Systemic Therapy for Advanced Bile Duct Malignancy

South Florida GI Cancer Symposium – 2025

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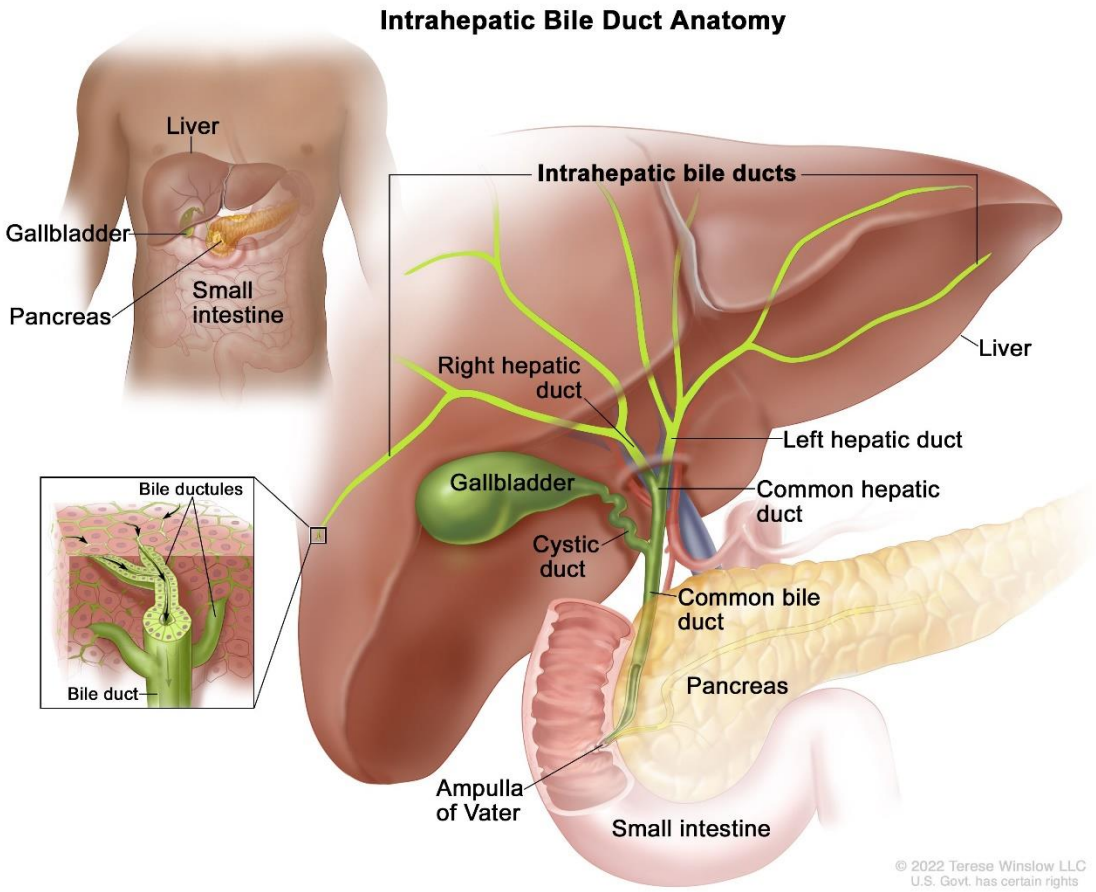
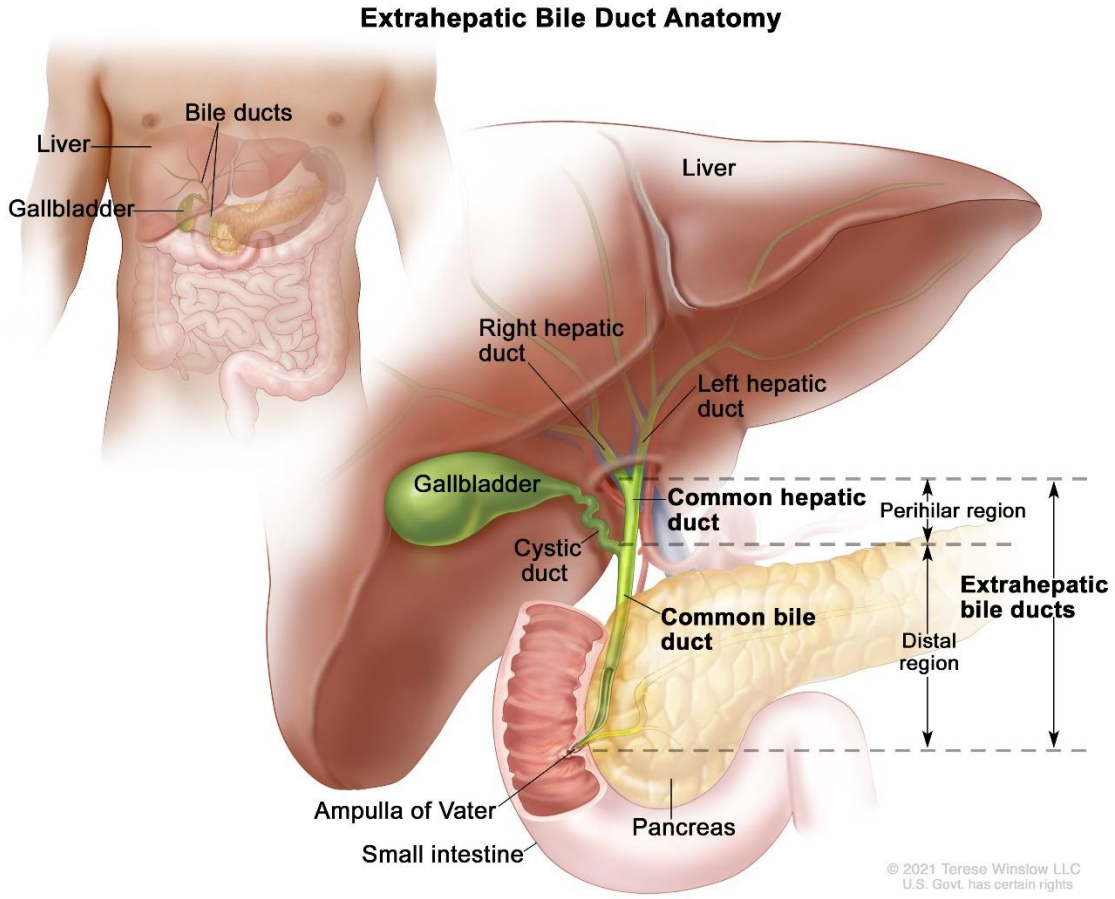
Anatomy and Classification



- A network of small tubes that carry bile inside the liver
- Right and left hepatic duct join outside the liver – common hepatic duct
- Cholangiocarcinoma is the epithelial cell tumor that arise from cholangiocytes of the biliary tract
- Cancer that forms within the bile ducts *inside the liver* are classified as intrahepatic cholangiocarcinoma (ICC)

Anatomy and Classification



- Cancer that forms within the bile ducts *outside the liver* are classified as extrahepatic cholangiocarcinoma

Perihilar (Klatskin)

Distal

Cholangiocarcinoma Outcomes by Stage

Intrahepatic Cholangiocarcinoma

SEER* stage	5-year relative survival rate
Localized	23%
Regional	9%
Distant	3%
All SEER stages combined	9%

Extrahepatic Cholangiocarcinoma

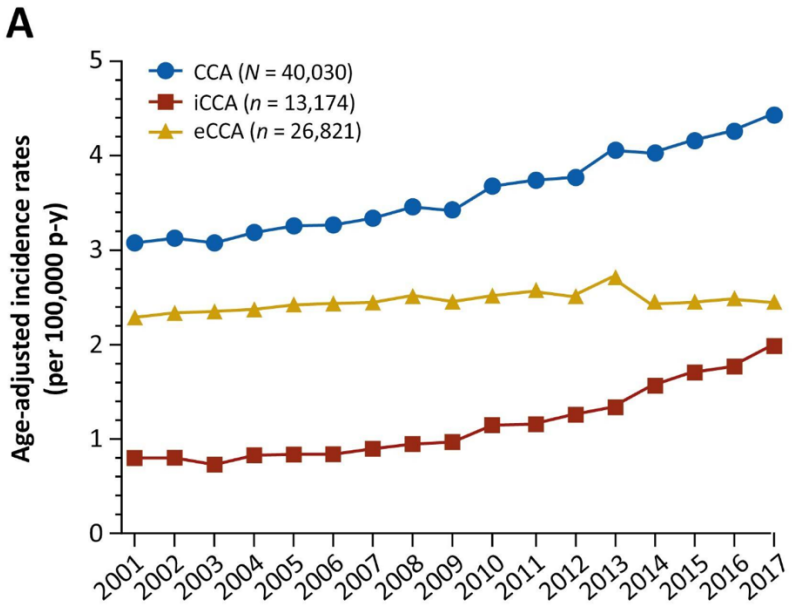
SEER stage	5-year relative survival rate
Localized	18%
Regional	18%
Distant	2%
All SEER stages combined	11%

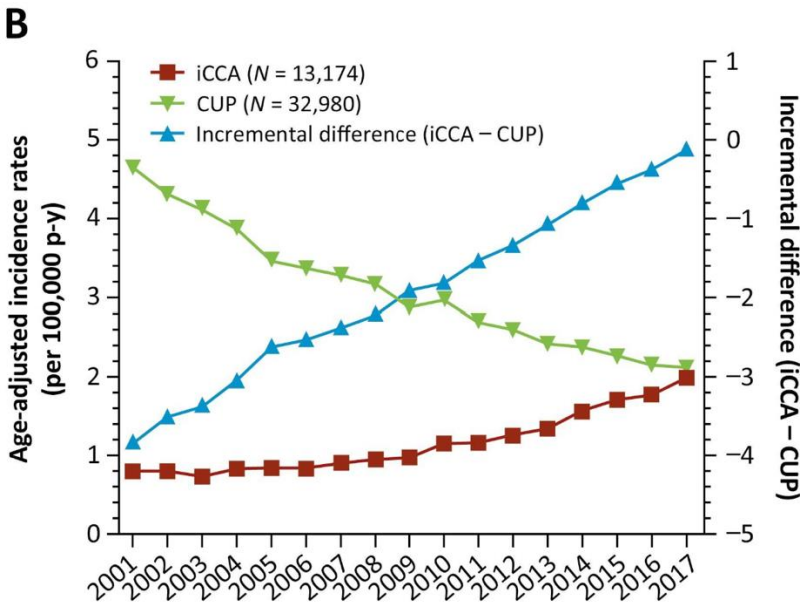
*SEER= Surveillance, Epidemiology, and End Results

