Year in Review in Pancreatico-Biliary Cancers

Tanios Bekaii-Saab, MD, FACP

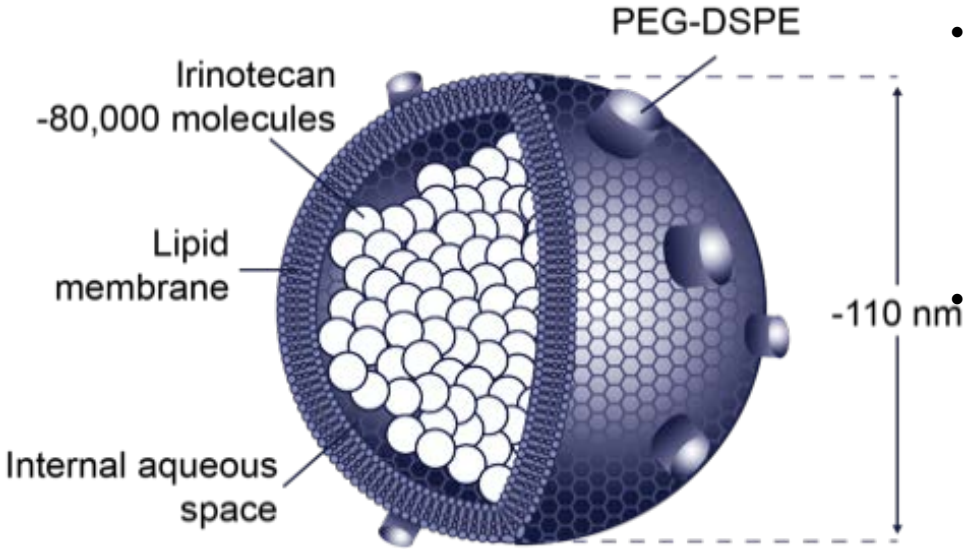
Agenda

- Liposomal Irinotecan in Pancreatic Cancer (PDAC)
- POLO trial (olaparib) in PDAC
- Platinums in PDAC
- FIGHT-202 (pemigatinib) and FOENIX-CCA2 (futibatinib) in intrahepatic cholangiocarcinoma
- ClarIDHy ivosidenib in intrahepatic cholangiocarcinoma

Courtesy of Tanios Bekaii-Saab, MD

Liposomal Irinotecan (nal-IRI): Drug Characteristics

nal-IRI is a stable nanoliposomal therapy



- The half-life (t½) of total irinotecan following administration of nal-IRI 70 mg/m^2 is 25.8 hours, >4 x longer than irinotecan (5.8 hours)[1,2]
- 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose[1]

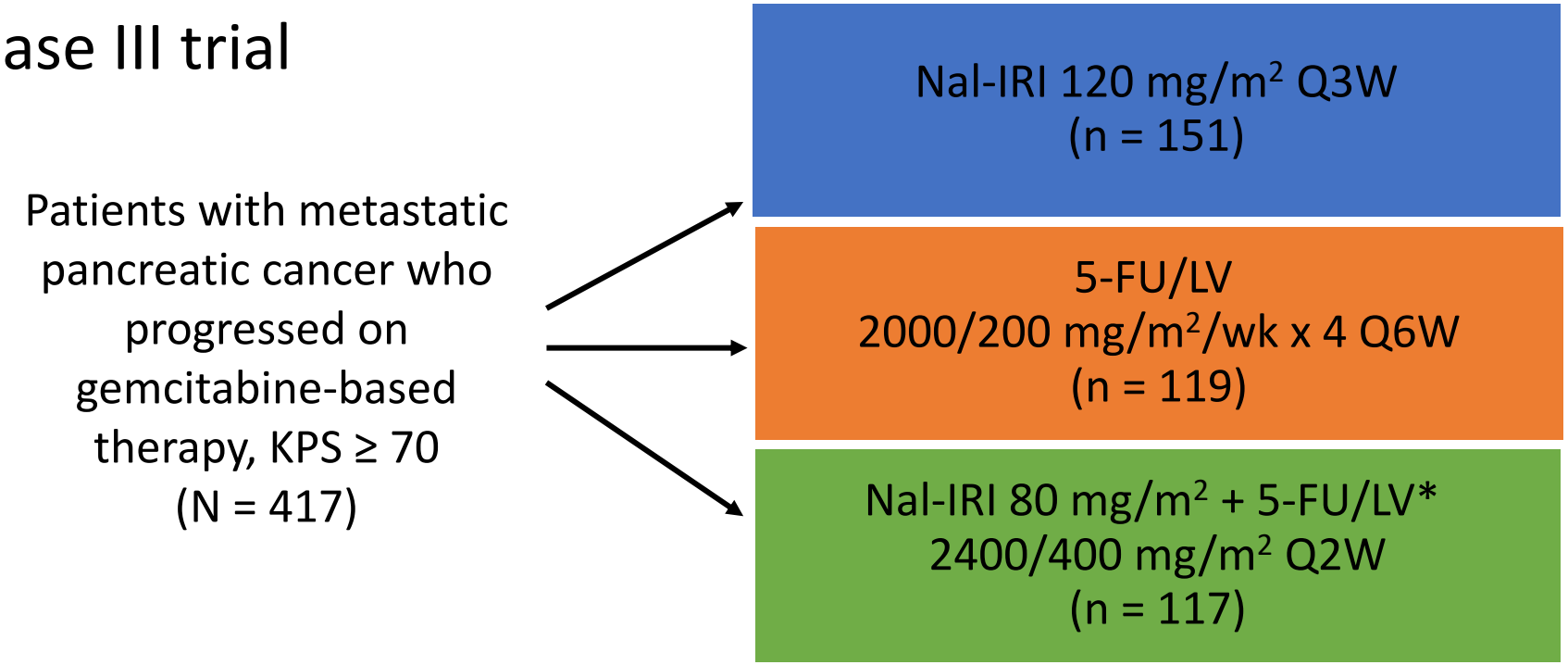
- In humans, nal-IRI results in 46-fold greater exposure of irinotecan in the blood than free irinotecan[3]
- In human tumor biopsies, SN-38 levels were substantially higher in tumor than plasma[4]
- nal-IRI resulted in SN-38 duration of exposure at site of tumor >3x longer than standard irinotecan in mouse model[5]
- nal-IRI had greater tumor volume reduction than free irinotecan in mouse models[5,6]

