Wake Forest®
School of Medicine

Pancreas and Biliary Cancers
Time to Overcome Challenges

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Wake Forest School of Medicine

Pancreas Cancer

RESECTABLE PDAC

Phase 3 trials

Trial	n	Treatment Arms	Primary endpoint	Results Survival in mos	HR
CONKO-001	368	Gemcitabine x observation	DFS	13.4 x 6.7 (median OS 22.8 x 20.2)	HR 0.76, p= 0.01
ESPAC-3	1088	5-FU x Gemcitabine	OS	23.0 x 23.6	HR 0.94, p=0.39
ESPAC-4	730	Gem/Capecitabine versus Gemcitabine	OS	28 x 25	HR 0.82 p=0·032
Prodige24-ACCORD	481	FOLFIRINOX x Gemcitabine	DFS OS	21.6 x 12.8 54.4 x 35	HR 0.58 p <0.001 HR 0.64 p =0.003

[1]Klinkenbijl JH et al Ann Surg 1999; [2]Neoptolemos JP et al N Engl J Med 2004;
[3]Neoptolemos JP et al JAMA 2010;
[4]Oettle H et al JAMA 2013; [5]Neoptolemos JP et al Lancet 2017

Adjuvant Therapy Pancreas Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy

- The CONKO-001 trial demonstrated significant improvements in disease-free survival (DFS) and overall survival (OS) with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.[1]
- ESPAC-3 study results showed no significant difference in OS between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.[2]
- Data from ESPAC-4 support the use of gemcitabine combined with capecitabine (1,660 mg/m^2/day days 1–21 every 4 weeks) with superiority demonstrated compared to gemcitabine alone (HR, 0.82; 95% CI, 0.68, 0.98; $P = .032$).[3]
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.[4]
- Recommended adjuvant therapy options apply to patients who did not receive prior neoadjuvant therapy. For those who received prior neoadjuvant therapy, the adjuvant therapy options are dependent on the response to neoadjuvant therapy and other clinical considerations.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Modified FOLFIRINOX (category 1)[a] • Gemcitabine + capecitabine (category 1)	• Gemcitabine (category 1) • 5-FU + leucovorin (category 1) • Continuous infusion 5-FU • Capecitabine (category 2B) • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] • Induction chemotherapy (gemcitabine, 5-FU + leucovorin, or continuous infusion 5-FU) followed by chemoradiation[b,c] followed by subsequent chemotherapy:[4] ▸ Gemcitabine followed by chemoradiation[b,c] followed by gemcitabine ▸ Bolus 5-FU + leucovorin followed by chemoradiation[b,c] followed by bolus 5-FU + leucovorin ▸ Continuous infusion 5-FU followed by chemoradiation[b,c] followed by continuous infusion 5-FU	• None

[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.

NEOADJUVANT THERAPY

Background

Study	Randomization	Resectablitiy	# Patients	OS in months	Other Endpoints
PREOPERATIVE					
PREOPANC-1 Versteijne E JCO38:1763,2020	G+XRT-S S- G	Resectable or borderline resectable	119 x 127	16 (N) x 14.3 (S) (HR 0.78. p=0.096)	R0 71% (N) x 40% (S) (p<.001)
Preop-02/JSA 05 JCO 37 S4;A189, 2019	GS1 x 2-S –GS1 x 6 S- GS1 x 6	Resectable	182 x 180	36.7 (9N) x 26.6(S) HR 0.72 p=0.015	No reported change in resection rates

NCCN Guidelines Accessed on 04/14/2023

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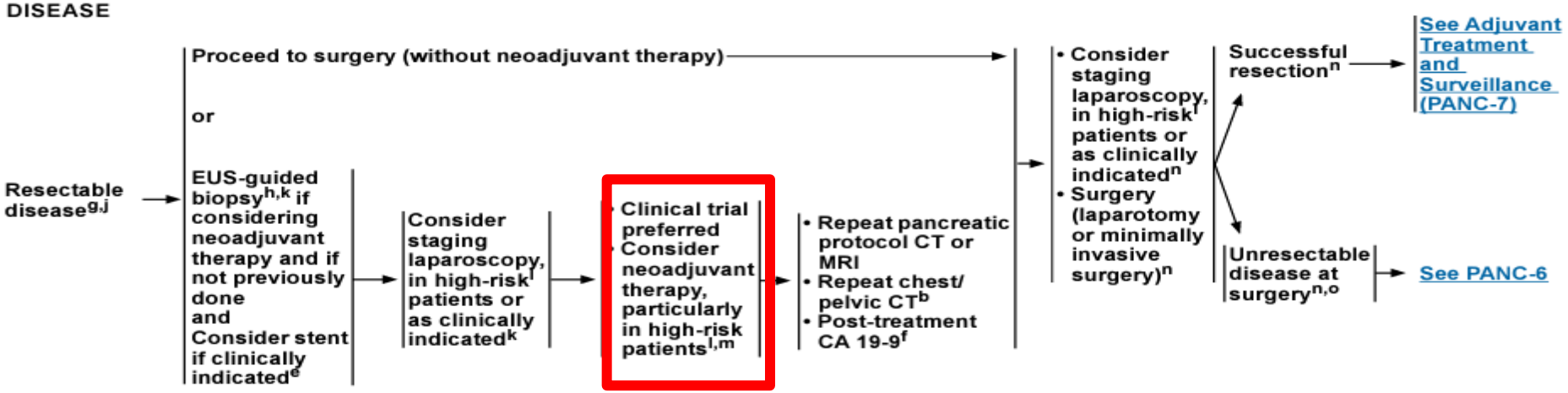

[k] High-risk features include imaging findings, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain.

[m] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation.

