



Wake Forest[®]
School of Medicine

Biliary, HCC, and Pancreatic Cancers : Moving the Bar Up

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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 22.8x 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	21.6 x 12.8	HR 0.58 p <0.001
			OS	54.4 x 35	HR 0.64 p =0.003

¹Klinkenbijl JH et al Ann Surg 1999; ²Neoptolemos JP et al N Engl J Med 2004;

³Neoptolemos JP et al JAMA 2010;

⁴Oettle H et al JAMA 2013; ⁵Neoptolemos JP et al Lancet 2017

Adjuvant Therapy Pancreas Cancer



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NCCN Guidelines Version 1.2021 Pancreatic Adenocarcinoma

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PRINCIPLES OF SYSTEMIC THERAPY

Adjuvant Therapy

- The CONKO 001 trial demonstrated significant improvements in DFS and 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/m²/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

Preferred Regimens

- Modified FOLFIRINOX (category 1)^a
- Gemcitabine + capecitabine (category 1)

Other Recommended Regimens

- 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

Useful in Certain Circumstances

- None

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

NEOADJUVANT THERAPY

Background

Study	Randomization	Resectability	# Patients	OS in months	Other Endpoints
PREOPERATIVE					
PREOPANC-1 Versteijne E JCO Jan, 2022	G+XRT-S S- G	Resectable or borderline resectable	119 x 127	15.7 (N) x 14.3 (S) (HR 0.78. p=0.025)	R0 71% (N) x 40% (S) (p<.001) 5 year: 20.5% x 6.5%
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 06/19/2022

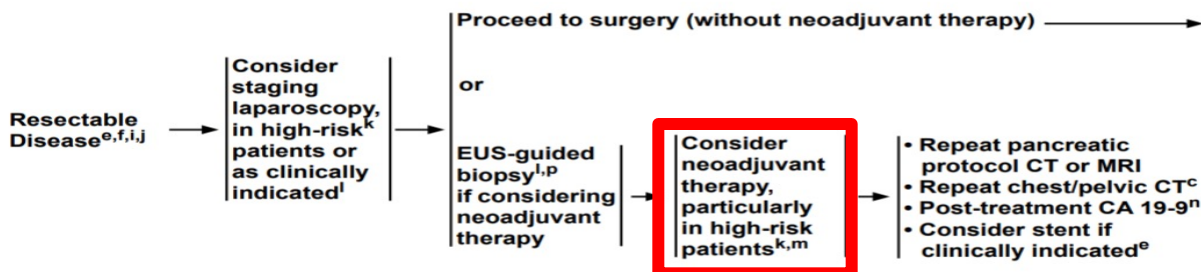


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NCCN Guidelines Version 1.2020 Pancreatic Adenocarcinoma

RESECTABLE DISEASE

TREATMENT



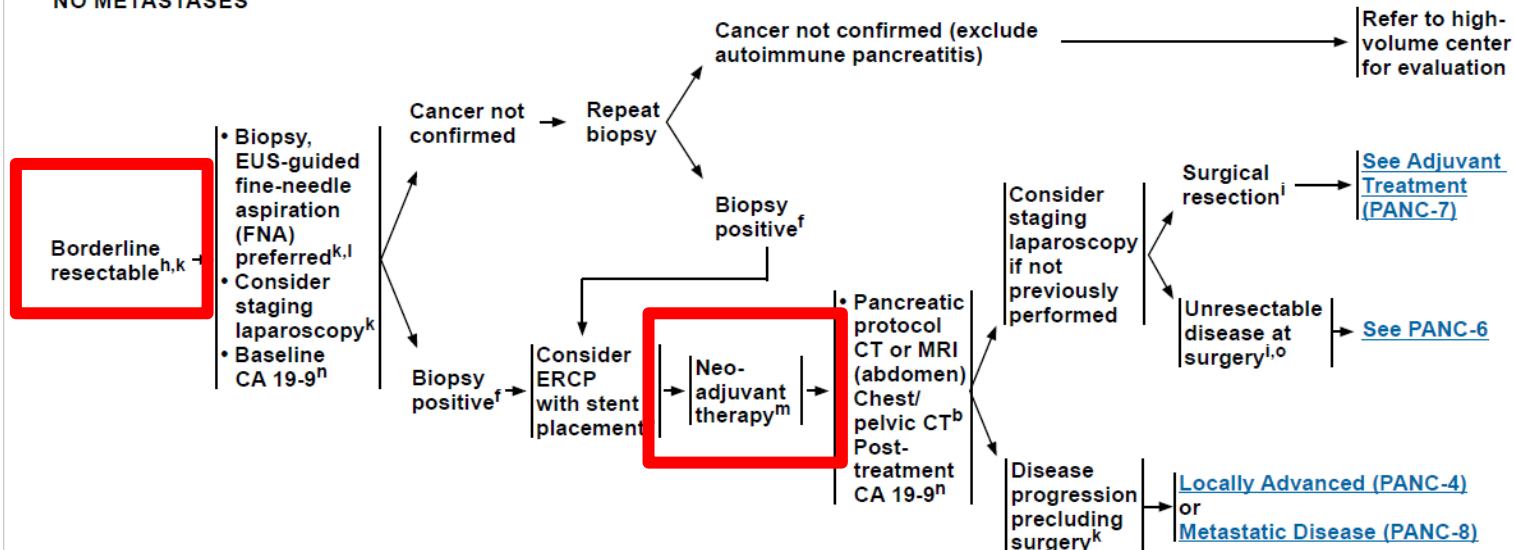
^k High-risk features include imaging findings, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain.

