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Landmark Analysis of Overall Survival by Objective Response in Patients With Previously Treated, Advanced HER2-Positive Biliary Tract Cancer: Post Hoc Analysis of the HERIZON-BTC-01 Trial

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Plain Language Summary

Why did we perform this research?

- People with advanced biliary tract cancers that have increased levels of a protein called HER2 do not have many treatment options and often have poor outcomes
- Zanidatamab is a medicine that targets HER2 and was recently approved in the US, the European Union, and China for use in patients who have advanced biliary tract cancer with increased levels of HER2 and have had their disease get worse after receiving at least 1 prior treatment

How did we perform this research?

- This analysis looked at whether patients who were treated as part of a clinical trial and had tumors shrink in response to zanidatamab treatment survived longer than those patients whose tumors did not shrink

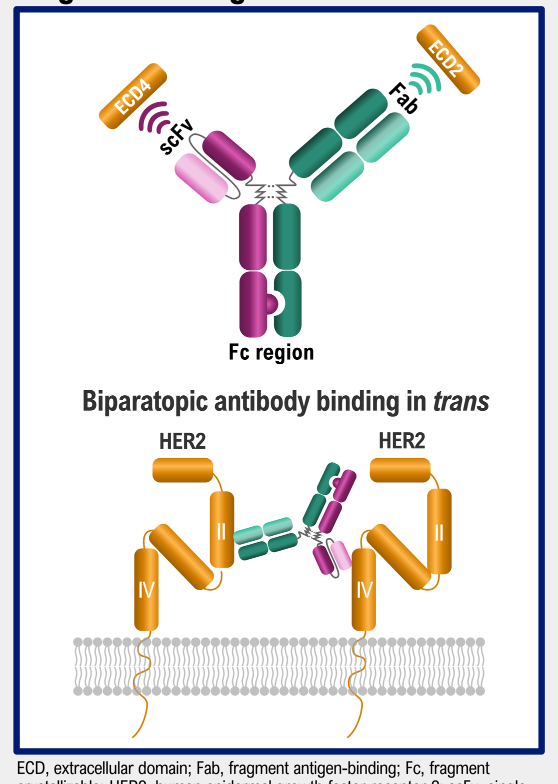
What were the results of this research?

- This follow-up analysis showed that patients with tumors that shrunk with zanidatamab treatment lived longer than patients with tumors that did not shrink
- Patients with tumors that did not shrink but also did not grow after 9 weeks of treatment lived longer than patients with tumors that grew despite zanidatamab treatment

Background

- Biliary tract cancer (BTC) is a heterogeneous group of rare (<1% of cancers worldwide) and aggressive gastrointestinal malignancies that includes gallbladder cancer (GBC) and intra- and extrahepatic cholangiocarcinoma (iCCA and eCCA, respectively)[1-3]
  - Median overall survival (OS) is typically <13 months with first-line therapies and 6 to 9 months for second-line chemotherapy[4,5]
- Human epidermal growth factor receptor 2 (HER2) protein overexpression and/or gene amplification, occurring in a subset of BTC cases (GBC: 19%–31%; iCCAs: 4%–5%; eCCAs: 17%–19%),[6,7] are actionable in BTC and represent a therapeutic target
- Zanidatamab is a dual HER2-targeted bispecific antibody that binds to extracellular domains 2 and 4 on HER2 in a *trans* configuration[8]
  - This biparatopic binding enables zanidatamab to crosslink neighboring HER2 proteins, leading to receptor clustering
  - In preclinical studies, zanidatamab enhanced HER2 internalization, reduced downstream signaling, and promoted immune-mediated cytotoxicity (complement-dependent cytotoxicity, as well as antibody-dependent cellular cytotoxicity and phagocytosis)
- Zanidatamab has received accelerated approval in the US and conditional approvals in the European Union and China for patients with previously treated, advanced HER2 immunohistochemistry (IHC) 3+ BTC based on the results of the phase 2 HERIZON-BTC-01 trial[9-11]
  - In 62 patients with IHC 3+ tumors, zanidatamab demonstrated manageable long-term safety, a confirmed objective response rate (cORR) of 52%, a median progression-free survival of 7.2 months, and a median OS of 18.1 months[11]

Figure 1. Zanidatamab Structure and Targeted Binding[8]



ECD, extracellular domain; Fab, fragment antigen-binding; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; scFv, single-chain variable fragment.

