PRACTICAL INSIGHTS FOR EARLY DIAGNOSIS AND MANAGEMENT OF BILIARY TRACT CANCERS

Advances in the Treatment of advanced Biliary Tract Cancer: What Clinicians Need to Know

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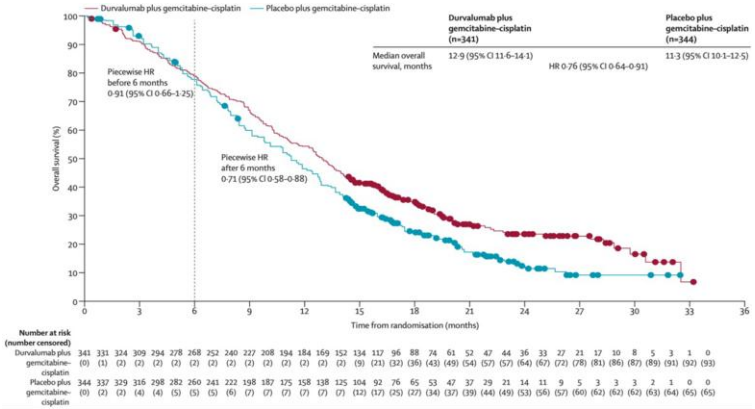
Advanced BTC: Standard of care in L1

Before 2022, the standard of care in advanced BTC was CISGEM based on ABC-02 trial results

TOPAZ-1 randomized phase 3 trial

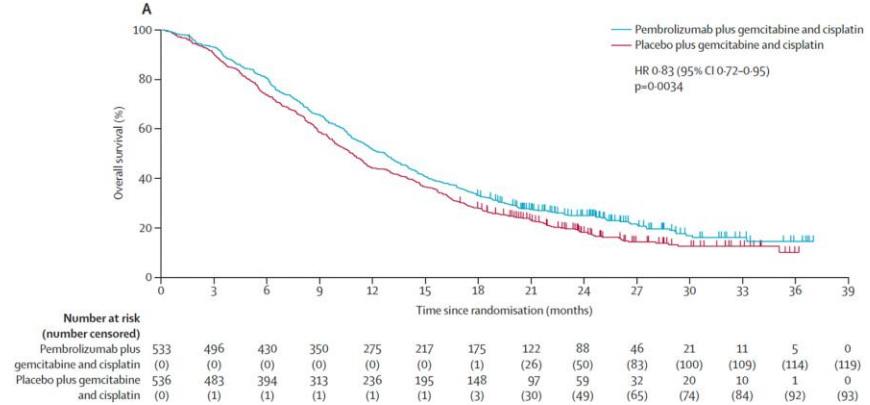
CISGEM + Durvalumab vs CISGEM placebo



OS: 12.9 vs 11.3 mo (HR = 0.76; 95% CI [0.64-0.91])
24-month OS: 23.6% vs.11.5%

KEYNOTE-966 randomized phase 3 trial

CISGEM + Pembrolizumab vs CISGEM placebo



Median OS: 12.7 vs 10.9 mo (HR =0.83; 95% CI [0·72-0·95])

→ Superiority of CISGEM-anti-PD1/PDL1 in OS, PFS and ORR without increased toxicity

Standard L1 therapy of advanced BTC is a combination of Cisplatin-Gemcitabine + anti-PDL1/PD1 inhibitor

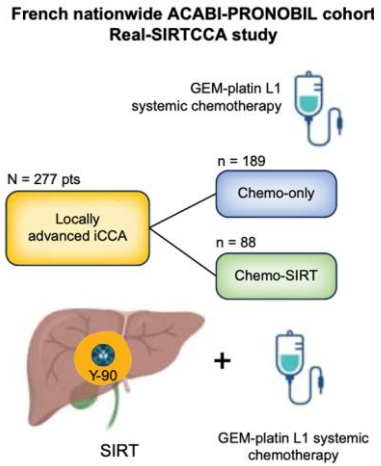
CISGEM: cisplatin-gemcitabine; **mo:** months; **OS:** overall survival.