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



**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.

Ongoing Neoadjuvant Trials

Trial	Population	Treatment	Primary endpoint	Identifier
NorPACT-1 ¹⁵	Resectable	Neoadjuvant FOLFIRINOX vs adjuvant FOLFIRINOX	18-mo OS	NCT02919787
PANACHE01-PRODIGE48 ¹⁶	Resectable	Neoadjuvant FOLFIRINOX or FOLFOX vs adjuvant FOLFIRINOX	12-mo OS	NCT02959879
Alliance A021806	Resectable	Neoadjuvant FOLFIRINOX/adjuvant FOLFOX vs adjuvant FOLFIRINOX	OS	NCT04340141
PREOPANC-3	Resectable	Neoadjuvant FOLFIRINOX/adjuvant FOLFIRINOX vs adjuvant FOLFIRINOX	OS	NCT04927780
PREOPANC-2 ¹⁷	Resectable Borderline resectable	Neoadjuvant FOLFIRINOX vs gemcitabine/CRT and adjuvant gemcitabine	OS	EudraCT: 2017-002036-17
PRIMUS002 ¹⁸	Resectable Borderline resectable	Neoadjuvant FOLFOX/nab-paclitaxel vs neoadjuvant Gem/nabP	TTP	NCT04176952
SOFT	Resectable Borderline resectable Locally advanced	Neoadjuvant chemotherapy and CRT vs neoadjuvant chemotherapy and SBRT	pN-positive status	NCT03704662
PANDAS-PRODIGE 44	Borderline resectable	Neoadjuvant FOLFIRINOX/adjuvant gemcitabine or 5-FU vs neoadjuvant FOLFIRINOX plus CRT/adjuvant gemcitabine or 5-FU	R0 resection	NCT02676349
MASTERPLAN ¹⁹	Borderline resectable Locally advanced	Neoadjuvant FOLFIRINOX vs neoadjuvant FOLFIRINOX plus SBRT	Locoregional control	NCT04089150

TAKE HOME MESSAGES

- Neoadjuvant treatment in resectable pancreas cancer is an attractive option for many patients
- Neoadjuvant treatment should be considered for borderline resectable tumors.
- Alliance 021806 and other ongoing trials will address the role of FOLFIRINOX in the neoadjuvant setting

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;

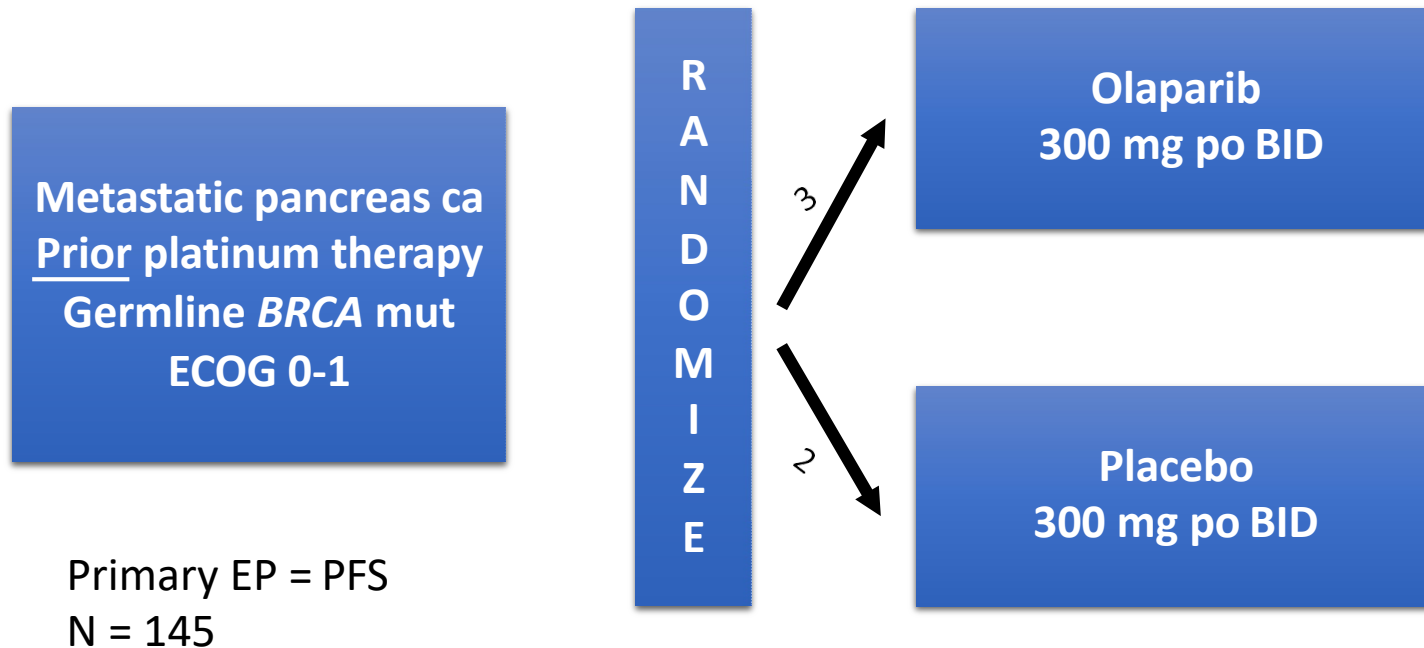
2. Burris HA, et al. J Clin Oncol 1997;15:2403;

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;

