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

Technology appraisal committee C [3 March 2026]

PART 1
Confidential information redacted

Chair: James Fotheringham

External assessment group: Aberdeen HTA Group

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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 recap of appraisal committee meeting 1**
- ❑ Response to consultation

NICE National Institute for Health and Care Excellence

Background of zanidatamab (ZIIHERA®, Jazz Pharmaceuticals)

Background

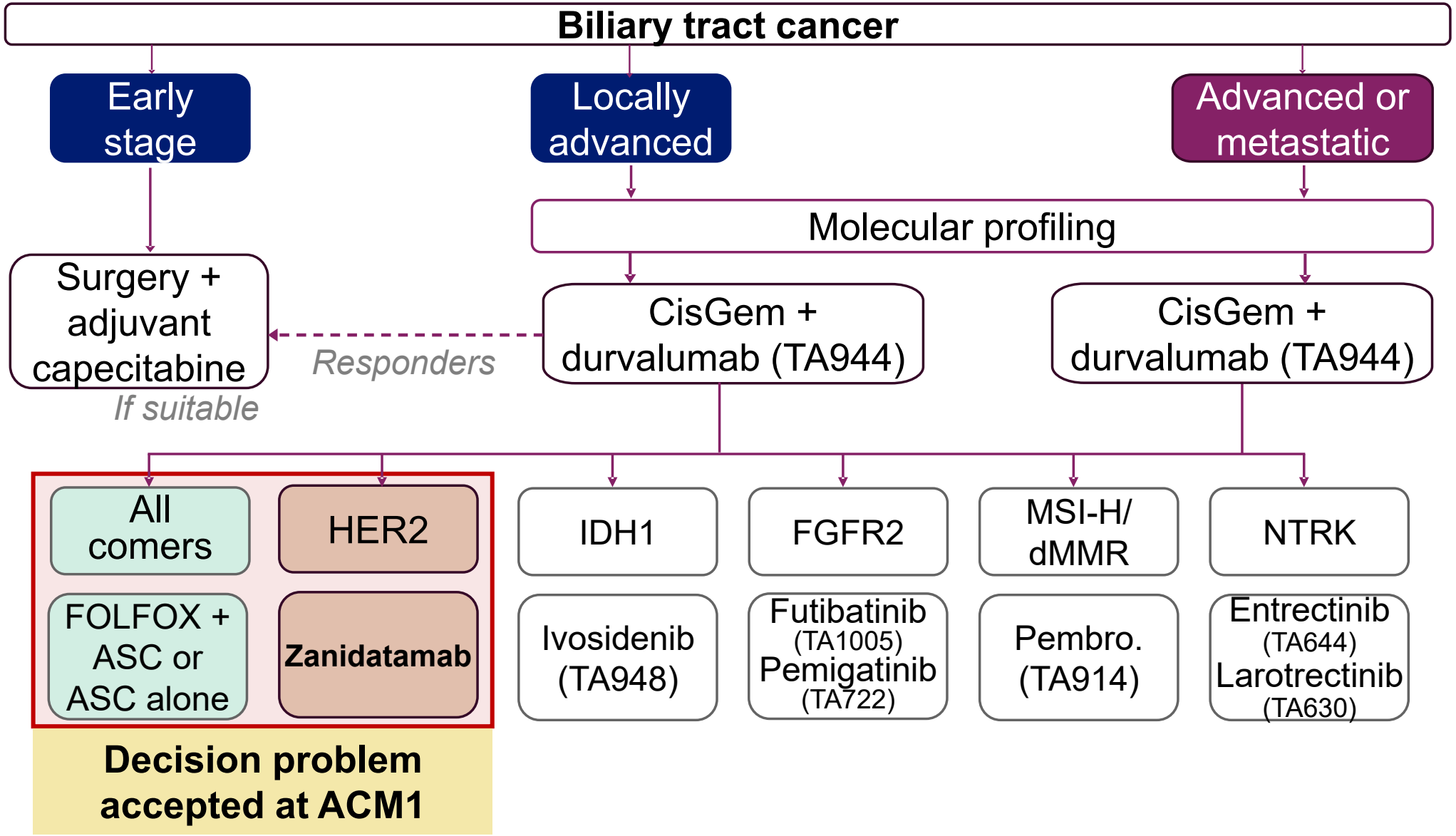
- HER2 alterations in ~5-20% of BTC; 80% of HER2+ BTC are IHC3+ (high HER2)
- ~50 people would be eligible for 2nd line zanidatamab in England per year

Marketing authorisation	• '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' • MHRA marketing authorisation granted February 2026
Mechanism of action	• Bispecific antibody that targets HER2 • HER2 stimulates cancer cells to grow
Administration	Recommended dose is 20 mg/kg, administered as an IV infusion every 2 weeks (every 14 days) until disease progression or unacceptable toxicity
Price	• Patient access scheme (PAS) discount accepted by NHS England

NICE

BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency.

Treatment pathway



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

ACM1 – Draft recommendation and uncertainties

Zanidatamab **should not be used** to treat HER2-positive (IHC3-positive) unresectable locally advanced or metastatic biliary tract cancer in adults after at least 1 line of systemic treatment

Uncertainties:

- Non-NHS subsequent treatments may have affected overall survival in HERIZON-BTC-01
- Naive comparison was used to estimate the relative clinical effectiveness of zanidatamab
- It was unclear to what extent zanidatamab improved quality of life

Requested analysis:

- Scenarios exploring treatment-specific and non-specific utility values, with simplified disutilities
- Cardiac monitoring costs that are most reflective of NHS practice

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

- ❑ Background and recap of appraisal committee meeting 1
- ✓ **Response to consultation**

NICE National Institute for Health and Care Excellence

Summary of consultation responses received (1/2)

AMMF – The Cholangiocarcinoma Charity (patient)

- HER2+ BTC is a rare condition – not possible to do multi-arm trials
- Patients report stable utility throughout disease, until rapid deterioration before death – would support time-to-death utility approach
- Model should consider possibility of response, re-staging and curative surgery
- Grade 1+2 adverse events can have significant effect on quality of life
- Agree with committee's conclusions on the benefits of zanidatamab for carers

Web comments (2 responses, both NHS clinicians [including a clinical expert from ACM1])

- Poor outcomes of HER2+ BTC and unmet need for treatments
- Long-term survival benefit likely due to zanidatamab and not subsequent treatments
- Positive results of a real-world expanded access programme for zanidatamab*
- New evidence that HER2 is associated with worse outcomes in BTC (unpublished)
- Reiterate small eligible population and low decision risk

*Note that this study was described in the company's submission.

ACM1, appraisal committee meeting 1; BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2.

