4101

Survival Outcomes for Zanidatamab Compared to Chemotherapy in Previously Treated HER2-Positive (IHC 3+) Biliary Tract Cancer: HERIZON-BTC-01 vs a Real-World External Control Arm

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Background

- Biliary tract cancer (BTC) encompasses a group of aggressive tumors, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder cancer (GBC)[1,2]
- BTC has poor prognosis as most patients present with unresectable, locally advanced, and/or metastatic disease,[3] and treatment options are limited
- Historically, survival is poor with a median overall survival (OS) of 12-13 months with first-line (1L) gemcitabine-based therapies and 6-9 months for subsequent chemotherapy[4]
- Current guidelines recommend chemotherapy, such as FOLFOX (leucovorin, fluorouracil and oxaliplatin), as the second-line (2L) treatment approach for BTC following 1L chemotherapy[5]
- Zanidatamab, a dual human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody, received accelerated approval for adults with previously treated, unresectable, or metastatic HER2-positive (HER2+; immunohistochemistry [IHC] 3+) BTC based on results from the single-arm phase 2 HERIZON-BTC-01 trial[6]

Objective

- To better contextualize the HERIZON-BTC-01 trial and provide additional support for the trial data, this study compared the outcomes with zanidatamab in the HERIZON-BTC-01 trial with a real-world cohort of patients with HER2+ (IHC 3+) BTC who received 2L chemotherapy (external control arm [ECA])

Methods

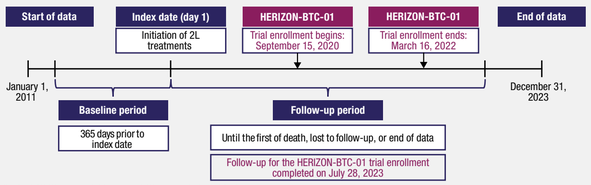
- This study compared 2 cohorts:
  - **Zanidatamab** - patients from the HERIZON-BTC-01 trial (NCT04466891) with HER2+ (IHC 3+), unresectable, locally advanced, or metastatic BTC (iCCA, eCCA, GBC) who had received prior gemcitabine-containing therapy
    - Patients had received zanidatamab 20 mg/kg intravenously every 2 weeks
  - **ECA** - constructed using data from the Flatiron Health Research Analytic Database (longitudinal, deidentified, patient-level database derived from electronic health records [EHRs] at community and academic cancer clinics in the USA)
    - Patients had received 2L chemotherapy, as defined in the database

Table 1. Key Inclusion and Exclusion Criteria From the HERIZON-BTC-01 Trial and Applied to the ECA

Inclusion Criteria	Exclusion Criteria
Evidence of iCCA, eCCA, or GBC identified from EHRs by a machine learning model and confirmed by evidence explicit documentation in physician notes	ECOG PS >1 within 6 months prior to initiation of 2L therapy
Medical record and chart-review confirmed diagnosis of locally advanced or metastatic iCCA, eCCA, or GBC	Diagnosis of metastases to brain or central nervous system site <30 days prior to 2L therapy
Received 2 or more lines of systemic therapies in the advanced disease setting, with 2L therapy initiated ⩾6 months prior to December 31, 2023, and ⩾2 distinct visits on/after January 11, 2011	
Evidence of HER2+ (IHC 3+) at any time prior to initiation of 2L therapy	

2L, second-line; ECA, external control arm; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EHR, electronic health record; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; GBC, gallbladder cancer.

Figure 1. Study Schema



Note: A total of 29,000 patients were initially assessed, with 290 patients meeting the criteria listed.
2L, second-line

Outcomes

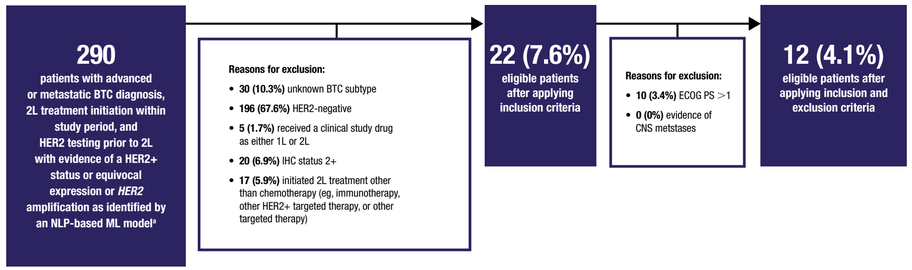
- Outcomes assessed included OS, progression-free survival (PFS), and adverse events (specifically Common Terminology Criteria for Adverse Events grade 3 or higher)
  - OS was defined as the length of time from the date the patient initiated 2L treatment to the date of death (from any cause); in the ECA cohort, death was a composite variable derived from EHR data, Social Security Death Index data, and obituary data[7]
  - PFS was defined as the length of time from the date the patient initiated 2L treatment to the date of disease progression or death from any cause. In the zanidatamab cohort, progression was determined by independent central review and investigator assessment. In the ECA cohort, disease progression was defined as a distinct episode in which the treating clinician concluded that there had been growth or worsening in the disease of interest

