Zanidatamab for treating HER2-positive (IHC3+) advanced biliary tract cancer after 1 or more systemic treatments [ID6388]

Technology appraisal committee C [9 December 2025]

PART 1
For screen – confidential data redacted

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Company: Jazz Pharmaceuticals

Zanidatamab for treating HER2-positive (IHC3+) advanced biliary tract cancer after 1 or more systemic treatments

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Biliary tract cancer (BTC) background

Background

- BTC includes 3 cancers of the biliary system: cholangiocarcinoma (CCA), gallbladder cancer (GBC), and Ampulla of Vater (AoV) cancer
- HER2 alterations in ~5-10% CCAs + ~20% GBCs
- 80% HER2 BTC are IHC3+ (high HER2 expression)

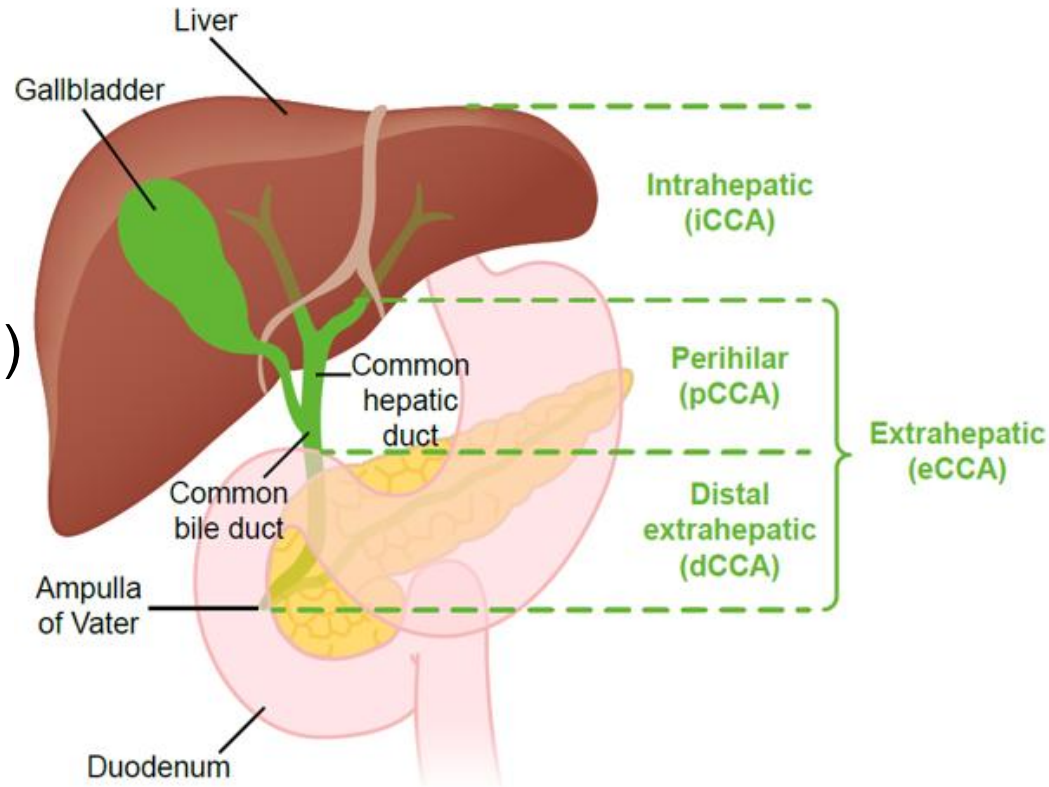
Epidemiology

- ~50 people eligible for 2nd line zanidatamab in England per year – due to advanced cancer at diagnosis, low prevalence of HER2, poor 1st line outcomes

Symptomology

- Often asymptomatic but can include jaundice, itchy skin, weight loss, abdominal pain, fatigue and fever

Anatomy of BTC



AoV, Ampulla of Vater; BTC, biliary tract cancer; CCA, cholangiocarcinoma; dCCA, distal CCA; eCCA, extrahepatic CCA; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic CCA; IHC, immunohistochemistry; pCCA, perihilar CCA.

Patient perspectives

AMMF – The Cholangiocarcinoma Charity and patient expert statements, included responses to online survey

- Most people diagnosed in advanced stages, when inoperable
- Challenging for people knowing that treatment options are limited and they have little time left
- Using chemotherapy, which may only extend life for a few months, comes at the expense of quality of life
- Unmet need for well-tolerated targeted treatment for HER2 BTC
- Zanidatamab not curative but is effective in extending survival more than current 2nd line standard care, FOLFOX
- Molecular profiling tests are not carried out until after a patient has progressed on 1st line → delay in initiating targeted therapy for actionable gene faults

"Zanidatamab has been life-altering and life-saving. I was out of options with current treatments and was given only a few months to live… I have hardly any side effects compared to other treatments"

"The side effects for current…chemotherapy [makes] it increasingly difficult to tolerate over time and the effectiveness wears off between 5-7 months."

"[Side effects of zanidatamab include] Very mild diarrhoea for a few days and a feeling of bloating immediately after treatment…"

NICE BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2.

Clinical perspectives

Clinical expert statements

- A clinically significant treatment benefit involves, at least, stabilisation of tumour growth and improvement of symptoms
- Less than 6 months survival with standard care 2nd line FOLFOX which has modest ~1 month survival benefit over best supportive care → must balance this against chemotherapy toxicity
- Standard care delivered by central line over ~50 hours – zanidatamab much easier to receive for patients
- Zanidatamab is effective for people with HER2 IHC3+* BTC only, HER2 IHC2 is significantly less impressive
- Any approval of HER2 targeted therapy needs mandatory testing at diagnosis, better care pathway

"Uptake of previously approved targeted therapies at second-line treatment for biliary tract cancer…has been poor, with less than third of potentially treatable patients receiving targeted therapy."

"Zanidatamab would significantly improve survival and quality of life for these patients with high unmet need"

*IHC3+ means high expression of the HER2 protein

BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

Equality considerations

No equality issues raised relating to NICE's obligations under the Equality Act 2010

Company

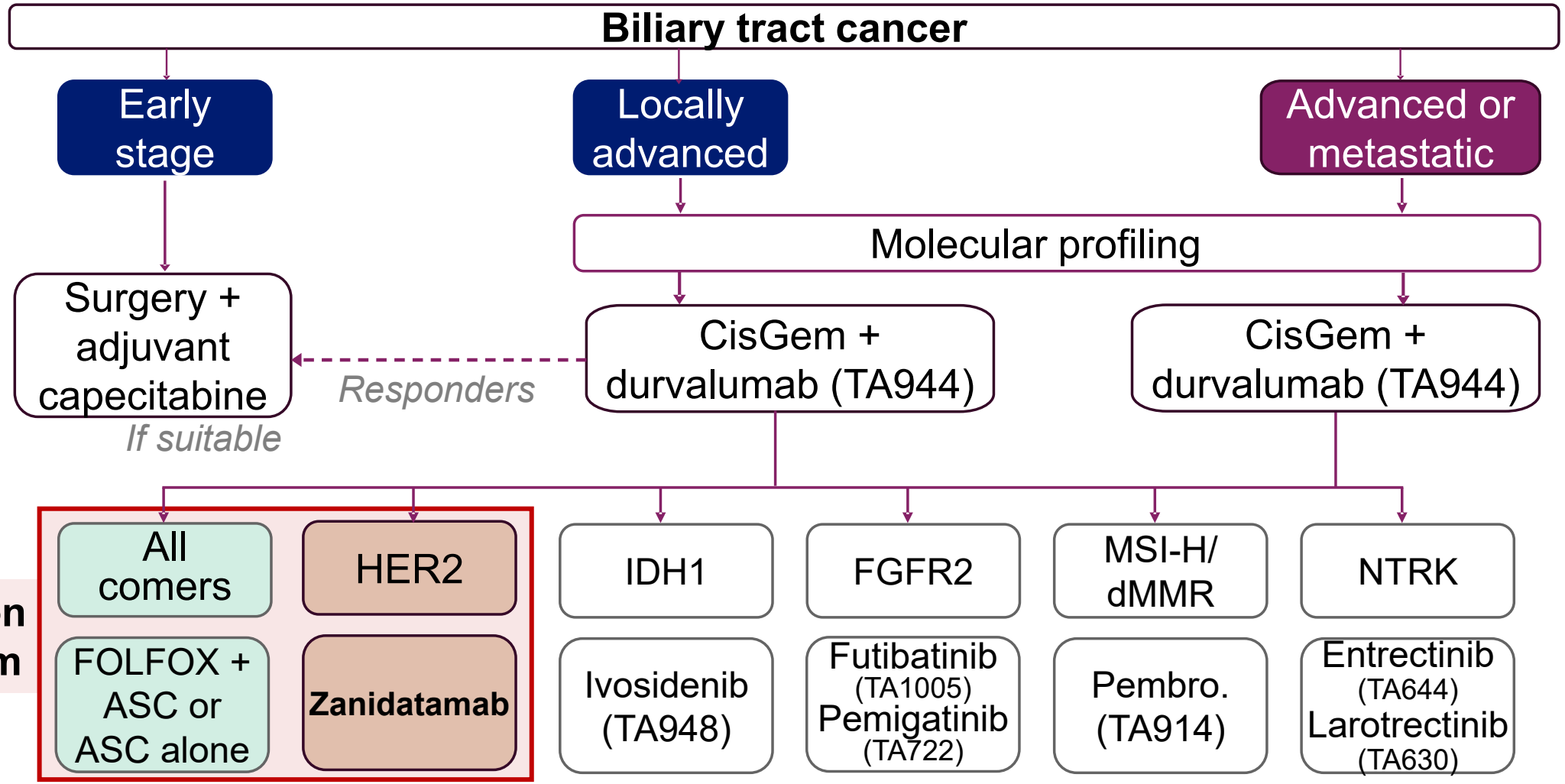
- Highlight that zanidatamab may address important health inequalities:
  - Recent study showed difference in age-standardised mortality rates for CCA:
    - ↳ Most deprived group: 5.9 per 100,000 person-years
    - ↳ Least deprived group: 4.3 per 100,000 person-years
- Highest incidence and mortality in the North of England