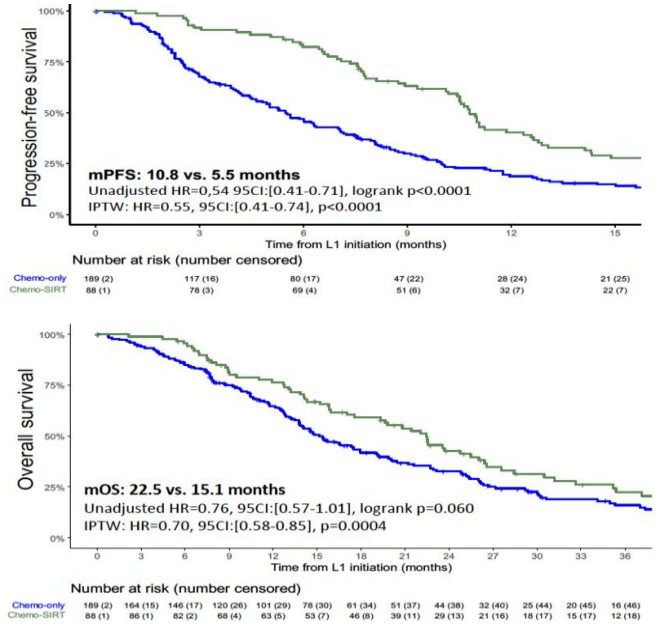
Valle et al. N Engl J Med 2010 2010. Oh et al. NEJM Evidence 2022. Oh et al Lancet Gastroenterol Hepatol 2024. Kelley et al. Lancet 2023; 401: 1853-65.

Is there a place for intensification in L1?

Selective internal radiation therapy combined with L1 in iCCA

- **Mysphec Trial (Phase II, single arm): CISGEM with SIRT.**
- **Meta-analysis (6 prospective trials): superiority in ORR, PFS, OS, resection rate of CISGEM-SIRT vs CISGEM.**





Improved PFS and OS
Improved ORR (58.3 vs 28.5 %; p<0.0001)
and resection rate (18.7 vs 8.8 %; p<0.0001)

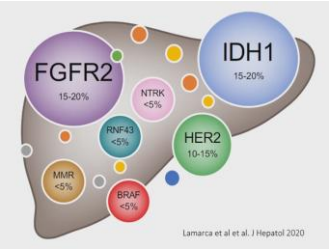
- **SIRT may improve survival outcomes and access to surgery via downstaging**

- **Consider SIRT with systemic L1 in patients ECOG 0-1 with liver only iCCA**

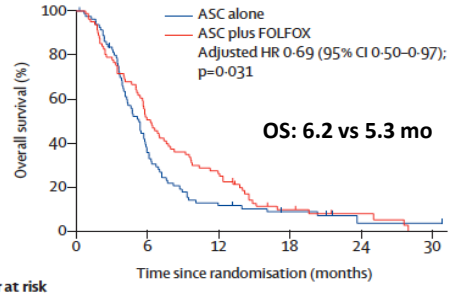
Chemo: chemotherapy; **PFS:** progression-free survival; **ORR:** objective response rate; **OS:** overall survival.

Edeline et al. Jama Oncol 2020. Edeline et al. Hepatology 2023. Adamus et al. JHEP Reports 2025.

Advanced BTC: Options in L2 and +



ABC-06 trial: FOLFOX vs BSC only



Low survival gain vs. best supportive care

BSC: best supportive care; **CISGEM:** cisplatine-gemcitabine; **OS:** overall survival.

Lamarca et al Lancet Oncol 2021. Roth et al Eur J of Cancer 2023.

