Oncology Review 2024: Biliary Tract Cancers

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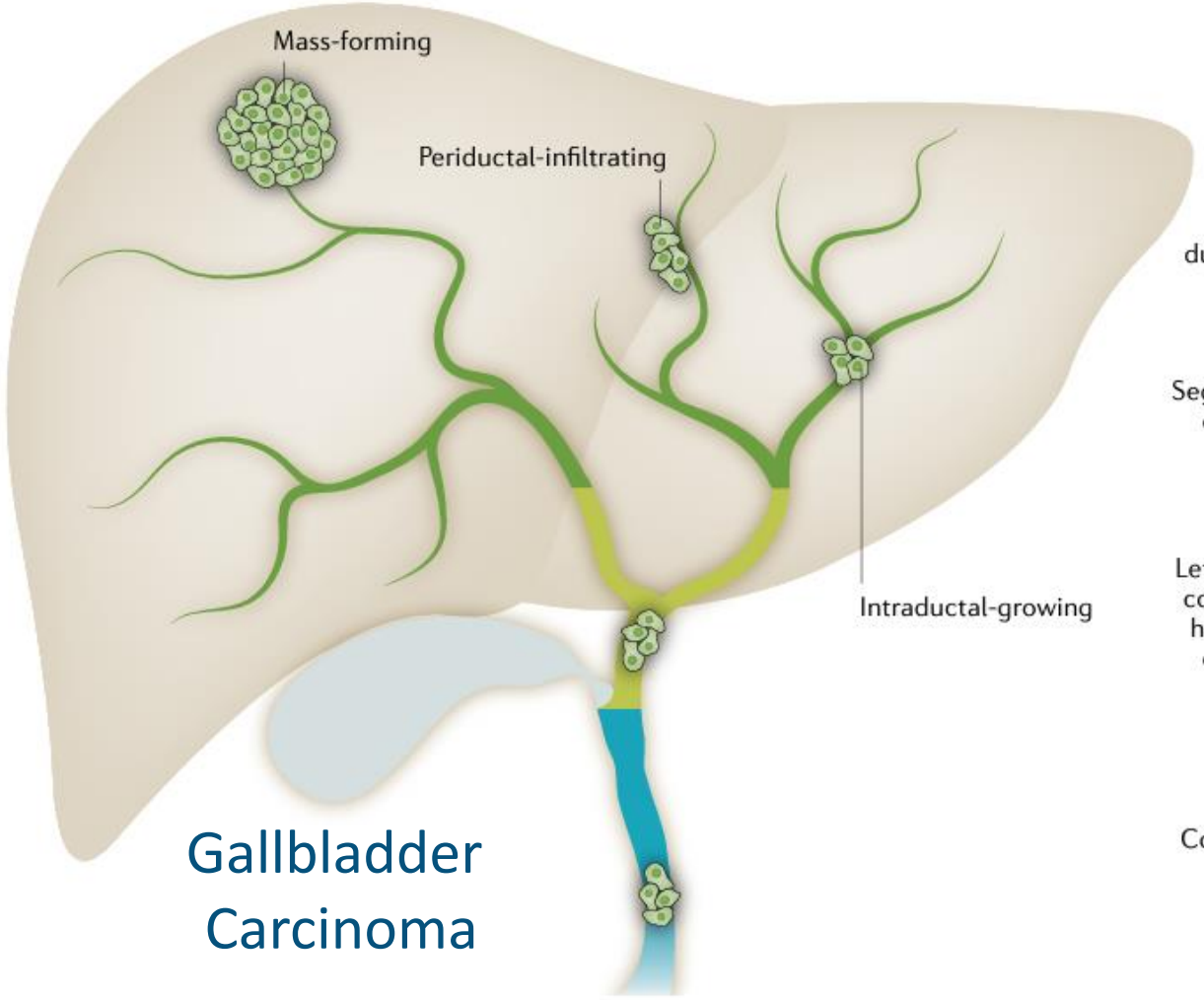
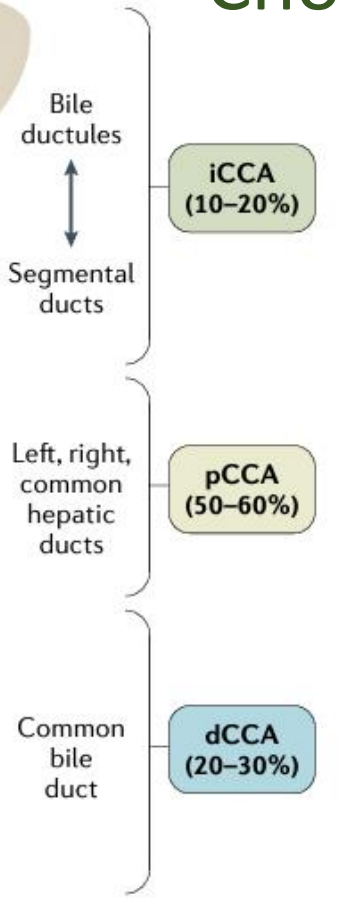
Distinct Anatomic Subtypes



Gallbladder Carcinoma

Cholangiocarcinoma



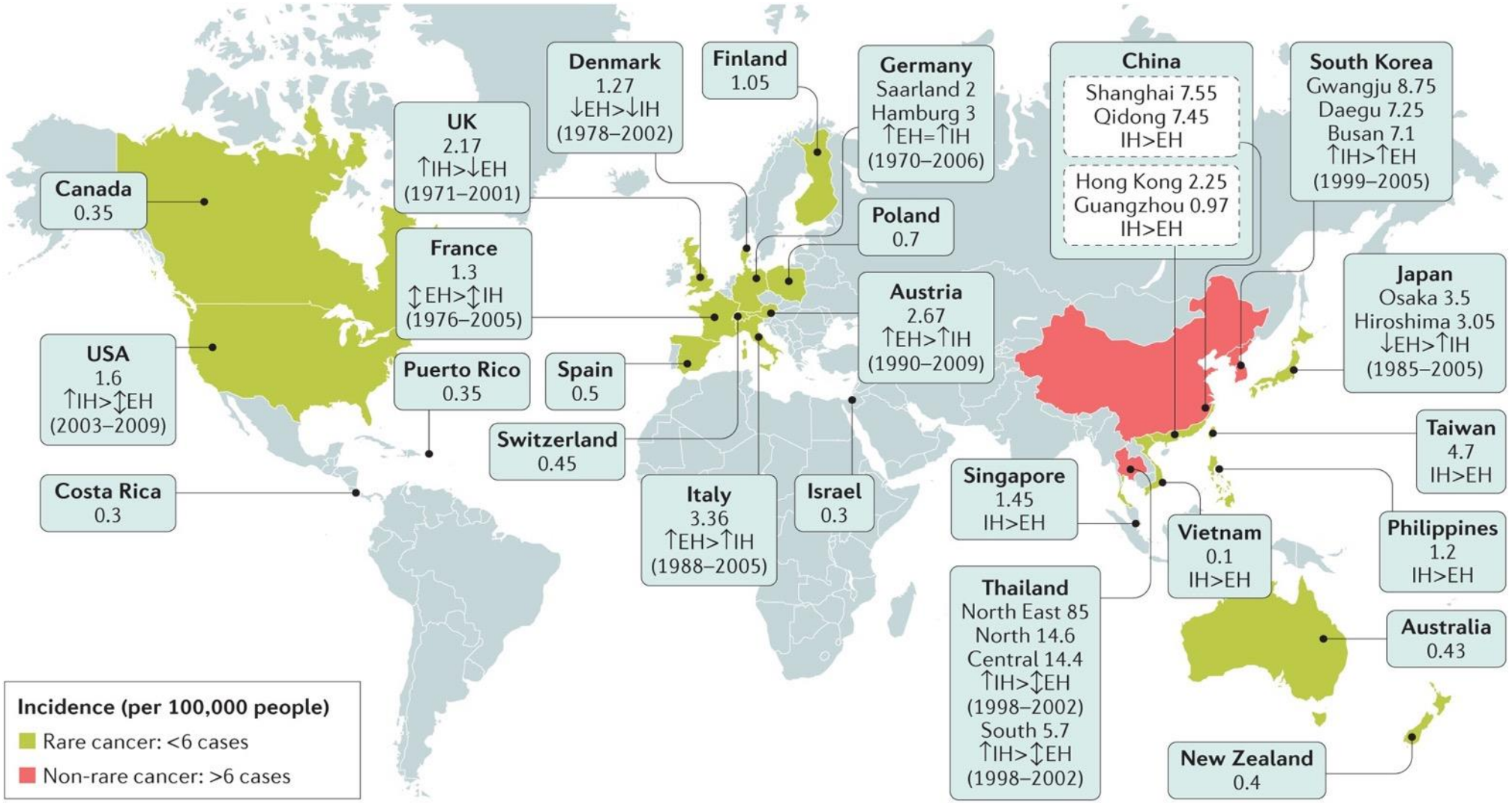
Intrahepatic CCA

Perihilar CCA (Klatskin Tumor)

Distal CCA

Banales et al Nature Reviews Gastroenterology, 2020

Cholangiocarcinoma: Low Incidence in West, Higher in East



Nature Reviews | Gastroenterology & Hepatology

*Banales, J.M., Marin, J.J.G., Lamarca, A. et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol **17**, 557–588 (2020)*

Cholangiocarcinoma Risk Factors: East vs West

Great for clinical vignettes

West	East
Primary Sclerosing Cholangitis (pCCA) (15% lifetime risk)	**Liver Fluke infestation** **Opisthorcihis viverini* **Clonorchis sinensis* *Schistosoma japonicum*
Congenital Fibropolycystic Disease (Caroli Syndrome, choledochal cyst) (pCCA) (15% lifetime risk)	**Hepatolithiasis** (SEA, Taiwan)
Cirrhosis / Hepatitis, Obesity, DM, Etoh	**Recurrent Cholangitis**

**Group 1: definite human carcinogen*

GBC Risk Factors: Chronic Inflammation

Chronic Cholecystitis **Chronic Salmonella Typhi**

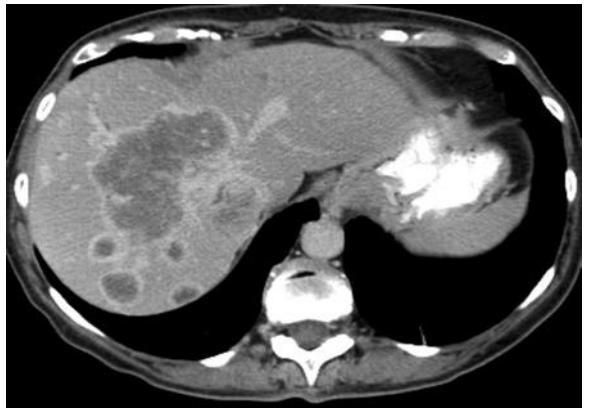
CCA Clinical Presentation: Depends on Location

- **Intrahepatic CCA:**
  - **Mass-forming tumor**
  - **Incidental finding**, tumor of uncertain primary
  - Abd pain, anorexia, weight loss
  - Alk Phos high, Bili often normal

