PCR203

Quality-Adjusted Time Without Symptoms or Toxicity Estimates in Previously Treated HER2-Positive Biliary Tract Carcinoma Using the Zanidatamab HERIZON-BTC-01 Study

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Background

- Biliary tract cancer (BTC) is a rare, heterogenous group of tumours that is frequently diagnosed at an advanced stage and is associated with a poor prognosis[1]
- Zanidatamab is a dual human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody that received accelerated approval by the US Food and Drug Administration and conditional marketing approval by the European Medicines Agency for the treatment of previously treated patients with HER2-positive BTC (immunohistochemistry [IHC] 3+) on the basis of the HERIZON-BTC-01 trial[1-4]
- In the global, single-arm, phase 2b HERIZON-BTC-01 trial (NCT04466891), 87 patients aged ≥18 years with *HER2*-amplified, locally advanced, unresectable or metastatic BTC and ≥1 prior treatment with gemcitabine-containing systemic chemotherapy were treated with zanidatamab (20 mg/kg intravenously every 2 weeks [Q2W])[1]
  - The primary endpoint was confirmed objective response rate
  - Overall survival (OS), progression-free survival (PFS), and the incidence and severity of adverse events (AEs) were assessed as secondary endpoints
- In the HERIZON-BTC-01 trial, zanidatamab monotherapy demonstrated rapid and durable responses in 80 patients with previously treated, unresectable or metastatic HER2-positive BTC (defined as *HER2*-amplified and IHC 3+ or IHC 2+)[1,5]
  - The median OS was 15.5 months in patients with HER2-positive BTC and 18.1 months in the IHC 3+ subgroup
- The safety profile of zanidatamab was manageable, with a low incidence of high-grade and serious treatment-emergent AEs and few treatment discontinuations due to AEs[1]
- The quality-adjusted time without symptoms or toxicity (Q-TWiST) method provides a framework for evaluating the trade-offs between survival, quality of life (QoL), and treatment side effects in a single metric.[6,7] Therefore, evaluating Q-TWiST in HERIZON-BTC-01 provides an additional level of assessment of the benefits and risks associated with zanidatamab treatment

Objective

- The objective of this research was to perform a Q-TWiST analysis of zanidatamab using HERIZON-BTC-01 trial data

Methods

- Q-TWiST integrates patient survival and QoL by partitioning patient survival time into 3 key health states
  1. TOX – time spent experiencing treatment-related toxicity
  2. TWiST – time without symptoms of disease or treatment-related toxicity
  3. REL – time following disease progression (ie, relapse), often associated with a notable deterioration in QoL compared with time before progression
- Duration in each state was calculated using Kaplan-Meier analysis to estimate restricted mean survival time (RMST) on AEs, OS, and PFS. The restricted time was set to the longest individual duration for each state to incorporate the full data
- As some AEs occurred concurrently, a TOX day was defined as a day where a patient experienced ≥1 grade ≥3 AE prior to progression. The TOX RMST was adjusted by scaling to the proportion (40/87) of patients with observed TOX

Figure 1. Definition of Q-TWiST Health States

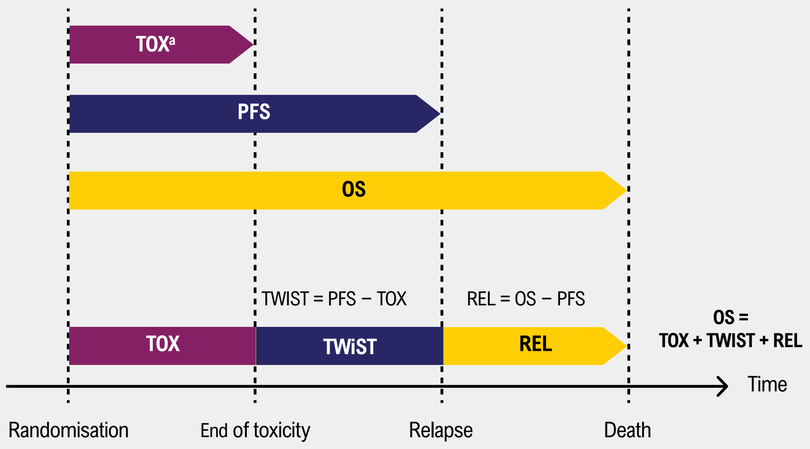


Figure adapted from Tabernero J, et al.[8]
[a]The placement of the TOX arrow bar does not indicate that toxicities occur first in a patient's PFS journey.
OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted TWiST; REL, postprogression survival; RMST, restricted mean survival time; TOX, time with treatment-related toxicity; TWiST, time without symptoms of disease or treatment-related toxicity.