1. Irinotecan liposome Prescribing Information. https://www.onivyde.com/_assets/pdf/ONIVYDE_USPI.pdf. Accessed January 10, 2020.
2. Irinotecan Prescribing Information. https://www.pfizermedicalinformation.com/en-us/camptosar. Accessed January 10, 2020. 3. Adiwijaya BS et al. *Clin Pharmacol Ther*. 2017;102:997-1005. 4. Ramanathan RK et al. American Association for Cancer Research Annual Meeting 2014 (AACR 2014). Poster CT224. 5. Kalra AV et al. *Cancer Res*. 2014;74:7003-7013. 6. Goldwasser F et al. *Cancer Res*. 1995;55:2116-2121.

Courtesy of Tanios Bekaii-Saab, MD

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV in PDAC

- Phase III trial



*Combination arm added after safety data were available.
Patients in 5-FU/LV arm used as controls for combination arm.

Wang-Gillam A, et al. Lancet. 2016;387:545-557.

Courtesy of Tanios Bekaii-Saab, MD

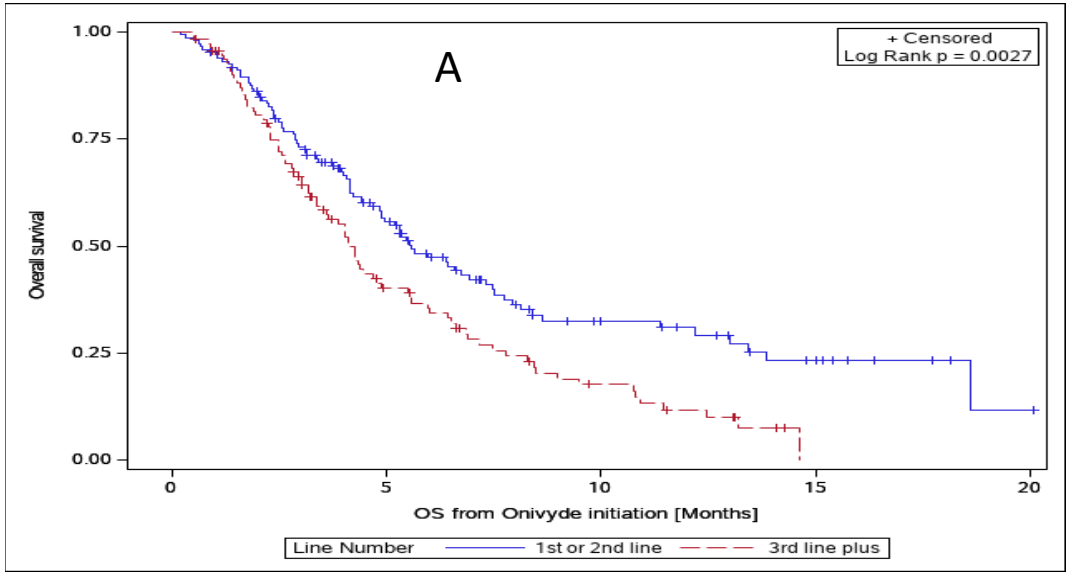
NAPOLI-1: Results

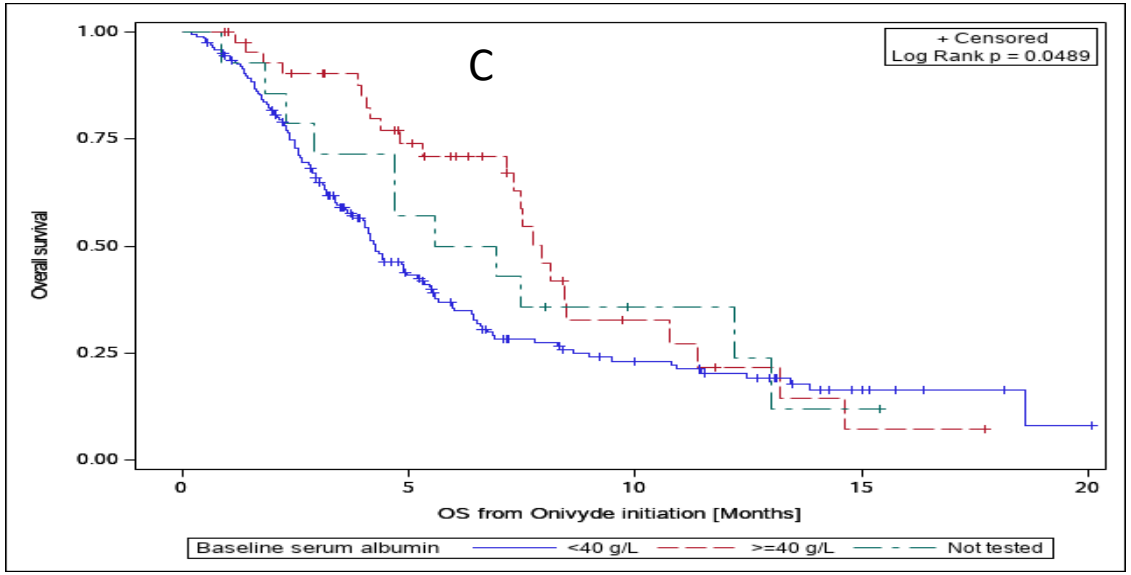
Tumor Response and Control	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 119)
Median OS, mos	6.1	4.2
	P = .0009	
Median PFS, mos	3.1	1.5
	P = .0001	
ORR, %	16	1
	P < .001	
CA19-9 reduction, %	36	12
	P = .0009	

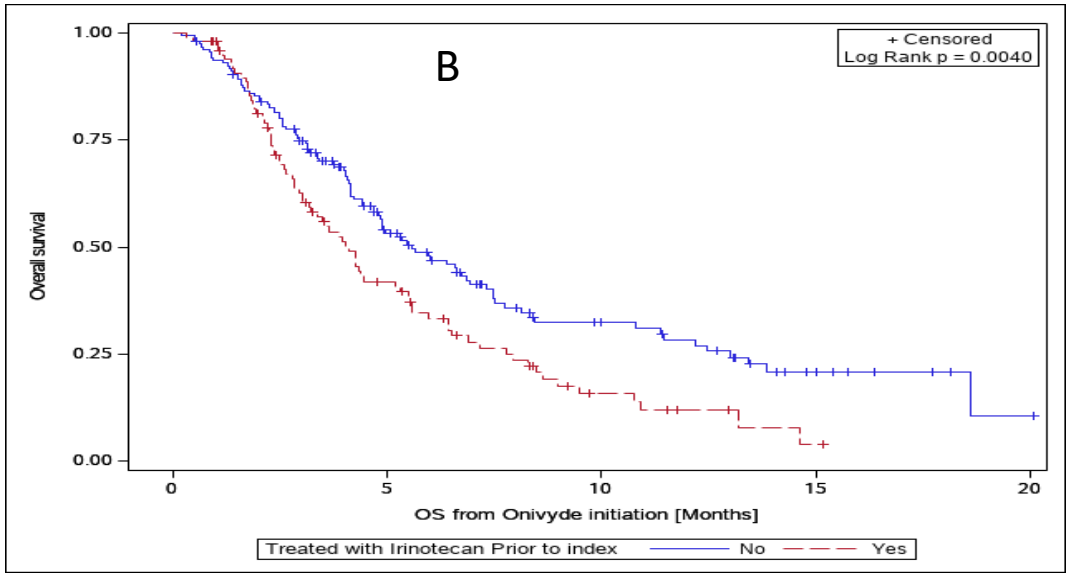
Wang-Gillam A, et al. Lancet. 2016;387:545-557.

