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Real-World Second-Line Treatment Patterns and Clinical Outcomes in Patients With HER2-Overexpressing Biliary Tract Cancer

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Background

- Biliary tract cancer (BTC), including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder cancer (GBC), is an aggressive, rare disease that typically presents at an advanced stage with a high symptom burden and a poor prognosis[1-3]
- The standard-of-care (SOC) therapy for first-line (1L) treatment is cisplatin + gemcitabine with or without the addition of pembrolizumab or durvalumab, which is associated with a median overall survival (OS) of approximately 13 months[3-6]
- Folinic acid, fluorouracil, and oxaliplatin (FOLFOX) as the second-line (2L) SOC provides minimal efficacy (median OS of 6 months) coupled with a high frequency of adverse events[7]
- Human epidermal growth factor 2 (HER2) overexpression has recently emerged as a target for precision therapies, addressing an unmet need for additional treatment options[8-10]
- There are currently no HER2 testing guidelines established for BTC
  - Various testing modalities, such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS), have been utilized in practice[11]

Objectives

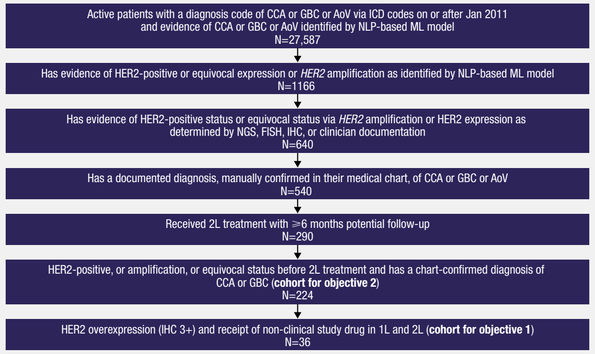
- To assess real-world treatment patterns and OS of patients with HER2-overexpressing (IHC 3+) advanced BTC who received 2L treatments
- To assess the HER2 testing patterns and concordance of HER2 overexpression (IHC 3+) and HER2-positive status (IHC 3+ or IHC 2+ with *HER2* gene amplification) and *HER2* amplification determined by NGS or FISH

Methods

- This is a retrospective observational study using custom data curated from the Flatiron Health Electronic Health Record (EHR) de-identified database covering the period of 01/2011 to 12/2023
- We included patients diagnosed with advanced/metastatic BTC who received 2L treatment and had at least 6 months of potential follow-up time (the latest date of 2L initiation needs to be 6 months before the latest date cut, 12/2023)
  - We then identified cohorts based on their HER2 status for each study objective
- Inclusion criteria included:
  - A chart-confirmed diagnosis of iCCA, eCCA, or GBC from the EHR data
  - Receipt of 2 or more lines of systemic therapies for advanced disease with a date of initiation of 2L therapy ⩾6 months before December 31, 2023, allowing potential ⩾6 months follow-up
  - Evidence of HER2-positive status (IHC 3+ or IHC 2+ with *HER2* amplification) or equivocal status (FISH-) via *HER2* amplification or *HER2* gene expression as defined by NGS, FISH, IHC, or clinician documentation (**objective 2**)
  - Evidence of HER2 overexpression defined as IHC test with a score of 3+, at any time prior to initiation of 2L therapy (**objective 1**)
- Exclusion criteria included:
  - A chart-confirmed diagnosis of ampullary cancer (excluded due to attrition)
  - Receipt of clinical study drug in 1L and 2L, but not for third line (3L)+
- Patients were grouped into the following treatment groups:
  - Received chemotherapy alone
  - Received regimens containing any HER2-targeted therapy, regardless of other combination therapies
  - Received regimens containing immune checkpoint inhibitors (ICIs) and other targeted therapy (excluding any HER2-targeted therapy)
- Follow-up start: Initiation of 2L treatment (index date)
- Follow-up end: The earliest of last recorded activity, death, or end of data (December 31, 2023)
- Descriptive statistics for baseline characteristics and 2L treatment patterns
- Kaplan-Meier estimator for OS, with censoring at last recorded activity/end of data
- Concordance of HER2 status and testing results estimated by percent agreement (+/+ or -/-)

Results

Figure 1. Flatiron External Control Arm Custom Data Attrition Diagram



1L, first-line; 2L, second-line; AoV, Ampulla of Vater; CCA, cholangiocarcinoma; FISH, fluorescence in situ hybridization; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; ICD, International Classification of Diseases; IHC, immunohistochemistry; ML, machine learning; NGS, next-generation sequencing; NLP, natural language processing.

