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School of Medicine

Pancreatic and Biliary Cancers: Moving the Bar Up?

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Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Celgene, Ipsen, Taiho, Merck

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 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	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

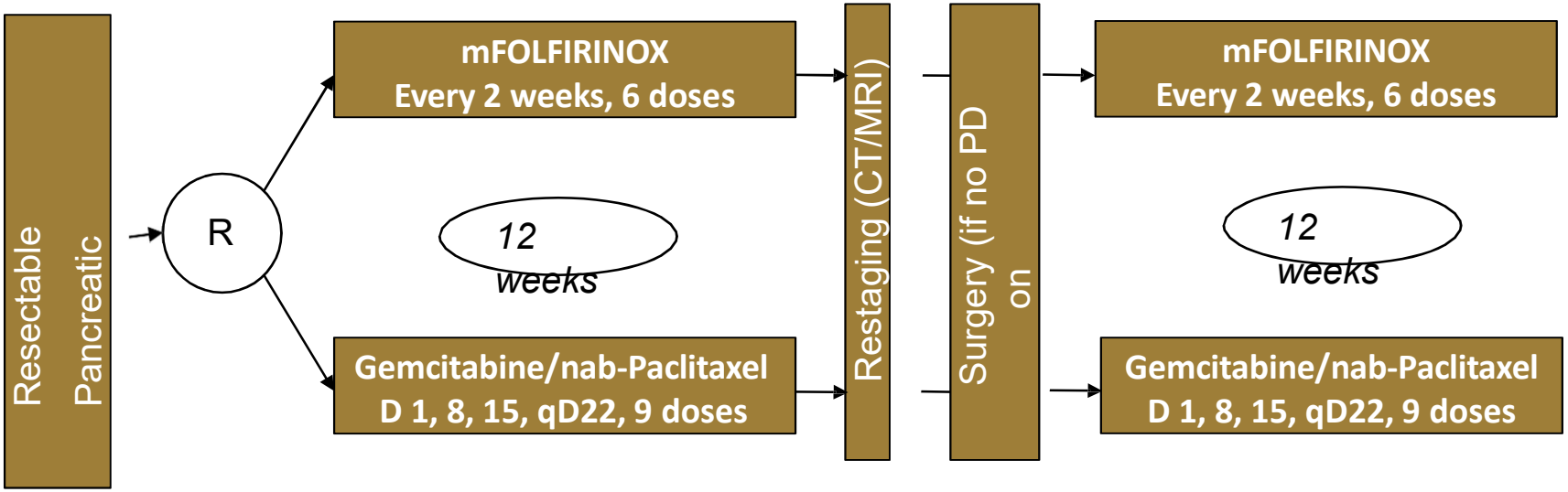
[a] FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1.

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

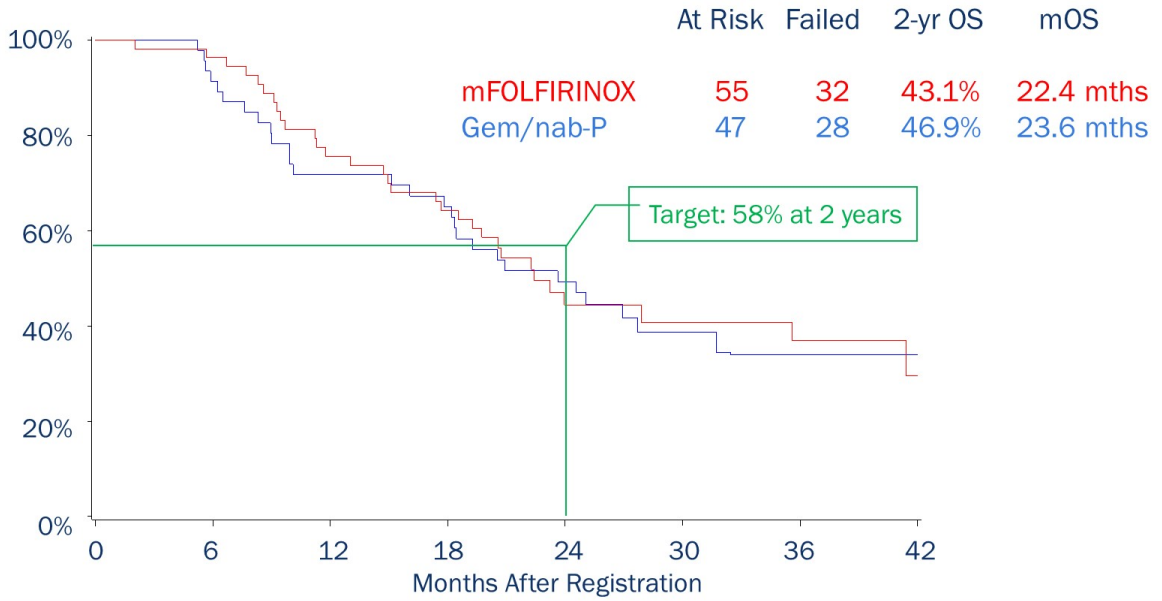
SWOG S1505: Perioperative neoadjuvant phase II randomized trial with Folfirinox or Gem/nab-P



Primary objective: 2-year overall survival > 58%

Retrospective central review of imaging to confirm resectability

Primary Endpoint: Two-year OS



PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Davendra Sohal, MD, MPH

SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network a National Cancer Institute program | NCI Community Oncology Research Program

Sohal D *et al.* J Clin Oncol 2020; 38,15 Suppl : 4504

Surgery Results

	mFOLFIRINOX (N=40)	Gem/nab-P (N=33)
R0 Resection	34 (85%)	28 (85%)
Complete or Major Pathologic Response	10 (25%)	14 (42%)
Total Nodes Resected, median (range)	19 (1-56)	18 (3-45)
Node Negative Resection	16 (40%)	15 (45%)
Disease-Free Survival after Resection	10.9 mths	14.2 mths

Sohal D *et al.* J Clin Oncol 2020; 38,15 Suppl : 4504

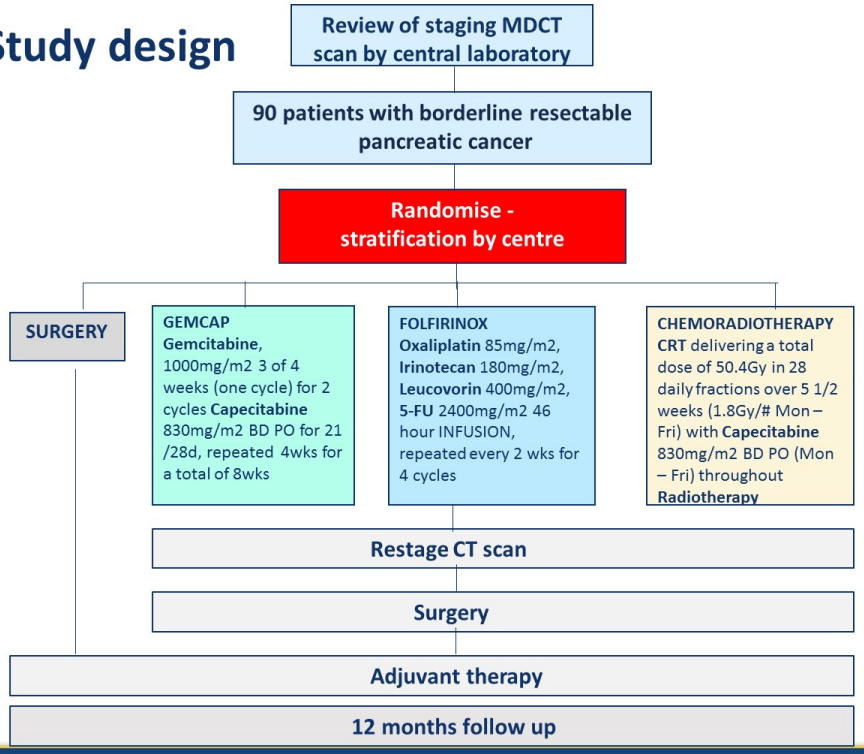
ESPAC-5F: Four arm, prospective, multicentre, international randomised phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer.