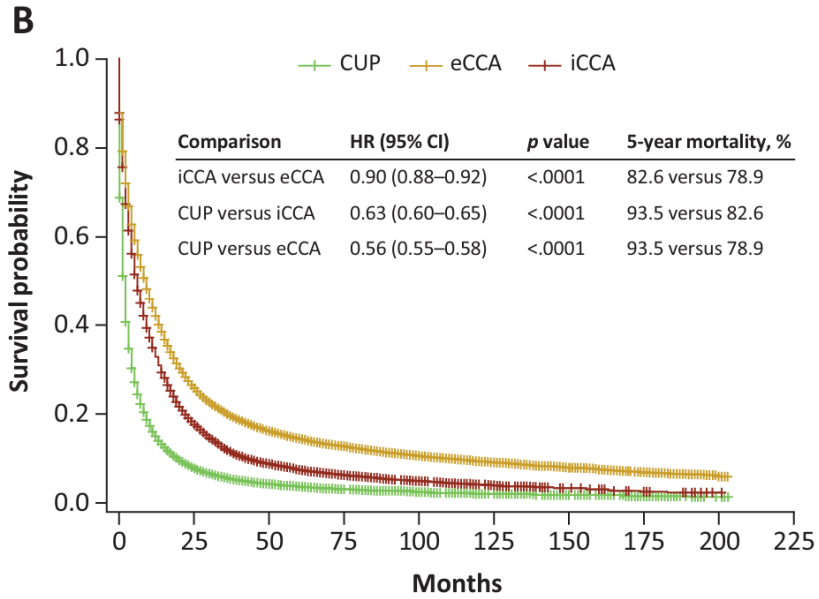
Data from 2012 – 2018. American Cancer Society

Incidence of Cholangiocarcinoma (2001 – 2017)

National Cancer Institute Surveillance, Epidemiology, and End Results 18 cancer registry







Comparison	HR (95% CI)	*p* value	5-year mortality, %
iCCA versus eCCA	0.90 (0.88–0.92)	<.0001	82.6 versus 78.9
CUP versus iCCA	0.63 (0.60–0.65)	<.0001	93.5 versus 82.6
CUP versus eCCA	0.56 (0.55–0.58)	<.0001	93.5 versus 78.9

- Incidence of cholangiocarcinoma is increasing
- Incidence of Cancer of Unknown Primary is declining while iCCA is increasing

Javle et al. *The Oncologist*, 2022

Risk Factors

Established

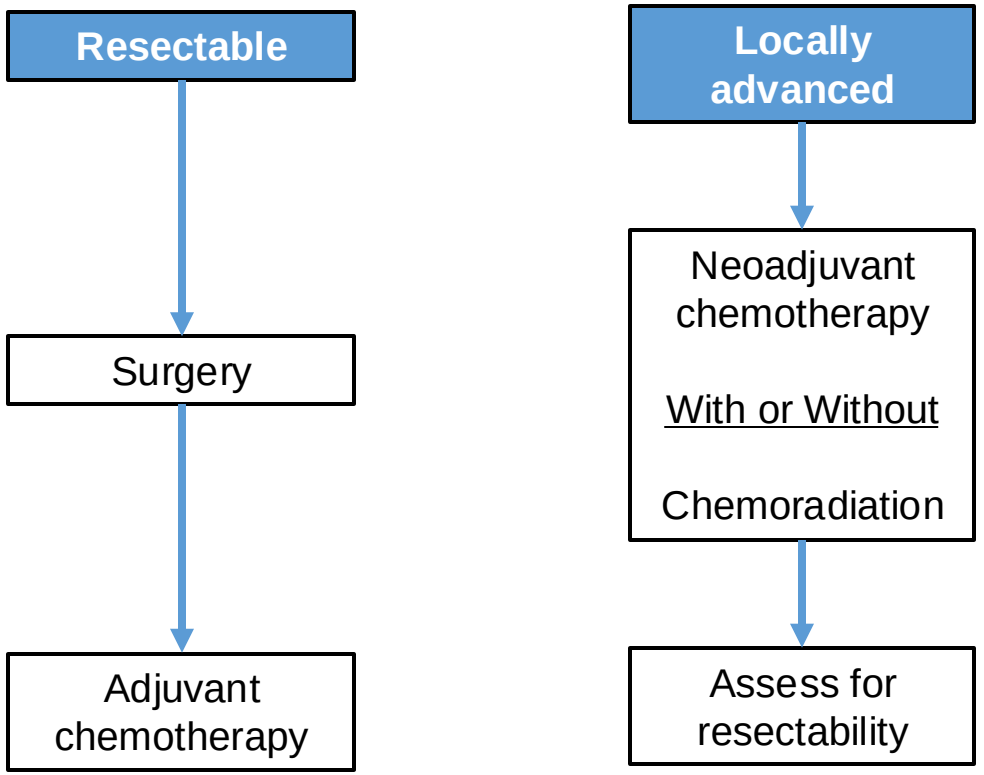
- Parasitic infections (Chinese liver fluke)
- Primary sclerosing cholangitis (PSC)
  - Inflammation and scarring of ducts
- Biliary duct cysts
- Hepatolithiasis

Being Considered

- Inflammatory bowel disease
  - Inflammatory bowel disease
- Hepatitis C or B virus
- Metabolic dysfunction
  - Diabetes
- Cirrhosis
  - Non-alcoholic fatty liver disease

Tyson GL et al. *Hepatology*. 2011
Wirth TC, Vogel A. *Best Pract Res Clin Gastroenterol*. 2016;

Bile Duct Cancer – Perioperative Chemotherapy

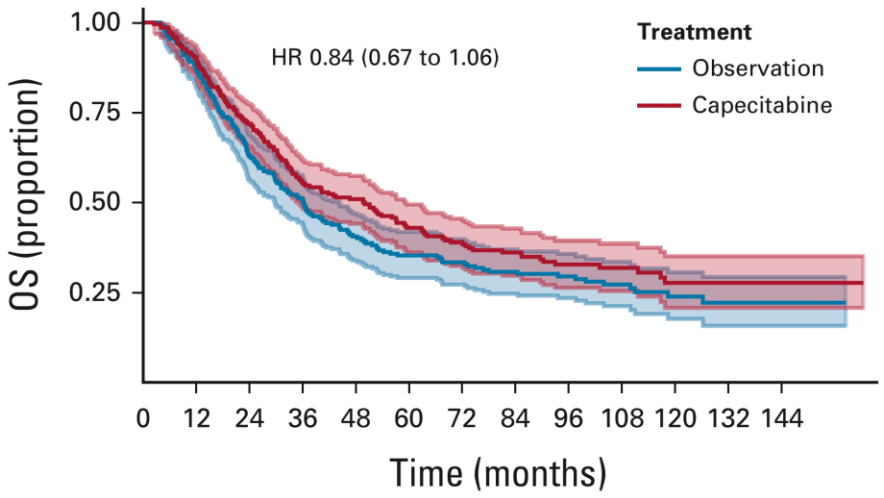


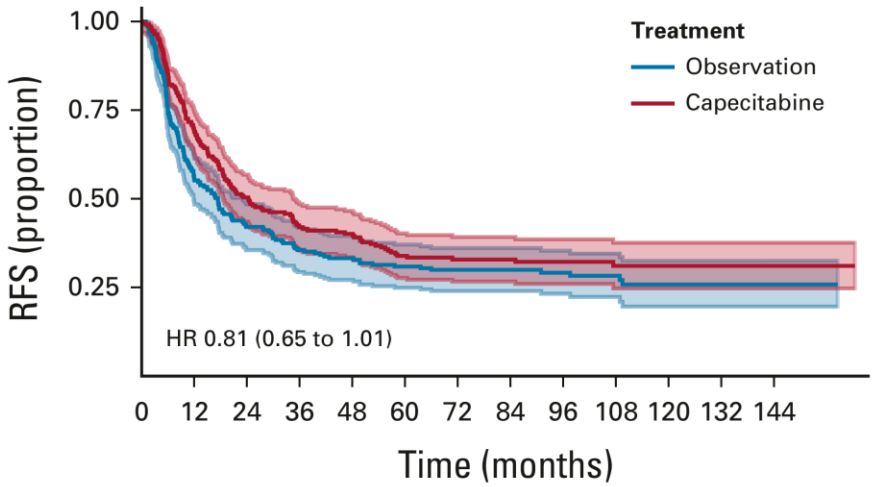
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Biliary Tract Cancers. Version 1.2025.