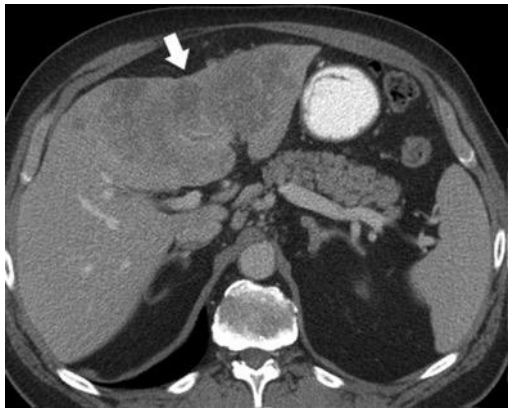
- **Perihilar / Extrahepatic CCA**:
  - **Biliary obstruction**: jaundice, cholangitis
  - Perihilar mass or stricture (pCCA)
  - Sometimes initially thought to be pancreas cancer (distal CCA)
  - **PSC patients: rising CA 19-9**

One of the GI cancers that present as hypercalcemia of malignancy (hypercalcemia, hypophosphatemia, low parathyroid hormone levels, and low vitamin D levels)

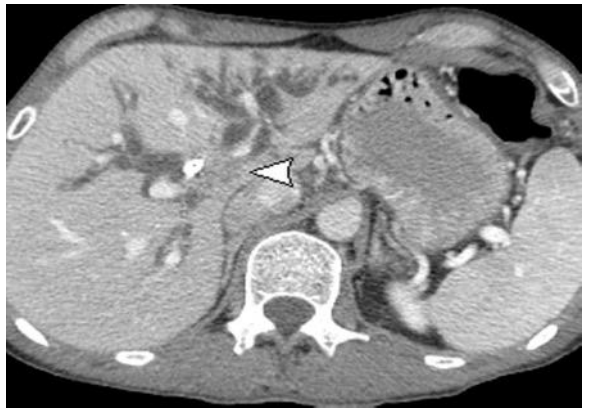
Mass forming: fibrotic enhancement



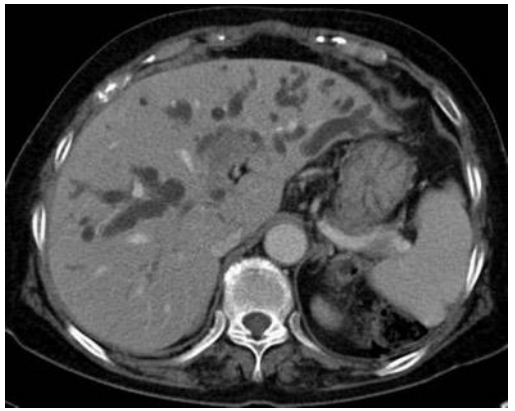
Capsular retraction



Klatskin tumor, bilateral bil dil



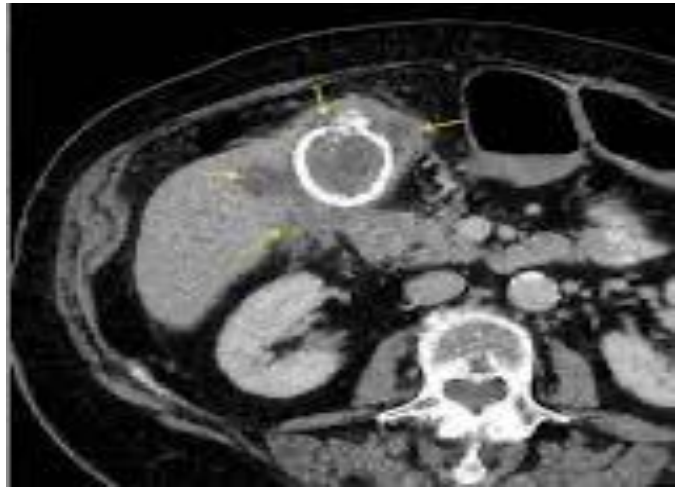
Intraductal growth

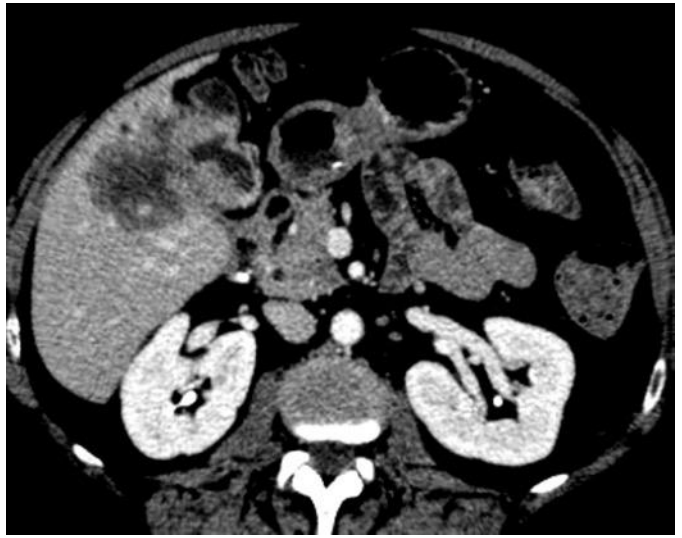


https://liveratlas.org/

Clinical Presentation: Depends on Location

- **Gall Bladder** Carcinoma:
  - Most common presentation is **incidental** cancer found on routine cholecystectomy (1-2% of cholecystectomies)
  - Otherwise, typically advanced on presentation
  - **Porcelain gall bladder:** risk of GB CA





http://www.svuhradiology.ie/case-study/porcelain-gallbladder-with-carcinoma/ https://liveratlas.org/

BTC Staging (AJCC 8th): Depends on type

	Intrahepatic	Perihilar	Extrahepatic	Gallbladder
T1	1 tumor w/o vascular invasion and is , T1a = ≤5 cm, T1b = ≥5 cm	Confined to bile duct	Bile duct wall invasion <5 mm	T1a: Invade lamina propria **T1b: Invade muscularis propria**
T2	One tumor w/ **vascular invasion** or **Multiple tumors** +/- vascular invasion	T2a/b: Invades adipose or liver tissue	Bile duct wall invasion 5-12 mm	T2a/b: Invades perimuscular connective tissue
T3	Any tumor perforating visceral peritoneum	Invades unilateral branches portal v or hepatic aa	Bile duct wall invasion >12 mm	Involvement of serosa or invasion of liver or adjacent organs
T4	Any tumor with direct invasion of local extrahepatic structures	Invades main PV or bilateral branches or CHA	Involves celiac axis, SMA, and/or CHA	Invades portal v, hepatic aa, or two or more extrahepatic organs
N1	**Any + regional nodes**	1-3	1-3	1-3
N2	N/A	≥4	≥4	≥4

Surgical Management

- **Intrahepatic**: Hepatic resection +/- portal LN dissection
- **Perihilar CCA**: Bile duct resection or **liver transplant**
- **Distal CCA**: Bile duct resection + cholecystectomy + **Whipple**
- **Gallbladder:** Cholecystectomy + **hepatic segmental resection (IVB/V), lymphadenectomy,** possible bile duct excision.

Resectable GBC: T1b and above is high risk

- **T1a:** no invasion of muscularis propria:
  - 75-100% long term survival
  - **Only simple cholecystectomy** needed, no adjuvant therapy
- **T1b:** muscle invasive disease
  - High risk of recurrence
  - **Cholecystectomy + hepatic segmental resection (segments IVB/V), lymphadenectomy, possible bile duct excision + adjuvant chemo**

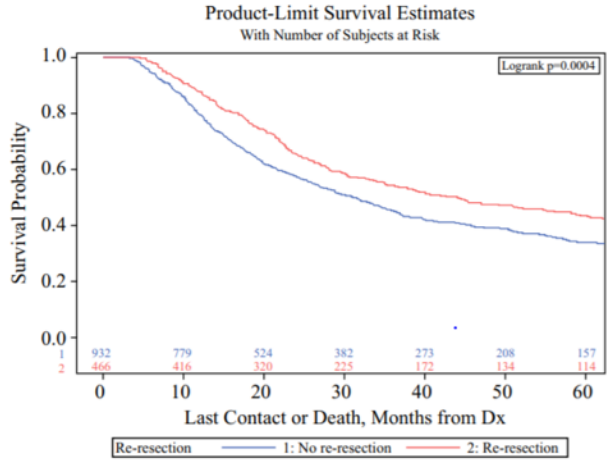
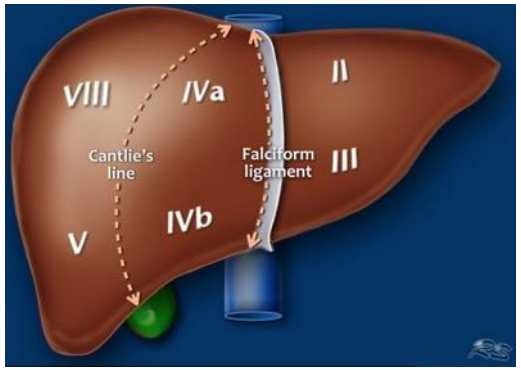


FIG. 5 Kaplan-Meier survival curves for gallbladder adenocarcinoma patients who did and did not undergo re-resection after matching

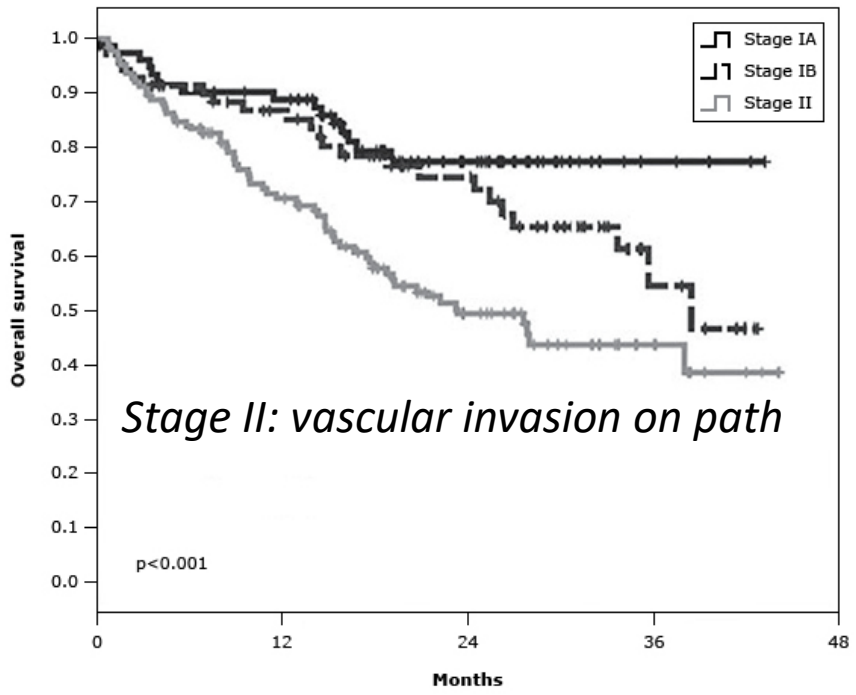


Papageorge MV, et al. Ann Surg Oncol (2021) 28:2949–2957

High Risk Features for Recurrence

Main factors are stage**, nodal** involvement and **margin**

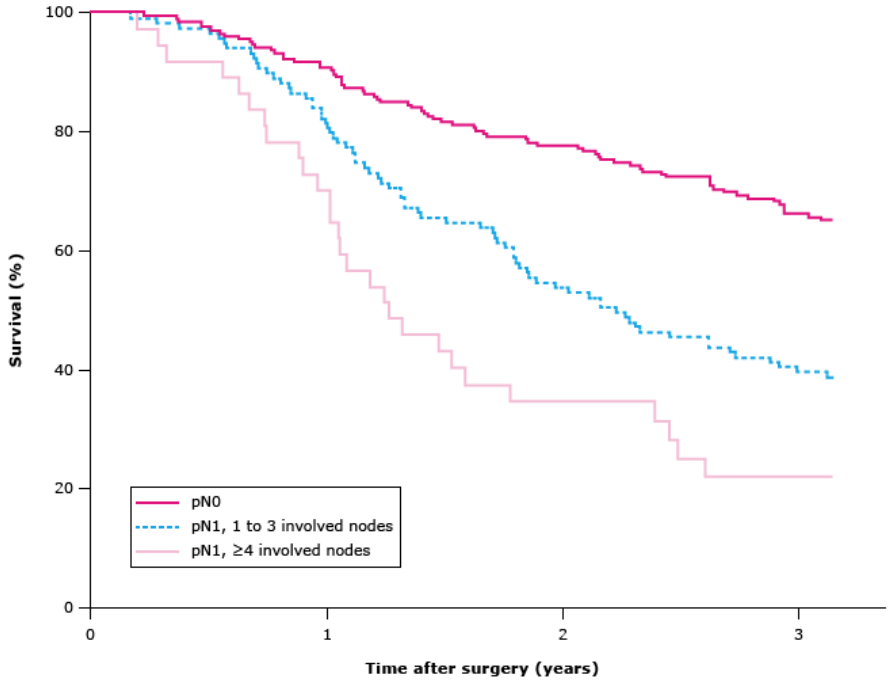
Stratification for survival in a series of 861 patients with intrahepatic cholangiocarcinoma based on revised AJCC/UICC 8th edition definitions for stage IA, IB, and II disease