P Ghaneh, D Palmer, S Cicconi, C Halloran, E Psarelli, C Rawcliffe, R Sripadam, S Mukherjee, J Wadsley, A Al-Mukhtar, L Jiao, H Wasan, R Carter, J Graham, F Ammad, J Evans, C Tjaden, T Hackert, M Büchler, J Neoptolemos for the European Study Group for Pancreatic Cancer (ESPAC)

ISRCTN: 89500674
EudraCT: 2013-003932-56
CRUK: C20203/A16186

Ghaneh P ASCO 2020

Study design



Primary
1. Recruitment rate
2. Resection rate (R1 + R0)

Secondary
1. R0 resection margin rate
2. Toxicity
3. Overall survival
4. Post operative complication rate
5. Post operative mortality rate
6. Response rate
7. Disease free survival rate
8. Local disease free survival rate
9. Quality of life

- Two patients excluded from the Full Analysis Set (one Immediate surgery, one CRT)
- Some data cleaning ongoing

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Primary outcome - resection rate (R0 + R1)

	No of resections	No of patients	Rate* (95% CI)	P-value
Immediate Surgery	20	32	62% (44% , 79 %)	0.668
Neoadjuvant treatment	31	56	55% (41% , 69%)	
Overall	51	88	58% (47% , 68%)	

*Defined as R0 + R1 resections in patients included in the Full Analysis Set

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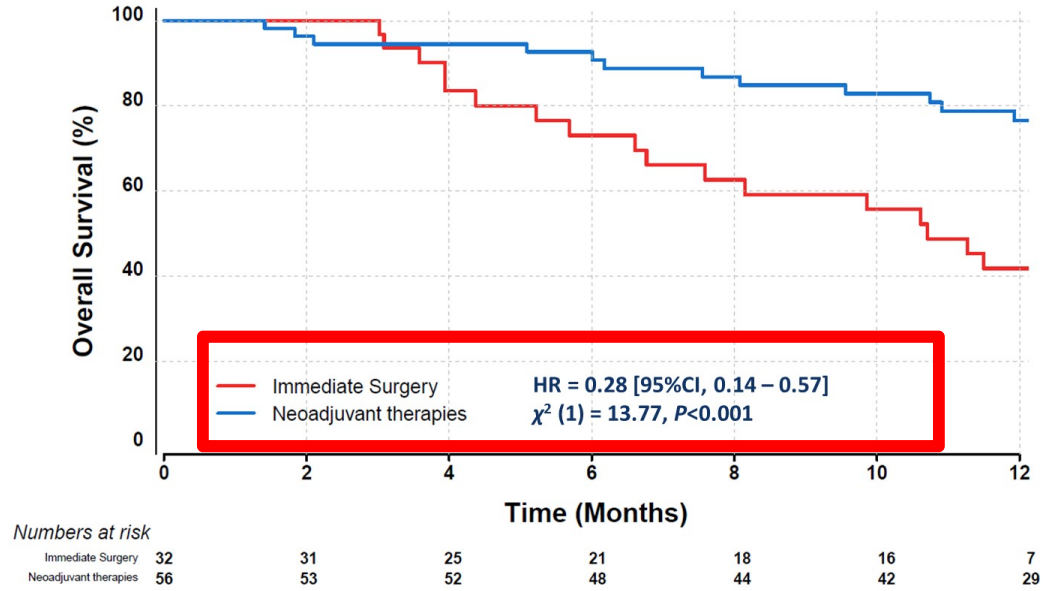
Secondary outcomes - overall survival (I)



12-months survival estimate (95% CI)

Immediate Surgery	42% (27% , 64%)
Neoadjuvant therapy	77% (66% , 89%)

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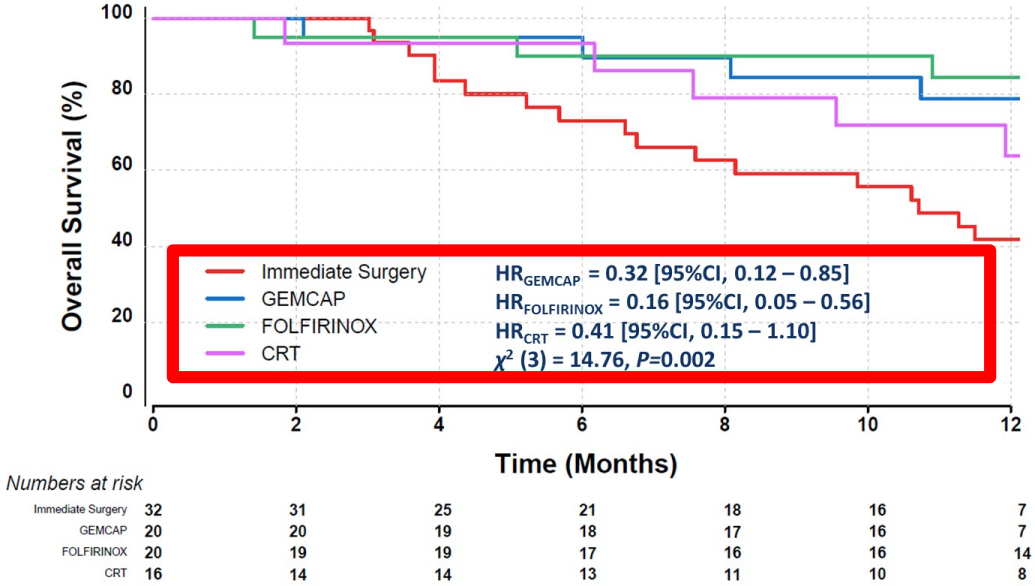
Secondary outcomes - overall survival (II)



Numbers at risk

Immediate Surgery	32	31	25	21	18	16	7
GEMCAP	20	20	19	18	17	16	7
FOLFIRINOX	20	19	19	17	16	16	14
CRT	16	14	14	13	11	10	8

12-months survival estimate (95% CI)

Immediate Surgery	42% (27% , 64%)
GEMCAP	79% (62% , 100%)
FOLFIRINOX	84% (70% , 100%)
CRT	64% (43% , 95%)

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TAKE HOME MESSAGES

- Both gemcitabine and nabpaclitaxel and FOLFIRINOX are promising neoadjuvant treatments
- Chemotherapy and radiation in combination appears less appealing
- Gemcitabine and nabpaclitaxel in combination showed promising complete pathologic response in resectable pancreatic cancer patients
- Alliance 021806 will address the role of FOLFIRINOX in the neoadjuvant setting

NCCN Guidelines Accessed on 11/13/2020

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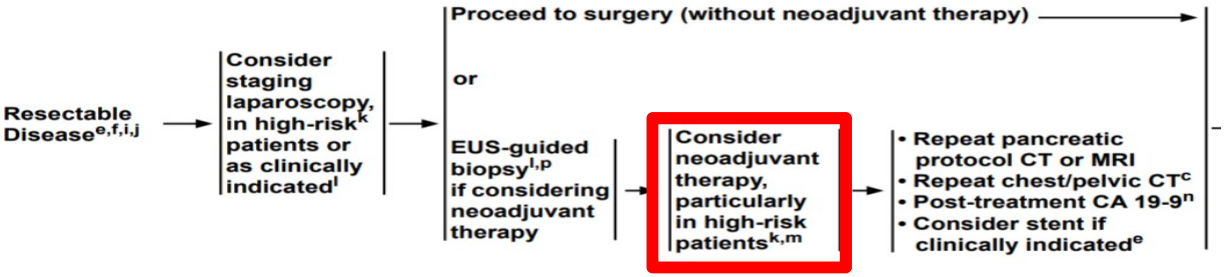
Pancreatic Adenocarcinoma

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.