Zanidatamab (ZIIHERA®, Jazz Pharmaceuticals)

Marketing authorisation	• EMA wording: 'Zanidatamab as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+*) biliary tract cancer previously treated with at least one prior line of systemic therapy' • EMA MA granted June 2025 • MHRA MA expected [redacted]
Mechanism of action	• Bispecific antibody that targets HER2 • HER2 stimulates cancer cells to grow
Administration	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
Price	• List price per pack: £[redacted]; per month of treatment: £[redacted]** • List price per average treatment course: £[redacted]† • A patient access scheme discount is proposed

*IHC3+ means high expression of the HER2 protein
**Assuming 70 kg person. Dose will also vary due to relative dose intensity and drug wastage
†Company's base case assumptions, undiscounted
EMA, European Medicines Agency; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; MA, marketing authorisation; MHRA, Medicines and Healthcare products Regulatory Agency.

Treatment pathway



What are the appropriate comparators for zanidatamab?
When does molecular profiling happen? Is it consistent across different centres?

ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2. Other abbreviations in notes.

Key issues

Issues	ICER impact
Clinical effectiveness issues	
Robustness of clinical effectiveness evidence	Unknown
Cost-effectiveness issues	
Overall survival extrapolations	Medium
Treatment acquisition costs for zanidatamab and FOLFOX	Medium
Utility estimation approach	Medium
Frequency of echocardiography monitoring for FOLFOX	Small

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

Zanidatamab for treating HER2-positive (IHC3+) advanced biliary tract cancer after 1 or more systemic treatments

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Key clinical trial: HERIZON-BTC-01

Efficacy data for zanidatamab from HERIZON-BTC-01
Supportive evidence provided from 2 RWE studies (England n=20, France n=12)

Design	Phase 2b, open-label, single-arm, multi-centre international study
Population	HER2-amplified, unresectable, locally advanced or metastatic BTC, with progression on previous line • Full population: n=87 ↳ Cohort 1 (IHC2/3+): n=80 ↳ **HER2+ IHC3+:* n=62** → **Submission population**
Intervention	Zanidatamab
Comparator	None
Primary outcome	Confirmed objective response rate
Secondary outcomes	Disease control rate, duration of response, PFS, OS, adverse events
Location	32 sites across 9 countries (1 UK site, 2 patients)

Prior therapy

	Cohort 1 (n=80)	IHC3+ (n=62)
No. of regimens		
1	58.8%	[redacted]
2 or more	41.3%	[redacted]
PD1/PDL1i	26.3%	[redacted]

Does lower than expected previous PD1/PDL1i use affect generalisability?

Outcomes

July 2024 final data cut

PFS	(per ICR)
Median	7.2 months
95% CI	5.4 to 9.4 months
OS	
Median	18.1 months
95% CI	12.2 to 22.9 months

*IHC3+ means high expression of the HER2 protein

BTC, biliary tract cancer; CI, confidence interval; ICR, independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival; PD1/PDL1, programmed cell death protein 1/programmed death ligand 1; PFS, progression-free survival.

Indirect treatment comparisons

Company + EAG prefer naïve comparison due to limitations with other methods

Company: HERIZON-BTC-01 was single-arm → need to use indirect comparison for the model
- Considered unanchored MAIC, external control arm analysis, and naïve comparison
- All analyses have limitations but show survival benefit for zanidatamab (see appendix)

Unanchored MAIC (results 1,2,3)
- ABC-06 as comparator – an RCT of FOLFOX + ASC (n=81) vs. ASC (n=81)
- Could not match on all patient characteristics, including HER2 status
- Used HERIZON 2nd line only population to match ABC-06 (n=[redacted] in HERIZON)
- Further matching reduced sample size more (n=[redacted] in HERIZON)
- Uncertainty about whether prognostic factors selected were truly prognostic
- Potential confounding due to subsequent treatments

External control arm
- Flatiron used for external control arm – this is a US patient database
- Compared with HERIZON IHC3+ 2nd line+ population (n=62 in HERIZON)
- Small Flatiron sample (n=12), limited adjustments to match with HERIZON

Naïve comparison
- Unadjusted comparison of HERIZON (IHC3+ 2nd line+, n=62) vs. ABC-06 (FOLFOX: n=81, ASC: n=81)
- Company + EAG consider most appropriate given limited data
- EAG concerned about robustness; effect estimates may be unreliable

What is the committee's preferred indirect treatment comparison?

ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

Naïve comparison

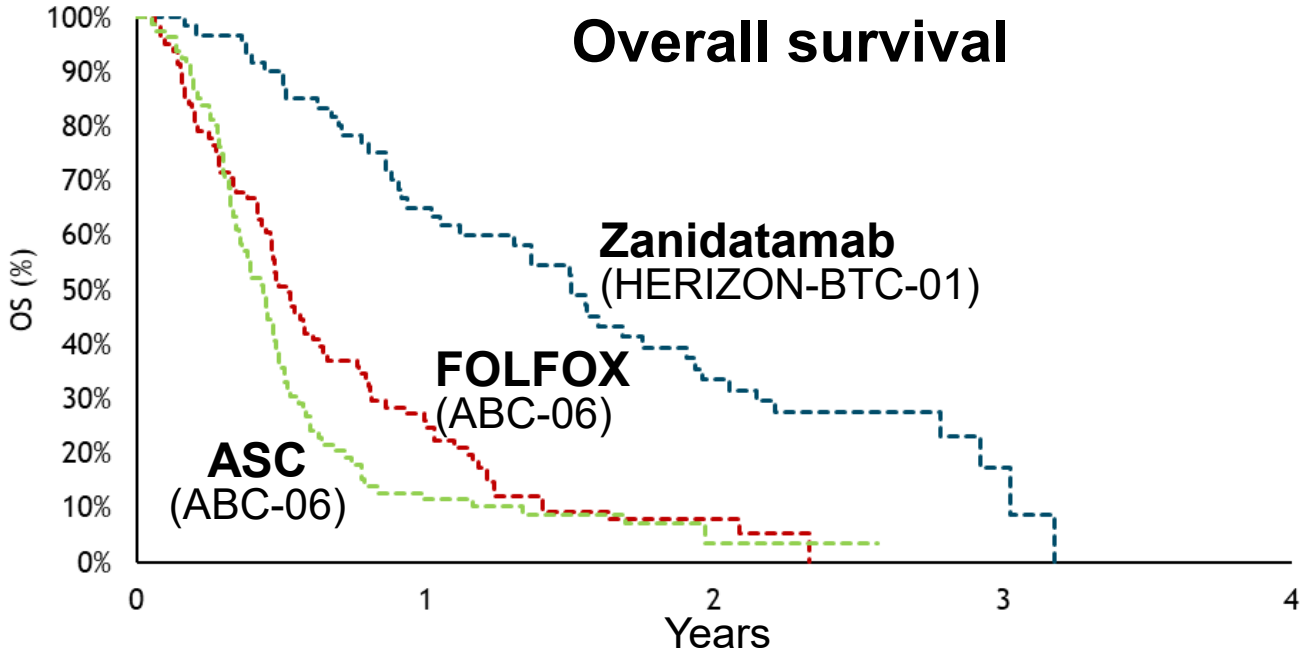
See appendix for comparison of baseline characteristics

Naïve comparison shows PFS and OS benefit for zanidatamab

Progression-free survival

[redacted]

Overall survival



	Zanidatamab	FOLFOX + ASC
Median PFS (INV) months (95% CI)	[redacted]	**4.0** (3.2, 5.0)
6-month PFS, %	[redacted]	32.1
12-month PFS, %	[redacted]	8.6

	Zanidatamab	FOLFOX + ASC	ASC
Median OS, months (95% CI)	**18.1** (12.2, 22.9)	**6.2** (5.4, 7.6)	**5.3** (4.1, 5.8)
6-month OS, %	[redacted]	50.6	35.5
12-month OS, %	[redacted]	25.9	11.4

NICE ASC, active symptom control; CI, confidence interval; FOLFOX; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; INV, investigator; OS, overall survival; PFS, progression-free survival.

