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The current clinical landscape for BTC

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BTC, biliary tract cancer.

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The global burden of BTC

Worldwide incidence of BTC is 0.3–6.0 per 100,000 people per year[1]

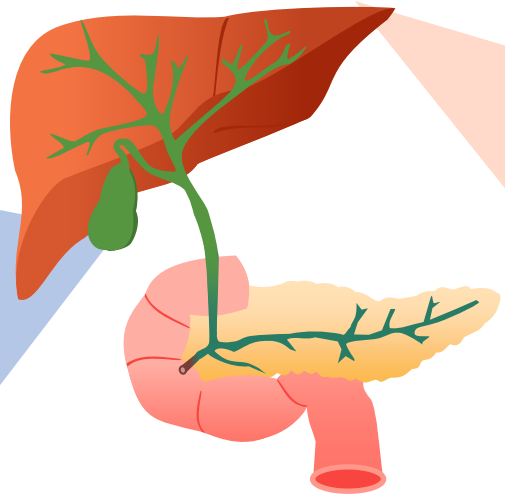
Incidence is higher in specific regions, such as Korea, China and Thailand[1]

BTC, biliary tract cancer.

1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol.* 2020. doi: 10.1038/s41575-020-0310.z [Online ahead of print].

Molecular genetics of BTC vary by site of origin

Example of prevalence of *IDH*, *FGFR* and *HER2* aberrations in intrahepatic cholangiocarcinoma versus gallbladder cancer



Gallbladder cancer

- *IDH1/2* mutation: **1.5%**[1]
- *FGFR1–3* fusions, mutations and amplifications: **3%**[1]
- *HER2* overexpression or amplification: **10–16%**[2]

Intrahepatic cholangiocarcinoma

- *IDH1/2* mutation: **4.9–36%**[1]
- *FGFR1–3* fusions, mutations and amplifications: **11–45%**[1]
- *HER2* overexpression: **<5%**[3]

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

1. Valle J, et al. *Cancer Discov.* 2017;7:943–62; 2. Nam A-R, et al. *Oncotarget.* 2016;7:58007–21;
3. Galdy S, et al. *Cancer Metastasis Rev.* 2017;36:151–7.

NCCN guidelines: Systemic therapy for unresectable/metastatic BTC[1]

First-line preferred regimen: Gemcitabine plus cisplatin

Subsequent-line preferred regimen: FOLFOX

Useful in certain circumstances:

- Entrectinib or larotrectinib for NTRK gene fusion-positive tumours
- Pembrolizumab for MSI-high or dMMR tumours

Useful in certain circumstances:

- Entrectinib/larotrectinib for NTRK gene fusion-positive tumours
- Pembrolizumab for MSI-high or dMMR tumours
- Pemigatinib for CCA with FGFR2 fusions or rearrangements
- Ivosidenib for CCA with IDH1 mutations

Other recommended regimens:

- FOLFIRI
- Regorafenib
- Preferred and other recommended regimens for unresectable and metastatic disease, including 5-FU-based regimens

5-FU, 5-fluorouracil; BTC; biliary tract cancer; CCA, cholangiocarcinoma; dMMR, deficient mismatch repair; FGFR, fibroblast growth factor receptor; FOLFOX, oxaliplatin, L-folinic acid and 5-fluorouacil; IDH, isocitrate dehydrogenase; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic tyrosine receptor.

1. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary cancers. Version 5.2020 - August 4, 2020. Available at: www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (accessed 24 August 2020).

Examples of ongoing clinical development

Targeted agents	➢ *HER2*: trastuzumab, lapatinib or pertuzumab; pertuzumab + trastuzumab; trastuzumab deruxtecan, ZW25 (zanidatamab)[1–4] ➢ *BRAF*: vemurafenib; dabrafenib plus trametinib[5]
Chemotherapy combinations	➢ Gemcitabine, cisplatin and nab-paclitaxel[4]
Immunotherapy combinations	➢ Immunotherapy and cytotoxic chemotherapy combinations, e.g. durvalumab plus gemcitabine and cisplatin (TOPAZ-1), bintrafusp alfa plus gemcitabine and cisplatin[7,8]

BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER2, human epidermal growth factor receptor 2.