Stage II: vascular invasion on path

AJCC 8th Ed

Survival after potentially curative resection in a multi-institutional series of 370 patients undergoing pancreaticoduodenectomy for a distal bile duct cancer



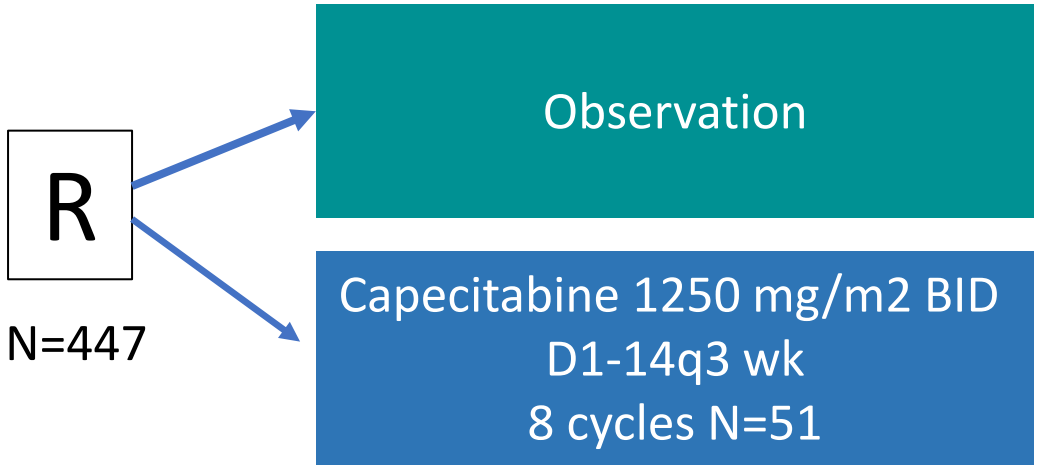
Kiriyama M, Ebata T, Aoba T, et al. Br J Surg 2015; 102:399.

Adjuvant Therapy: BILCAP

something is better than nothing

- Randomized open-label multi-center UK ph III trial: Cape vs Obs
- Took 10 years to complete

CCA or muscle-invasive GBC cancer
macroscopic complete resection
ECOG 0-2
Within 16 weeks of surgery



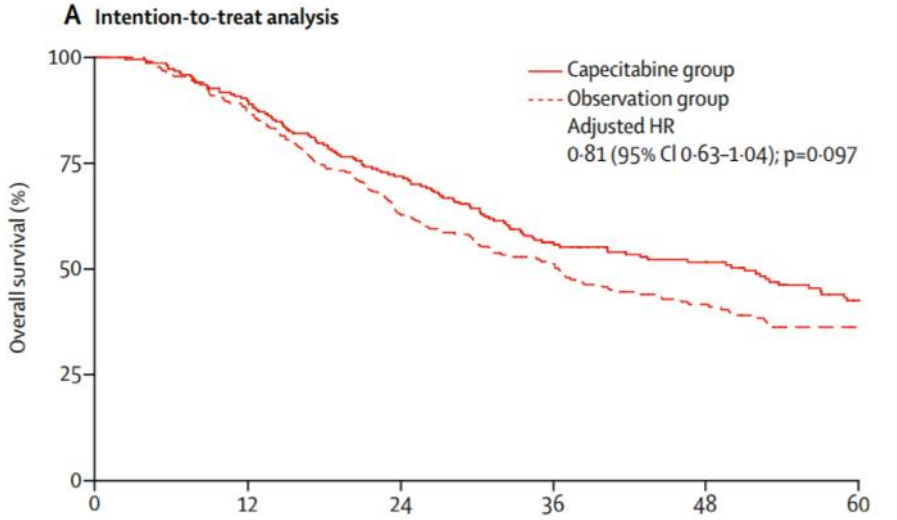
Primary: Overall survival (OS) by **intention-to-treat**

Secondary: Outcome by **per-protocol analysis**
Relapse free survival (RFS)
Toxicity, Quality of life, Health economics

Primrose JN et al. Lancet Oncol 2019; 20: 663-73

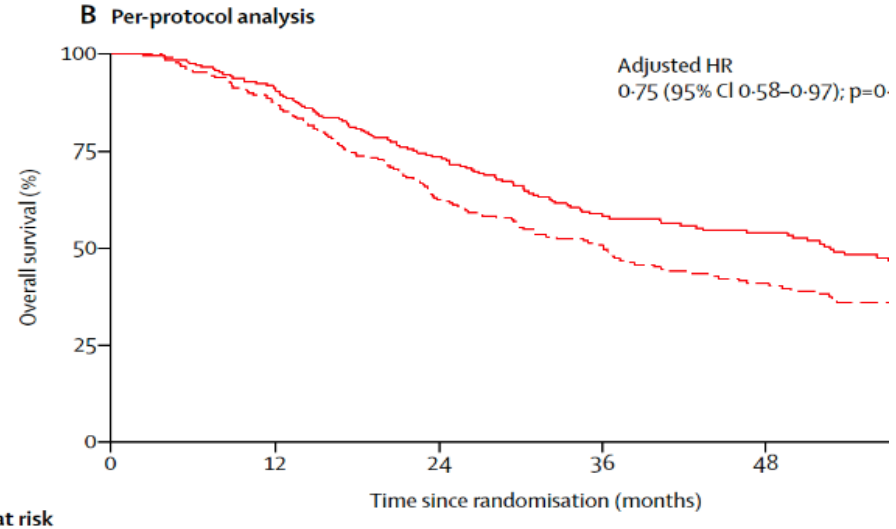
BILCAP: Highest level of evidence in adjuvant tx

Intention-to-treat analysis



Number at risk (number censored)						
Capecitabine group	223 (0)	195 (6)	155 (7)	105 (25)	83 (39)	56 (53)
Observation group	224 (0)	193 (3)	137 (5)	95 (23)	67 (34)	46 (47)

Per-protocol analysis

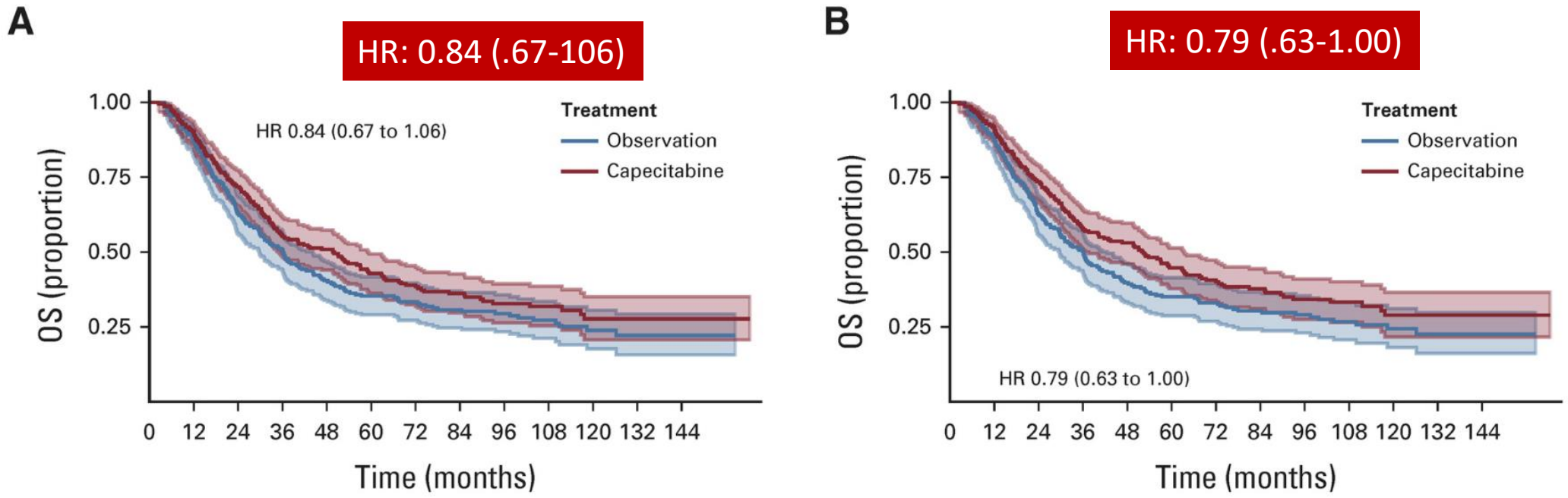


Number at risk (number censored)					
Capecitabine group	210 (0)	190 (2)	152 (3)	105 (21)	83 (35)
Observation group	220 (0)	190 (3)	134 (5)	92 (23)	64 (34)

- No OS benefit in ITT analysis, but **OS benefit seen in Per-protocol Analysis**
- Difference of 17 patients ineligible/withdrawal of consent prior to starting treatment
- **Median OS: 53 mo vs 36 months**
- **Median RFS: 25.9 mo vs 17.5 mo (similar for both ITT and per-protocol analysis)**

Primrose JN et al. Lancet Oncol **2019**; 20: 663-73

BILCAP: Highest level of evidence in adjuvant tx



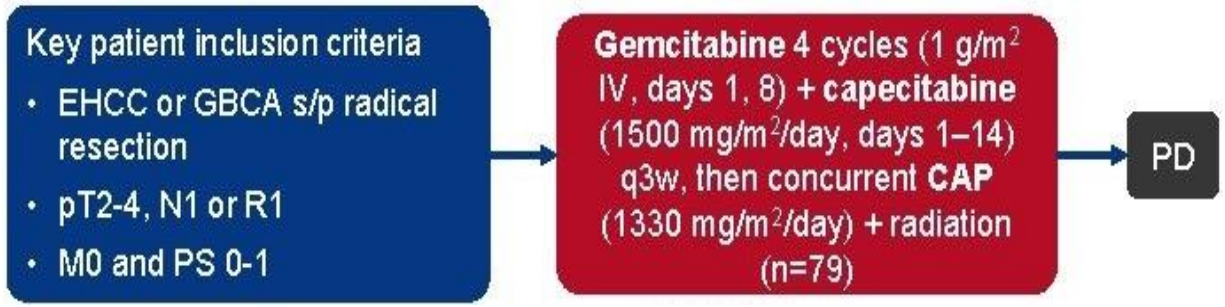
- **IIT:** OS 49.6 months (95% CI, 35.1 to 59.1) for capecitabine vs 36.1 months (95% CI, 29.7 to 44.2) in obs
- PP: OS 52.3 months (36.5 to 63.3) for capecitabine vs 36.1 (29.6 to 42.5) in obs)
- Adjusted RFS HR was 0.74 (0.57 to 0.96) in the first 24 months, with insufficient evidence of a difference from 24 months onward: HR 1.47 (0.86 to 2.52)