Summary of consultation responses received (2/2)

Jazz Pharmaceuticals (company)

Committee's preferred assumptions at ACM1:

- Disagree with committee's preferred assumptions for survival extrapolation, time-on-treatment, and approach to estimate utility values

Uncertainties (subsequent treatments, naive comparison and QoL):

- Disagree with the committee's assessment of the uncertainties, present further evidence to support generalisability of the trial, cite real-world evidence

Requested analysis:

- Provide both treatment-specific and non-treatment-specific utility values
- Provide updated costs for cardiac monitoring

Other analysis:

- Present distributional cost-effectiveness analysis to quantify health inequalities effect
- Include carer QALYs in base case

ACM1, appraisal committee meeting 1; QALY, quality-adjusted life year.

Large ICER impact

ACM1 assumptions: progression-free + overall survival

ACM1 committee preferred assumptions

- Company's expert elicitation suggested <10% survival at 5 years with zanidatamab
- Committee note that naïve comparison and non-NHS subsequent treatments add uncertainty
- Committee concerned that the log-logistic OS curve was too optimistic in the long term
- So, chose gamma OS curve – more pessimistic than company's log-logistic in long term, but this reduced some of the uncertainty in the appraisal
  - ↳ Committee considered EAG's log-normal OS curve as a plausible optimistic scenario
- Log-normal PFS curve chosen to avoid OS/PFS curves crossing in long-term

Company response:

- Gamma OS is too pessimistic and use of log-normal PFS does not avoid crossing issue
- Committee selected more pessimistic survival estimations than comparable 2L BTC appraisals – clinical advice expects similar survival between different targeted treatments for 2L BTC
- Highlight analysis of subsequent treatments + positive real-world evidence that support benefit

EAG: Maintain that log-normal OS curve better reflects long-term clinical expectation

Web comments: New, unpublished evidence that HER2 is prognostic factor in BTC – favourable to zanidatamab in naïve comparison as comparator trial did not specify HER2 in eligibility criteria

What is the committee's preferred PFS and OS extrapolation?

Abbreviations in notes.

Medium ICER impact

ACM1 assumptions: Zanidatamab time on treatment

ACM1 committee preferred assumptions

- Company's gamma ToT curve for zanidatamab lacked face validity – without a cap, ToT exceeded PFS for a significant period, before steeply decreasing
- Log-normal ToT curve meant higher % people in PFS remained on treatment for longer

Company response:

- All ToT curves exceed PFS at some point – capping in the model prevents this
- In HERIZON-BTC-01, all patients stopped by 3 years

EAG: Company's approach suggests increasing rate of discontinuation from zanidatamab prior to progression

- Zanidatamab's favourable toxicity and lack of stopping rule suggests people would continue on treatment when progression-free and experiencing benefit

- Clinical experts – do you expect people will be on treatment at 5 years? Would a 3-year stopping rule be appropriate?
- What is the committee's preferred ToT extrapolation?

ToT curve (PFS curve)	% PFS on treatment		
	1 y	2 y	5 y
Gamma* (Log-logistic)	[redacted]	[redacted]	[redacted]
Log-normal† (Log-logistic)	[redacted]	[redacted]	[redacted]
Log-normal‡ (Log-normal)	[redacted]	[redacted]	[redacted]

[redacted]

Proportion of progression-free who are on treatment (uncapped)

*Company's preferred gamma ToT curve and log-logistic PFS curve
†EAG's preferred log-normal ToT curve and log-logistic PFS curve
‡Committee's preferred log-normal ToT and log-normal PFS curve

PFS, progression-free survival; ToT, time on treatment.

Small ICER impact

ACM1 assumptions: Utility estimation approach

ACM1 committee preferred assumptions

- Merits to both progression-based and time-to-death, but limitations with time-to-death included:
  - ↳ The difference in time in progressed disease between zanidatamab and comparators meant lower utility values (from being close to death) were applied in comparator progression-free
  - ↳ There were a small number of high utility observations close to death – lacked face validity
- Greater internal consistency in the model using progression-based

AMMF – The Cholangiocarcinoma Charity (patient)

- Patients with BTC report stable utility throughout condition until rapid deterioration before death

Company response:

- Time-to-death utilities applied regardless of progression status – incorrect to say lower utility values applied in progression-free state for comparators
- High utility before death is known phenomenon and does not undermine time-to-death

EAG:

- Time-to-death method means QALYs generated in FOLFOX PFS are reduced – but the same is not true for zanidatamab (due to a significantly longer time in progressed disease for zani.)
- Restate preference for progression-based utilities

What is the committee's preferred utility estimation approach?

BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival; QALY, quality-adjusted life year.

Small ICER impact

Requested analysis: Utility values (1/2)

ACM1 committee requested analysis

- Company's base case included treatment-specific disutility, admin disutility, and AE disutility
- Two scenarios requested to better reflect expected quality of life benefit of zanidatamab:
  - ↳ Treatment-specific utility values that are fully justified
  - ↳ Non-treatment-specific utility values with simplified disutilities to avoid double-counting

Company response:

- For treatment-specific, ABC-06 IPD not available, but baseline and 4-month utility values reported
  - ↳ Assuming baseline utility is progression-free, and 4-month utility is combination of progression-free + progressed utility, progressed utility can be calculated
- Alternative approach, simplify disutilities by only applying the treatment-specific disutility from ACM1 (and not admin or AE disutilities) – this is the company's preferred approach
  - ↳ Reiterate that only accounting for AEs and admin is insufficient to capture FOLFOX disutility

*Treatment-specific **utility** values*

Health state	Zani.	FOLFOX	ASC
Progression-free	[redacted]	0.77	0.75
Progressed disease	[redacted]	0.41	0.47

*Treatment-specific **disutility** values*

Health state	Zani.	FOLFOX	ASC
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

NICE AE, adverse event; ASC, active symptom control; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IPD, individual patient data.

Small ICER impact

Requested analysis: Utility values (2/2)

ACM1 committee requested analysis

- Company's base case included treatment-specific disutility, admin disutility, and AE disutility
- Two scenarios requested to better reflect expected quality of life benefit of zanidatamab:
  - ↳ Treatment-specific utility values that are fully justified
  - ↳ Non-treatment-specific utility values with simplified disutilities to avoid double-counting

EAG:

- Approach to estimate treatment-specific utilities requires assumption that baseline utility is equal to progression-free utility
- Baseline utility in ABC-06 was assessed *before* treatment started – so may miss any benefits (e.g. remaining progression-free) or negatives (e.g. adverse events)
- Agree that company's revised approach is reasonable, provide scenario where treatment-specific disutility is only applied in PFS

NICE tech team:

- Previous 2L BTC appraisals with FOLFOX comparator have used non-treatment-specific utilities, with disutilities for AEs and administration, but no treatment-specific disutility

What are the committee's preferred utility values?

