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Zanidatamab in Previously-Treated HER2-Positive Biliary Tract Cancer (BTC): Impact on Patient-Reported Pain Outcomes in the Phase 2b HERIZON-BTC-01 Study

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Background

- Most patients with biliary tract cancer (BTC) have locally advanced or metastatic disease at first diagnosis, which is associated with poor prognosis[1-3]
  - BTC disease burden negatively affects patient quality of life and substantially impacts activities of daily living[4,5]
  - Pain is one of the most commonly reported symptoms of BTC,[4] and pain management is often inadequate for patients with BTC;[6] therefore, more effective treatments are needed to adequately target the underlying disease and improve disease-related pain
- Zanidatamab is a bispecific antibody that simultaneously binds to two nonoverlapping HER2 epitopes (known as biparatopic binding) in a *trans* configuration, thereby crosslinking HER2 molecules.[7] HER2 crosslinking results in zanidatamab-HER2 clustering and drives multiple antitumor mechanisms of action, including:[7]
  - Receptor internalization and downregulation
  - Inhibition of cell signaling and tumor growth
  - Immune-mediated effects
- In the pivotal phase 2b HERIZON-BTC-01 trial (NCT04466891), zanidatamab led to a clinically meaningful benefit with rapid, durable responses and improved health-related quality of life (HRQoL) from baseline (BL) with a manageable safety profile[5,8]
  - Here, we report the disease-related pain outcomes and opioid use for pain control in patients with HER2-positive BTC in the HERIZON-BTC-01 trial

Methods

- HERIZON-BTC-01 is an ongoing, open-label, global, phase 2b study of zanidatamab in patients with *HER2*-amplified BTC
  - Patients with centrally-confirmed *HER2*-amplified tumors (assessed by in situ hybridization) were prospectively assigned into one of two cohorts:
    - HER2-positive: Cohort 1 (centrally-confirmed immunohistochemistry [IHC] 2+ or 3+)
    - Others: Cohort 2 (centrally-confirmed IHC 0 or 1+)
  - Due to limited sample size (n=7) and no confirmed responses in Cohort 2, the disease-related pain and opioid use analyses reported here are focused on Cohort 1 only (HER2-positive)
- Zanidatamab 20 mg/kg IV once every 2 weeks was administered; mandatory infusion-related reaction prophylaxis included corticosteroids (hydrocortisone 100 mg IV or dexamethasone 10 mg IV), antihistamines (diphenhydramine 50 mg per oral or IV), and acetaminophen (650-1000 mg per oral)
- Disease-related pain and opioid use were predefined exploratory endpoints and were assessed using the following:
  - **European Quality of Life 5 Dimensions (EQ-5D) visual analog scale (VAS)**: assesses overall current health using a scale of 0-100 (a higher score indicates better health)
    - Minimal important difference is a change of 7 points[9]
  - **Brief Pain Inventory short form questionnaire (hereafter referred to as BPI)**: disease-related pain including worst and least pain in the last 24 hours (1-4, mild pain; 5-6, moderate pain; 7-10, severe pain); and pain interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life
    - Minimal important difference for pain and pain interference based on the chronic pain Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus recommendations is a change of 1 point[10]
  - **Opioid use in the last 24 hours**: recorded with concomitant medications

Results

- This study is ongoing and recruitment is complete (data cutoff for this analysis was October 10, 2022); from September 2020 to March 2022, 80 patients were enrolled in Cohort 1
- The primary results and HRQoL of HERIZON-BTC-01 have previously been reported, and are summarized in **Tables 1-2** and **Figure 1**[5,8]

Table 1. Baseline Demographics and Patient Disease Characteristics in Cohort 1[8]

Characteristic	n=80
Age, median (range)	64 (58-70)
Female, n (%)	45 (56)
Race, n (%)	
Asian	52 (65)
White	23 (29)
Other	5 (6)
ECOG PS, n (%)[a]	
0	22 (28)
1	58 (73)
Disease subtype, n (%)	
GBC	41 (51)
ICC	23 (29)
ECC	16 (20)
HER2 status by central assessment, n (%)[a]	
IHC 3+	62 (78)
IHC 2+	18 (23)
AJCC tumor stage at study entry, n (%)	
III	9 (11)
IV	71 (89)
Prior radiotherapy, n (%)	13 (16)
Prior surgery with curative intent, n (%)	25 (31)
Lines of prior therapy for metastatic or locally advanced disease, median (range)[b,c]	1 (1-2)
Previous systemic therapy, n (%)	
Gemcitabine-based[b]	80 (100)
Gemcitabine + cisplatin[d]	61 (76)
Fluoropyrimidine-based[d,e]	27 (34)
PD-1/PD-L1 inhibitor[d]	21 (26)
Fluoropyrimidine[d]	5 (6)

