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Pancreas and Biliary Ca: Advances

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Wake Forest School of Medicine

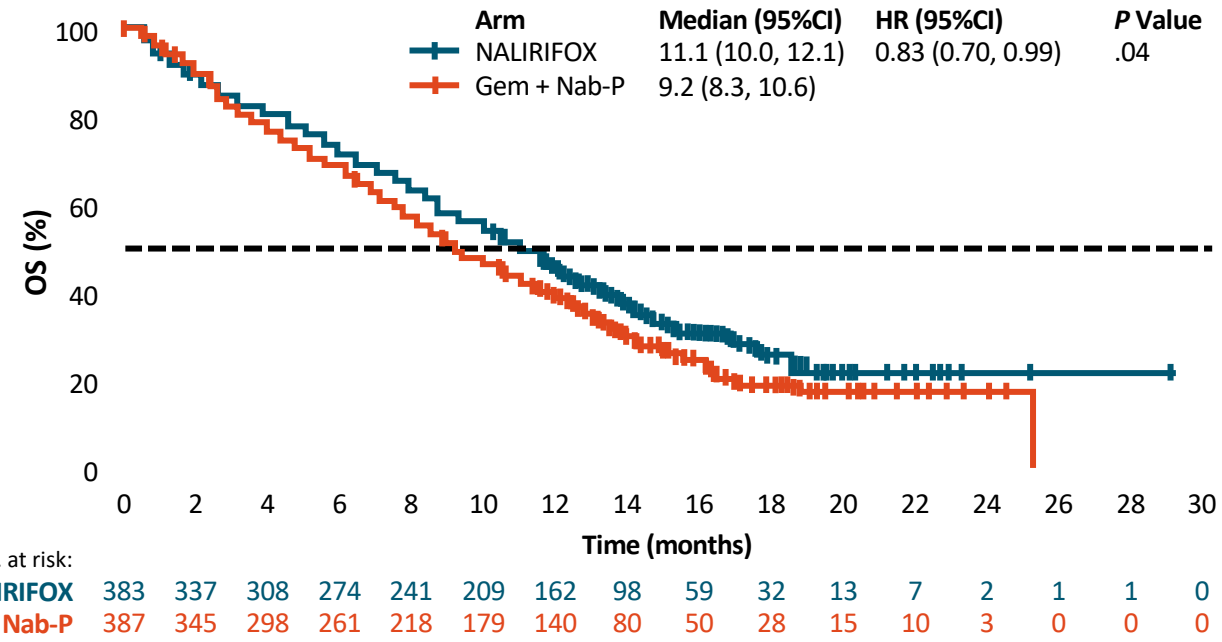
We Have Made Progress in the 1st-Line Pancreas Adeno in the Metastatic Setting

Trial[1]	Date	Patients (n)	Treatment	Median survival (mo)	P value
Burris et al[2]	1997	126 (unresectable, LA or metastatic pancreatic cancer)	5-FU vs. gemcitabine	4.41 5.65*	Log-Rank Test 0.0025
NCIC[3]	2007	569 (unresectable, LA or metastatic pancreatic cancer)	gemcitabine vs. gemcitabine + erlotinib	5.91 6.24	0.038 (HR = 0.82 [95% CI, 0.69–0.99])
PRODIGE[4]	2011	342 (metastatic)	gemcitabine vs. FOLFIRINOX	6.8 11.1	<0.001 (HR = 0.57 [95% CI, 0.45–0.73])
Ueno, et al[5]	2013	834 (LA, or metastatic pancreatic cancer)	gemcitabine vs. S-1 vs. gemcitabine + S-1	8.8 9.7 10.1	gemcitabine vs. S-1: <0.001 (non-inferiority; HR = 0.96 [97.5% CI, 0.78–1.18]) gemcitabine vs. gemcitabine + S-1: 0.15 (superiority; HR = 0.88 [97.5% CI, 0.71–1.08])
MPACT[6]	2013	861 (metastatic)	gemcitabine vs. gemcitabine + nab-paclitaxel	6.7 8.5	<0.001 (HR = 0.72 [95% CI, 0.62–0.83])

1. Ryan DP, et al. N Engl J Med 2014;371:1039;
2. Burris HA, et al. J Clin Oncol 1997;15:2403;
3. Moore MJ, et al. J Clin Oncol 2007;25:1960;

4.Conroy T, et al. N Engl J Med 2011;364:1817;
5. Ueno H, et al. J Clin Oncol 2013;31:1640;
6. Von Hoff DD, et al. N Engl J Med 2013;369:1691.

NAPOLI: OS (Primary Endpoint)



NALIRIFOX x FOLFIRINOX

	NALIRIFOX	FOLFIRINOX (PRODIGE)
Median OS	11.2 Months	11.1 Months
Median PFS	7.4 Months	6.4 Months
ORR	41.8%	31.6%
Toxicity	Myelotoxicity, peripheral neuropathy, and GI Toxicity	

Maintenance Therapy May Be Considered

PRODIGE 35
LV5FU2 after 3 to 6 mo of induction

	FOLFIRINOX	Maintenance	FIRGEM
PFS (mo)	**6.3**	**5.7**	**4.5**
9 mo PFS (%)	**32**	**29**	**16**
12 mo PFS (%)	**15**	**15**	**13**

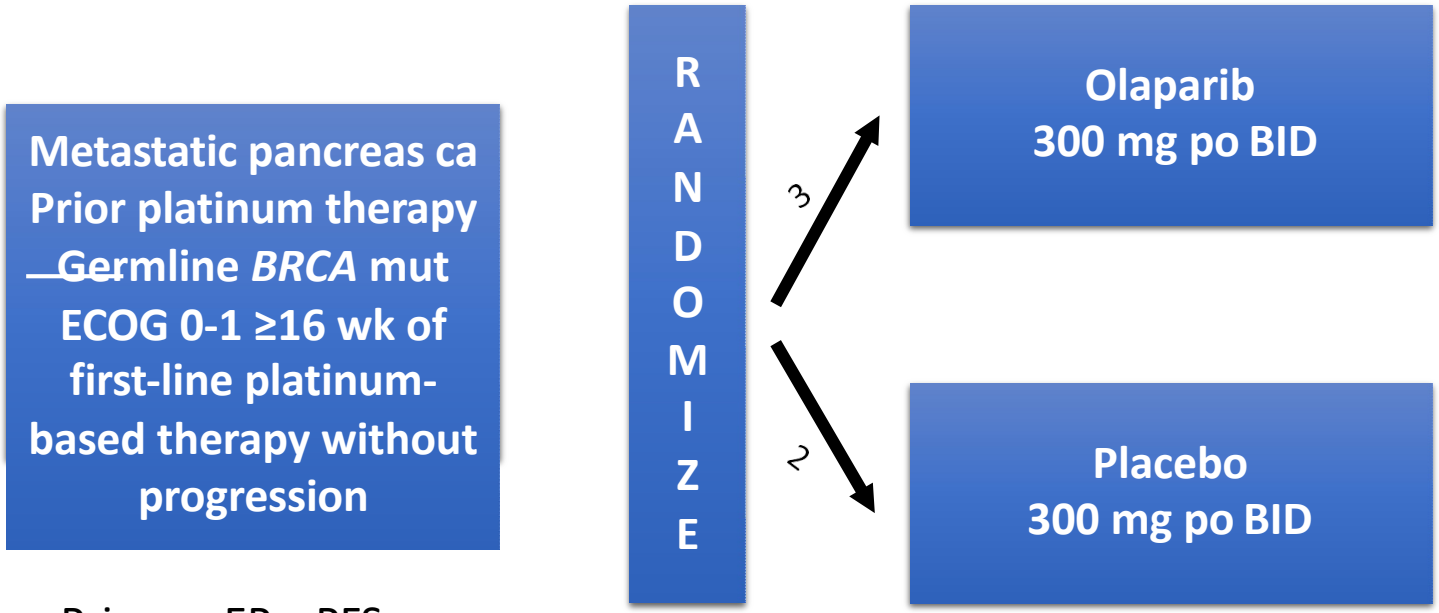
	FOLFIRINOX	Maintenance	FIRGEM
OS (mo)	**10.1**	**11.0**	**7.3**
9 mo OS(%)	**74**	**75**	**60**
12 mo OS(%)	**43**	**44**	**28**