Bile Duct Cancer – Adjuvant Therapy

BILCAP

- Randomized phase 3 (N = 447)
- CC and GB after resection with curative intent
- Capecitabine (1,250mg/m2 oral twice daily on days 1-14 every 21 days for 8 cycles) versus observation



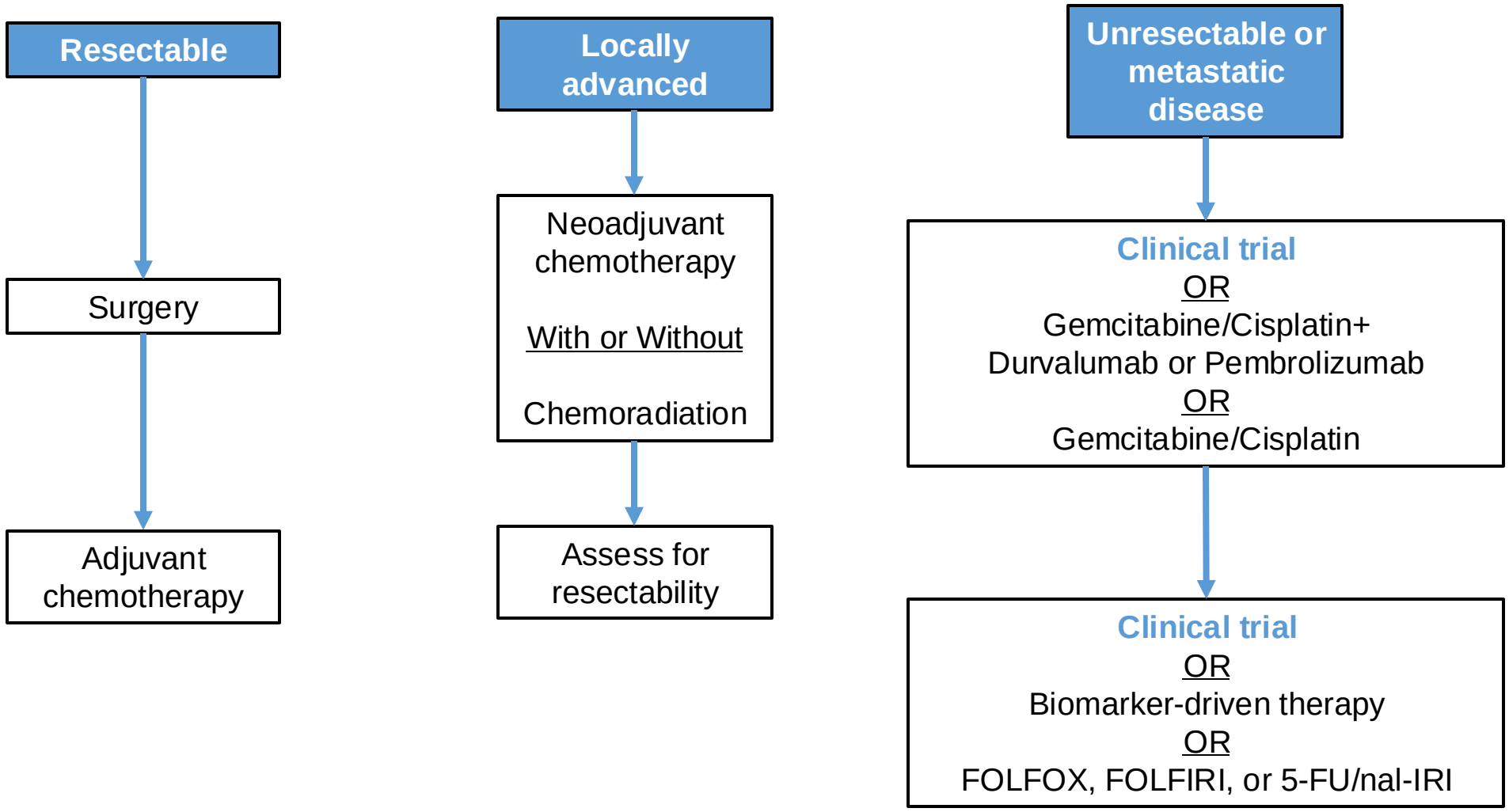


mOS: 49.6 vs 36.1 mo (HR: 0.84)

mPFS: 24.3 vs 17.4 mo (HR: 0.81)

Bridgewater J, et al. JCO. 2022

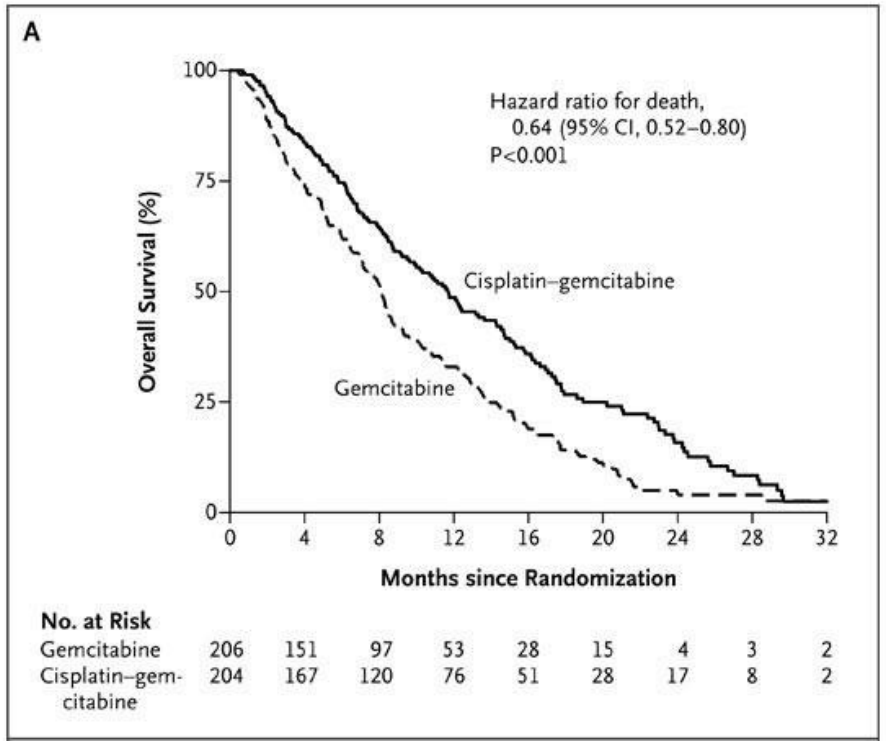
Treatment Paradigm for Cholangiocarcinoma

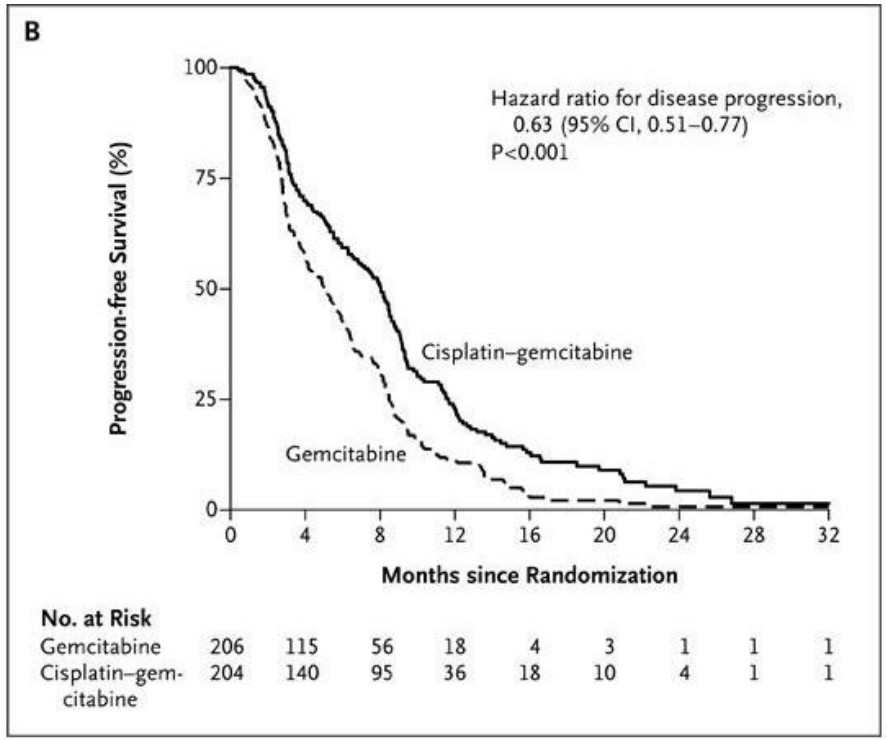


National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Biliary Tract Cancers. Version 1.2025.

Advanced BTC – Gemcitabine with Cisplatin

- ABC-02. Randomized phase 3 (N = 410)
- Locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary carcinoma
- Gemcitabine versus Gemcitabine with cisplatin for up to 24 weeks





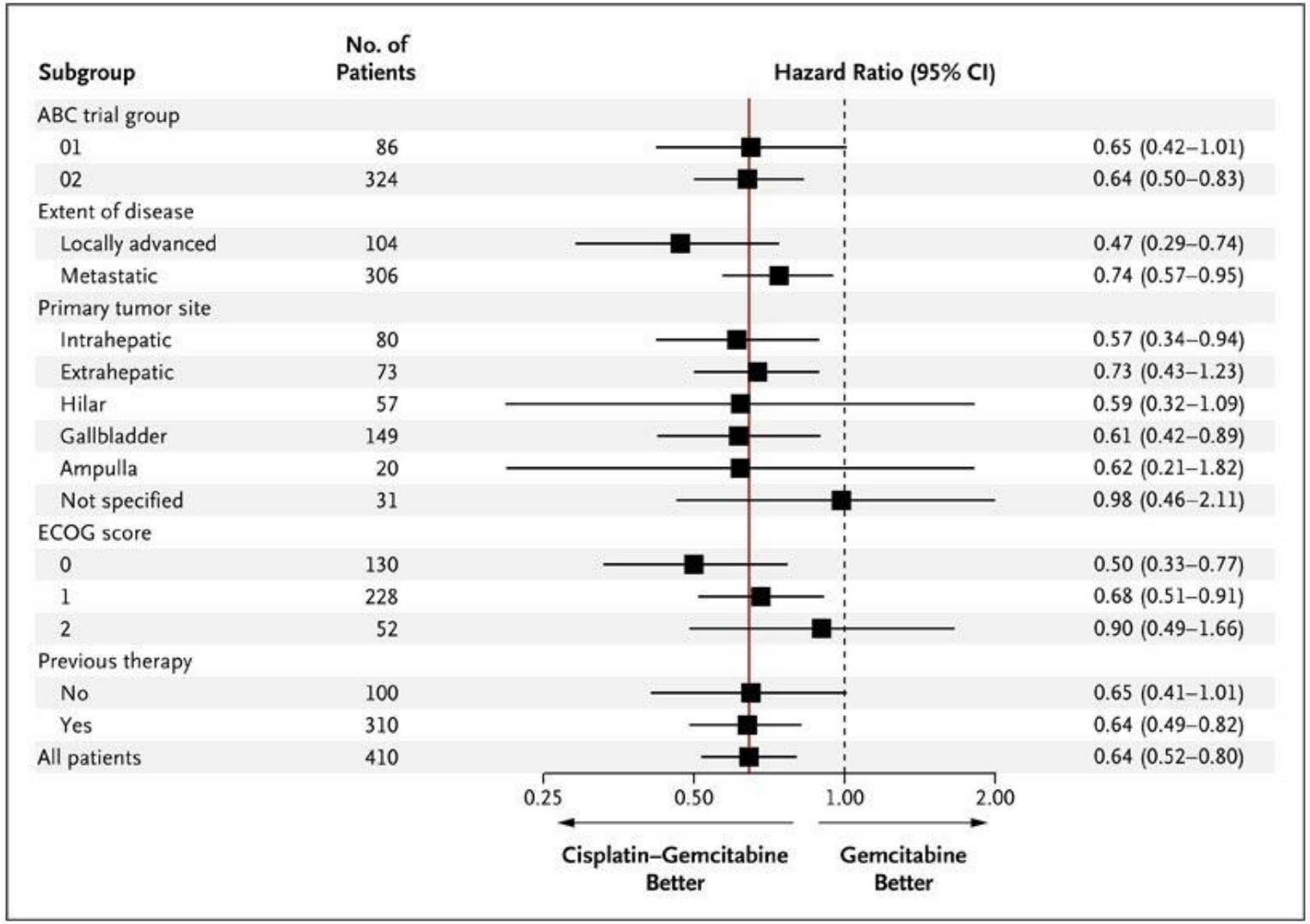
mOS: 11.7 vs 8.1 mo
(HR: 0.64; *P* <.001)