[a]Numbers may not sum to 100% due to rounding to the nearest integer. [b]Includes gemcitabine-based therapies received in the adjuvant/neoadjuvant setting if progression occurred within 6 months of completion of therapy or surgery. [c]Total regimens as designated by the investigator. [d]Patients are counted at most once under each regimen type received and may be counted in multiple categories. [e]Excludes regimens in combination with gemcitabine.

AJCC, American Joint Committee on Cancer; ECC, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; ICC, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 2. Disease Response Endpoints Following Zanidatamab Treatment in Cohort 1[8]

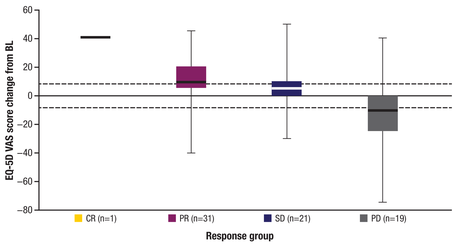
Disease Response Endpoints[a]	n=80
Confirmed objective response rate, n (%) [95% CI]	33 (41) [30, 53]
CR, n (%)	1 (1)
PR, n (%)	32 (40)
SD, n (%)	22 (28)
PD, n (%)	24 (30)
NE, n (%)	1 (1)
Median duration of response, months (range) [95% CI][b-d]	13 (2-17+) [6, NE]
Disease control rate, n (%) [95% CI][e]	55 (69) [57, 79]
Median progression-free survival, months (range) [95% CI][d]	6 (0-19+) [4, 7]

[a]Disease response endpoints are per independent central review. [b]Only patients who had a confirmed objective response were included in the analysis. [c]Confirmed best overall response of partial response or complete response. [d]Estimates per the Kaplan-Meier method; 95% CIs were based on the Brookmeyer and Crowley method with log-log transformation. [e]Best overall response of SD or confirmed CR or PR.

+, data censored at time of data cutoff; CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- Median (range) time to first response was 2 (2-6) months; 76% of responses were observed at the first tumor assessment after the start of zanidatamab treatment
- Treatment-related adverse events (TRAEs) were evaluated in Cohorts 1 and 2 (N=87) and previously published[8]
  - The most common TRAEs were diarrhea (37%) and infusion-related reactions (33%), with no grade 4 or 5 TRAEs reported
  - Serious TRAEs were reported in 8% of patients

Figure 1. Change in EQ-5D VAS Scores From BL at Time of BONT by Tumor Response[5,a]



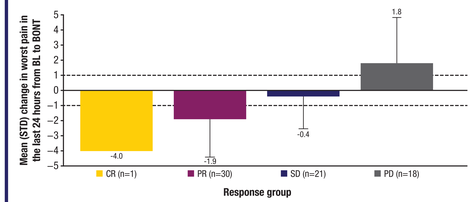
[a]BONT was defined as the lowest post-BL value observed.

Bars represent quartiles 1 and 3. Lines represent median values. Capped lines represent minimum and maximum values. Dotted lines represent clinically meaningful improvement (+7) and clinically meaningful deterioration (-7).

BL, baseline; BONT, best on-treatment score; CR, complete response; EQ-5D, European Quality of Life 5 Dimensions; PD, progressive disease; PR, partial response; SD, stable disease; VAS, visual analog scale.

- Clinically meaningful improvements in EQ-5D VAS scores from BL (≥7 points)[9] were reported by patients who responded to zanidatamab (complete response [CR] and partial response [PR]) at the time of best on-treatment score (BONT)
  - Patients with progressive disease (PD) had clinically meaningful deterioration, with a median reduction of 10 points in EQ-5D VAS scores from BL to BONT

Figure 2. Change From BL in Worst Pain in the Last 24 Hours at Time of BONT[a]



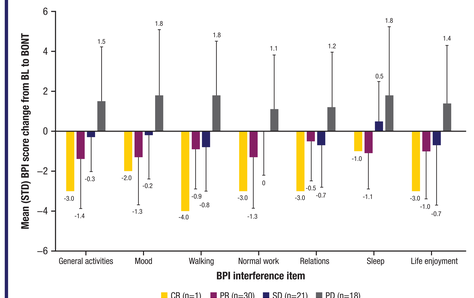
[a]BONT was defined as the lowest post-BL value observed. Negative values from BL to change at time of BONT indicate decreased pain, and positive values indicate worsening pain.