- The values of TOX, TWiST, and REL states sum to the value of OS for each patient

Figure 2. Q-TWiST Equations

Equation 1

$$TWiST_{MEAN} = PFS_{RMST} - TOX_{RMST^a}$$

Equation 2

$$REL_{MEAN} = OS_{RMST} - PFS_{RMST}$$

Equation 3

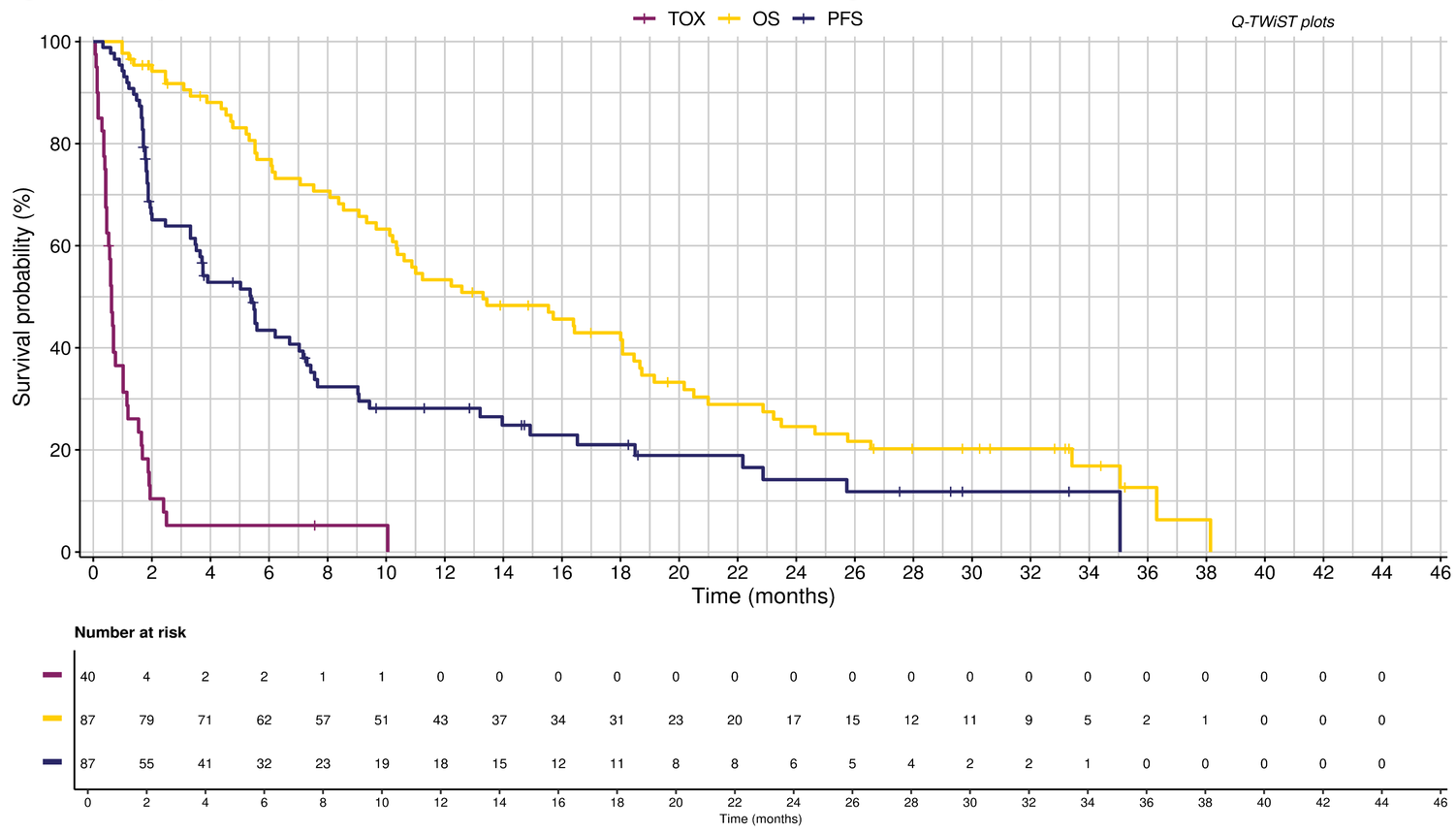
$$Q\text{-}TWiST = (U_{TOX} \times TOX) + (U_{TWiST} \times TWiST) + (U_{REL} \times REL)$$

[a]RMST for TOX adjusted to account for non-zero values excluded from the initial RMST calculation.
OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted TWiST; REL, postprogression survival; RMST, restricted mean survival time; TOX, time with treatment-related toxicity; TWiST, time without symptoms of disease or treatment-related toxicity; U, utility.