L1: CISGEM + anti-PDL1/PD1

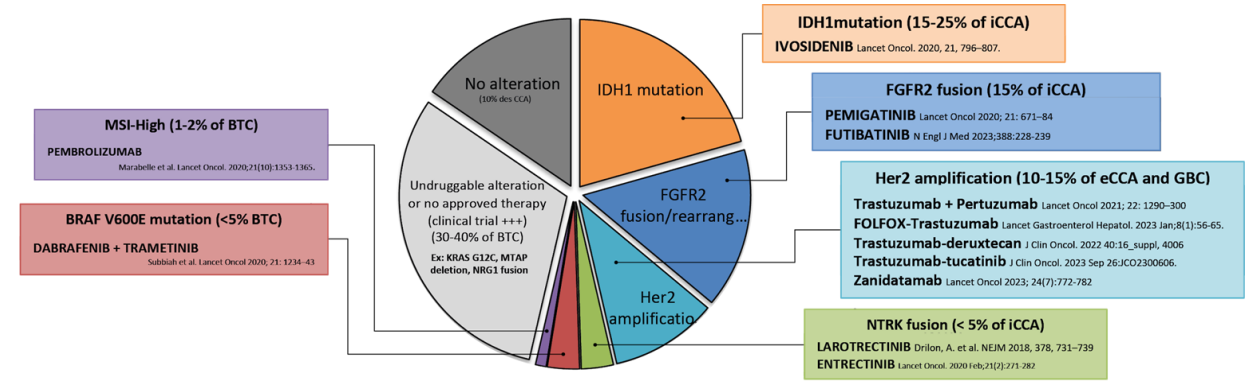
All patient with advanced CCA, ECOG 0-1

Molecular profiling

- **MMR** (IHC) + MSI in PCR or NGS if dMMR.
- **HER2** (IHC) 3+ or 2+ + ISH.
- **NGS (DNA et RNAseq)** : mutations (*IDH1*, *BRAF*, *KRAS, etc*), fusions/rearrangments (*FGFR2*, *NTRK, etc).*

Early molecular profiling for access to personalised medicine

Druggable alterations?



IDH1-mutated BTC: L2 and +

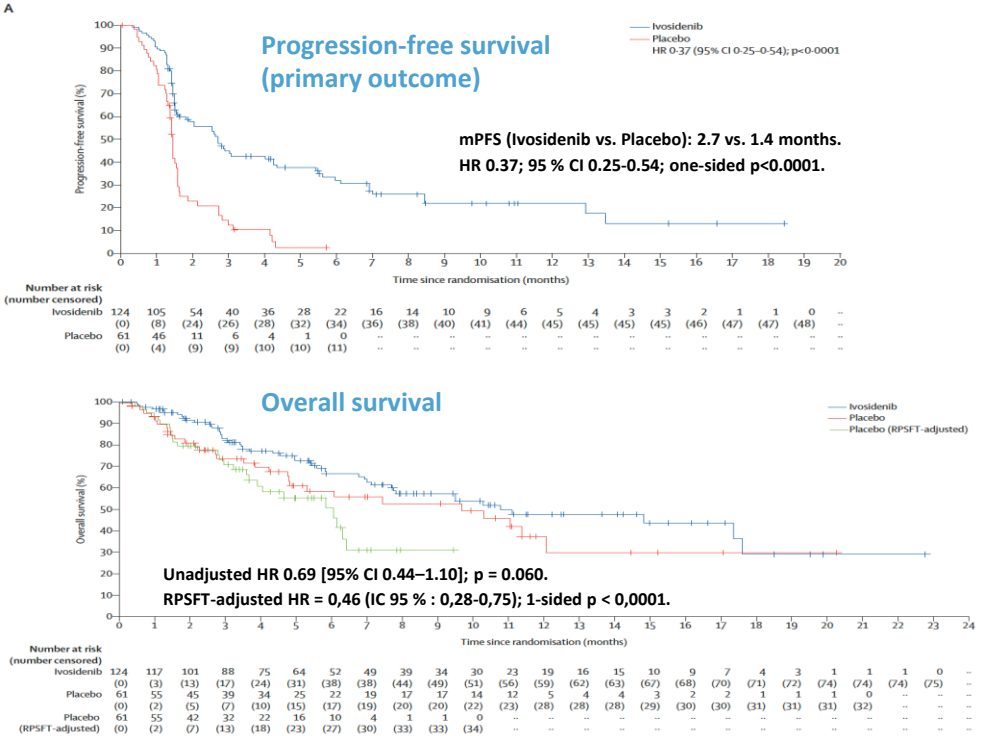
ClarIDHy multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Patients characteristics	Ivosidenib (n = 126)	Placebo (n = 61)
L2, n (%) **L3, n (%)**	66 (52,4) 60 (47,6)	33 (54,1) 28 (45,9)
R132C-IDH1 mutation, n (%)	86 (68,3)	45 (73,8)
iCCA, n (%)	113 (89,7)	58 (95,1)
Metastatic disease, n (%)	117 (92,9)	56 (91,8)

