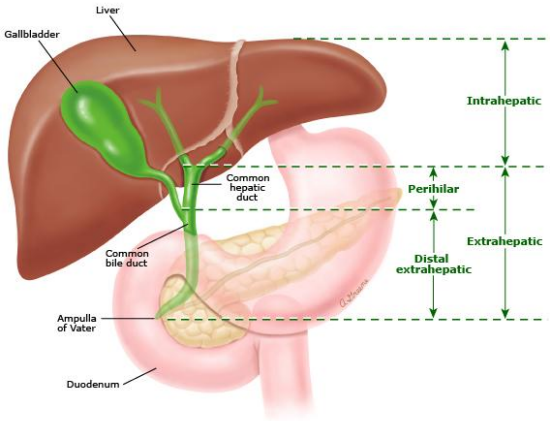
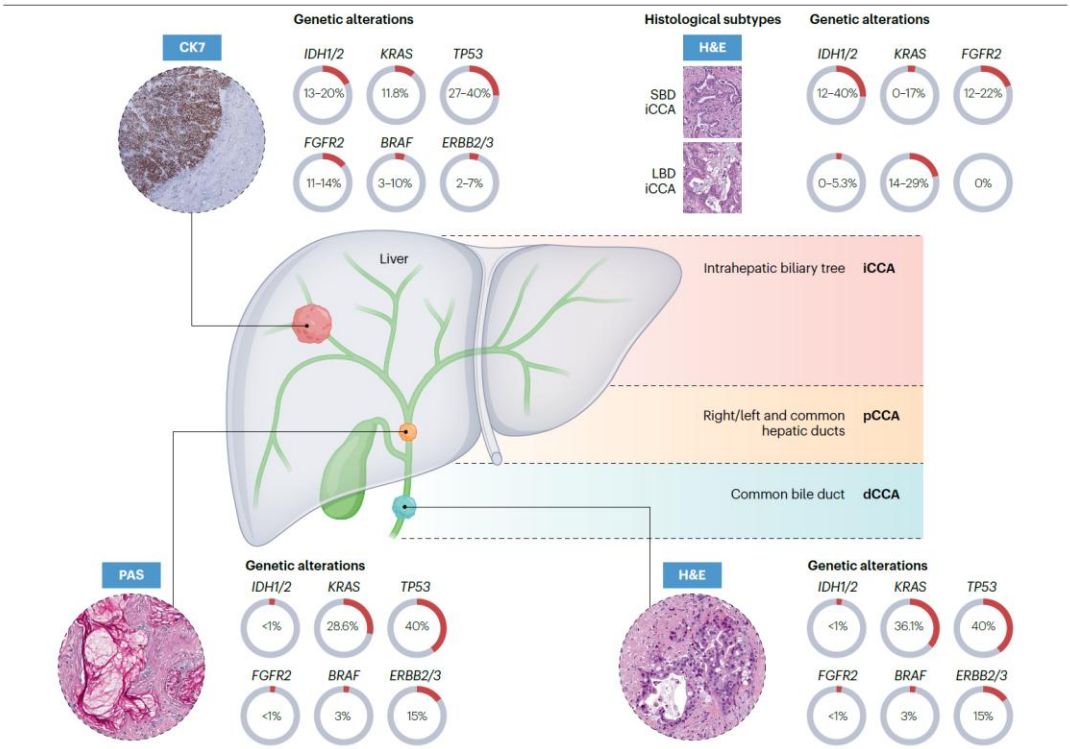
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GENERAL OVERVIEW

- **Subtypes.** Intrahepatic CCA (iCCA), perihilar CCA (pCCA) and distal CCA (dCCA).
- **Risk factors.** PSC, fibropolycystic liver disease, hepatolithiasis, chronic liver disease/cirrhosis, hepatotropic viruses, obesity and alcohol.
- **Hereditary associations.** Lynch syndrome, BAP1 tumour-predisposition syndrome and selected other cancer-predisposition syndromes.
- **Presentation.** Abdominal pain, weight loss, fever and/or biliary obstruction (jaundice, pruritus, pale stools, dark urine).