NCCN Guidelines Accessed on 04/14/2023

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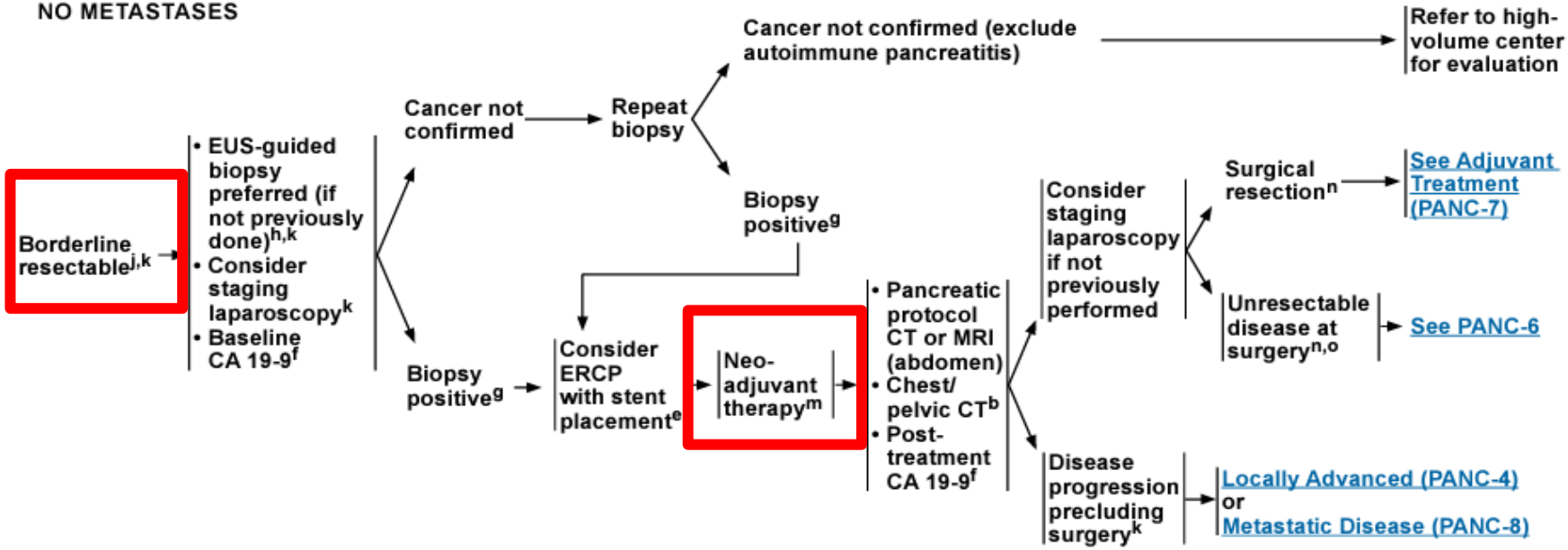
BORDERLINE RESECTABLE DISEASE NO METASTASES

TREATMENT



[m] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Systemic Therapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles of Radiation Therapy (PANC-G). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.

We Have Made Progress in the 1st-Line 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.

NCCN Guidelines Since 2019

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

BRCA1/2 Mutations in Pancreatic Cancer

- Germline *BRCA1* or *BRCA2* mutation observed in 5-7%

- **More importantly, up to 40% of patients who are germline *BRCA1/2* gene mutation positive do NOT have a family history**

Chaffee KG et al. Genet Med. 2018;20:119-127; Petersen GM et al. Semin Oncol. 2016;43:548-553

DNA damage response and repair (DDR) Genes in Pancreas Ca

- 17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes
  - *BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51…*

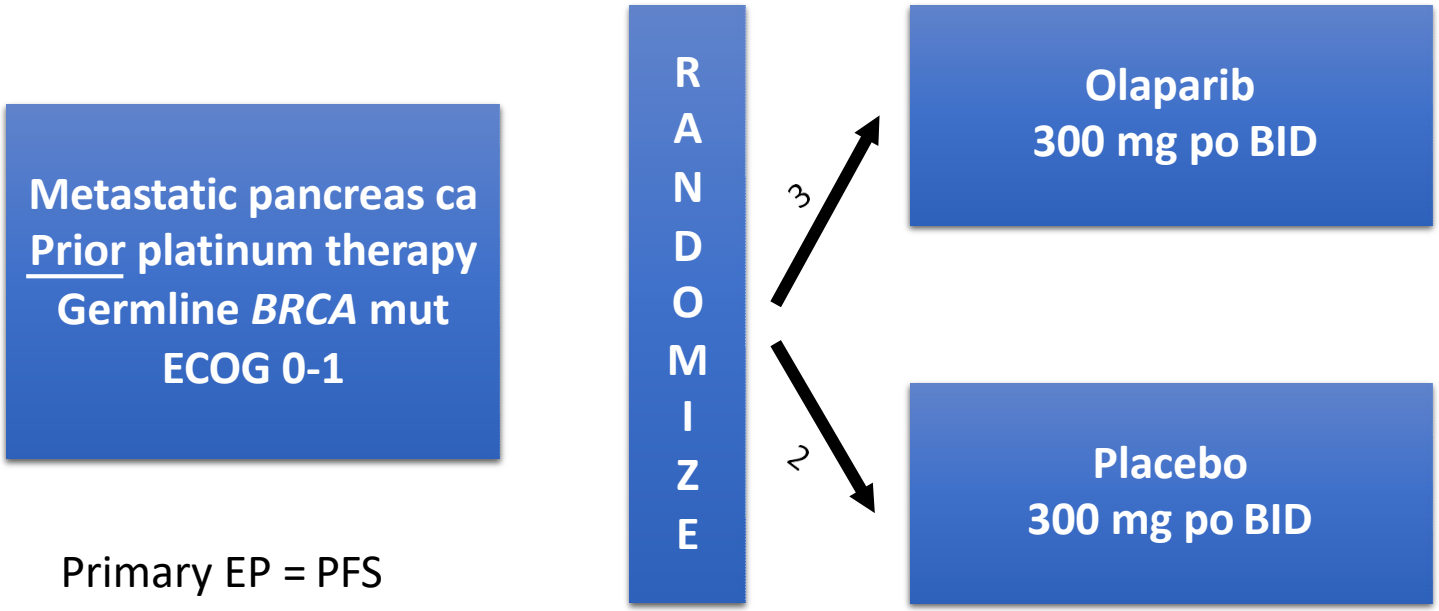
Pishvaian, et al, Clinical Cancer Research, 2018; Heeke, et al, JCO Precision Oncology, 2018;

DDR genes and Treatment Selection in Pancreas Cancer

- DDR mutated Met Pancreas Ca, platinum-based chemo may improve outcomes (RR, PFS, and OS)