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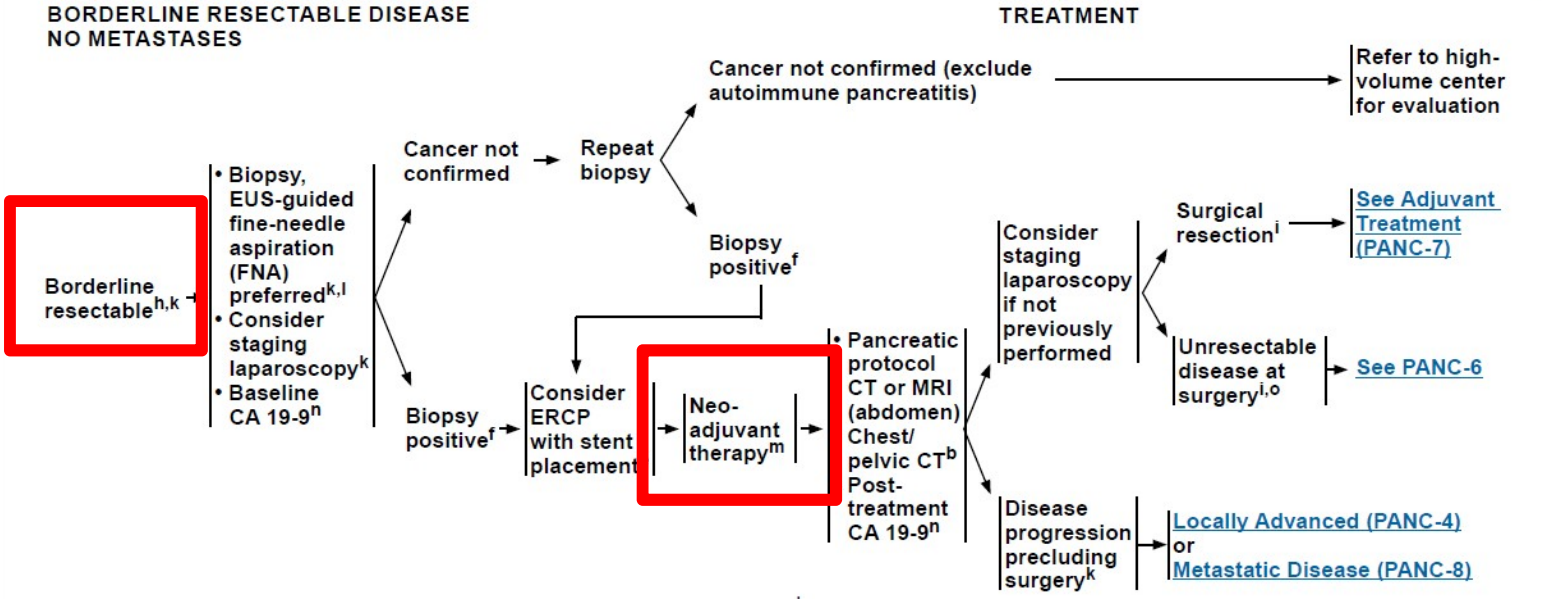


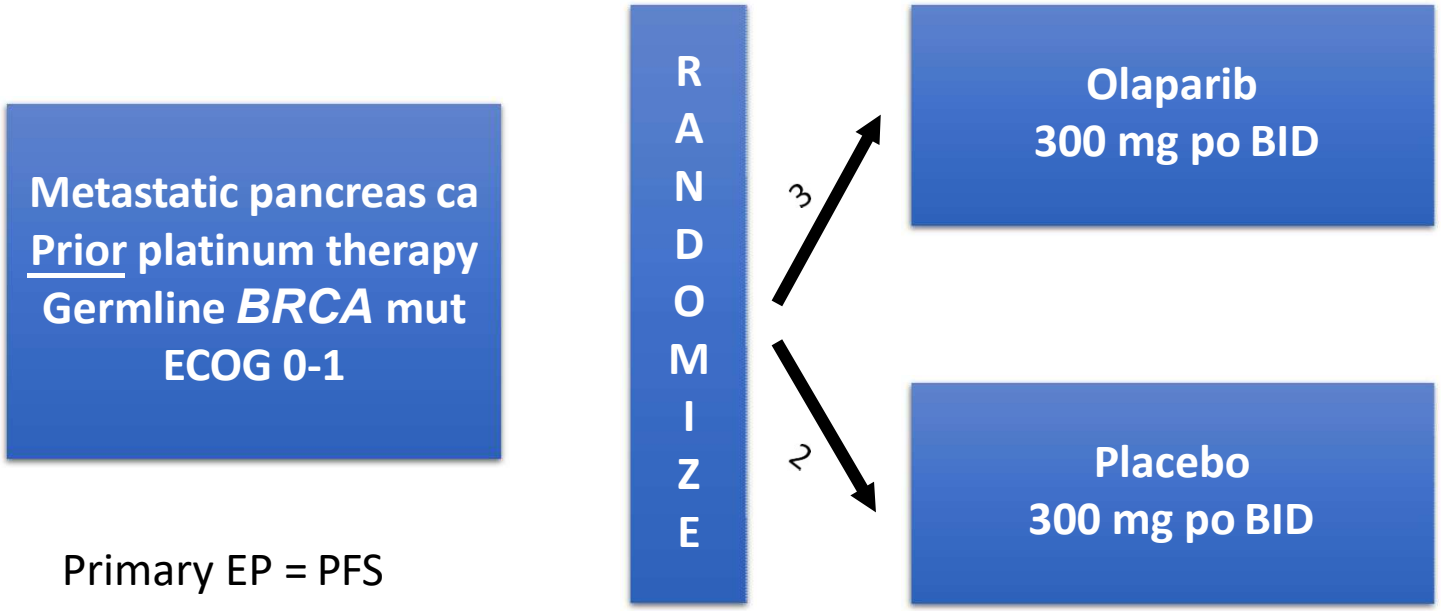
[m] There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Systemic Therapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles 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.

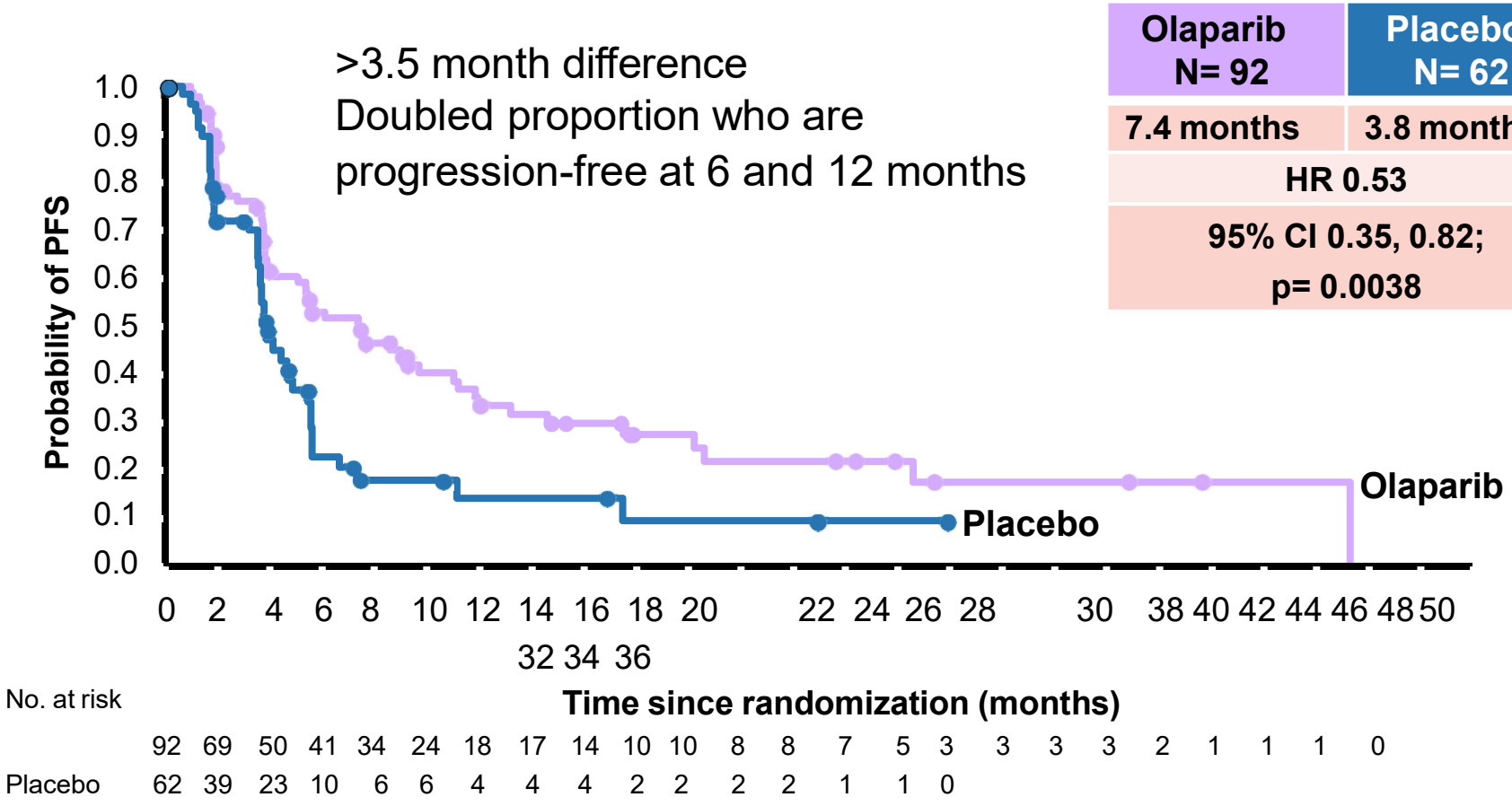
POLO: Phase 3 international PARPi maintenance study in gBRCA mutated patients