FIRGEM: FOLFIRI.3 followed by gemcitabine. Dahan L, *et al.* ASCO 2018; Abstract #4000.

NCCN Guidelines Since 2019

- Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes

POLO: Phase 3 international PARPi maintenance study in gBRCA mutated patients



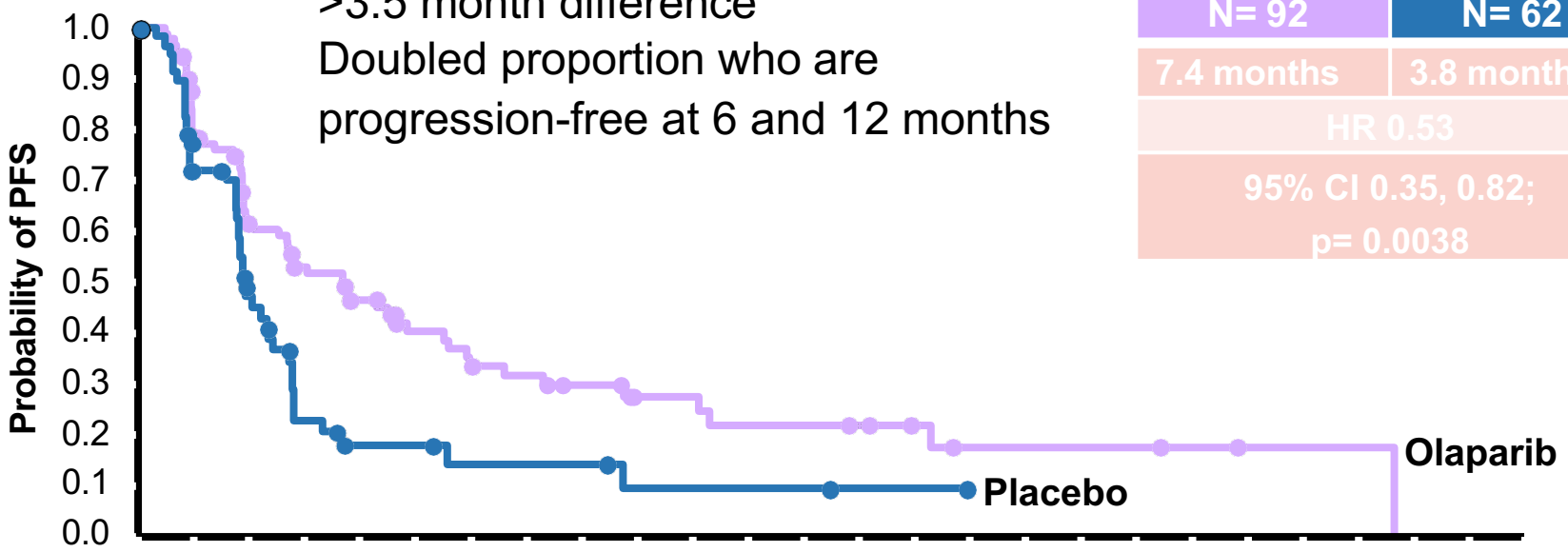
Primary EP = PFS
N = 154

NCT02184195

- 3315 patients screened; 247 had germline *BRCA* mutation (7.5%)

Golan. NEJM. 2019;381:317.

Primary Endpoint: Blinded Central Review

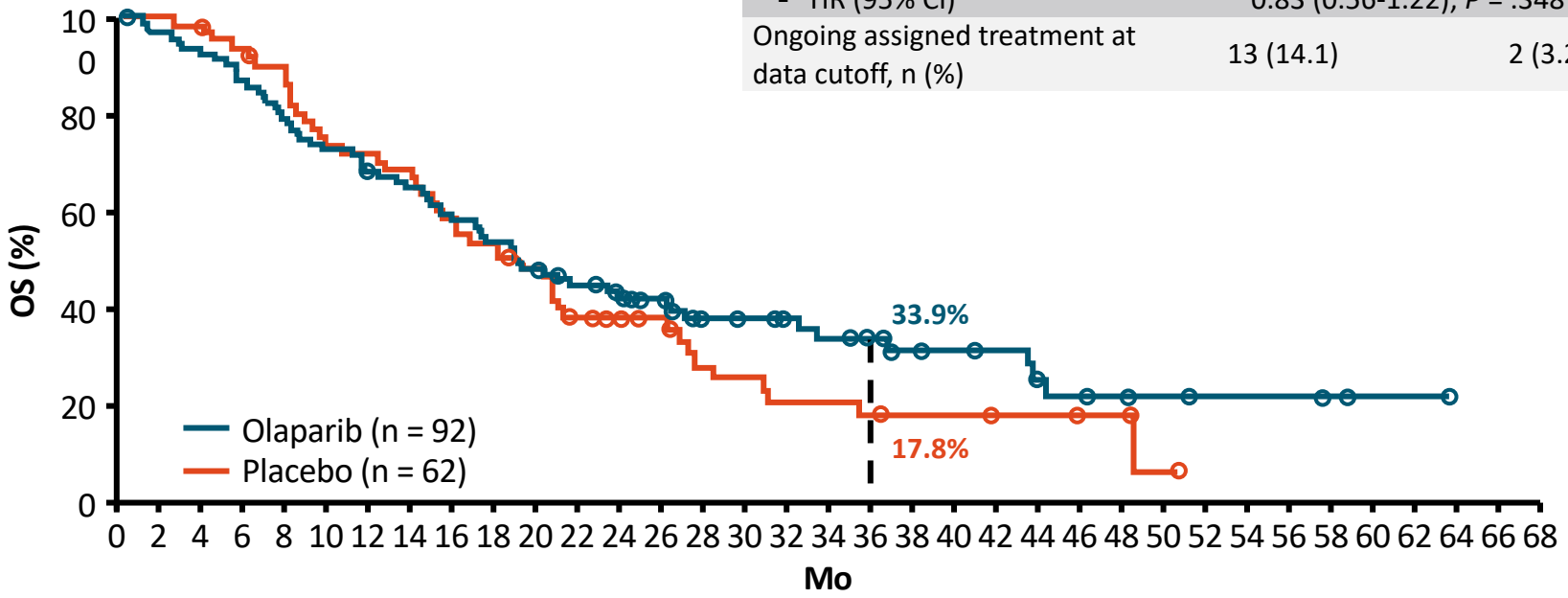


Olaparib N= 92	Placebo N= 62
7.4 months	3.8 months
HR 0.53	
95% CI 0.35, 0.82; p= 0.0038	