Pishvaian, et al, JCO Precision Oncology, October, 2019

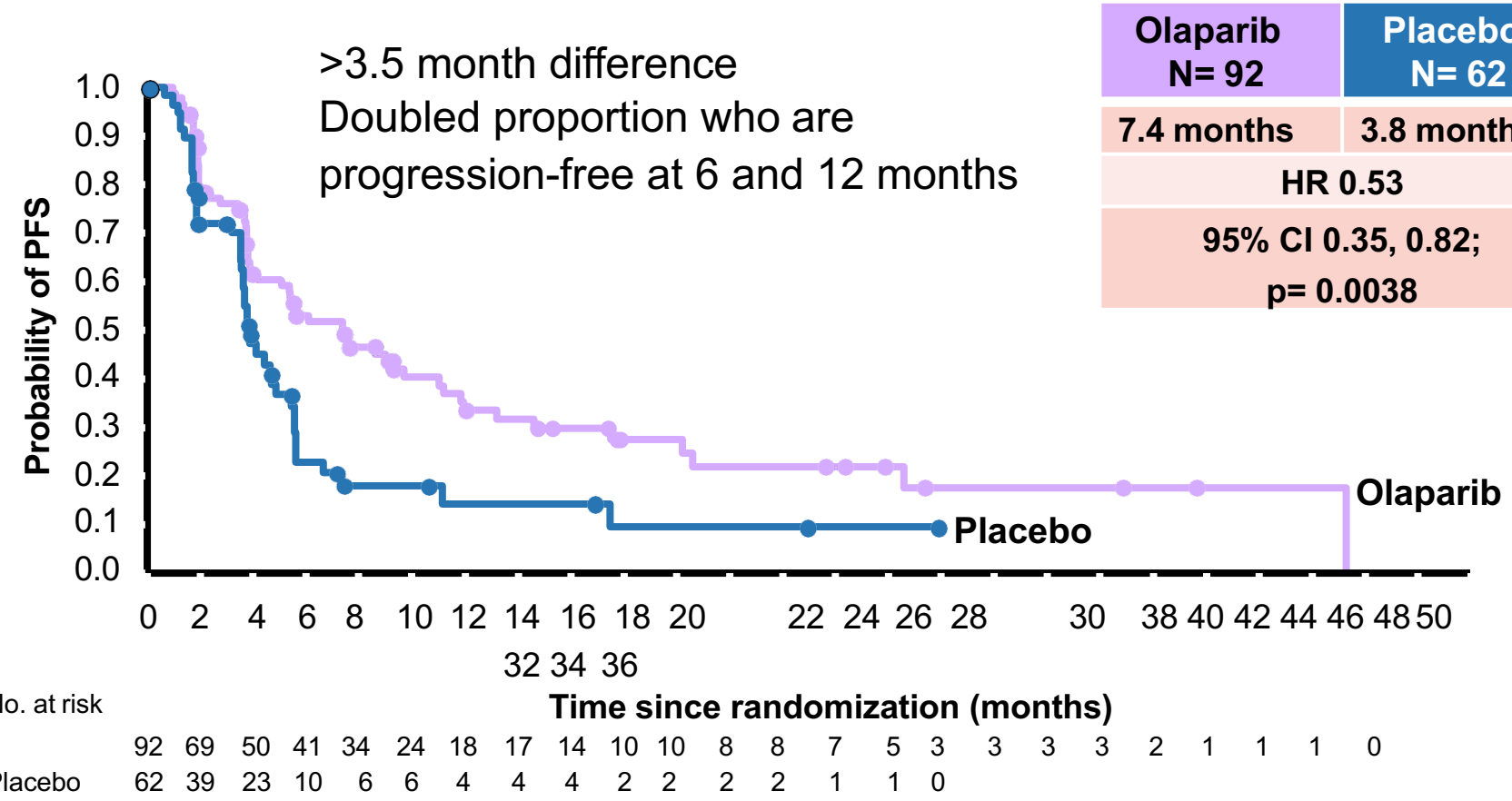
POLO: Phase 3 international PARPi maintenance study in gBRCA mutated patients



Primary EP = PFS
N = 145

NCT02184195

Primary Endpoint: Blinded Central Review

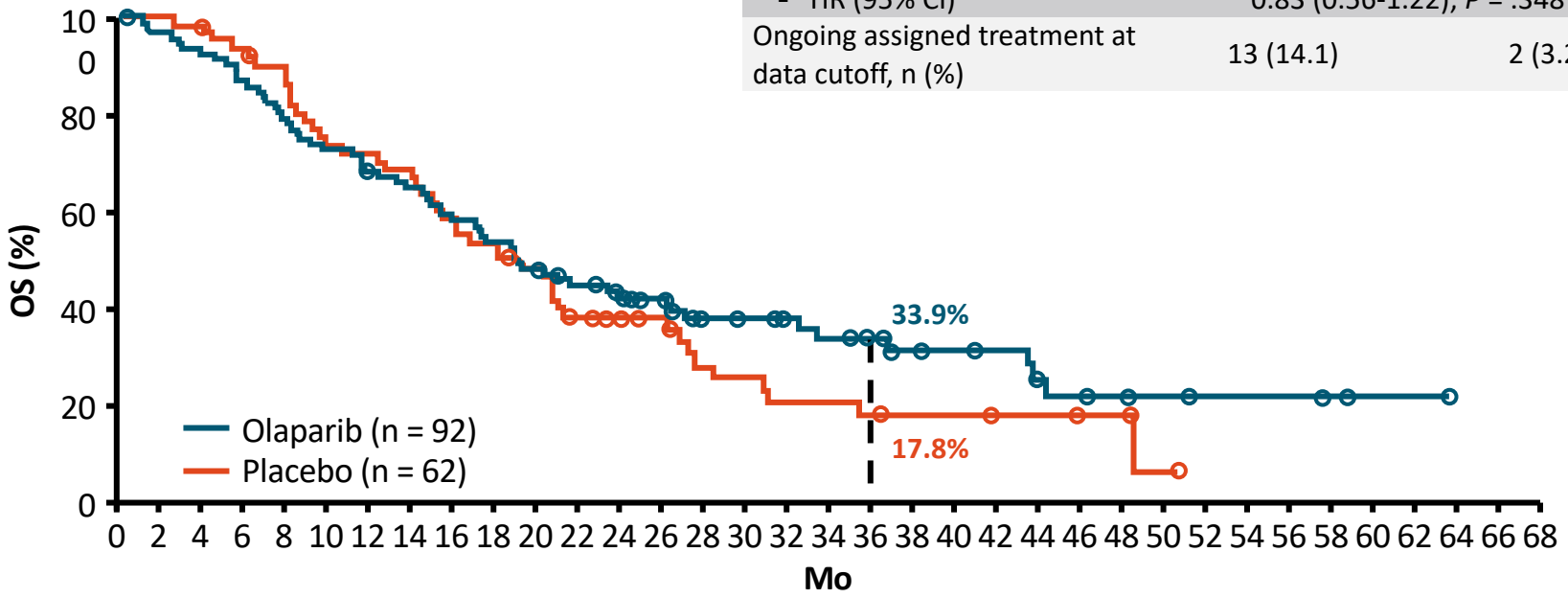


Olaparib N= 92	Placebo N= 62
7.4 months	3.8 months
HR 0.53	
95% CI 0.35, 0.82; p= 0.0038	

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)



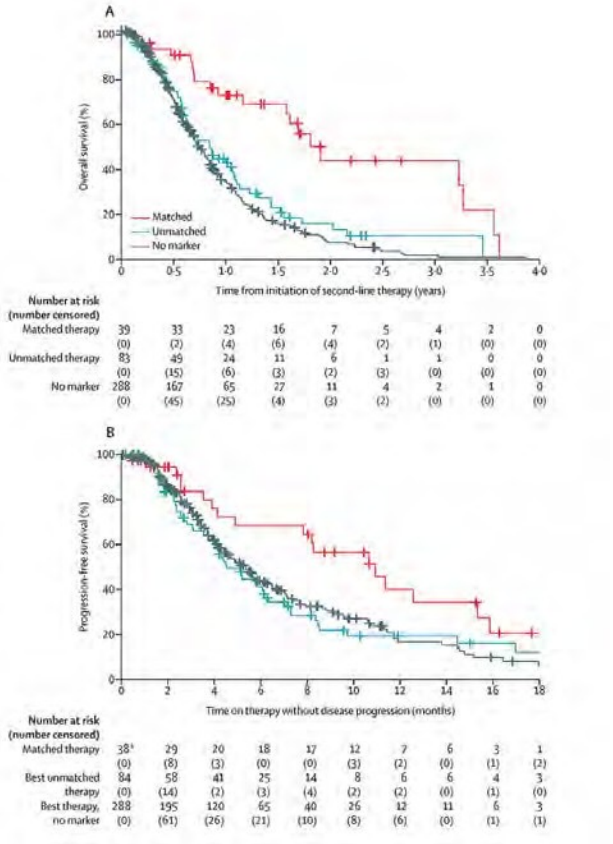
Golan. ASCO GI 2021. Abstr 378.

