Actionable targets by tumor genomic profiling in patients with cholangiocarcinoma

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Background

- Cholangiocarcinoma (CCA) is a rare and aggressive biliary tract malignancy, with up to 8000 new cases annually in the US and a median survival of less than 24 months from the time of diagnosis.[1]
- Technologies such as next-generation sequencing (DNA and RNA) and fluorescence *in situ* hybridization (FISH), coupled with the more conventional immunohistochemistry, have helped to unravel the complex genomic and transcriptomic landscape of CCA.
- Sequencing studies have revealed a very high prevalence of oncogenic alterations in CCA, of which several are targetable.[2,3]
- The first targeted drug for CCA, pemigatinib, was recently approved by the FDA for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement as detected by an FDA-approved test.[4] Other novel targeted therapies are in clinical development.
- However, barriers to molecular testing are still very high in CCA patients, particularly in the first-line setting, due to:
  - Insufficient tumor tissue collected at diagnosis
  - No opportunity to re-biopsy tumor
  - Time required for molecular testing may protract treatment decisions.

Purpose

- Review the published literature and the cBioPortal repository to estimate the prevalence of targetable genomic alterations, including point mutations, copy number variations and gene fusions/rearrangements in patients diagnosed with CCA.
- Better understand the percentage of patients with CCA who could benefit from targeted therapy based on their unique tumor profile.

Methods

- A systematic literature review was performed to define a list of actionable and potentially actionable genomic alterations in CCA, following a search process described in Figure 1:
  - Keyword search of major databases (PubMed, Medline) and conference archives (e.g. ASCO, ESMO, AACR, WCGIC) for the last 5 years
  - Keywords used included, but were not limited to, the following: cholangiocarcinoma, bile tract malignancy, bile tract cancer, BTC, fusion, rearrangement, translocation, mutation, SNV, amplification, genetic aberration/alteration, MSI-high, precision medicine, next-generation sequencing
  - Two scientific reviewers selected publications for full-text review.
- Mutations, copy number amplification/deletion, or fusions/rearrangements in a gene targeted by an FDA approved drug target were considered actionable. Genomic alterations in genes targeted by a drug in clinical trials was classified potentially actionable.
- cBioPortal analysis:
  - Analysis was performed on 28 May 2020 using cbioportal.org, v3.3.5[5,6]
  - Five non-overlapping 'CCA' datasets were included, comprising an *in silico* cohort of 305 patients
  - A list of 20 target genes was queried against this cohort
  - Germline mutations were excluded from the analysis.

Results

- A systematic literature review identified 11 publications that reported genetic alterations in at least 150 patients with CCA (Figure 1).
- 20 genes defined as actionable (FDA-approved drug, n=13) or potentially actionable (clinical trial, n=7) were identified in the 11 selected publications of CCA patient cohorts.
- Genes with actionable genetic alterations with a prevalence >5% in CCA included:
  - Mutations and fusions in *FGFR2*
  - Mutations in *PIK3CA, ERBB2, IDH1, and IDH2*
  - *EGFR* amplification.
- Potentially actionable mutations in *BAP1, ARID1A,* and *KRAS* are also frequently altered in CCA and have drugs in phase 1 or phase 2 clinical trials for CCA.
- Approximately 45% of patients are likely to have an actionable or potentially actionable alteration that may provide useful information for treatment planning.

Table 1. Actionable genetic alterations in CCA

Target gene	Gene function	Literature review Range[1], %	cBioPortal Prevalence, %
Fusions/rearrangements			
FGFR2	Kinase	8–14	7.8
ROS1[2]	Kinase	<1	–
Mutations			
FGFR2	Kinase	1–2	1.6
IDH1[3]	Oncogene	3–25	21
IDH2[3]	Oncogene	2–6	2.8
ERBB2[2]	Kinase	0.7–29	1.3
PIK3CA	Oncogene	5–8	7
BRAF[2]	Oncogene	3–5	4
BRCA1/BRCA2	DNA repair	1–3	4
MET[2]	Kinase	<1	<1
Amplifications			
EGFR	Kinase	5	2.1
MET[2]	Kinase	2	<1
ERBB2[2]	Kinase	3–4	2.2
FGFR1/3	Kinase	4	–
Microsatellite instability			
MSI-H	Neoantigen production	0.5–1.3	N/A

1. Range of prevalence in CCA is based on data from individual studies.
2. Variants that are typically mutually exclusive from *FGFR* fusions and IDH1/2 mutations.[2]
3. Variants that are typically mutually exclusive from *FGFR* fusions.[2]