Golan, T. New Engl J Med, 2019

POLO: Final OS

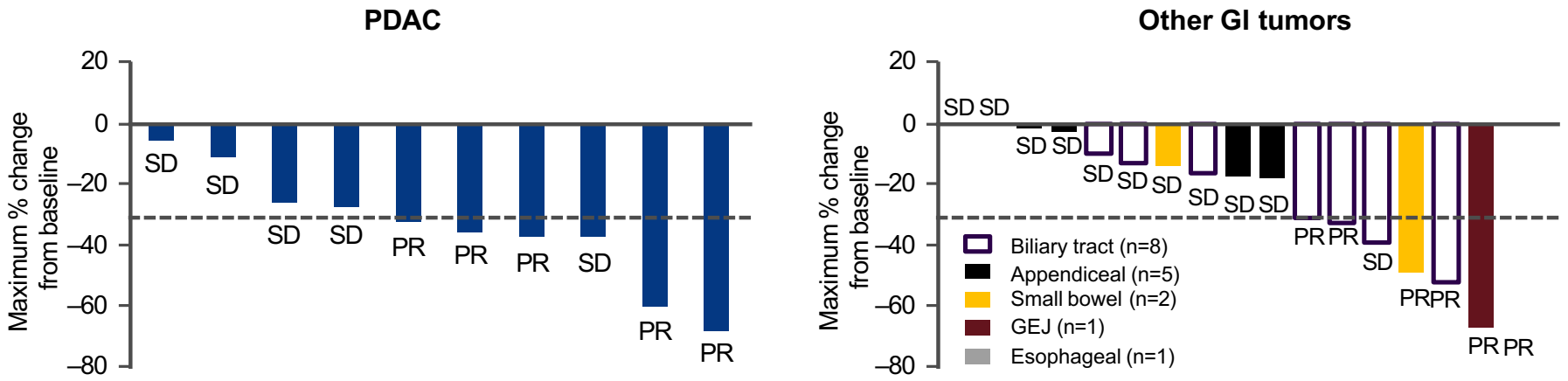
	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, mo	19.0	19.2
▪ HR (95% CI)	0.83 (0.56-1.22); *P* = .3487	
Ongoing assigned treatment at data cutoff, n (%)	13 (14.1)	2 (3.2)



Golan. ASCO GI 2021. Abstr 378.

KRYSTAL-1: Adagrasib (MRTX849) unresectable or metastatic pancreatic cancer and other gastrointestinal tumors with KRASG12C mutation

Best tumor change from baseline (evaluable patients)



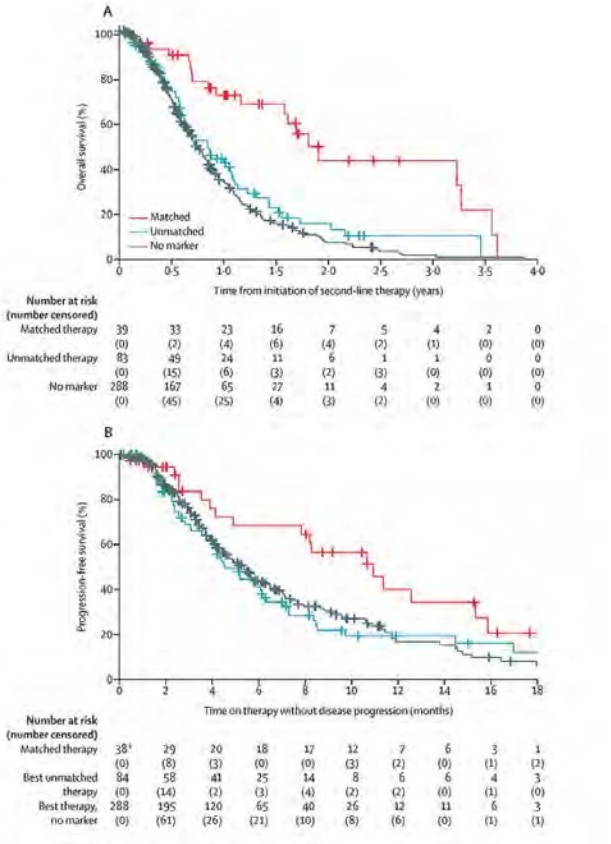
Bekaii-Saab TS, et al. J Clin Oncol 2022;40(suppl):abstr 519

Know Your Tumor Registry Trial
Advanced setting

- Post at least 2 lines

- **mOS**: Time from initiation of second line treatment
  - Matched treatment: **1.81 y**
  - Unmatched: 0.85 y
  - No match: 0.73 y

- **mPFS: Only one line of treatment with best outcome**
  - Matched treatment: **10.93 mo**
  - Unmatched: 4.53 mo
  - No match: 5.37 mo



OS

PFS

Pishvaian et al., Lancet Oncol 2020

CONCLUSIONS

- Systemic chemotherapy is beneficial for patients with metastatic pancreas cancer with good PS and adequate organ function
- Germline testing is recommended in patients with pancreas ca
- Somatic/tumor NGS testing should be performed in advanced/metastatic patients that are candidates to received systemic therapy
- Targeting actionable mutations may lead to significant benefit (including survival and QOL benefits)

Biliary Cancers Chemotherapy

Prospective, National, Multicenter Phase 3 Study: ABC-02 Schema

Eligible patients (n = 400[a])

+ QoL

Randomized 1:1

(stratified by center, primary site, PS, prior therapy and locally advanced vs metastatic)

Arm A

Gem *1000 mg/m²*
D1,8,15 q 28d
24 weeks (6 cycles)

Arm B

Cisplatin *25 mg/m²*
+ Gem *1000 mg/m²*
D1,8 q 21d
24 weeks (8 cycles)

Primary endpoint OS

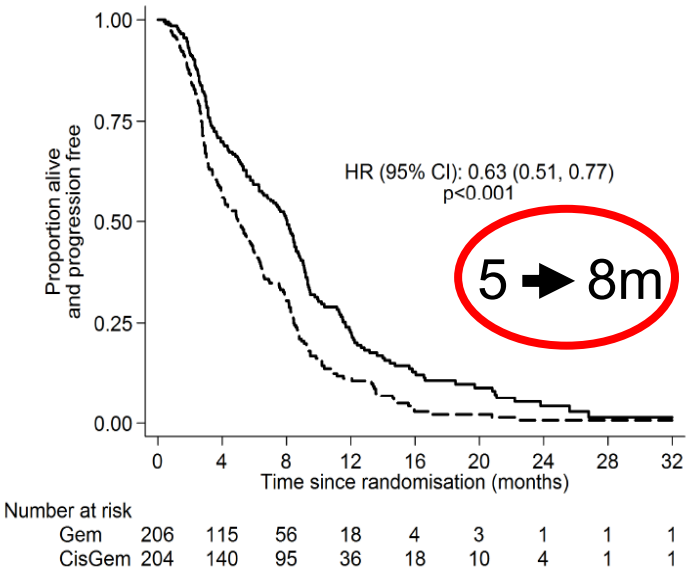
Inclusion criteria:

- Histologically / cytologically verified, non-resectable or recurrent/metastatic CCC, GB, or ampullary carcinoma
- Adequate biliary drainage, no uncontrolled infection
- ECOG PS 0-2
- LFTs: bilirubin ≤ 1.5 x ULN, ALT/ AST/ alk phos ≤ 3 x ULN (≤ 5 if liver metastases)
- No prior systemic treatment[b]
- Consenting informed-patients

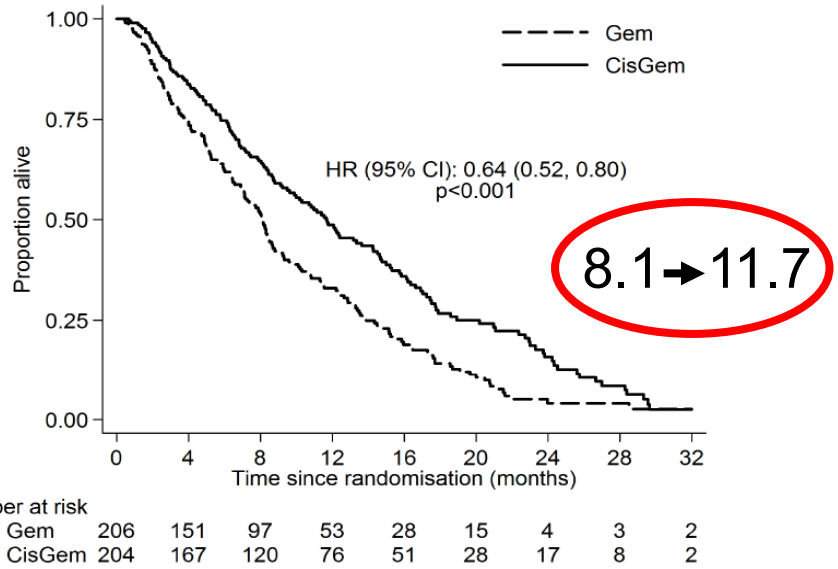
[a] Including 86 patients in ABC-01.
[b] Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)



Overall Survival (ITT)



Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

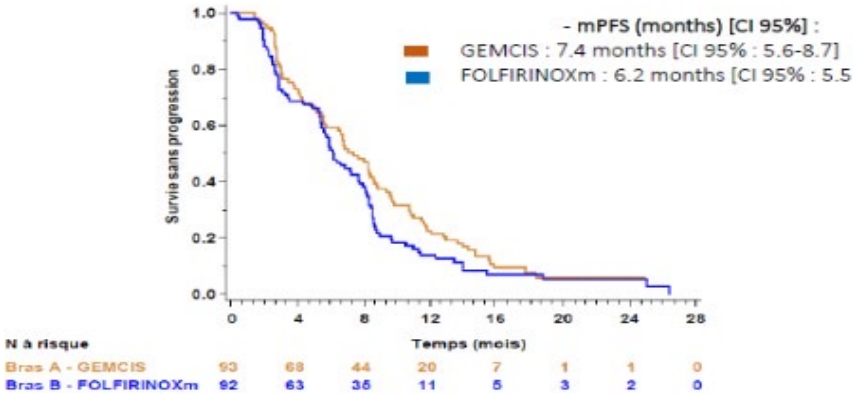
CHEMOTHERAPY TRIPLETS APPEAR NOT TO IMPROVE OUTCOMES

Random Phase II mFOLFIRINOX or CisGem

Primary end-point: PFS-rate at 6 months

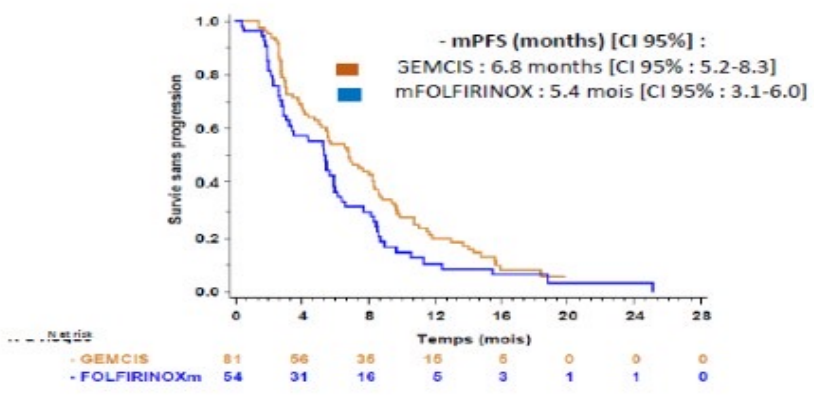
n=190.

PFS in modified ITT analysis (n= 185)



- PFS at 6 months [CI 95%] :
  - GEMCIS : 59.0% [CI 95% : 48.3-68.3]
  - FOLFIRINOXm : 51.1% [CI 95% : 40.5-60.7]

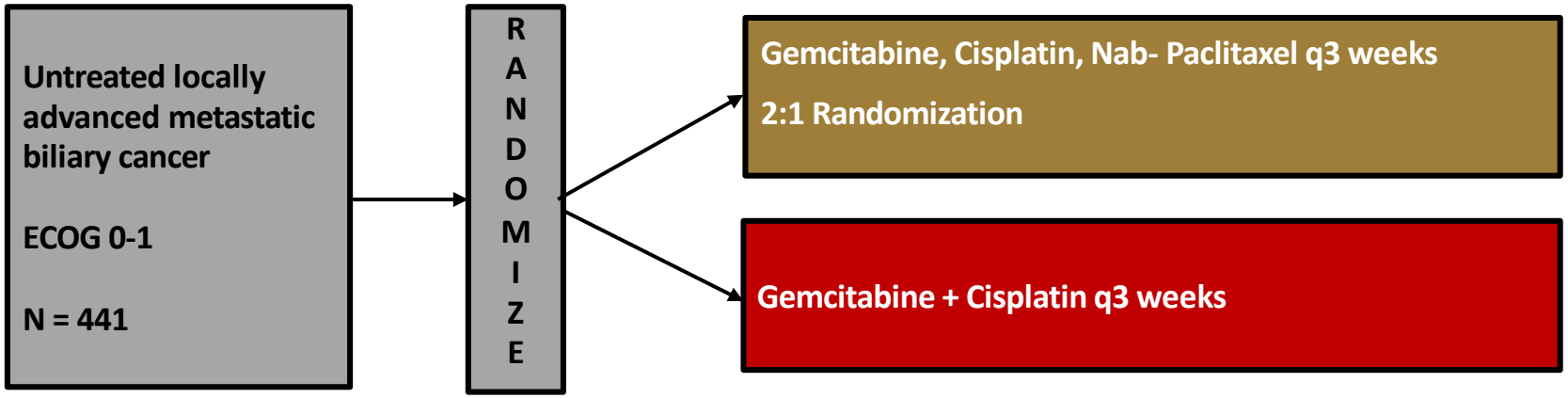
PFS in PP analysis (n= 135)