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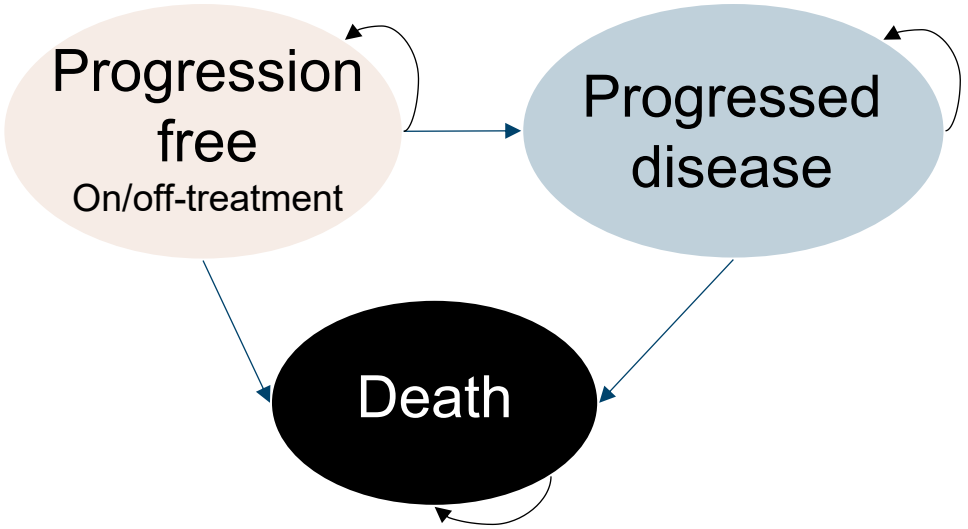
Company's model overview

3-state partitioned survival analysis



Zanidatamab affects *QALYs* by:

- Increasing overall survival
- Increasing the time spent in progression free

Zanidatamab affects *costs* by:

- Increasing treatment acquisition costs, with longer time on treatment

Assumptions that *most* affect the ICER:

- Time on treatment and relative dose intensity for zanidatamab and FOLFOX
- Method used to calculate utility values

EAG: satisfied that partitioned survival analysis is appropriate

Medium ICER impact

Survival analysis

EAG generally agree with curve selection, but disagree on zanidatamab OS

Company:

- Fit standard curves to unadjusted OS + PFS from HERIZON-BTC-01 + ABC-06 trials
- ASC PFS estimated using HR from MAIC (as PFS for ASC was not reported in ABC-06)

EAG: Agree with curve selection for zanidatamab PFS, FOLFOX PFS + OS, and ASC OS

- Disagree with log-logistic for zanidatamab OS – optimistic especially at longer follow-up
- Prefer log-normal, more modest long-term, tends to 0 more quickly
- Provide gamma (capped to PFS) as scenario – tends to 0 quickest

Long-term zanidatamab OS

[redacted]

Distribution	Landmark OS (%)		
	5y	7.5 y	10 y
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Gamma (cap.)	[redacted]	[redacted]	[redacted]

- What is the committee's preferred zanidatamab OS extrapolation?
- [redacted]% in HERIZON had subsequent treatment, could this have affected OS?

FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

Medium ICER impact

Key issue: Treatment acquisition costs – time on treatment

EAG prefer different ToT extrapolation for zanidatamab + adjusted FOLFOX ToT

Company:

- Fit standard parametric curves to ToT for zanidatamab IHC3+ population (n=62)
- Prefer gamma – most pessimistic long-term estimates, in line with observed ToT
- FOLFOX ToT assumed equal to PFS from ABC-06

EAG: Company's preferred ToT extrapolation means ToT exceeds PFS for first [redacted] months*, then rapidly drops off

↳ Gamma curve lacks face validity

↳ Prefer log-normal

- For FOLFOX – ToT equal to PFS may overestimate ToT. FOLFOX has significant toxicity and people discontinue for reasons other than progression

↳ Apply TTD/PFS ratio to PFS

% progression-free on treatment

How should ToT be modelled?

*Note that the model includes a cap that prevents ToT from exceeding PFS
FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival; ToT, time on treatment; TTD, time to discontinuation.

Medium ICER impact

Key issue: Treatment acquisition costs – RDI

EAG prefer lower RDI for FOLFOX to account for toxicity

Company:

- Apply RDI from trial ([redacted]%) to account for missed doses, reductions + interruptions
- The same RDI for FOLFOX was assumed due to limited literature
- Highlight that RDI for FOLFOX not considered in previous 2nd line BTC appraisals

EAG:

- FOLFOX has significant toxicity – greater than expected for zanidatamab
- Prefer to use lower RDI from Korean real-world study of 2nd line BTC

Treatment	Company preferred RDI	Source	EAG preferred RDI	Source
Zanidatamab	[redacted]	HERIZON-BTC-01	[redacted]	HERIZON-BTC-01
FOLFOX	[redacted]	Assume = zanidatamab	78%	Korean real-world study

To experts: how common are discontinuations or reductions of FOLFOX due to toxicity?

- Should RDI be applied for FOLFOX?
- If so, which value does the committee prefer?

BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; RDI, relative dose intensity.

Medium ICER impact

Key issue: Utility estimation approach

Company prefer time-to-death; EAG prefer progression-based utilities

Company:

- Provided progression-based and time-to-death (TTD) utility values
- Limitation of progression-based is small number of observations post-progression, they are usually at or around time of progression, and utility modelled as constant over time
- Prefer TTD, where utility rapidly decreases in days before death, as may be expected

EAG:

- TTD method undermined by large difference in time in progressed disease health state between treatments – zanidatamab ([redacted] days), FOLFOX (28 days), ASC (77 days)*
  - ↳ Uncertain whether applying zanidatamab-derived TTD utilities to FOLFOX + ASC is appropriate given substantial difference in time in progressed disease
- TTD lacks face validity – small number of high utility observations close to death
- Costs and treatments in model determined by progression status – internal consistency of applying progression-based utility values

How should utility values be estimated – progression-based or time-to-death?

*Under company preferred assumptions. With Gamma curve for zanidatamab, time in progressed disease is [redacted] days.
ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; TTD, time-to-death.

Small ICER impact

Key issue: Frequency of echocardiography* monitoring

Clinical advice suggests lower frequency of echocardiography in NHS

Company:

- Assume echocardiography for FOLFOX patients before + after each administration
- Supported by oxaliplatin and fluorouracil licences →

EAG:

- EAG and company clinical advice suggest echocardiography not routinely performed in NHS for FOLFOX patients
- EAG base case assumes echocardiography once, prior to FOLFOX initiation
- Also provide scenario of 2 echocardiographies – 1 before and 1 after treatment

SmPC wording

Oxaliplatin:

'QT interval should be closely monitored on a regular basis before and after administration'

Fluorouracil:

'Cardiac function should be regularly monitored during treatment'

In the NHS, how often is echocardiography done for FOLFOX patients?

*Company note echocardiogram (echo) included mistakenly instead of electrocardiogram (ECG)

NICE FOLFOX, folinic acid, fluorouracil, and oxaliplatin; SmPC, summary of product characteristics.

Other issues raised by EAG

Assumption	Company base case	EAG base case	ICER impact
Source for AE rates	HERIZON-BTC-01 full cohort	HERIZON-BTC-01 (IHC3+ pop.)	Small
Source for utilities	HERIZON-BTC-01 full cohort	HERIZON-BTC-01 (IHC3+ pop.)	Small
Disutility for central line for FOLFOX	Apply full annual disutility per cycle	Adjust disutility by cycle length	Medium*
Treatment-specific disutility	Included • FOLFOX: [redacted] (due to need for central line, high incidence of grade 1/2 AEs that are not captured in AE disutilities) • ASC: [redacted] (due to lack of disease control)	Excluded • Company's calculation subject to uncertainty, involves further naïve comparison between HERIZON-BTC-01 + ABC-06 • Risk of double-counting disutility – as disutilities already applied for grade 3/4 AEs and administration (for FOLFOX)	Small
End-of-life morphine cost	Included	Excluded – would likely be included in the company's end-of-life cost	Small

*TTD approach only, does not affect EAG base case.
AE, adverse event; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC, immunohistochemistry.

QALY weightings for severity

Background

- General population QALYs based on ONS 2017-19 National life tables for England and Wales
- Population EQ-5D-3L data adjusted by age and sex derived from the Health Survey from England 2014

	QALYs of people without condition	QALYs with condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Company base case				
FOLFOX + ASC	14.75	0.41	14.34	97.22%
ASC		0.36	14.75	97.56%
EAG base case				
FOLFOX + ASC	14.75	0.60	11.42	95.01%
ASC		0.45	11.57	96.26%

>95% = 1.7x QALY weight

Does the committee agree it is appropriate to apply a 1.7x QALY weighting for severity?

NICE ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ONS, Office for National Statistics; QALY, quality-adjusted life year.

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

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Zanidatamab OS	Log-logistic	Log-normal
Zanidatamab ToT	Gamma	Log-normal
FOLFOX ToT	Equal to PFS	Ratio of number of cycles/PFS
AE population source	HERIZON-BTC-01 full cohort	HERIZON-BTC-01 (IHC3+ pop.)
Admin. disutility	Apply full annual disutility per cycle	Adjust disutility by cycle length
Utility population source	HERIZON-BTC-01 full cohort	HERIZON-BTC-01 (IHC3+ pop.)
Utility estimation	Time-to-death	Progression based
Treatment-specific disutility	Included	Excluded
FOLFOX RDI	Equal to zanidatamab ([redacted])	Real-world study (78%)
Echocardiography for FOLFOX	Before and after each admin	Once before treatment initiation
End-of-life morphine cost	Included	Excluded

NICE AE, adverse event; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment.

