746P A 2-Year Follow-Up of Zanidatamab + mFOLFOX6 ± Bevacizumab in First-Line Treatment of Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced/Metastatic Colorectal Cancer

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Plain Language Summary

Why did we perform this research?

- People with advanced colorectal cancer that has too much of a protein called HER2 often have a short life expectancy and limited treatment options when first diagnosed

How did we perform this research?

- This study looked at whether a medicine called zanidatamab, which targets HER2, added to standard chemotherapy (a mix of 5-fluorouracil [5-FU], oxaliplatin, and leucovorin), could help treat these patients

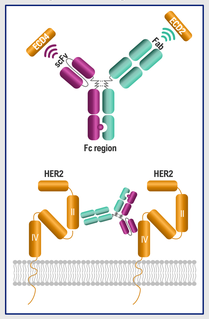
What were the results of this research?

- After 2 years of follow-up, the study showed that patients may benefit from the addition of zanidatamab to their treatment
- Nearly all patients who received treatment in the study had their tumours shrink and survived for many months without any extra safety concerns
- Side effects were usually manageable and did not cause any of the patients to stop zanidatamab treatment

Background

- HER2 is amplified and/or overexpressed in approximately 2%–6% of colorectal cancer (CRC) cases and is a treatment target[1-3]
- Although HER2 testing is encouraged, ESMO guidelines only recommend HER2-directed therapy, such as trastuzumab, for the treatment of HER2-positive metastatic CRC (mCRC) in second-line and beyond[4]; in separate studies, trastuzumab plus tucatinib and trastuzumab deruxtecan each demonstrated a confirmed objective response rate (cORR) of 38% in patients with pretreated HER2-positive mCRC[5,6]
- With promising results in later lines of treatment, there is justification for broader incorporation of HER2-targeted therapies in the first-line (1L) setting for patients with HER2-positive mCRC

Figure 1. Zanidatamab Structure and Targeted Binding



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

- Zanidatamab is a dual HER2-targeted bispecific antibody that binds to 2 distinct domains on HER2, promoting HER2 crosslinking not observed with trastuzumab or trastuzumab plus pertuzumab[7]
- In preclinical studies, zanidatamab drove multiple antitumour mechanisms of action, including[7]
  - Facilitation of HER2 internalisation and degradation
  - Reduction of HER2 on the cell surface and inhibition of HER2 signalling pathways
  - Activation of immune-mediated antitumour effects (complement-dependent cytotoxicity as well as antibody-dependent cellular cytotoxicity and phagocytosis)
- Zanidatamab received accelerated approval in the US and conditional approvals in China and the EU for adults with previously treated, unresectable, or metastatic HER2-positive (immunohistochemistry [IHC] 3+) biliary tract cancer (BTC) based on the phase 2 HERIZON-BTC-01 trial[8-10]
- In a first-in-human, phase 1 study across a range of HER2-positive solid tumours, zanidatamab monotherapy demonstrated promising antitumour activity (cORR, 38%) and a manageable safety profile in 26 patients with heavily pretreated mCRC[11]
- This study evaluated zanidatamab plus 5-FU plus oxaliplatin and the folinic acid leucovorin (mFOLFOX6) ± bevacizumab for the 1L treatment of patients with HER2-expressing mCRC
  - At an earlier data cutoff (31 October 2023), the cORR was 91%; 23% of patients experienced dose-limiting toxicities (DLTs), and grade 3–4 treatment-related adverse events (TRAEs) were reported in 38% of patients[12]

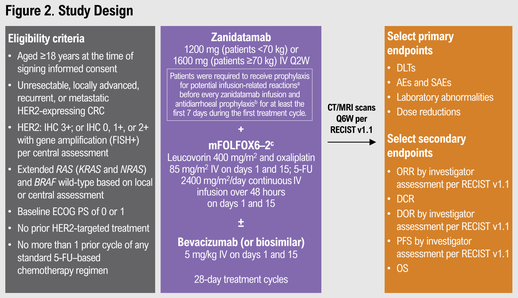
Objective

- To present updated (2 years of follow-up) antitumour activity and safety of 1L zanidatamab combined with mFOLFOX6-2 with or without bevacizumab in patients with HER2-expressing mCRC

Methods (CRC Cohort)