NICE AE, adverse event; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survival.

Small ICER impact

Requested analysis: Cardiac monitoring costs

ACM1 committee requested analysis

- Committee asked that the company update the model with costs for ECG and echocardiography that were most reflective of NHS practice

Company response:

- Updated model to include ECG cost from NHS reference costs 2023/24
- Applied before + after each treatment

EAG:

- Company's cost for ECG is average of all settings – instead, prefer to use reference cost for when ECG would be directly accessed during FOLFOX treatment and would not require a further appointment
- Apply cost twice per course of FOLFOX treatment, at start and end

	Echo. (zanidatamab)	**ECG** (FOLFOX)
Company	£116	£118 (average of all attendances)
EAG	£116	£54 (directly accessed diagnostic services)

What are the committee's preferred costs and frequency for cardiac monitoring?

NICE ECG, electrocardiogram; Echo., echocardiogram; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

Medium ICER impact

Other analysis: Carer quality-of-life

ACM1 committee considerations

- Patient experts noted the significant burden on carers for people with BTC
- Committee agreed that zanidatamab was likely to have a positive impact on carers
- Committee had not seen robust quantitative evidence, so chose to consider this qualitatively

Company response:

- Updated base case includes 'multiplier approach' to capture carer utility
- Apply multiplier of 0.16 to patient QALYs to get carer QALYs – then add both together

EAG: 0.16 multiplier taken from study of patients with long-term after-effects of meningitis and their carers – uncertain whether this is transferable to BTC

  ↳ Company approach from Pennington 2026 – which considers multiple approaches for determining carer utility, not clear why chosen method and value is most appropriate here

- EAG not aware of studies looking at carer utility impacts in a relevant population
- Prefer to capture carer quality of life qualitatively so remove from base case

NICE tech team: "*Manual 4.3.17: When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health related quality of life and how the technology affects carers… Preference for EQ-5D*"

How would the committee prefer to consider carer quality of life?

BTC, biliary tract cancer; EQ-5D, Euroqol-5-dimensions; QALY, quality-adjusted life year.

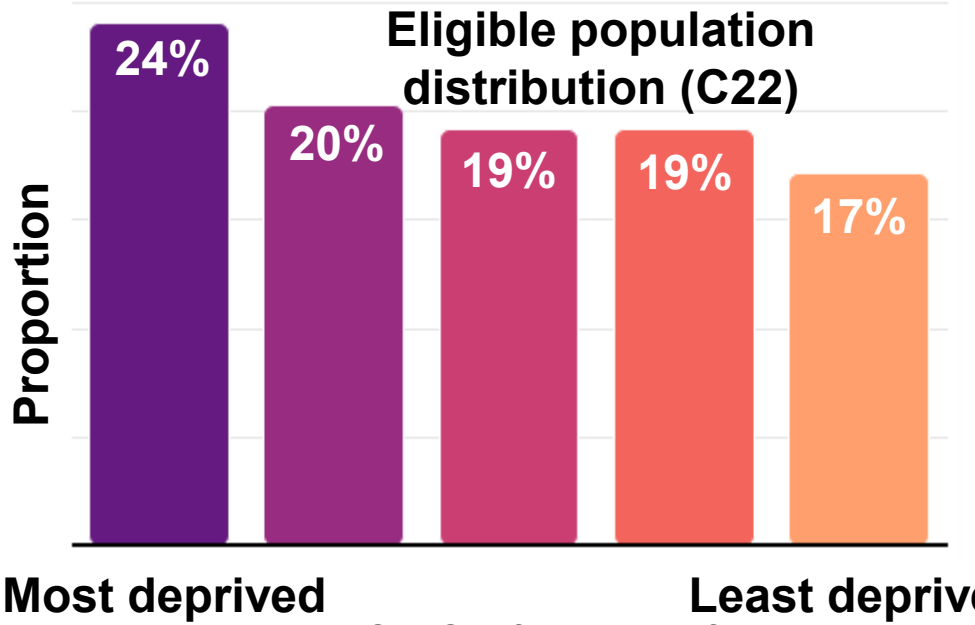
Other analysis: Distributional cost-effectiveness analysis (DCEA)

Company:

- Cite study showing higher incidence and mortality of BTC in the population group with highest socioeconomic deprivation
- Present a DCEA to quantify benefit of zanidatamab on this health inequality
- ICD-10 code C22 (malignant neoplasm of liver + intrahepatic bile ducts) to model distribution

NICE tech team:

- Eligible population is small ~50 people
- Zanidatamab compared with FOLFOX has a net health inequality benefit (NHIB) of [redacted] QALYs across the entire population
- Assumes flat opportunity cost gradient – equally distributed across social groups
- NHIB negative for moderate + steep gradients



Net health inequality benefit *(30k threshold)*

Opportunity cost gradient	Company	EAG
Flat	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Steep	[redacted]	[redacted]

- Is there evidence of a significant burden of health inequalities in the eligible population?
- Is the ICD-10 code appropriate? Any difference expected with the indicated population?
- Does zanidatamab address inequality or unfairness in the societal distribution of health?

N BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ICD-10, International Classification of Diseases 10.

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
- Starting age of 62 years, 55% female (reflective of HERIZON-BTC-01)

	QALYs of people without condition	QALYs with condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Company base case				
FOLFOX + ASC	12.03	0.54	11.49	95.51%
ASC		0.37	11.66	96.92%
EAG base case				
FOLFOX + ASC	12.03	0.56	11.47	95.34%
ASC		0.39	11.64	96.76%

>95% = 1.7x QALY weight

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

ASC, active symptom control; EQ-5D, Euroqol-5-dimensions; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; ONS, Office for National Statistics; QALY, quality-adjusted life year.

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**

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Summary of differences in preferred assumptions

Assumption	Committee (ACM1)	Company base case	EAG base case
ECG frequency (FOLFOX)	No preference stated	Twice per administration	Twice per treatment course
ECG cost	Cost reflective of NHS	£118 (average of all settings)	£54 (directly accessed services)
FOLFOX RDI	78% Not specified whether to acquisition, admin or both	78% Applied to acquisition costs	78% Applied to acquisition and administration costs
Carer QoL	Consider qualitatively	0.16 multiplier	Consider qualitatively
Zanidatamab OS curve	Gamma	Log-logistic	Log-normal
Zanidatamab PFS curve	Log-normal	Log-logistic	Log-logistic
Zanidatamab ToT curve	Log-normal	Gamma	Log-normal
Utility approach	Progression-based	Time-to-death	Progression-based

NICE ECG, electrocardiogram; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RDI, relative dose intensity; ToT, time on treatment.