Results – cost-effectiveness ranges

Confidential discounts for other treatments in pathway – ICERs in Part 2 slides
ICER ranges presented below

Zanidatamab versus FOLFOX + ASC

Company base case probabilistic ICER:

- <£30,000 per QALY gained*

EAG base case probabilistic ICER:

- >£30,000 per QALY gained

Zanidatamab versus ASC

Company base case probabilistic ICER:

- >£30,000 per QALY gained*

EAG base case probabilistic ICER:

- >£30,000 per QALY gained

*3.5% discount rate.
ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Committee decision making slide

Assumption	Question for committee
Comparators	What are the appropriate comparators for zanidatamab? When does molecular profiling happen? Is it consistent across different centres?
Trial	Does lower than expected previous PD1/PDL1i use affect generalisability?
ITC	What is the committee's preferred indirect treatment comparison?
Survival analysis	What is the committee's preferred zanidatamab OS extrapolation? Could subsequent treatments in the trial have affected OS?
	How should ToT be modelled?
Costs	Should RDI be applied for FOLFOX? If so, which value does the committee prefer?
	In the NHS, how often is echocardiography done for FOLFOX patients?
Utilities	How should utility values be estimated – progression-based or time-to-death?
Other factors	• What are the committee's preferred assumptions for the EAG's other issues? • Is it appropriate to apply a 1.7 QALY weighting for severity? • Are there any equality or health inequalities considerations that need to be accounted for? • Are there any uncaptured benefits of zanidatamab? • Is there any uncertainty in the modelling that needs to be accounted for?
ICER	What is the committee's preferred ICER threshold?
	What is the committee's preferred ICER?

Supplementary appendix

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HERIZON-BTC-01 IHC3+ – PFS – July 2024 datacut

[redacted]

NICE IHC, immunohistochemistry; PFS, progression-free survival.

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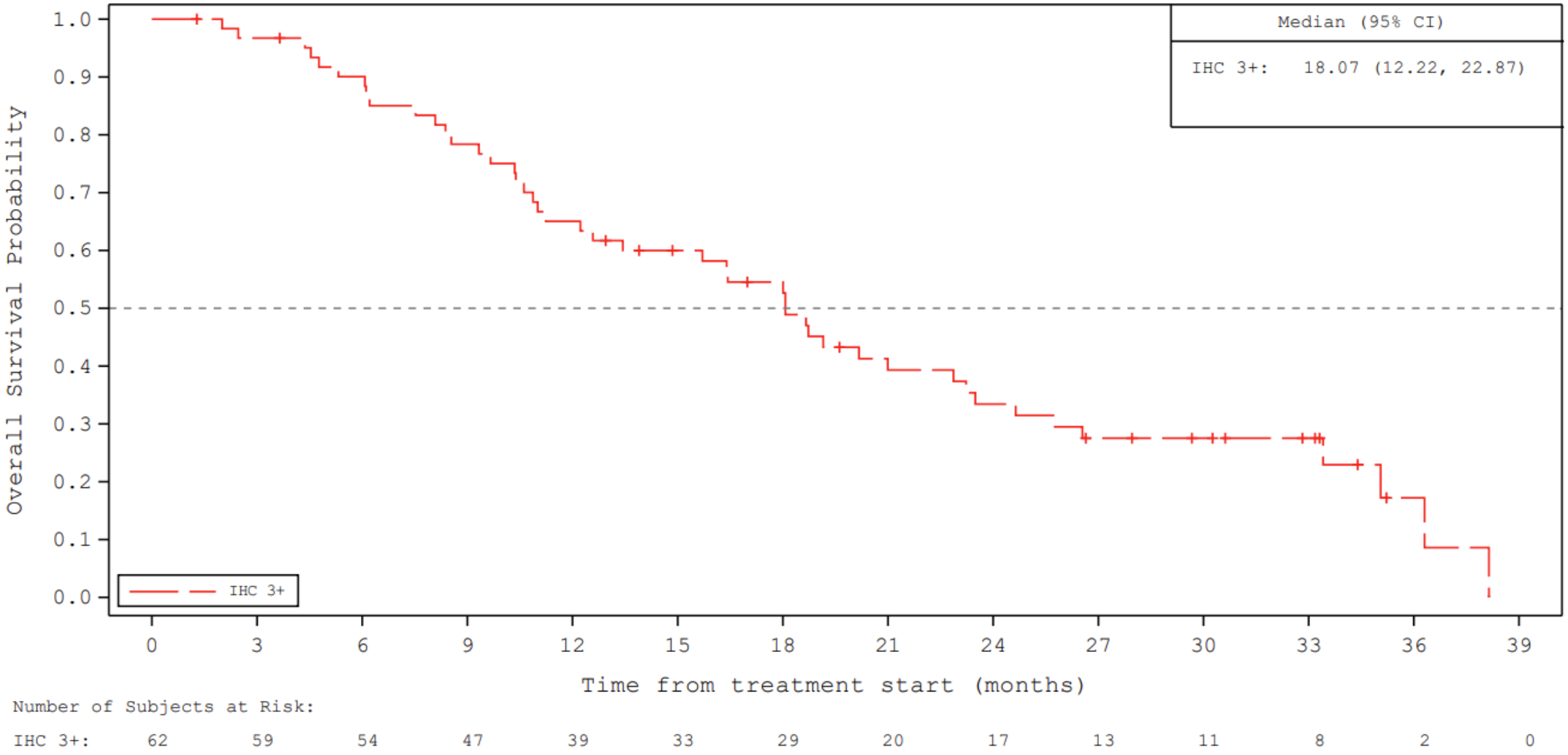
HERIZON-BTC-01 IHC3+ – OS – July 2024 datacut



IHC, immunohistochemistry; OS, overall survival.

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HERIZON-BTC-01 subsequent treatment use

Any subsequent treatment: [redacted]/62 ([redacted]%)

Subsequent treatment, n (%)	IHC3+ population of HERIZON-BTC-01 (n=62)
FOLFOX	[redacted]
FOLFIRI	[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]

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

NICE FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC, immunohistochemistry

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ABC-06 trial

Design	Phase 3, open-label, randomised controlled trial
Population	Locally advanced or metastatic BTC with progression on 1st line treatment (n=162) HER2 positivity **not** known
Intervention	FOLFOX + active symptom control
Comparator	Active symptom control alone
Primary outcome	Overall survival
Secondary outcomes	Progression-free survival, overall response, adverse events, quality of life, health economics
Location	UK only (20 sites)

Outcomes

Final analysis

PFS	FOLFOX + ASC
Median	4.0 months
95% CI	3.2 to 5.0

OS	FOLFOX + ASC	ASC
Median	6.2 months	5.3 months
95% CI	5.4 to 7.6	4.1 to 5.8
HR	0.69	
95% CI	(0.50 to 0.97); p=0.031	
6-month	50.6%	35.5%
12-month	25.6%	11.4%

NICE ASC, active symptom control; BTC, biliary tract cancer; CI, confidence interval; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry

HERIZON-BTC-01 + ABC-06 baseline characteristics

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Characteristic		Zanidatamab HERIZON-BTC-01 IHC3+ (n=62)	Zanidatamab HERIZON-BTC-01 IHC3+, 2L only (n=[redacted])	FOLFOX + ASC or ASC ABC-06 (n=162)
Median age, years (range)		[redacted]	[redacted](NR)	65 (26 to 84)
Race, n (%)	White	[redacted]	NR	NR
	Asian		NR	NR
	Other		NR	NR
Region, n (%)	North America	[redacted]	NR	0
	Asia		[redacted]	0
	Other		NR	162 (100)
Female, n (%)		[redacted]	[redacted]	82 (50.6)
ECOG PS, n (%)	0	[redacted]	[redacted]	53 (32.7)
	1		[redacted]	107 (66.0)
	2		[redacted]	0
Previous radiotherapy, n (%)		[redacted]	NR	NR
Previous surgery, n (%)		[redacted]	NR	72 (44.4)
Previous lines of therapy, n (%)	1	[redacted]	NR	NR
	2+		NR	NR
	Median (range)		NR	NR
Disease stage at study entry, n (%)	Locally advanced	[redacted]	[redacted]	29 (17.9)
	Metastatic			133 (82.1)
Tumour site, n (%)	GBC	[redacted]	NR	134 (21.0)
	iCCA		NR	72 (44.4)
	eCCA		NR	45 (27.8)

ASC, active symptom control; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, and oxaliplatin

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HERIZON-BTC-01 + ABC-06 baseline characteristics

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
Median age, years (range)	[redacted]	[redacted](NR)	65 (26 to 84)
Race, n (%)	[redacted]		
White		NR	NR
Asian		NR	NR
Other		NR	NR
Ethnicity, n (%)	[redacted]		
Hispanic/Latino		NR	NR
Other		NR	NR
Region, n (%)	[redacted]		
North America		NR	0
Asia		[redacted]	0
Other		NR	162 (100)
Female, n (%)	[redacted]	[redacted]	82 (50.6)
ECOG PS, n (%)	[redacted]		
0		[redacted]	53 (32.7)
1			107 (66.0)
2			0