Dotted lines represent clinically meaningful improvement (≥1 point decrease) and clinically meaningful deterioration (≥1 point increase).

BL, baseline; BONT, best on-treatment score; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; STD, standard deviation.

- Patients with CR and PR reported clinically meaningful improvements in worst pain in the last 24 hours (≥1 point decrease),[10] while patients with PD reported clinically meaningful deterioration in worst pain from BL to BONT

Figure 3. Change in Individual BPI Items by Tumor Response From BL to Time of BONT[a,b]



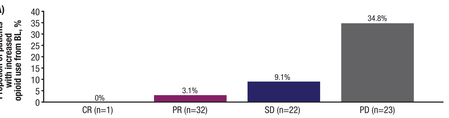
[a]BONT was defined as the lowest post-BL value observed. Negative BPI values from BL to change at time of BONT indicate better outcomes, and positive values indicate worse outcomes. [b]BPI domain scores were summarized as the change from BL over time and at the time of BONT.

BL, baseline; BONT, best on-treatment score; BPI, Brief Pain Inventory; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; STD, standard deviation.

- Patients reported mean BPI scores ≤4 at BL
- The largest improvements in pain interference for the patient with CR were reported in walking; for patients with PR, the largest improvements were reported in general activities, mood, and normal work
- The main improvements in pain interference for patients with SD were in walking, relations, and life enjoyment
- Patients with PD reported worsening pain interference across all BPI items

Figure 4. Opioid Use for Disease-Related Pain[a] (A) in the 24 Hours Prior to Completing Their Physician Visit by Tumor Response, (B) by MME, and (C) Post-BL

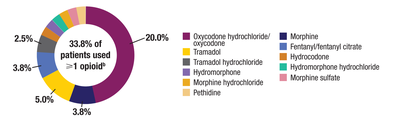
A)



B)

Opioid Use, Mean (STD)	n=80			
	CR (n=1)	PR (n=32)	SD (n=22)	PD (n=24)
BL MME	0.0 (NA)	5.0 (14.3)	162.1 (745.6)	9.9 (21.7)
BONT MME	0.0 (NA)	4.3 (16.3)	225.6 (1053.0)	12.8 (19.3)
MME change from BL	0.0 (NA)	−0.6 (18.6)	63.5 (307.5)	5.4 (21.2)

C)



[a]Opioid use was summarized as the change from BL over time and in the last 24 hours. [b]For opioids used by <2% of patients, each section of the chart equals 1.3%.

BL, baseline; BONT, best on-treatment score; CR, complete response; MME, morphine milligram equivalents per day; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; STD, standard deviation.

- Fewer patients with CR and PR increased opioid use overall post-BL compared with patients with SD or PD
- The most used opioid post-BL among patients was oxycodone hydrochloride/oxycodone

Conclusions

- Zanidatamab led to reduced pain, less pain interference, and clinically meaningful improvements in EQ-5D VAS scores in patients who responded to treatment from BL to time of BONT, suggesting zanidatamab may potentially improve patient HRQoL through disease control
- Patients with CR, PR, and SD generally reported the most improvements in pain and BPI outcomes, with fewer patients with these responses needing increased opioid use compared with patients with PD
- Study limitations include a moderate sample size and single-arm design
- The results of HERIZON-BTC-01, including the BPI results, support the continued development of zanidatamab as a promising treatment option for HER2-positive, locally advanced/metastatic BTC

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Support and Acknowledgments: This study was supported by Zymeworks, BeiGene, and Jazz Pharmaceuticals. The authors would like to thank all patients and their families, all investigators, clinical trial researchers, personnel, and staff who contributed to or participated in the HERIZON-BTC-01 trial. Medical writing support, under the direction of the authors, was provided by Ellen Woon, PhD, of CMC Affinity, a division of IPG Health Medical Communications, with funding from Jazz Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines.

