HSD26

Descriptive Landscape for Targeted Treatments in Second-Line Biliary Tract Cancer: A Targeted Literature Review

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Background

- Biliary tract cancer (BTC) is a heterogenous and rare group of malignancies, including gallbladder cancer, intrahepatic and extrahepatic cholangiocarcinoma,[1,2] that represents less than 1% of all cancers[3]
- BTC often harbors clinically actionable molecular alterations including isocitrate dehydrogenase (IDH), fibroblast growth factor receptor (FGFR), and human epidermal growth factor receptor 2 (HER2), with expression varying by anatomical subtype[4,5]

Objective

- A targeted literature review (TLR) was conducted to:
  - Understand the current standard of care (SOC) in second-line (2L) BTC and contextualize genetic targets of interest for targeted treatments
  - Summarize ongoing clinical trials for treatments targeting HER2, FGFR, and IDH in BTC across all treatment lines

Methods

- A search strategy ensured retrieval of evidence aligned with research objectives
- Searches were conducted in August 2023 covering the previous 5 years (2018–2023), including MEDLINE (PubMed version), Trip, WHO, GIN, and National Comprehensive Cancer Network (NCCN). Screening, prioritization, and extraction followed Cochrane guidance[6,7]
- Thirty articles were selected for extraction and reporting, guided by the quality articles including study type, and focus on answering the research questions of interest (see below):
  - Clinical guidelines were prioritized based on countries of interest (US, UK, EU, and Japan) and publication date
  - Primary and full-text screening of articles was conducted based on pre-specified inclusion/exclusion criteria by a single reviewer, with any uncertainties consulted and resolved by a second reviewer
  - Articles were selected for extraction and reporting via a scoring system. Pre-specified prioritization factors included coverage of subtypes, publication date, study type, and reference to clinical pathways
- Supplementary electronic searches supported and contextualized findings
- Clinicaltrials.gov was searched for HER2, IDH, and FGFR terms in the 'biliary tract cancer', 'bile tract cancer' (which includes cholangiocarcinoma), and 'gallbladder cancer' categories across all treatment lines on March 19, 2024
- Search findings are subject to indexing rules and may not capture 100% of the trials for the indications, especially for basket trials

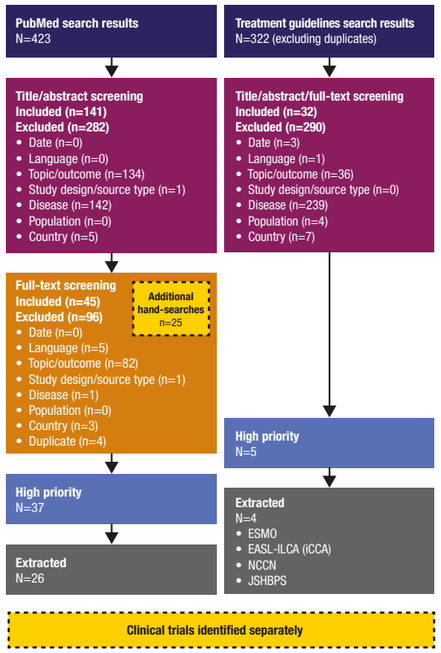
Results

- **Figure 1** summarizes identified and included studies
  - Clinical guidelines: European Society for Medical Oncology (ESMO), European Association for the Study of the Liver-International Liver Cancer Association (EASL-ICLA), NCCN, and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS)
  - Wider literature: 19 articles were expert reviews, 5 articles were systematic literature reviews or meta-analyses, and 2 articles contained real-world evidence
  - Clinical trials: 57 unique ongoing clinical trials identified for patients with HER2-positive, FGFR-positive, or IDH-positive BTC

Overview of clinical guidelines included in TLR (2L BTC)

- Treatment options in 2L BTC are similar across the 4 guidelines
  - FOLFOX is recommended in ESMO, EASL-ICLA, and NCCN guidelines.[3,17,18] JSHBPS guidelines indicate fluoropyrimidines as standard 2L treatment[19]
  - Targeted- and immuno- therapies are referenced as an alternative option to FOLFOX across all 4 clinical guidelines, when disease is linked to actionable alterations and/or checkpoint blockade

Figure 1. Search and Screening Results for PubMed and Treatment Guideline Searches



EASL-ILCA, European Association for the Study of the Liver and International Liver Cancer Association; ESMO, European Society for Medical Oncology; iCCA, intrahepatic cholangiocarcinoma; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; NCCN®, National Comprehensive Cancer Network®.