NICE ASC, active symptom control; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC, immunohistochemistry

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HERIZON-BTC-01 + ABC-06 baseline characteristics

Characteristic	HERIZON-BTC-01 IHC3+ (n=62)	HERIZON-BTC-01 IHC3+ 2L only patients (n=[redacted])	ABC-06 (n=162)
Previous radiotherapy, n (%)	[redacted]	NR	NR
Previous surgery, n (%)	[redacted]	NR	72 (44.4)
Previous lines of therapy, n (%)	[redacted]	[redacted]	
1			162 (100)
2+			0
Median (range)			1.0 (1 to 1)
IHC result, n (%)		[redacted]	
IHC3+	62 (100)		NR
IHC0/1+/2+	0		NR
Disease stage at study entry, n (%)	[redacted]	[redacted]	
Locally advanced (Stage III)			29 (17.9)
Metastatic (Stage IV)			133 (82.1)
Tumour site, n (%)	[redacted]		
GBC		NR	134 (21.0)
iCCA		NR	72 (44.4)
eCCA		NR	45 (27.8)
Albumin levels, n (%)			
<35 g/L	NR	NR	40 (24.7)
≥35 g/L	NR	NR	122 (75.3)

eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry

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Indirect comparison – unanchored MAIC

Company:

- Population of HERIZON-BTC-01 matched to ABC-06
- Matching was achieved on 4 criteria

Characteristic	ABC-06	HERIZON-BTC-01 unweighted (2L)	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 2nd line	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]	✗

2L, 2nd line; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MAIC, matching-adjusted indirect comparison.

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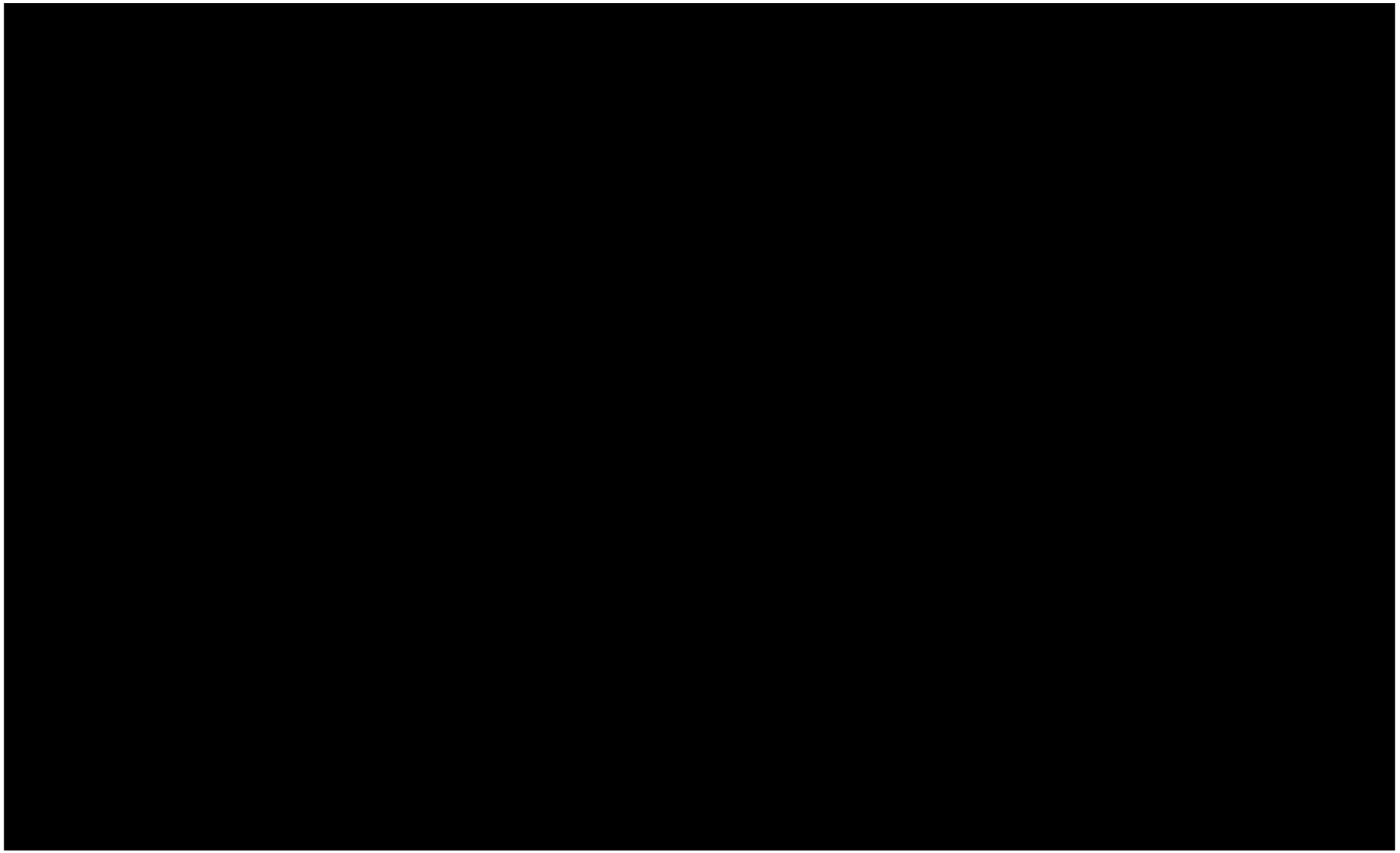
Indirect comparison – unanchored MAIC – PFS



Company:

- Used 2nd line only subgroup from HERIZON-BTC-01 (n=[redacted])
- Weighted analysis further trimmed to match ABC-06 (n=[redacted])
- Both weighted and unweighted PFS estimates favoured zanidatamab vs. FOLFOX and were statistically significant

NICE FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

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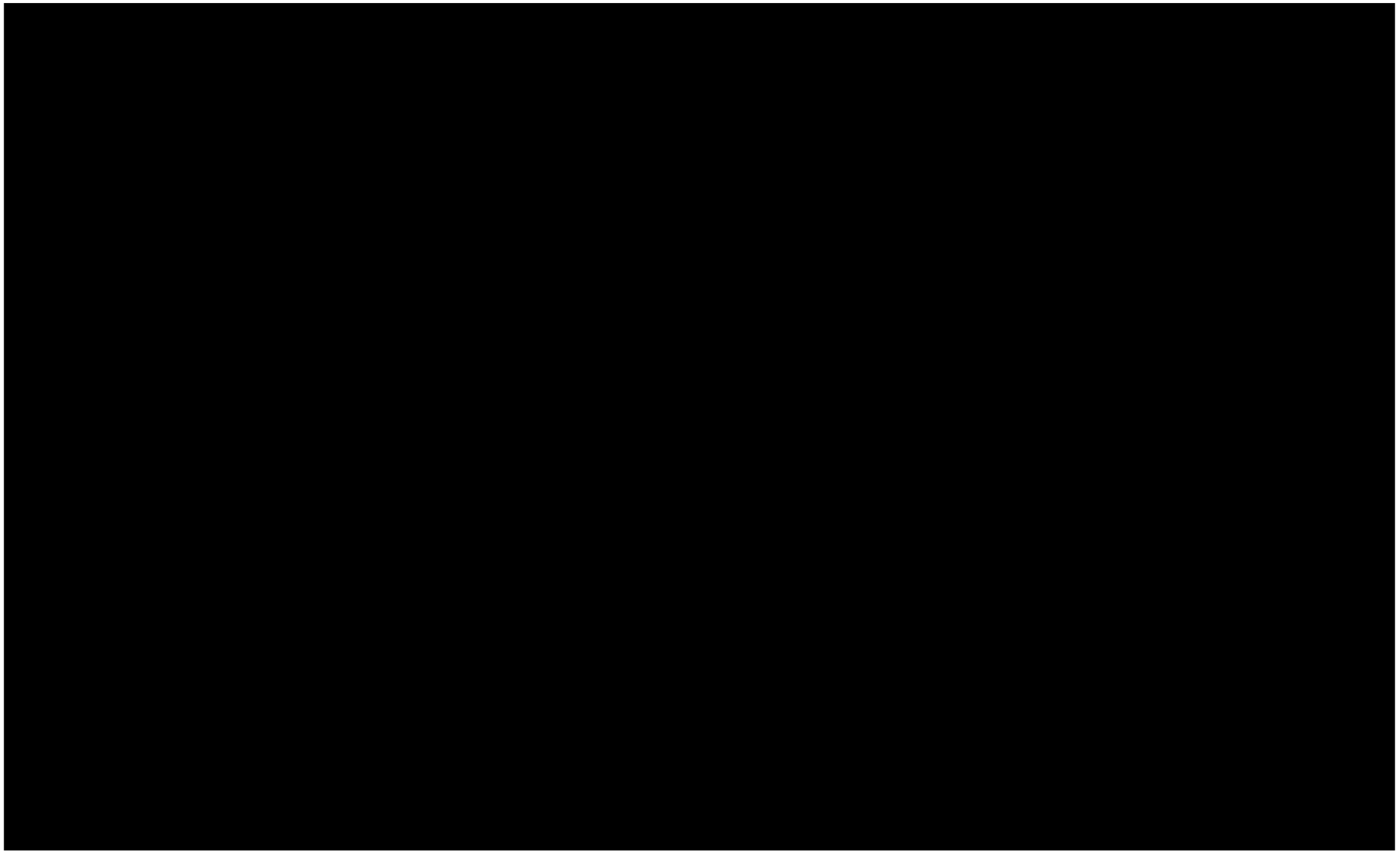
Indirect comparison – unanchored MAIC – OS



Company:

- Used 2nd line only subgroup from HERIZON-BTC-01 (n=[redacted])
- Weighted analysis further trimmed to match ABC-06 (n=[redacted])
- Both weighted and unweighted OS favoured zanidatamab vs. FOLFOX and were statistically significant

NICE FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival.