Disclosures: S Pant has consulted for AskGene Pharma, Boehringer Ingelheim, Ipsen, Janssen, Novartis, and Zymeworks, and has received funding from 4D Pharma, Amal Therapeutics, Arcus Biosciences, Astellas Pharma, Boehringer Ingelheim, BioNtech, Bristol Myers Squibb, Eli Lilly, Elicio Therapeutics, Framewave, Immuneering, ImmunoMET, Ipsen, Janssen, Mirati Therapeutics, NGM Biopharmaceuticals, Novartis, Pfizer, Rgenix, Xencor, and Zymeworks. **DY Oh** has been an advisory board member for Arcus Biosciences, ASLAN, AstraZeneca, Bayer, Basilea, BeiGene, BMS/Celgene, Genentech/Roche, Halozyme, IQVIA, Merck Serono, Novartis, Taiho, Turning Point, Yuhan, and Zymeworks; and has received funding from Array, AstraZeneca, BeiGene, Eli Lilly, Handok, MSD, Novartis, and Servier. **HJ Choi** has consulted for AstraZeneca and Roche. **JW Kim** has consulted for AstraZeneca, Beyond Bio, BeiGene, Bristol Myers Squibb/Celgene, Eisai, GC Cell, Merck Sharp & Dohme, ONO, Sanofi-Aventis, Servier, and TOJIBEI; and has received funding from Inno.N and Jeil Pharm. **HM Chang** has received funding from Zymeworks. **HC Sun** has consulted for TopAlliance; and has received funding from AstraZeneca and TopAlliance. **T Macarulla** has an advisory role at Ability Pharmaceuticals SL, AstraZeneca, Basilea Pharma, Baxter, BioLineRX, Celgene, Eisai, Incyte, and Ipsen; has received speaker's fees from Janssen and Lilly; and has received direct research funding from Merck Sharp & Dohme, Novocure, QED Therapeutics, Roche Farma, Sanofi-Aventis, Servier, and Zymeworks. **JP Metges** has received honoraria from Astellas, Bayer, Bristol Myers Squibb, and Merck Sharp & Dohme. **JA Bridgewater** has consulted for Bristol Myers Squibb, Incyte, Servier, and Taiho; received funding from Incyte; and received honoraria from Incyte and Servier. **MA Tejani** has received honoraria from Caris and Natera. **H Wasan** is an advisory board member and/or invited speaker at Amgen, Bayer, BMS/Celgene, BTG, Erytech Pharma, Incyte, Merck KGaA, Pierre Fabre, Pfizer, Roche/Genentech/FM, Servier, SIRTEX Medical, Seagen, and Zymeworks; has consultancies at Bayer, Celgene, Incyte, NICE/BSI, ONCOSIL, and Pierre Fabre; is a member of the Global Trials steering committee at ARCAD (Pancreas Academic), Merck KGaA, Pfizer (Array), SIRTEX, and Zymeworks; and has received research funding from Merck Serono, MSD, Pfizer and SIRTEX. **M Ducreux** has been an advisory board member for Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, MSD, Pierre Fabre, Roche, and Servier; received speaker in symposia from Bayer, Daiichi Sankyo, Merck Serono, MSD, Pierre Fabre, Roche, and Servier; has received funding from Keocyt, Merck Serono, and Roche; and has participated in independent data monitoring committees for Pancan and Roche. M Ducreax's spouse is the head of oncology business unit at Sandoz France. **J Ma** is an employee of, and owns stock or stock options in, BeiGene. **PM Garfin** is a former employee of, and owned stock or stock options in, Zymeworks; owns stock or stock options in Seagen; and is a current employee of, and owns stock or stock options in, Jazz Pharmaceuticals. **JJ Harding** has consulted or been an advisory board member for Adaptimmune, AstraZeneca, Bristol Myers Squibb, Eisai, Elevar, Exelexis, Genoscience, Hepion, Imvax, Merck, Medivir, QED, Tyra, and Zymeworks; and has received funding from Bristol Myers Squibb, Boehringer Ingelheim, CytomX, Debiopharm, Eli Lilly, Genoscience, Incyte, Loxo@Lilly, Novartis, Polaris, Pfizer, Yivia, and Zymeworks. **J Fan, L Bao, F Xie, JE Ying,** and **EY Chen** have nothing to disclose.

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Presented at the ASCO Gastrointestinal Cancers Symposium; January 18-20, 2024; San Francisco, CA