Table 1. Overview of the Clinical Guidelines Included in the TLR

Guideline (Year)	Population(s) Stated in Guideline	Diagnostic Pathway	Recommends Biomarker Testing?	Treatment Pathway
ESMO (2022)	BTC and its subclassifications	✓	✓	✓
EASL-ILCA (2023)	Intrahepatic CCA	✓	No	✓
NCCN (2023)	BTC and its subclassifications	✓	✓	✓
JSHBPS (2021)	Bile duct (including CCA, gallbladder, and ampullary cancer)	✓	NR	✓

BTC, biliary tract cancer; CCA, cholangiocarcinoma; EASL-ILCA, European Association for the Study of the Liver and International Liver Cancer Association; ESMO, European Society for Medical Oncology; JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; NCCN®, National Comprehensive Cancer Network®; NR, not reported; TLR, targeted literature review.

- There are important differences in the level and type of detail of diagnostic testing recommendations in BTC (**Table 1**). The NCCN and ESMO guidelines specifically recommend testing for a range of biomarkers (**Table 2**), unlike EASL-ILCA, which does not recommend biomarker testing, and JSHBPS, which does not report on biomarker testing
  - ESMO recommends that testing should be conducted before or during first-line systemic therapy
  - NCCN does not explicitly mention the time point in the pathway for molecular testing

Table 2. ESMO and NCCN Recommendations for Molecular Testing in BTC

Guideline	Biomarker (Per Guideline)										
	BRAF	CA 19-9	c-MET	FGFR2	HER2	IDH1	MSI/MMR	NTRK	PD-L1	RET	TMB
ESMO	✓	✓	✓	✓	✓	✓	✓	✓	NR	NR	NR
NCCN	✓	NR	NR	✓[a]	✓	✓[a]	✓	✓	✗	✓	✓

[a]Testing for IDH1 and FGFR2 fusions or rearrangements is recommended for patients with unresectable or metastatic intrahepatic or extrahepatic CCA and should be considered for patients with unresectable or metastatic gallbladder cancer.

✓= recommended; ✗ = not recommended; NR = not reported.

BRAF, v-raf murine sarcoma viral oncogene homolog B1; BTC, biliary tract cancer; CA 19-9, cancer antigen 19-9; CCA, cholangiocarcinoma; cMET, mesenchymal epithelial transition factor; ESMO, European Society for Medical Oncology; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; MMR, mismatch repair; MSI, microsatellite instability; NCCN®, National Comprehensive Cancer Network®; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death-ligand 1; RET, rearranged during transfection; TMB, tumor mutational burden.

- **Table 2** demonstrates that despite many actionable alterations in BTC, ESMO and NCCN clinical guidelines currently differ in recommendations for testing for these specific targets in patients with BTC
  - There is consensus in testing for FGFR2, IDH1, v-raf murine sarcoma viral oncogene homolog B1 (BRAF), microsatellite instability/mismatch repair (MSI/MMR), HER2, and neurotrophic tyrosine kinase receptor (NTRK) alterations across both guidelines
- ESMO and NCCN provide some guidance on the diagnostic approach for molecular testing
  - ESMO focuses on the use of next generation sequencing (NGS) but states the preferred technology depends on the targets, and the availability of material for testing (e.g. tissue or circulating tumor DNA). Immunohistochemistry (IHC) is only mentioned as an option for MSI testing, with no reference to fluorescent in situ hybridization (FISH) for any biomarker testing
  - NCCN is the only guideline providing details for recommended testing techniques within each anatomic subtype, as well as by gene mutation/biomarker type
  - NCCN recommends NGS assays to test for FGFR2 mutations and tumor NGS using a multi-gene panel or hotspot mutation testing to identify IDH1 mutations. It is noted that NGS can be considered for HER2 testing when limited diagnostic tissue is available, however IHC/FISH are most utilized

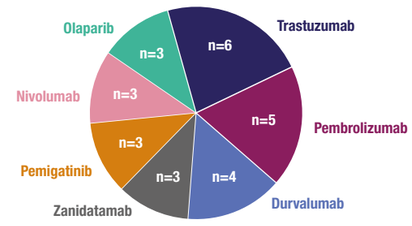
Definition of 2L SOC in wider literature

- 2L SOC is not consistently defined across articles
- Four articles identified FOLFOX (fluorouracil, leucovorin plus oxaliplatin) as the SOC in 2L BTC (publication years 2021–2023)[8-11]
- Six articles concluded there is no global SOC in 2L BTC (publication years spanning 2018–2023)[5,12-16]
  - One paper identified was published in 2018, prior to the FOLFOX pivotal trial publication
- Within a TLR setting, it is not possible to make any accurate or unbiased inferences of how views may have changed over time. Nonetheless, within this TLR, a higher proportion of articles identifying FOLFOX as the SOC tended to be published in more recent years, compared with articles concluding no SOC, which were slightly older