mPFS: 8.0 vs 5.0 mo
(HR: 0.63; *P* <.001)

ORR: 26.1% vs 15.5% (NR)

Valle, J et al. NEJM. 2010; 362:1273

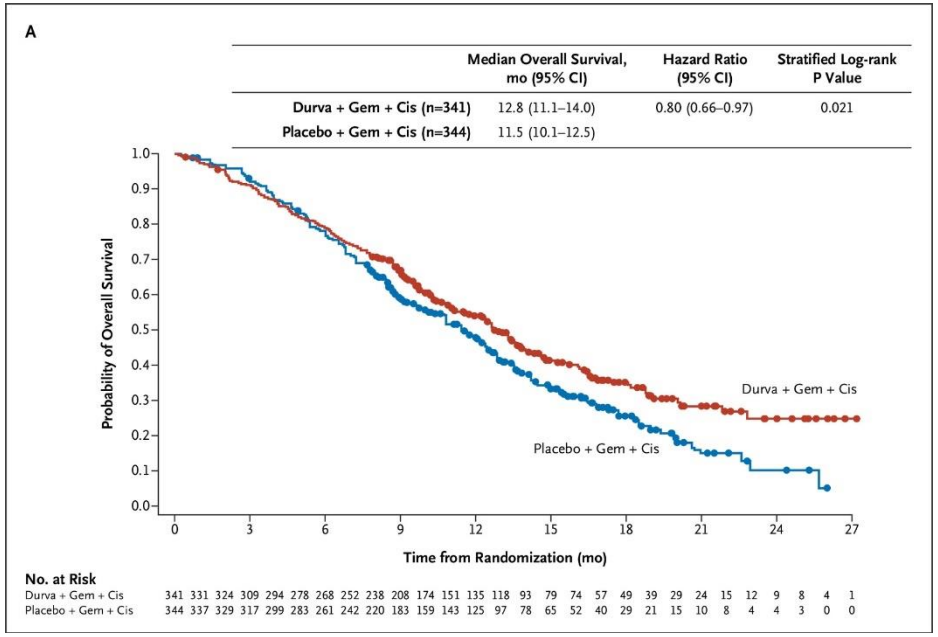
HR According to Trial and Prespecified Baseline Factors

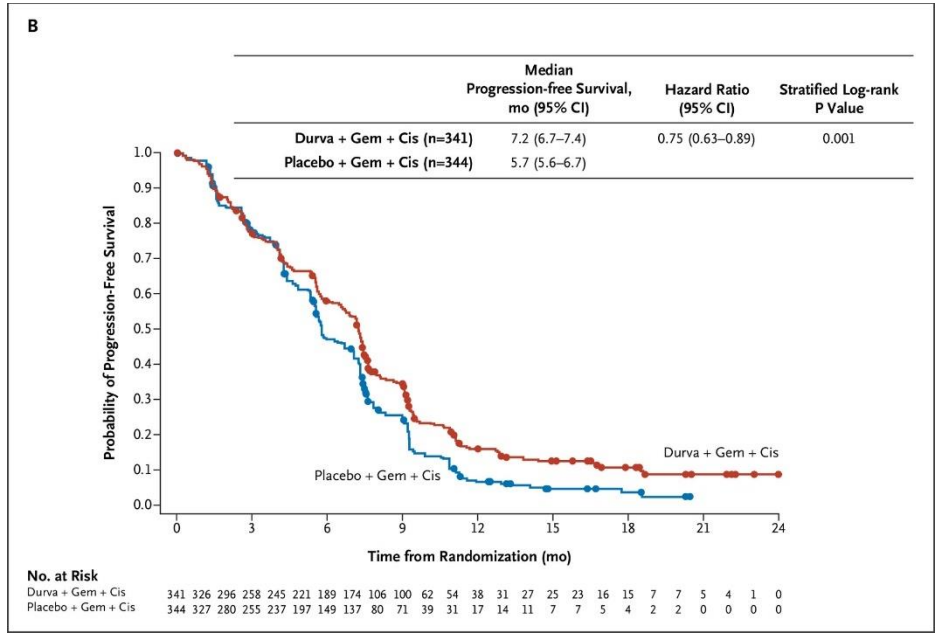


Valle, J et al. NEJM. 2010; 362:1273

Advanced BTC – Gemcitabine/Cisplatin/Durvalumab

- TOPAZ-01. Randomized phase 3 (N = 685)
- Unresectable or metastatic biliary tract cancer
- Gemcitabine/cisplatin with durvalumab or placebo for up to 8 cycles





mOS: 12.8 vs 11.5 mo (HR: 0.80; *P*=0.021)

mPFS: 5.7 vs 7.2 mo (HR: 0.75; *P*=0.001)

ORR: 26.7% vs 18.7% (NR)

Oh D-Y et al. NEJM Evid 2022

Advanced BTC – Gemcitabine/Cisplatin/Durvalumab

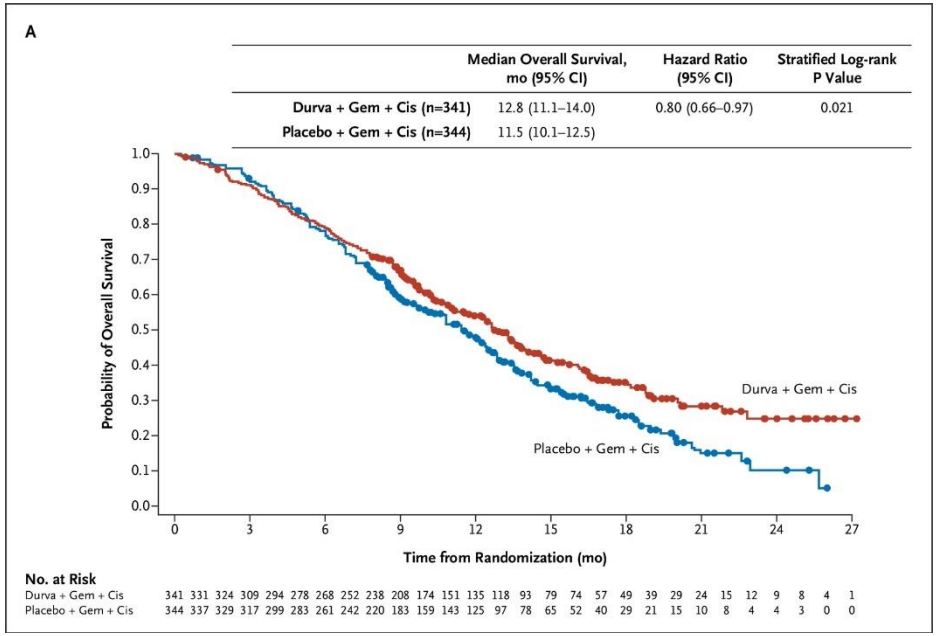
Table 3. Summary of Safety Data in the Safety Analysis Set.

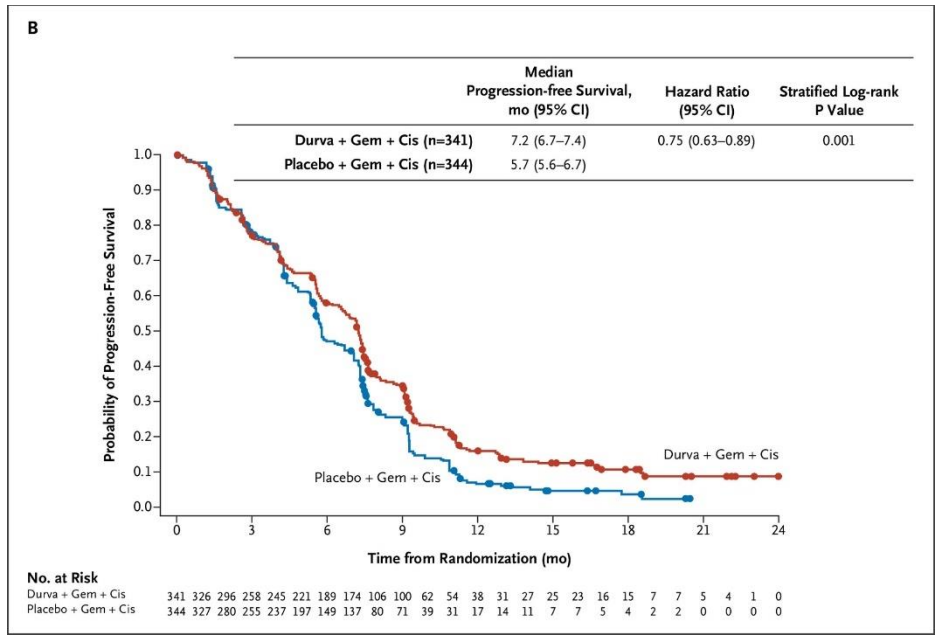
Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=338)	Placebo plus Gemcitabine and Cisplatin (n=342)
Adverse events — no. (%)		
Any grade	336 (99.4)	338 (98.8)
Serious	160 (47.3)	149 (43.6)
Grade 3 or 4	256 (75.7)	266 (77.8)
Leading to discontinuation of any study treatment	44 (13.0)	52 (15.2)
Leading to death	12 (3.6)	14 (4.1)
Treatment-related adverse events — no. (%)		
Any grade	314 (92.9)	308 (90.1)
Serious	53 (15.7)	59 (17.3)
Grade 3 or 4	212 (62.7)	222 (64.9)
Leading to discontinuation of any study treatment	30 (8.9)	39 (11.4)
Leading to death*	2 (0.6)	1 (0.3)

* Treatment-related adverse events leading to death were ischemic stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group.

