Molecular Profiling, Treatment Patterns, and Healthcare Resource Utilization in Patients in the USA With Unresectable Locally Advanced/Metastatic Biliary Tract Cancer

EE416

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Background

- Biliary tract cancer (BTC) encompasses rare hepatic and perihepatic tumors, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder cancer (GBC); at diagnosis, most patients present with unresectable, locally advanced or metastatic disease[1]
- Advanced stage presentation (AdvBTC) and limited treatment options lead to a poor prognosis; 5-year overall survival (OS) is 3% for distant disease[2]
- Recently, anti-programmed death-ligand 1 (PD-L1) antibodies have demonstrated improved 2-year OS from 10% to 24% when used as add-on immunotherapy to cisplatin plus gemcitabine in first-line (1L) treatment of AdvBTC[3,4]; subsequent lines of therapy for AdvBTC, such as FOLFOX (leucovorin, fluorouracil and oxaliplatin), show incremental survival benefits and significant toxicity[5]
- Overexpression of human epidermal growth factor 2 ([HER2] also known as ERBB2) has recently emerged as a target for precision therapies in second-line (2L) AdvBTC and beyond[6]
- Healy et al[7] reported a real-world analysis of treatment patterns, healthcare resource utilization (HCRU), healthcare costs, and mortality among people with BTC in the USA from January 2016 to June 2020; the present study builds on this knowledge by creating an AdvBTC cohort and presenting post-2020 data and molecular profiling patterns

Objective

- To describe real-world demographics and clinical characteristics, molecular profiling, treatment patterns, HCRU, and healthcare costs in patients with AdvBTC in the USA

Methods

- This was a retrospective, observational study of adult patients with AdvBTC using data from the Optum Market Clarity+ database, which includes USA electronic health records (EHR) and administrative claims linked database, from January 2007 to December 2023

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Diagnosis of BTC (ie, diagnosis of iCCA, eCCA, or GBC) on 1 non-diagnostic inpatient or 2 non-diagnostic outpatient medical claims (1-90 days apart) • Evidence of AdvBTC: stage III without resection, metastatic disease, or relapse after resection • Continuous health insurance enrollment in both medical and prescription drug insurance plans (allowing a 45-day gap in insurance coverage for any reason) from 182 days before (baseline period) to 30 days after the index date (date of the first AdvBTC diagnosis), unless a patient died within 30 days after the index date • ⩾18 years of age at index date	• Diagnosis of primary malignancy other than BTC, except for non-melanoma skin cancer, within 182 days prior to the index date • Clinical trial participation within 182 days prior to the index date

- Patients' records were analyzed from the first AdvBTC diagnosis date (**index date**) to the end of continuous enrollment in an insurance plan, death, or end of study date (December 2023), whichever came first
- Patients were assigned into cohorts according to: HER2-positive status (**HER2+**); index date (**indexed pre-2020; indexed in/after 2020**); and line of therapy (**1L; 2L; third-line and beyond [3L+]**); cohorts were not mutually exclusive, and patients could be included in more than 1 cohort based on stratification variables
  - Patients were included in the HER2+ cohort if their tumor was immunohistochemistry [IHC] 3+, or IHC 2+ with gene amplification (determined by fluorescence in situ hybridization and/or next generation sequencing [NGS]), as reported in the EHRs, or if the patient had received any HER2-targeted agent(s)
- Descriptive statistics were calculated for baseline characteristics, molecular profiling, treatment patterns, HCRU, and costs

Results

Figure 1. Optum Market Clarity+ Data[a] Attrition Diagram

[a]Optum Market Clarity+ data from January 1, 2007, to December 31, 2023, with 112 million patients in the database; [b]Defined as any one of the following: stage III disease without resection, metastatic disease, or relapse after resection; [c]First unresectable locally advanced/metastatic iCCA, eCCA, or GBC diagnosis date.