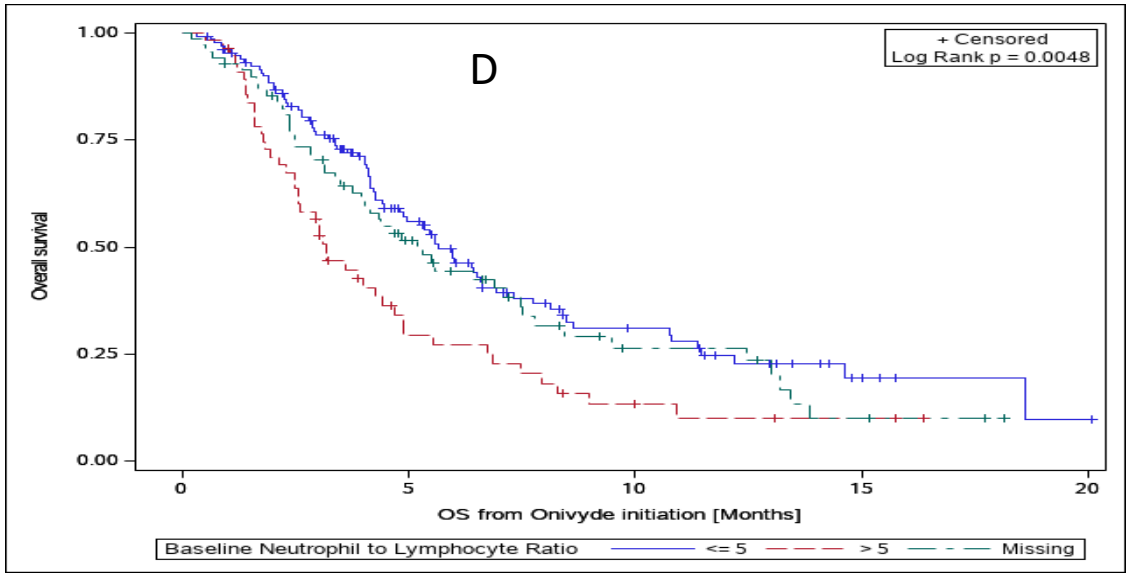
Courtesy of Tanios Bekaii-Saab, MD

RW Outcomes: Overall survival curves among patients by: (A) nal-IRI as first-/second-line therapy compared with third-line-or-later therapy, (B) prior treatment with irinotecan, (C) baseline serum albumin level, and (D) baseline neutrophil to lymphocyte ratio









Barzi A et al . *Pancreas* • Volume 49, Number 2, February 2020

Courtesy of Tanios Bekaii-Saab, MD

First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Primary analysis from a phase 1/2 study

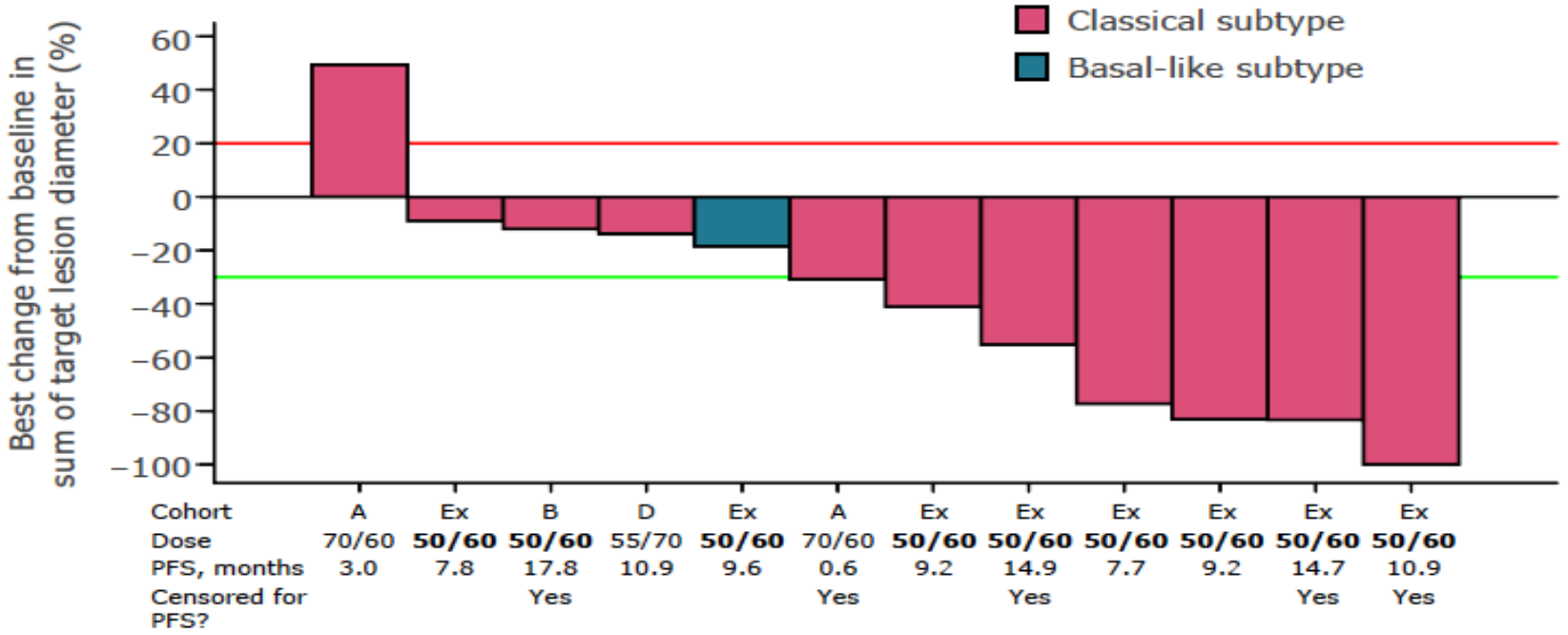
Outcome	NALIRIFOX (n=32)
Clinical Efficacy	
Median progression-free survival	9.2 months
Median overall survival	12.6 months
Objective response rate	34.4%
Disease control rate at week 16	71.9%
Median duration of response	9.4 months
Grade ≥3 Adverse Events	
Neutropenia	31.3%
Febrile neutropenia	12.5%
Hypokalemia	12.5%
Diarrhea	9.4%
Neutrophil count decreased	9.4%
Nausea	9.4%