- This is a global, open-label, phase 2 trial (NCT03929666) evaluating zanidatamab plus standard combination chemotherapy for HER2-expressing gastrointestinal cancers, including gastro-oesophageal adenocarcinoma,[13] BTC,[14] and CRC

Figure 2. Study Design



[a]Acetaminophen, diphenhydramine, and corticosteroid. [b]Loperamide. [c]Per protocol, chemotherapy was required for 6 cycles unless patients experienced unacceptable toxicity, withdrew consent, had clinical disease progression, or had radiological progression per RECIST v1.1. Continuation of chemotherapy was at the discretion of the investigator and patient after cycle 6. Patients who stopped oxaliplatin without disease progression and for reasons that were not related to zanidatamab toxicity could continue on to receive 5-FU with zanidatamab with or without bevacizumab. Patients who discontinued 5-FU also had to discontinue oxaliplatin. When both 5-FU and oxaliplatin were discontinued, bevacizumab was also stopped. Patients could continue on zanidatamab monotherapy if chemotherapy was discontinued due to toxicity unrelated to zanidatamab. 5-FU, 5-fluorouracil; AE, adverse event; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; CRC, colorectal cancer; CT, computed tomography; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; *KRAS*, KRAS proto-oncogene, GTPase; mFOLFOX6-2, modified dose of 5-FU and leucovorin and oxaliplatin; MRI, magnetic resonance imaging; *NRAS*, NRAS proto-oncogene, GTPase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q6W, every 6 weeks; *RAS*, RAS type GTPase family of genes; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious AE.

- Patients received a modified dose of FOLFOX6 (mFOLFOX6-2) that does not include the 5-FU 400 mg/m² intravenous bolus

Results

Table 1. Demographics and Baseline Disease Characteristics in Patients With HER2-Positive mCRC

	Zanidatamab + mFOLFOX6-2 (n = 6)	Zanidatamab + mFOLFOX6-2 + bevacizumab (n = 7)	Total (N = 13)
Age, median, years (range)	50.5 (35–64)	58.0 (36–83)	55.0 (35–83)
<65 years, n (%)	6 (100)	5 (71)	11 (85)
≥65 years, n (%)	0	2 (29)	2 (15)
Male, n (%)	3 (50)	6 (86)	9 (69)
Race, n (%)			
Asian	4 (67)	6 (86)	10 (77)
White	2 (33)	1 (14)	3 (23)
Ethnicity, n (%)			
Hispanic or Latino	1 (17)	0	1 (8)
Not Hispanic or Latino	5 (83)	7 (100)	12 (92)
ECOG PS, n (%)			
0	2 (33)	2 (29)	4 (31)
1	4 (67)	5 (71)	9 (69)
Primary diagnosis, n (%)			
Colon adenocarcinoma	3 (50)	4 (57)	7 (54)
Rectal adenocarcinoma	3 (50)	3 (43)	6 (46)
Disease stage at initial diagnosis, n (%)			
IIB	0	1 (14)	1 (8)
IIIA	0	1 (14)	1 (8)
IV	6 (100)	5 (71)	11 (85)
Centrally confirmed HER2 status, n (%)			
IHC 2+/FISH+	2 (33)	3 (43)	5 (38)
IHC 3+	4 (67)	4 (57)	8 (62)
Measurable disease per RECIST v1.1, n (%)	6 (100)	6 (86)	12 (92)

ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

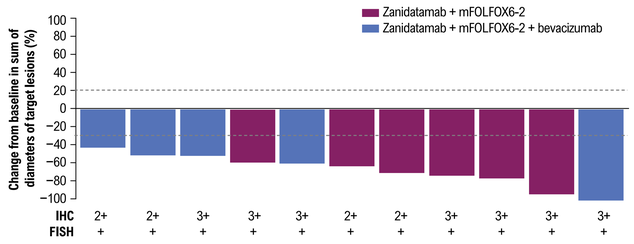
- The trial enrolled patients at investigational sites in 4 countries (Canada, Chile, Republic of Korea, and the US)
- Between 3 May 2022 and 21 August 2023, 13 patients with mCRC were enrolled and treated (zanidatamab + mFOLFOX6-2, n = 6; zanidatamab + mFOLFOX6-2 + bevacizumab, n = 7)
- As of the last patient last visit (30 August 2025), the median (range) duration of follow-up was 39.2 (24.3–40.0) months for zanidatamab in combination with mFOLFOX6-2 and 33.6 (26.8–39.5) months for zanidatamab in combination with mFOLFOX6-2 and bevacizumab
  - Nine (69%) patients were still on study at time of termination by the sponsor; prior to study end, 3 (23%) patients withdrew consent and 1 (8%) patient from the zanidatamab + mFOLFOX6-2 group died
- The median (range) duration of zanidatamab treatment was 22.7 (8.1–39.6) months for the zanidatamab + mFOLFOX6-2 group and 10.2 (0–34.7) months when bevacizumab was included; the median (range) number of zanidatamab treatment cycles was 23.5 (9–42) for the zanidatamab + mFOLFOX6-2 group and 11.0 (1–37) when bevacizumab was included