Demographics and Clinical Characteristics

Table 2. Demographics and Clinical Characteristics During the Baseline Period

	Overall N=5480	HER2+ n=61	Indexed Pre-2020 n=2516	Indexed In/After 2020 n=2964
Age at index (years), mean (SD)	66.8 (11.7)	61.3 (14.3)	66.4 (11.5)	67.2 (12.0)
Female, n (%)	2963 (54.1)	40 (65.6)	1385 (55.0)	1578 (53.2)
Race/ethnicity, n (%)				
White/Caucasian	3504 (63.9)	31 (50.8)	1649 (65.5)	1855 (62.6)
African American	629 (11.5)	10 (16.4)	281 (11.2)	348 (11.7)
Asian	152 (2.8)	4 (6.6)	65 (2.6)	87 (2.9)
Other/unknown/missing	1195 (21.8)	16 (26.2)	521 (20.7)	674 (22.7)
Region, n (%)				
Northeast	1413 (25.8)	20 (32.8)	683 (27.1)	730 (24.6)
Midwest	2066 (37.7)	20 (32.8)	956 (38.0)	1110 (37.4)
South	1193 (21.8)	9 (14.8)	537 (21.3)	656 (22.1)
West	585 (10.7)	10 (16.4)	233 (9.3)	352 (11.9)
Other/unknown/missing	223 (4.1)	2 (3.3)	107 (4.3)	116 (3.9)
Insurance type, n (%)				
Commercial	1848 (33.7)	33 (54.1)	888 (35.3)	960 (32.4)
Medicaid	522 (9.5)	7 (11.5)	244 (9.7)	278 (9.4)
Medicare	2873 (52.4)	21 (34.4)	1227 (48.8)	1646 (55.5)
Multiple payer types/unknown/missing	237 (4.3)	0 (0)	157 (6.2)	80 (2.7)
NCI Comorbidity Index, mean (SD)[a]	2.6 (2.5)	1.6 (1.9)	2.5 (2.4)	2.7 (2.5)
Weight (kg), mean (SD)[b]	81.6 (22.1)	81.5 (19.4)	80.7 (21.2)	82.6 (23.0)
Missing, n (%)	3492 (63.7)	37 (60.7)	1404 (55.8)	2088 (70.4)
Tumor location of first BTC diagnosis, n (%)				
Intrahepatic	3345 (61.0)	29 (47.5)	1484 (59.0)	1861 (62.8)
Extrahepatic	617 (11.3)	2 (3.3)	303 (12.0)	314 (10.6)
Gallbladder	1250 (22.8)	27 (44.3)	606 (24.1)	644 (21.7)
Mixed	178 (3.2)	2 (3.3)	83 (3.3)	95 (3.2)
Not specified	90 (1.6)	1 (1.6)	40 (1.6)	50 (1.7)
Time since first BTC diagnosis (days), mean (SD)	102.8 (321.7)	87.3 (378.3)	105.1 (296.0)	100.9 (342.1)

[a]Higher NCI Comorbidity Index scores indicate a higher mortality risk; [b]If multiple weight records were observed on the same day, average weight was calculated.

- Demographics/clinical characteristics were similar in patients indexed pre- vs in/after 2020 (**Table 2**)
- Slightly younger age and lower comorbidity burden occured in the HER2+ cohort compared with the overall cohort

Molecular Profiling

Table 3. Molecular Profiling for Any Genetic Mutations by Time Period

	Overall N=5480			Patients Indexed In/After 2022[a] n=1402		
	All Patients[b]	Pre-Index Date[b]	Post-Index Date[b]	All Patients[b]	Pre-Index Date[b]	Post-Index Date[b]
Overall, n (%)[c]	3694 (67.4)	1061 (19.4)	3151 (57.5)	985 (70.3)	327 (23.3)	812 (57.9)
IHC	3604 (65.8)	1013 (18.5)	3066 (55.9)	948 (67.6)	310 (22.1)	774 (55.2)
ISH/FISH	625 (11.4)	145 (2.6)	493 (9.0)	219 (15.6)	60 (4.3)	166 (11.8)
NGS	486 (8.9)	71 (1.3)	426 (7.8)	225 (16.0)	39 (2.8)	190 (13.6)

[a]Molecular testing first recommended in National Comprehensive Cancer Network guidelines in 2022; [b]Pre-index date refers to the period from the first diagnosis of BTC to the first diagnosis of AdvBTC (index date) (exclusive). Post-index date refers to the period from the first diagnosis of AdvBTC (index date) (inclusive) to the end of follow-up. There were 1047 de novo metastatic patients with AdvBTC date earlier than the BTC date which were excluded from the pre-index analysis; [c]Categories are not mutually exclusive. Some patients may have ⩾1 test type.