1. Javle M, et al. *J Hematol Oncol*. 2015;8:58; 2. NCT02091141; 3. NCT04482309; 4. NCT04466891; 5. Wainberg ZA, et al. J Clin Oncol. 2019;37(Suppl 4):187; 6. NCT03768414; 7. NCT03875235; 8. NCT04066491. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 August 2020).

How genetic alterations and the tumour microenvironment are driving the development of new therapies

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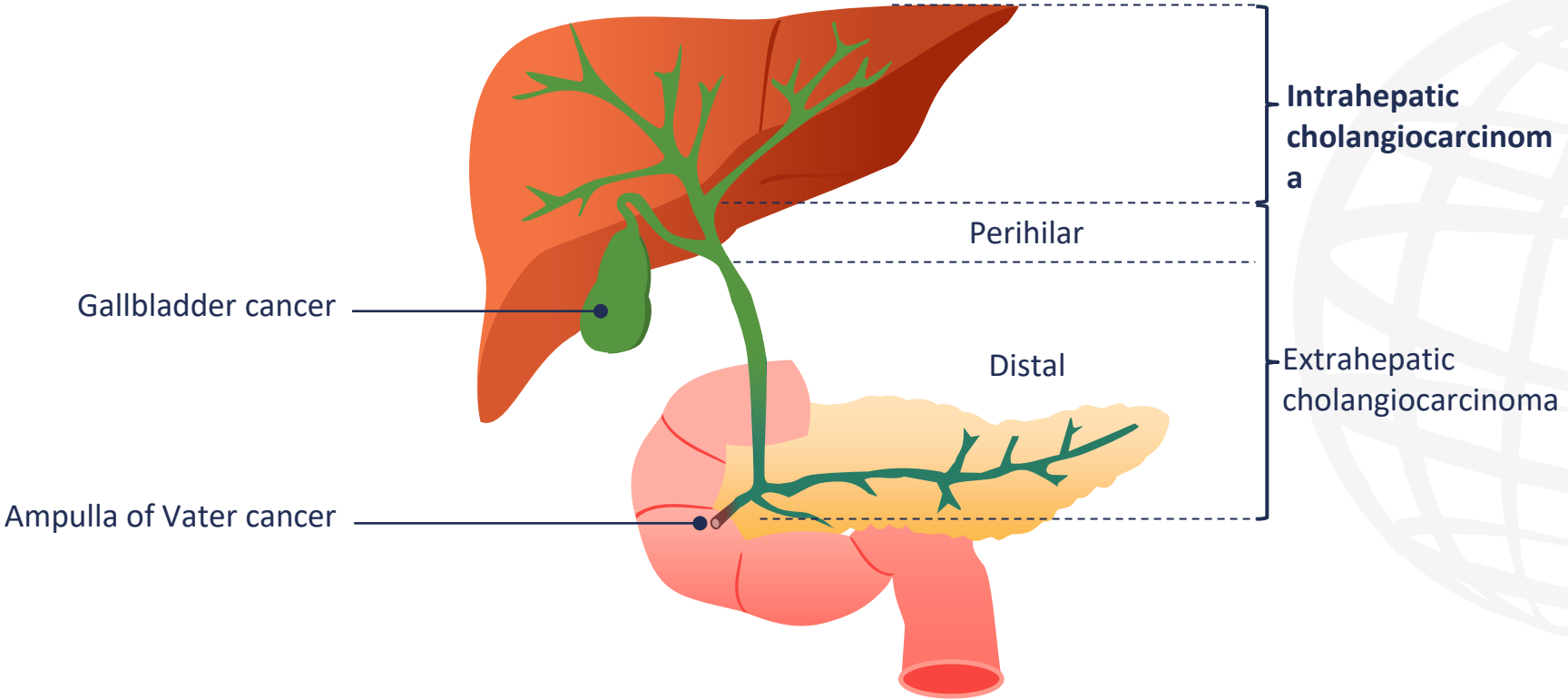
Anatomical classification of BTCs[1]



BTC, biliary tract cancer.