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

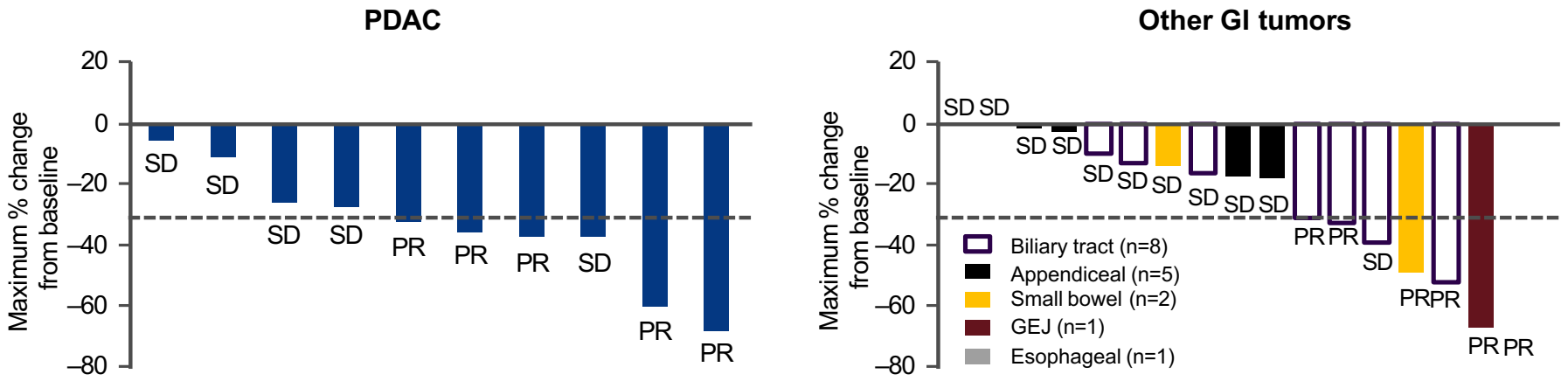
Pishvaian et al., Lancet Oncol 2020

NTRK, NRG (Neuregulin) 1, RET Fusions, BRAF mutation

- Entrectinib: case reports in patients with NTRK and ROS fusion
  - Pishvaian, et al, JCO-PO, 2018
- Pan-HER inbitors (afatinib) and HER2-3 inhibitors (seribantumab or zenocutuzumab) NRG 1 Fusions. Responses in case reports
  - Jones MR, et al. Clin Cancer Res 2019;25:4674–81
- RAF alterations 2.2% (84 of 3,781) in large retrospective series.
  - BRAF/MEK/ERK inhibitors active in V600 subgroup, fusions, and Exon 11 mutations
    - Hadifar a, et al JCO PO no. 5 (2021) 1325
- Pralsetinib (BLU-667) RET fusion-positive tumors.
  - Subbiah V, et al,, J Clin Oncol 39, 2021 (suppl 3; abstr 467)

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

KRAS G12D

- MRTX 1133 shows promise in targeting and inhibiting KRAS G12D activation
  - Trials Underway

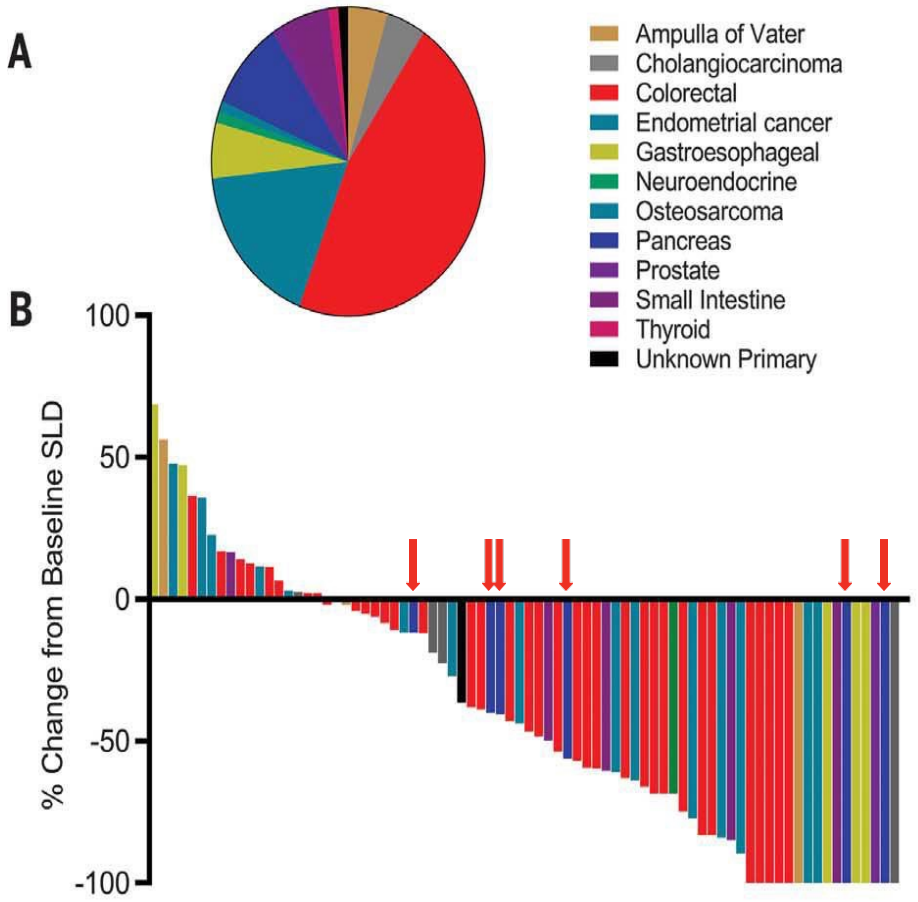
- Agents under development targeting G12R, G12V, G12A, G12S, G13D

Wang et al., J Med Chemistry 2022

IMMUNOTHERAPY

Checkpoint Inhibitors

- Pembrolizumab in MSI-high disease
- Response or SD in 6 out of 6 patients



Le DT, et al. Science 2017; 357: 409-413

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/metasatatic patients that are candidates to received systemic therapy
- Targeting actionable mutations may lead to significant benefit (including survival and QOL benefits)