- In the overall cohort, 67% (3694/5480) of patients had ⩾1 molecular test since the first diagnosis, and most occurred post-index (**Table 3**)
- IHC (for any biomarker) was the most common testing type used to investigate the molecular profile of patients with AdvBTC; NGS testing increased for patients in/after 2022 vs the overall cohort in both the pre-index (1.3% vs 2.8%) and post-index (7.8% vs 13.6%) periods, albeit of low utilization (**Table 3**)

Surgical Procedures/Treatment Patterns

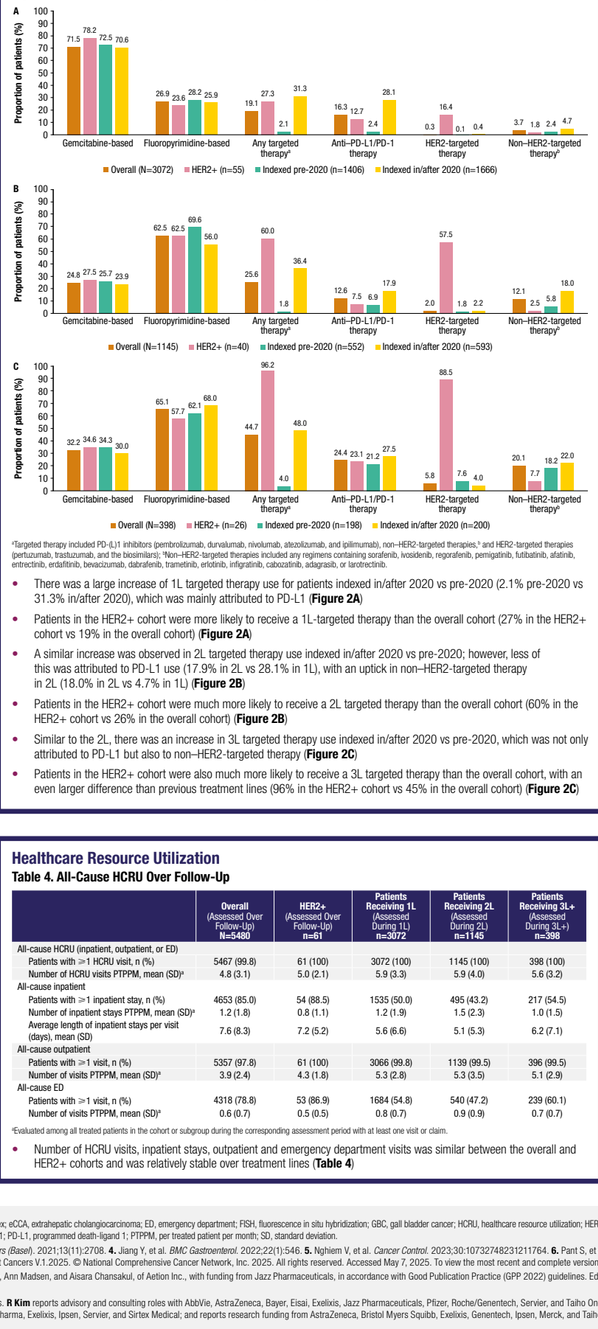
- In the overall cohort, 20% (1092/5480) of patients had surgical procedures from the date of the first BTC diagnosis to the index date
- 56% (3072/5480) of patients had any Systemic Anti-Cancer Therapy (SACT), with 21% (1145/5480) progressing from 1L to 2L treatment, and 7% (398/5480) progressing to 3L+
- The percentage of patients in the HER2+ cohort who had SACT was higher vs the overall cohort

Patient Characteristics by Line of Therapy

- Demographic/clinical characteristics for 1L, 2L, and 3L+ patients were assessed within 3 months prior to the start of 1L, 2L, and 3L+ treatments, respectively
- Compared to 1L (n=3072), 2L patients (n=1145) had:
  - A higher percentage of commercial insurance (53% in 2L vs 43% in 1L) and lower Medicare coverage (36% in 2L vs 44% in 1L)
  - A lower mean NCI Comorbidity Index score (average of 1.9 in 2L vs 2.4 in 1L) and a lower frequency of mild liver disease (42% in 2L vs 65% in 1L)