Figure 2. cBioPortal analysis

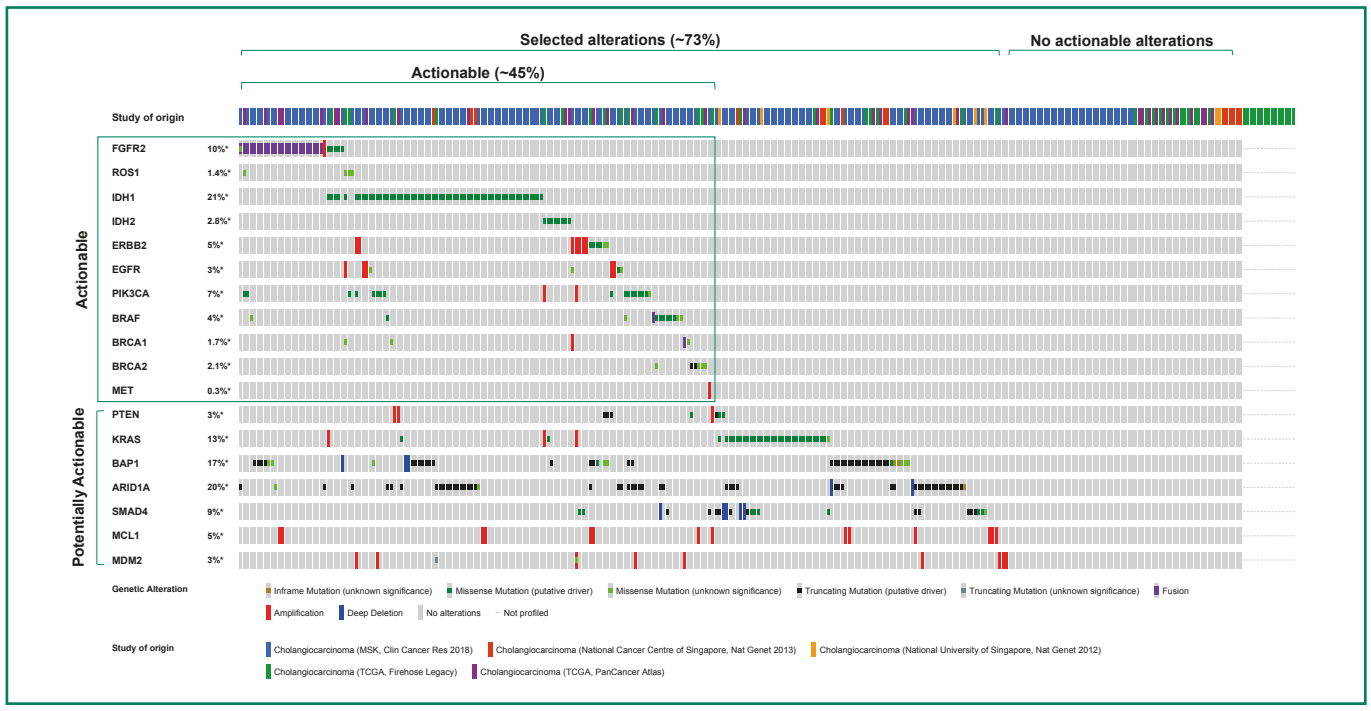
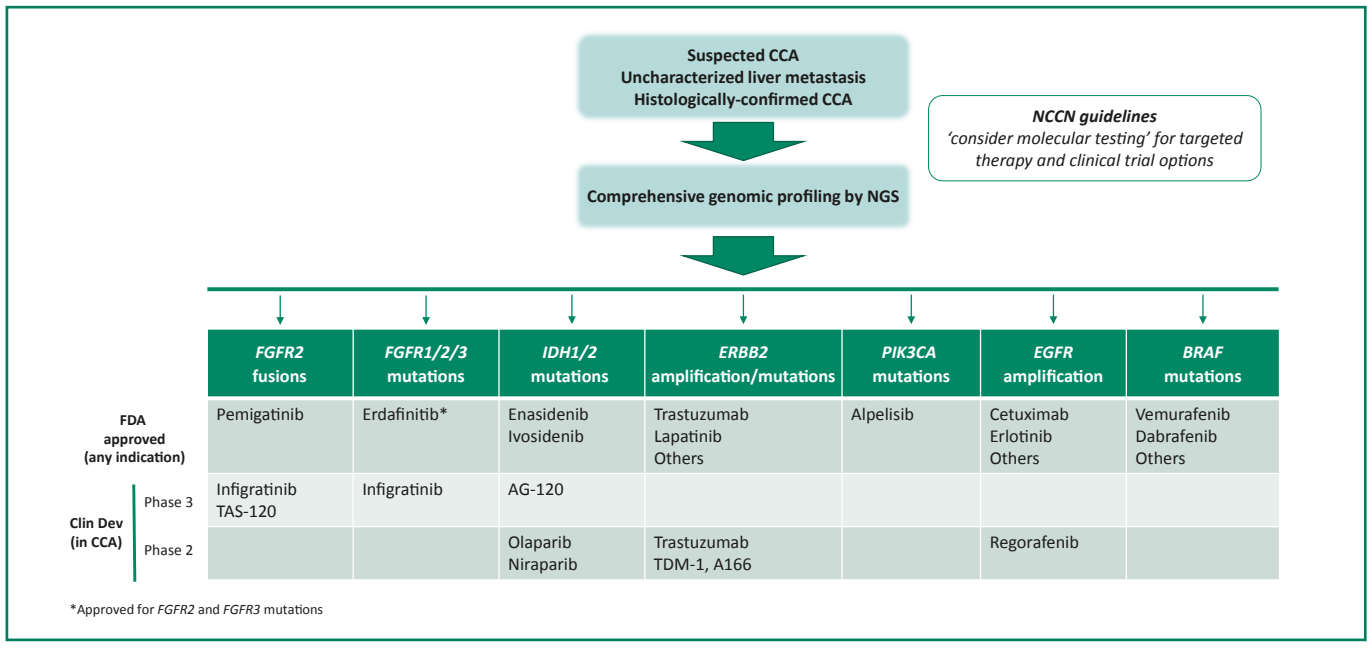