Committee decision making slide

Assumption	Question for committee
Survival analysis	What is the committee's preferred PFS and OS extrapolation?
Time on treatment	• Clinical experts – do you expect people will be on treatment at 5 years? Would a 3-year stopping rule be appropriate? • What is the committee's preferred ToT extrapolation?
Utility values	• What is the committee's preferred utility estimation approach? • What are the committee's preferred utility values?
Monitoring costs	What are the committee's preferred costs and frequency for cardiac monitoring?
Carer QoL	How would the committee prefer to consider carer quality of life?
Health inequalities	• Is there evidence of a significant burden of health inequalities in the eligible population? • Is the ICD-10 code appropriate? Any difference expected with the indicated population? • Does zanidatamab address inequality or unfairness in the societal distribution of health?
Other factors	• Is it appropriate to apply a 1.7 QALY weighting for severity? • 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?

NICE

ECG, electrocardiogram; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RDI, relative dose intensity; ToT, time on treatment.

Results – cost-effectiveness ranges

Due to confidential prices for treatments in the model, 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

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

Supplementary appendix

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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)

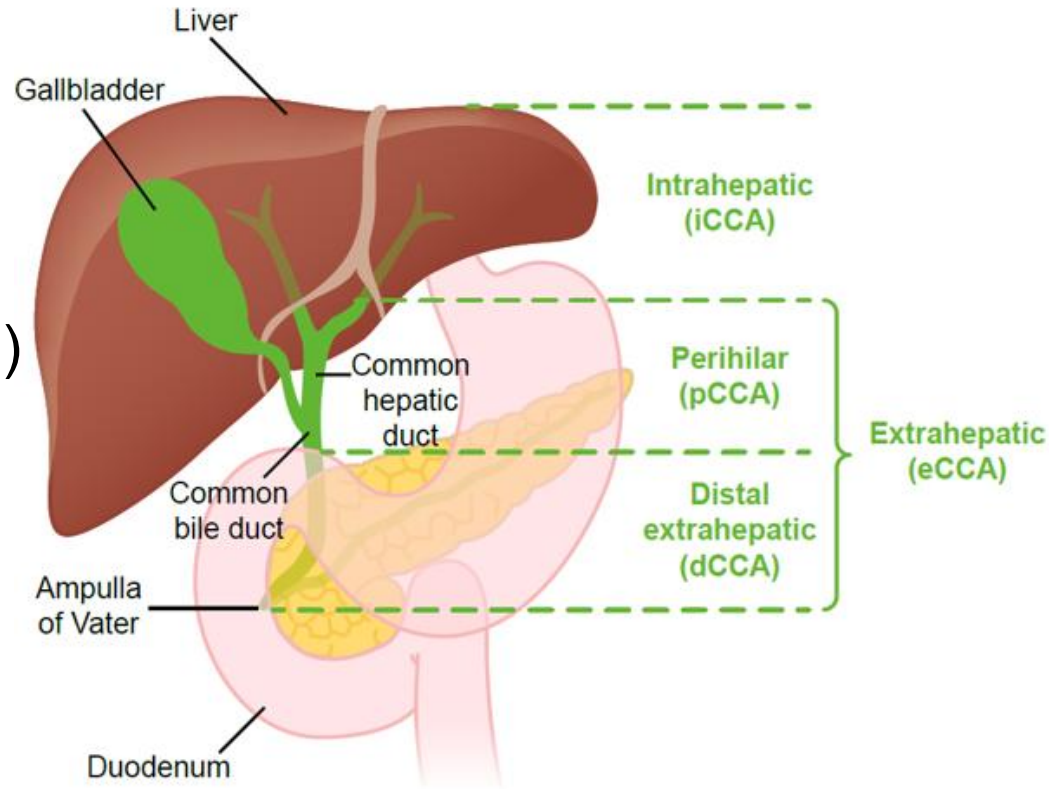
Epidemiology

- ~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



NICE

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.

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

Unanchored MAIC

- 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.

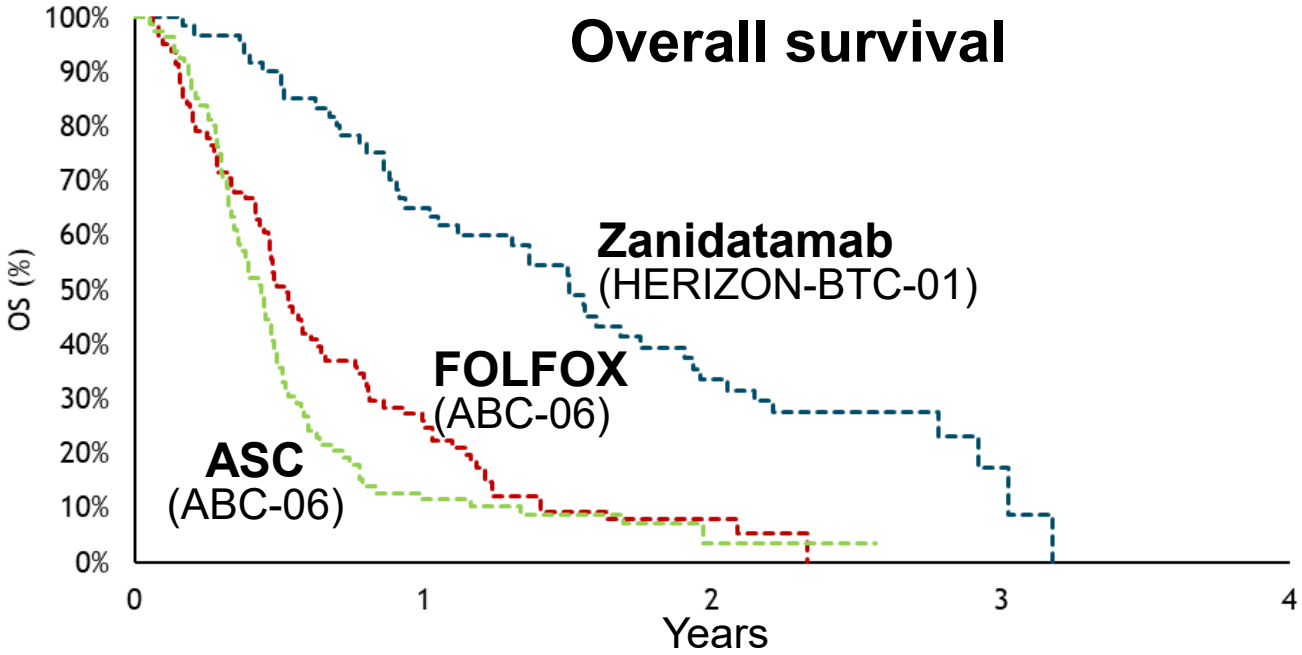
Naïve comparison

Naïve comparison shows PFS and OS benefit for zanidatamab

Progression-free survival

[redacted]