Objective

- To assess whether the antitumor activity observed with zanidatamab in patients with advanced HER2 IHC 3+ BTC in HERIZON-BTC-01 was prognostic of longer survival

Methods

Figure 2. Study Design for HERIZON-BTC-01

Eligibility criteria
- Locally advanced, unresectable, or metastatic *HER2*-amplified BTC that progressed on or following prior gemcitabine-containing therapy
- Aged ≥18 years at the time of signing informed consent
- HER2 status: *HER2* amplification determined by in situ hybridization and overexpression by IHC per central testing
- Baseline ECOG PS of 0 or 1
- No prior HER2-targeted treatment

Zanidatamab administration

20 mg/kg IV Q2W

Patients received mandatory prophylaxis[a] for potential infusion-related reactions before every zanidatamab infusion

28-day treatment cycles

Week 9 landmark → **Week 25 landmark**

CT/MRI scans Q8W per RECIST v1.1

Only patients with HER2 IHC 3+ tumors were included in post hoc analysis

Primary endpoint
- Objective response rate per independent central review

Post hoc analysis
- Post-landmark overall survival by response status prior to
  - 9 weeks
  - 25 weeks

[a]Acetaminophen, antihistamines, and corticosteroids.
BTC, biliary tract cancer; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; MRI, magnetic resonance imaging; Q2W, every 2 weeks; Q8W, every 8 ± 1 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- HERIZON-BTC-01 was a global, single-arm, phase 2b trial
- Patients were prospectively assigned into cohorts based on HER2 IHC scores (cohort 1 [IHC 3+ or 2+]; cohort 2 [IHC 1+ or 0])
- Only patients with HER2 IHC 3+ tumors were included in this post hoc analysis
- Landmark survival models were employed at week 9 (initial response evaluation) and week 25 (time point by which all responses occurred)
- Responders included all patients with a best response of confirmed or unconfirmed complete response (CR) or partial response (PR) prior to the landmark
- Nonresponders included patients with stable disease (SD), progressive disease (PD), or no assessment prior to the landmark

Results

Table 1. Baseline Demographics and Disease Characteristics by Best Overall Response in Patients With HER2-Positive (IHC 3+) Advanced BTC

	All (N = 62)	CR or PR[a] (n = 35)	SD (n = 14)	PD (n = 13)
Age, median (range), years	64.0 (38–79)	64.0 (38–74)	65.0 (47–79)	63.0 (42–73)
Male, n (%)	28 (45)	13 (37)	11 (79)	4 (31)
Race, n (%)[b]				
Asian	38 (61)	24 (69)	6 (43)	8 (62)
White	19 (31)	7 (20)	7 (50)	5 (38)
Other[c]	5 (8)	4 (11)	1 (7)	0
ECOG PS, n (%)				
0	20 (32)	8 (23)	6 (43)	6 (46)
1	42 (68)	27 (77)	8 (57)	7 (54)
Disease subtype, n (%)				
GBC	33 (53)	22 (63)	4 (29)	7 (54)
iCCA	17 (27)	7 (20)	8 (57)	2 (15)
eCCA	12 (19)	6 (17)	2 (14)	4 (31)
Disease stage at initial diagnosis, n (%)				
I	2 (3)	1 (3)	1 (7)	0
II	8 (13)	6 (17)	1 (7)	1 (8)
III	16 (26)	7 (20)	5 (36)	4 (31)
IV	34 (55)	19 (54)	7 (50)	8 (62)
Unknown	2 (3)	2 (6)	0	0