1. Tariq NU, et al. *Cancer Manag Res*. 2019;11:2623–42.

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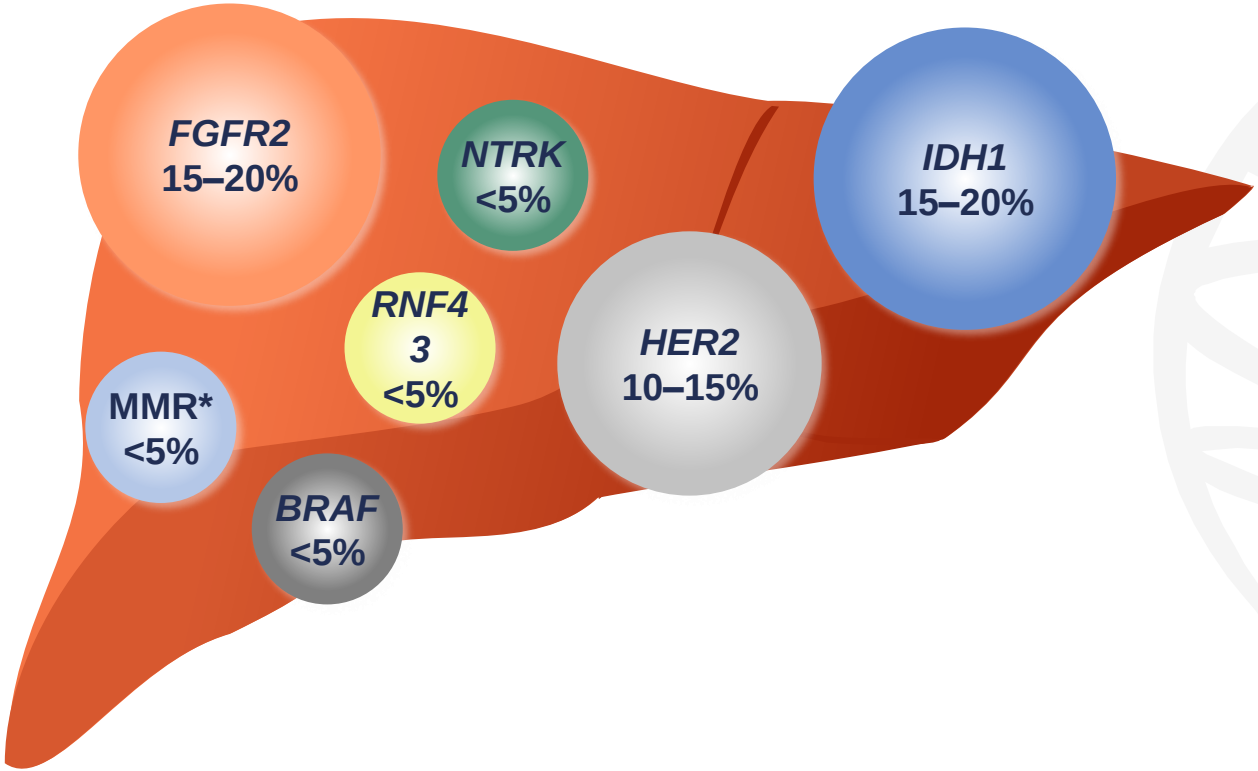
Genetic alterations in BTCs[1]



*Includes microsatellite instability.

BTC, biliary tract cancer; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; NTRK, neurotrophic tyrosine receptor kinase; MMR, mismatch repair deficiency; RNF43, ring finger protein 43.