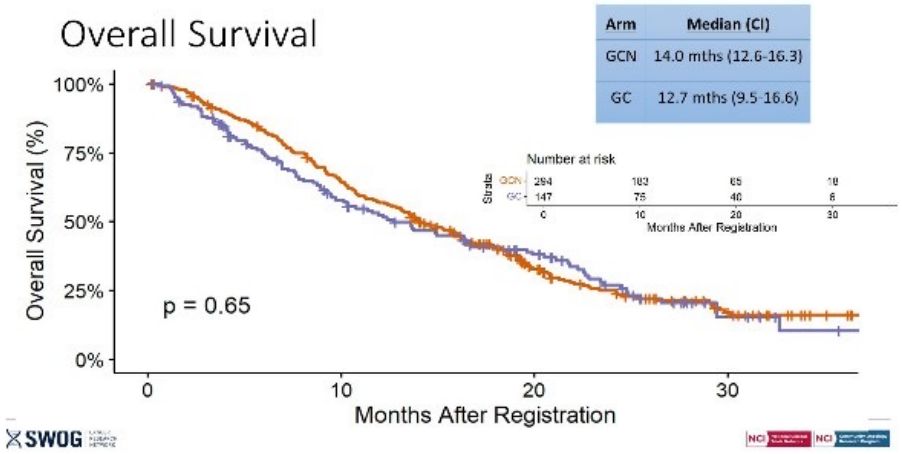
- **PFS at 6 months [CI 95%] :**
  - GEMCIS : 54.2% [CI 95% : 42.7-64.3]
  - mFOLFIRINOX : 37.0% [CI 95% : 24.4-49.7]

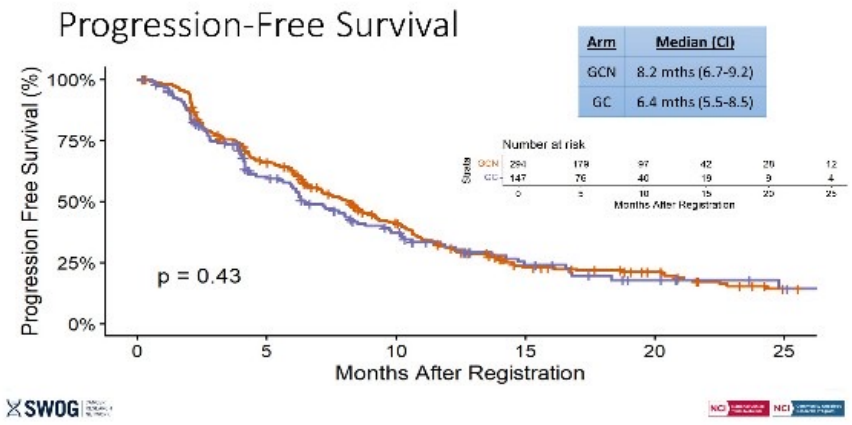
Phelip et al, ESMO 2020

Phase 3 SWOG 1815



Primary endpoint: overall survival

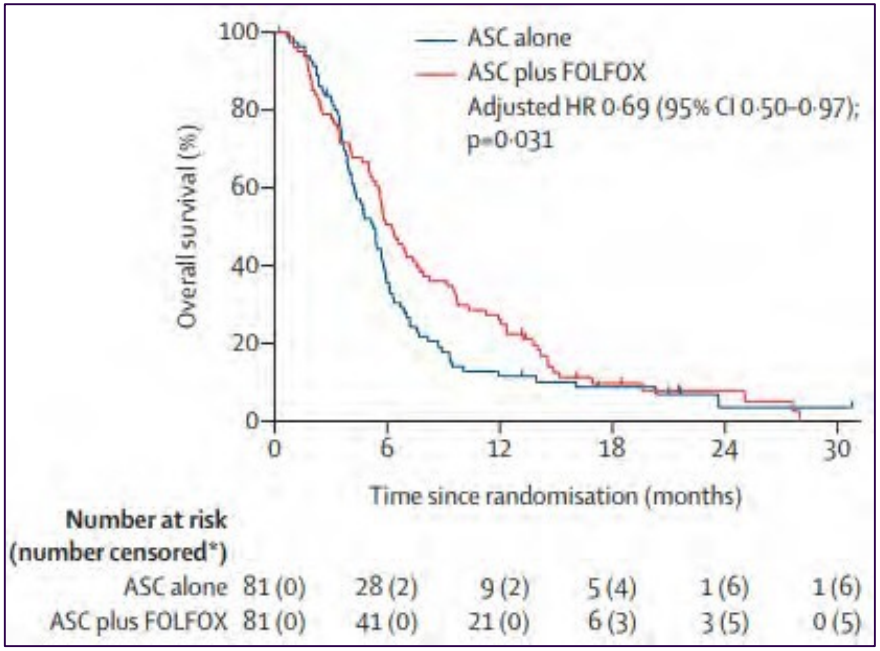




Shroff et al, ESMO-GI 2023

Second-line Chemotherapy in Biliary tract cancers

FOLFOX (ABC-06)



Overall Survival

- **Arm A** (ASC alone)
- **Arm B** (ASC + mFOLFOX)

- **Median OS**
  - 5.3 months
  - 6.2 months
- **6-month survival rate**
  - 35.5%
  - 50.6%
- **12-month survival rate**
  - 11.4%
  - 25.9%

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

Targets Biliary Tract Cancers

- IDH-1 mutations
- FGFR2 fusions
- BRAF
- Her-2 (ERBB2)
- Immunotherapy

Ivosidenib Phase 1 and Phase 3 Studies

Phase 1 Study

CCA, chondrosarcoma, glioma, others [NCT02073994]

CCA cohort[1]: n = 73 [dose escalation (n = 24); dose-expansion 500 mg QD (n = 49)]

No DLTs; drug-related AEs: fatigue, nausea, diarrhea, vomiting

Activity:

Median PFS 3.8 months

6-month PFS: 40.1%

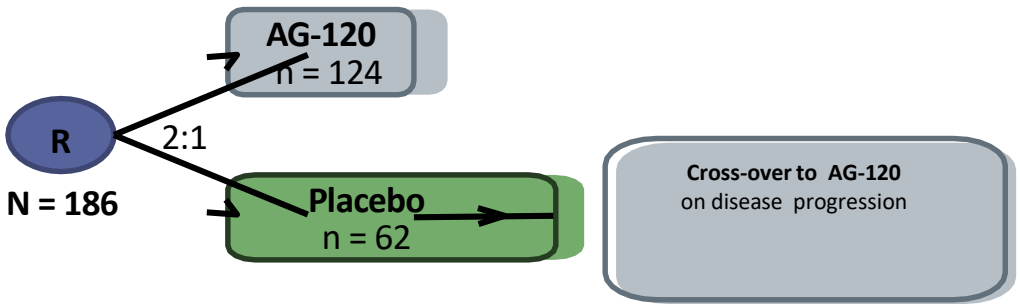
12-month PFS: 21.8%

RR 5% (4 PRs)

OS: 13.8 m

Phase 3 Study (ClarIDHy)

Second-line, placebo- controlled
[NCT02989857][2]