Table 2. Disease Response in Patients With HER2-Positive mCRC by Investigator Assessment per RECIST v1.1 (Response-Evaluable Patients)[a]

	Zanidatamab + mFOLFOX6-2 (n = 6)	Zanidatamab + mFOLFOX6-2 + bevacizumab (n = 5)	Total (n = 11)
Confirmed objective response rate, n (%)	6 (100)	5 (100)	11 (100)
(95% CI)	(54–100)	(48–100)	(72–100)
Confirmed best overall response, n (%)			
Partial response	6 (100)	5 (100)	11 (100)
Disease control rate,[b] n (%)	6 (100)	5 (100)	11 (100)
(95% CI)	(54–100)	(48–100)	(72–100)

[a]All treated patients who had ≥1 measurable target lesion (per RECIST v1.1) at baseline and ≥1 evaluable postbaseline disease assessment (per RECIST v1.1) or discontinued study treatment due to death or clinical progression. [b]Disease control was defined as a best overall response of stable disease, partial response, or complete response.
HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

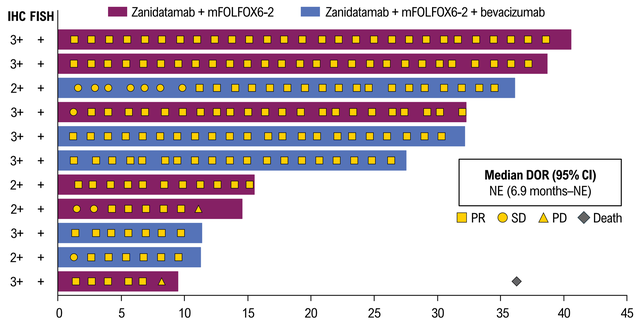
Figure 3. Change in Target Lesion Size in Patients With HER2-Positive mCRC (Response-Evaluable Set)[a]



[a]All treated patients who had ≥1 measurable target lesion (per RECIST v1.1) at baseline and ≥1 evaluable postbaseline disease assessment (per RECIST v1.1) or discontinued study treatment due to death or clinical progression.
Dotted lines indicate thresholds for progressive disease (20% increase in sum of diameters of target lesions) and partial response (30% decrease in sum of diameters of target lesions) per RECIST v1.1.
FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

- All response-evaluable patients (100%) achieved a partial response

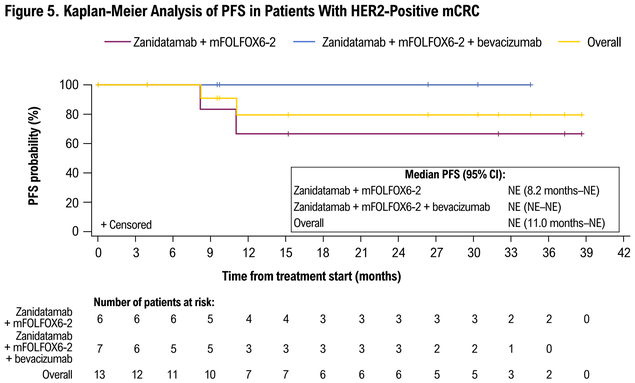
Figure 4. Treatment Duration and Response in Patients With HER2-Positive mCRC (Response-Evaluable Set)[a]



[a]All treated patients who had ≥1 measurable target lesion (per RECIST v1.1) at baseline and ≥1 evaluable postbaseline disease assessment (per RECIST v1.1) or discontinued study treatment due to death or clinical progression.
DOR, duration of response; FISH, fluorescence in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; NE, not estimable; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

- The overall median duration of response was not reached (median [range] duration of follow-up: 36.2 [24.3–40.0] months)

Figure 5. Kaplan-Meier Analysis of PFS in Patients With HER2-Positive mCRC



HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; NE, not estimable; PFS, progression-free survival.