No OS benefit in ITT analysis, but **OS benefit seen in Per-protocol Analysis…but barely made the cut and the benefit mostly in the first 2 years**

Prospective Data: SWOG 0809 for eCCA /GBC

Phase II trial, single arm trial attempted to establish a standard practice (2014) for adjuvant therapy of **eCCA & GBC**, N=79 pT2-4 AND either N+ or R1 resection

4 cycles Gem/Cape → cape chemoradiation 54-59 Gy



	All pts (%, 95% CI)	Extrahepatic	Gallbladder
2-yr OS	65 (53-74)	**68 (54-79)**	**56 (35-73)**
2-yr DFS	54 (40-66)	**54 (39-66)**	**48 (28-66)**
2-yr LR	11 (4-18)	13 (4-22)	8 (0-19)

Primary endpoint: OS
Secondary Endpoints: DFS, Safety

86% completed therapy
mOS 34 months
Applicability limited due to single arm

Ben-Josef E et al. J Clin Oncol, 2014;33:261-2622

STAMP: More Adjuvant Chemo not better for eCCA

Multicenter, open-label, randomized Ph II, 3 Korean centers

Extrahepatic CCA (pCCA,dCCA)
Adenocarcinoma histology
Macroscopic Resection (R0, R1)
≥1 regional LN met
ECOG 0-1

R

N=101

Gemcitabine 1000mg/m2
Cisplatin 25mg/m2, D1,8
8 cycles N=50

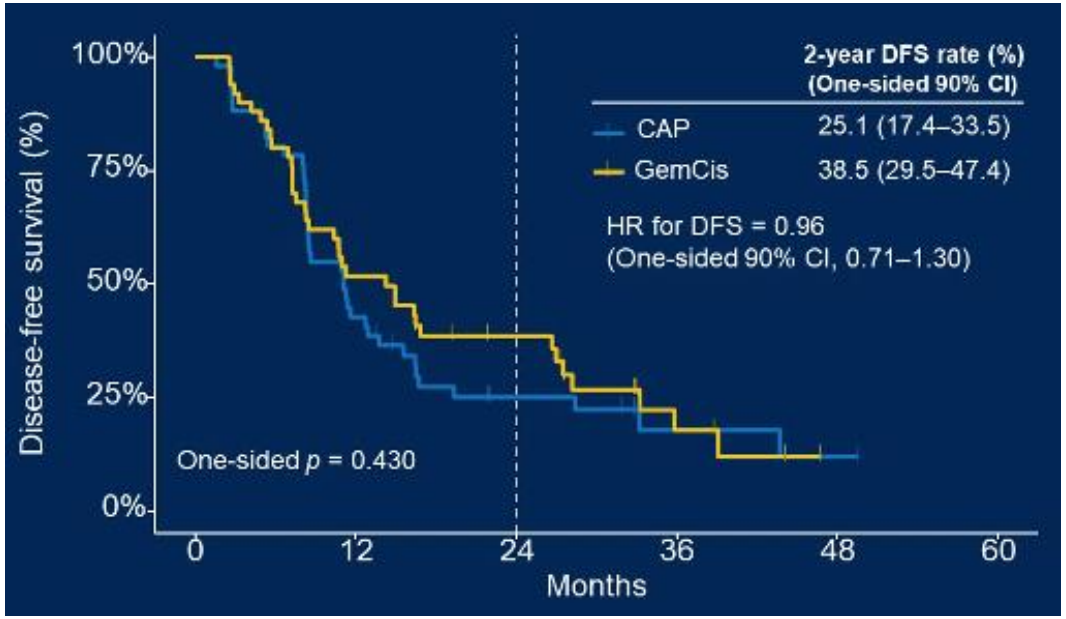
Capecitabine 1250 mg/m2 BID
D1-14q3 wk
8 cycles N=51

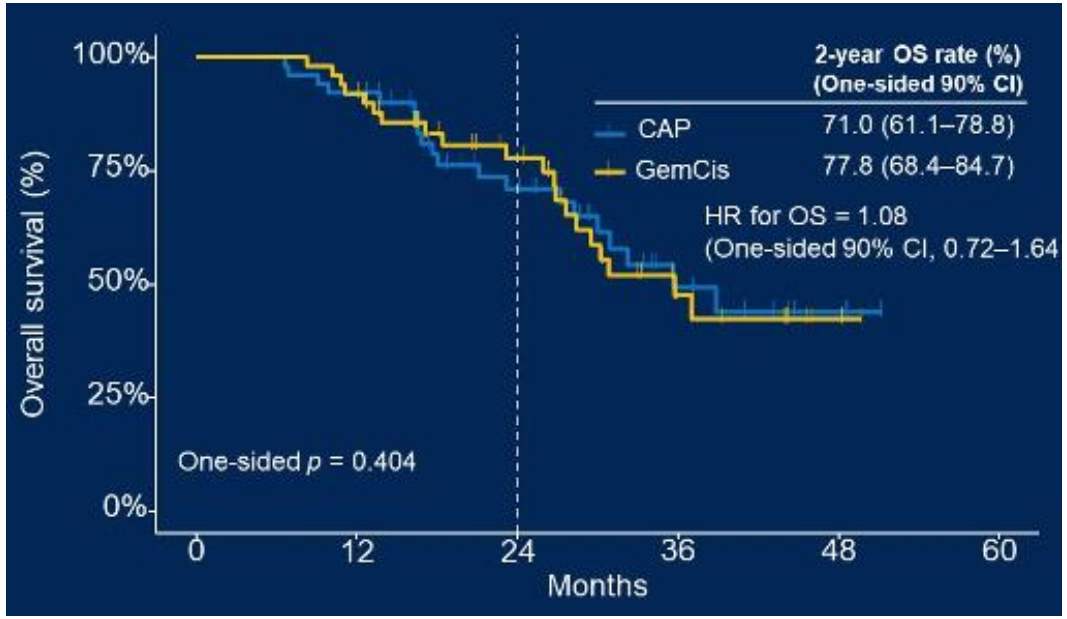
Primary Endpoint: DFS
Secondar Endpoint OS, Safety, EORTC QLQ

Yoo et al Journal of Clinical Oncology 2022 40:16_suppl, 4019-4019

Adjuvant Therapy: More not Better for eCCA

STAMP: Multicenter, open-label, randomized Ph II, 3 Korean centers





Negative study: no statistical difference in PFS or OS
No trends in subgroup analysis
More grade 3 AE with GemCis (42%) vs Cape (16%), mostly cytopenias

Unknown for iCCA

Yoo et al Journal of Clinical Oncology 2022 40:16_suppl, 4019-4019

Systemic Therapy for BTC: Rapidly Evolving

First-line

Gemcitabine Cisplatin
ABC-02 (included ampullary)
ORR: 26% (vs 21%), mOS: 11mo
2010

Gemcitabine Cisplatin Durvalumab
TOPAZ-1
ORR: 26.7% (vs 18.7%) ,mOS 12.8mo
2022

Gemcitabine Cisplatin Pembrolizumab
Keynote 966
ORR: 29% ,mOS 12.7mo
2023

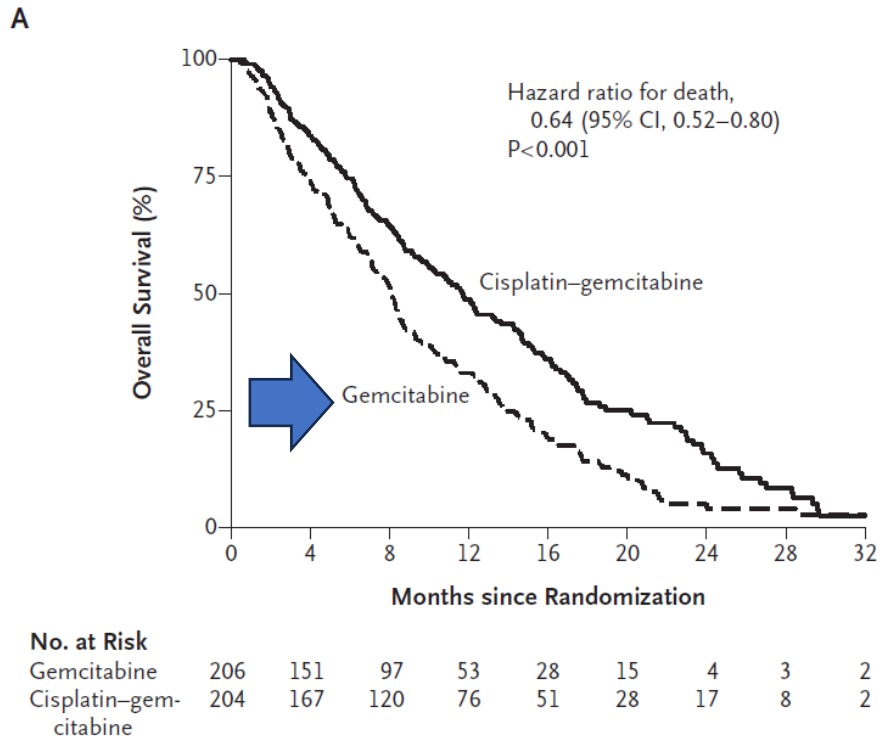
Gemcitabine Cisplatin
Nab-Paclitaxel ? SWOG 1815 was negative