Anatomical subtypes and recurrent molecular alterations. Source figure: Nature Reviews Gastroenterology & Hepatology, 2026.

DIAGNOSIS, STAGING AND PROGNOSIS

- **Diagnostic work-up.** Multiphasic CT and/or MRI/MRCP; ERCP when tissue sampling or biliary drainage is required; CA19-9 and CEA; liver tests; viral serology and IgG4 when clinically indicated.
- **Pathology.** Histological confirmation is recommended before systemic treatment. In potentially resectable pCCA, biopsy strategy should be discussed with the hepatobiliary MDT because of implications for selected transplant pathways.
- **Prognostic factors.** Resection margin, nodal status, vascular invasion, tumour burden and performance status.

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PERIHILAR CCA — AJCC 8

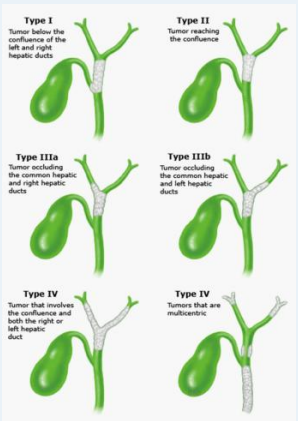
Primary tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: cannot be assessed T0: no evidence of primary tumour Tis: carcinoma in situ / high-grade dysplasia T1: confined to bile duct, up to muscle layer or fibrous tissue T2a: beyond bile duct wall into surrounding adipose tissue T2b: invades adjacent hepatic parenchyma T3: unilateral portal vein or hepatic artery branch involvement T4: main portal vein/bilateral branches, common hepatic artery, or unilateral second-order bile ducts with contralateral portal vein/hepatic artery involvement	NX: cannot be assessed N0: no regional LN metastasis N1: 1–3 positive regional LN N2: ≥4 positive regional LN	M0: no distant metastasis M1: distant metastasis

Stage grouping

Stage	TNM
0	Tis N0 M0
I	T1 N0 M0
II	T2a–b N0 M0
IIIA	T3 N0 M0
IIIB	T4 N0 M0
IIIC	Any T N1 M0
IVA	Any T N2 M0
IVB	Any T Any N M1

BISMUTH–CORLETTE CLASSIFICATION

- **Type I.** Below the confluence of the right and left hepatic ducts.
- **Type II.** Reaches the confluence.
- **Type IIIa.** Involves the confluence and right hepatic duct.
- **Type IIIb.** Involves the confluence and left hepatic duct.
- **Type IV.** Multifocal disease or involvement of the confluence with both right and left hepatic ducts.



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DISTAL AND INTRAHEPATIC CCA — AJCC 8

Distal CCA

Primary tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: cannot be assessed Tis: carcinoma in situ / high-grade dysplasia T1: depth of invasion <5 mm T2: depth 5–12 mm T3: depth >12 mm T4: involvement of major arterial structures (celiac axis/SMA ± common hepatic artery, according to local pathology staging convention)	NX: cannot be assessed N0: no regional LN N1: 1–3 regional LN N2: ≥4 regional LN	M0: no distant metastasis M1: distant metastasis

Stage	TNM
I	T1 N0 M0
IIA	T1 N1 M0 OR T2 N0 M0
IIB	T2 N1 M0 OR T3 N0–1 M0
IIIA	T1–3 N2 M0
IIIB	T4 Any N M0
IV	Any T Any N M1

Intrahepatic CCA

Primary tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: cannot be assessed T0: no evidence of primary tumour Tis: carcinoma in situ T1: solitary tumour without vascular invasion T1a: ≤5 cm T1b: >5 cm T2: solitary tumour with intrahepatic vascular invasion OR multiple tumours, with/without vascular invasion T3: perforates visceral peritoneum T4: direct invasion of local extrahepatic structures	NX: cannot be assessed N0: no regional LN N1: regional LN metastasis	M0: no distant metastasis M1: distant metastasis