Acceptable toxicity

	Ivosidenib (n = 121)		Placebo (n = 59)	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Nausea	40 (33 %)	3 (2 %)	14 (24 %)	1 (2 %)
Diarrhoea	37 (31 %)	0	9 (15 %)	0
Fatigue	28 (23 %)	4 (3 %)	9 (15 %)	1 (2 %)
Cough	25 (21 %)	0	5 (8 %)	0
Abdominal pain	23 (19 %)	3 (2 %)	7 (12 %)	1 (2 %)
Decreased appetite	21 (17 %)	2 (2 %)	11 (19 %)	0
Vomiting	20 (17 %)	3 (2 %)	10 (17 %)	0

Ivosidenib is the standard in L2 and more in IDH1-mutated CCA



IDH: isocitrate deshydrogenase; **L:** line; **RPSFT:** rank preserving structural failure time.

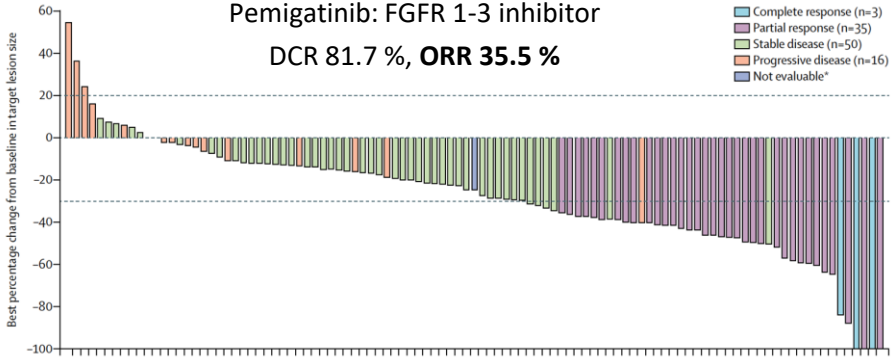
Abou-Alfa et al. Lancet Oncol 2020.

FGFR2-rearranged BTC: L2 and +

FIGHT-202 single-arm phase 2 trial[1]

Pemigatinib: FGFR 1-3 inhibitor

DCR 81.7 %, **ORR 35.5 %**

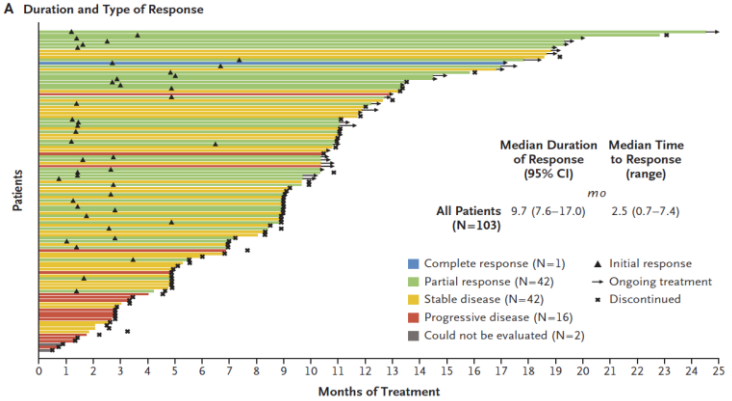


FGFR2 alterations	ORR	PFS	OS
Fusion (n = 100)	**35.5 %**	**6.9 m**	**21.1 m**
Other (ampl,mut) (n=20)	0	2.1	6.7
No alteration (n=20)	0	1.7 m	4.0 m

FOENIX-CCA2 single-arm phase 2 trial[2]

Futibatinib: Irreversible FGFR 1-4 inhibitor

DRC: 83 %, **ORR: 42 %**



Median PFS: 9.0 mo (95 % CI, 6.9–13.1)

Median OS: 21.7 mo (95 % CI, 14.5–NE)

→ FGFR2 inhibitors related adverse events: hyperphosphatemia, diarrhea, fatigue, mucitis, hand-foot syndrom, nauseas, arthralgia, dry skin, mouth and eyes

Pemigatinib and futibatinib are the 2 available standard in FGFR2-f/r BTC in L2 and +

DCR: disease control rate; **PFS:** progression-free survival; **ORR:** objective control rate; **OS:** overall survival.