1. Lamarca A, et al. *J Hepatol.* 2020;73:170–85.

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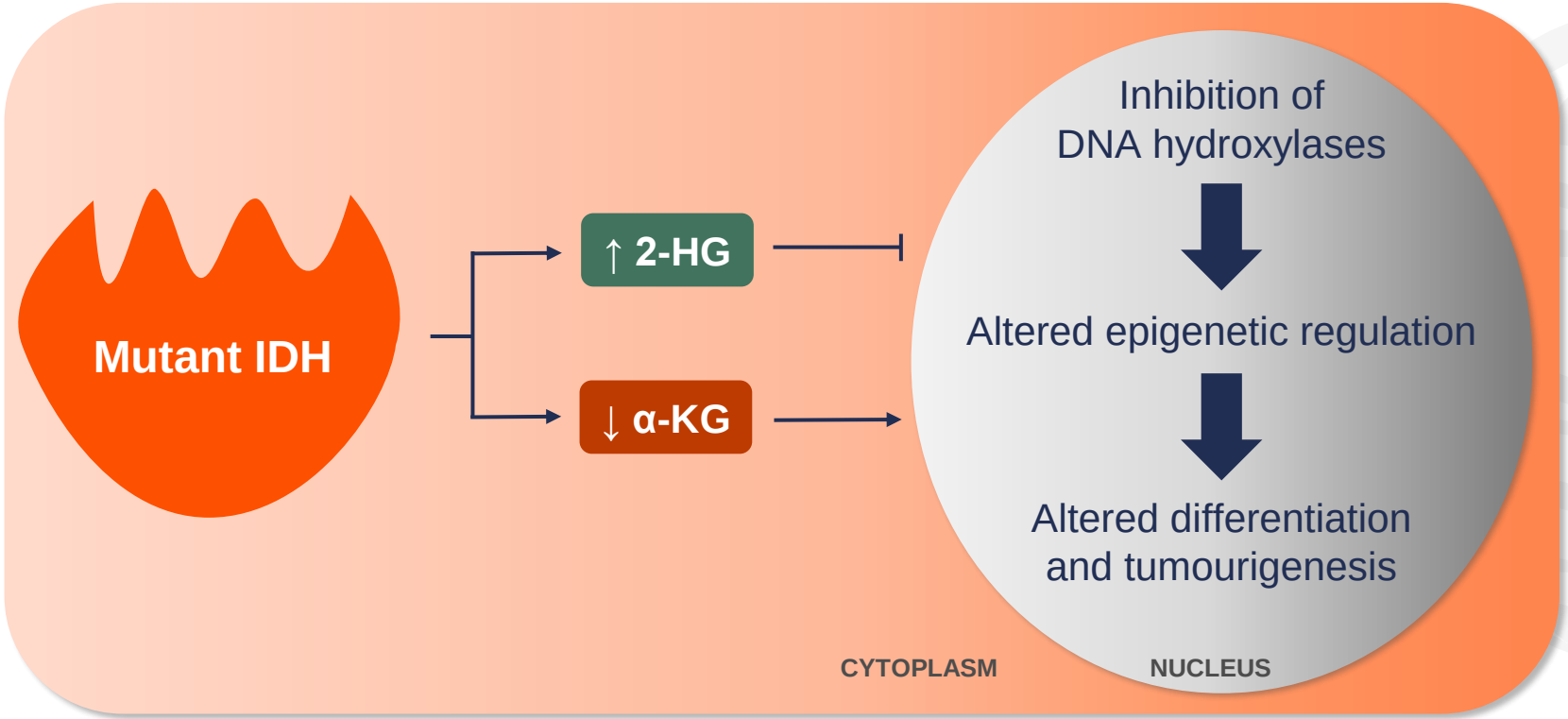
IDH1 as a target in BTCs[1]



2-HG, 2-hydroxyglutarate; α-KG, α-ketoglutarate; BTC, biliary tract cancer; DNA, deoxyribonucleic acid; IDH, isocitrate dehydrogenase.