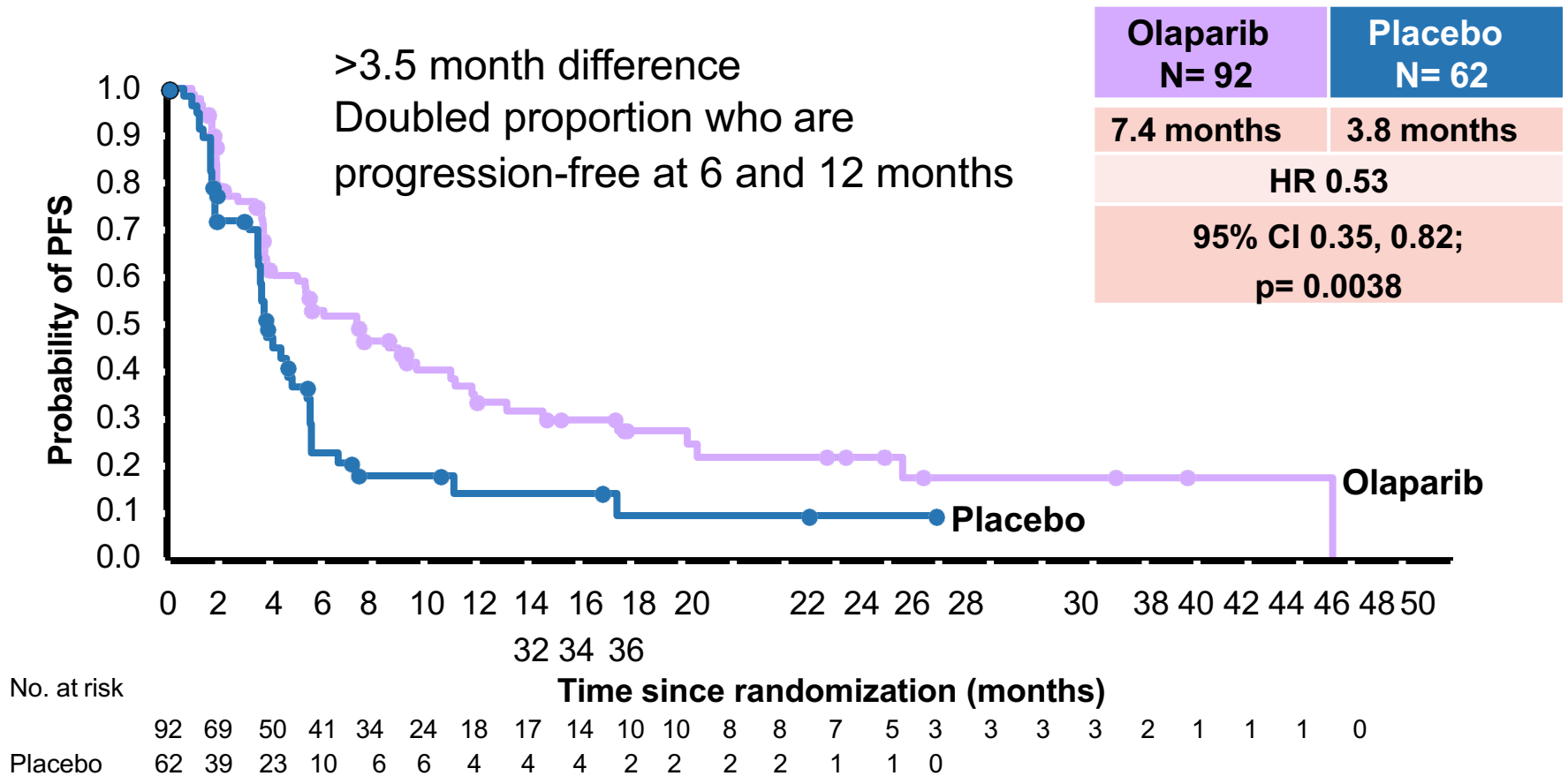
6. Von Hoff DD, et al. N Engl J Med 2013;369:1691.