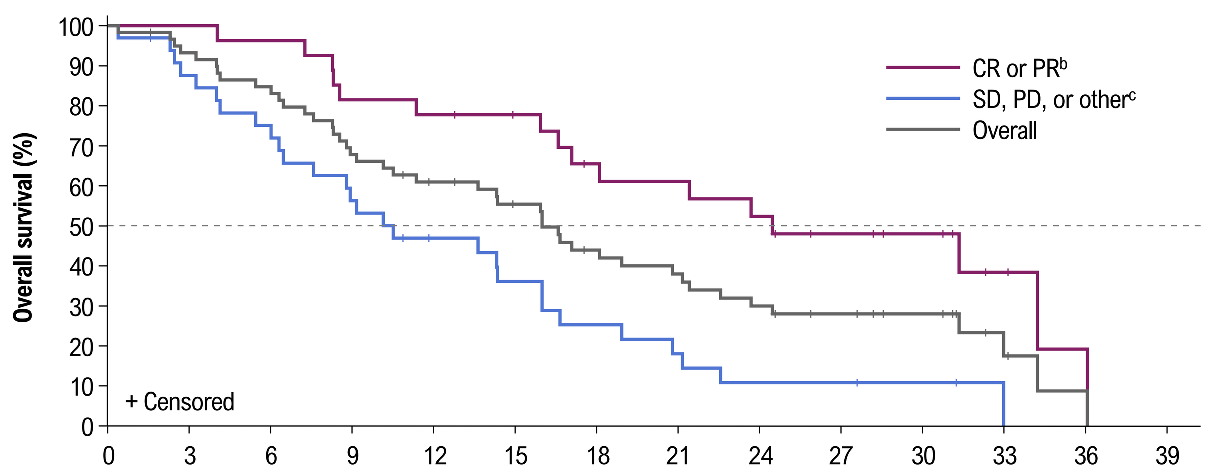
[a]Includes patients with confirmed or unconfirmed CRs and PRs. Best overall response determined using all study follow-up.
[b]Patients could have reported more than 1 race category.
[c]Includes 1 patient reported as American Indian or Alaskan Native, 2 patients for whom collection and/or reporting of this information was prohibited by local and/or regional laws or regulations, and 2 patients with unknown race.
BTC, biliary tract cancer; CR, complete response; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

- Between September 15, 2020, and March 16, 2022, 62 patients with HER2 IHC 3+ tumors were enrolled
- Of these patients, 56% achieved a best overall response (BOR) of CR or PR, 23% achieved SD, and 21% of patients had a BOR of PD
- The median (range) duration of follow-up was 34.0 (28.0–45.0) months

Figure 3. Landmark Analysis of OS[a] Based on Best Response Prior to Week 9 of Treatment in Patients With HER2-Positive (IHC 3+) BTC

A. OS[a] from week 9 of treatment in responders (CR or PR)[b] and nonresponders (SD, PD, or other[c])

	n	OS, median (95% CI), months	HR (95% CI)
CR or PR:	27	24.5 (16.6–NE)	0.30 (0.16–0.59) vs all others
SD, PD, or other:	33	10.5 (6.3–16.0)	
Overall:	60	16.0 (10.5–21.2)	

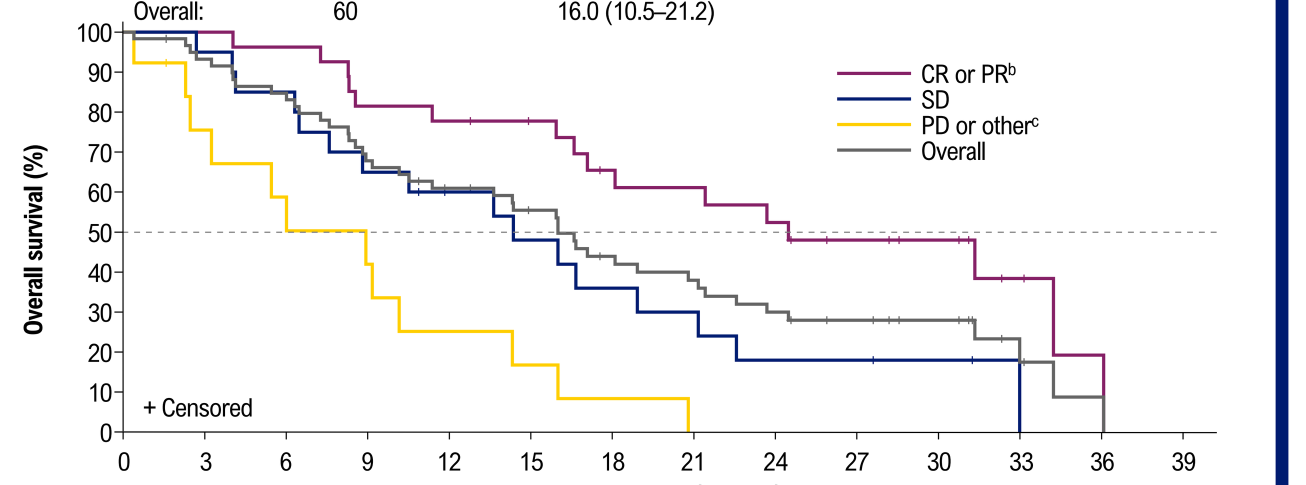


Number of patients at risk:

Time since landmark (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CR or PR:	27	27	26	22	21	19	15	14	12	9	7	3	1	0
SD, PD, or other:	33	28	24	18	13	10	7	5	3	3	2	0	0	0
Overall:	60	55	50	40	34	29	22	19	15	12	9	3	1	0