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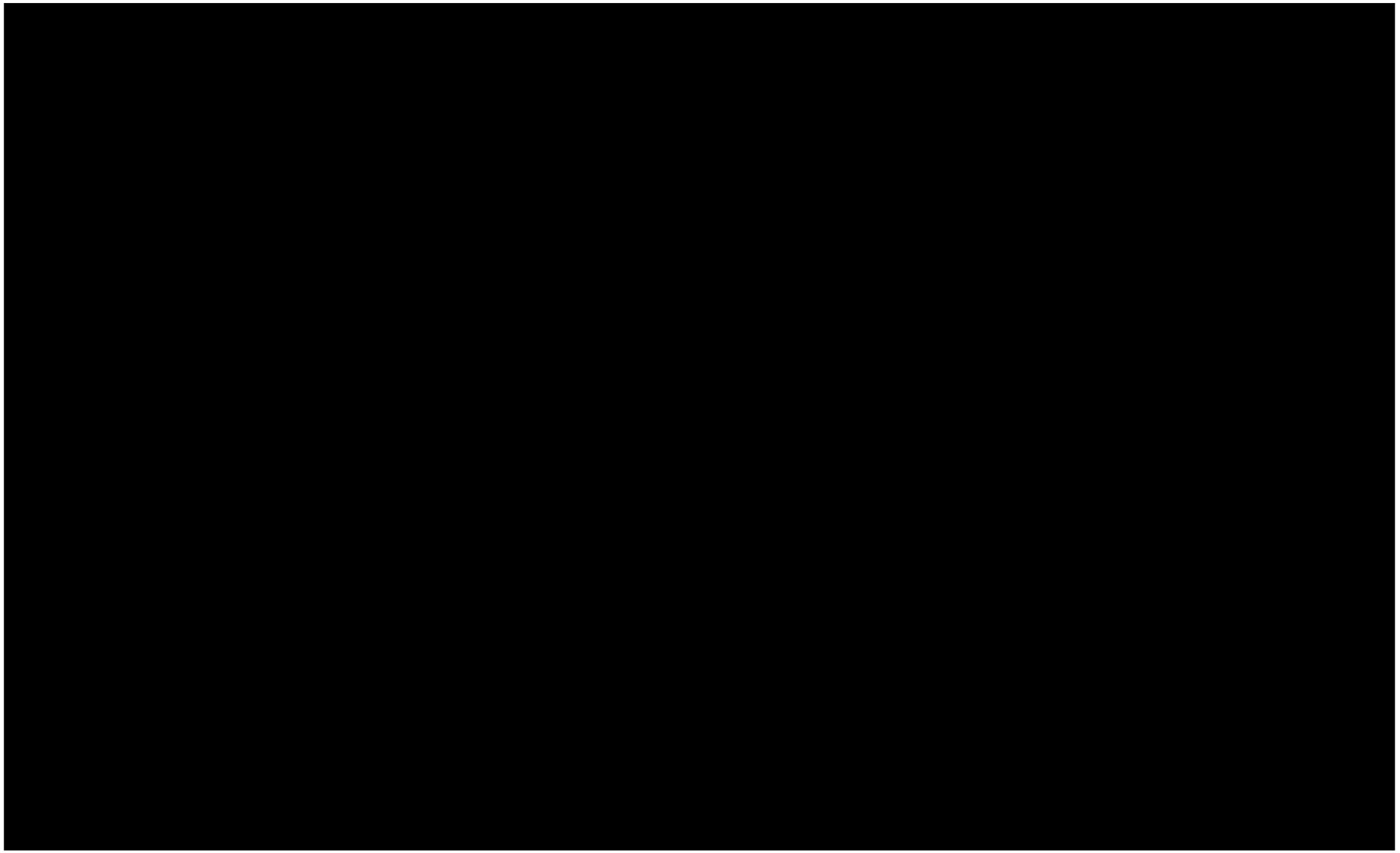
Indirect comparison – unanchored MAIC – OS



Company:

- Used 2nd line only subgroup from HERIZON-BTC-01 (n=[redacted])
- Weighted analysis further trimmed to match ABC-06 (n=[redacted])
- Both weighted and unweighted OS favoured zanidatamab vs. ASC and were statistically significant

NICE ASC, active symptom control; OS, overall survival.

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Flatiron database

Design	Retrospective observational analysis of the Flatiron database – a US-based patient-level database
Population	Patients were identified in Flatiron: • **n≈27,000,** patients with BTC ↳ **n=290,** advanced or metastatic, 2nd line treatment + HER2 tested ↳ **n=12,** HER2+ IHC3+ BTC who had chemo 2nd line + ECOG 0 or 1 • Locally advanced or metastatic BTC with HER2 expression (IHC3+), who had 2nd line treatment (n=12)
Intervention	Any systemic chemotherapy (50% had FOLFOX)
Comparator	None
Primary outcome	PFS and OS
Location	US only

BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival.

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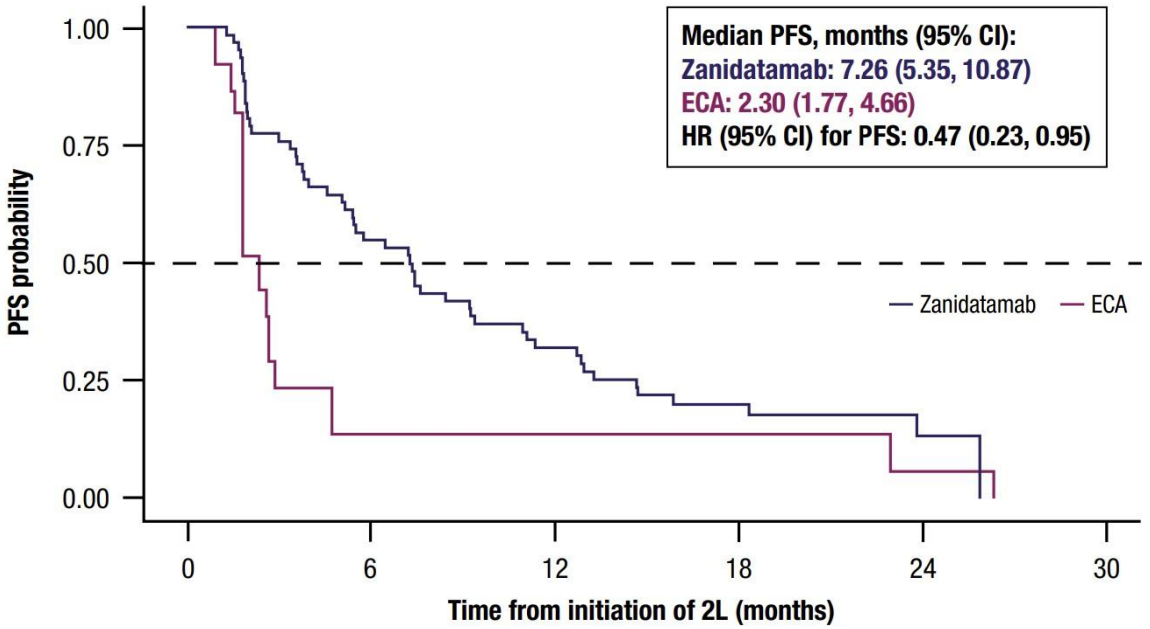
Indirect comparison – external control arm