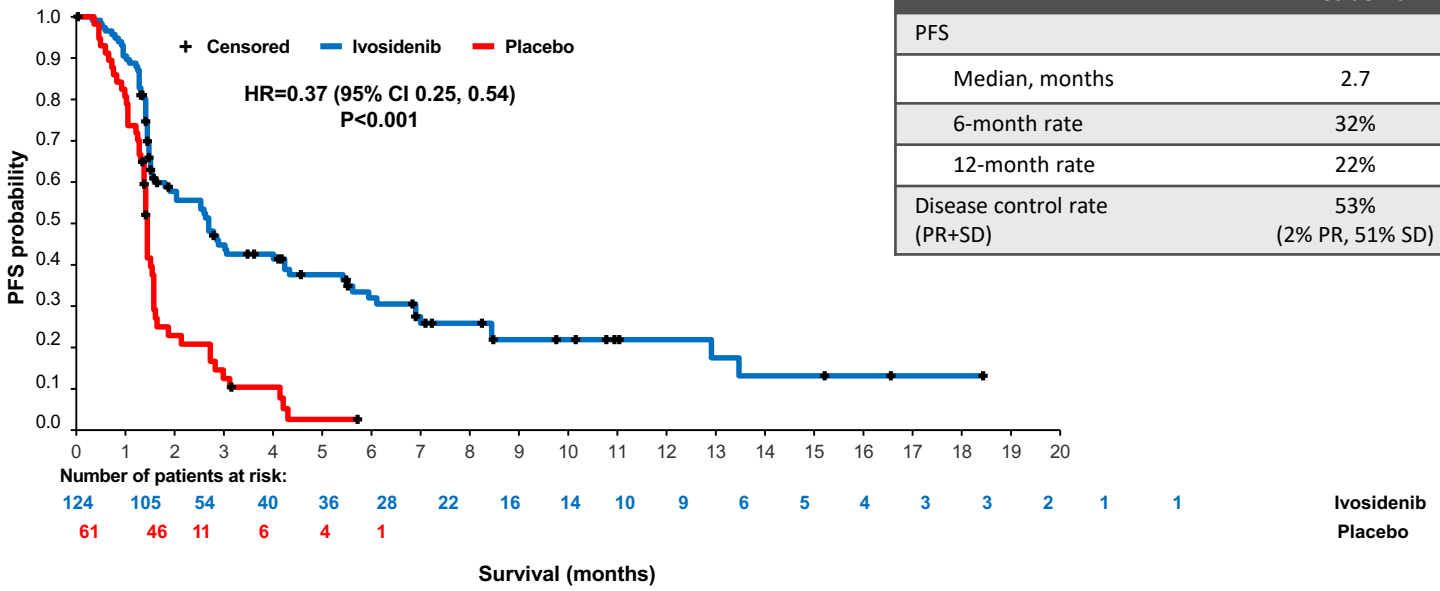
AG-120 is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

IDH1 Mutations

- IHCCA (22%)
- Chondrosarcoma (50%)
- Glioma (80%)

Abou-Alfa, GK. Lancet Oncol, 2020
Zhu, AK et al. JAMA Oncol 2021

ClarIDHy: PFS



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

NE = not estimable; PR = partial response; SD = stable disease.

- mOS (months; adjusted for cross-over): 10.8 vs 6 months (9.7 months unadjusted)

Abou-Alfa, GK. Lancet Oncol, 2020

FGFR2 inhibitors

Agent	Trial N size	RR (%)	PFS (m)
Pemigatinib	107	35.5	6.9
Infigratinib (withdraw)	108	23.1	7.3
Futibatinib	103	41.7	8.9
Derazantinib	103	21.4	7.8

First Line Trials with FGFR2 Inhibitors
Pemigatinib , Infigratinib, and Futibatinib

All four are not selective FGFR inhibitors (FGFR 1-4)

Lancet Onc 2020
Lancet Gastro Hepato 2021
ASCO 2022
ESMO 2021

FUTIBATINIB

Irreversible inhibitor FGFR 1-4

Activity against cells with mutations associated with resistance to FGFR inhibitors

Phase 1 with 83 CCA

28 pts prior FGFRi - ORR 17.9%

Cancer Discov. 2022 Feb 1; 12(2): 402–415

FGFR 2 Inhibitors toxicity

- Hyperphosphatemia (FGFR1)
- Eye disorders
- Stomatitis
- Fatigue
- Diarrhea (FGFR4)

REFOCUS TRIAL:
RYL-4008 Highly Selective FGFR2 Inhibitor Activity Resistance Mutations

	FGFRi-naïve CCA N = 25	Prior-FGFRi CCA N = 50
ORR n(%) [95% CI]	13 (52% [31.3%-72.2%])	7 (14% [5.8%-26.7%])
mDOR mo (range)	8.2 (1.9-18.6)	5.6 (1.9-7.4)
DCR n (%)	22 (88%)	40 (80%)

No reported G3 or G4 Hyperphosphatemia or G3 or G4 Diarrhea

Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 4009-4009.

The Phase 2 Dabrafenib and trametinib: BRAF ^{V600E}-mutated BTC Rare Oncology Agnostic Research (ROAR) basket trial

- *BRAF* mutations have been reported in approximately 5%-7% of iCCAs; these mutations may be enriched in iCCA vs other types of biliary cancers
- **Phase 2 study in 43 pts**
  - **ORR 47% (95% CI, 31–62)** – central review
  - Duration of response: 9 months (95% CI, 6–14)
  - PFS: 9 months (95% CI, 5–10)
  - OS: 14 months (95% CI, 10–33)

Subbiah V, et al. *Lancet Oncol.* 2020;21:1234–43.

Targeting HER-2

- **Pertuzumab and trastuzumab: phase 2a study (**Javle Lancet Oncol 2021**)**
  - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
  - RR 23 %. Median DOR: 10.8 months. Median OS: 10.9 months
    - Higher activity in extrahepatic BTC RR: 40% (ampullary); 31% (GBC)

- **Zanidatamab – HER-2 bispecific antibody (Herizon BTC-01).** Harding, Lancet Oncol 2023
  - 87 patients. RR 36%. Median DOR 11 months
  - Median PFS: 5.4 months. OS at 9 months: 69.9%
    - **Appears not active in 2+IHC**

- **Neratinib, a pan-HER irreversible tyrosine kinase inhibitor** Harding ASCO 2022
  - 25 pts with activating somatic HER2 mutations (GB 40%, ICC24%, EHCC20%, AV 16%)
  - RR 16% and PFS 2.8 months. Median OS 5.4 months

Targeting HER-2
Trastuzumab deruxtecan

- 30 pts recurrent or unresectable:
- RR 36.4% and 12.5%. PFS 5.1 and 3.2 months in HER 2 + and HER 2 low
- DOR in Her 2 +: 7.4 months
- ILD: ≥ Grade 3: 12.5%