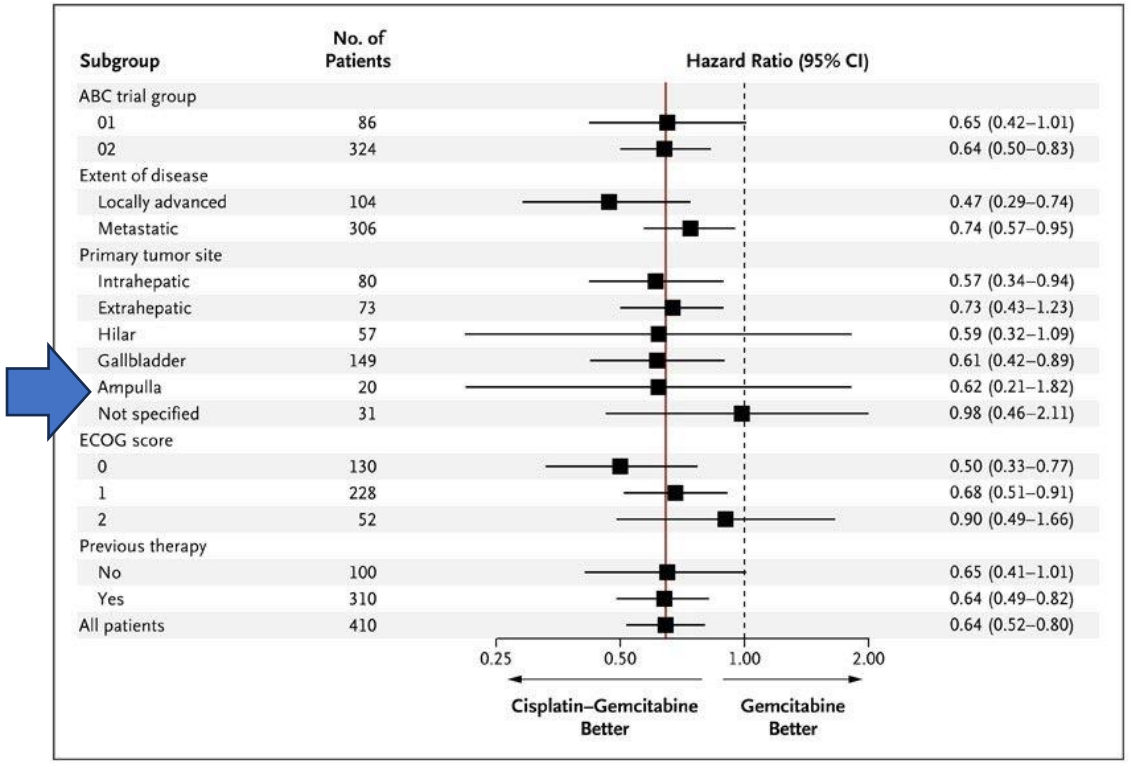
Second-line

No Targets	**FOLFOX** ABC-06 ORR: 5%, mOS 6.2mo	2018	**5-FU Nal-IRI** Nifty ORR: 14.8%, mOS 8.6mo	2021
FGFR2 fusion	***Pemigatinib** FIGHT-302 ORR: 35.5%, mOS 21.2mo	2020	***Futibatinib** FOENIX-CCA2 ORR: 42%, mOS 21.7mo	2022
IDH-1 mutation	**Ivosidenib** ClarIDHy ORR: 2%, mOS 10.3	2022		
BRAF V600E	**Dabrafenib/Trametinib** ROAR tissue agnostic, ORR: 36%, DCR 76%	2022		
ERBB2 amplification HER 2 “positive’	**⁺Trastuzumab/Pertuzumab** MyPathway, ORR: 40%		**T-Dxd (Enhertu)** DESTINY Pan-Tumor02 ORR:22%, mOS 7mo	
MSI-H	**Pembrolizumab** KEYNOTE cohorts ORR:39.6%	2017	**Dostarlimab-glxy** GARNET ORR: 41.6%	2021
NTRK fusion	**Larotrectinib** LoxoTRK, SCOUT, NAVIGATE ORR: ~60-70%	2018	**Entrectinib** STARTRK1,2 ORR: 57%	2019
RET Fusion	**⁺Pralsetinib** BLU-667, tumor agnostic, 2B rec	2022		

Systemic Therapy for BTC: The Early Days

ABC-02 trial: Randomized Ph III trial Gemcitabine vs Gemcitabine + Cisplatin in **first-line BTC**



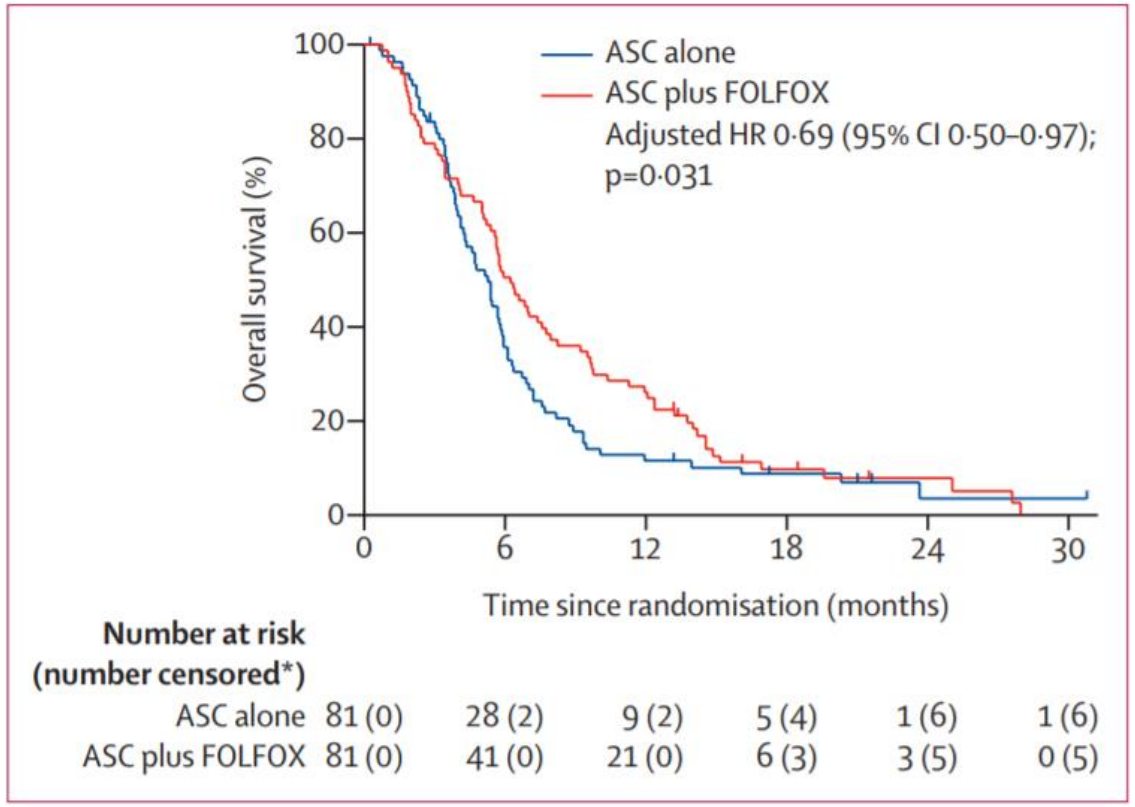


Improved DCR: 81.4% vs. 71.8% (p=0.049), ORR: 26% vs 21 %

mOS 11.7 vs. 8.1 months (p<0.001), Treatment compliance better with Gem Cis

Valle et al N Engl J Med 2010

ABC-06: FOLFOX is **2L** option for Metastatic CCA



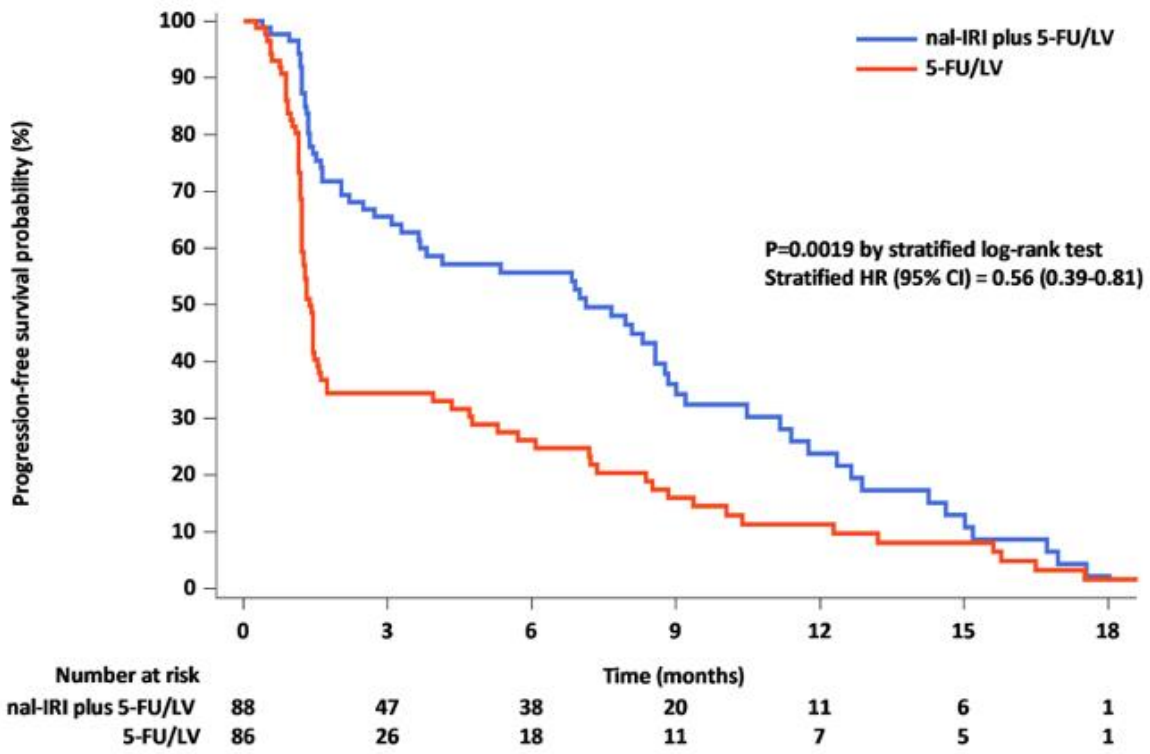
*ASC: Active Supportive Care

	FOLFOX	ASC
Median OS	**6.2 mo**	5.3 mo
1-year OS rate	25.9%	11.4%
Median PFS	4.0 mo	N/A
6-month PFS rate	32.1%	N/A
ORR	**5%**	N/A

*Benefit seen regardless of platinum sensitivity

Lamarca A, et al. Lancet Oncol 2021; 22:690-701.

NIFTY: 5-FU + NAL-IRI is a 2nd Line Option



	Nal-IRI + 5-FU/LV	5-FU-/LV
Investigator median PFS	3.9 mo	1.6 mo
Investigator 6-month PFS rate	30.6%	11.6%
Median OS	8.6 mo	5.5 mo
1-year OS rate	35.4%	22.4%
BICR ORR	**14.8%**	**5.8%**
Investigator ORR	19.3%	2.3%

HR 0.56 95% CI 0.39-0.81, p=0.0019

Multicenter, Open-label, randomized Ph IIB study (**Korean Centers**)

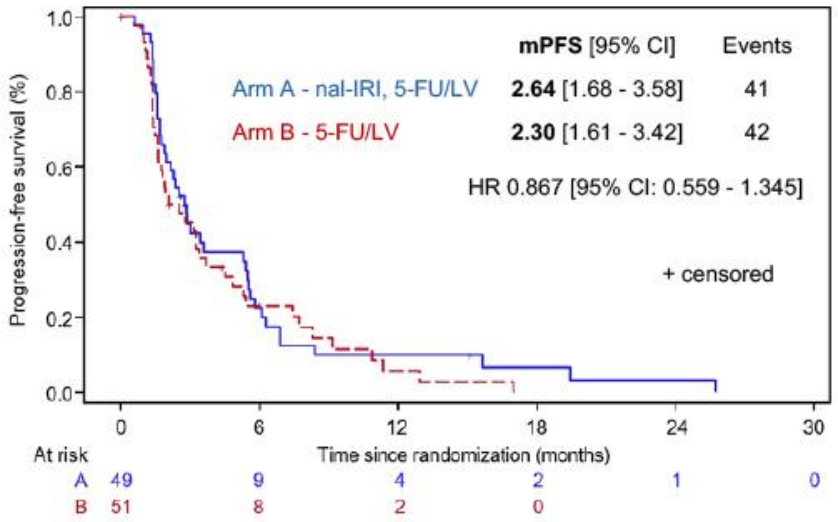
Yoo C, et al. Abstract 4006. 2021 ASCO Annual Meeting