Table 1. Baseline Characteristics and Demographics in the BTC IHC 3+ Total Cohort and by 2L Treatment Groups

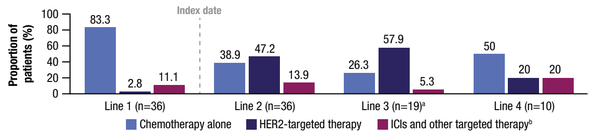
	IHC 3+ Total	Chemotherapy Alone	Regimens Containing HER2-Targeted Therapy	Regimens Containing ICIs and Other Targeted Therapy[a]
	N=36	n=14	n=17	n=5
Age at index date (years), median (25th, 75th percentile)	67 (57, 73)	68 (63, 73)	66 (57, 73)	67 (63, 71)
Female, n (%)	24 (66.7)	10 (71.4)	11 (64.7)	3 (60.0)
Race/Ethnicity, n (%)				
White	18 (56.2)	7 (53.8)	9 (64.3)	2 (40.0)
Black or African American	7 (21.9)	3 (23.1)	2 (14.3)	2 (40.0)
Other	7 (21.9)	3 (23.1)	3 (21.4)	1 (20.0)
Missing	4 (11.1)	1 (7.1)	3 (17.6)	0
Disease subtype, n (%)				
GBC	22 (61.1)	10 (71.4)	11 (64.7)	1 (20.0)
iCCA	11 (30.6)	4 (28.6)	4 (23.5)	3 (60.0)
eCCA	3 (8.3)	0	2 (11.8)	1 (20.0)
ECOG status within 30 days prior to index,[b] n (%)				
0	6 (21.4)	4 (33.3)	2 (15.4)	0
1	15 (53.6)	6 (50.0)	7 (53.8)	2 (66.7)
2	5 (17.9)	1 (8.3)	3 (23.1)	1 (33.3)
3	2 (7.1)	1 (8.3)	1 (7.7)	0
Missing	8 (22.2)	2 (14.3)	4 (23.5)	2 (40.0)
Stage at initial diagnosis, n (%)				
II	6 (22.2)	2 (20.0)	4 (30.8)	0
III	7 (25.9)	3 (30.0)	2 (15.4)	2 (50.0)
IV	14 (51.9)	5 (50.0)	7 (53.8)	2 (50.0)
Missing	9 (25.0)	4 (28.6)	4 (23.5)	1 (20.0)

[a]Other non–HER2-targeted therapies included bevacizumab + erlotinib, olaparib, pemigatinib, regorafenib.
[b]ECOG assessed at the most recently recorded value from 30 days prior to index date through index date (inclusive).

2L, second-line; BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; HER2, human epidermal growth factor 2; iCCA, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitors; IHC, immunohistochemistry.

- In 36 patients with HER2 overexpression (IHC 3+) who received 2L treatment, 14 (38.9%) patients received chemotherapy only, 17 (47.2%) patients received regimens containing HER2-targeted therapy (alone or in combination with other therapies), and 5 (13.9%) patients received regimens containing ICIs and other targeted therapy as a 2L treatment (**Table 1**)
- Baseline demographics and clinical characteristics were generally similar across the chemotherapy only and HER2-targeted therapy treatment groups
- Comorbidities such as diabetes, chronic pulmonary disease, and congestive heart failure were more frequent in patients who received chemotherapy only and non–HER2-targeted therapy than in patients who received HER2-targeted therapy
- Across all treatment groups, there were no patients that had central nervous metastasis

Figure 2. Treatment Types per Line of Therapy



[a]10.5% (2/19) of patients in line 3 received a clinical study drug.
[b]Other non–HER2-targeted therapies included bevacizumab + erlotinib, olaparib, pemigatinib, regorafenib.
HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor.