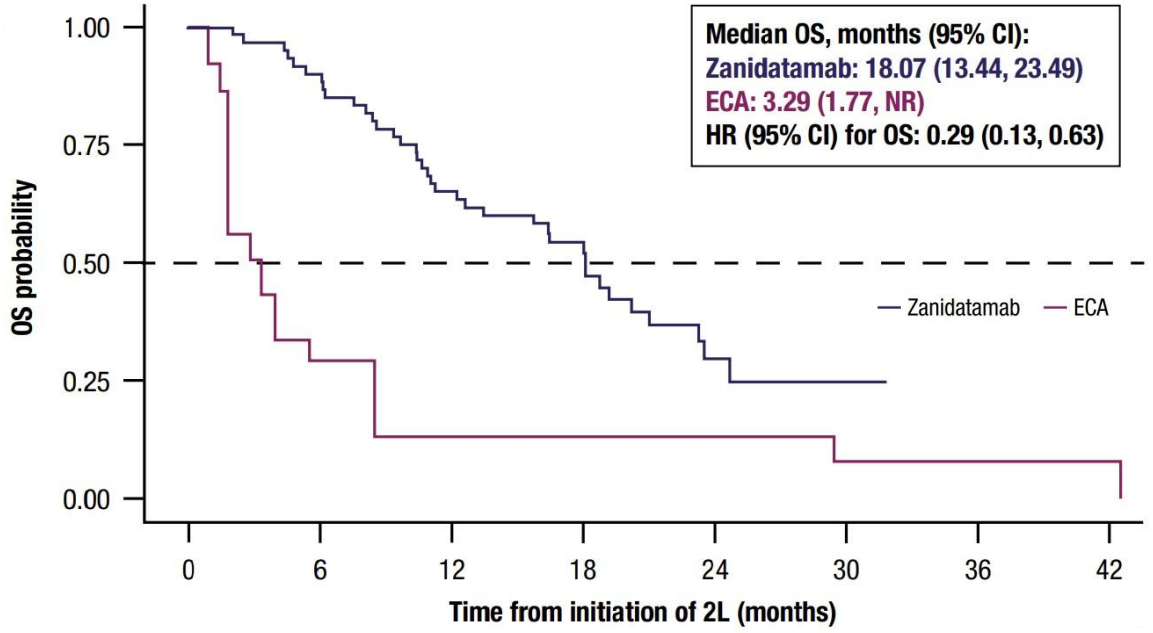
Company:

- Standardised mortality ratio (SMR) weighting was applied to account for baseline imbalance of key prognostic factors
- Median survival and HRs were estimated using SMR-weighted KM and Cox proportional hazards regression
- Results showed significantly longer PFS and OS with zanidatamab

PFS



OS



CI, confidence interval; ECA, external control arm; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

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Indirect treatment comparisons – hazard ratios

Unanchored MAIC

Analysis	Zanidatamab HR vs. comparator	
	FOLFOX + ASC	ASC
PFS		
Zanidatamab 2L unweighted (n=[redacted])	[redacted]	NR
Zanidatamab 2L weighted (n=[redacted])	[redacted]	NR
OS		
Zanidatamab 2L unweighted (n=[redacted])	[redacted]	[redacted]
Zanidatamab 2L weighted (n=[redacted])	[redacted]	[redacted]

External control arm

Analysis	Zanidatamab HR vs. comparator
	External control arm
PFS	
Zanidatamab 2L+ (n=62)	0.47 [95% CI: 0.23, 0.95]
OS	
Zanidatamab 2L+ (n=62)	0.29 [95% CI: 0.13, 0.63])

NICE ASC, active symptom control; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

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Zanidatamab PFS extrapolation

[redacted]

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

Distribution	Landmark PFS (%)			
	6 m	1 y	3 y	5 y
Exponential	[redacted]			
Generalised gamma	[redacted]			
Gompertz	[redacted]			
Log-logistic	[redacted]			
Log-normal	[redacted]			
Weibull	[redacted]			
Gamma	[redacted]			

Company + EAG: agree that the log-logistic curve is appropriate for PFS

NICE AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

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Zanidatamab OS extrapolation

[redacted]

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**

Distribution	Landmark OS (%)			
	6 m	1 y	3 y	5 y
Exponential	[redacted]			
Generalised gamma	[redacted]			
Gompertz	[redacted]			
Log-logistic	[redacted]			
Log-normal	[redacted]			
Weibull	[redacted]			
Gamma	[redacted]			

Company: prefer log-logistic

EAG: prefer log-normal

NICE AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival.

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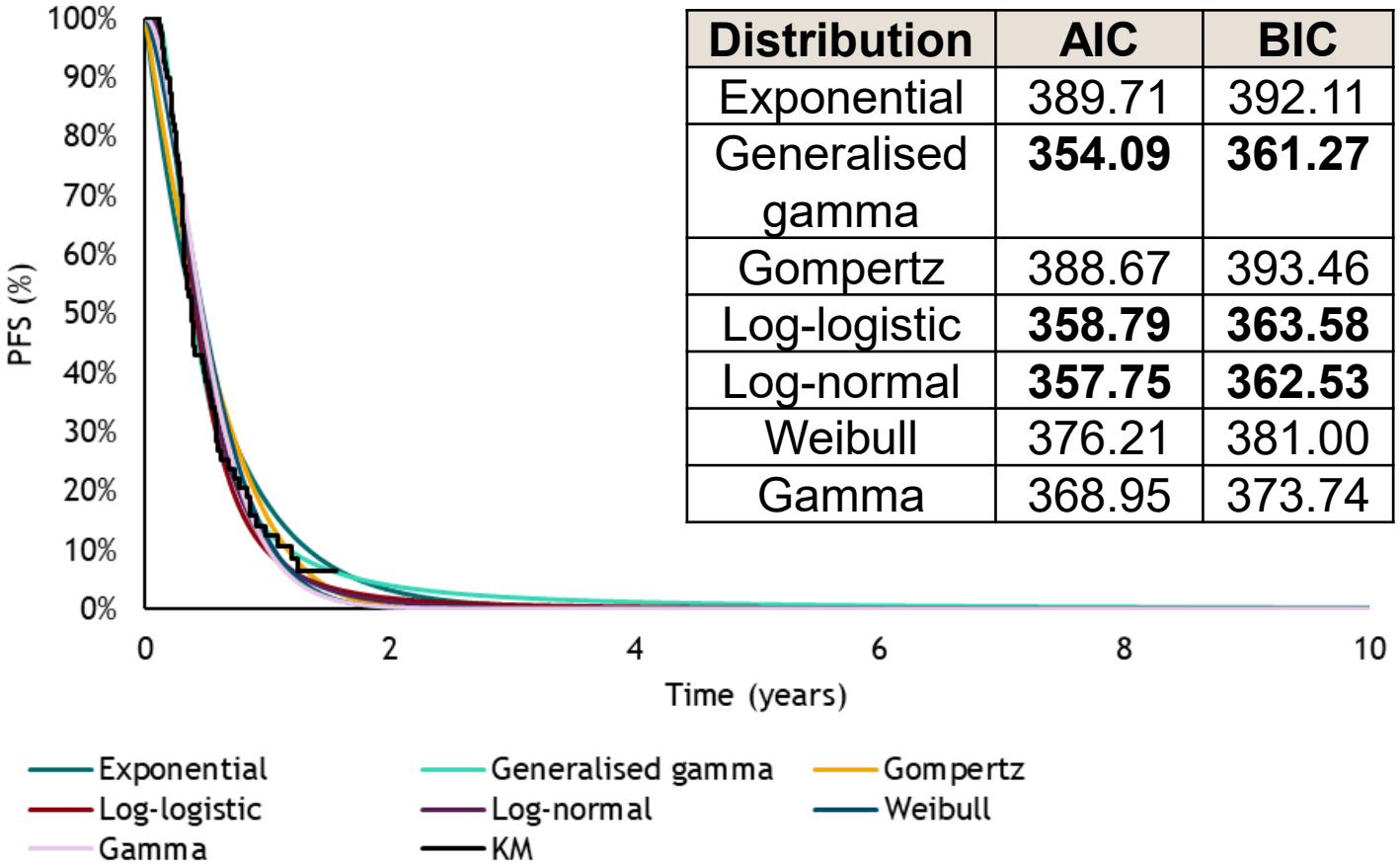
FOLFOX + ASC PFS extrapolation



Distribution	AIC	BIC
Exponential	389.71	392.11
Generalised gamma	**354.09**	**361.27**
Gompertz	388.67	393.46
Log-logistic	**358.79**	**363.58**
Log-normal	**357.75**	**362.53**
Weibull	376.21	381.00
Gamma	368.95	373.74

Distribution	Landmark PFS (%)			
	6 m	1 y	3 y	5 y
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
Weibull	47.0	12.0	0.0	0.0
Gamma	45.7	10.3	0.0	0.0

Company + EAG: agree that the log-normal curve is appropriate for PFS

AIC, Akaike Information Criterion; ASC, active symptom control; BIC, Bayesian Information Criterion; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

