacted] | [redacted] |
| Utility approach | TTD – continuous (inverse square root) | Progression-based | [redacted] | [redacted] |
| | | TTD – continuous (TTD days) | [redacted] | [redacted] |
| | | TTD – continuous (log TTD) | [redacted] | [redacted] |
| | | TTD – continuous (inverse exponential) | [redacted] | [redacted] |
| | | TTD – continuous (TTD) | [redacted] | [redacted] |
| | | TTD groupings | [redacted] | [redacted] |
| | | McCarthy (2024) | [redacted] | [redacted] |
| Age-adjusted disutilities | Included | Excluded | [redacted] | [redacted] |

| Topic | Base case | Scenario | ICER (zanidatamab versus comparator), £ | |
|---|---|---|---|---|
| | | | FOLFOX | ASC |
| Treatment-related disutility | Included | Excluded | [redacted] | [redacted] |
| Zanidatamab OS curve | Log-logistic | Exponential | [redacted] | [redacted] |
| Zanidatamab PFS curve | Log-logistic | Generalised gamma | [redacted] | [redacted] |
| | | Gompertz | [redacted] | [redacted] |
| Zanidatamab ToT curve | Gamma | Gompertz | [redacted] | [redacted] |
| | | Weibull | [redacted] | [redacted] |
| FOLFOX + ASC OS curve | Log-normal | Exponential | [redacted] | [redacted] |
| | | Generalised gamma | [redacted] | [redacted] |
| FOLFOX + ASC PFS curve | Log-normal | Log-logistic | [redacted] | [redacted] |
| | | Gamma | [redacted] | [redacted] |
| FOLFOX + ASC ToT approach | Equal to PFS | Median ToT and PFS HR | [redacted] | [redacted] |
| ASC OS curve | Log-logistic | Log-normal | [redacted] | [redacted] |
| PFS definition for zanidatamab | INV | ICR | [redacted] | [redacted] |
| Efficacy approach | Naive comparison | MAIC | [redacted] | [redacted] |