Statistical analysis

- Standardized mortality ratio (SMR) weighting was used to account for potential imbalance of key prognostic factors at baseline
  - Baseline variables for ECA weighting were age at 2L initiation, sex, disease subtype, and history of chronic liver disease; these factors were selected through a systematic literature review and medical insights
- Covariate balance before and after weighting was assessed using standardized mean differences
- Median survival and hazard ratios (HRs) were estimated using SMR-weighted Kaplan-Meier and Cox proportional hazards regression, respectively
  - Patients in the HERIZON-BTC-01 trial were assigned a weight of 1 to preserve the distribution of trial participants and study results
  - Patients in the ECA cohort were assigned weights based on propensity scores to make their characteristics more comparable with those of the patients in the HERIZON-BTC-01 trial

Results

Figure 2. Study Flow Diagram for the ECA Cohort



[a]A total of 29,000 patients were initially assessed.
1L, first-line; 2L, second-line; BTC, biliary tract cancer; CNS, central nervous system; ECA, external control arm; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ML, machine learning; NLP, natural language processing.

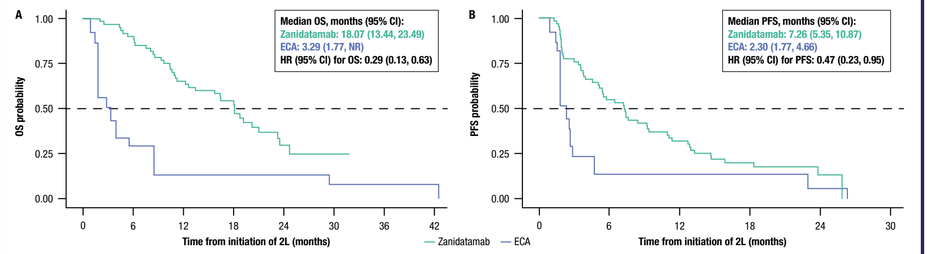
Table 2. Baseline Demographics/Clinical Characteristics Before and After Baseline Adjustment For Confounding Factors[a]

Characteristics	Before Adjustment for Baseline Confounding Factors			After Adjustment for Baseline Confounding Factors, SMR-Weighted		
	Zanidatamab (n=62)	ECA (n=12)	Standardized Mean Difference[b]	Zanidatamab (n=62)	ECA (n=62)	Standardized Mean Difference[b]
Age at 2L initiation, years (mean [SD])[b]	62.7 (9.3)	66 (8.6)	0.37	63 (9.3)	63 (8.1)	0.07
Female, n (%)[c]	34 (54.8)	8 (66.7)	0.24	34 (54.8)	34 (54.9)	0.00
Disease subtype, n (%)[c]						
GBC	33 (53.2)	9 (75.0)	-0.47	33 (53.2)	31 (50.4)	0.06
iCCA or eCCA	29 (46.8)	3 (25.0)		29 (46.8)	31 (49.6)	
History of chronic liver disease, n (%)[c]	11 (18.0)	2 (17.0)	0.03	11 (18)	7 (11)	0.20
Group stage at initial diagnosis, n (%)[d]						
Stage I-II	10 (16.7)	2 (22.2)	0.14	10 (16.7)	8 (22.2)	0.14
Stage III-IV	50 (83.3)	7 (77.8)		50 (83.3)	28 (77.8)	
Missing	2	3		2	3	
ECOG PS, n (%)[e]						
0	20 (32.3)	4 (40.0)	-0.16	20 (32.2)	15 (26.8)	0.11
1	42 (67.7)	6 (60.0)		42 (67.7)	40 (73.2)	
Missing	0	2		0	2	
Calendar year of index, n (%)						
2011-2013	0 (0)	1 (8.3)	0.82	0 (0)	5 (7.3)	0.58
2014-2016	0 (0)	0 (0)		0 (0)	0 (0)	
2017-2019	0 (0)	2 (16.7)		0 (0)	6 (10.4)	
2020-2023	62 (100)	9 (75.0)		62 (100)	51 (82.3)	

[a]Percentages were calculated based on the number of patients with available data for each characteristic, except for comorbidities. Patients from the HERIZON-BTC-01 cohort were assigned a weight of 1 while patients in the ECA cohort were weighted. [b]Multinominal SMDs were calculated using Mahalanobis distance as suggested by Yang et al (2015); [c]Covariate included in the propensity score model used to generate the SMR weights; [d]Data were missing for 2 patients in the zanidatamab cohort and 3 patients in the ECA cohort before adjustment for baseline confounding; [e]Data were missing for 2 patients in ECA cohort, before and after adjustment for baseline confounding.
2L, second-line; ECA, external control arm; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; SD, standard deviation; SMR, standardized mortality ratio.