Advanced BTC – Gemcitabine/Cisplatin/Pembrolizumab

- KEYNOTE-966. Randomized phase 3 (N = 1069)
- Locally advanced or metastatic biliary tract cancer
- Gemcitabine/cisplatin with durvalumab or placebo for up to 8 cycles





mOS: 12.7 vs 10.9 mo (HR: 0.83; *P*=0.0034)

mPFS: 6.5 vs 5.6 mo (HR: 0.86; *P*=0.023)

Systemic steroids required for immune-related AEs – 9% vs. 5%

Kelley RK, et al. *Lancet*.2023

Key Differences – TOPAZ-1 and KEYNOTE-966

TOPAZ-1

Allowed recurrent (> 6m after curative surgery or adjuvant therapy)

Durvalumab/Placebo allowed to progression after ≤ 8 cycles of Gem/Cis

KEYNOTE-966

No prior systemic therapy allowed

Gemcitabine with Pembrolizumab/Placebo allowed to ≤ 35 cycles of Pembrolizumab/Placebo

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Biliary Tract Cancers

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PRINCIPLES OF SYSTEMIC THERAPY[a]

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Durvalumab + gemcitabine + cisplatin (category 1)[e-h,4,5]
- Pembrolizumab + gemcitabine + cisplatin (category 1)[e,g,h,4,6]

Other Recommended Regimens

- Gemcitabine + cisplatin (category 1)[e,4,7]
- Capecitabine + oxaliplatin
- FOLFOX
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[i]

Preferred Regimens

- FOLFOX[8]

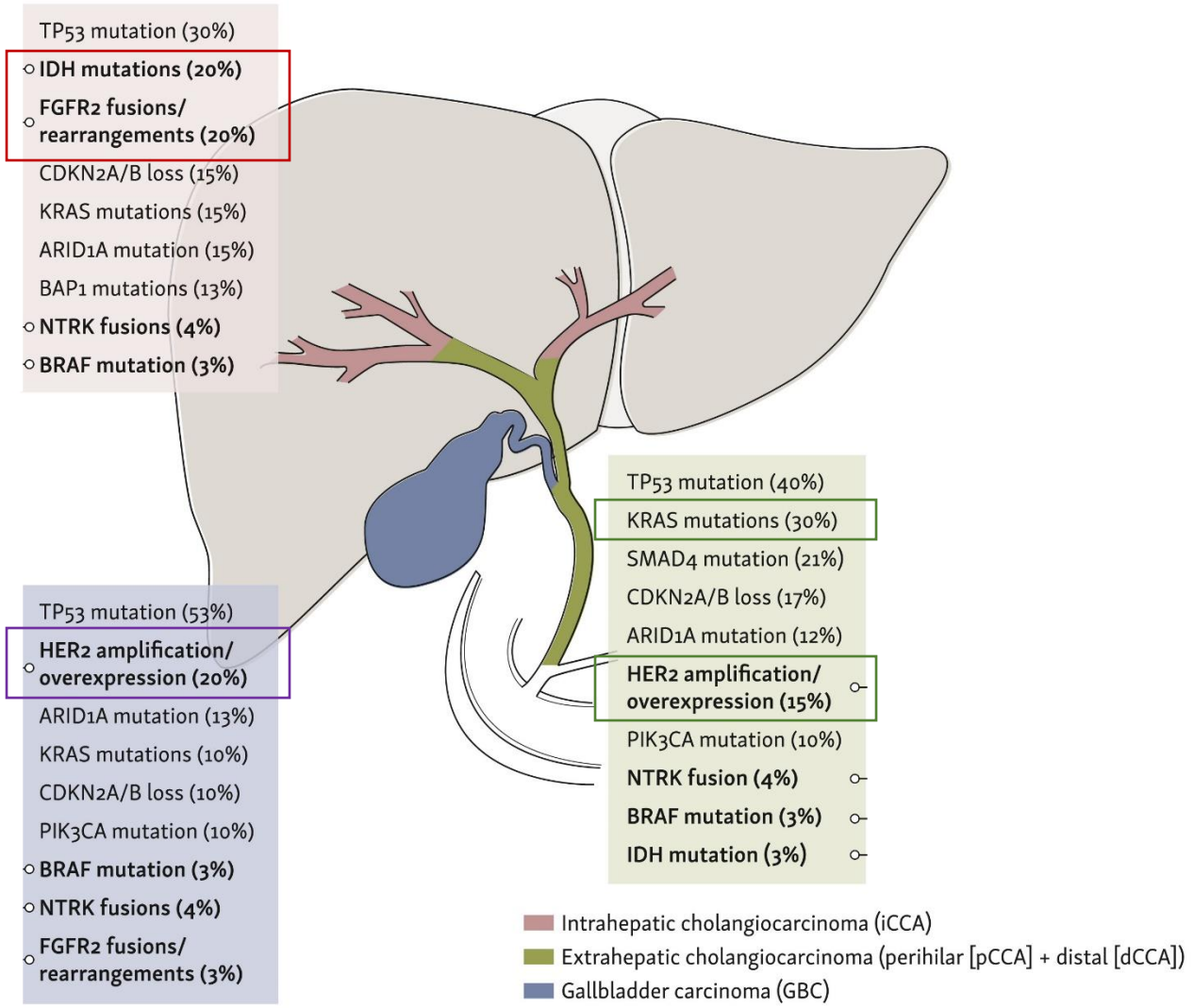
Other Recommended Regimens

- FOLFIRI[9]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[10]
- Regorafenib (category 2B)[11]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)
- Nivolumab (category 2B)[g,h,j,12]

Molecular Landscape of Bile Duct Tumors



Approximately 50% of ICC and ECC harbor potentially targetable mutations

ICC

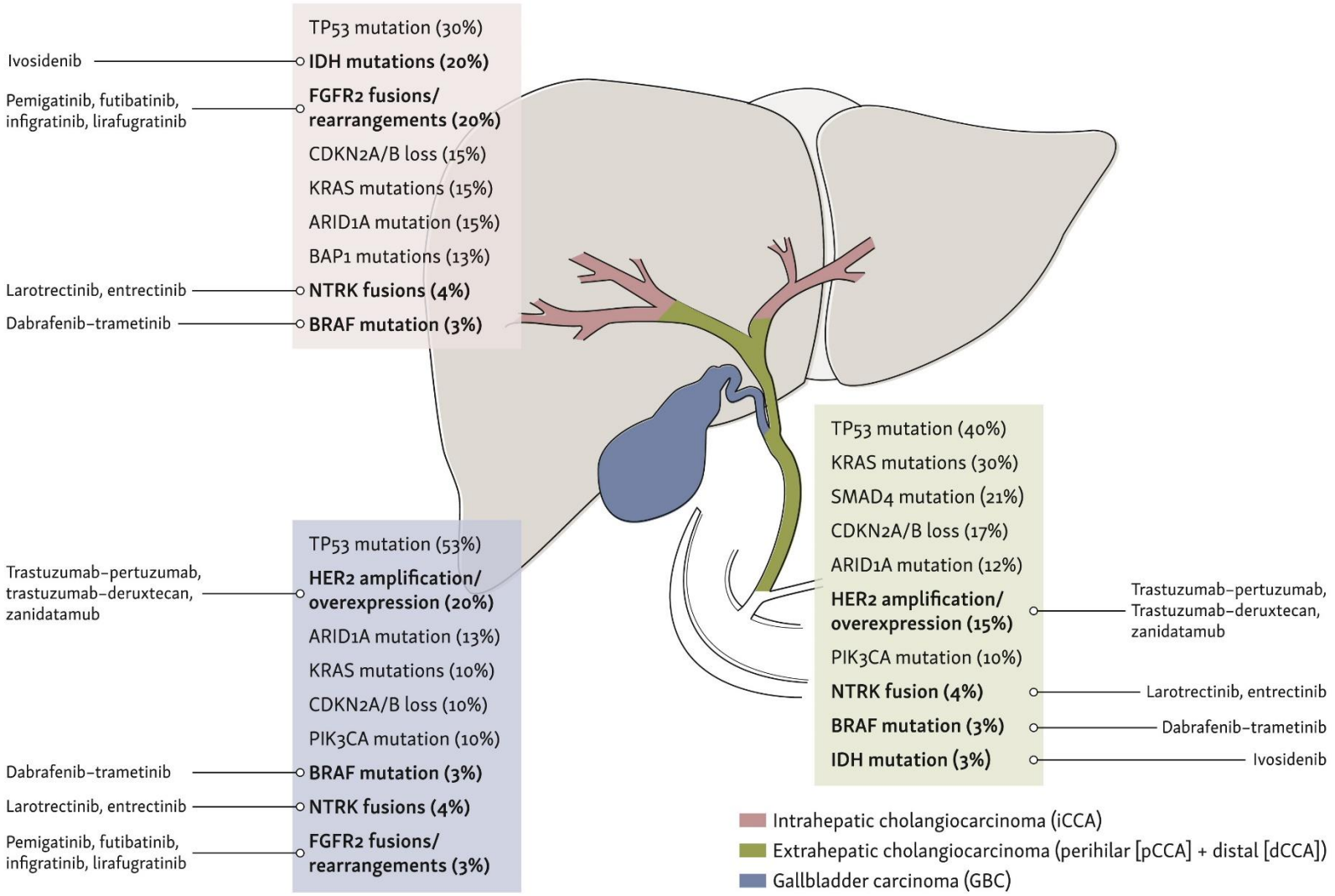
IDH1, FGFR2, NTRK, BRAF

ECC

HER2, *BRAF, IDH*

Kehmann L, et al. 2024. ESMO OPEN

Molecular Landscape of Cholangiocarcinoma



- Approximately 50% of ICC and ECC harbor potentially targetable mutations
- **ICC**