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

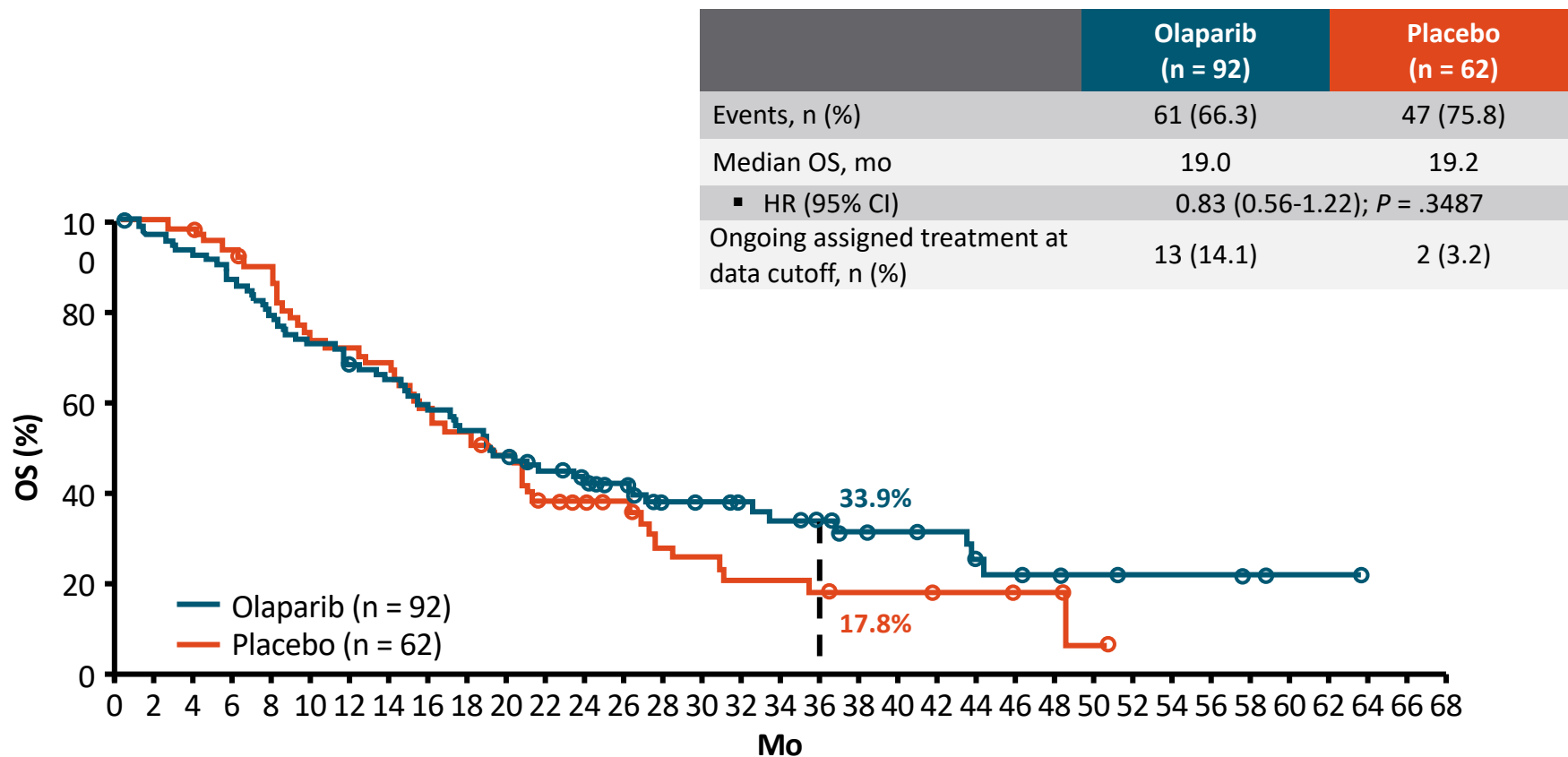


NCT02184195

Primary Endpoint: Blinded Central Review



POLO: Final OS



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:

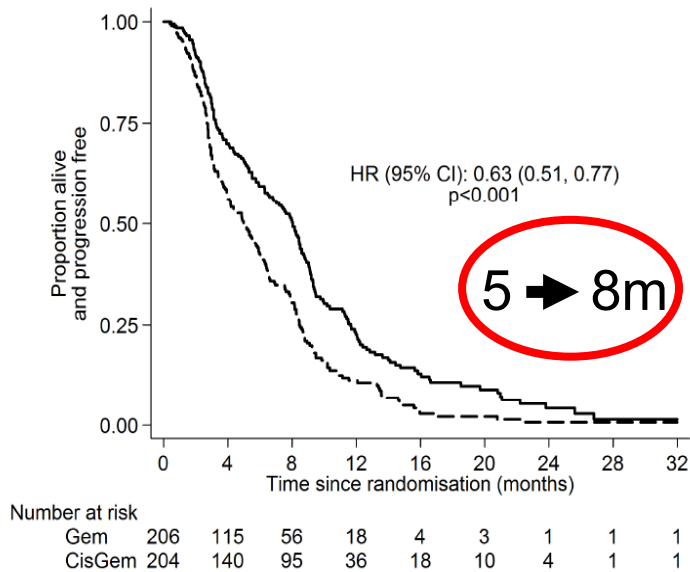
- Histologically / cytologically verified, non-resectable or recurrent/metastatic CCC, GB, or ampullary carcinoma
- Adequate biliary drainage, no uncontrolled infection
- ECOG PS 0-2
- LFTs: bilirubin $\leq 1.5 \times \text{ULN}$, ALT/ AST/ alk phos $\leq 3 \times \text{ULN}$ (≤ 5 if liver metastases)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

^a Including 86 patients in ABC-01.

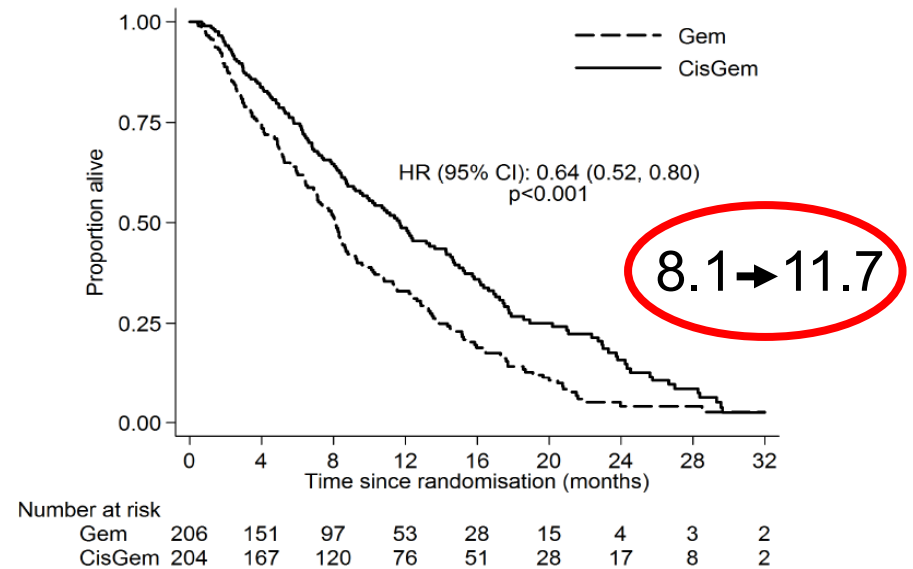
^b Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med.* 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)