**Issue 10 Minor corrections**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 2.2, Page 1:**<br>"…(choangiocarcinoma…)" | *"…cholangiocarcinoma…"* | Spelling correction. | Typo corrected |
| **Section 2.2, Page 1:**<br>*"In the UK each year, around 3,100 people are diagnosed with CCA and around 1,100 with GBC."* | *"In the UK each year, around 3,100 people are diagnosed with CCA, around 1,100 with GBC, and around 550 with ampullary cancer."* | The text currently omits patients with ampullary cancer. | Accepted |
| **Section 3.2, Page 9/10:**<br>"The study design of HERIZON-BTC-101 is presented in Figure 9, Section 2.3.1.1.1 of the CS."<br><br>"Eligibility criteria for HERIZON-BTC-101 are presented in Table 6 of the CS." | *"The study design of HERIZON-BTC-01 is presented in Figure 9, Section 2.3.1.1.1 of the CS."*<br><br>*"Eligibility criteria for HERIZON-BTC-01 are presented in Table 6 of the CS."* | Correction of trial name spelling. | Typos corrected |
| **Section 3.2.1 (Table 8), Pages 14–17:**<br>**Section 3.2.2 (Table 9), Page 18:** | Align row labels with correct data | Potential for data to be read incorrectly and misinterpreted. | The rows in the two table have been realigned |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Misalignment of row labels and data | | | |
| **Section 3.4.3, Page 31:**<br>"…ICH3+…" | *"…IHC3+…"* | Spelling correction. | Typo corrected |
| **Section 3.6, Page 36:**<br>*"If using data from ABC-06, the EAG observed that this publication includes a data sharing agreement - this might allow the use of fully patient-level analyses rather than analyses using published data."* | The company request the EAG remove this statement. | The company submitted requests for information for patient-level data from the authors of the publication but received no response. If possible, this should be reflected in the report. | Added, "although the EAG understands that the company requested data but received no response from the authors." |
| **Section 4.2.2, Page 39:**<br>*"All treatments are assumed to be discontinued at the point of progression in the model, with those who have progressed disease incurring treatment acquisition costs that are based on UK clinical expert opinion."* | *"All treatments are assumed to be discontinued at the point of progression (or maximum treatment duration) in the model, with those who have progressed disease incurring treatment acquisition costs that are based on UK clinical expert opinion."* | For factual accuracy that FOLFOX is treated for a maximum of 12 cycles if patients had not progressed beforehand. | Text updated as requested. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.6, Page 44:**<br>*"FOLFOX ToT was based on an estimated HR between median PFS and ToT as reported in the ABC-06 study."* | *"FOLFOX ToT was based on PFS in the base case with a scenario exploring an estimated HR between median PFS and ToT as reported in the ABC-06 study."* | To accurately represent that the company base case assumes the same as PFS for FOLFOX ToT. | Text updated as requested. |
| **Section 4.2.7, Page 51:**<br>*"One UK study, McCarthy (2024)…"* | *"One UK cost-effectiveness analyses, McCarthy (2024)…"* | McCarthy reported a UK cost-effectiveness analysis using the KEYNOTE-158 trial and therefore wasn't a specific UK-based study as there were no UK patients in KEYNOTE-158. | Text updated as requested. |
| **Section 4.2.7, Page 53, Table 17:**<br>PD value for the IHC3+ subgroup "[redacted]" | "[redacted]" | The correct value for the progressed disease utility value for the IHC3+ subgroup using the INV PFS is [redacted]. This was misreported by the company in Table 11 of the clarification questions response, and for this we apologise. The value is correct in the cost-effectiveness model and | Thank you for identifying and correcting this. The EAG has been updated accordingly. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| | | therefore does not impact any results. | |
| **Section 4.2.7, Page 56:**<br>*"However, the company argued that treatment-specific utilities are justified, partially due to the higher rate of grade 1 and 2 AEs in FOLFOX and ASC, which are not captured in AE disutilities applied in the model, and also due to the lack of disease control in ASC."* | *"However, the company argued that treatment-specific utilities are justified, partially due to the higher rate of grade 1 and 2 AEs in FOLFOX and ASC, which are not captured in AE disutilities applied in the model, the administration of patients via a PICC line (not captured in the administration disutility) and also due to the lack of disease control in ASC."* | To accurately represent that the administration disutility only captures the proportion of patients administered via a portacath. disutility for those patients having a PICC with FOLFOX vs an IV infusion with zanidatamab is considered to be already accounted for in the treatment-specific disutility. | Text amended to improve clarity. |
| **Section 4.2.7, Page 59, Table 21:**<br>*"Administration disutility (FOLFOX)"* | *"Administration disutility for portacath (FOLFOX)"* | To provide accuracy that the disutility is only applied to the proportion of patients who are administered via a portacath. | Text updated as requested. |
| **Section 4.2.8, Page 61:**<br>*"Patk et al. …"* | *"Park et al. …"* | Spelling correction. | Text updated as requested. |

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| **Section 4.2.8, Page 62, Table 22:** *"Lamarca 2021"* | *"Assumed same as zanidatamab from HERIZON-BTC-01"* | The source for the RDI values for FOLFOX was assumed same as zanidatamab from HERIZON-BTC-01 in company's base case, in line with other targeted therapies' appraisals. | Not a factual inaccuracy, but text updated to include both base case and scenario assumption source. |
| **Section 4.2.8, Page 65:** *"The model assumes that all adverse events (AEs)…"* | *"The model assumes that all Grade 3+ adverse events (AEs)…"* | To accurately describe that only Grade 3+ adverse events were costed for. | Text updated as requested. |
| **Section 6.2, Page 88, Table 33:** *"Company preferred base case analysis"* | *"EAG preferred base case analysis"* | To correctly reflect which base case is being presented. | Text updated as requested. |

## References


1. National Institute for Health and Care Excellence (NICE). Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced HER2-negative gastric or gastro-oesophageal junction adenocarcinoma (TA997). 2024. Available from: https://www.nice.org.uk/guidance/ta997. Accessed on: 6th October 2025.
2. National Institute for Health and Care Excellence (NICE). Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma (TA983). 2024. Available from: https://www.nice.org.uk/guidance/ta983. Accessed on: 6th October 2025.