Treatment Regiments by Line of Therapy

Figure 2. Distribution of Regimens in (A) 1L, (B) 2L, and (C) 3L+ for Different Cohorts



[a]Targeted therapy included PD-(L)1 inhibitors (pembrolizumab, durvalumab, nivolumab, atezolizumab, and ipilimumab), non–HER2-targeted therapies,[b] and HER2-targeted therapies (pertuzumab, trastuzumab, and the biosimilars); [b]Non–HER2-targeted therapies included any regimens containing sorafenib, lvosidenib, regorafenib, pemigatinib, futibatinib, afatinib, entrectinib, erdafitinib, bevacizumab, dabrafenib, trametinib, erlotinib, infigratinib, cabozatinib, adagrasib, or larotrectinib.

- There was a large increase of 1L targeted therapy use for patients indexed in/after 2020 vs pre-2020 (2.1% pre-2020 vs 31.3% in/after 2020), which was mainly attributed to PD-L1 (**Figure 2A**)
- Patients in the HER2+ cohort were more likely to receive a 1L-targeted therapy than the overall cohort (27% in the HER2+ cohort vs 19% in the overall cohort) (**Figure 2A**)
- A similar increase was observed in 2L targeted therapy use indexed in/after 2020 vs pre-2020; however, less of this was attributed to PD-L1 use (17.9% in 2L vs 28.1% in 1L), with an uptick in non–HER2-targeted therapy in 2L (18.0% in 2L vs 4.7% in 1L) (**Figure 2B**)
- Patients in the HER2+ cohort were much more likely to receive a 2L targeted therapy than the overall cohort (60% in the HER2+ cohort vs 26% in the overall cohort) (**Figure 2B**)
- Similar to the 2L, there was an increase in 3L targeted therapy use indexed in/after 2020 vs pre-2020, which was not only attributed to PD-L1 but also to non–HER2-targeted therapy (**Figure 2C**)
- Patients in the HER2+ cohort were also much more likely to receive a 3L targeted therapy than the overall cohort, with an even larger difference than previous treatment lines (96% in the HER2+ cohort vs 45% in the overall cohort) (**Figure 2C**)

Healthcare Resource Utilization

Table 4. All-Cause HCRU Over Follow-Up

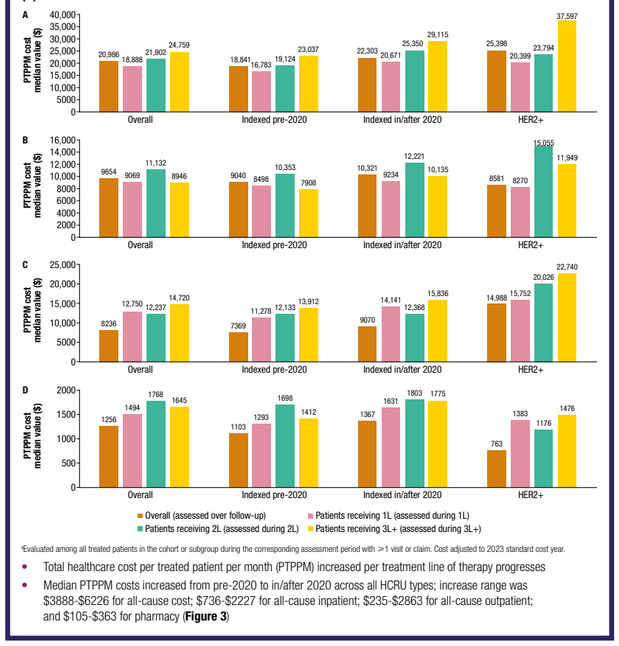
	Overall (Assessed Over Follow-Up) N=5480	HER2+ (Assessed Over Follow-Up) n=61	Patients Receiving 1L (Assessed During 1L) n=3072	Patients Receiving 2L (Assessed During 2L) n=1145	Patients Receiving 3L+ (Assessed During 3L+) n=398
All-cause HCRU (inpatient, outpatient, or ED)					
Patients with ⩾1 HCRU visit, n (%)	5467 (99.8)	61 (100)	3072 (100)	1145 (100)	398 (100)
Number of HCRU visits PTPPM, mean (SD)[a]	4.8 (3.1)	5.0 (2.1)	5.9 (3.3)	5.9 (4.0)	5.6 (3.2)
All-cause inpatient					
Patients with ⩾1 inpatient stay, n (%)	4653 (85.0)	54 (88.5)	1535 (50.0)	495 (43.2)	217 (54.5)
Number of inpatient stays PTPPM, mean (SD)[a]	1.2 (1.8)	0.8 (1.1)	1.2 (1.9)	1.5 (2.3)	1.0 (1.5)
Average length of inpatient stays per visit (days), mean (SD)	7.6 (8.3)	7.2 (5.2)	5.6 (6.6)	5.1 (5.3)	6.2 (7.1)
All-cause outpatient					
Patients with ⩾1 visit, n (%)	5357 (97.8)	61 (100)	3066 (99.8)	1139 (99.5)	396 (99.5)
Number of visits PTPPM, mean (SD)[a]	3.9 (2.4)	4.3 (1.8)	5.3 (2.8)	5.3 (3.5)	5.1 (2.9)
All-cause ED					
Patients with ⩾1 visit, n (%)	4318 (78.8)	53 (86.9)	1684 (54.8)	540 (47.2)	239 (60.1)
Number of visits PTPPM, mean (SD)[a]	0.6 (0.7)	0.5 (0.5)	0.8 (0.7)	0.9 (0.9)	0.7 (0.7)