Stage	TNM
IA	T1a N0 M0
IB	T1b N0 M0
II	T2 N0 M0
IIIA	T3 N0 M0
IIIB	T4 N0 M0 OR Any T N1 M0
IV	Any T Any N M1

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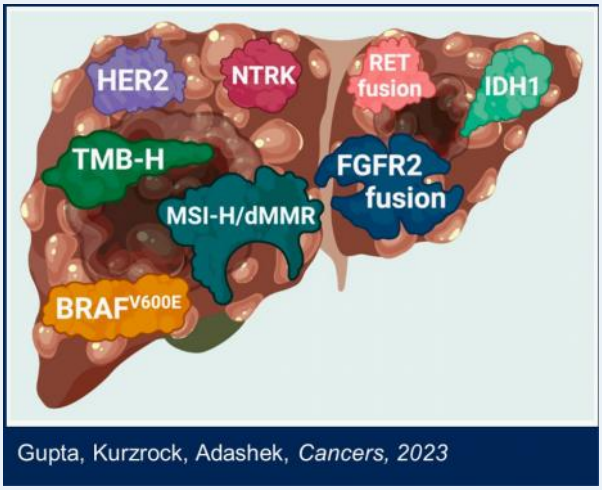
TREATMENT

RESECTABLE DISEASE

- **Surgery.** Aim for R0 resection; procedure depends on tumour location and local extent.
- **Adjuvant evidence.** PRODIGE 12 (GEMOX) and BCAT (gemcitabine) were negative. In BILCAP, capecitabine did not significantly improve OS in the primary ITT analysis, but sensitivity/per-protocol analyses supported benefit (per-protocol median OS 53 vs 36 months).
- **UZA recommendation.** Offer/consider adjuvant capecitabine for 6 months (8 cycles) after curative resection, taking postoperative recovery, comorbidity and recurrence risk into account.
- **R1 resection.** Discuss in hepatobiliary MDT. For extrahepatic CCA, adjuvant chemoradiotherapy may be considered in selected R1 cases; evidence remains limited.
- **Follow-up.** Every 3–6 months during the first 2 years, then every 6–12 months up to 5 years.

MOLECULAR TESTING — ADVANCED DISEASE

- **Perform early.** Obtain broad molecular profiling before or during first-line therapy so that biomarker-directed options are available at progression.
- **Core alterations.** IDH1 mutation; FGFR2 fusion/rearrangement; MSI-H/dMMR; NTRK fusion.
- **Also assess.** HER2 overexpression/amplification (especially pCCA/dCCA), BRAF V600E, RET fusion, KRAS G12C and NRG1 fusion when covered by the local NGS panel.



Actionable alterations in biliary tract cancer (Gupta, Kurzrock, Adashek. Cancers. 2023).

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ADVANCED DISEASE

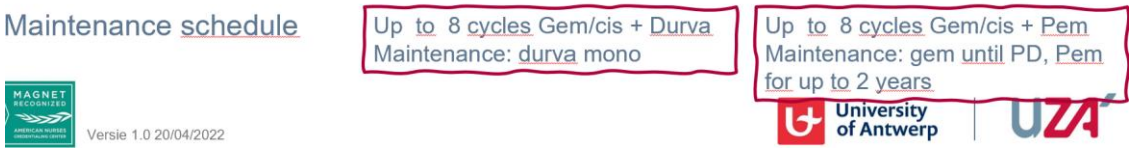
FIRST-LINE TREATMENT

- **Preferred standard.** Cisplatin + gemcitabine + durvalumab (TOPAZ-1) — reimbursed for first-line unresectable/metastatic biliary tract cancer.
- **Alternative standard.** Cisplatin + gemcitabine + pembrolizumab (KEYNOTE-966) — reimbursed for first-line locally advanced unresectable/metastatic biliary tract cancer.
- **If cisplatin unsuitable.** Consider oxaliplatin-based substitution when clinically appropriate; evidence is less robust than for cisplatin. Gemcitabine monotherapy may be considered in selected frail/ECOG PS 2 patients.