  IDH1, FGFR2, NTRK, BRAF
- **ECC**

  HER2, BRAF, IDH

Kehmann L, et al. 2024. ESMO OPEN

Molecular Testing NCCN Recommendations

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PRINCIPLES OF MOLECULAR TESTING

Table 2: Incidence of Therapeutic Targets in Advanced Biliary Tract Cancers

Aberration	Approximate Incidence[e]
NTRK fusion	<1%
MSI-H/dMMR	1%–3%
TMB-H	<5%
BRAF V600E mutation	1%–5%
FGFR2 fusion or rearrangement	9%–15% of intrahepatic CCAs and rare in other subsites
IDH1 mutation	10%–20% of intrahepatic CCAs and rare in other subsites
HER2 (*ERBB2*) overexpression and/or amplification	5%–20% of CCAs, 15%–30% of gallbladder cancer
RET fusion	<1%
KRAS G12C mutation	1%

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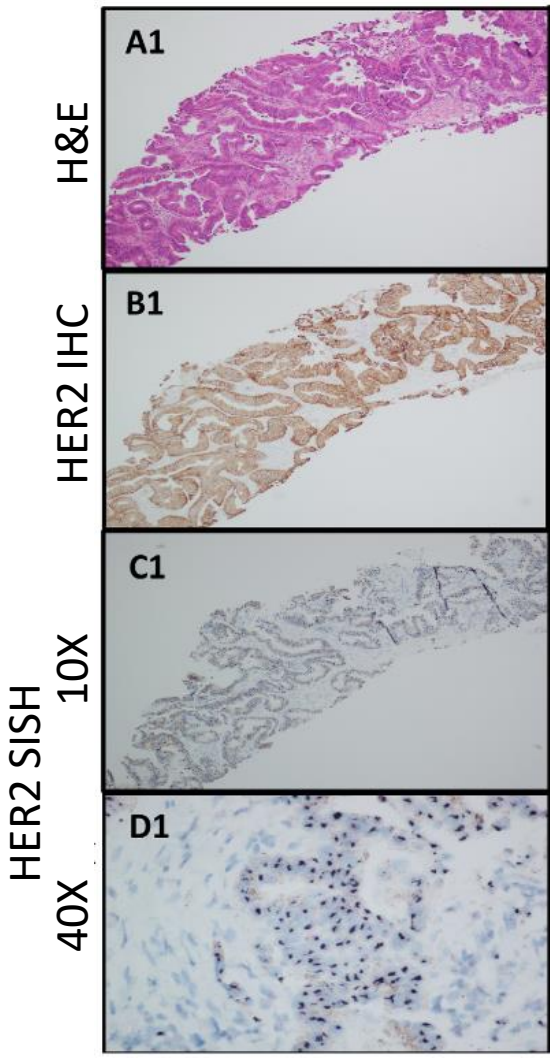
PRINCIPLES OF MOLECULAR TESTING

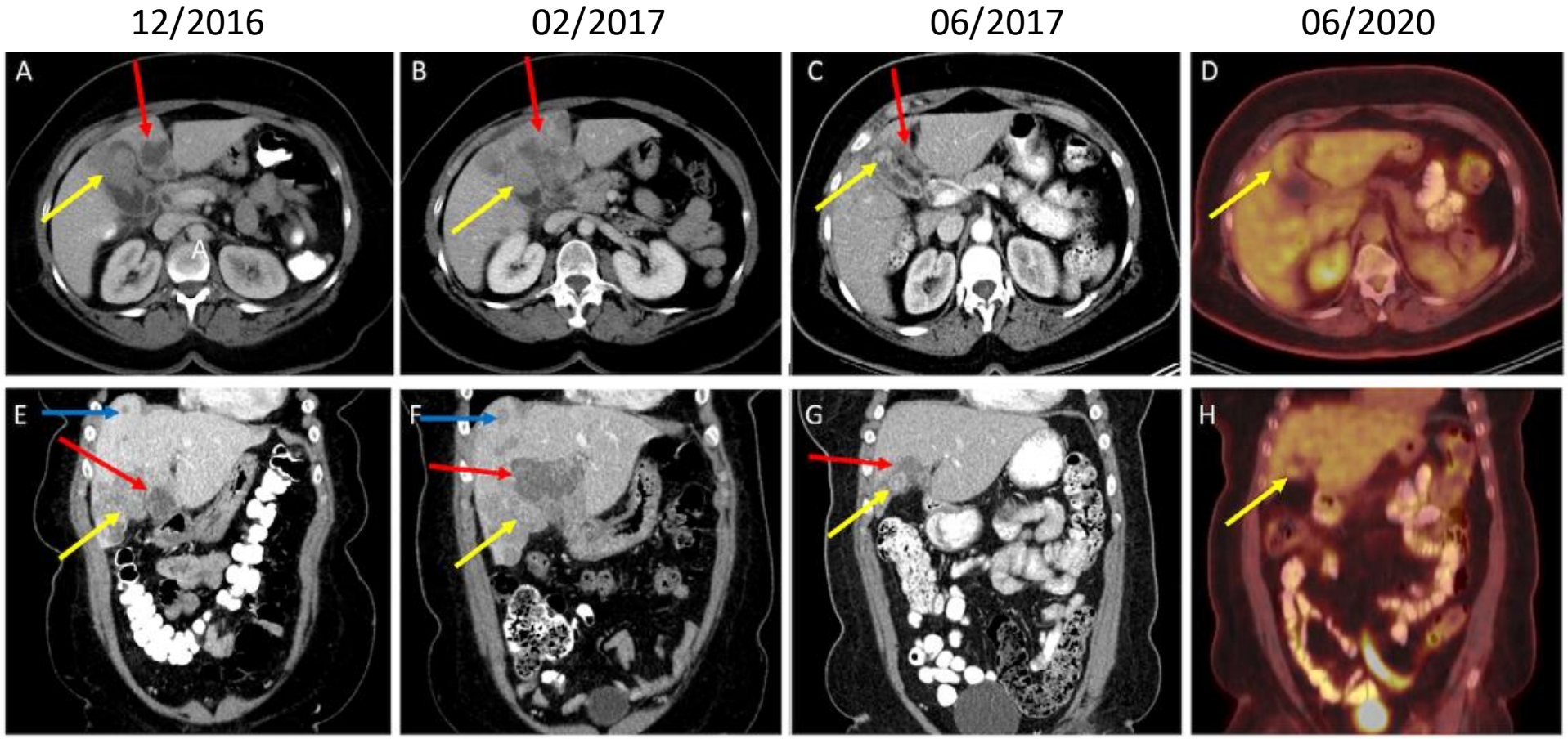
Table 1: Recommendations for Molecular Testing in Unresectable or Metastatic Biliary Tract Cancers[a-d]

Recommended Molecular Testing	Anatomic Subsite		
	Gallbladder	Intrahepatic CCA	Extrahepatic CCA
NTRK gene fusion	X	X	X
MSI-H/dMMR	X	X	X
TMB-H	X	X	X
BRAF V600E mutation	X	X	X
FGFR2 fusion or rearrangement	–	X	X
IDH1 mutation	–	X	X
HER2 *(ERBB2)* overexpression and/or amplification	X	X	X
RET gene fusion	X	X	X
KRAS G12C mutation	X	X	X

MSI-H: microsatellite instability-high
dMMR: mismatch repair deficient
TMB-H: tumor mutational burden-high