Ohba A et al: A 4006, ASCO 2022

- 41pts recurrent or unresectable:
- RR 22%
- DOR 8.6 months

Meric-Bernam ASCO 2023

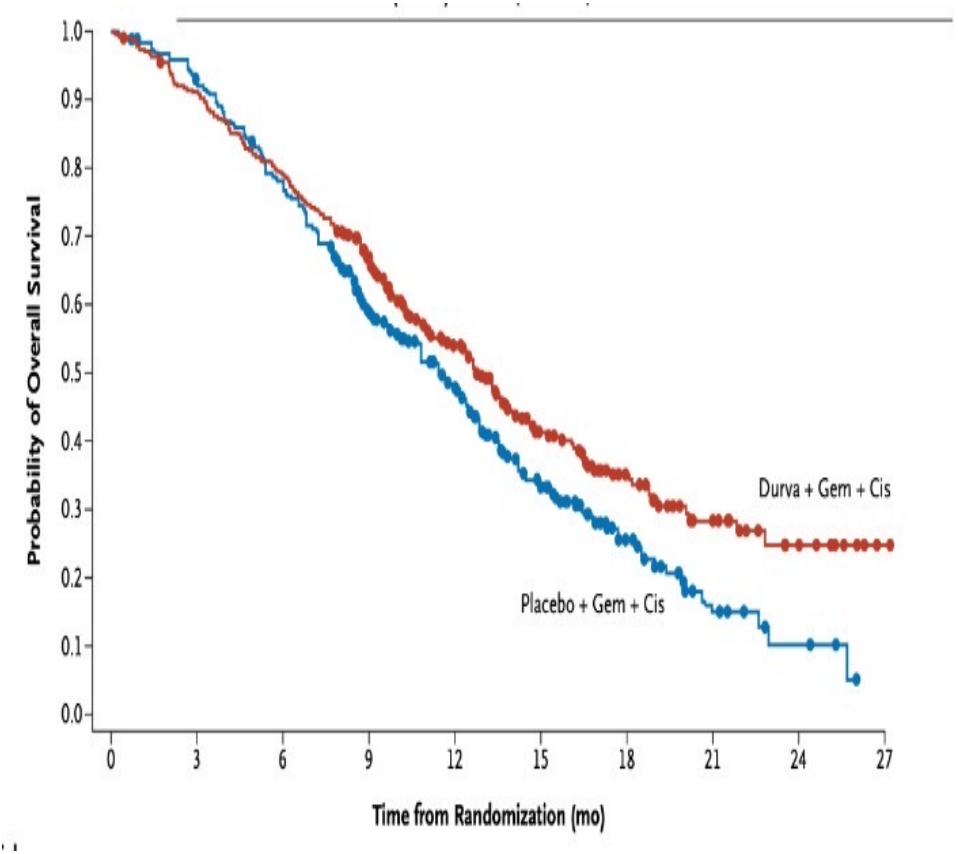
Immunotherapy

TOPAZ-1 Study

- 685 chemo naïve for met, locally advanced or metastatic BTC (ICC, ECC, and GBC)
- ECOG PS 1
- Randomized 1:1 Gem/DDP +/- Durvalumab or Placebo up to 8 cycles. Follower by D or P to progression

Do-Youn O et al, N Engl J Med Evidence June 2022

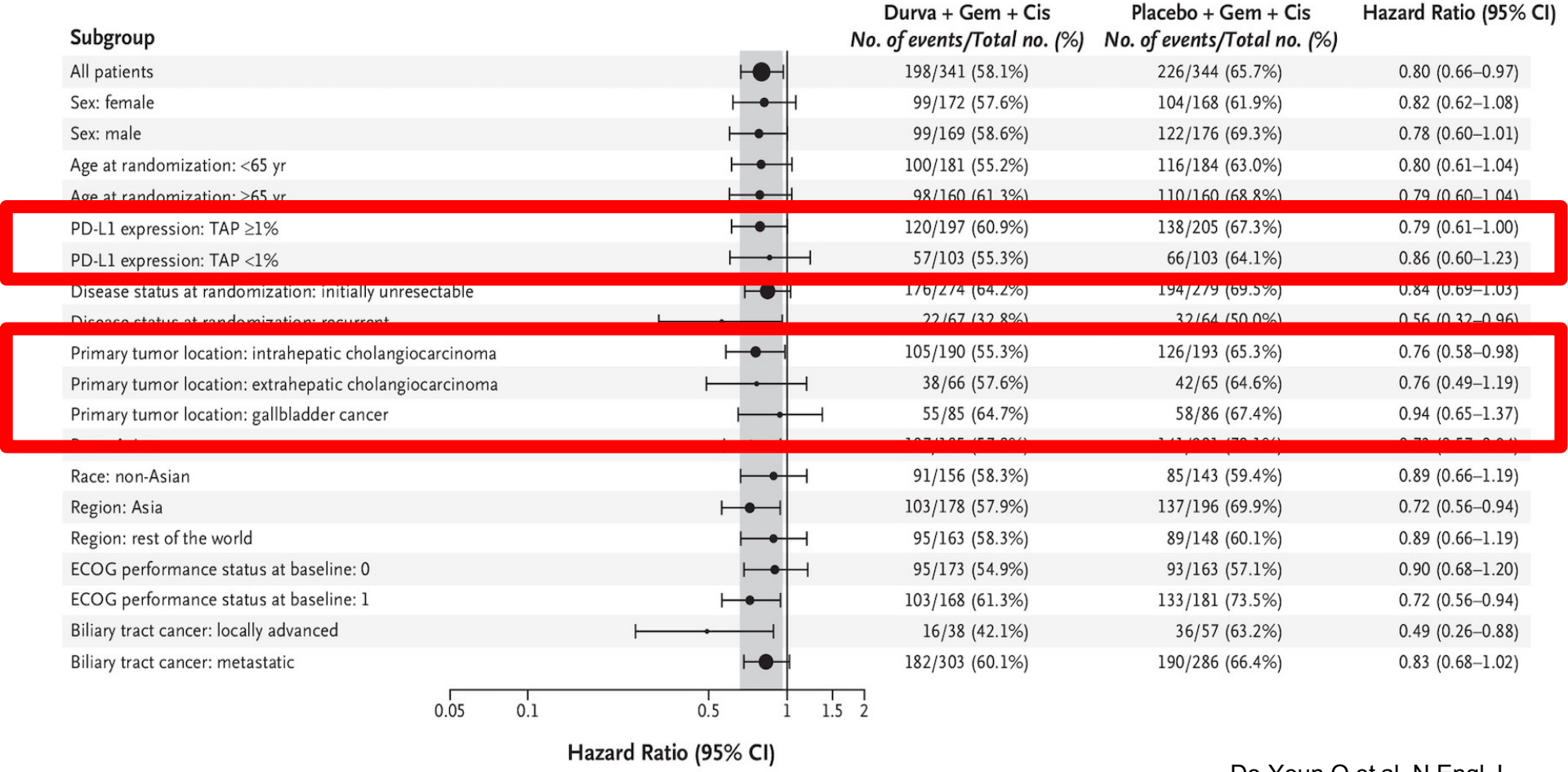
TOPAZ-1
Efficacy Results



	GEM/DDP/D (n=341)	GEM/DDP/P (n=343)	HR (C.I.) [P Value]
mOS (months)	12.8	11.5	0.8 (0.66-0.97) [0.021]
PFS (months)	7.2	5.7	0.75(0.63-0.89) [0.001]
ORR (%)	26.7	18.7	
DCR	85.3	82.6	