Primary EP = PFS
N = 145

NCT02184195

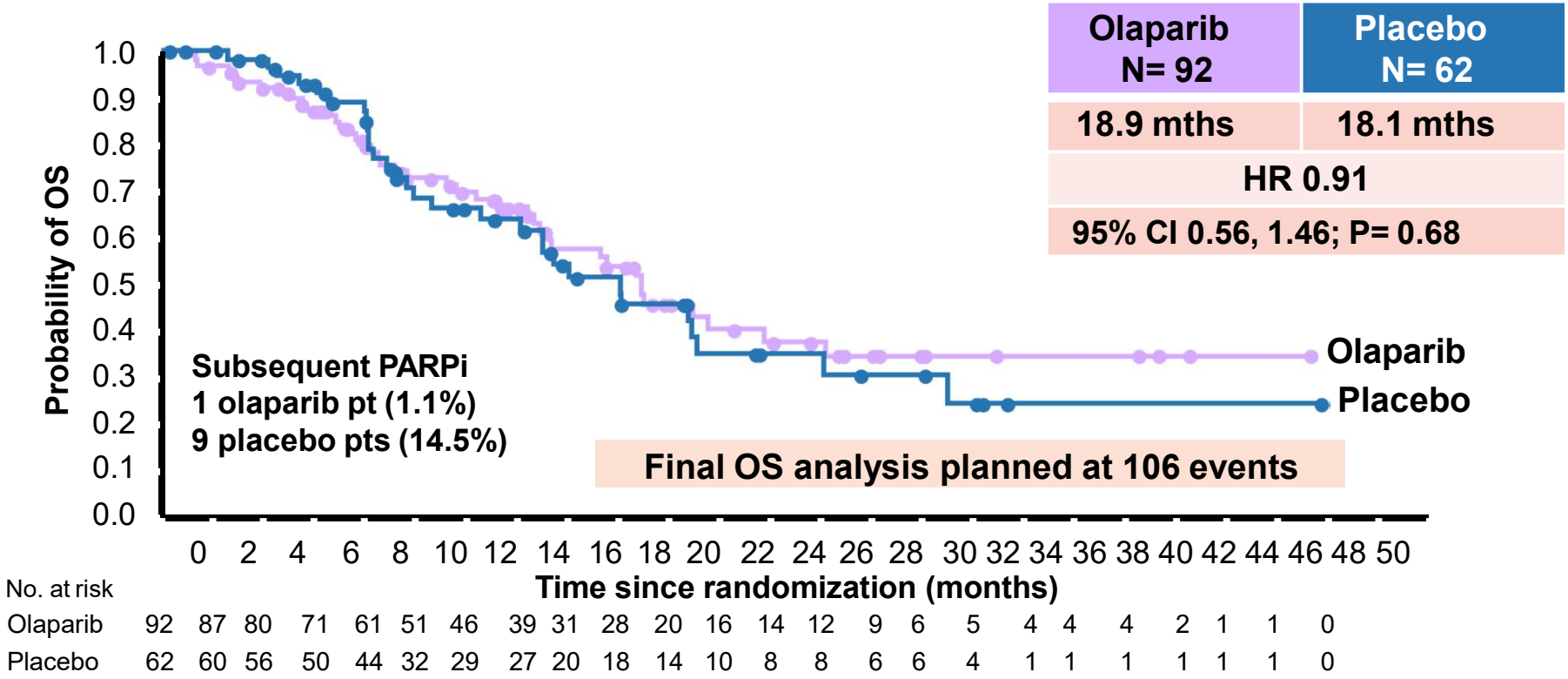
Primary Endpoint: Blinded Central Review



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

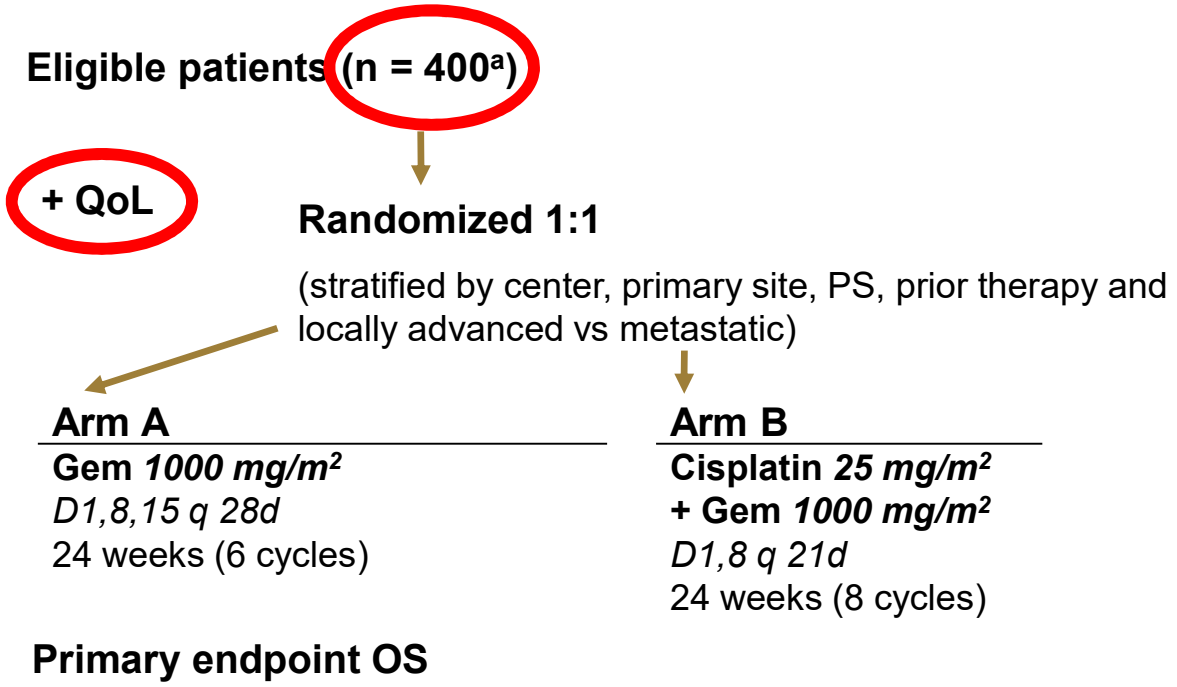
Overall Survival (46% Maturity)