- TWiST duration was derived as PFS minus adjusted TOX, and REL duration was derived as OS minus PFS
- To calculate the Q-TWiST values, weights were assigned to each of the 3 health states, which are interpreted as health state utility values
- To represent the uncertainty around health state duration estimates, 1000 bootstrap samples were taken with replacement, and the average health state duration was used to construct 95% CIs
- The final Q-TWiST value was derived using the standard approach in the literature which assumes a weight (health state utility value) of 1 for the TWiST state and weights of 0.5 for the TOX and REL states as a base case[9]
- Additionally, Q-TWiST threshold analysis was performed wherein each of the REL and TOX weights were varied between 0 and 1 in 0.25 increments and all 25 combinations input into the Q-TWiST calculation
  - This method results in an increasing Q-TWiST value between the TWiST value and the OS value, which represents the range of possible Q-TWiST values

Results

Figure 3. Kaplan-Meier Estimates of OS, PFS, and TOX – ICR Progression



ICR, independent central review; OS, overall survival; PFS, progression-free survival; Q-TWiST, quality-adjusted time without symptoms; TOX, time with treatment-related toxicity.

- The Kaplan-Meier estimate for each state was used to calculate RMST as an estimate of health state duration

Table 1. Health State RMST – ICR Progression

Health State	RMST, Months
OS	16.57
PFS	9.90
TOX[a] (unadjusted)	1.32
TOX[a] (adjusted)	0.60

[a]The unadjusted value refers to the RMST for only patients with ≥1 day of recorded TOX. The adjusted value also accounts for patients with a value of zero for TOX.
ICR, independent central review; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time; TOX, time with treatment-related toxicity.

- The adjusted RMST value was used for TOX

Table 2. Health State Durations – ICR Progression

Health State	Duration, Months
OS	16.57
PFS	9.90
TOX	0.60
TWiST	9.30
REL	6.67

ICR, independent central review; OS, overall survival; PFS, progression-free survival; REL, postprogression survival; TOX, time with treatment-related toxicity; TWiST, time without symptoms of disease or treatment-related toxicity.

- The adjusted RMST value was used for TOX. TWiST and REL values were calculated based on these RMST values using equations 1 and 2, respectively

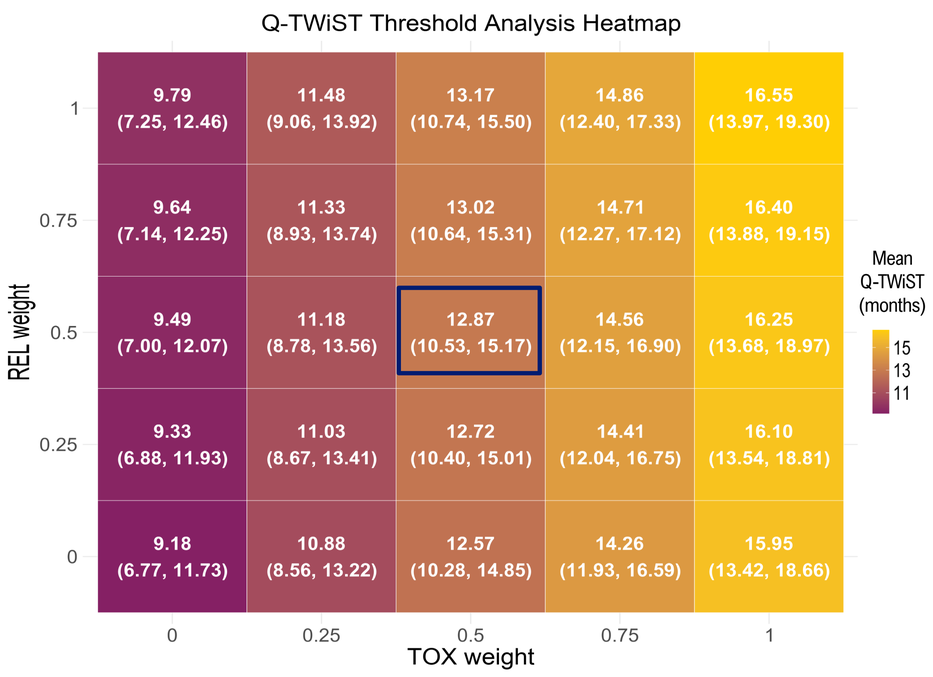
Table 3. Bootstrap Analysis Health State Durations – ICR Progression