Targeting HER2 in Bile Duct Tumors

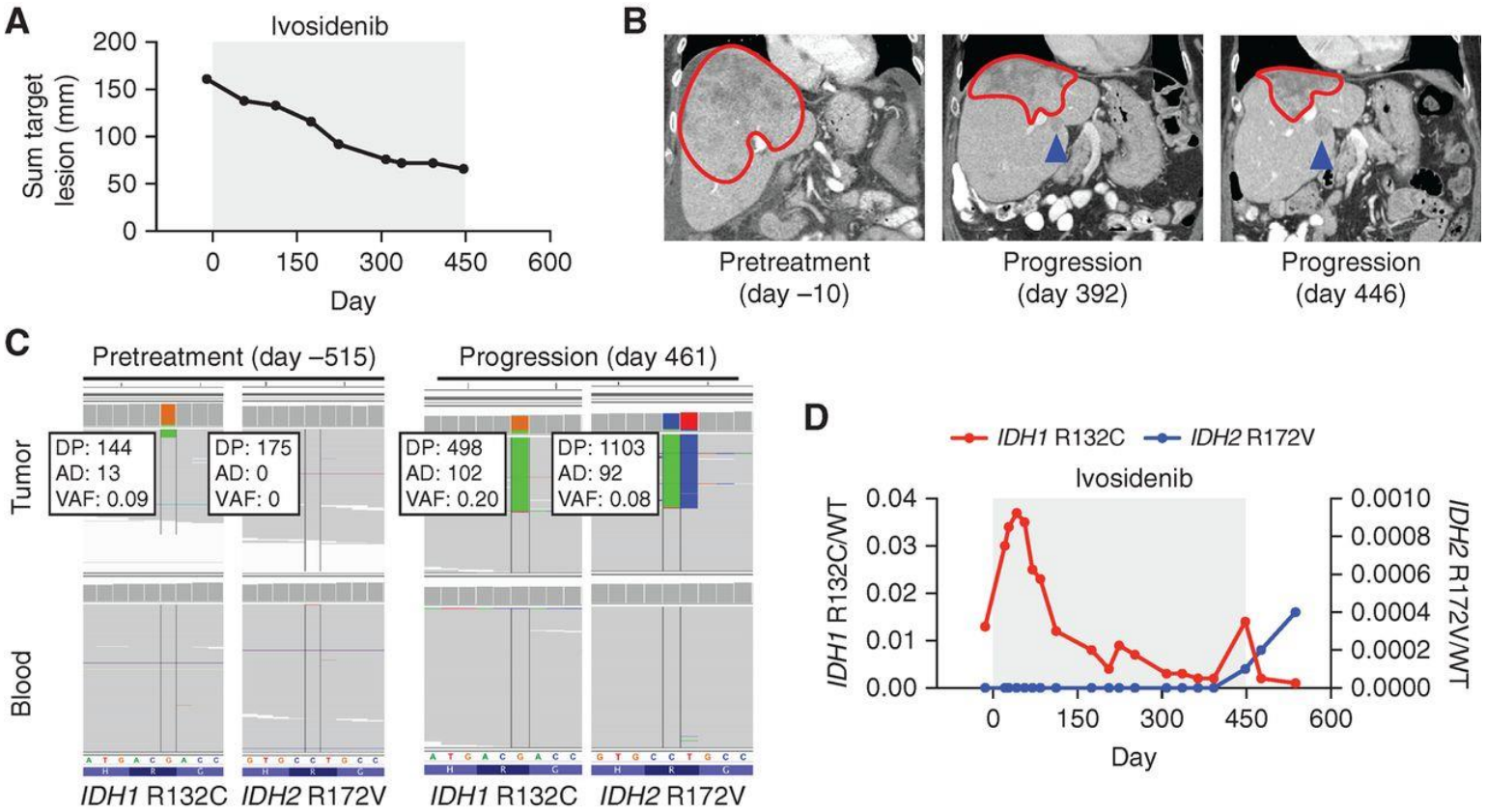




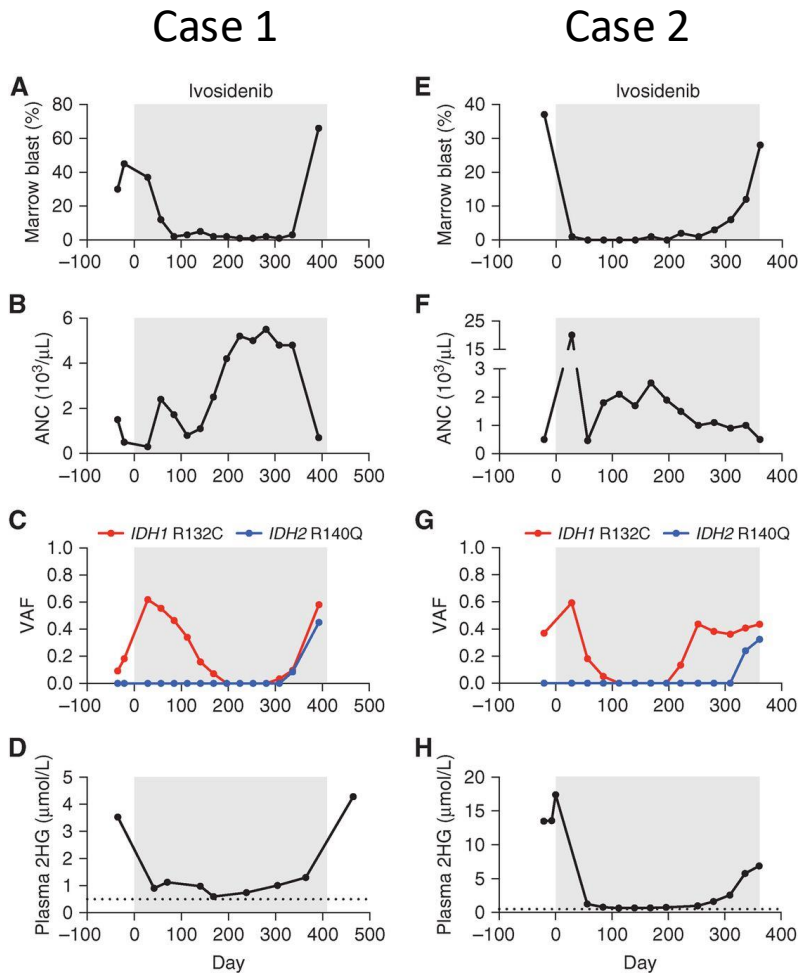
May M, 2021. *The Oncologist*

IDH1 Resistance – Isoform Switching

IDH1 R132C-mutant ICC



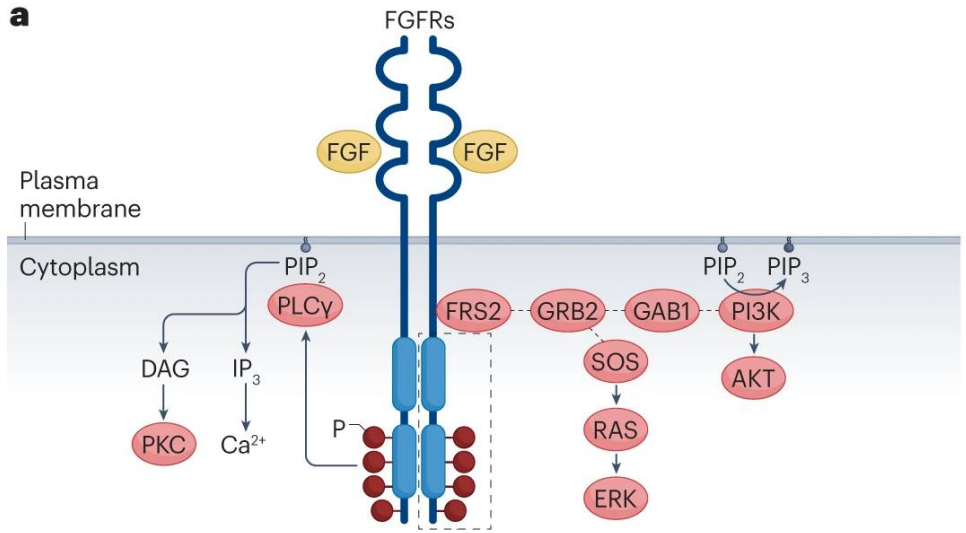
IDH1 R132C-mutant AML

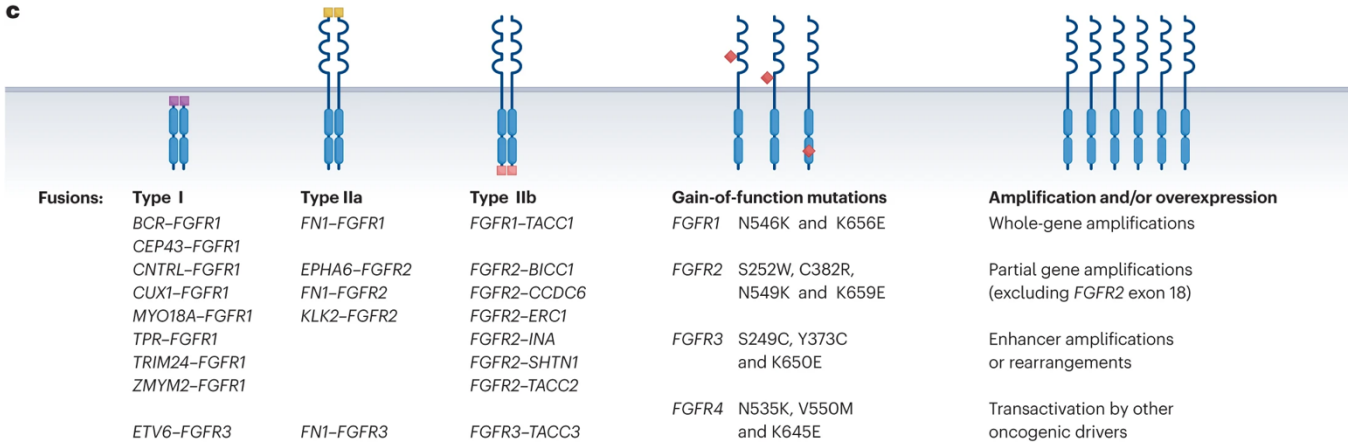


Harding J, et al. Cancer Discov. 2018

Fibroblast Growth Factor Receptor 2

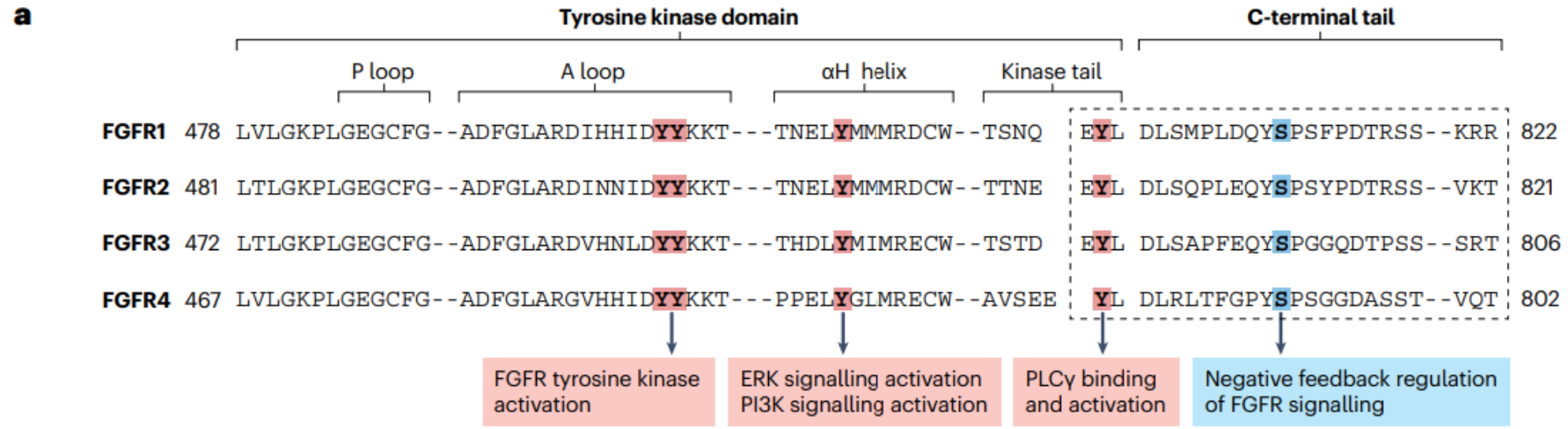
- FGFR 1 – 4 receptor tyrosine kinases
  - Proliferation, angiogenesis, differentiation, survival, and repair
- Activation of FGFR2 observed in 10-15% ICC
  - Fusions, rearrangements, point mutations, and in-frame deletions
- Fusions result in ligand-independent dimerization and downstream activation