- In the 1L, 75% (27/36) of patients received gemcitabine-based chemotherapy (69.4% [25/36] received gemcitabine + cisplatin), 25% (9/36) received fluoropyrimidine-based chemotherapy, and 11.1% (4/36) received programmed cell death protein 1 (PD-1) or programmed death ligand 1 inhibitor (PD-L1)
- In the 2L:
  - A total of 47.2% (17/36) of patients received regimens containing HER2-targeted therapy (alone or in combination)
    - HER2-targeted therapy included trastuzumab (T) + pertuzumab (P) (41.2% [7/17]) and trastuzumab deruxtecan (11.8% [2/17])
    - Combinations of HER2-targeted therapy included T + chemotherapy (35.3% [6/17]), T + P + chemotherapy (5.9% [1/17]), and T + P + ICI (5.9% [1/17])
  - 2L chemotherapy only group (38.9% [14/36]) included FOLFOX (50% [7/14]), folinic acid; 5-fluorouracil (5-FU); irinotecan (FOLFORI; 14.3% [2/14]), gemcitabine + capecitabine/carboplatin/cisplatin (21.4% [3/14]), and 5-FU + leucovorin (7.1% [1/14])
  - ICIs and other targeted therapies included chemotherapy + ICIs (8.3% [3/36]), and other non-HER2 tyrosine kinase inhibitors ± bevacizumab (5.6% [2/36])

Table 2a. Real-World Overall Survival in the Total BTC IHC 3+ Cohort and by 2L Treatment Groups

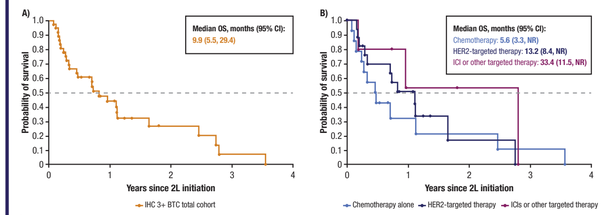
	IHC 3+ Total N=36	Chemotherapy Only n=14	Regimens Containing HER2-Targeted Therapy n=17	Regimens Containing ICIs and Other Targeted Therapy n=5
Events, N	27	12	12	3
Censored, N	9	2	5	2
Median overall survival, months (95% CI)	9.9 (5.5, 29.40)	5.6 (3.3, NR)	13.2 (8.4, NR)	33.4 (11.5, NR)

Table 2b. Real-World Overall Survival in Patients With ECOG 0 or 1 in the Total BTC IHC 3+ Cohort and by 2L Treatment Groups

ECOG 0 or 1	IHC 3+ Total N=21	Chemotherapy Only n=10	Regimens Containing HER2-Targeted Therapy n=9	Regimens Containing ICIs and Other Targeted Therapy n=2
Events, N	17	8	7	2
Censored, N	4	2	2	0
Median overall survival, months (95% CI)	8.7 (3.3, NR)	6.2 (2.8, NR)	9.9 (4.0, NR)	6.9 (2.2, NR)

2L, second-line; BTC, biliary tract cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; NR, not reached.

Figure 3. Real-World Overall Survival in (A) BTC IHC 3+ Total Cohort and (B) 2L Treatment Groups



Dotted line shows median overall survival.

2L, second-line; BTC, biliary tract cancer; CI, confidence interval; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; NR, not reached; OS, overall survival.

Positive or Equivocal Status Defined by NGS, FISH, or IHC

Table 3. Testing patterns in patients with positive or equivocal status defined by NGS, FISH, or IHC

IHC	FISH	NGS	Number of Patients
			N=224 (100%)
√	√	√	80 (35.7)
		√	66 (29.5)
√		√	29 (12.1)
√	√		27 (12.9)
√			11 (4.9)
	√		7 (3.1)
	√	√	4 (1.8)

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing.

- The testing cohort for *HER2* amplification or overexpression consisted of 224 patients (**Table 3**)
  - 65.6% had IHC results with or without confirmatory FISH or NGS
  - 35.7% had IHC, FISH, and NGS testing results
  - 29.5% had NGS results only

Table 4. Concordance Between HER2 Overexpression Status by IHC and *HER2* Amplification by NGS

		NGS			Concordance[b]
		Amplification	No Amplification	Total	76.2% (15+46/80)
HER2 overexpression (IHC 3+)	Count	15	4	19	
	% within NGS[a]	79.0	21.1	100.0	
No HER2 overexpression (IHC 2+, 1+, or 0)	Count	15	46	61	
	% within NGS	24.6	75.4	100.0	
Total	Count	30	50	80	
	% within NGS	37.5	62.5	100	

Green shading indicates the proportion of patients with or without *HER2* amplification, as determined by NGS, among patients with HER2 overexpression and those without, respectively.

[a]Cell count divided by total number of patients with amplification and non-amplification by NGS in each IHC group; eg, IHC 3+ patients with amplification by NGS divided by IHC 3+ with and without amplification by NGS; [b]Concordance was defined as both tests being positive or negative (HER2+ and FISH+; HER2- and FISH-).

FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing.