Biliary Cancer

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

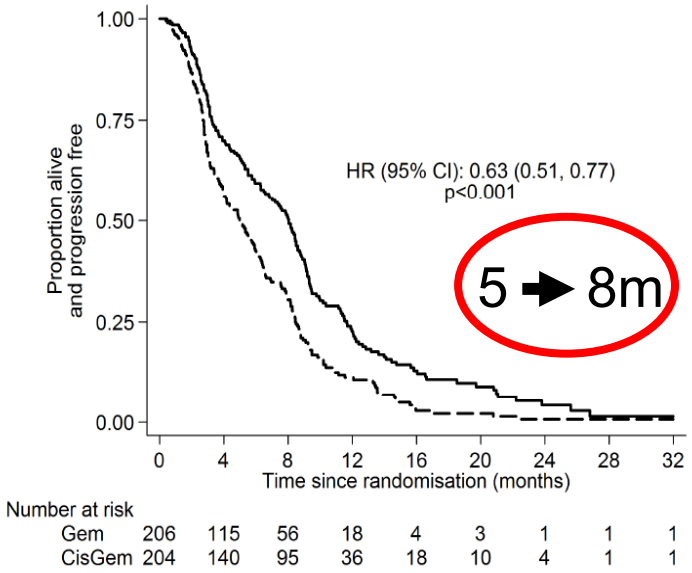
Inclusion criteria:

- 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

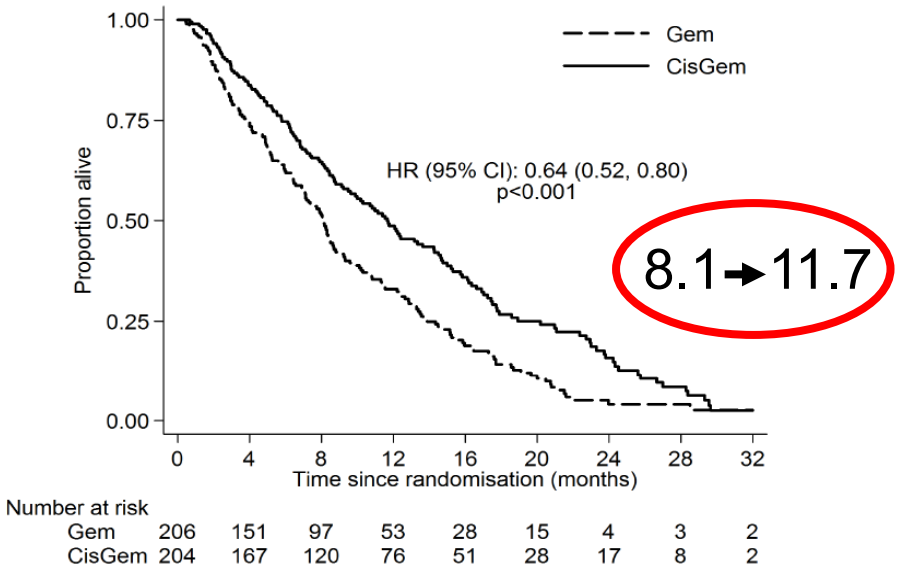
[a] Including 86 patients in ABC-01.
[b] Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)

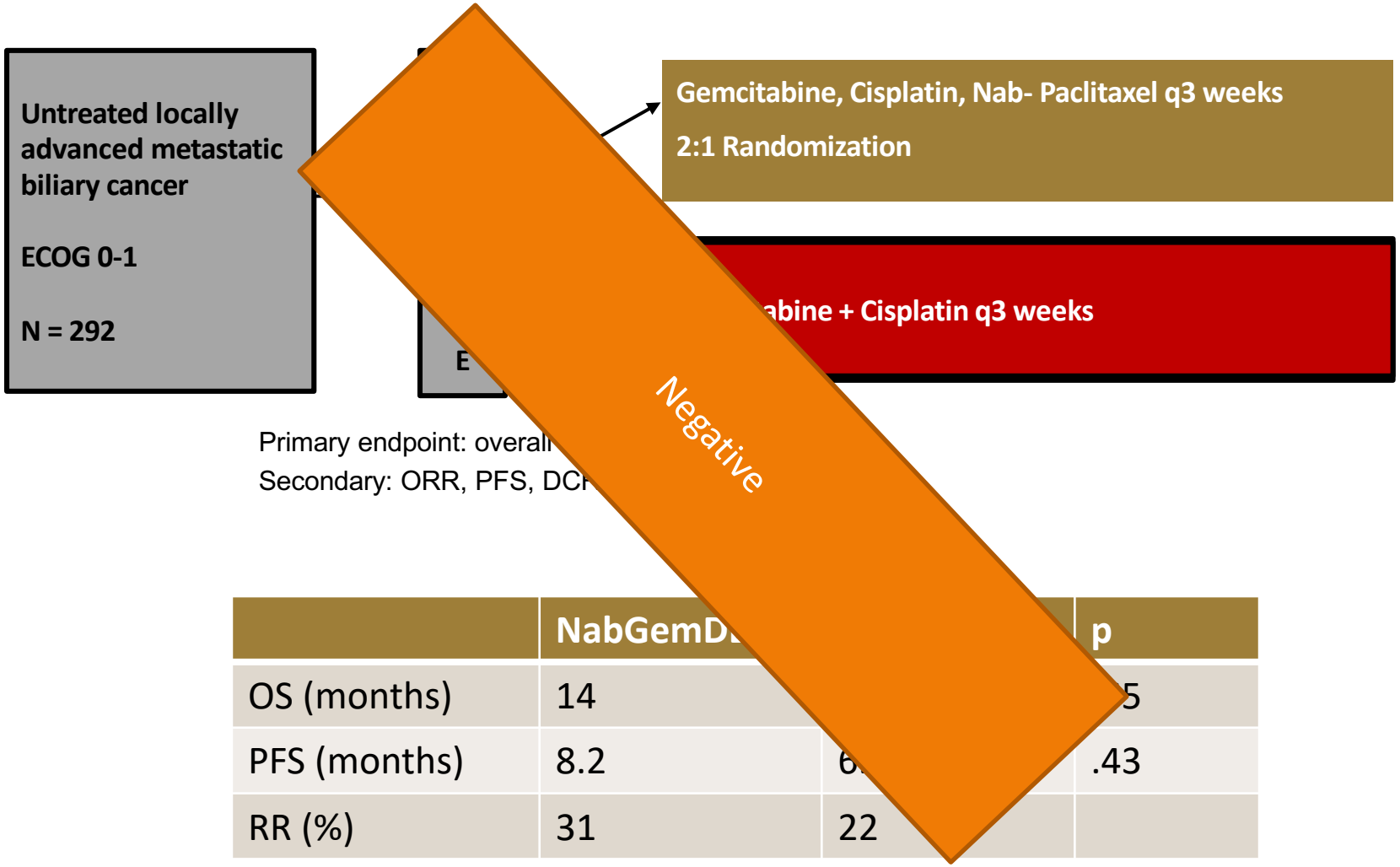


Overall Survival (ITT)



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

Phase 3 SWOG 1815



	NabGemD		p
OS (months)	14		5
PFS (months)	8.2	6.	.43
RR (%)	31	22	

Shroff R et al: LBA490, ASCO GI 2023

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

Oh D-Y et al NEJM Evid. June 1, 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	
Survival 24 months %	24.9	10.4	

Oh D-Y et al NEJM Evid. June 1, 2022

TOPAZ-1 Toxicity

- No clear additional Non-immune Toxicity
- Immune mediated toxicity G 3 or G4 were infrequent;
  - Pneumonitis (0.3%), Dermatitis (.9%), hepatic (0.6 %).