Treatments frequently discussed in 2L BTC

- Chemotherapies were most frequently discussed, with FOLFOX or FOLFIRI (fluorouracil, leucovorin plus irinotecan) regimens mentioned in 46% of articles
- Alternatives such as fluoropyrimidine, 5-fluorouracil, and irinotecan combination were mentioned in 27% of articles
- A wide range of actionable alterations were identified
  - HER2, FGFR2, Kirsten rat sarcoma virus (KRAS)/mitogen-activated protein kinase (MAPK), IDH1/IDH2, BRAF, breast cancer gene (BRCA), and MSI-H were the most discussed actionable alterations, for which IHC tests and NGS have an important role[6,12,20,21]
  - IHC and NGS testing is critical to understanding the molecular heterogeneity of BTC to support optimal consideration of treatments for patients, including emerging targeted therapies for HER2
- Many targeted therapies were discussed across the literature[5,10,20,22-26] including, but not limited to, those affecting the following pathways:
  - Programmed cell death protein-1/programmed cell death-ligand 1: pembrolizumab, nivolumab, dostarlimab (also programmed cell death-ligand 2), and durvalumab
  - HER2: trastuzumab, trastuzumab deruxtecan, tucatinib, pertuzumab, lapatinib, neratinib, afatinib, and zanidatamab
  - IDH: ivosidenib and enasidenib
  - FGFR: derazantinib, infigratinib, pemigatinib, and futibatinib
  - Neurotrophic tropomyosin-receptor kinase: larotrectinib and entrectinib
- Targeted therapies with Food and Drug Administration (FDA)/European Medicines Agency (EMA) approval for biomarker selected patients with BTC are currently limited to those targeting the IDH1 and FGFR pathways

Figure 2. Targeted Therapies Investigated in 3 or More HER2, IDH, or FGFR Clinical Trials

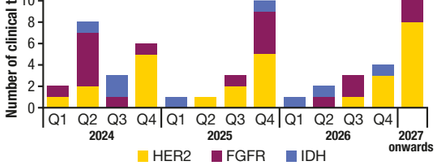


FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase 1.

Ongoing clinical trials in BTC (HER2, IDH, and FGFR)

- 57 studies were identified for the 3 targets searched: HER2 (n=28), IDH (n=9), and FGFR (n=20)
- Many HER2, IDH, or FGFR targeted therapies are being investigated in 3 or more clinical trials, as presented in **Figure 2**
- Almost half of the identified ongoing clinical trials are in patients with HER2-positive BTC, including combination therapies with multiple investigatory products and chemotherapies

Figure 3. Expected Completion Dates for BTC Clinical Trials (HER2, IDH1/2, and FGFR)



BTC, biliary tract cancer; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase.

- The landscape for targeted therapy is rapidly evolving, with completion dates spanning from 2024 until 2029 (**Figure 3**)
- Within 2024, 8 clinical trials in patients with HER2 positivity are expected to complete; 8 in patients with FGFR positivity and 3 in patients with IDH positivity
- In 2025, 15 trials are expected to complete (HER2: n=8, FGFR: n=5, IDH: n=2), and in 2026 a further 10 are expected to complete (HER2: n=4, FGFR: n=3, IDH: n=3)

Conclusions

- FOLFOX/FOLFIRI are the most studied and recommended treatment options in 2L BTC based on this TLR
- There are many actionable alterations in BTC. HER2, FGFR2, KRAS/MAPK, IDH1/IDH2, BRAF, BRCA, and MSI were most discussed
- Biomarker testing and treatment recommendations in the US, European, and Japanese guidelines are not consistent, calling for further research to understand the SOC and targeted treatments on a country level
- The increased focus on identifying and researching actionable targets in BTC across the literature and guidelines demonstrates how IHC and NGS testing are critical to support optimal consideration of treatments for patients
- Despite many actionable alterations in BTC, there is currently limited evidence from clinical trials to support the approval of new targeted treatments; FDA/EMA-approved targeted therapies are only available for BTC patients with IDH1 and FGFR alterations. There is a high unmet need for patients with other actionable targets, including HER2, where there are almost 30 active or planned clinical trials
- The targeted treatment landscape in BTC is rapidly evolving, with many clinical trial read-outs expected in the near future

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