Health State	Mean Duration, Months (95% CI)
OS	16.55 (13.97, 19.30)
PFS	9.79 (7.25, 12.46)
TOX	0.60 (0.32, 0.98)
REL	6.77 (4.61, 9.13)
TWiST	9.18 (6.77, 11.73)

ICR, independent central review; OS, overall survival; PFS, progression-free survival; REL, postprogression survival; TOX, time with treatment-related toxicity; TWiST, time without symptoms of disease or treatment-related toxicity.

- Given the random aspect of bootstrap sampling, small differences were expected in the mean values compared to using the whole data

Figure 4. Q-TWiST Threshold Analysis – ICR Progression



ICR, independent central review; Q-TWiST, quality-adjusted time without symptoms; REL, postprogression survival; TOX, time with treatment-related toxicity.

- For this analysis, TOX, REL, and TWiST mean values from the bootstrap analysis were input into the Q-TWiST formula (equation 3)
- The change in REL and TOX weights with TWiST weight set to 1 generated Q-TWiST values ranging from the mean TWiST duration to the mean OS duration
- The base case value (blue box) provided a Q-TWiST estimate for zanidatamab using data from the HERIZON-BTC-01 trial of 12.87 months (95% CI: 10.53, 15.17)
- Threshold analysis showed a broad range of Q-TWiST values; however, this was expected given that the analysis represents the range of possible values rather than those clinically plausible
  - For example, some scenarios use an estimate of average health state utility of zero for TOX or REL states, which is not plausible

Conclusions

- To the authors' knowledge, this is the first Q-TWiST analysis in a single-arm study and, based on a targeted literature review, the first Q-TWiST analysis in BTC
- The health state values derived in the Q-TWiST analysis demonstrate that considerably more PFS time was spent in the TWiST state than TOX state, highlighting zanidatamab's manageable safety and positive benefit-risk profile
- The longer TWiST vs REL duration suggests Q-TWiST was primarily driven by time spent without disease symptoms or toxicity (ie, TWiST), reflecting the notable symptom-free survival achieved by patients receiving zanidatamab
- The results of the Q-TWiST analysis should be interpreted with caution due to limitations inherent to the methodology and the specific approach employed
  - Standard Q-TWiST assumptions include disregarding lower-grade AEs in TOX calculation and assuming all qualifying AEs are treated with equal weight, regardless of their severity
  - Arbitrary utility values based on previously published examples, although necessary for the calculations, may not fully capture the true QoL impacts experienced by patients
  - Given the single-arm nature of the HERIZON-BTC-01 trial, neither the health state values nor the uncertainty around each estimate can be assessed comparatively

References: 1. Harding JJ, et al. *Lancet Oncol.* 2023;24(7):772-82. **2.** Weisser NE, et al. *Nature Commun.* 2023;14(1):1394. **3.** Jazz Pharmaceuticals, Inc. Ziihera® (zanidatamab-hrii) for injection, for intravenous use [package insert]. July 2025. Accessed 14 October 2025. https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf. **4.** Jazz Pharmaceuticals. 1 July 2025. Accessed 14 October 2025. https://investor.jazzpharma.com/node/21951/pdf. **5.** Pant S, et al. Presented at ASCO; 31 May–4 June 2024; Chicago, IL, USA. Poster 4091. **6.** Goldhirsch A, et al. *J Clin Oncol.* 1989;7:36-44. **7.** Gelber RD, et al. *J Clin Oncol.* 1986;4:1772-9. **8.** Tabernero J, et al. *ESMO Open*. 2017;2:e000284. **9.** Solem CT, et al. *Expert Rev Pharmacoecon Outcomes Res.* 2018;18:245-53.

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