Zanidatamab (ZW25) in HER2-positive Biliary Tract Cancer (BTC): Results From a Phase 1 Study

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Background

- Biliary tract cancers (BTC), including cholangiocarcinoma (CC) and gallbladder cancer, are aggressive, rare tumors
- Patients with unresectable, locally advanced or metastatic BTCs have a poor prognosis and treatment options are limited after first line treatment[1]
- Second line chemotherapy yields objective response rates (ORR) of < 10% and the median overall survival of these patients is ~6 months[2]
- Approximately 19% of gallbladder cancers, 17% of extrahepatic CC and 5% of intrahepatic CC overexpress human epidermal growth factor receptor 2 (HER2)[3]
- Zanidatamab (ZW25) is a novel HER2-targeted, bispecific antibody that simultaneously binds two distinct sites on HER2: the ECD4 (same target as that of trastuzumab) and the ECD2 (same target as that of pertuzumab)
- Unique binding of zanidatamab to HER2 results in multiple mechanism of action, including: improved binding, clustering, and receptor internalization and downregulation, inhibition of ligand-dependent and -independent proliferation, and potent activation of antibody-dependent cellular cytotoxicity

Methods

ZW25-101 (NCT02892123) is a first-in-human, 3-part, Phase 1 study (**Figure 1**) that evaluates zanidatamab in HER2-expressing cancers, including BTCs.

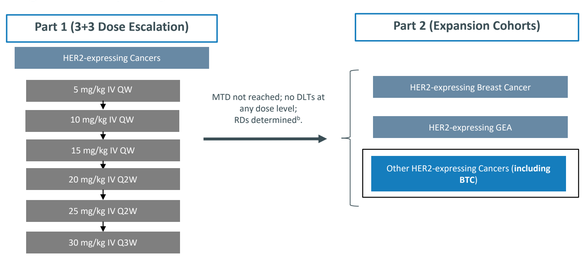
Objectives

- Determine maximum tolerated dose (MTD) and recommended dose (RD) of zanidatamab
- Characterize safety and tolerability of zanidatamab
- Evaluate potential anti-tumor effects of zanidatamab

Key Eligibility Criteria

- Advanced HER2-expressing cancer with progression after standard of care therapy
  - BTC patients were required to be HER2 immunohistochemistry (IHC) 3+ or IHC2+/ fluorescence in situ hybridization (FISH)+ per central assessment
- Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[4]
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1

Figure 1: Study Design (Parts 1 & 2)[a]



GEA=gastroesophageal adenocarcinoma; IV=intravenous; QW=weekly; Q2W=every 2 weeks; Q3W=every 3 weeks.
a, in Part 3 (not shown), patients with HER2-expressing breast cancers or GEAs were treated with zanidatamab + select chemotherapy; b, see Results.

Results

- Part 1:
  - RD for zanidatamab monotherapy was determined to be 10 mg/kg QW and 20 mg/kg Q2W
- Part 2: 21 patients with BTC were treated in Part 2 of the study at the RD of 20 mg/kg Q2W
- BTC patient characteristics are presented in **Table 1**

Table 1: Patient Characteristics

	(N = 21)
Median age (range), years	63 (42–78)
Sex: Female, n (%)	14 (67)
Race, n (%)	
Asian	14 (67)
White	5 (24)
Black or African American	1 (5)
Unknown	1 (5)
Diagnosis, n (%)	
Gallbladder	12 (57)
Intrahepatic cholangiocarcinoma	5 (24)
Extrahepatic cholangiocarcinoma	4 (19)
Median prior systemic therapies (range)	2 (1–8)
Patients with prior HER2-targeted therapy, n (%)	5 (24)
ECOG PS, n (%)	
0	2 (10)
1	19 (90)

Data extracted on: Nov 16, 2020 (data are from an unlocked database and subject to change).

Safety

Zanidatamab was well-tolerated in patients with BTCs with no patient experiencing a Grade 3 or higher zanidatamab-related AE (**Table 2**).