Golan, T. New Engl J Med, 2019

Biliary Cancer

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



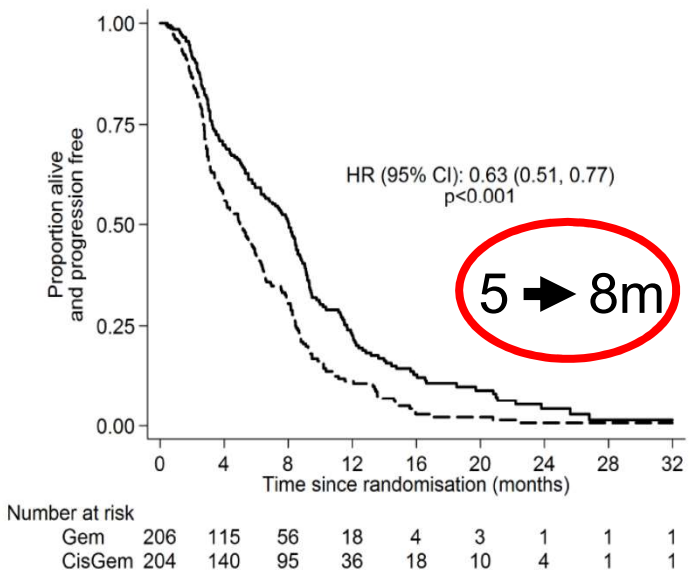
Inclusion criteria:

- 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

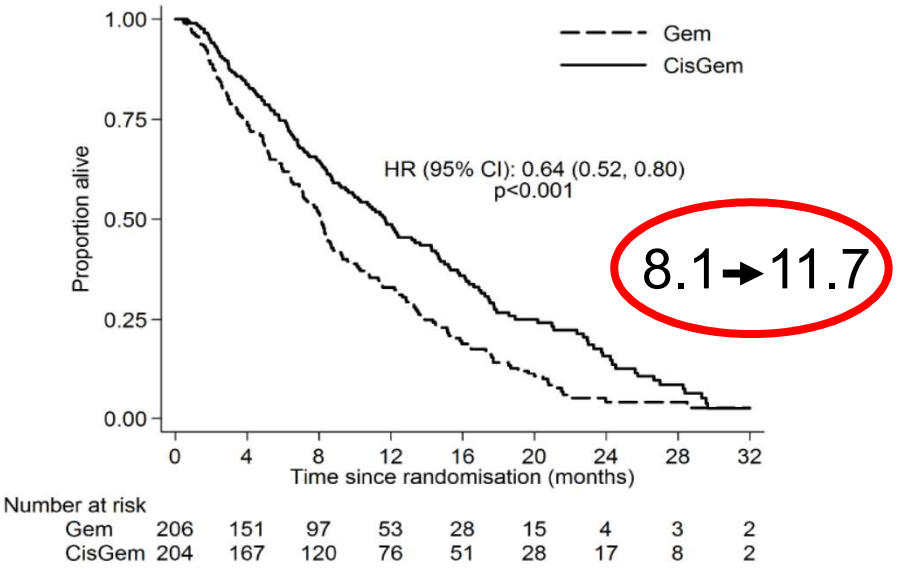
[a] Including 86 patients in ABC-01.
[b] Allowed: palliative surgery, relapse following curative surgery, PDT, radiotherapy with documented progression.
Valle J, et al. *N Engl J Med*. 2010;362(14):1273-1281.

ABC-02 Results

Progression-free Survival (ITT)



Overall Survival (ITT)



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

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

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

Gemcitabine/DDP/Nab-paclitaxel

GCN regimen

Gem/Cis/nab-paclitaxel[1]
[NCT02392637]
USA (MDA and Mayo)
Single-arm, phase 2
N =61

Schedule | gemcitabine 800mg/m^2 + cisplatin 25 mg/m^2 + nab-paclitaxel 100 mg/m^2; D1,8 q21d

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

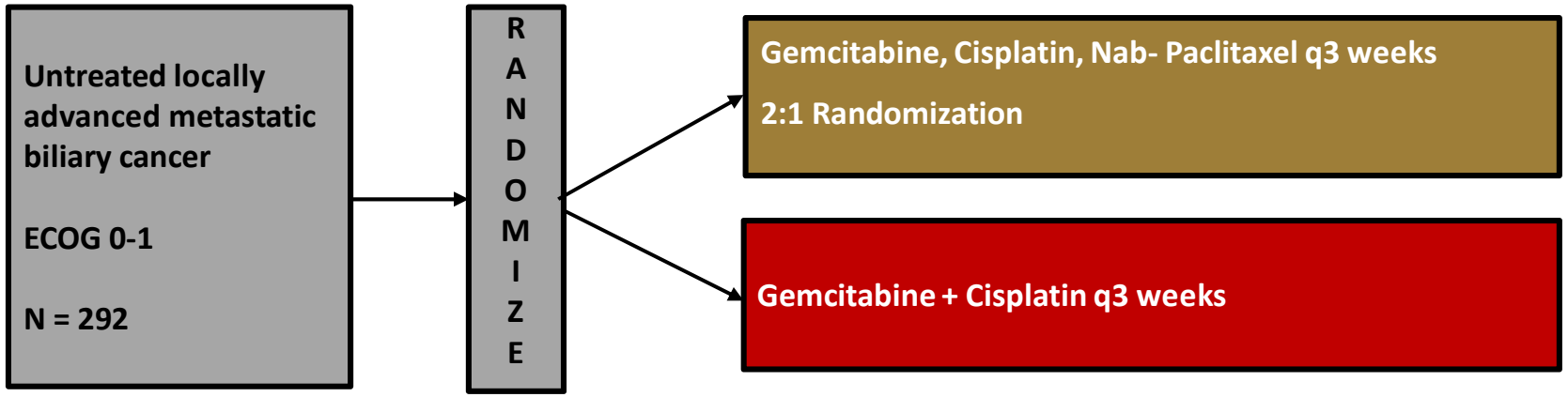
PFS: 11.8 months

PR: 45%

OS: 19.2 months

Rachna T et al *JAMA Oncol.* 2019;5(6):824

Phase 3 SWOG 1815



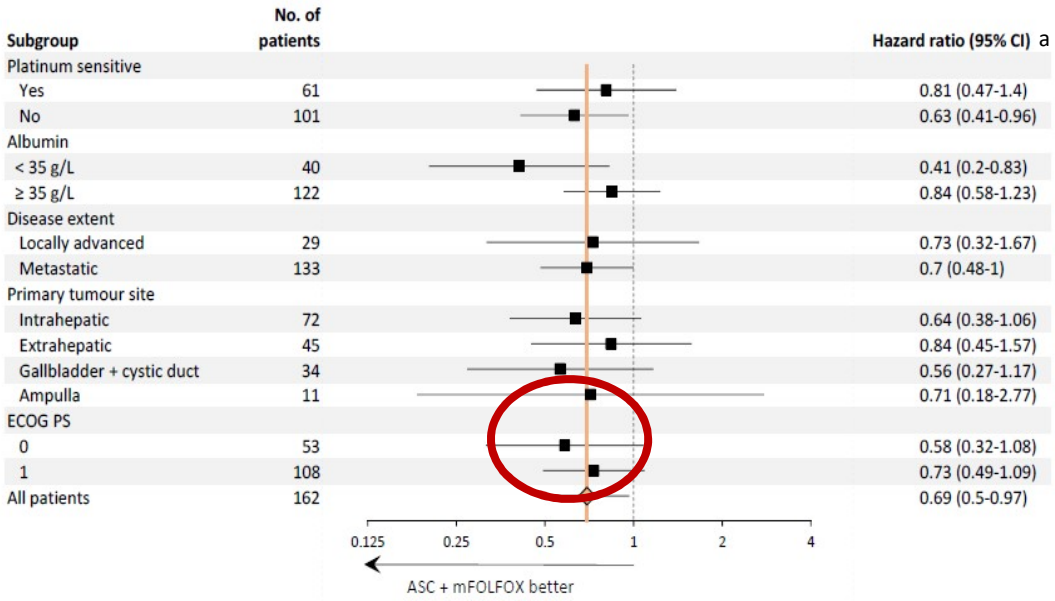
Primary endpoint: overall survival
Secondary: ORR, PFS, DCR, Safety, Ca 19-9 response