NALIRICC: Different results in Germany

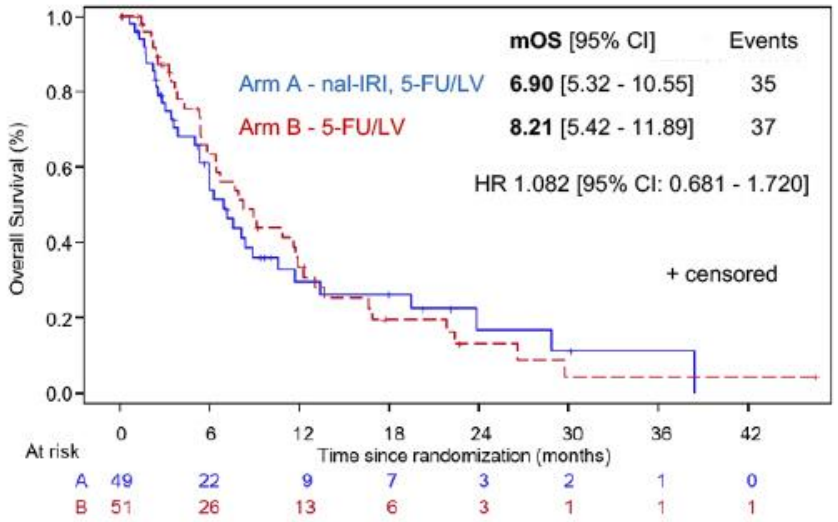
NALIRICC I Efficacy Results

Response was evaluated per RECIST v1.1, every 6 weeks

Progression-free survival



Overall Survival



		CR Complete remission	PR Partial remission	SD Stable disease	PD Progressive disease	Missing value	ORR	DCR
Arm A - Nal-IRI, 5-FU/LV	N = 49	1 (2.0%)	6 (12.2%)	18 (36.7%)	12 (24.5%)	12 (24.5%)	7 (14.3%)	25 (51.0%)
Arm B - 5-FU/LV	N = 51	1 (2.0%)	1 (2.0%)	21 (41.2%)	20 (39.2%)	8 (15.7%)	2 (3.9%)	23 (45.1%)

https://dailyreporter.esmo.org/esmo-congress-2022/upper-gi-tumours/second-line-chemotherapy-for-advanced-biliary-tract-provides-modest-efficacy-but-quality-of-life-benefit

X-trial Comparison of 2L Treatments for Advanced BTC

	Nal-IRI + 5-FU/LV[1]	5-FU-/LV[1]	FOLFOX[2]	Best Supportive Care[2]
Median OS (mo)	8.6	5.5	6.2	5.3
1 year OS rate (%)	35.4	22.4	25.9	11.4
Median PFS (mo)	7.1	1.4	4.0	N/A
6-month PFS rate (%)	55.7	26.2	32.1	N/A
Investigator median PFS (mo)	3.9	1.6	N/A	N/A
Investigator 6-month PFS rate (%)	30.6	11.6	N/A	N/A
ORR (%)	14.8	5.8	5.0	N/A

- **Second line options not that good, low ORRs**
- **Combination therapy is more active** than monotherapy chemotherapy regimens
- Nal-IRI + 5-FU/LV appears more active than FOLFOX, but Korean population limits applicability in west

[1]Lamarca A, et al. Lancet Oncol 2021; 22:690-701 [2]Yoo C, et al. Abstract 4006. 2021 ASCO Annual Meeting [3]Mizrahi J et al. Abstract 451. 2019 GI ASCO Meeting

TOPAZ-1: ICI now in front-line treatment of BTC

Randomized, double blind, placebo-controlled, global, multi-center Ph III study

Locally Advanced or Metastatic BTC (CCA, GBC)
Treatment Naïve or >6mo from curative intent surgery
ECOG 0-1

R

N=685

Gemcitabine 1000mg/m2
Cisplatin 25mg/m2, D1,8
+ Durvalumab 1500mg D1
8 cycles

→ Durvalumab 1500mg D1

Gemcitabine 1000mg/m2
Cisplatin 25mg/m2, D1,8
+ placebo 8 cycles

→ placebo

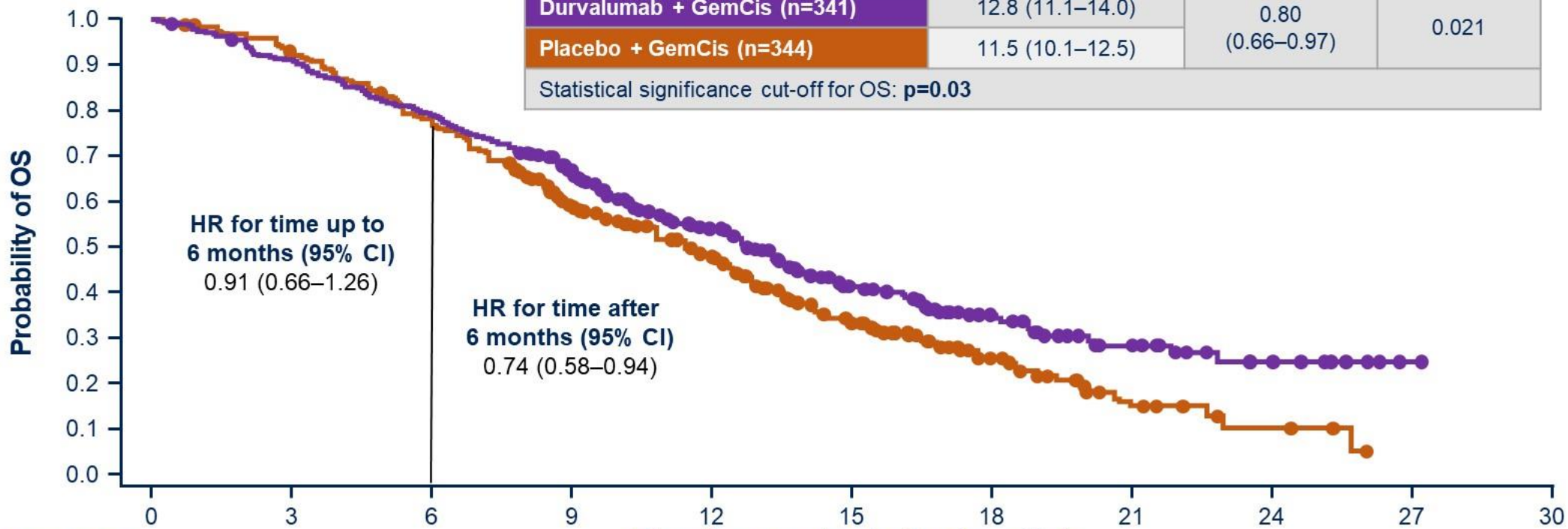
Stratification:
- Anatomy: iCCA vs eCCA vs GBC
- Locally advanced vs metastatic

Primary Endpoint: OS
Secondar Endpoints: PFS, ORR, DoR, Safety, ORR by PD-L1

Do-Youn et al GI ASCO 2022

Primary endpoint: OS

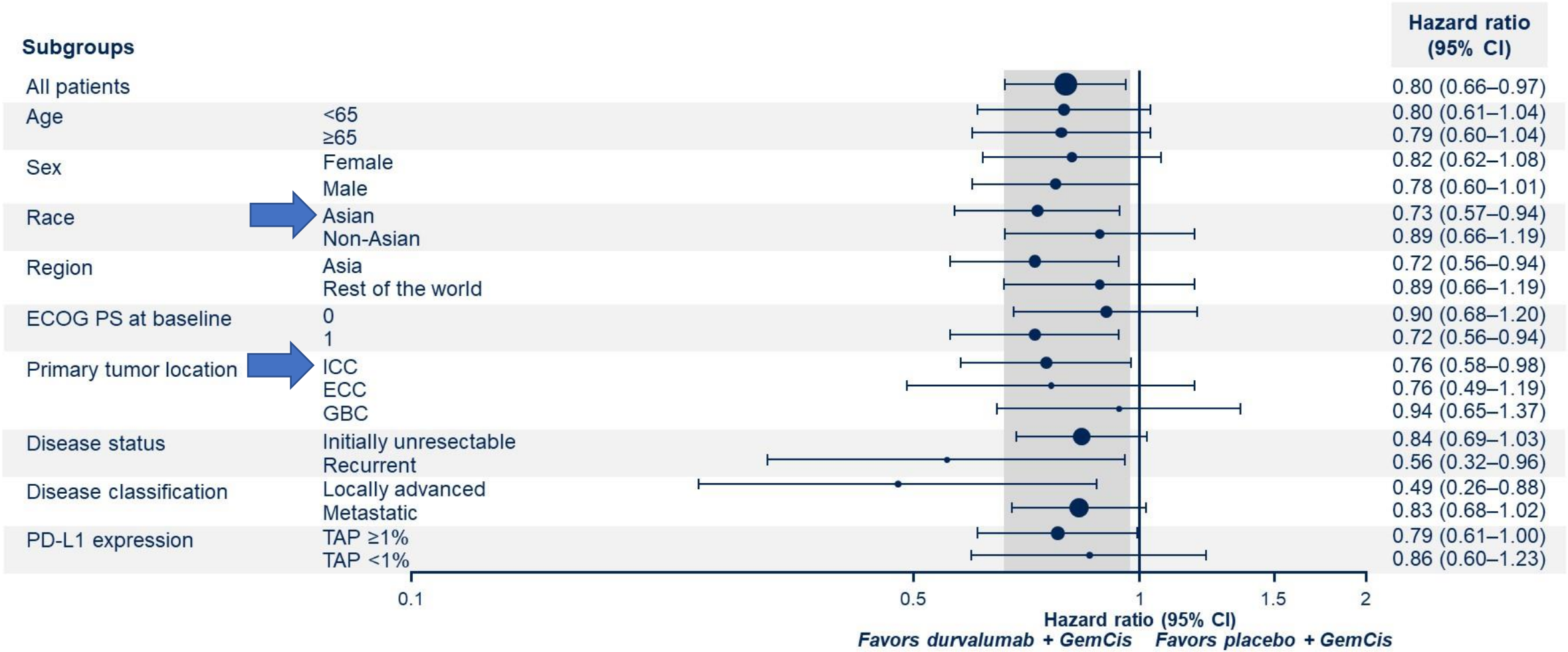
	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

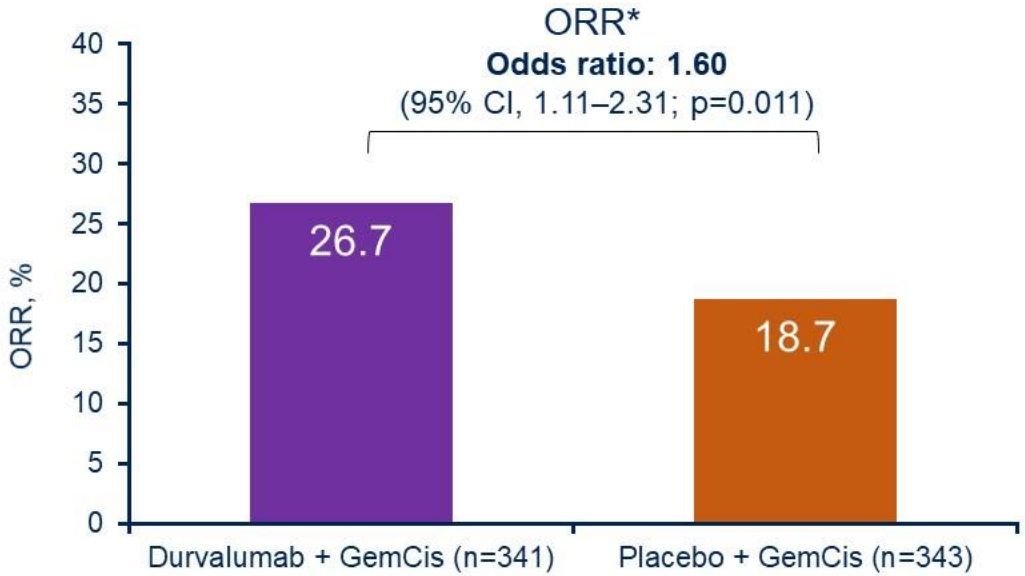
Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