Courtesy of Tanios Bekaii-Saab, MD

Wainberg, Z.A., et al. Presented at the ESMO World Congress on Gastrointestinal Cancer (WCGI 2020, abstract #LBA-1)

NALIRIFOX: Biomarkers – Genomic Profiling

Tumour response data were available for 12 patients



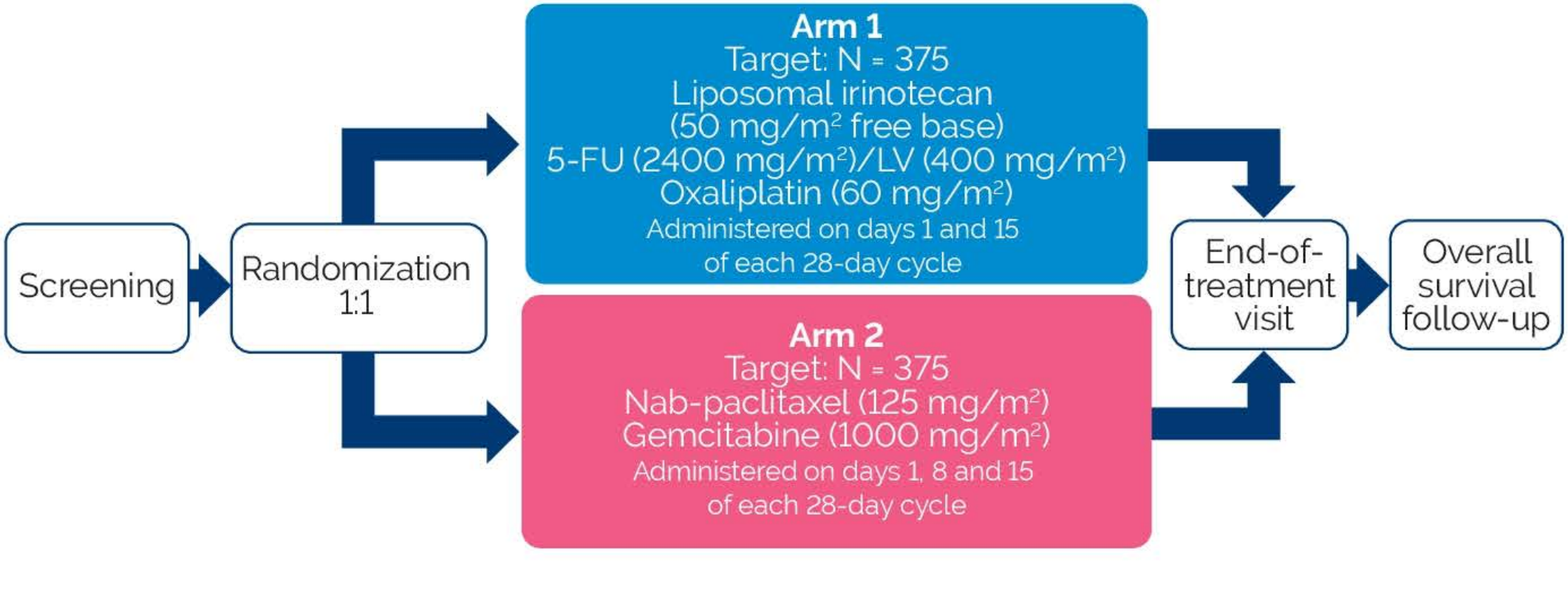
PFS in the pooled population 50/60

- Classical subtype: range 7.7–17.8 months (n = 8)
- Basal-like subtype: 9.6 months (n = 1)

Courtesy of Tanios Bekaii-Saab, MD

- Wainberg, Z.A., et al. Presented at the ESMO World Congress on Gastrointestinal Cancer (WCGI 2020, abstract #LBA-1)

NAPOLI-3: An open-label, randomized, phase III study of first-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin versus nab-paclitaxel + gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma



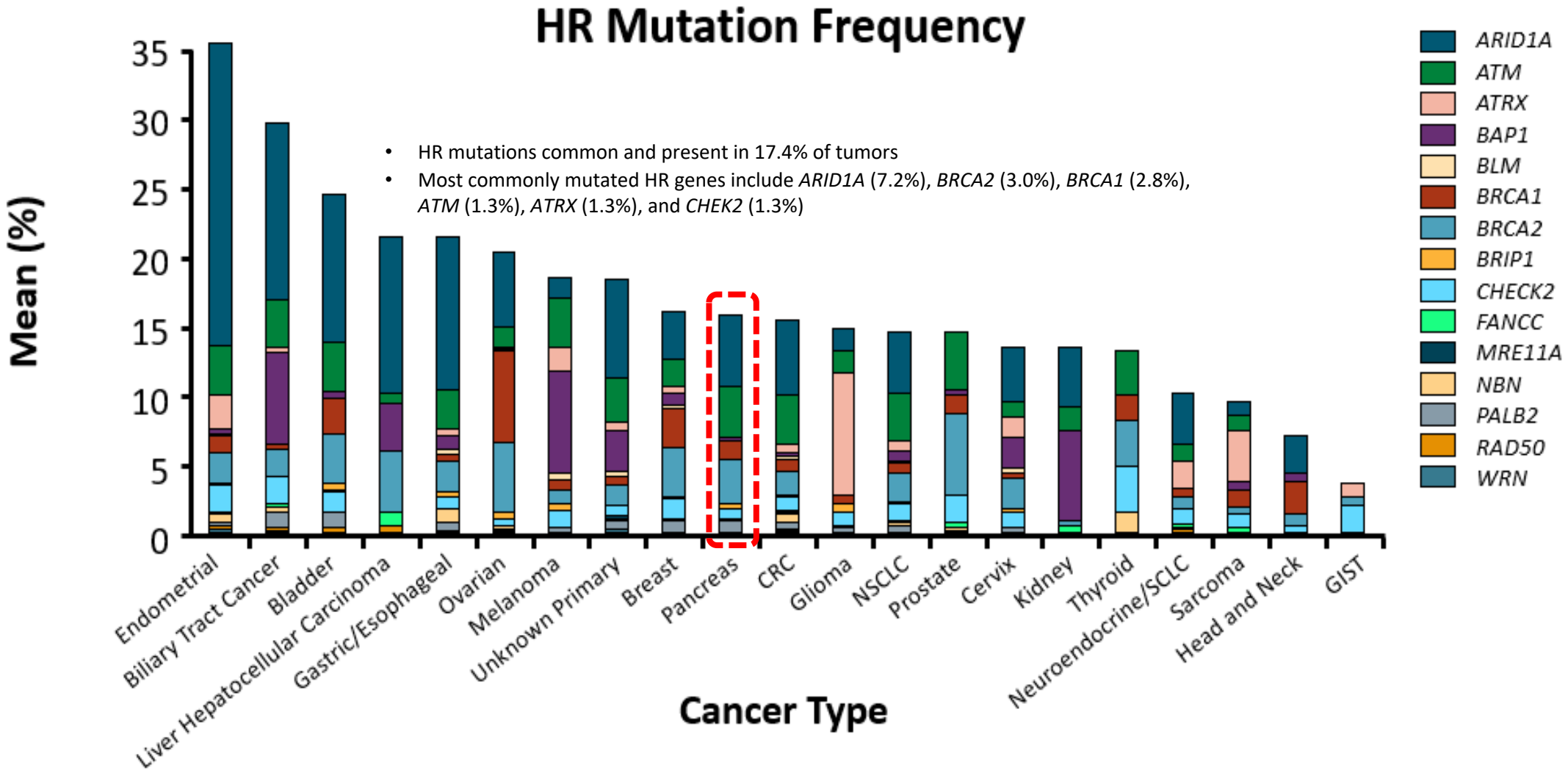
Wainberg, Z.A., et al. J Clin Oncol 38: 2020 (suppl; abstr TPS4661)

Courtesy of Tanios Bekaii-Saab, MD

Conclusions

- Clinical Implications
  - ❑Gemcitabine and nab-paclitaxel in first line allows for a better sequencing strategy with Liposomal Irinotecan plus 5-FU as a preferred option in second line
  - ❑Most patients will require dose modifications that will lead to at least equally good if not improved outcomes with Liposomal Irinotecan plus 5-FU
- Future Directions
  - ❑NAPOLI-3 assessing the role of NALIRIFOX in 1L PDAC
  - ❑New approaches to molecularly subclassify pancreatic cancer may allow for smarter treatment decisions