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

ABC-06: Active Symptom Control ± 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



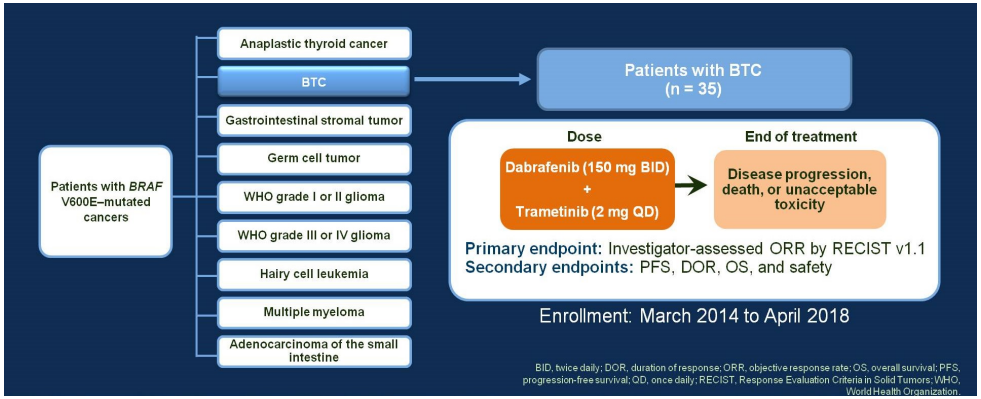
[a] HRs are adjusted for platinum sensitivity, albumin and stage.

ASC, active symptom control.

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

The Phase 2 ROAR Study Evaluated Combined BRAF and MEK Inhibition in *BRAF*-Mutated Cancers, Including BTC

- *BRAF* mutations have been reported in approximately 5%-7% of iCCAs; these mutations may be enriched in iCCA vs other types of biliary cancers



ROAR Study Design (NCT02034110)

Baseline Demographics – BTC Cohort (n = 35)

Parameter	BTC Cohort (n = 35)
Age, median (range), years	57.0 (26-77)
Male, n (%)	15 (43)
ECOG PS, n (%)	
0	14 (40)
1	20 (57)
2	1 (3)
Histology, n (%)	
Adenocarcinoma	26 (74)
Hepatocholangiocarcinoma	6 (17)
Cholangiocarcinoma	3 (9)
Measurable disease present at screening, n (%)	35 (100)
Stage at enrollment[a]	
Stage II	1 (3)
Stage IV	26 (74)
Stage IVA	1 (3)
Stage IVB	6 (17)
Time since diagnosis, median (range), years	1.1 (0.1-8.8)

Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

The Phase 2 ROAR Study Results of the BTC Cohort

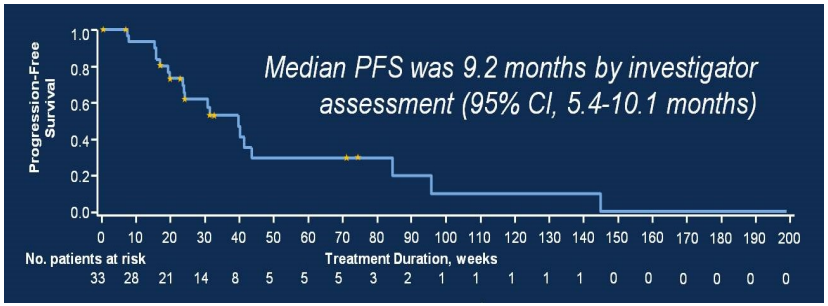
Best Overall Response

Response	Investigator-Assessed Response ITT/Evaluable Population (n = 33)	Response by Independent Review ITT/Evaluable Population (n = 33)
Best overall response, n (%)		
CR	0	0
PR	14 (42)	12 (36)
SD	15 (45)	13 (39)
PD	4 (12)	4 (12)
Not evaluable[a]	0	2 (6)
Missing	0	2 (6)
ORR (CR + PR), n (%)	14 (42)	12 (36)
95% CI	25.5-60.8	20.4-54.9

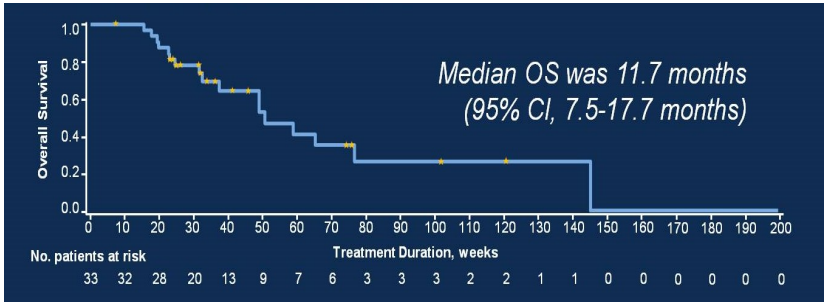
- DOR at 6 months was 66% (95% CI, 32%-86%)
- The most common AEs were pyrexia (40%), rash (29%), nausea, diarrhea, fatigue (23% each), chills (20%)
  - 57% of patients had at least Grade 3/4

Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

Progression-Free Survival



Overall Survival



Presented By Zev Wainberg at 2019 Gastrointestinal Cancer Symposium

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%

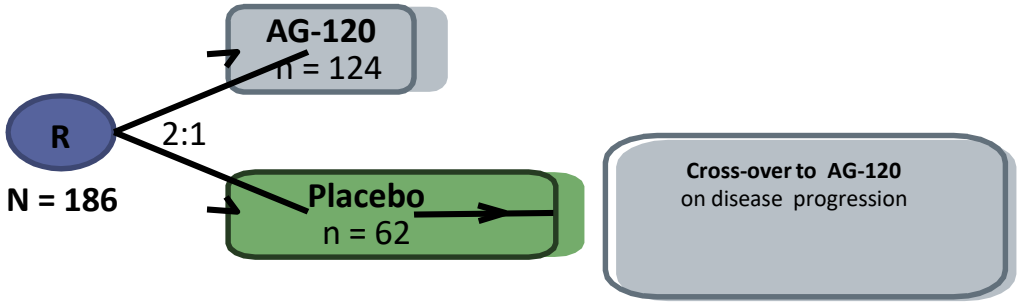
RR 5% (4 PRs)

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: End Points, Sample Size, and Key Eligibility Criteria

Endpoints

- Primary endpoint: PFS by blinded independent radiology center (IRC)
- Secondary endpoints included: safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL); pharmacokinetics/pharmacodynamics