1. Yang H, et al. *Clin Cancer Res.* 2012;18:5562–71.

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FGFR inhibitors have demonstrated efficacy in phase II studies

- Advanced or metastatic cholangiocarcinoma[1–3]
- Disease progression on ≥1 prior therapy[1–3]

Infigratinib overall response rate: **31.0%**[1]

Pemigatinib objective response rate: **35.5%** (n=38; 3 complete, 35 partial)[2]

Futibatinib objective response rate: **34.3%** (n=23; all partial)[3]

Phase III trials of FGFR inhibitors in the first-line setting versus gemcitabine and cisplatin are ongoing[4–6]

FGFR, fibroblast growth factor receptor.

1. Javle M, et al. *Hepatobiliary Surg Nutr.* 2019;8(Suppl. 1):AB051; 2. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671–84; 3. Goyal L, et al. *J Clin Oncol.* 2020;38(Suppl. 15):108; 4. NCT03773302; 5. NCT03656536; 6. NCT04093362. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 21 August 2020).

Tumour-agnostic strategies in BTC

MSI high tumours	➢ Immunotherapy has a role in patients with mismatch repair and MSI[1] ➢ Trials are ongoing, including combinations of checkpoint inhibitors with other immune modulators[1]
NTRK fusions	➢ Pooled analysis of three larotrectinib trials in patients with advanced *TRK* fusion-positive solid tumours (n=159): **OR=79%** (16% complete response)[2] ➢ Integrated analysis of three ongoing entrectinib trials of patients with metastatic or locally advanced *NTRK* fusion-positive solid tumours (n=54): **OR=57%** (7% complete and 50% partial) and **median duration of response was 10 months**[3]
BRAF mutations	➢ Dual inhibition of BRAF (dabrafenib) and MEK (trametinib) assessed in basket trial of solid tumours with *BRAF*^{V600E} mutation[4] ➢ 43 patients with *BRAF*^{v600E}-mutated BTC: **51% achieved investigator-assessed overall response**[4]

BRAF, v-raf murine sarcoma viral oncogene homolog B1; BTC, biliary tract cancer; MEK, mitogen-activated protein kinase kinase; MSI; microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; OR, objective response; TRK, tropomyosin receptor kinase.

1. Lamarca A, et al. *J Hepatol.* 2020;73:170–85; 2. Hong DS, et al. *Lancet Oncol.* 2020;21:531–40; 3. Doebele RC, et al. *Lancet Oncol.* 2020;21:271–82; 4. Subbiah V, et al. *Lancet Oncol.* 2020. doi: https://doi.org/10.1016/S1470-2045(20)30321-1 [Online ahead of print].

New hope from emerging therapies

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BTCs harbour well-characterized driver alterations[1,2]

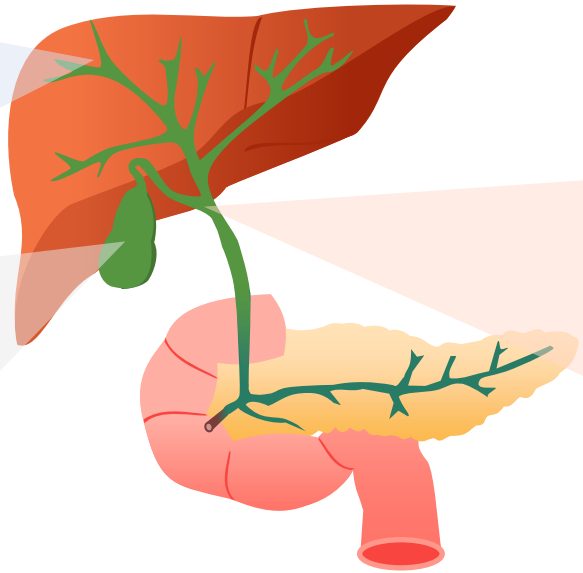
- Heterogeneous BTCs exhibit distinct and functionally important alterations
- Biomarker testing can help identify actionable alterations for molecular-targeted agents