Courtesy of Tanios Bekaii-Saab, MD



Heeke. *JCO Precis Oncol*. 2018

Courtesy of Tanios Bekaii-Saab, MD

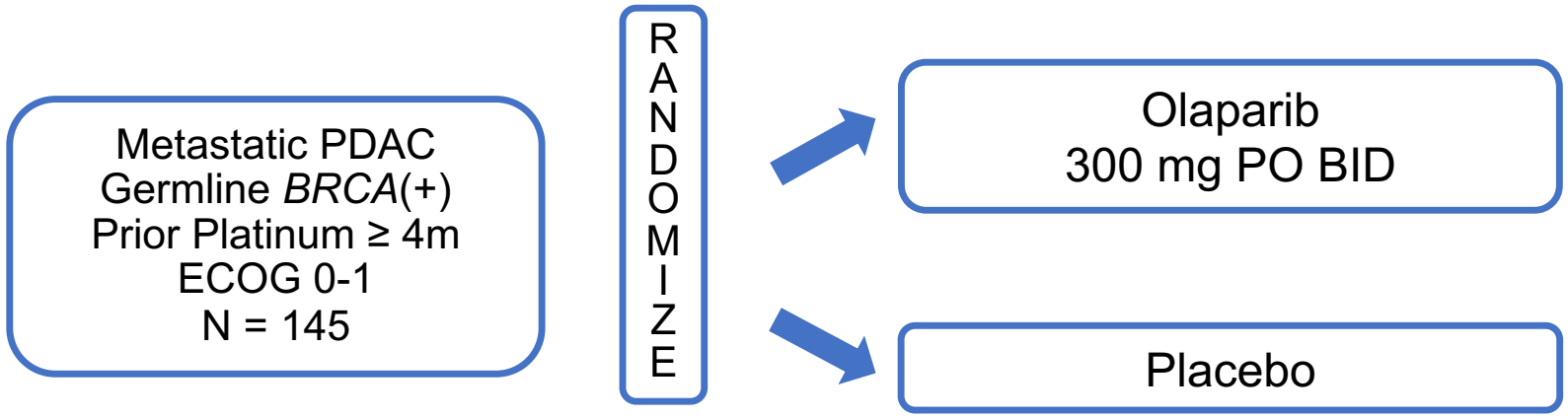
Single-Agent PARPi Trials in PDAC

	Olaparib	Veliparib	Talazoparib	Rucaparib
N	23	16	10	19
BRCA Type	Germline	Germline	Germline (including PALB2)	Germline (15)/ Somatic (4)
Lines of Therapy	Mean = 2	Mean = 2	1-2	1-2
Prior platinum	15/23 (65%)	14/16 (88%)	-	-
Response Rate	5/23 (22%)	**0%**	2/10 20%	3/19 (15%)
Stable Disease	8/22 (35%)	4/16 (25%) 4, 4, 10, 11 m	1/10 10%	4/19 (21%) 1 CR: 14 m+

Kaufmann, B. J Clin Oncol, 2014. Lowery, MA. Eur J Cancer, 2017. Domchek, S. J Clin Oncol, 2016 (34):4110

Courtesy of Tanios Bekaii-Saab, MD

POLO: Phase III Maintenance (Switch) in g*BRCA+* PDAC: Platinum Therapy → Olaparib/Placebo



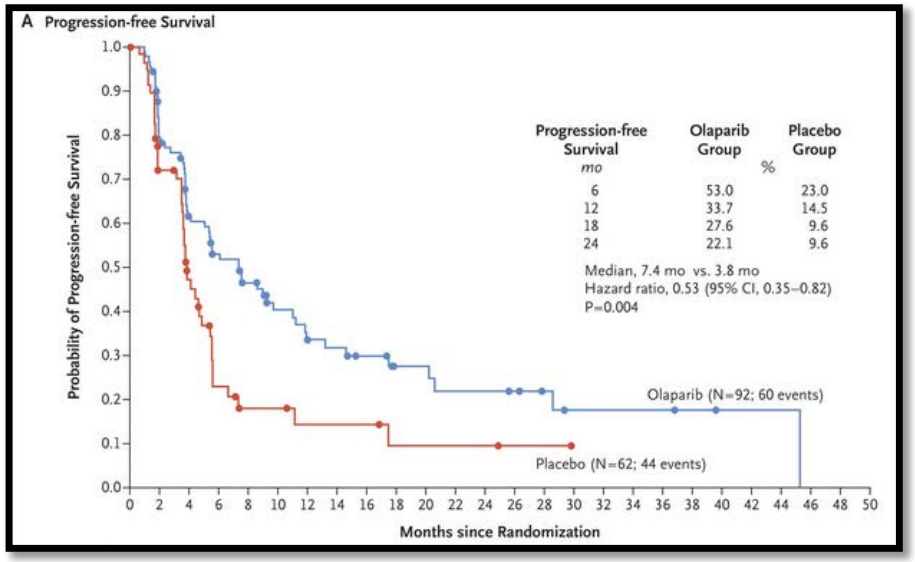
Randomization 3:2
Primary Endpoint: PFS (blinded independent central review mRECIST 1.1)
N ~ 3,500 screened

Golan T et al. *N Engl J Med.* 2019;381:317-327.