Subgroup analysis of OS

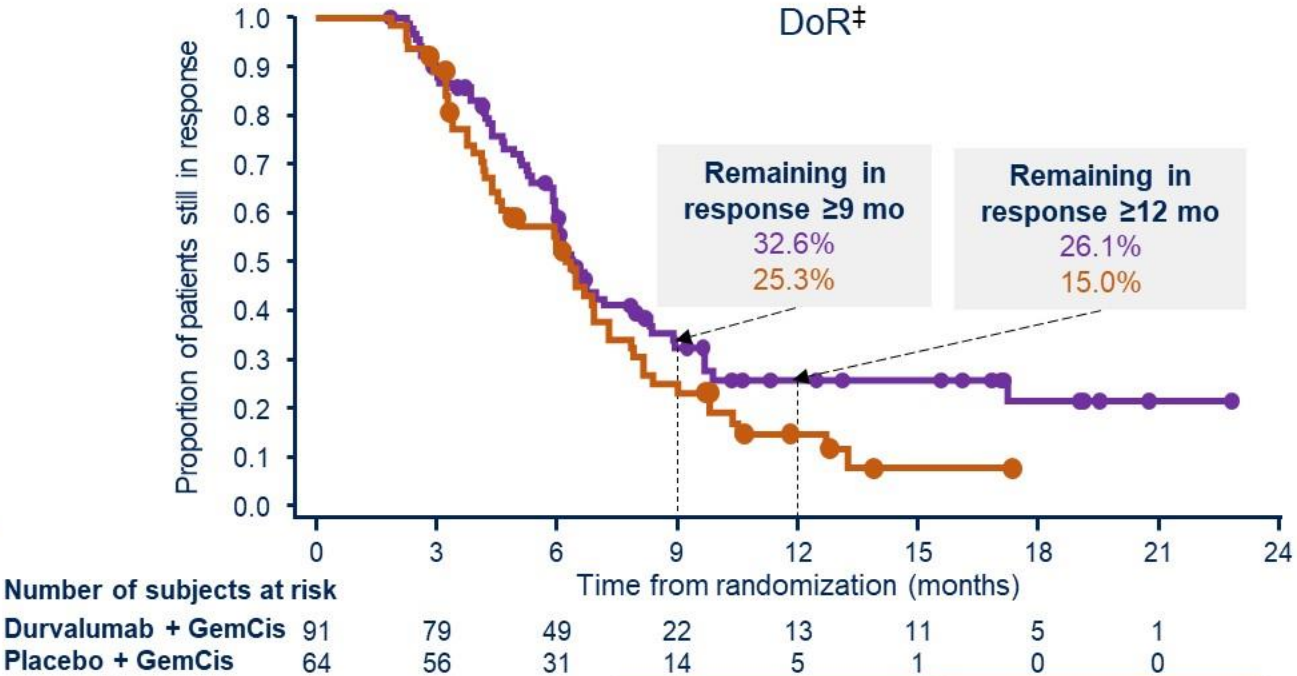


CI, confidence interval; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; OS, overall survival; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Secondary endpoint: Tumor response



	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)



	Durvalumab + GemCis (n=91)	Placebo + GemCis (n=64)
Median DoR (quartile 1–3), months	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Median time to response (quartile 1–3), months	1.6 (1.3–3.0)	2.7 (1.4–4.1)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, month; ORR, objective response rate; PR, partial response.

PRESENTED BY: Do-Youn Oh, MD, PhD

Keynote 966: Another Confirmation for ICI

Randomized, double blind, placebo-controlled, global, multi-center Ph III study

Locally Advanced or Metastatic BTC (CCA, GBC)
Treatment Naïve or >6mo from curative intent surgery
ECOG 0-1

R

N=1069

Gemcitabine 1000mg/m2
Cisplatin 25mg/m2, D1,8
+ Pembrolizumab 200mg D1
8 cycles

→ Gemcitabine + Pembro

Gemcitabine 1000mg/m2
Cisplatin 25mg/m2, D1,8
+ placebo 8 cycles

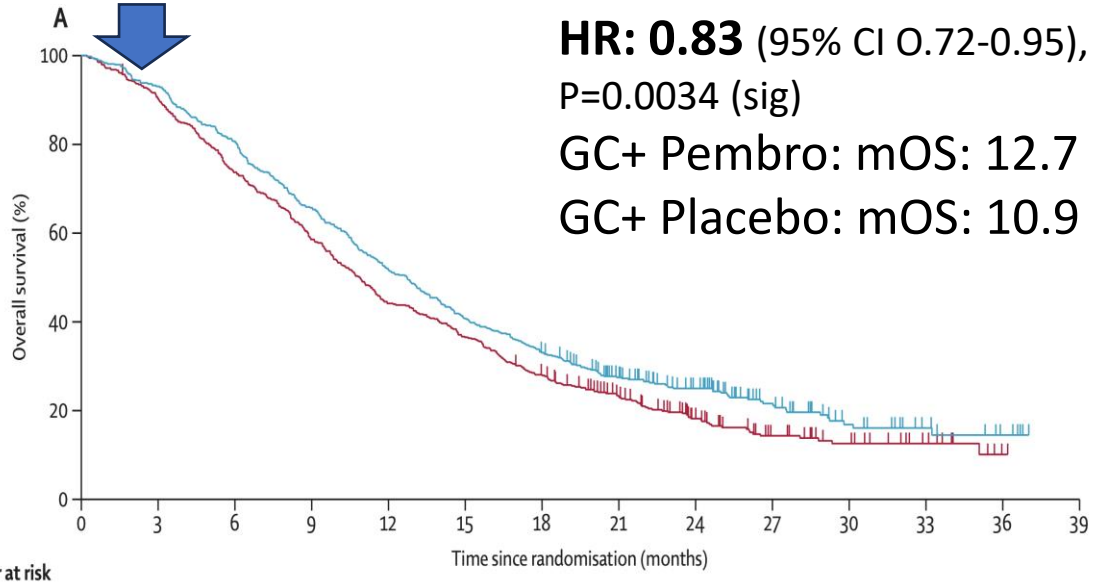
→ Gemcitabine + placebo

Stratification:
- Anatomy: iCCA vs eCCA vs GBC
- Locally advanced vs metastatic
- **Region: Asia vs non-Asia**

Primary Endpoint: OS
Secondar Endpoints: PFS, ORR, DoR, Safety, ORR
Blinded independent central review

1º endpoint OS and 2⁰ endpoint PFS

OS: stat sig (+), separated early



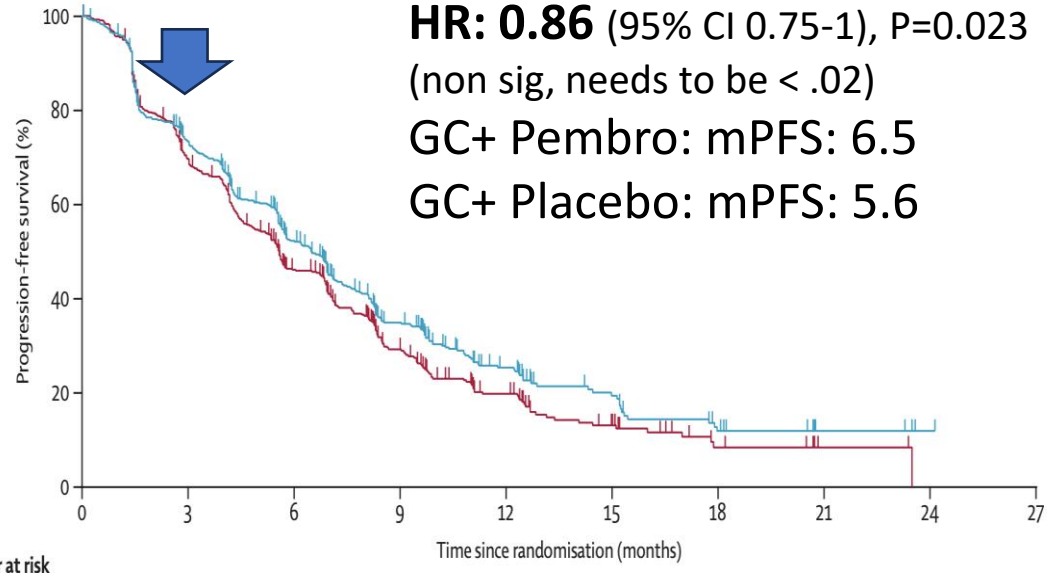
HR: 0.83 (95% CI O.72-0.95), P=0.0034 (sig)

GC+ Pembro: mOS: 12.7

GC+ Placebo: mOS: 10.9

Number at risk (number censored)														
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	496 (0)	430 (0)	350 (0)	275 (0)	217 (0)	175 (1)	122 (26)	88 (50)	46 (83)	21 (100)	11 (109)	5 (114)	0 (119)
Placebo plus gemcitabine and cisplatin	536 (0)	483 (1)	394 (1)	313 (1)	236 (1)	195 (1)	148 (3)	97 (30)	59 (49)	32 (65)	20 (74)	10 (84)	1 (92)	0 (93)

PFS: not stat sig (-), trend, separated early, sustained



HR: 0.86 (95% CI 0.75-1), P=0.023 (non sig, needs to be < .02)

GC+ Pembro: mPFS: 6.5

GC+ Placebo: mPFS: 5.6

Number at risk (number censored)										
Pembrolizumab plus gemcitabine and cisplatin	533 (0)	368 (27)	238 (55)	121 (101)	62 (131)	29 (153)	14 (158)	5 (167)	1 (171)	0 (172)
Placebo plus gemcitabine and cisplatin	536 (0)	352 (25)	211 (50)	99 (94)	51 (113)	21 (130)	7 (139)	2 (144)	0 (145)	0 (145)