Overall Survival (ITT)



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

ABC-02 Conclusions

- Cisplatin and gemcitabine for advanced biliary cancer significantly improved overall survival (by 3.6 m)
- Reduced risk of death by 36% (HR 0.64, $P < 0.001$)
- Significantly improved progression-free survival and tumour control
- CisGem is recommended as a standard of care and the backbone for future studies

Gemcitabine/DDP/Nab-paclitaxel

GCN regimen

Gem/Cis/nab-paclitaxel¹

[NCT02392637]

USA (MDA and Mayo)

Single-arm, phase 2

N =61

Schedule | gemcitabine 800mg/m² + cisplatin 25 mg/m² + nab-paclitaxel 100 mg/m²; D1,8 q21d

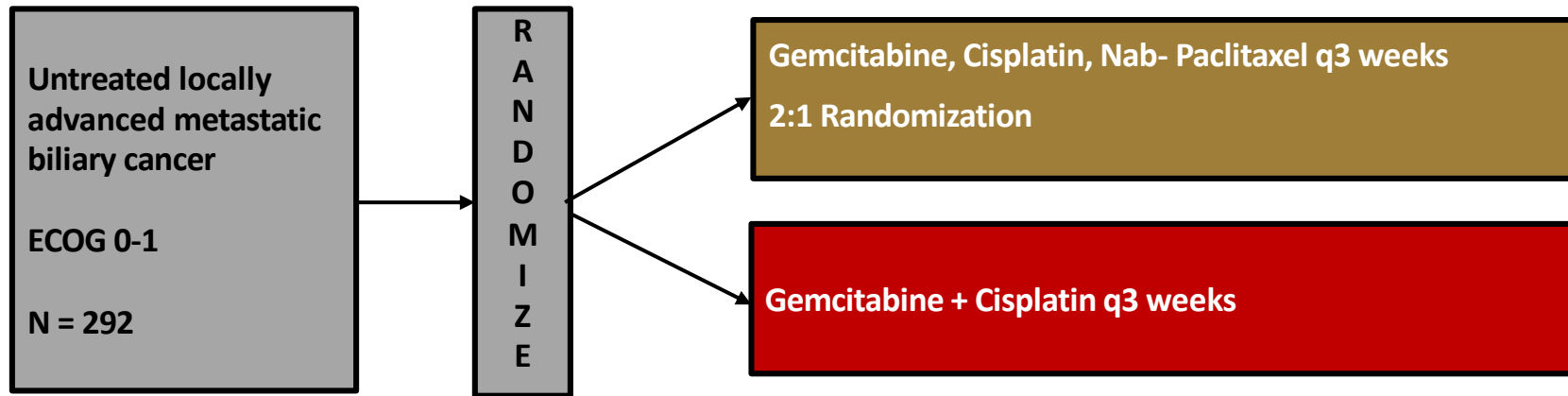
8 (63%) ICC, 9 (15%) ECC, 13 (22%) GBC, 47 (78%) had metastatic disease, and 13 (22%) had locally advanced disease

PFS: 11.8 months

PR: 45%

OS: 19.2 months

Phase 3 SWOG 1815



Primary endpoint: overall survival

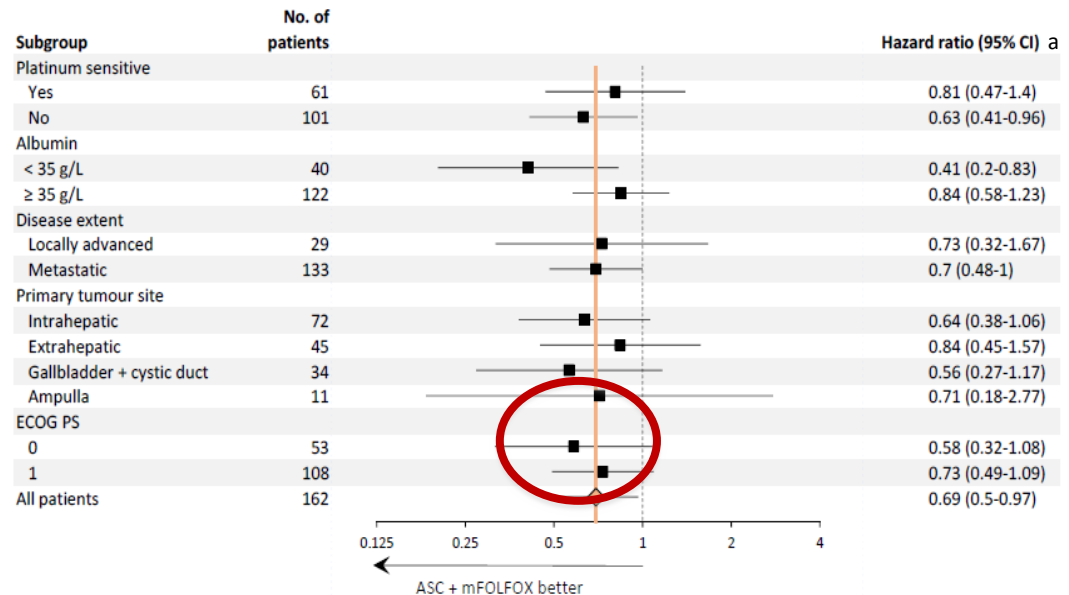
Secondary: ORR, PFS, DCR, Safety, Ca 19-9 response

<https://www.clinicaltrials.gov/ct2/show/NCT03768414>. Accessed October 7, 2019.