Maintenance schedule

- **TOPAZ-1:** up to 8 cycles of cisplatin + gemcitabine + durvalumab, then durvalumab monotherapy until progression or unacceptable toxicity.
- **KEYNOTE-966:** cisplatin for up to 8 cycles; gemcitabine may be continued beyond cycle 8, and pembrolizumab can continue for up to 35 cycles (approximately 2 years), according to the trial/label schedule.

	TOPAZ -1 (Cis/Gem + Durva vs Cis Gem)	KEYNOTE- 966 (Cis/Gem + Pembro vs Cis Gem)
Number of patients	685	1069
Overall Survival	12.8 m vs 11.5 m **HR 0.80** (0.66-0.97)	12.7 m vs 10.9 m **HR 0.83** (0.72-0.95)
24-month OS	**24.9 % vs 10.4%**	**26% vs 19% (calculated)**
Progression free survival	7.2 m vs 5.7 m HR 0.75 (0.63-0.89)	6.5 m vs 5.6 m HR 0.86 (NS)
Objective response rate	26.7% vs 18.7% (OR 1.6)	Similar between arms
Grade 3 AEs	**75.7% vs 77.8%**	**69% vs 70%**
HRQoL	No deterioration	No deterioration



TOPAZ-1 and KEYNOTE-966: key efficacy and maintenance differences (original UZA teaching figure).

SECOND-LINE CHEMOTHERAPY (ECOG PS 0–2)

- **Preferred evidence-based option.** FOLFOX (ABC-06).
- **Alternative.** CAPOX can be considered.
- **nal-IRI + 5-FU/LV.** Supported by the phase IIb NIFTY trial; consider depending on prior therapy, fitness and access.

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BIOMARKER-DIRECTED AND SUBSEQUENT THERAPY

BIOMARKER-DIRECTED OPTIONS

- **IDH1 R132-mutated iCCA.** Ivosidenib — reimbursed after progression following at least one prior systemic line.
- **FGFR2 fusion/rearranged iCCA.** Pemigatinib — reimbursed after progression following at least one prior systemic line. FIGHT-302 supports high first-line activity but does not currently reimbursed.
- **NTRK fusion.** Larotrectinib or entrectinib — tumour-agnostic reimbursement is available.
- **MSI-H/dMMR.** Pembrolizumab is active tumour-agnostically (no reimbursement), but in current practice most eligible patients will already have received anti-PD-1/PD-L1-containing first-line therapy
- **HER2 IHC 3+ advanced BTC.** Zanidatamab is now authorised in the EU after ≥1 prior systemic line, but no reimbursement. Other HER2 regimens (trastuzumab/tucatinib, trastuzumab deruxtecan, pertuzumab/trastuzumab) have clinical activity but are not standard reimbursed BTC options in Belgium.
- **BRAF V600E (5%).** Dabrafenib plus trametinib (no reimbursement)
- **RET fusions.** Selpercatinib (no reimbursement)