- Approximately 29,000 patients had evidence of a BTC diagnosis in the Flatiron Health's Research Analytic Database
  - As BTC is a rare cancer, and testing for HER2 overexpression is not universally conducted, there was a small eligible population for the ECA cohort, with only 12 patients included (**Figure 2**)
- Systemic treatments observed as 2L chemotherapy in the ECA cohort included fluorouracil, leucovorin, oxaliplatin, capecitabine, irinotecan, irinotecan liposomal, cisplatin, gemcitabine, paclitaxel, carboplatin, and docetaxel
- Patients in the zanidatamab and ECA cohorts had similar mean age at 2L initiation and similar history of chronic liver disease; both cohorts had >75% of patients with stage III/IV disease (**Table 2**)
- There was a higher proportion of female patients, patients with GBC, and a higher burden of comorbidities overall in the ECA vs the zanidatamab cohort (**Table 2**)
- Most patients in the zanidatamab cohort were Asian, but no Asian patients were reported in the ECA cohort

Figure 3. SMR-Weighted (A) OS and (B) PFS



Dotted line shows median overall survival.
2L, second-line; CI, confidence interval; ECA, external control arm; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio.

- Zanidatamab, compared to the ECA cohort, had longer median OS (18.07 vs 3.29 months) and median PFS (7.26 vs 2.30 months) (**Figure 3A and B**)
- Adjusted HRs (95% CIs) for OS and PFS were 0.29 (0.13, 0.63) and 0.47 (0.23, 0.95), respectively (**Figure 3A and 3B**)

Table 2. 6- and 12-Month Survival Proportions and Differences

	6 Months		12 Months	
	Survival	Difference in Survival	Survival	Difference in Survival
OS, % (95% CI)				
Zanidatamab	90 (83, 98)	61 (32, 90)	65 (54, 78)	52 (29, 74)
ECA	29 (11, 75)		13 (3, 55)	
PFS, % (95% CI)				
Zanidatamab	55 (44, 69)	41 (20, 62)	32 (22, 46)	18 (-2, 39)
ECA	14 (4, 47)		14 (4, 47)	

CI, confidence interval; ECA, external control arm; OS, overall survival; PFS, progression-free survival.

- At 6 and 12 months after initiation of 2L treatment, OS and PFS rates were higher in the zanidatamab vs the ECA cohort

Table 3. Documented Grade 3 AEs in the ECA Cohort[a]

Adverse events	ECA
Hematologic function, n (%)	
Anemia	0 (0)
Lymphopenia	0 (0)
Neutropenia	1 (12.5)
Thrombocytopenia	1 (10)
Maximum change in neutrophil-lymphocyte ratio, median (25th, 75th percentile)	0.91 (-0.51, 3.32)
Liver function, n (%)	
Alkaline phosphatase increase	1 (9.1)
Alanine aminotransferase increase	1 (10)
Aspartate aminotransferase increase	2 (18.2)
Blood bilirubin increase	2 (18.2)
Kidney function, n (%)	
Hypoalbuminemia	0 (0)
Creatinine increase	0 (0)
Maximum change in lactate dehydrogenase, median (25th, 75th percentile)	175 (175, 175)

[a]AEs are defined according to CTCAE.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECA, external control arm.

Limitations

- The small sample size of HER2+ (IHC 3+) BTC patients on 2L chemotherapy limited the ability to implement all the eligibility criteria from the HERIZON-BTC-01 trial and to adjust for all relevant prognostic factors in the ECA cohort. Therefore, the main analysis focused on maximizing comparability while maintaining sample size
- The ECA cohort did not include patients from Asia, while the majority of patients (63%) in the zanidatamab cohort were Asian; however, a subgroup analyses of HERIZON-BTC-01 by geographic region demonstrated relatively similar objective response rates between Asians and non-Asians[6]
- Sufficient precision to assess overall survival improvements with zanidatamab vs 2L chemotherapy in the IHC 3+ population was anticipated; however, due to smaller differences in outcomes, precision was insufficient to detect survival benefits compared with other HER2 agents

Conclusions

- Among patients with previously treated HER2+ (IHC 3+) BTC, the zanidatamab cohort experienced longer survival and PFS compared to the chemotherapy (ECA) cohort
  - The zanidatamab cohort had a median OS over 14 months longer than that of the ECA cohort
- OS of patients with HER2+ (IHC 3+) who received chemotherapy was consistent with previously reported OS for chemotherapy in 2L BTC[8]

References: 1. ten Haaft BH, et al. *Eur J Cancer.* 2024;199:113564. **2.** Valle JW, et al. *Lancet.* 2021;397(10272):428-444. **3.** Cillo U, et al. *Liver Int.* 2019;39(Supplement 1):143-155. **4.** Koshiol J, et al. *BMC Cancer.* 2022;22(1):1178. **5.** Rizzo A, et al. *Curr Oncol.* 2022:29(2):551-564. **6.** Harding JJ, et al. *Lancet Oncol.* 2023;24(7):772-782. **7.** Curtis MD, et al. *Health Serv Res.* 2018;53(6):4460-4476. **8.** Lamarca A, et al. *Lancet Oncol.* 2021;22(5):690-701.

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