B. OS[a] from week 9 of treatment in responders (CR or PR),[b] patients with SD, or patients with PD/other[c]

	n	OS, median (95% CI), months	HR (95% CI)
CR or PR:	27	24.5 (16.6–NE)	0.40 (0.19–0.83) vs SD
SD:	20	14.4 (6.5–21.2)	0.38 (0.17–0.82) vs PD or other
PD or other:	13	8.9 (2.3–14.3)	
Overall:	60	16.0 (10.5–21.2)	



Number of patients at risk:

Time since landmark (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
CR or PR:	27	27	26	22	21	19	15	14	12	9	7	3	1	0
SD:	20	19	17	13	10	8	6	5	3	3	2	0	0	0
PD or other:	13	9	7	5	3	2	1	0	0	0	0	0	0	0
Overall:	60	55	50	40	34	29	22	19	15	12	9	3	1	0

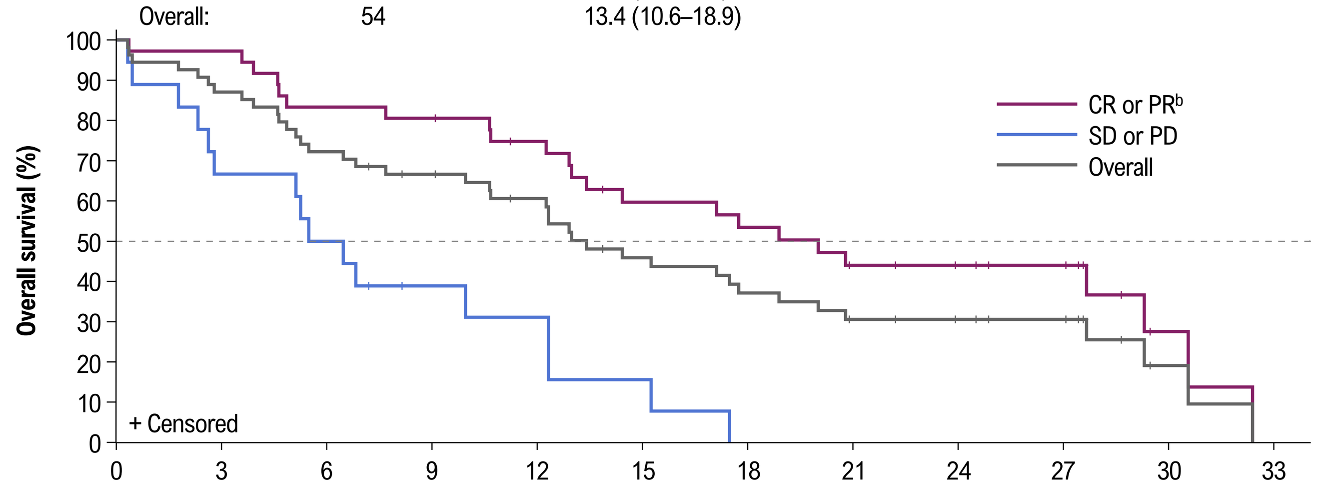
[a]OS was estimated using Kaplan-Meier methodology, with CIs based on the Brookmeyer and Crowley method with log-log transformation.
[b]Included patients with confirmed or unconfirmed CR and PR on or prior to the week-9 landmark.
[c]Other included 1 patient without a tumor assessment prior to week 9 who went on to achieve a PR.
BTC, biliary tract cancer; CR, complete response; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

- Patients with ≥1 CR or PR by week 9 had prolonged OS vs patients with SD, PD, or no evaluation (70% reduction in the risk of death) and those with SD (60% reduction in the risk of death)
- Patients with SD by week 9 had a 62% reduction in the risk of death vs patients with PD or no evaluation

Figure 4. Landmark Analysis of OS[a] Based on Best Response Prior to Week 25 of Treatment in Patients With HER2-Postive (IHC 3+) BTC

A. OS[a] from week 25 of treatment in responders (CR or PR)[b] and nonresponders (SD or PD)

	n	OS, median (95% CI), months	HR (95% CI)
CR or PR:	36	20.0 (13.0–29.3)	0.21 (0.10–0.44) vs SD or PD
SD or PD:	18	6.0 (2.6–12.3)	
Overall:	54	13.4 (10.6–18.9)	