- Concordance between HER2 overexpression status by IHC and *HER2* amplification by NGS was 76.2% (**Table 4**)
- Similar concordance between HER2 overexpression status by IHC and *HER2* amplification by FISH were found

Table 5. Concordance Between HER2-positive status and *HER2* Amplification by NGS

		NGS			Concordance[c]
		Amplification	No Amplification	Total	82.5% (26+40)/80
HER2+ (IHC 3+ or IHC 2+ with *HER2* amplification)	Count	26	10	36	
	% within NGS[a]	72.2	27.8	100.0	
	% within HER2[b]	86.7	20.0	45.0	
HER2- (IHC 2+ without *HER2* amplification or IHC 1+ or 0)	Count	4	40	44	
	% within NGS	9.1	90.9	100.0	
	% within HER2	13.3	80.0	55.0	
Total	Count	30	50	80	
	% within NGS	37.5	62.5	100.0	
	% within HER2	100.0	100.0	100.0	

Green shading indicates the proportion of patients with or without *HER2* amplification, as determined by NGS, among patients with HER2-positive status and those with HER2-negative status, respectively.

Purple shading indicates the proportion of patients with HER2-positive status among patients with *HER2* amplification as determined by NGS.

[a]Cell count divided by total number of patients with amplification and non-amplification by FISH in each HER2 group; eg, HER2-positive patients with amplification by FISH divided by HER2-positive with and without amplification by NGS; [b]Cell count divided by the total number of patients with HER2 status in each FISH group; eg, patients with HER2 status with amplification by FISH divided by patients with HER2 results with amplification by FISH; [c]Concordance was defined as both tests being positive or negative (HER2+ and FISH+; HER2- and FISH-).

FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing.

- Concordance between HER2-positive status and *HER2* amplification by NGS was 82.5% (**Table 5**)
- Similar concordance between HER2-positive status by IHC and *HER2* amplification by FISH were found

Study Limitations

- A substantial amount of the patients only received NGS for molecular profiling; however, detection by NGS is limited by lack of standardized cutoffs
- This study included the small sample size, which may be due to:
  - The rarity of the disease
  - Due to the lack of HER2-targeted therapies approved by the U.S. Food and Drug Administration at the start of database inclusion dates, HER2-specific molecular profiling was not performed in all patients, and therefore not established prior to study start

Conclusions

- In this US real-world retrospective study, the OS of patients with HER2-overexpressed BTC who received chemotherapy only was consistent with previous reports[7,12,13]
- HER2-targeted therapy demonstrated a numerical improvement in OS vs chemotherapy alone in patients with HER2-overexpressed BTC (median OS was 13.2 months vs 5.2 months)
- HER2-targeted therapies were mainly administered in 2L or 3L, aligning with current clinical practice guidelines for the use of targeted therapies
- Concordance between HER2 overexpression by IHC and *HER2* amplification by NGS was 76.2%
  - These findings suggest that both IHC (to detect HER2 protein overexpression) and NGS (to detect *HER2* gene amplification) should be utilized to accurately identify patients who can benefit from HER2-targeted therapy
    - NGS alone may underrepresent patients with HER2 overexpression who do not show *HER2* amplification
  - In cases where tissue availability is limited, NGS may provide insights into HER2 status

References: 1. Moeini A, et al. *JHEP Rep.* 2021;3(2):100226. **2.** Hunter LA, Soares HP. *Cancers (Basel).* 2021;13(20):5074. **3.** Koshiol J, et al. *BMC Cancer.* 2022;22(1):1178. **4.** Kelley RK, et al. *Lancet.* 2023;401:1853-1865. **5.** Oh DY, et al. *Lancet Gastroenterol Hepatol.* 2024;9(8):694-704. **6.** Vitale E, et al. *Front Oncol.* 2024;14:1409132. **7.** Lamarca A, et al. *Lancet Oncol.* 2021;22(5):690-701. **8.** Harding JJ, et al. *J Hepatol.* 2023;78:217-228. **9.** Kam AE, et al. *Lancet Gastroenterol Hepatol.* 2021;6:956-969. **10.** Harding JJ, et al. *Lancet Oncol.* 2023;24(7):772-782. **11.** Vogel A, Ducreux M. *ESMO Open.* 2025;10(1)104003. **12.** Caparica R, et al. *Autops Cas Rep.* 2019;9(2):e2019087. **13.** Mizrahi JD, et al. *World J Gastrointest Oncol.* 2020;12(1)83-91.

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