ABC-06: Active Symptom Control $\pm$ mFOLFOX

- ASC $\pm$ 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.

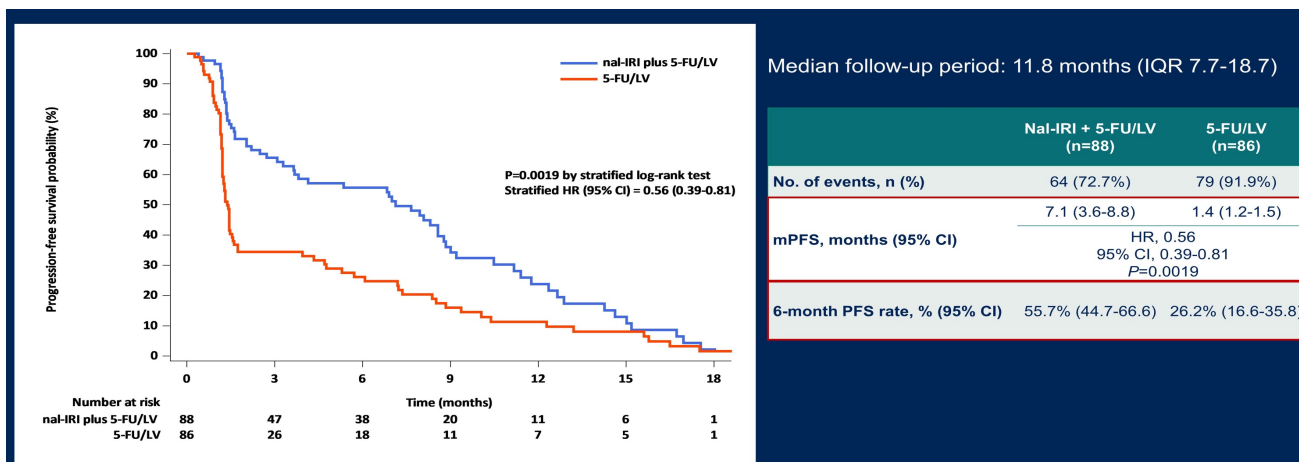
ASC, active symptom control.

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

Liposomal Irinotecan + 5FU

- NIFTY Phase IIb study: second-line biliary tract cancer, after progression to CisGem: 88 pts Nal-IRI/5FU vs 86 5FU

► Benefit in PFS



- Partial response rate: 14.8% vs 5.8%
- OS 8.6 vs 5.5 (HR 0.68 (0.48-0.98); p-value 0.039)

*

Yoo et al ASCO 2021

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 cohort¹: 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%

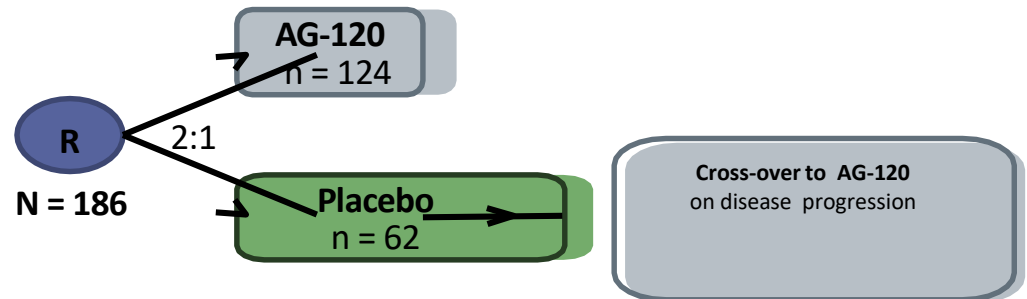
12-month PFS: 21.8%

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

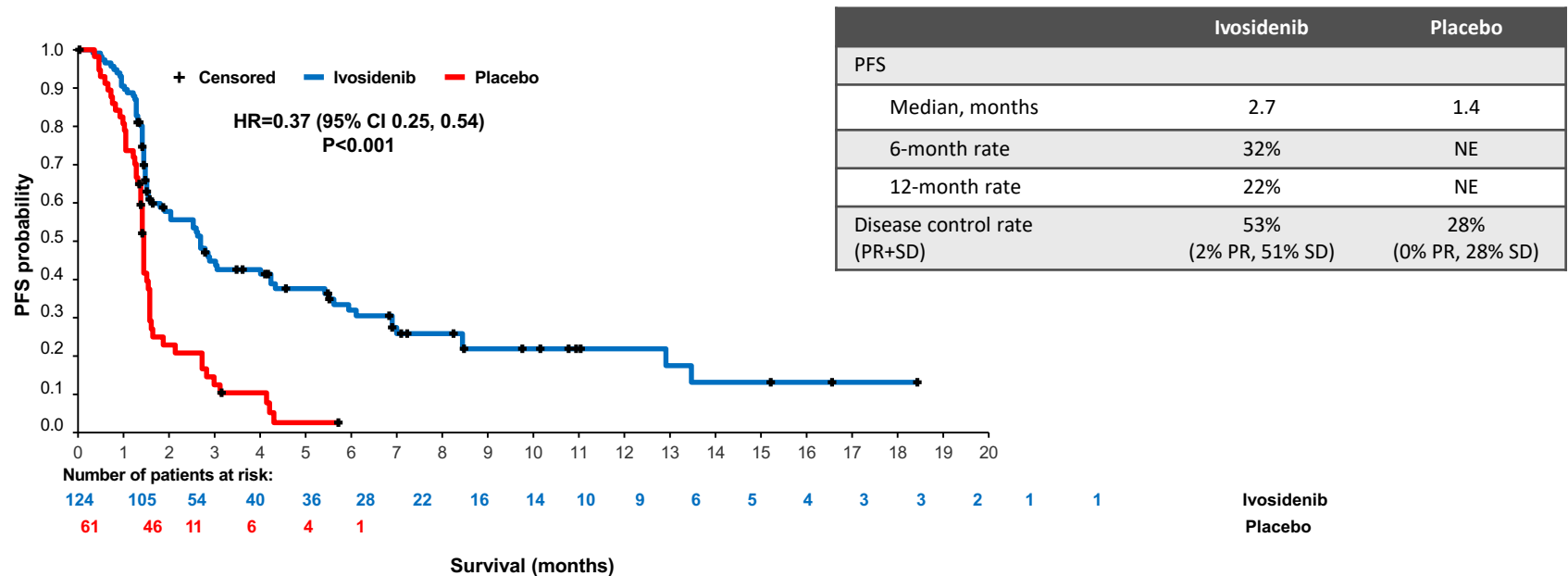
IHCCA (22%)