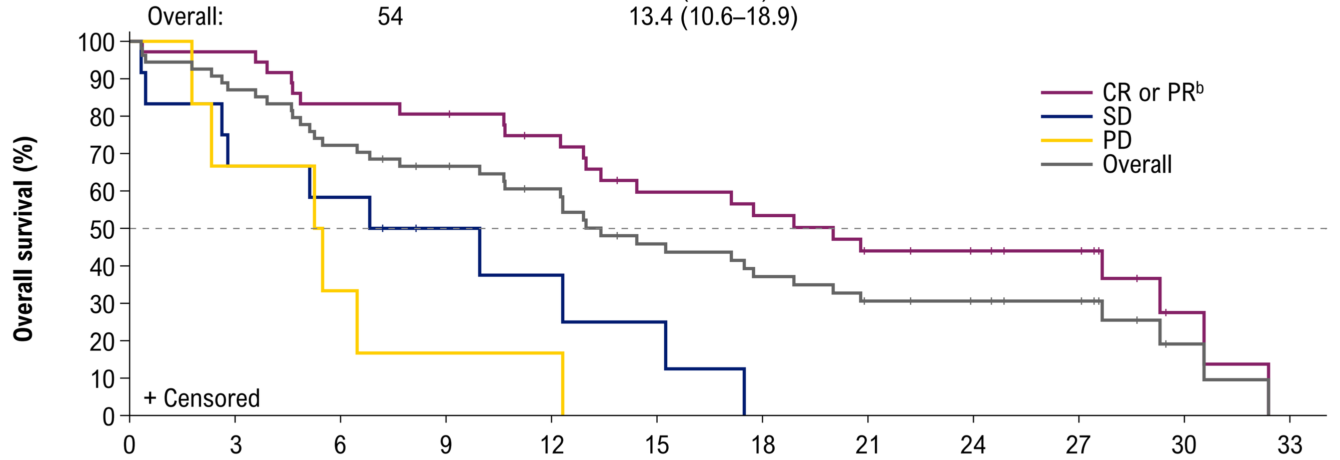


Number of patients at risk:

Time since landmark (months)	0	3	6	9	12	15	18	21	24	27	30	33
CR or PR:	36	35	30	29	25	19	17	13	11	9	2	0
SD or PD:	18	12	9	5	4	2	0	0	0	0	0	0
Overall:	54	47	39	34	29	21	17	13	11	9	2	0

B. OS[a] from week 25 of treatment in responders (CR or PR),[b] patients with SD, or patients with PD

	n	OS, median (95% CI), months	HR (95% CI)
CR or PR:	36	20.0 (13.0–29.3)	0.24 (0.11–0.56) vs SD
SD:	12	8.4 (0.5–15.2)	0.58 (0.21–1.63) vs PD
PD:	6	5.4 (1.8–NE)	
Overall:	54	13.4 (10.6–18.9)	



Number of patients at risk:

Time since landmark (months)	0	3	6	9	12	15	18	21	24	27	30	33
CR or PR:	36	35	30	29	25	19	17	13	11	9	2	0
SD:	12	8	7	4	3	2	0	0	0	0	0	0
PD:	6	4	2	1	1	0	0	0	0	0	0	0
Overall:	54	47	39	34	29	21	17	13	11	9	2	0

[a]OS was estimated using Kaplan-Meier methodology, with CIs based on the Brookmeyer and Crowley method with log-log transformation.
[b]Included patients with confirmed or unconfirmed CR and PR on or prior to the week-25 landmark.
BTC, biliary tract cancer; CR, complete response; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

- Week 25 landmark results were consistent with week 9, with longer survival in responders vs all other patients and patients with SD (79% and 76% reduction in the risk of death, respectively); 7/20 (35%) patients with SD at week 9 achieved a CR or PR by week 25

Conclusions

- In HERIZON-BTC-01, patients who responded to zanidatamab by week 9 or by week 25 demonstrated prolonged survival compared with all other patients (70% and 79% reduction in the risk of death, respectively)
- Patients who achieved SD by week 9 or by week 25 had a 62% and 42% reduction in the risk of death, respectively, vs patients with PD or no evaluation
  - Furthermore, patients with SD prior to week 9 demonstrated an encouraging median OS of 14.4 months, and 35% achieved a response by week 25
- These results show a prognostic association between objective response with zanidatamab and prolonged OS in BTC; additionally, findings suggest a clinical benefit for patients who achieve early SD and support continued zanidatamab treatment
- The efficacy of first-line zanidatamab combined with standard-of-care treatment in patients with HER2-positive (IHC 3+ or IHC 2+/amplified) BTC is being evaluated in the ongoing phase 3 HERIZON-BTC-302 trial (NCT06282575)[12]

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