[a]Evaluated among all treated patients in the cohort or subgroup during the corresponding assessment period with at least one visit or claim.

- Number of HCRU visits, inpatient stays, outpatient and emergency department visits was similar between the overall and HER2+ cohorts and was relatively stable over treatment lines (**Table 4**)

Healthcare Cost

Figure 3. All-Cause Cost Assessed in the (A) PTPPM, (B) Inpatient PTPPM, (C) Outpatient PTPPM, and (D) All-Cause ED PTPPM[a]



[a]Evaluated among all treated patients in the cohort or subgroup during the corresponding assessment period with ⩾1 visit or claim. Cost adjusted to 2023 standard cost year.

- Total healthcare cost per treated patient per month (PTPPM) increased per treatment line of therapy progresses
- Median PTPPM costs increased from pre-2020 to in/after 2020 across all HCRU types; increase range was $3888-$6226 for all-cause cost; $736-$2227 for all-cause inpatient; $235-$2863 for all-cause outpatient; and $105-$363 for pharmacy (**Figure 3**)

Strengths

- Use of a large USA representative database that integrates a vast network of EHRs with linked claims data
- AdvBTC definition was robust, encompassing not only diagnosis codes for metastasis and procedure codes for resection from claims but also staging information from EHRs
- Data from this study further advance the knowledge, building on Healy et al[7] by adding post-2020 data and results on treatment patterns and costs/HCRU, and by reflecting changes in treatment patterns and HCRU compared with pre-2020 data

Limitations

- Real-world data may be subject to incomplete coding of diagnoses, procedures, and variables of interest, which could lead to under-ascertainment, misclassification, or bias
- Findings related to HER2+ may not be generalizable to the whole HER2+ population due to most patients in the HER2+ cohort being identified by treatment and not gene amplification or protein expression
- NGS use may not be captured in claims

Conclusions

- Biomarker testing may not be optimally utilized in patients with AdvBTC, with ⩾30% receiving no testing in this study
- Use of targeted therapies was higher in later treatment lines (2L, 3L) compared to 1L; this may be due to the 2L+ approvals for most targeted therapies
- Healthcare costs generally increased with higher treatment lines (2L, 3L) and were slightly higher after 2020, and generally higher in the HER2+ cohort

Table and Figure Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; 3L+, third-line and beyond; AdvBTC, advanced biliary tract cancer; BTC, biliary tract cancer; BMI, body mass index; eCCA, extrahepatic cholangiocarcinoma; ED, emergency department; FISH, fluorescence in situ hybridization; GBC, gall bladder cancer; HCRU, healthcare resource utilization; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; ISH, in situ hybridization; NCI, National Cancer Institute; NMSC, non-melanoma skin cancer; NGS, next generation sequencing; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTPPM, per treated patient per month; SD, standard deviation.

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