Overall survival



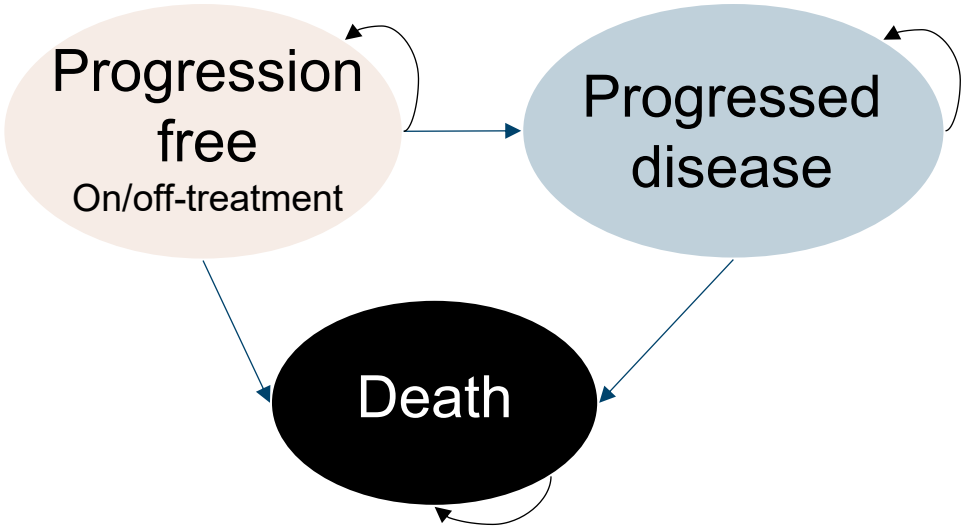
	Zanidatamab	FOLFOX + ASC
Median PFS (INV) months (95% CI)	[redacted]	**4.0** (3.2, 5.0)
6-month PFS, %	[redacted]	32.1
12-month PFS, %	[redacted]	8.6

	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.

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

Back to main deck

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	7 y	10 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

Committee ACM1: prefer gamma, log-normal is optimistic scenario

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

Back to main deck

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	7 y	10 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

Committee ACM1: prefer log-normal

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

Back to main deck

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

Committee ACM1: prefer log-normal

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

Back to main deck

Utility values estimation approaches

Progression-based

	HERIZON-BTC-01, IHC3+ sub-pop. (N=62)	Durvalumab, TA944 (N=806)	McCarthy et al, TA 914 (Cholangio-carcinoma) (N=Not reported)
PF	[redacted]	0.797	0.805
PD	[redacted]	0.679	0.702

Time to death (TTD)

[redacted]

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

Back to main deck

Company's treatment-specific utility calculation

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

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

Back to main deck

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.

Back to main deck

Real-world evidence (1/2)

Design	Retrospective observational study
Population	HER2+ BTC, after 1L treatment with CisGem, with or without durvalumab • Full population: n=20 ↳ Evaluated for outcomes: n=13
Intervention	Zanidatamab
Comparator	None
Primary outcome	Objective response rate
Secondary outcomes	OS, adverse events
Location	1 UK site

Outcome	N=13
Overall response (CR+PR)	7 (54%)
Disease control rate (CR+PR+SD)	8 (62%)
Best overall response:	
Complete	2 (16%)
Partial	5 (38%)
Stable disease	1 (8%)
Mixed	1 (8%)
Progressed	4 (30%)

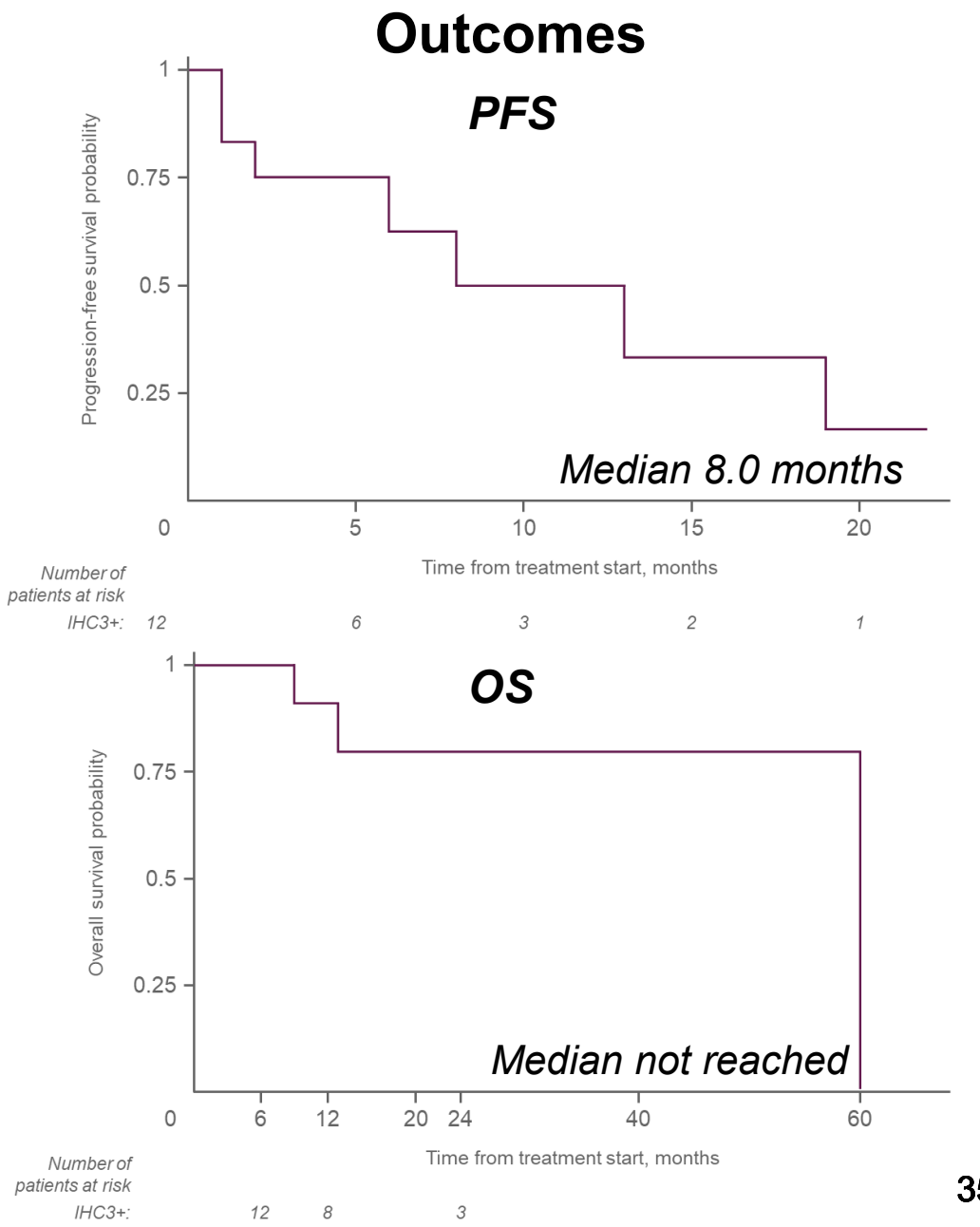
- OS not reached
- No serious adverse events