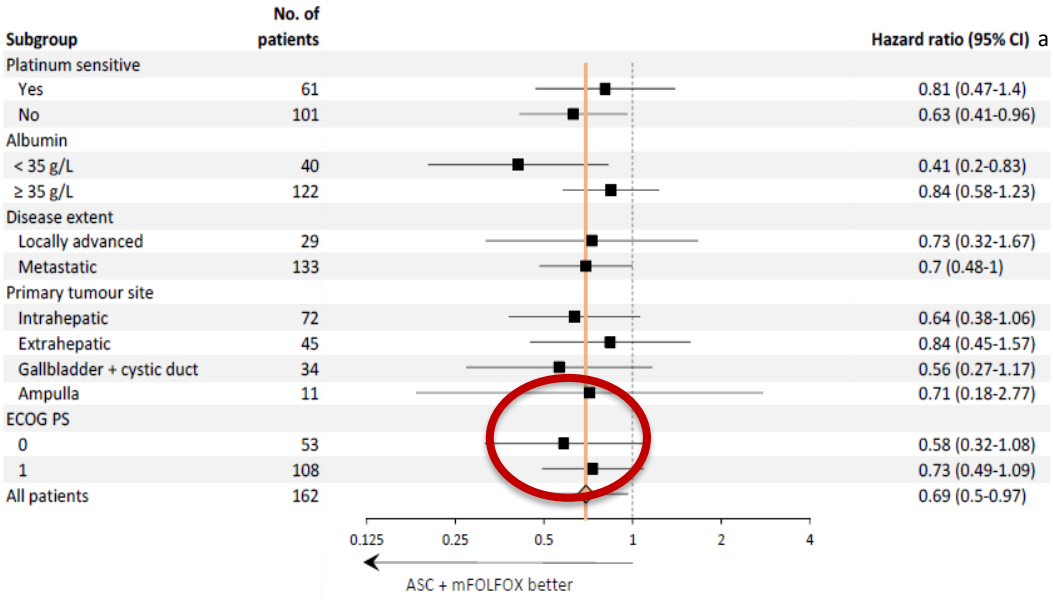
Oh D-Y et al NEJM Evid. June 1, 2022

Second Line

ABC-06: Active Symptom Control ± mFOLFOX

- ASC ± mFOLFOX in ABC after prior gemcitabine/cisplatin therapy
- 162 patients were randomized (1:1)
  - 44% intrahepatic, 28% extrahepatic, 21% gallbladder, and 7% ampullary
- Median OS: 5.3 mo ASC vs. 6.2 mo combo (adjusted HR 0.69 [95% CI 0.50-0.97]; *P* = 0.031)
  - 6-month survival rate: 35.5% vs 50.6%
  - 12-month survival rate: 11.4% vs 25.9%
- Grade 3/4 toxicities were reported in 32 (39%) and 48 (59%) patients in the ASC alone and combination groups, respectively

Supgroup Analyses All Favor the Combination Over ASC Alone

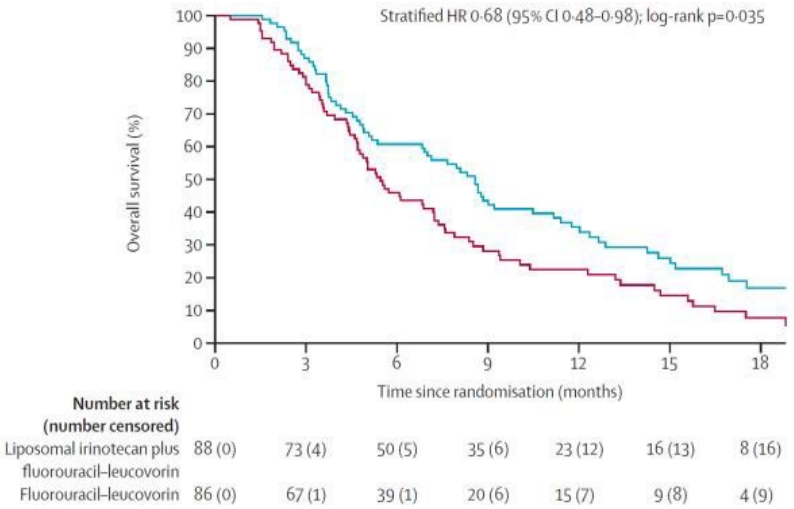


[a] HRs are adjusted for platinum sensitivity, albumin and stage.

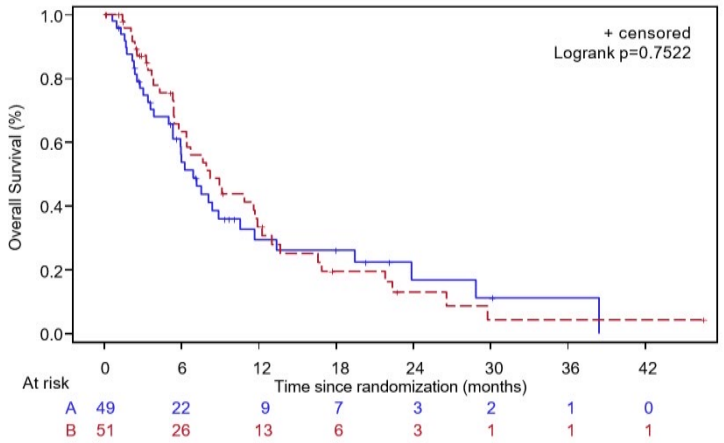
ASC, active symptom control.

Lamarca A, et al. *J Clin Oncol* 2019;37,(suppl; abstr 4003).