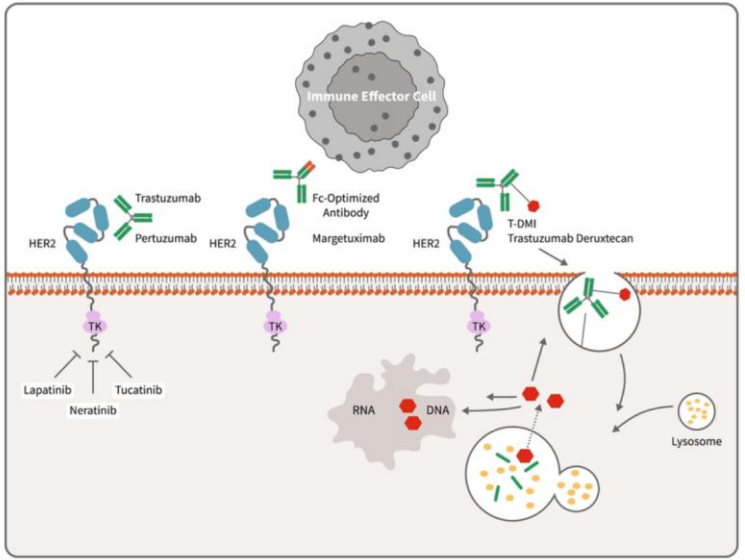
1. Abou-Alfa GK, et al. Lancet Oncol 2020;21:796-807. 2. Goyal et al. NEJM 2023 Jan 19;388(3):228-239.

Options in HER2-amplified BTCs in L2 and +

Drug name, *Drug class* Trial name and design	N	Results		
		ORR	PFS	OS
Trastuzumab-pertuzumab[1] *Anti-HER2 Ab* myPathway single-arm phase 2	39	23 %	4.0 m	10.9 m
FOLFOX-trastuzumab[2] *Chemo + anti-HER2 Ab* KCSG-HB19-14 single-arm phase 2	34	29 %	5.1 m	NR
Trastuzumab-tucatinib[3] *Anti-HER2 Ab + HER2 TKI* SGNTUC-019 single-arm phase 2	33	47 %	5.5 m	NA (12-m OS = 53.6 %)
Trastuzumab-deruxtecan[4] *Anti-HER2 Ab conjugated with TOP1 inhibitor* HERB trial single-arm phase 2	32	HER2+: 36 % HER2-low: 13 %	HER2+: 4.4 m HER2-low: 4.2 m	HER2+: 7.1 m HER2-low: 8.9 m
Zanidatamab[5,6] *Bi specific anti-HER2 Ab* HERIZON-BTC-01 single-arm phase 2	87	41 %	5.5 m HER2+: 7.2 m HER2-low: 1.7 m	15.5 HER2+: 18.1 m HER2-low: 5.2 m

1. Meric-Bernstam et al. Lancet Oncol. 2021. 2. Lee et al. Lancet Gastro & Hep 2023. 3. Nakamura et al. J Clin Oncol. 2023. 4. Ohba et al. J Clin Oncol. 2024. 5. Harding et al. Lancet Oncol 2023. 6. Pant S, et al. ASCO 2024. Póster 4091

Adapted from Roth et al Eur J of Cancer 2023.



Wynn et al. Cancer and Metastasis Reviews 2022.