Katoh M, et al. Nat Rev Clin Oncol. 2024

FGFR Tyrosine Kinase Domain and Drug Binding Site



Katoh M, et al. Nat Rev Clin Oncol. 2024

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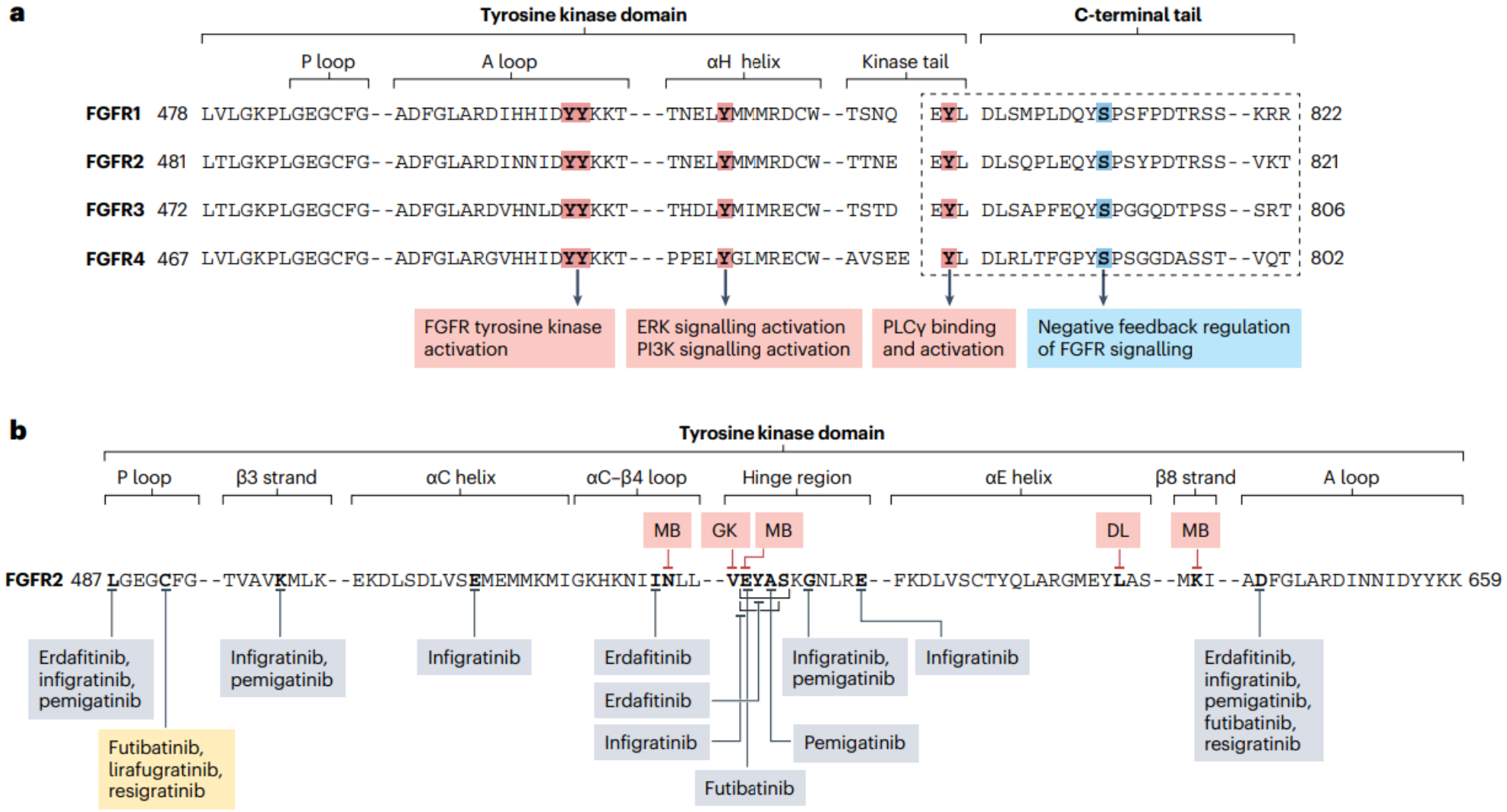
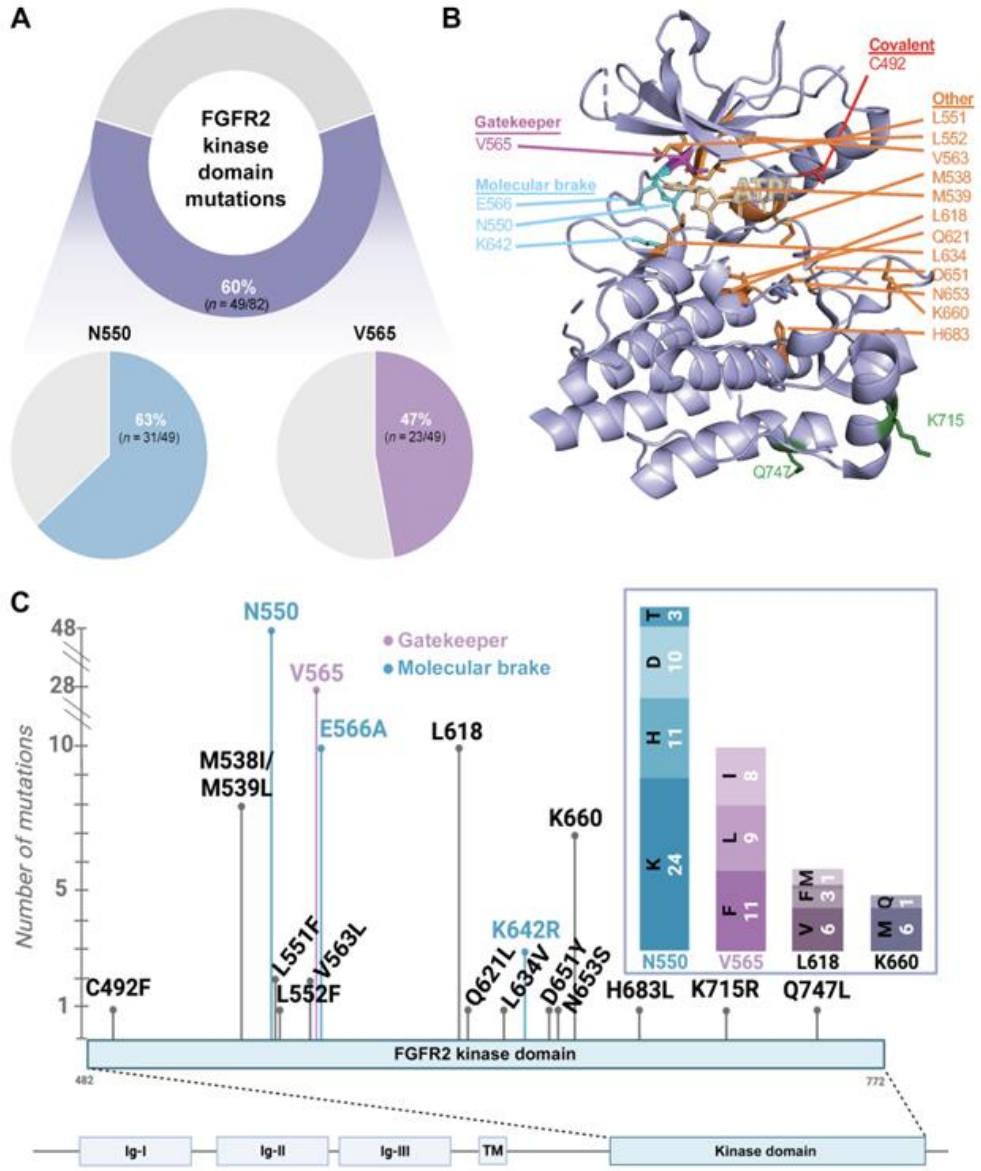


Katoh M, et al. Nat Rev Clin Oncol. 2024

FGFR Resistance

- Circulating DNA or tumor tissue upon disease progression following FGFR inhibitor therapy
  - 82 FGFR2-altered CC patients
- 49 of 82 (60%) had *FGFR2* kinase domain mutations on acquired resistance
  - N550 (63%) and V565 (47%)
- Secondary mutations within *FGFR2* kinase domain is the primary mode of acquired resistance



Wu Q, et al. Clin Cancer Res 2024

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BRAF V600E mutation	X	X	X
FGFR2 fusion or rearrangement	–	X	X
IDH1 mutation	–	X	X
HER2 *(ERBB2)* overexpression and/or amplification	X	X	X
RET gene fusion	X	X	X
KRAS G12C mutation	X	X	X

MSI-H: microsatellite instability-high
dMMR: mismatch repair deficient
TMB-H: tumor mutational burden-high

Summary

- Cholangiocarcinoma may clinically present as cancer of unknown primary
- Capecitabine is the current standard of care in the adjuvant setting
- Gemcitabine and cisplatin with either durvalumab or pembrolizumab is the current standard of care in advanced disease
- IDH, FGFR2, Her2, BRAF, and NTRK are clinically meaningful targets
- Second generation inhibitors of IDH and FGFR need to tackle treatment resistance
- Yet to establish whether KRAS inhibitors will have meaningful clinical benefit in CC