Sample size

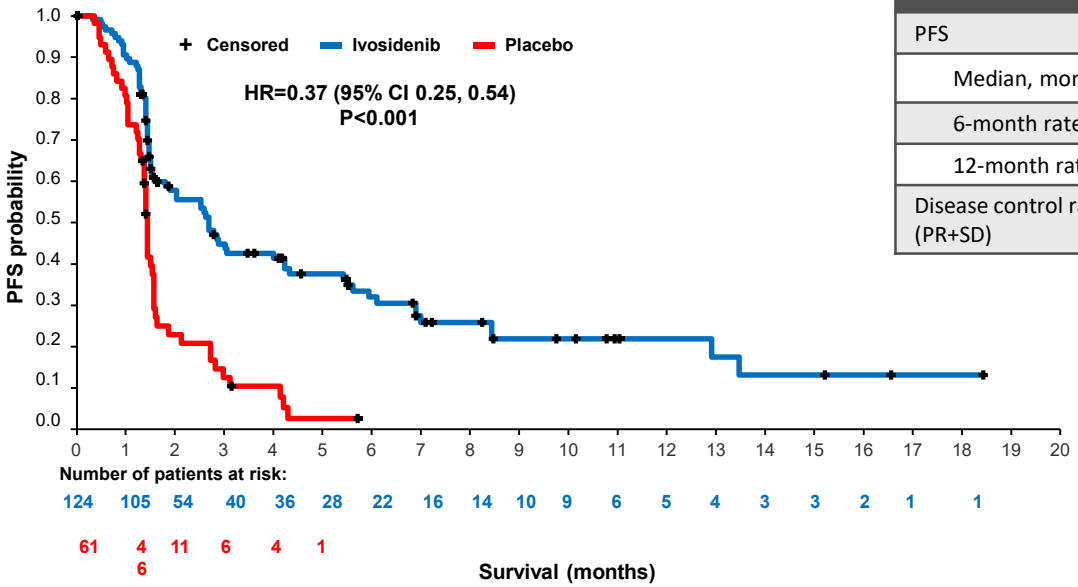
- ~186 patients based on HR 0.5, 96% power, 1-sided alpha = 0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

Eligibility

- ≥18 years of age
- Histologically confirmed diagnosis of CCC
- Centrally confirmed mIDH1 status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU- containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

Abou-Alfa, GK. Lancet Oncol, 2020

ClarIDHy: PFS by IRC

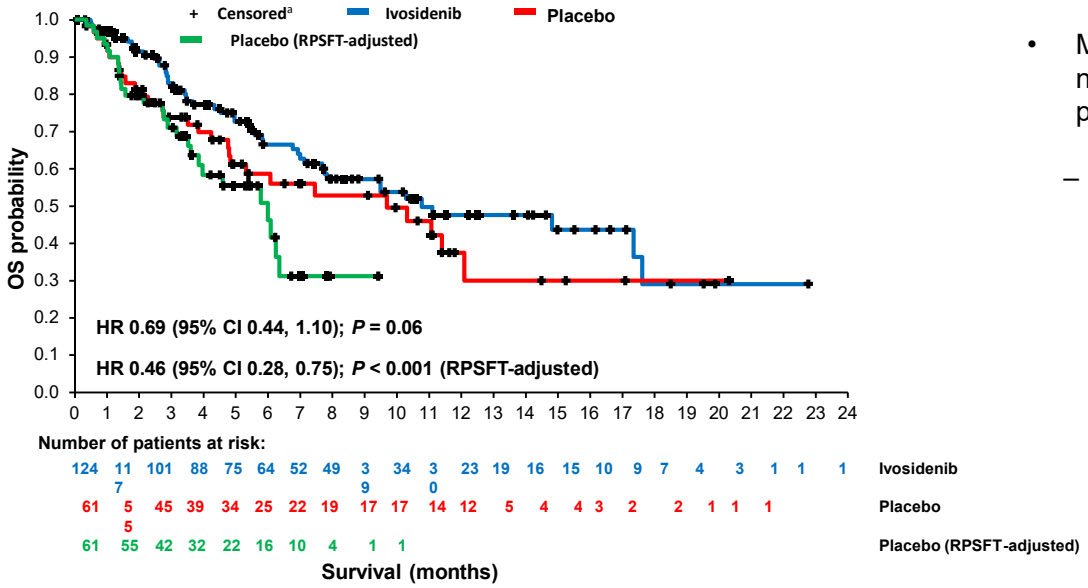


	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

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

Abou-Alfa, GK. Lancet Oncol, 2020

ClarIDHy: OS by ITT



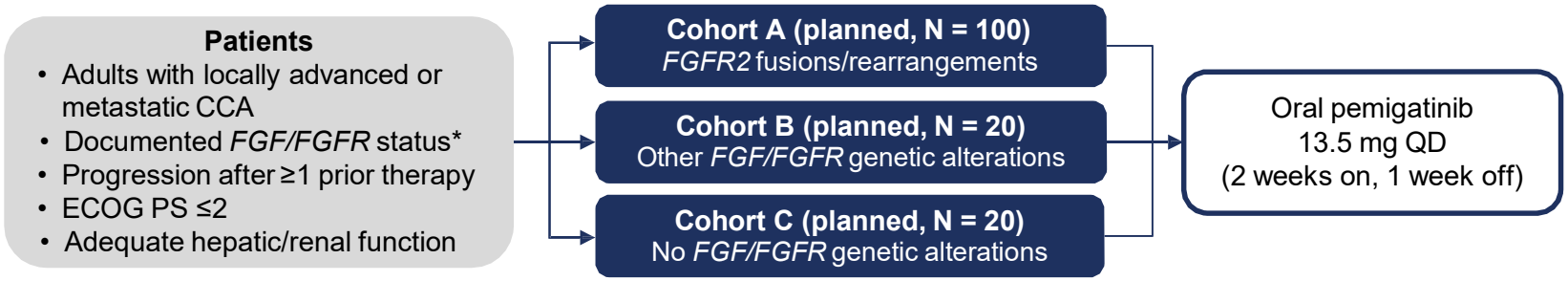
- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
    - Rank-preserving structural failure time (RPSFT)1,2 method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
    - With the RPSFT method, the median OS with placebo adjusts to 6 months

[a] Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier.

Abou-Alfa GK, et al. ESMO 2019:abstract LBA10_PR.

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

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RESPONSE

Variable	Cohort A (n = 107) *FGFR2* Fusions/ Rearrangements	Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations	Cohort C (n = 18) No *FGF/FGFR* Genetic Alterations
ORR (95% CI), %	**35.5 (26.50–45.35)**	0	0
Best OR,* n (%)	3 (2.8)	0	0
CR	35 (32.7)	0	0
PR	50 (46.7)	8 (40.0)	4 (22.2)
SD	16 (15.0)	7 (35.0)	11 (61.1)
PD	3 (2.8)	5 (25.0)	3 (16.7)
Not evaluable†			
Median DOR (95% CI), mo	7.5 (5.7–14.5)	—	—
DCR (CR + PR + SD) (95% CI), %	82 (74–89)	40 (19–64)	22 (6–48)

* Assessed and confirmed by independent central review.
† Postbaseline tumor assessment was not performed owing to study discontinuation (2 participants in cohort A, 4 participants in cohort B, 3 participants in cohort C) or was performed prior to the minimum interval of 39 days for an assessment of SD (1 participant in cohort A, 1 participant in cohort B).

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ADVERSE EVENTS OCCURRING IN ≥25% OF PATIENTS