NICE 1L, 1st line; BTC, biliary tract cancer; CisGem, cisplatin and gemcitabine; CR, complete response; HER2, human epidermal growth factor receptor 2; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Back to main deck

Real-world evidence (2/2)

Design	Retrospective observational study
Population	HER2+ BTC • Full population: n=20 ↳ HER2+ IHC3+ BTC: n=12
Intervention	Zanidatamab
Comparator	None
Primary outcome	PFS
Secondary outcomes	OS, response, adverse events
Location	France



BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival.

HERIZON-BTC-01 subsequent treatment use

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

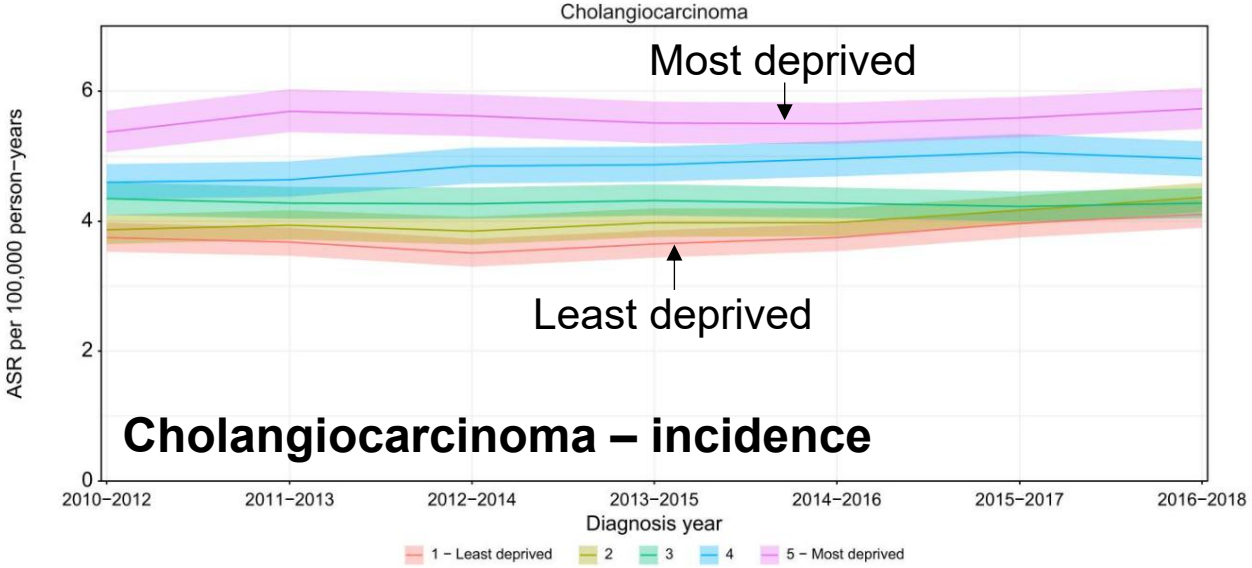
Subsequent treatment, n (%)	IHC3+ population of HERIZON-BTC-01 (n=62)
FOLFOX	[redacted]
FOLFIRI	[redacted]
Lenvatinib mesilate	[redacted]
Nivolumab	[redacted]
Pyrotinib maleate	[redacted]
All other non-therapeutic products	[redacted]
Fluorouracil	[redacted]
Sintilimab	[redacted]
Capecitabine	[redacted]
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]

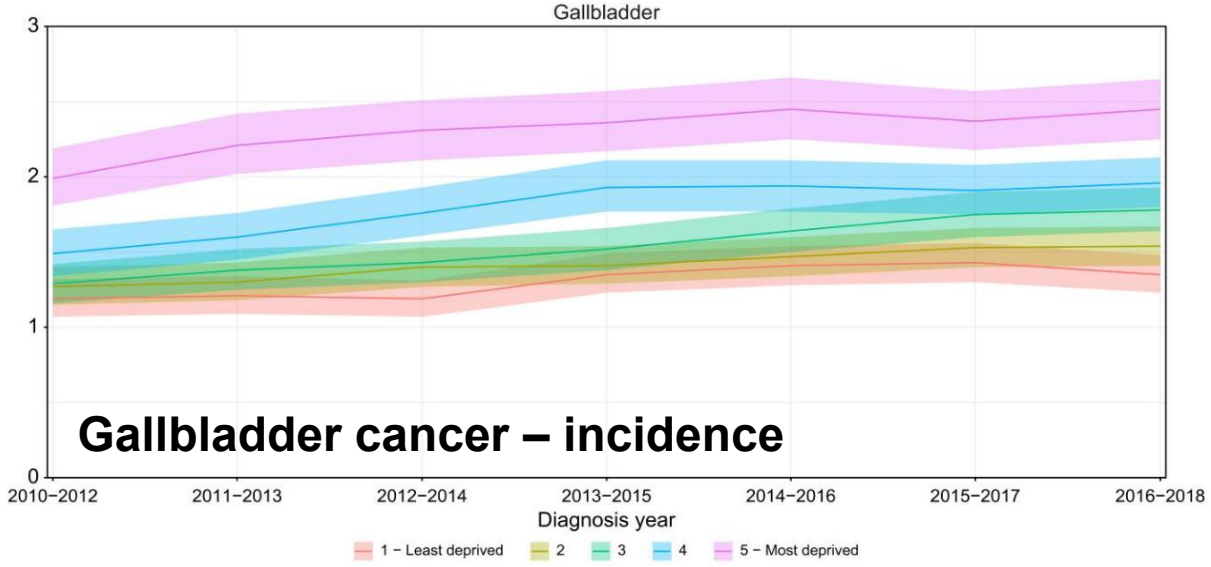
Subsequent treatment, n (%)	IHC3+ population of HERIZON-BTC-01 (n=62)
Combinations of antineoplastic agents	[redacted]
Gemcitabine hydrochloride	[redacted]
Gimeracil; oteracil potassium; tegafur	[redacted]
Herbal anticancer remedies	[redacted]
Investigational antineoplastic drugs	[redacted]
Irinotecan 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]