Chondrosarcoma (50%)

Glioma (80%)

Abou-Alfa, GK. Lancet Oncol, 2020

ClarIDHy: PFS by IRC



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

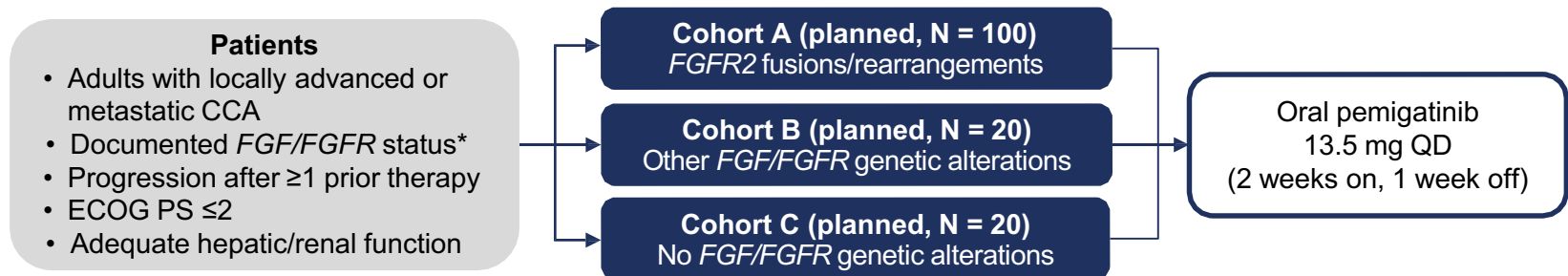
- FGFR2 Fusions

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

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

CONCLUSIONS

- 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

Other FGFR Inhibitors in Development

- **Futibatinib (TAS-120):** irreversible 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

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)

Targeting HER-2

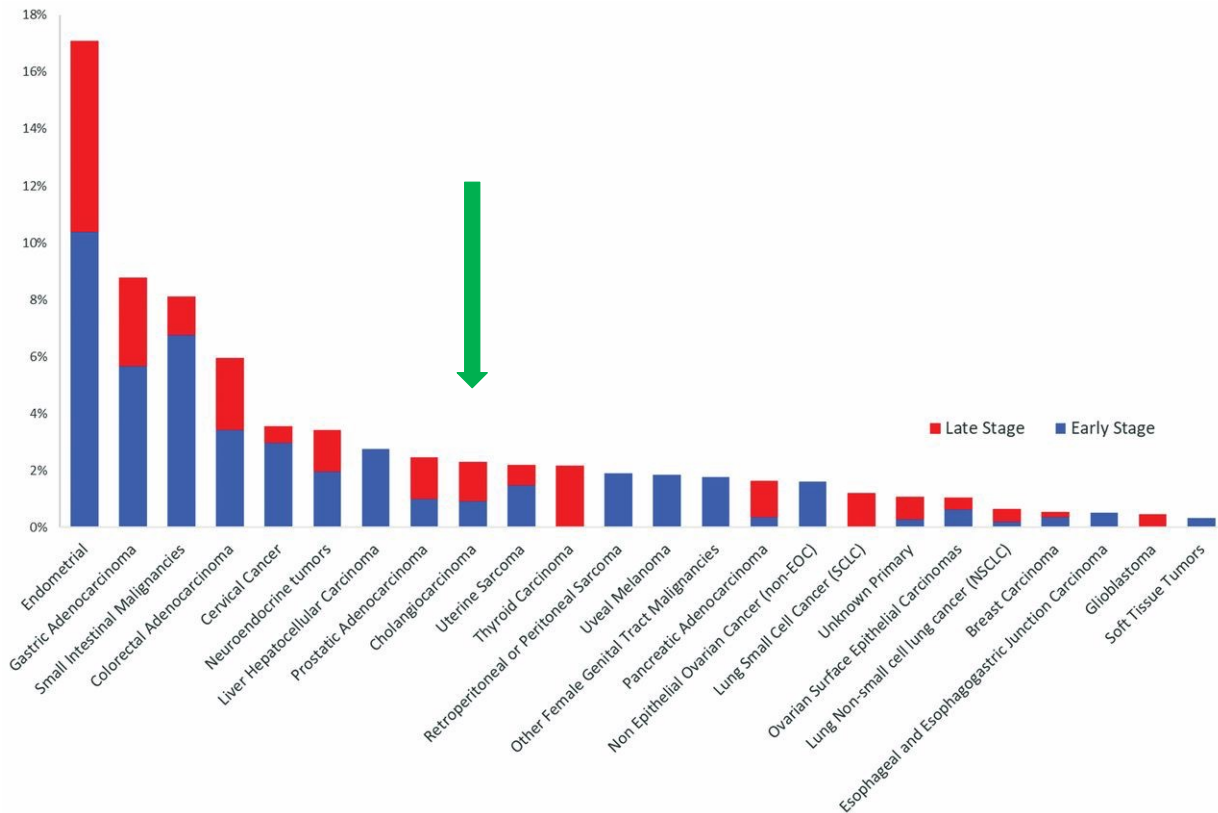
- **Pertuzumab and trastuzumab: phase 2a study**
 - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
 - RR 23 %
- **Zanidatamab – HER-2 bispecific antibody**
 - 20 patients (11 gallbladder cancers, 5 intra- and 4 extra-hepatic cholangiocarcinoma)
 - RR 47%; median duration 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: $\geq$ Grade 3 12.5%