Liposomal Irinotecan + 5FU



Yoo et al. The Lancet Oncology 22, 1560



Vogel et al. ESMO 2022, Abstr. 53

Targets

- Specific
  - IDH-1 mutations
  - FGFR2 fusions
  - BRAF
  - Her-2
- Tumor agnostic
  - NTRK fusions
  - MMR-deficiency

IDH-1

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%

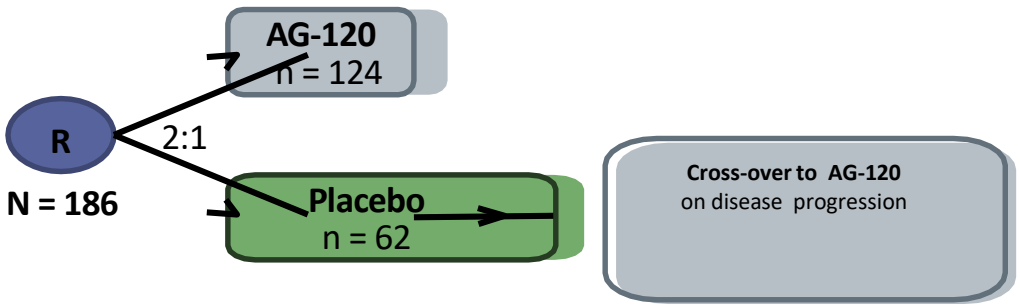
12-month PFS: 21.8%

RR 5% (4 PRs)

OS: 13.8 m

Phase 3 Study (ClarIDHy)

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



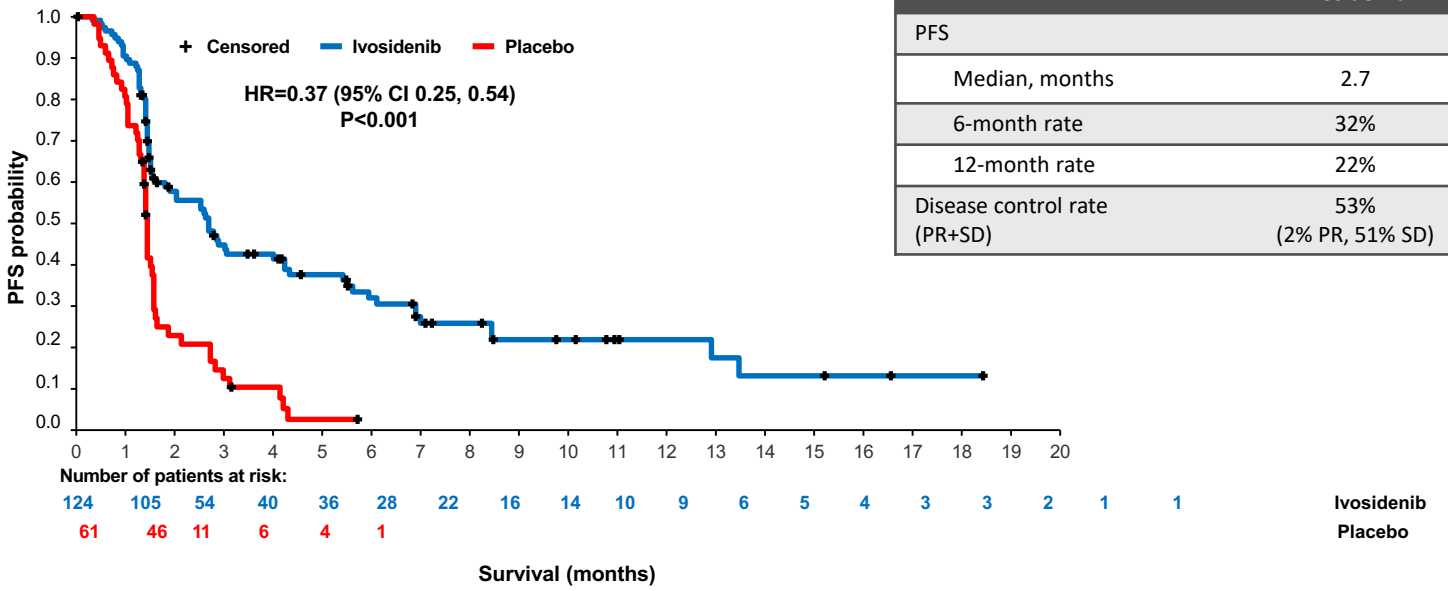
AG-120 is a first-in-class, potent, oral inhibitor of the mutant IDH1 enzyme

IDH1 Mutations

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

Abou-Alfa, GK. Lancet Oncol, 2020

ClarIDHy: PFS by IRC



	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 Fusions

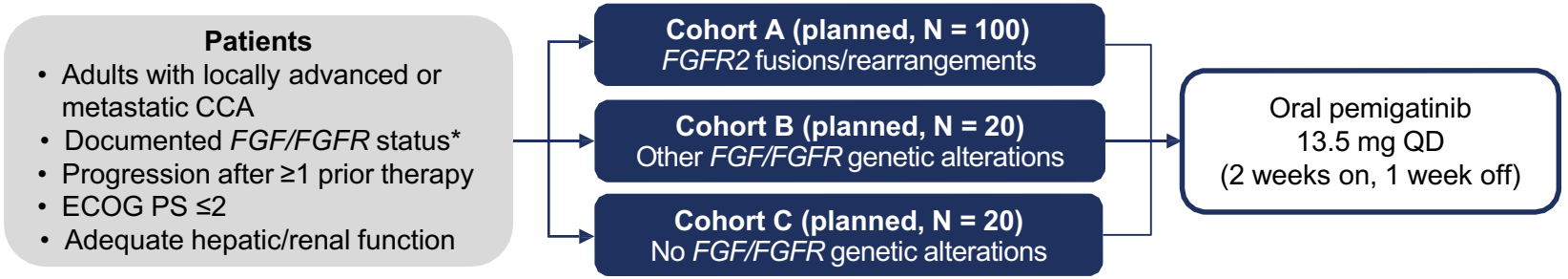
  At the time of initial diagnosis, CA19-9 was < 35U/mL in 42.6% of pts.

  Bone metastases were observed in 41 (30.6%) pts with advanced disease

Goyal et al ASCO 2020

FIGHT-202 STUDY DESIGN

- Phase 2 open-label, single-arm study evaluating the efficacy and safety of pemigatinib in patients with previously treated locally advanced or metastatic CCA (NCT02924376)
  - Sites opened in the United States, Europe, Middle East, and Asia



FGFR2

- Physiologic roles: cell proliferation, differentiation, migration, angiogenesis
- Approx. 10-15% IHCCA
- FGFR fusions: ligand independent activation of FGFR

Abou-Alfa, GK. Lancet Oncol, 2020

RESULTS

- 56 unique *FGFR2* fusion genes were observed in cohort A (*FGFR2* fusions or rearrangements).
- In cohort A, pemigatinib treatment resulted in
  - ORR of 35.5% with durable responses
  - Median PFS of 6.9 months
- A phase 3 study is ongoing in the first-line setting to evaluate pemigatinib versus gemcitabine plus cisplatin in patients with CCA and *FGFR2* fusions or rearrangements (NCT03656536)