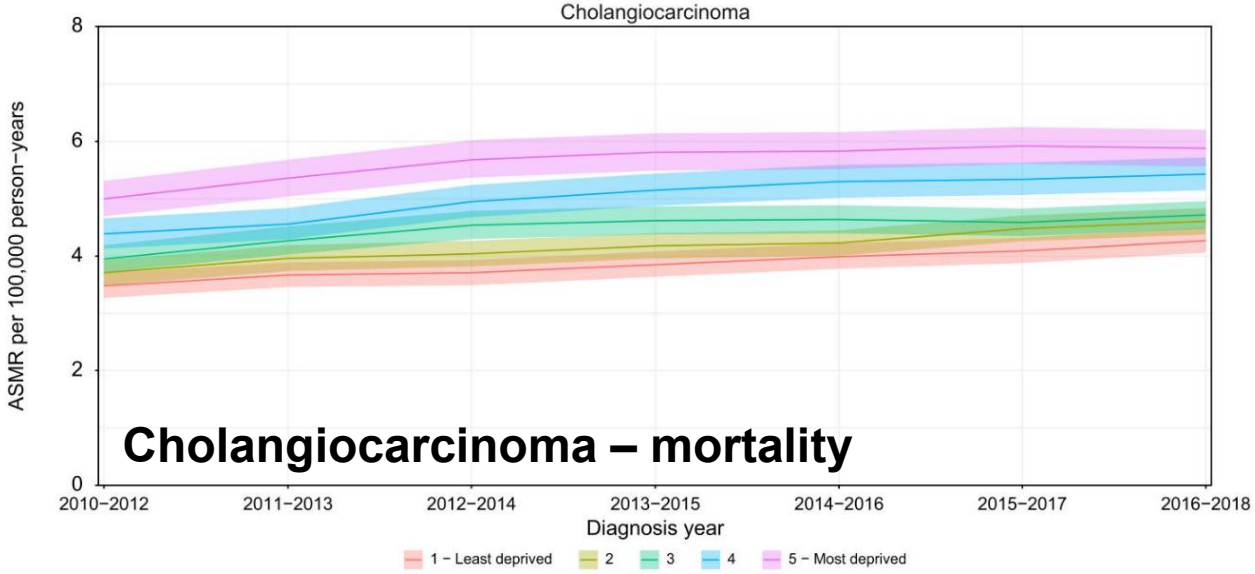
NICE FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IHC, immunohistochemistry

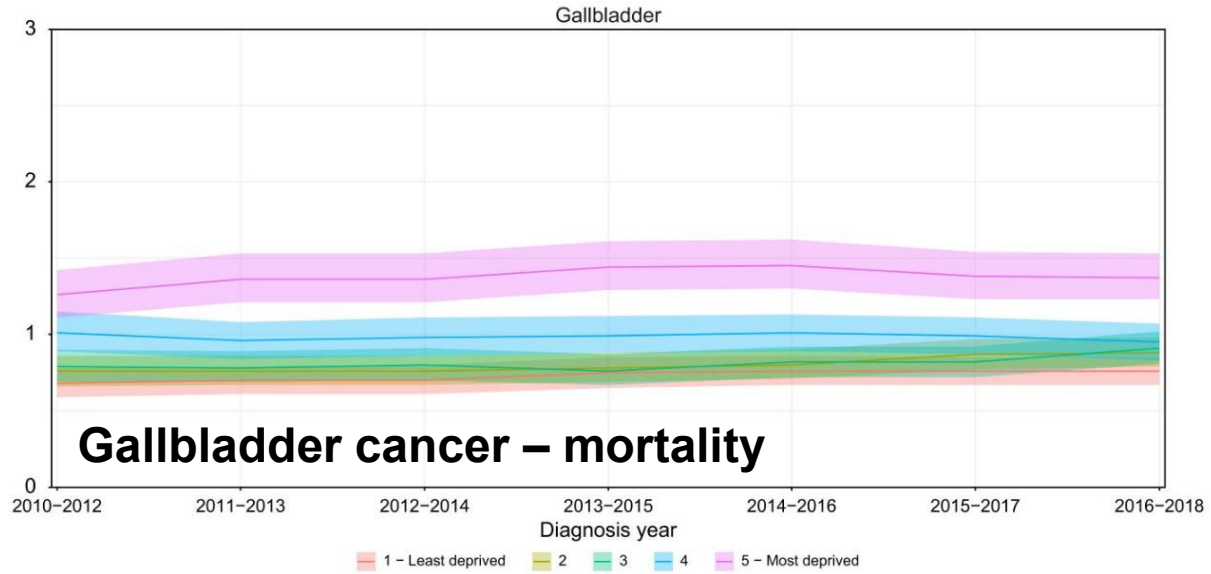
Back to main deck

DCEA: Evidence of socioeconomic differences









NICE

Tataru D, Khan SA, Hill R et al. (2023) Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation. JHEP Rep. 2023 Dec 15;6(3):100983. doi: 10.1016/j.jhepr.2023.100983.

Back to main deck

Distributional cost-effectiveness analysis (1/4)

- Benefits and costs of new health technologies may not be equally distributed across social groups, which can impact health inequalities
- DCEA is an economic evaluation framework for synthesising evidence on health inequalities
- Determines how costs and benefits vary across population groups
- Can be used to show the potential impact of a new technology on health inequalities and specifically the health inequality gap in the general population
- Needs clear evidence of a significant burden of health inequalities in the eligible population, supported by quantitative evidence

– NICE health technology evaluations: the manual (section 4.12)

Back to main deck

DCEA inputs (2/4)

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

ICD-10, International Classification of Diseases-10; IMD, index of multiple deprivation; QALY, quality-adjusted life year

Back to main deck

DCEA outputs – company's preferred assumptions (3/4)

- NHB not positive in any scenario (as ICER above cost-effective threshold)
- NHIB positive only when assuming flat opportunity cost gradient (preferred by NICE)

Opportunity cost gradient	Measure (in QALYs)	IMD1	IMD2	IMD3	IMD4	IMD5	Total	NHIB (QALYs)
Flat	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Moderate	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Steep	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

- NHIB: population-level net modelled difference in QALY benefit between IMD1 and IMD5. If opportunity cost gradient is flat, a change in drug price does not affect NHIB
- Steeper gradients = higher proportion of opportunity cost in more disadvantaged groups

NICE

ICER, incremental cost-effectiveness ratio; IMD, index of multiple deprivation; NHB, net health benefit; NHIB, net health inequality benefit; QALY, quality-adjusted life year

Back to main deck

DCEA outputs – EAG's preferred assumptions (4/4)