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

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. Followed by D or P to progression

Do-Youn Oh ASCO GI 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 Oh ASCO GI 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 %).

Do-Youn Oh ASCO GI 2022

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin⁴ (category 1)

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 paclitaxel¹ (category 2B)
- Durvalumab + gemcitabine + cisplatin (category 2B)^{d,5}

Single Agents

- ▶ 5-fluorouracil
- ▶ Capecitabine
- ▶ Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
 - ▶ Entrectinib⁶⁻⁸
 - ▶ Larotrectinib⁹
- For MSI-H/dMMR tumors:
 - ▶ Pembrolizumab^{e,f,10,11}
- For *RET* fusion-positive tumors:
 - ▶ Pralsetinib (category 2B)¹²

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression⁹

Preferred Regimens

- FOLFOX¹³

Other Recommended Regimens

- FOLFIRI¹⁴ (category 2B)
- Regorafenib¹⁵ (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)¹⁶
- Durvalumab + gemcitabine + cisplatin (category 2B)^{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:
 - ▶ Entrectinib⁶⁻⁸
 - ▶ Larotrectinib⁹
- For MSI-H/dMMR tumors:
 - ▶ Pembrolizumab^{e,f,h,10,11}
 - ▶ Dostarlimab-gxly^{f,h,i,17,18} (category 2B)
- For TMB-H tumors:
 - ▶ Pembrolizumab^{e,f,h,19}
- For *BRAF*-V600E mutated tumors:
 - ▶ Dabrafenib + trametinib^{20,21}
- For CCA with *FGFR2* fusions or rearrangements:
 - ▶ Pemigatinib²²
 - ▶ Infigratinib²³
- For CCA with *IDH1* mutations:
 - ▶ Ivosidenib^{24,25}
- For *RET* fusion-positive tumors:
 - ▶ Pralsetinib (category 2B)¹²
- For HER2-positive tumors:
 - ▶ Trastuzumab + pertuzumab²⁶
- Nivolumab^{f,h,27} (category 2B)
- Lenvatinib + pembrolizumab^{f,h,28} (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 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.

^f See [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^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.

Summary

- Advanced or metastatic Biliary Cancers
 - Clinical trials are paramount
 - Tissue is the issue:
 - MSI testing and NGS routine to direct therapy
 - IDH mutation, FGF fusions/re-arrangements, BRAF, HER-2. MSI-H, TMB, PD-LI(+)
 - Gem/DDP + Durvalumab (?) (a first-line standard)
 - Gem/DDP+Nabpaclitaxel in selected pts?
 - FOLFOX (is it a second line standard in pt with no targetable mutations?)
 - 5FU + Nanoliposomal Irinotecan (?)

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)^{a,b,c,1}

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A) ([category 1] or B7)^{d,e,2,3}
- Lenvatinib (Child-Pugh Class A only)^{4,5} (category 1)
- Durvalumab⁶
- Pembrolizumab⁷ (category 2B)

Useful in Certain Circumstances

- Nivolumab^{b,8} (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)

Subsequent-Line Therapy^f if Disease Progression^g

Options

- Regorafenib (Child-Pugh Class A only) (category 1)^{h,9}
- Cabozantinib (Child-Pugh Class A only) (category 1)^{i,4}
- Ramucirumab (AFP ≥400 ng/mL and Child-Pugh Class A only) (category 1)^{i,11}
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)^{d,e}

Other Recommended Regimens

- Nivolumab + ipilimumab (Child-Pugh Class A only)^{b,i,12}
- Pembrolizumab (Child-Pugh Class A only) (category 2B)^{b,j,k,13-15}

Useful in Certain Circumstances

- Nivolumab (Child-Pugh Class B only)^{b,j,16-19} (category 2B)
- Dostarlimab-gxly^{b,j,l,20,21} for MSI-H/dMMR tumors (category 2B)

^a An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

^b See [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^c Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk.

^d See Child-Pugh Score ([HCC-C](#)) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

^e Caution: There are limited safety data available for patients with Child-Pugh Class B or C liver function and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, et al. J Clin Oncol 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.

^f Larotrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)

^g There are no comparative data to define optimal treatment after first-line systemic therapy.

^h The data reflect use on or after sorafenib in patients who previously tolerated sorafenib at a dose of at least 400 mg per day.

ⁱ The data reflect use on or after sorafenib.

^j 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.

^k Pembrolizumab is a recommended treatment option for patients with or without MSI-H HCC.

^l 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.

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.

Thanks for the attention!
Questions???