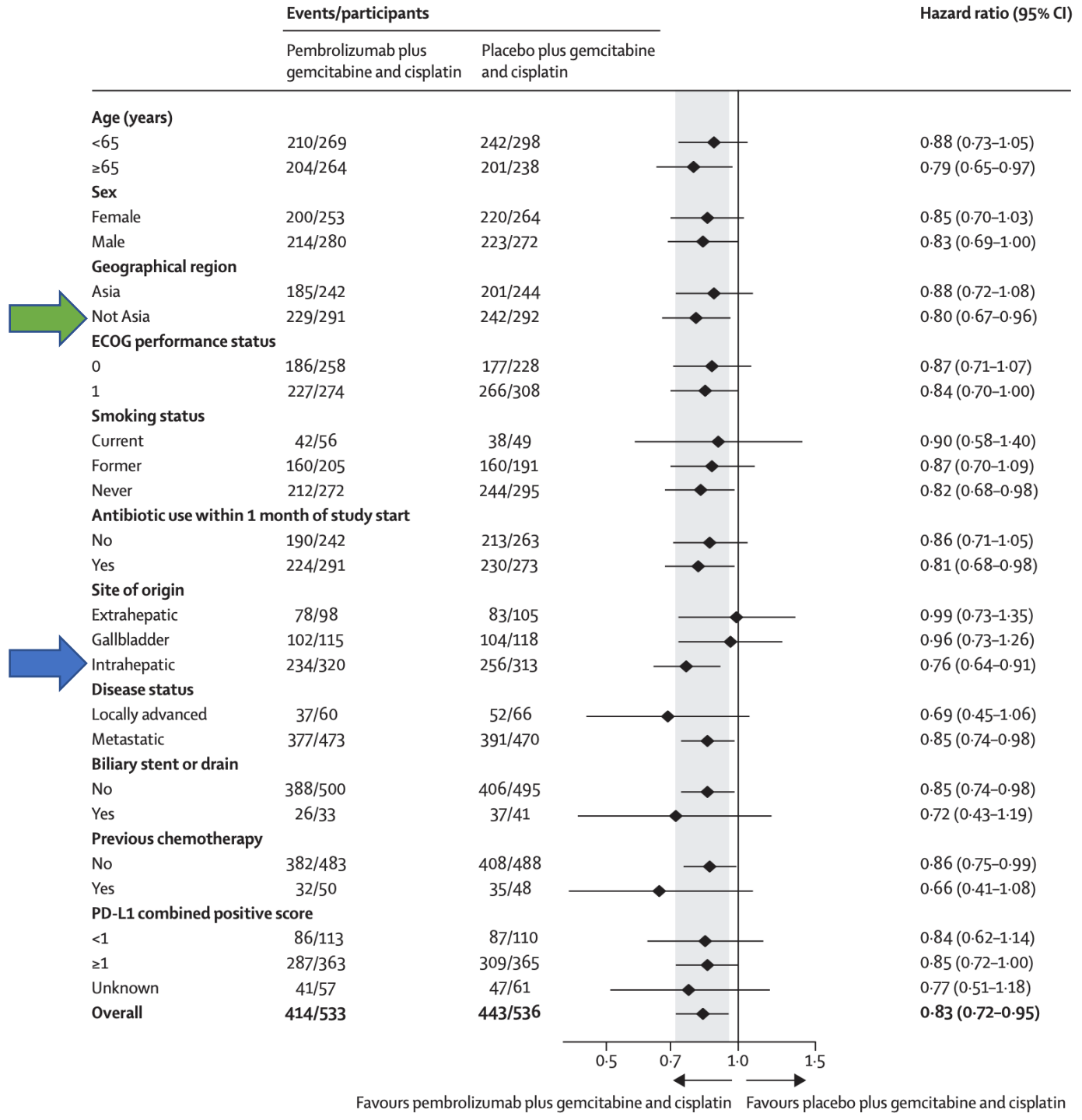
Keynote 966: Subgroup Analysis

- Geographic: more benefit non-Asian
- Type: iCCA benefits more, GBCA and eCCA not really
- PD-L1 useless

Response Rate:

	GC + Pembro	GC + Placebo
ORR	**29%**	**29%**
DoR	9.7	6.9
24mo ongoing RR	18%	6%

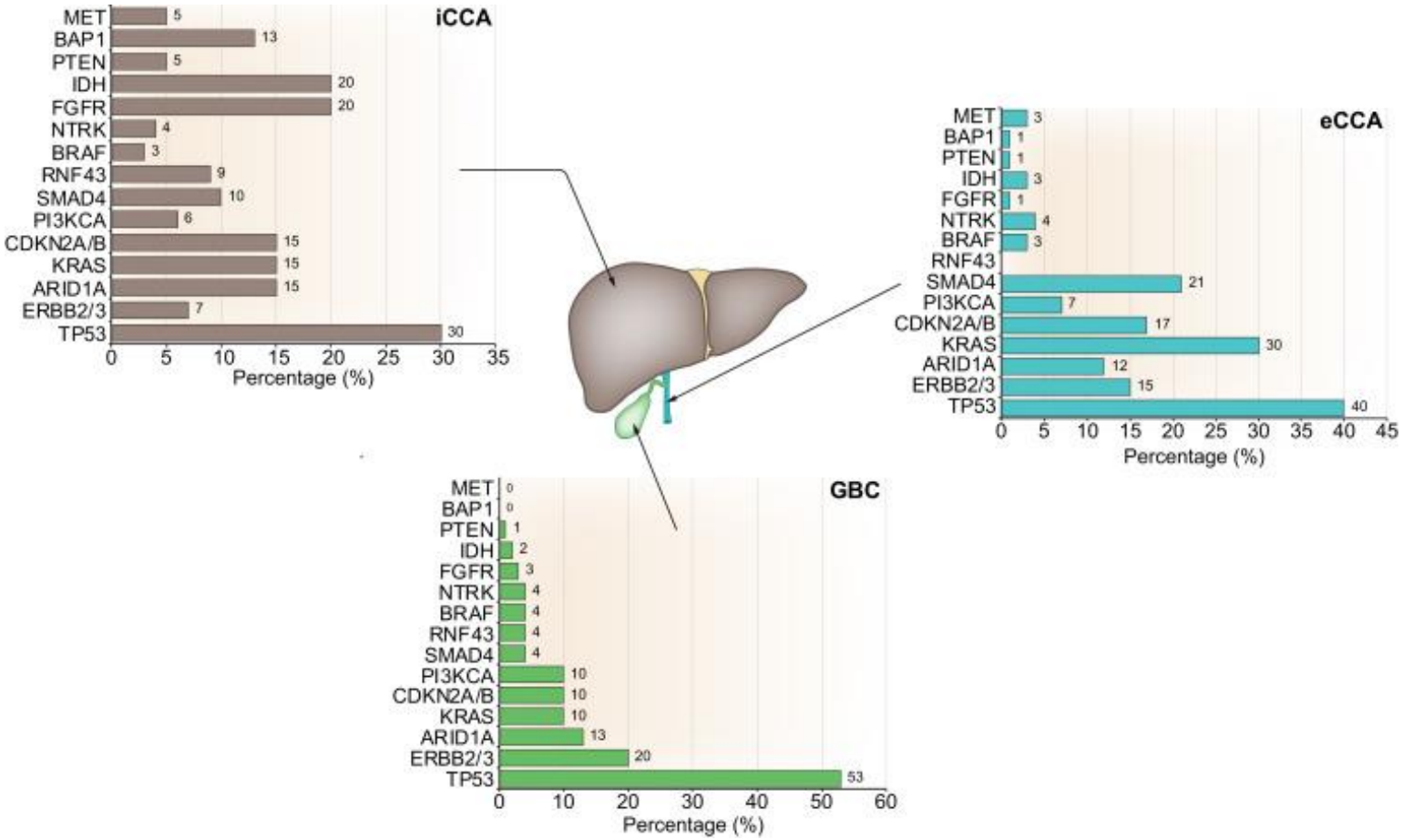
Blinded central review

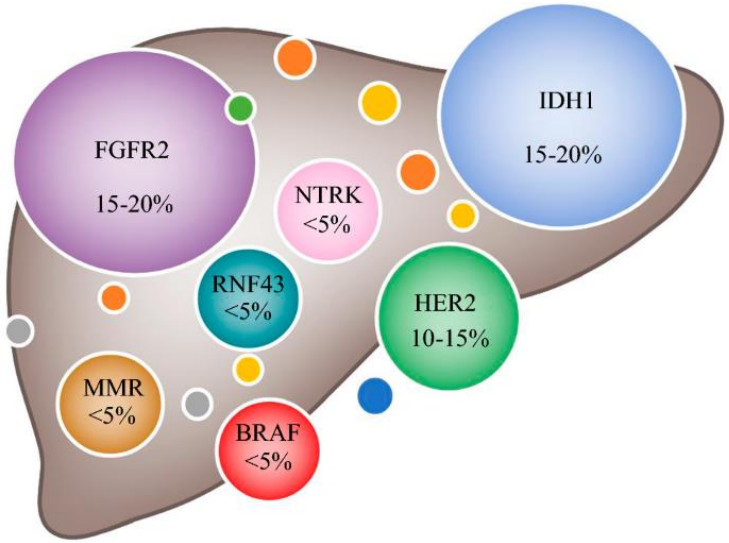


TOPAZ vs Keynote 966

	TOPAZ (GC+D)	KEYNOTE 966 (GC+P)
Maintenance	ICI vs placebo	G+ICI vs G+placebo
Demographics		
Asia	52%	45%
Intrahepatic CCA	56%	60%
HBV infection	22.5%	31%
Response Review	Investigator	Blinded Central
ORR vs Control	26.7% vs 18.7%	29% both

Molecular Targets for Therapy in BTC





Lamarca et al J Hepatol. 2020 Jul;73(1):170-185

*Fong et al Ann Surg Oncol **28**, 2660–2674 (2021).*

Systemic Therapy for BTC: Rapidly Evolving

First-line

Gemcitabine Cisplatin
ABC-02 (included ampullary)
ORR: 26% (vs 21%), mOS: 11mo
2010

Gemcitabine Cisplatin Durvalumab
TOPAZ-1
ORR: 26.7% (vs 18.7%) ,mOS 12.8mo
2022

Gemcitabine Cisplatin Pembrolizumab
Keynote 966
ORR: 29% ,mOS 12.7mo
2023

Gemcitabine Cisplatin
Nab-Paclitaxel ? SWOG 1815 was negative

Second-line

No Targets	**FOLFOX** ABC-06 ORR: 5%, mOS 6.2mo	2018	**5-FU Nal-IRI** Nifty ORR: 14.8%, mOS 8.6mo	2021
FGFR2 fusion	***Pemigatinib** FIGHT-302 ORR: 35.5%, mOS 21.2mo	2020	***Futibatinib** FOENIX-CCA2 ORR: 42%, mOS 21.7mo	2022
IDH-1 mutation	**Ivosidenib** ClarIDHy ORR: 2%, mOS 10.3	2022		
BRAF V600E	**Dabrafenib/Trametinib** ROAR tissue agnostic, ORR: 36%, DCR 76%	2022		
ERBB2 amplification HER 2 “positive’	**⁺Trastuzumab/Pertuzumab** MyPathway, ORR: 40%		**T-Dxd (Enhertu)** DESTINY Pan-Tumor02 ORR:22%, mOS 7mo	
MSI-H	**Pembrolizumab** KEYNOTE cohorts ORR:39.6%	2017	**Dostarlimab-glxy** GARNET ORR: 41.6%	2021
NTRK fusion	**Larotrectinib** LoxoTRK, SCOUT, NAVIGATE ORR: ~60-70%	2018	**Entrectinib** STARTRK1,2 ORR: 57%	2019
RET Fusion	**⁺Pralsetinib** BLU-667, tumor agnostic, 2B rec	2022		

Low Hanging Fruit Board Questions/Tips

- **Peculiar Toxicities of targeted therapies**
  - **FGFR2 Inhibitors (Pemigatinib, Futibatinib)**: Hyperphosphatemia, Retinal (Central Serous Retinopathy / Retinal Pigment Epithelium Detachment CSR/RPED)
  - **IDH inhibitors (Ivosidenib)**: myositis, QT prolongation
  - **Dabrafenib/Trametinib**: pyrexia, CSR/RPED
  - **Pertuzumab:** diarrhea
  - **Enhertu**: ILD
- What to avoid with liver dysfunction
  - Irinotecan
  - Targeted therapies (FGFR2i, IDHi, NTRKi): no data in severe liver dysfunction
- Avoid ICI: autoimmune disease
- Targeted therapies only indicated in 2nd line, chemo still 1st line

Low Hanging Fruit Board Questions/Tips

- Chemotherapy vignettes:
  - Avoid cisplatin in patients with significant kidney dysfunction
  - LATE Anaphylactic reactions can happen in patients who are receiving oxaliplatin or carboplatin for many months
  - 5-FU cardiac vasospasm
  - Gemcitabine associated HUS
  - All sorts of potential toxicity with cisplatin: kidney, hearing, hemorrhagic cystitis etc.

Good Luck!

Think like a question maker (not necessarily a clinician) for the boards