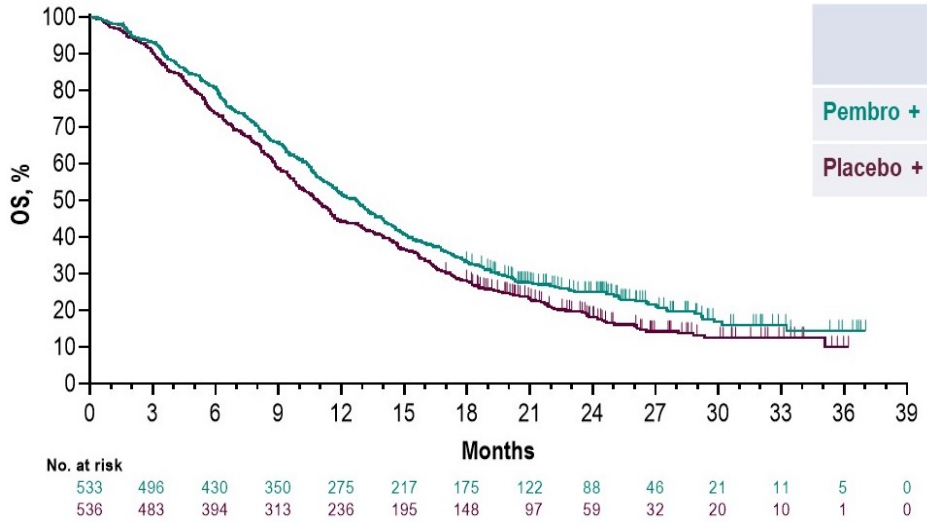
Do-Youn O et al, N Engl J Med Evidence June 2022

TOPAZ FOREST PLOT



Do-Youn O et al, N Engl J Med Evidence June 2022

KEYNOTE 966
Pembro+Gem+Cis vs GemCis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**

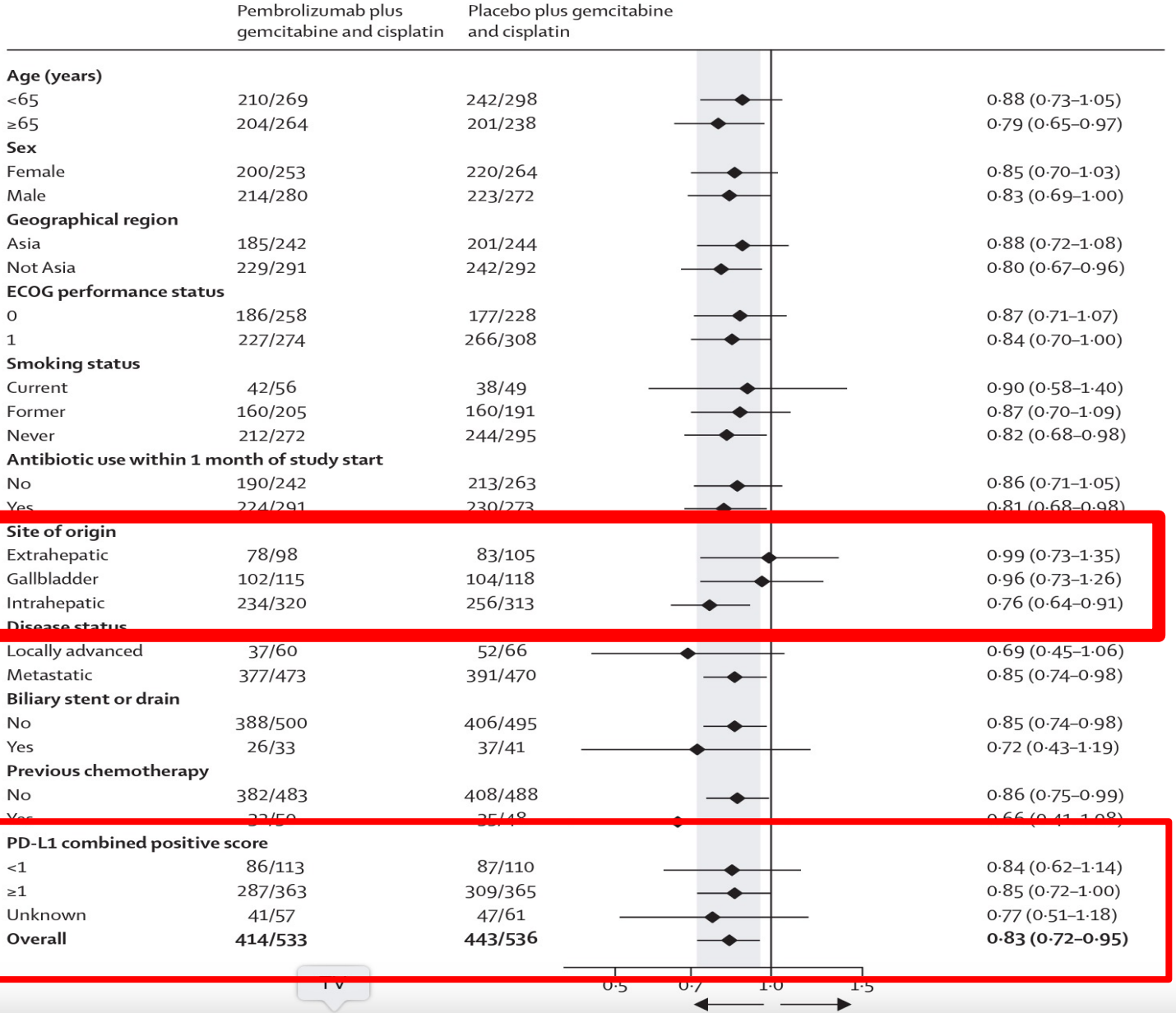
Below the signficance boundary of
P = 0.0200

- KEYNOTE-966 showed similar safety profiles between the pembrolizumab and placebo groups[1]
  - 70% of patients treated with pembrolizumab + gem/cis had grade 3 or 4 treatment-related adverse events vs 69% for placebo + gem/cis

[1]Kelley et al. Lancet 2023; 2023;S0140-6736(23)00727-4.

ORR: 29% vs 29%

KEYNOTE-966 FOREST PLOT



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Biliary Tract Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Durvalumab + gemcitabine + cisplatin (category 1)[d,e,f,4]

Other Recommended Regimens

- Gemcitabine + cisplatin (category 1)[5]
- FOLFOX
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel (category 2B)[1]
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)

GEM +CIS+ PEMBRO
Keynote 966 - ???

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[9]

Preferred Regimens

- FOLFOX[6]

Other Recommended Regimens

- FOLFIRI (category 2B)[7]
- Regorafenib (category 2B)[8]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[9]
- 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)[e,f,10]
- Lenvatinib + pembrolizumab (category 2B)[e,f,11]

Summary Metastatic Biliary Ca

- Clinical trials are paramount
- Tissue is the issue:
  - MSI/dMMR, HER 2 testing and NGS “routine” to direct therapy
    - IDH mutation, FGF fusions/re-arrengements,RET, NTRK, BRAF, HER-2. MSI-H, TMB, PD-LI(+)
- First-line Gem/DDP + Durvalumab or GEMDDP + Pembrolizumab
  - Gem/DDP+Nabpaclitaxel in selected pts?
- FOLFOX (is it really a second line standard in pts with no targetable mutations?)
  - 5FU + Nanoliposomal Irinotecan (?)

Thanks For The Attention!