- The estimated overall 18- and 24-month (95% CI) progression-free survival (PFS) rates were both 80% (39–95)

Table 3. Summary of Safety in Patients With HER2-Positive mCRC

	Zanidatamab + mFOLFOX6-2 (n = 6)		Zanidatamab + mFOLFOX6-2 + bevacizumab (n = 7)		Total (N = 13)	
Any TRAE,[a] n (%)	6 (100)		7 (100)		13 (100)	
Grade 1–2	3 (50)		4 (57)		7 (54)	
Grade ≥3	3 (50)		3 (43)		6 (46)	
Serious TRAE,[a] n (%)	1 (17)		1 (14)		2 (15)	
AEs leading to zanidatamab dose reduction, n (%)	1 (17)		0		1 (8)	
AEs leading to zanidatamab dose discontinuation, n (%)	0		0		0	
AESI, n (%)	**Grade 1–2**	**Grade ≥3**	**Grade 1–2**	**Grade ≥3**	**Grade 1–2**	**Grade ≥3**
Infusion-related reaction	3 (50)	0	2 (29)	0	5 (38)	0
Noninfectious pulmonary toxicities	1 (17)	0	0	0	1 (8)	0
Left ventricular dysfunction	0	0	0	0	0	0

[a]TRAEs could be related to zanidatamab and/or mFOLFOX6-2 and/or bevacizumab.
AE, adverse event; AESI, AE of special interest; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

- No new safety concerns were observed with longer-term follow-up
- No serious TRAEs occurred in more than 2 patients
- There were no zanidatamab discontinuations due to AEs of any cause, and 1 patient received a reduced zanidatamab dose due to AEs

Table 4. TRAEs Occurring in ≥20% of Patients With HER2-Positive mCRC

	Zanidatamab + mFOLFOX6-2 (n = 6)		Zanidatamab + mFOLFOX6-2 + bevacizumab (n = 7)		Total (N = 13)	
Preferred term, n (%)	**Grade 1–2**	**Grade ≥3**	**Grade 1–2**	**Grade ≥3**	**Grade 1–2**	**Grade ≥3**
Diarrhoea	3 (50)	1 (17)	5 (71)	2 (29)	8 (62)	3 (23)
Nausea	4 (67)	0	4 (57)	1 (14)	8 (62)	1 (8)
Peripheral sensory neuropathy	5 (83)	0	3 (43)	1 (14)	8 (62)	1 (8)
Ejection fraction decreased	2 (33)	0	2 (29)	1 (14)	4 (31)	1 (8)
Infusion-related reaction	3 (50)	0	2 (29)	0	5 (38)	0
Stomatitis	3 (50)	0	2 (29)	0	5 (38)	0
Fatigue	1 (17)	0	2 (29)	1 (14)	3 (23)	1 (8)
Vomiting	2 (33)	0	1 (14)	1 (14)	3 (23)	1 (8)
Neutrophil count decreased	0	1 (17)	1 (14)	1 (14)	1 (8)	2 (15)

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; mFOLFOX6-2, modified dose of 5-fluorouracil and leucovorin and oxaliplatin; TRAE, treatment-related adverse event.

- Diarrhoea was the most common grade ≥3 TRAE, occurring in 1/6 (17%) patients receiving zanidatamab + mFOLFOX6-2 and in 2/7 (29%) patients receiving zanidatamab + mFOLFOX6-2 + bevacizumab

Conclusions

- After 2 years of additional follow-up, zanidatamab plus chemotherapy ± bevacizumab continued to demonstrate encouraging antitumour activity and a generally manageable safety profile as 1L treatment for patients with HER2-positive mCRC
  - No patients discontinued zanidatamab due to TRAEs
  - At the last patient last visit, the cORR was 100%, with an additional partial response since the previously reported data cutoff (31 October 2023)[12]
  - Median PFS and duration of response were not reached; there was 1 death reported
- Clinical investigation of zanidatamab monotherapy in previously treated, HER2-positive mCRC is ongoing in the phase 2 tumour-agnostic DiscovHER PAN-206 study[15]

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