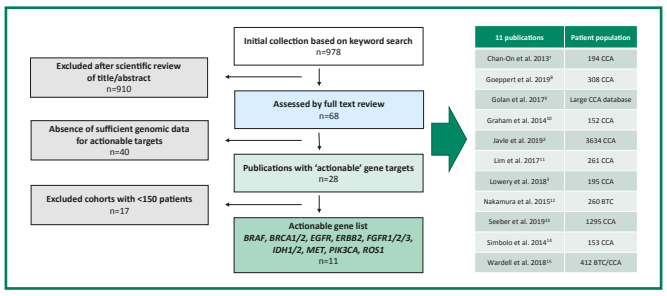
Figure 3. Actionable gene targets observed in ≥5% of CCA



		FGFR2 fusions	*FGFR1/2/3* mutations	*IDH1/2* mutations	*ERBB2* amplification/mutations	*PIK3CA* mutations	*EGFR* amplification	*BRAF* mutations
FDA approved (any indication)		Pemigatinib	Erdafinitib*	Enasidenib Ivosidenib	Trastuzumab Lapatinib Others	Alpelisib	Cetuximab Erlotinib Others	Vemurafenib Dabrafenib Others
Clin Dev (in CCA)	Phase 3	Infigratinib TAS-120	Infigratinib	AG-120				
	Phase 2			Olaparib Niraparib	Trastuzumab TDM-1, A166		Regorafenib	

*Approved for *FGFR2* and *FGFR3* mutations

Figure 1. Schema of the literature analysis



- The cBioPortal database was queried for the 20 targeted genes (Figure 2):
  - 305 patients with CCA; median age at diagnosis 59 years (29–86 years); 49.3% male/48.7% female (2% NA); Stage IV 48.8%; 72.3% iCCA, 14.2% eCCA, 1.5% pCCA, 11.9% CCA NOS.
- The most prevalent alterations included *FGFR2* fusions (7.8%) and *IDH1* mutations (21%), as shown in Table 1. Only a small proportion of patients (0.5–1.3%) were classified as MSI-high.
- Mutations in *ARID1A* (20%), *BAP* (17%), and *KRAS* (13%) may allow patients to meet eligibility criteria for ongoing clinical trials of targeted therapies (Table 2).
- cBioPortal analysis indicates that 73% of patients have at least one of the selected genetic alterations, and ~45% patients have at least one 'actionable' alteration.

Table 2. Potentially actionable gene targets in CCA

Target gene	Gene function	Literature review prevalence range, %	cBioPortal prevalence, %	Development stage for CCA
PTEN	Tumor suppressor	2–3	3	Phase 3 (NCT03345303)
BAP1	Chromatin remodeling	4–15	17	Phase 2 (NCT03207347)
ARID1A	Chromatin remodeling	6–21	14	Phase 1/2 (NCT03297424)
KRAS	Oncogene	13–28	18	Phase 1/2 (NCT03785249)
SMAD4	Transcription factor	6–13	9	In development for other solid tumors
MCL1	Oncogene	4	5	In development for other solid tumors
MDM2	Tumor suppressor	4–5	3	In development for other solid tumors

Conclusions

- The literature review and cBioPortal analysis consistently demonstrate that CCA tumors harbor a high proportion of actionable or potentially actionable genetic alterations.
- Our assessment that ~45% of patients with CCA harbor an actionable genetic alteration is in agreement with other studies (35–47%),[2,3] demonstrating the potential benefit of molecular profiling of patients with advanced CCA.
- However, despite the high number of patients that may benefit from molecularly targeted treatment, only a minority of newly diagnosed patients currently undergo comprehensive genomic profiling.
- These data suggest that genomic profiling at the time of diagnosis provides timely and actionable information to assist in treatment management of patients with CCA, which may also accelerate clinical trial enrollment.

Clinical relevance:

Given the totality of the evidence, actionable genetic alterations are present in at least 45% of patients with CCA.

Further integration of genomic profiling into the CCA treatment plan is warranted to ensure full access to targeted therapy and clinical trials for patients.

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