- A single zanidatamab-related serious AE (Grade 2 fatigue) was reported in one patient. The patient was hospitalized, treated with IV fluids, and recovered within a day.
- Two deaths were reported during the study — one due to progressive disease and one due to an unrelated AE (cardiac arrest in the setting of bowel perforation)

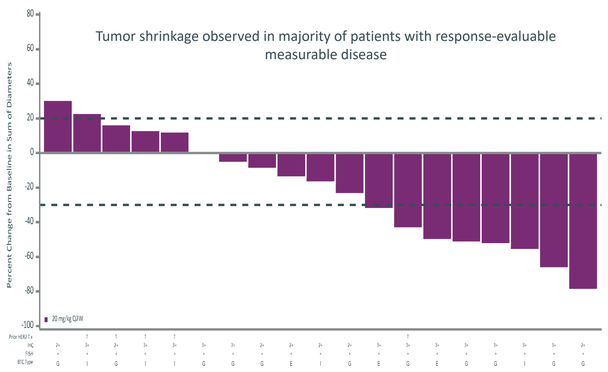
Table 2: Zanidatamab-related AEs

	(N = 21)
Patients with treatment-emergent AEs, n (%)	21 (100)
Patients with zanidatamab-related AEs (occurring in ≥ 15% of BTC patients)	
Any, n (%)	15 (71)
Diarrhea	9 (43)
Infusion-related reaction	7 (33)

Efficacy

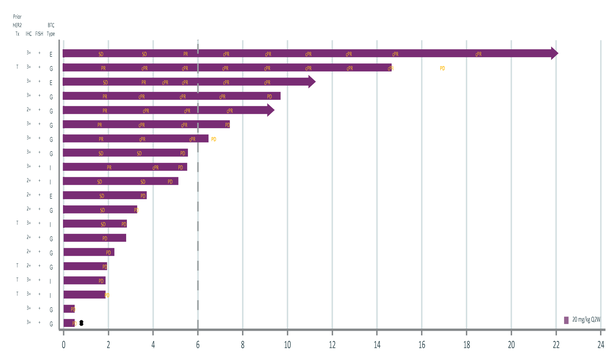
- Twenty (95%) patients were response-evaluable

Figure 2: Anti-tumor Activity: Zanidatamab



E = Extrahepatic Cholangiocarcinoma, FISH=fluorescence in situ hybridization; I = Intrahepatic Cholangiocarcinoma, IHC=; immunohistochemistry; G = Gallbladder; T=trastuzumab; Tx=treatment.
Note: 1 patient in the response-evaluable set died prior to the post-baseline tumor measurement and is not included in the plot (this patient is included in Figure 3 and Table 3; this patient was counted as PD). One patient was not response evaluable because they withdrew from the study. Response-evaluable: all treated patients with measurable disease who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to death or clinical progression.

Figure 3: Duration of Treatment



(c)PR=(confirmed) partial response; E = Extrahepatic Cholangiocarcinoma, FISH=fluorescence in situ hybridization; I = Intrahepatic Cholangiocarcinoma, IHC=; immunohistochemistry; G = Gallbladder; PR= partial response; PD=progressive disease; SD=stable disease; T=Trastuzumab; Tx=treatment.
*, Death.

Table 3: Disease Response Endpoints[a] and DOR

	(N = 20)
Confirmed objective response, n (%) (95% CI)	8 (40) (19.1, 63.9)
Partial response	8 (40)
Stable disease	5 (25)
Progressive disease	7 (35)
Disease control rate, n (%)	13 (65)

Duration of response,[b] months	(N=8)
Median (95% CI)	7.4 (3.2, NE)

DOR=duration of response; NE= not estimable.
a, per Investigator Assessment using RECIST 1.1 in response-evaluable patients; b, in response-evaluable patients who had a complete or partial response followed by at least one more response assessment.

Conclusions

- Zanidatamab was well tolerated and demonstrated promising anti-tumor activity in patients with HER2+ BTC that has progressed after prior therapies, including HER2-targeted agents
- All zanidatamab-related AEs were mild or moderate in severity (Grade 1 or 2)
- The confirmed objective response was 40% (8/20), disease control rate was 65% (13/20), and median duration of response was 7.4 months
- Based on these results, zanidatamab has the potential to address unmet need in patients with HER2+ BTC
- A registration-enabling global Phase 2 study (ZW25-203; HERIZON-BTC-01) in HER2-amplified BTC is now open for enrollment. For further information:
  - Please visit www.ClinicalTrials.gov (NCT04466891)
  - Details of the ZW25-203 study design are being presented at ASCO-GI 2021 (Pant S, et al., abstract #TPS352)

References

1. Valle JW, et al. Cancer Discov. 2017;7(9):943-962; 2. Lamarca A, et al. J Clin Oncol. 2019;37(suppl; abstr 4003); 3. Galdy S, et al. Cancer Metastasis Rev. 2017 Mar;36(1):141-157; 4. Eisenhauer EA, et al. Eur J Cancer. 2009;45(2):228-247.

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