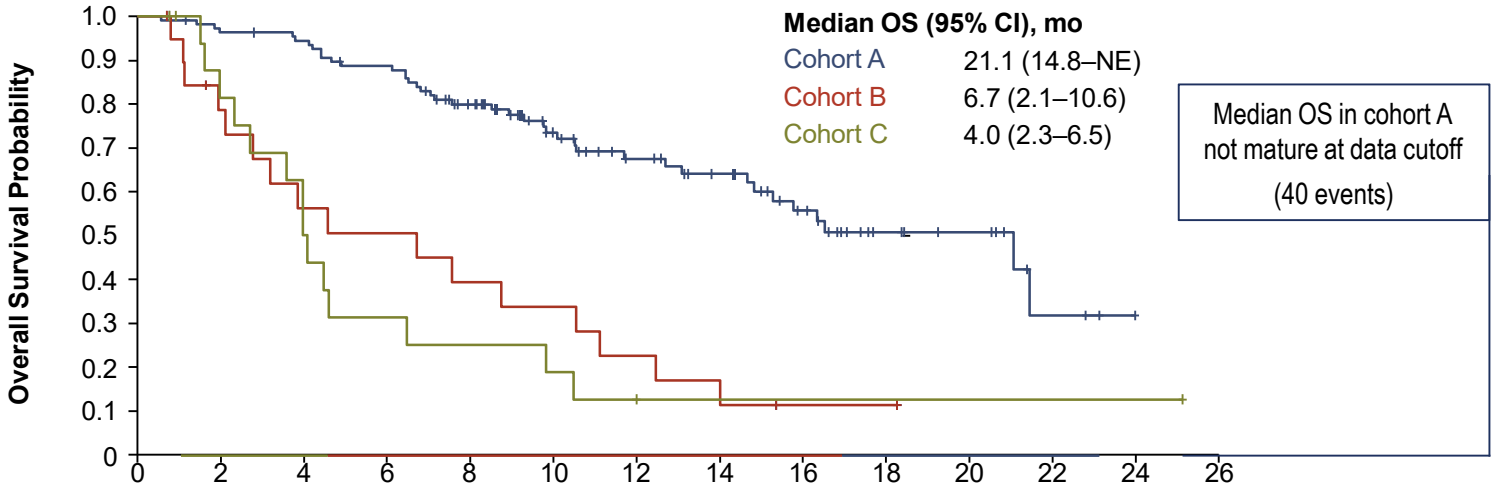
	Any AEs (N = 146)*	
Hyperphosphatemia†	**88 (60)**	**0**
Alopecia	72 (49)	0
Diarrhea	68 (47)	4 (3)
Fatigue	**62 (42)**	**7 (5)**
Nail toxicities†	62 (42)	3 (2)
Dysgeusia	59 (40)	0
Nausea	58 (40)	3 (2)
Constipation	51 (35)	1 (1)
Stomatitis	**51 (35)**	**8 (5)**
Dry mouth	49 (34)	0
Decreased appetite	48 (33)	2 (1)
Vomiting	40 (27)	2 (1)
Dry eye	37 (25)	1 (1)
Arthralgia	36 (25)	9 (6)

- **Hyperphosphatemia**† managed with a low phosphate diet, phosphate binders, and diuretics, or dose reduction/interruption
  - All grade 1 or 2
  - Few (n = 3) required dose reductions/interruptions
- **Hypophosphatemia**† occurred in 23% of patients
  - Most common grade ≥3 AE (12%)
  - None clinically significant/serious; none led to discontinuation/dose reduction
- **Serous retinal detachment**† occurred in 4% of patients
  - Mostly grade 1/2 (grade ≥3, 1%)
  - None resulted in clinical sequelae

* Safety analysis includes 1 patient who did not have confirmed *FGF/FGFR* status by central laboratory and was not assigned to any cohort.
† Combined MedDRA Preferred Terms.

Abou-Alfa, GK. Lancet Oncol, 2020

OVERALL SURVIVAL



No. at Risk						Time	o	ts (Months)					
Cohort A	107	102	99	92	73	t	Even	34	24	12	9	3	0	0
						52	41							
Cohort B	20	14	10	9	7	6	4	2	1	1	0	0	0	0

	Cohort A	Cohort B	Cohort C
Median (range) duration of follow-up, mo	15.4 (7.0–24.7)	19.9 (16.2–23.5)	24.2 (22.0–26.1)
Median (range) duration of treatment, mo	7.2 (0.2–24.0)	1.4 (0.2–12.9)	1.3 (0.2–4.7)

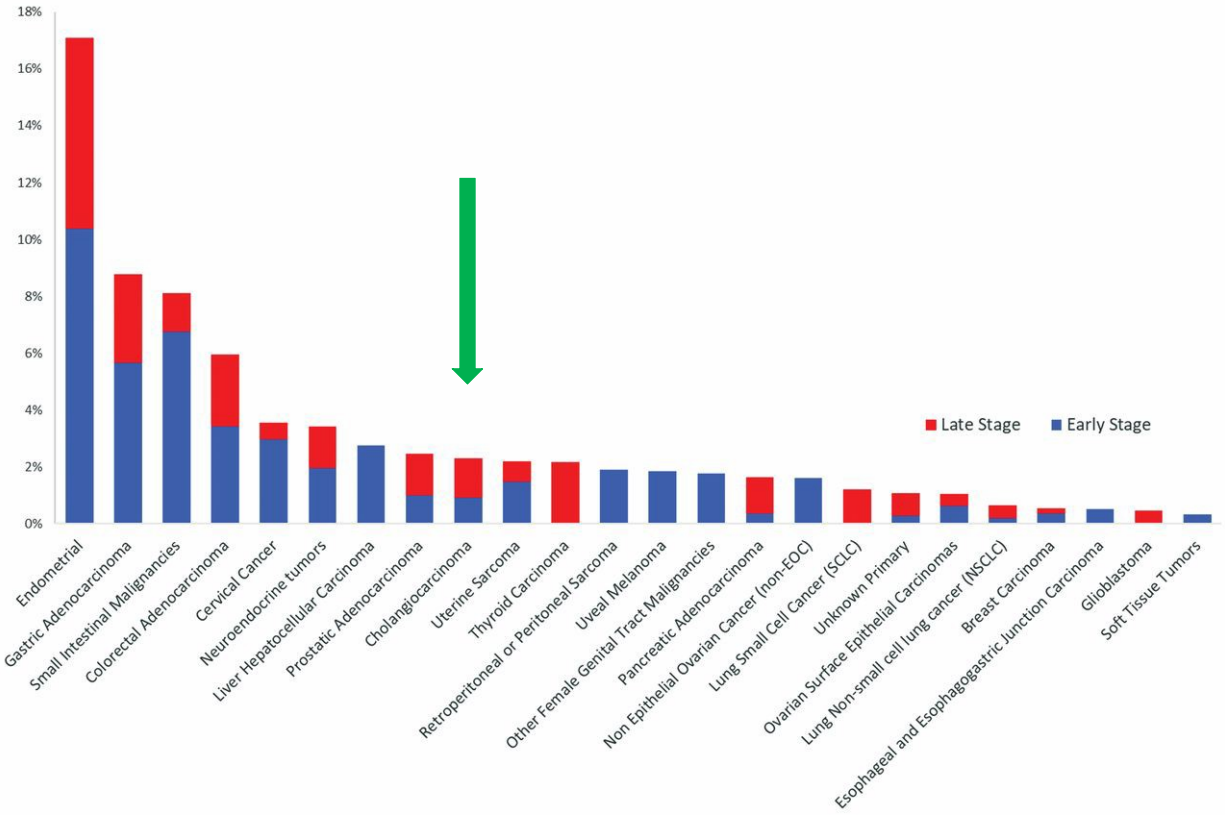
The study was not designed to compare cohorts.

Abou-Alfa, GK. Lancet Oncol, 2020

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)

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

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin
- Capecitabine + cisplatin
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel (cholangiocarcinoma only)
- 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[5–7]
  - Larotrectinib[8]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[d,e,9]

Subsequent-line Therapy for Biliary Tract Cancers if Disease Progression

Preferred Regimens

- FOLFOX[10]

Other Recommended Regimens

- FOLFIRI[11] (category 2B)
- Regorafenib[12] (category 2B)
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above[f]

Useful in Certain Circumstances[f]

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[5–7]
  - Larotrectinib[8]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[d,e,9]
- For cholangiocarcinoma with *FGFR2* fusions or rearrangements:
  - Pemigatinib[13]
- For cholangiocarcinoma with *IDH1* mutations
  - Ivosidenib[14]

[d] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Leyland-Jones B, Kato S, et al. Personalized, molecularly matched combination therapies for treatment-naïve, lethal malignancies: the I-PREDICT Study. J Clin Oncol 2017;35:2512.
[e] See Management of Immunotherapy-Related Toxicities.
[f] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.

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.

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-arrengements, BRAF, HER-2. MSI-H, TMB, PD-LI(+)
  - Gem/DDP (a first-line standard)
    - Gem/DDP+Nabpaclitaxel in selected pts?
  - FOLFOX (is it a second line standard in pt with no targetable mutations?)