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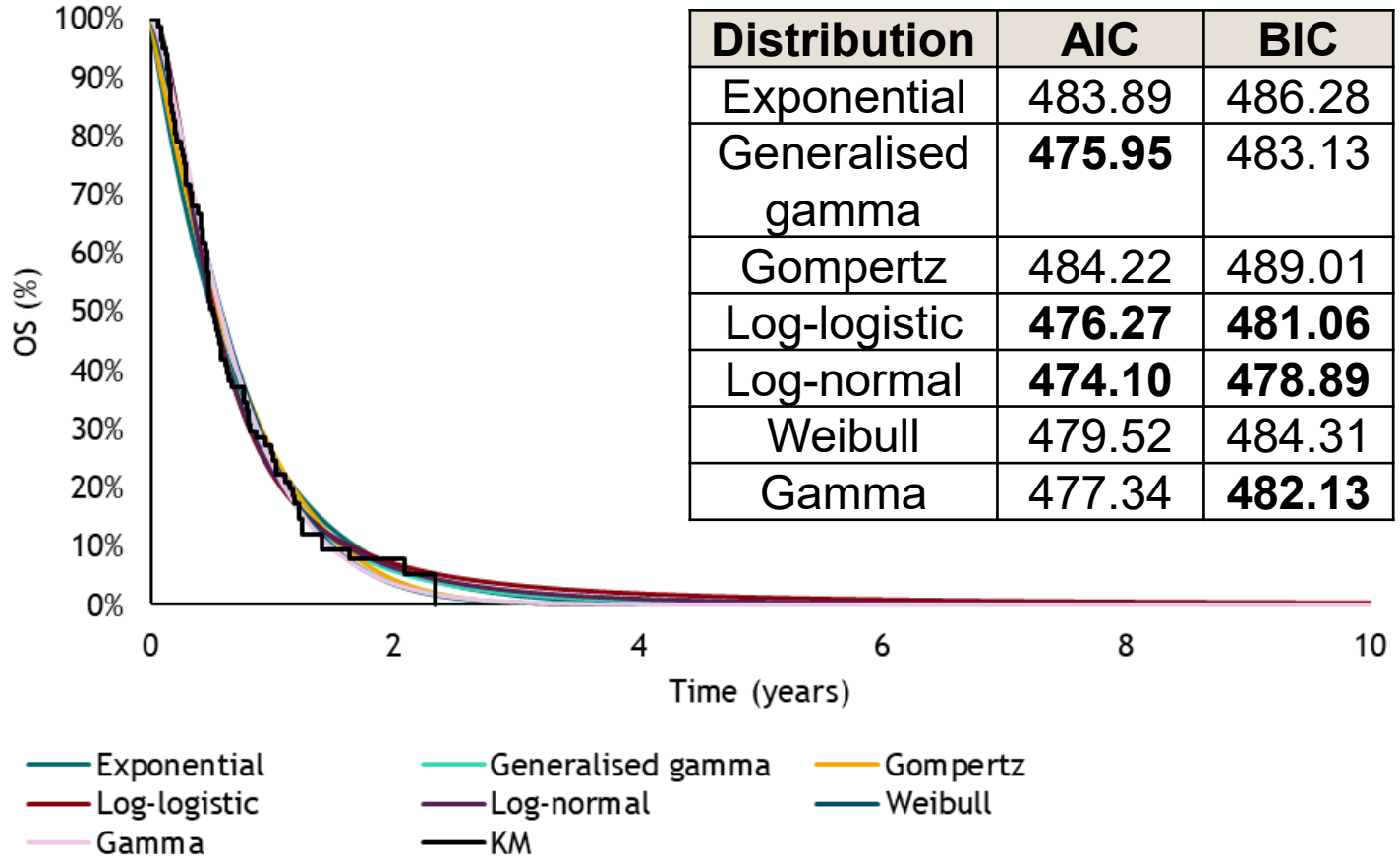
FOLFOX + ASC OS extrapolation



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**

Distribution	Landmark OS (%)			
	6 m	1 y	3 y	5 y
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

Company + EAG: agree that the log-normal curve is appropriate for OS

AIC, Akaike Information Criterion; ASC, active symptom control; BIC, Bayesian Information Criterion; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival.

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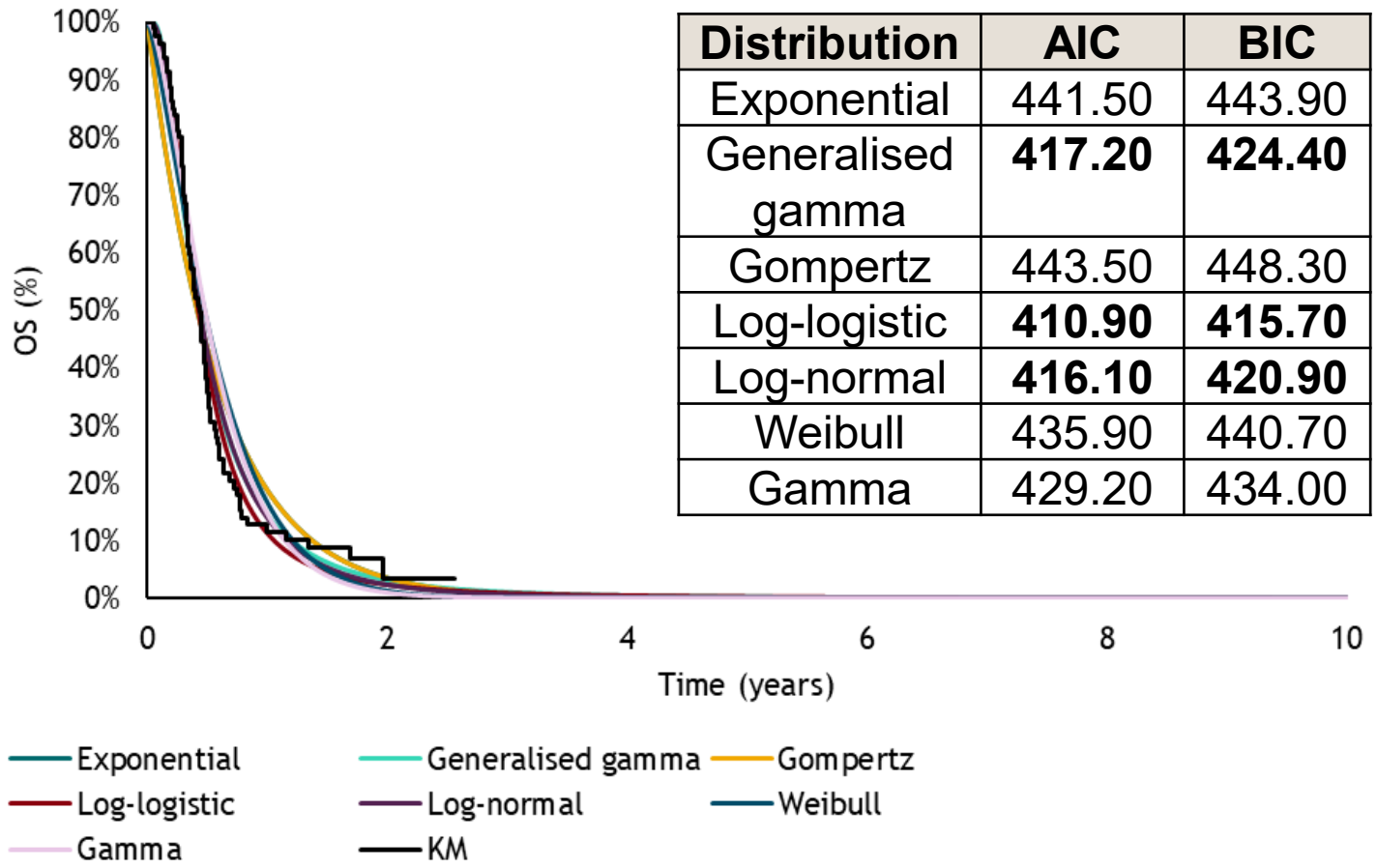
ASC OS extrapolation



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

Distribution	Landmark OS (%)			
	6 m	1 y	3 y	5 y
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

Company + EAG: agree that the log-normal curve is appropriate for OS

AIC, Akaike Information Criterion; ASC, active symptom control; BIC, Bayesian Information Criterion; OS, overall survival.

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Zanidatamab ToT extrapolation

[redacted]

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**

Distribution	Landmark ToT (%)			
	6 m	1 y	3 y	5 y
Exponential	[redacted]			
Generalised gamma	[redacted]			
Gompertz	[redacted]			
Log-logistic	[redacted]			
Log-normal	[redacted]			
Weibull	[redacted]			
Gamma	[redacted]			

Company: prefer gamma

EAG: prefer log-normal

NICE AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ToT, time on treatment.

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Utility values estimation approaches

Progression-based

	Company preferred HERIZON-BTC-01 (N=80)	EAG preferred HERIZON-BTC-01, IHC 3+ sub-pop. (N=62)	Durva-lumab, TA944 (N=806)	McCarthy et al, TA 914 (Cholangiocarcinoma) (N=Not reported)
PF	[redacted]	[redacted]	0.797	0.805
PD	[redacted]	[redacted]	0.679	0.702

Time to death (TTD)

[redacted]

NICE IHC, immunohistochemistry; PD, progressed disease; PF, progression-free.

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Company and EAG clinical advice on echocardiography

Company clinician interview transcripts:

Interviewee 1:

- [redacted]

Interviewee 6:

- [redacted]

EAG clinical adviser:

- 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

NICE FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

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Company's treatment-specific disutility calculation

Calculation step	Utility Value	Source
(a) HERIZON-BTC-01 baseline utility	[redacted]	HERIZON-BTC-01
FOLFOX disutility		
(b) FOLFOX baseline utility	0.77	ABC-06
(c) FOLFOX 4-month utility	0.70	ABC-06
(d) FOLFOX % progression-free at 4 months	56.7%	ABC-06
(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] [progression-free utility] + (1-d)*[redacted] [progressed disease utility]
FOLFOX + ASC decrement	[redacted]	Calculation (g-f)
ASC disutility		
(h) ASC baseline utility	0.75	ABC-06
(i) ASC 4-month utility	0.62	ABC-06
(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] [progression-free utility] + (1-j)*[redacted] [progressed disease utility]
ASC decrement	[redacted]	Calculation (m-l)

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

Ratio of OS hazards over time

ASC, active symptom control; FF, FOLFOX (folinic acid, fluorouracil, and oxaliplatin); LL, log-logistic; LN, log-normal, OS, overall survival