Phase II study of infigratinib cholangio *FGFR2* gene fusion/rearrangement

- 108 pts advanced/metastatic CCA post ≥1 line of systemic therapy
- Infigratinib 125 mg orally for 21 days of each 28-day cycle
  - ORR 23.1% (1 CR/24PRs). DOR 5 months
  - TEAEs any grade: hyperphosphatemia (76.9%), eye disorders (67.6%), stomatitis (54.6%), and fatigue (39.8%).
  - A phase III infigratinib versus gem/DDP is ongoing in the front-line setting

Javie M: JCO 2021, 39(suppl 3):265

Other FGFR Inhibitors in Development

- **Futibatinib (TAS-120): i**rreversible FGFR1–4 inhibitor
  - RR 41.7% (FGFR2 fusion)
  - Duration of response 9.7 months AND mPFS was 9.0 months
- **Derazantinib; ARQ 087**
  - RR 20.7%
- **ICP-192 (gunagratinib)**
  - Preclinical studies demonstrated potential to overcome resistance to first generation agents

Goyal et al, AACR 2021 DOI: 10.1158/1538-7445

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**
  - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
  - RR 23 %

- **Zanidatamab – HER-2 bispecific antibody**
  - 20 patients (11 gallbladder cancers, 5 intra- and 4 extra-hepatic cholangiocarcinoma)
  - RR 47%; median duration of response 6.6 months

- **Neratinib, a pan-HER irreversible tyrosine kinase inhibitor**
  - 25 pts with activating somatic HER2 mutations (GB 40%, ICC24%, EHCC20%, AV 16%)
  - RR 12% and PFS 2.8 months

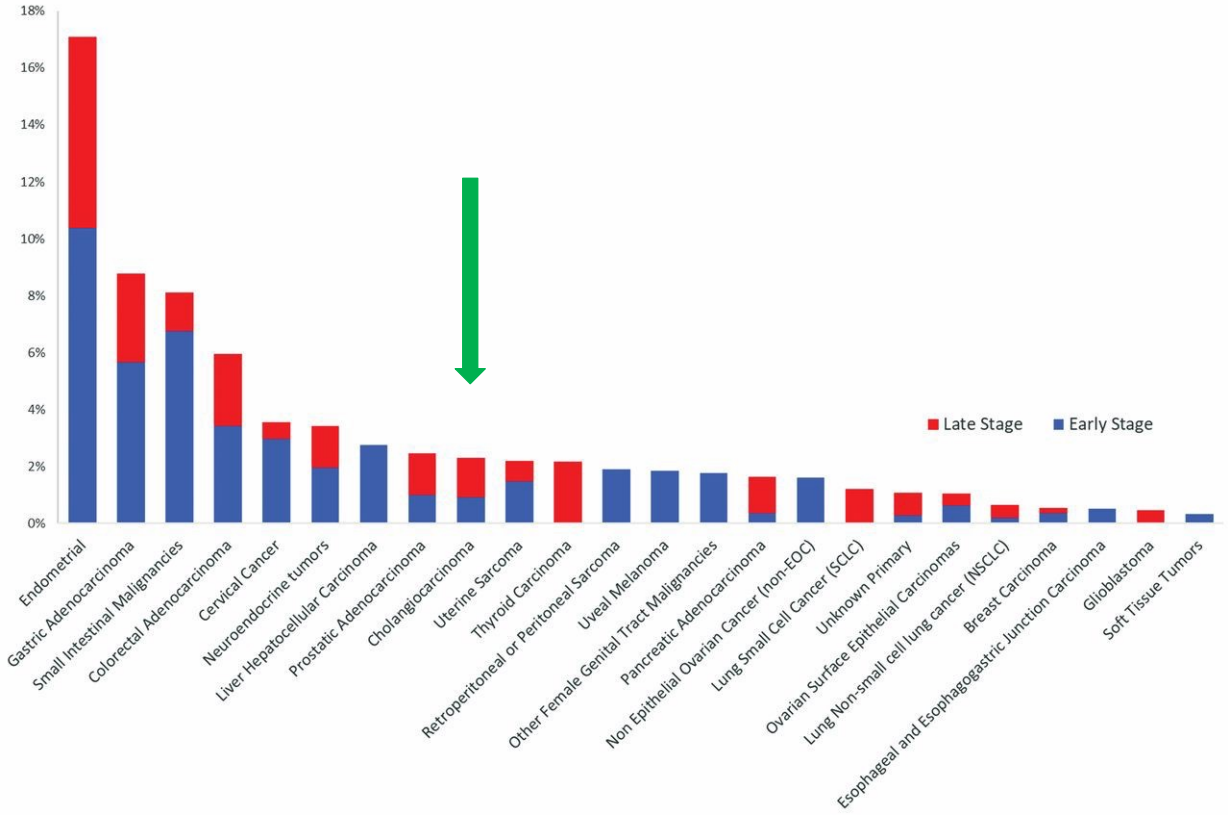
Javle Lancet Oncol 2021
Meric-Bernstam ASCO GI 2021
Harding et al ASCO GI 2021

Targeting HER-2

- Trastuzumab deruxtecan
- 30 pts recurrent or unresectable: 22 HER2+(10 IHC 3+ and 12 IHC 2+) and 8 HER2-low (6 IHC 2+ and 2 IHC1+)
- RR 36.4% and 12.5%. PFS 5.1 and 3.2 months
- DOR in Her 2 +: 7.4 months
- ILD: ≥ Grade 3 12.5%

Ohba A et al: A 4006, ASCO 2022

MSI-High Frequency: Multiple Cancers



Le, D et al. Science, 2017

Immune Biomarkers in Biliary Cancers

- MMR deficiency
  - KEYNOTE-16: Biliary tract cancers; RR 53%, 21% CR
  - KEYNOTE-158: Cholangiocarcinoma RR 37% (N= 9)
- Tumor mutation burden (TMB)
  - >10 mutations/Mb 3.5- 5.5% - highest in gallbladder cancer

Le, DT. NEJM, 2015. Silva, VW. CCO, 2016. Lee, H. Ther Adv Gastroenterol, 2017. Diaz, L. ESMO, 2017, Abstr 386P

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2022
Biliary Tract Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,e,5]

Other Recommended Regimens

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

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[12]
  - Selpercatinib for CCA (category 2B)[13]

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

Preferred Regimens

- FOLFOX[14]

Other Recommended Regimens

- FOLFIRI[15] (category 2B)
- Regorafenib[16] (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[17]
- Durvalumab + gemcitabine + cisplatin (category 2B)[e,h,5]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[e,h,i,18,19] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,20]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[21,22]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[23]
  - Infigratinib[24]
  - Futibatinib[25]
- For CCA with *IDH1* mutations
  - Ivosidenib[26,27]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[13]
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[28]
- Nivolumab[e,h,29] (category 2B)
- Lenvatinib + pembrolizumab[e,h,30] (category 2B)

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[h] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[j] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References
Continued

Thanks for the attention!
Questions???