SUBSEQUENT-LINE THERAPY

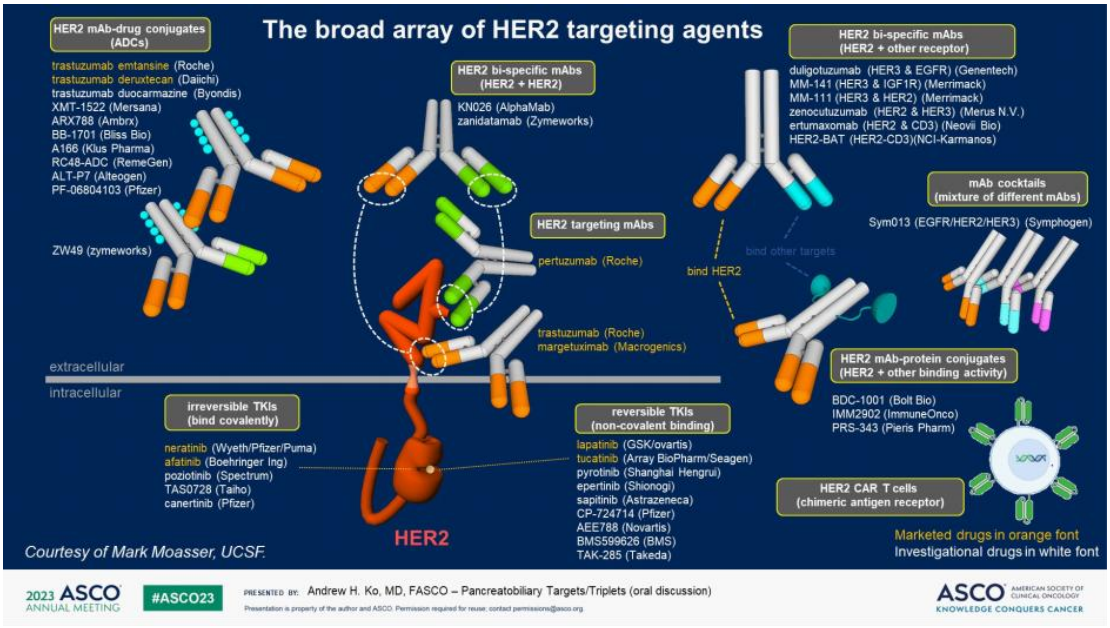
- **FOLFIRI.** Reasonable option in fit patients after prior platinum/fluoropyrimidine exposure, although randomized BTC-specific evidence is limited.
- **Regorafenib.** Activity reported in the randomized phase II REACHIN study; not reimbursed for BTC in Belgium.
- **Clinical trial.** Strongly consider whenever available, particularly for rare molecular subsets or after standard chemotherapy and matched targeted options.

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WHAT'S NEW?

HER2-POSITIVE BILIARY TRACT CANCER

- **Frequency.** HER2 overexpression/amplification is enriched in extrahepatic CCA and gallbladder cancer; prevalence varies by assay and tumour site.
- **Pertuzumab + trastuzumab.** MyPathway: objective response rate approximately 23%.
- **Tucatinib + trastuzumab.** SGNTUC-019: confirmed ORR 46.7% in previously treated HER2-positive BTC.
- **Trastuzumab deruxtecan.** HERB phase II: clinically meaningful activity in HER2-positive BTC; monitor carefully for ILD/pneumonitis.
- **Zanidatamab.** HERIZON-BTC-01: final data show strongest activity in IHC 3+ disease; EU-authorised for previously treated unresectable locally advanced/metastatic HER2 IHC 3+ BTC.



HER2-targeted therapeutic landscape (ASCO teaching figure retained from the original guideline).

RECENT PRACTICE-CHANGING / PRACTICE-INFORMING DATA

- **Neoadjuvant GOLP — ZSAB-neoGOLP (NEJM 2026).** In resectable high-risk iCCA, neoadjuvant GEMOX + lenvatinib + toripalimab improved median event-free survival (18.0 vs 8.7 months). OS remains immature and the unexpectedly short control-arm EFS plus single-country population warrant caution; not current UZA standard.
- **FIGHT-302 (JCO 2026).** First-line pemigatinib versus gemcitabine/cisplatin in FGFR2-rearranged advanced CCA: PFS 8.3 vs 6.8 months (HR 0.58), ORR 47% vs 15%, OS 24.4 vs 25.0 months; crossover and absence of first-line immunotherapy comparator limit direct practice change.
- **Zenocutuzumab — eNRGy (JCO 2026).** In NRG1-fusion-positive cholangiocarcinoma, ORR 36.8% and median PFS 9.2 months; compelling rare-subset activity, but Belgian access/reimbursement needs individual verification.
- **RAGNAR.** Erdafitinib demonstrated tumour-agnostic activity across FGFR-altered solid tumours; useful biologic signal but not a Belgian standard option for BTC.

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