ICC

Targetable GAs	Prevalence
FGFR2 fusions	10–20%
IDH1/2	22–28%
BAP1	15–25%

GBC

Targetable GAs	Prevalence
EGFR	4–13%
HER2 (amp)	10–15%
PIK3CA	6–13%
HER3	0–12%
PTEN	0–4%



EHCCA

Targetable GAs	Prevalence
HER2 (mut)	11–20%
PRKACA and *PRKACB*	9%
ARID1A	5–12%

Amp, amplification; ARID1A, AT-rich interaction domain 1A; BAP1, BRCA1 (breast cancer type 1 susceptibility protein) associated protein-1; BTC, biliary tract cancer; EGFR, epidermal growth factor receptor; EHCCA, extrahepatic cholangiocarcinoma; FGFR2, fibroblast growth factor receptor 2; HER2/3, human epidermal growth factor receptor 2/3; IDH1/2, isocitrate dehydrogenase 1/2; GA, genetic aberration; GBC, gallbladder carcinoma; ICC, intrahepatic cholangiocarcinoma; mut, mutation; PIK3CA, phosphoinositide-3-kinase, catalytic, alpha polypeptide; PRKACA/B, protein kinase cAMP-activated catalytuc subunit alpha/beta; PTEN, phosphate and tensin homolog.

1. Verlingue L, et al. *Eur J Cancer*. 2017;81:161–73; 2. Jain A, Javle M. *J Gastrointest Oncol*. 2016;7:797–803.

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Phase II clinical trials of FGFR inhibitors for BTCs

Infigratinib (BGJ398)[1]

Infigratinib 125 mg OD

Advanced IHC containing *FGFR2* fusions (n=71)

31% ORR
(95% CI 20.5–43.1%)

(confirmed and unconfirmed)

Most common any-grade TEAEs:
- Hyperphosphataemia (73%)
- Fatigue (49%)
- Stomatitis (45%)

Pemigatinib (INCB054828)[2]

Pemigatinib 13.5 mg OD

LA/metastatic CCA with *FGFR2* translocations and fusions (n=146)

36% ORR
(95% CI 26.5–45.4%)

(per RECIST v1.1 based on independent review)

Most common any-grade TEAEs:
- Hyperphosphataemia (55%)
- Alopecia (46%)
- Dysgeusia (38%)

Futibatinib (TAS-120)[3]

Futibatinib 20 mg OD

LA/metastatic ICC with *FGFR2* rearrangements and fusions (n=103)

34% ORR
(n=23; CI unreported)

(based on independent central radiology reviewed)

Most common any-grade TEAEs:
- Hyperphosphataemia (79%)
- Diarrhoea (37%)
- Dry mouth (33%)

BTC, biliary tract cancer; CI, confidence interval; CCA, cholangiocarcinoma; FGFR, fibroblast growth factor receptor; IHC, intrahepatic cholangiocarcinomas; LA, locally advanced; OD, once daily; ORR, overall response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment-emergent adverse events.

1. Javle M, et al. *Hepatobiliary Surg Nutr*. 2019;8(Suppl. 1):AB051; 2. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:671–84; 3. Goyal L, et al. *J Clin Oncol.* 2020;38(Suppl. 15):108.

ClarIDHy (phase III): Study design and outcomes[1]

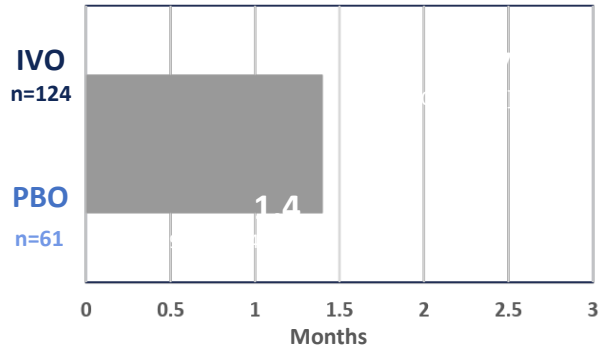
ClarIDHy: Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma

- 185 adult patients with histologically confirmed, advanced, *IDH1*-mutant cholangiocarcinoma
- ≤2 previous treatment regimens for advanced disease
- ECOG performance status: 0 or 1
- Measurable lesion as defined by RECIST v1.1

2:1

Oral ivosidenib 500 mg OD (or matched placebo) in continuous 28-day cycles

PFS was significantly improved with ivosidenib versus placebo



HR: 0.37
(95% CI 0.25–0.54)
p<0.0001

Decline in EORTC QLQ-C30 physical functioning subscale from baseline was significantly lower for ivosidenib-treated patients (n=62)
Least squares mean: -3.4 (SE 1.81)

The most common grade 3–5 AE in both treatment groups was ascites:
Placebo: 4/59 (7%)
Ivosidenib: 9/121 (7%)

AE, adverse event; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; IVO, ivosidenib; OD, once daily; PFS, progression-free survival; PBO, placebo; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SE, standard error.

1. Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21:796–807.

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Strategic FGFR inhibitor sequencing may overcome acquired resistance in BTCs[1]

- Acquired resistance is often associated with the emergence of secondary *FGFR2* kinase domain mutations
- Treatment with a second FGFR inhibitor may provide clinical benefit in these patients

***FGFR2* fusion**	**First FGFR inhibitor**	**Interval between inhibitors** (months)	**Second FGFR inhibitor**	**PFS** (months)	**Best overall response**
FGFR2–SORBS1	Infigratinib	1.2	Futibatinib	15.8	-76.7%
FGFR2–ZMYM4	Infigratinib	1.6	Futibatinib	7.2	+8.3%
FGFR2–INA	Debio 1347	3.0	Futibatinib	5.1	-22.1%
FGFR2–NRAP	Infigratinib	7.4	Futibatinib	17.2	-47.7%

Four patients showed a benefit with second FGFR inhibitor futibatinib

- Two achieved a partial response
- Two had stable disease with a duration of benefit of 5.1–17.2 months

Strategic sequencing of FGFR inhibitors may prolong the duration of benefit from FGFR inhibition in patients with *FGFR2* fusion–positive ICC

BTC, biliary tract cancer; FGFR, fibroblast growth factor receptor; ICC, intrahepatic cholangiocarcinoma; INA, alpha-internexin; NRAP, nebulin-related-anchoring protein; PFS, progression-free survival; SORBS1, sorbin and SH3 domain containing 1; ZMYM4, zinc finger MYM-type containing 4.

1. Goyal L, et al. *Cancer Discov*. 2019;9:1064–79.

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Ongoing clinical trials evaluating immunotherapies for BTCs

Checkpoint inhibitor monotherapies

- **Pembrolizumab** in unresectable and/or metastatic BTC that has progressed on standard of care therapy (NCT02628067; phase II)[1]
- **Nivolumab** in advanced refractory BTCs (NCT02829918; phase II)[2]

Combination therapies

- **Nivolumab with gemcitabine + cisplatin or ipilimumab** as first-line therapy in advanced unresectable BTC (NCT03101566; phase II)[3]
- **Durvalumab +/- tremelimumab** in advanced BTC (NCT01938612; phase I)[4]

Bifunctional immunotherapy

- **Bintrafusp alfa monotherapy** in locally advanced/metastatic BTC in the second-line setting (NCT03833661; phase II)[5]
- **Gemcitabine plus cisplatin +/- bintrafusp alfa** in the first-line setting for locally advanced/metastatic BTC (NCT04066491; phase II/III)[6]

BTC, biliary tract cancer; PD-L1, programmed death-ligand 1.

1. NCT02628067; 2. NCT02829918; 3. NCT03101566; 4. NCT01938612; 5. NCT03833661; 6. NCT04066491. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 24 August 2020).