- NHB not positive in any scenario (as ICER above cost-effective threshold)
- NHIB positive only when assuming flat opportunity cost gradient (preferred by NICE)

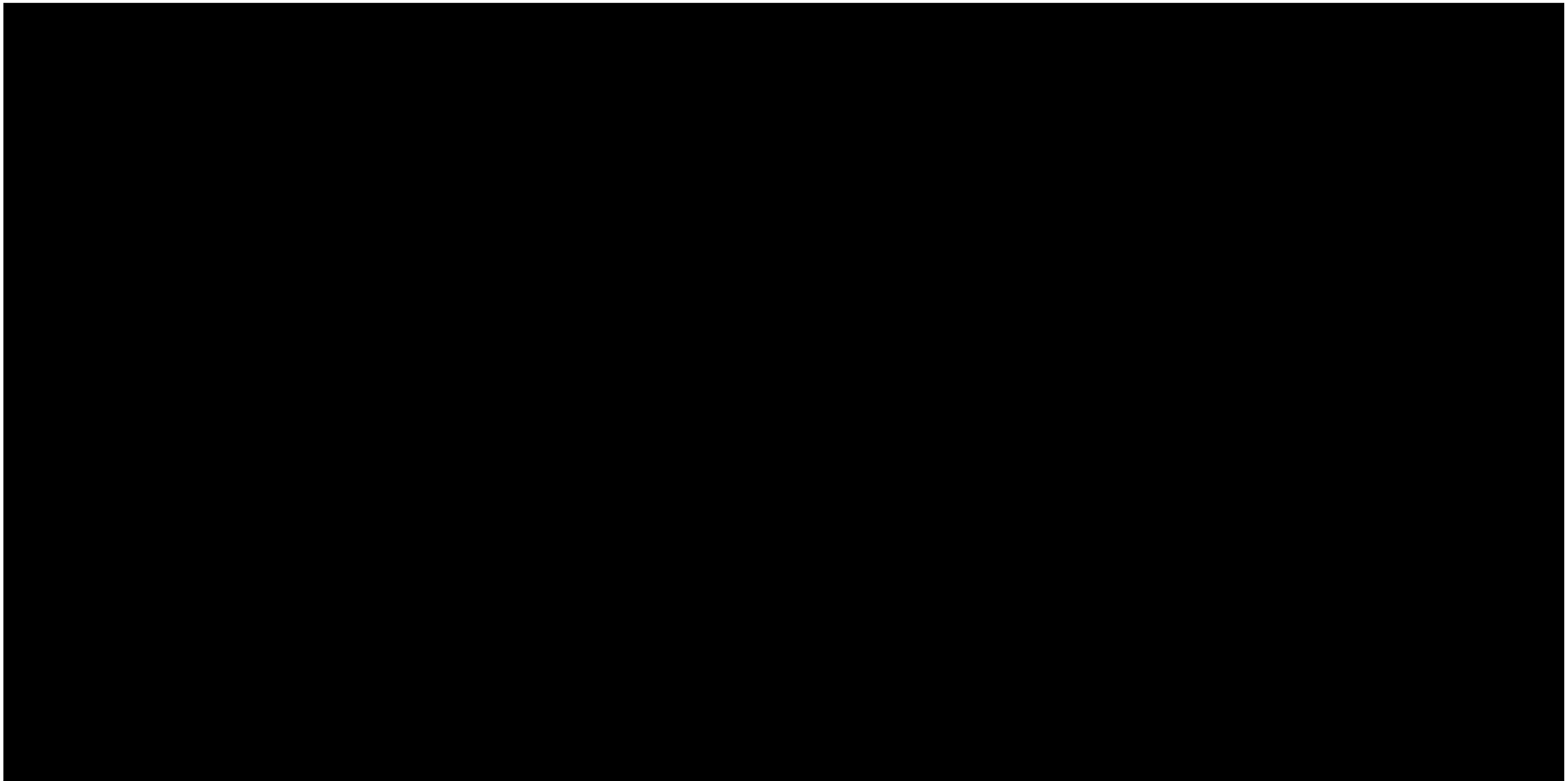
Opportunity cost gradient	Measure (in QALYs)	IMD1	IMD2	IMD3	IMD4	IMD5	Total	NHIB (QALYs)
Flat	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Moderate	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Steep	Gross health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Opportunity costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Net health benefit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

- NHIB: population-level net modelled difference in QALY benefit between IMD1 and IMD5. If opportunity cost gradient is flat, a change in drug price does not affect NHIB
- Steeper gradients = higher proportion of opportunity cost in more disadvantaged groups

NICE ICER, incremental cost-effectiveness ratio; IMD, index of multiple deprivation; NHB, net health benefit; NHIB, net health inequality benefit; QALY, quality-adjusted life year

Back to main deck

HERIZON-BTC-01: overall survival by first subsequent treatment



NPT, non-protocol therapy.

HERIZON-BTC-01: overall survival by prior anti-PD-1/PD-L1 use

IHC, immunohistochemistry; PD-L1, programmed death ligand 1

Patient testimony on quality-of-life benefits of zanidatamab (1/2)

"For me it has been life-altering and literally life-saving. I was out of options with current treatments and was given only a few months to live as my cancer was so aggressive. I have hardly any side effects compared to other treatments and feel better and better each day. My cancer is continuing to shrink in size... I am able to live a normal life and no longer feel completely defined by my cancer."

"My mother has had 4 years of good quality life due to [zanidatamab]. She regained her independence... she has had some time to recover from her year on chemo... I was able to return to work and … able to maintain my job at 80% LTFT and look after my family."

"My outlook on life has changed, as I can now see/hope for a long-term future. I don't worry so much about my wife becoming incidentally ill as this treatment is not so aggressive on the immune system compared to other treatments."

"[Zanidatamab] gave me my life back. There are almost no side effects apart from mild gastric issues occasionally. I stay in excellent health and have done throughout my time on this treatment. I am back at work and feel strong mentally and physically. My quality of life is excellent: people would think there was nothing wrong with me..."

Patient testimony on quality-of-life benefits of zanidatamab (2/2)

"[Zanidatamab] changed everything for [my wife] and for our family. She was quickly independent again and everyone felt better. [My wife] is back to full strength and lives a normal life with a busy social life and family life: a thing we thought we had lost…She experiences little or no side effects."

"From our experience, [my partner] has less side effects than the Gem/Cis/Durva treatment. The infusion time is quicker … He has more energy, and our lives are far more 'normal' since he started the zanidatamab treatment. [He] has also been able to go back to work part-time."

"I feel the advantage for this treatment is that there are a lot fewer side effects compared to chemotherapy alternatives... It has also improved my quality of life, reducing my tumour size significantly and improving my pain (I have reduced my pain medication significantly since starting zanidatamab)."