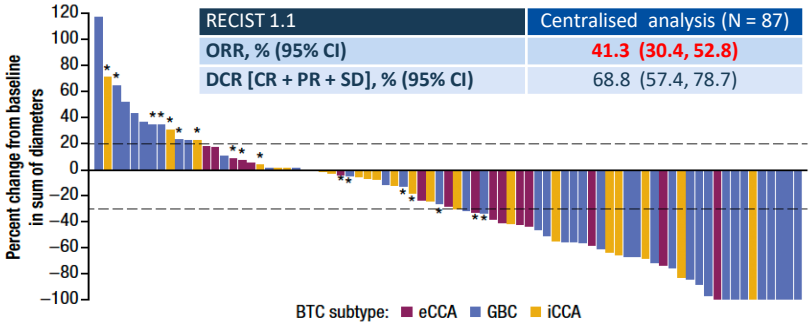
Ab: antibody; **Chemo:** chemotherapy; **L:** line; **M:** months; **NA:** not available; **NR:** not reached; **Pts:** patients.

HERIZON-BTC-01: Zanidatamab (Bispecific anti-HER2 Ab)

Single-arm phase 2b trial

FDA and EMA approved

A tumor size decrease was observed in 68.4 % of patients



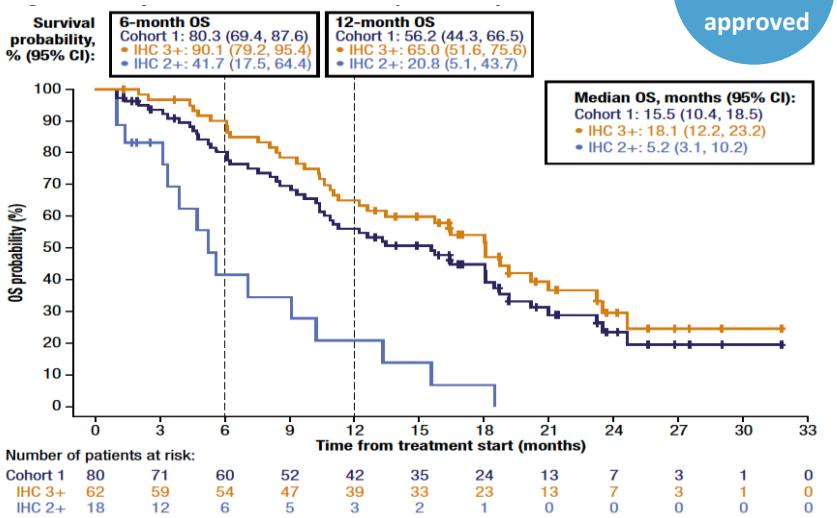
RECIST 1.1	Centralised analysis (N = 87)
ORR, % (95% CI)	41.3 (30.4, 52.8)
DCR [CR + PR + SD], % (95% CI)	68.8 (57.4, 78.7)

*Indicates patients with tumors of IHC 2+ status; all other patients had tumors with IHC status of 3+.

[a]Only patients with measurable disease at baseline and at least 1 post-baseline assessment were included (n=79).

Dotted lines indicated 20% increase and 30% decrease in sum of diameters of target tumors.

BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry.



→ **mPFS: 5,5 months and mOS: 15.5 months**

Acceptable toxicity: diarrhea, infusion-related reaction, nausea, decrease of the ventricular ejection fraction

Phase 3 trial HERIZON-BTC (CISGEM-durvalumab +/- Zanidatamab) in L1 in HER2 amp BTC

DCR: disease controle rate; **ORR:** objective response rate.

Harding JJ et al. Lancet Oncol 2023; Pant S et al. ASCO 2024. Poster 4091.

Advanced BTC: Take home messages

- Gemcitabine + Cisplatin + Durvalumab or pembrolizumab is the first-line standard.
- Consider intensification with SIRT in liver-only advanced iCCA.
- Early molecular profiling is essential to organize L2.
- In the absence of druggable molecular alteration, FOLFOX is the standard in L2.
- In case of druggable molecular alteration: prioritize access to matched targeted therapy
  - ✓ Ivosidenib in IDH1-mutated BTC.
  - ✓ Pemigatinib or futibatinib in FGFR2 rearranged BTC.
  - ✓ Anti HER2-therapy (trastuzumab with pertuzumab or tucatinib or deruxtecan; zanidatamab).
- Early palliative care and clinical trial enrollment are essential in this severe disease.