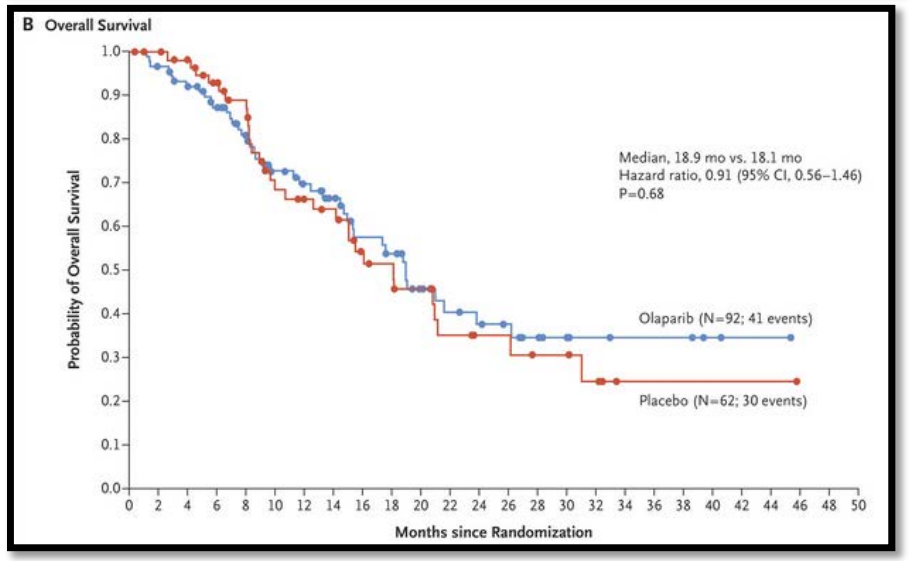
Courtesy of Tanios Bekaii-Saab, MD

POLO Trial Results

- 3315 patients screened to identify 154 eligible patients



Median PFS: 7.4 vs 3.8 mos
HR: 0.53 (*P* = .004)



No difference in OS on interim analysis
(Median OS, 18.9 vs 18.1 mos)
HR: 0.91 (*P* = 0.68)

Golan et al. N Engl J Med 2019;381(4):317-327;
Hochhauser et al. ESMO 2020;Abstract 1527P.

Courtesy of Tanios Bekaii-Saab, MD

Maintenance olaparib in patients aged ≥ 65 years with a germline *BRCA* mutation and metastatic pancreatic cancer: POLO trial

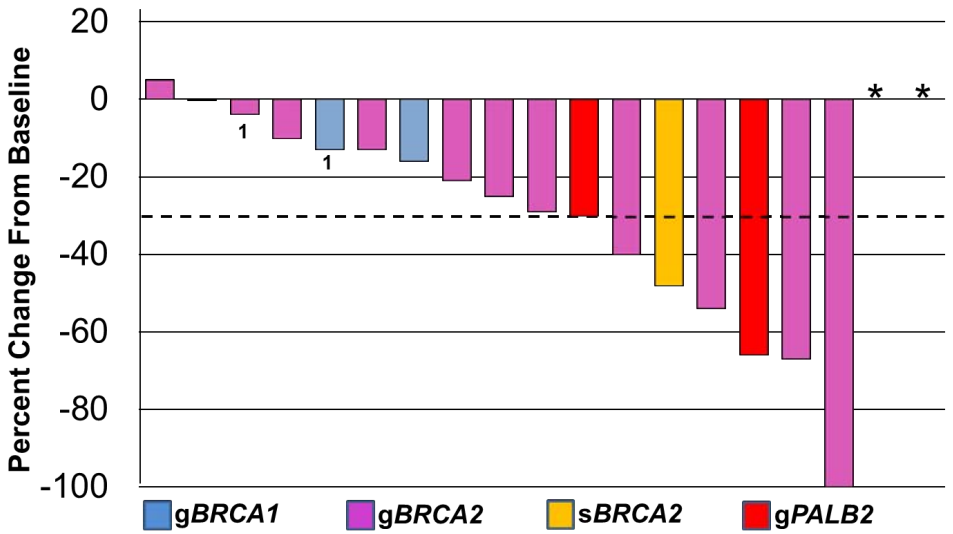
	Olaparib		Placebo	
	Age < 65 years (n = 63)	Age ≥ 65 years (n = 28)	Age < 65 years (n = 48)	Age ≥ 65 years (n = 12)
Any grade	59 (93.7)	28 (100)	44 (91.7)	12 (100)
CTCAE grade ≥ 3	24 (38.1)	12 (42.9)	10 (20.8)	4 (33.3)
AEs leading to death	0	0	0	0
SAEs	16 (25.4)	6 (21.4)	7 (14.6)	2 (16.7)
AEs leading to dose interruption	22 (34.9)	10 (35.7)	2 (4.2)	1 (8.3)
AEs leading to dose reduction	13 (20.6)	2 (7.1)	1 (2.1)	1 (8.3)
AEs leading to treatment discontinuation	3 (4.8)	2 (7.1)	1 (2.1)	0

Age at baseline, years	Duration of first-line treatment, months	Best response to maintenance therapy	Duration of maintenance therapy, months
37	5.9	SD	30.0
39	3.7	PR	28.1
47	3.7	PR	39.4
54	6.6	NED	45.4
56	3.7	PR	24.1
56	3.3	PR	25.6
57	11.8	CR	26.6
68	5.4	PR	33.0
70	5.0	PR	40.6
76	5.1	SD	24.1

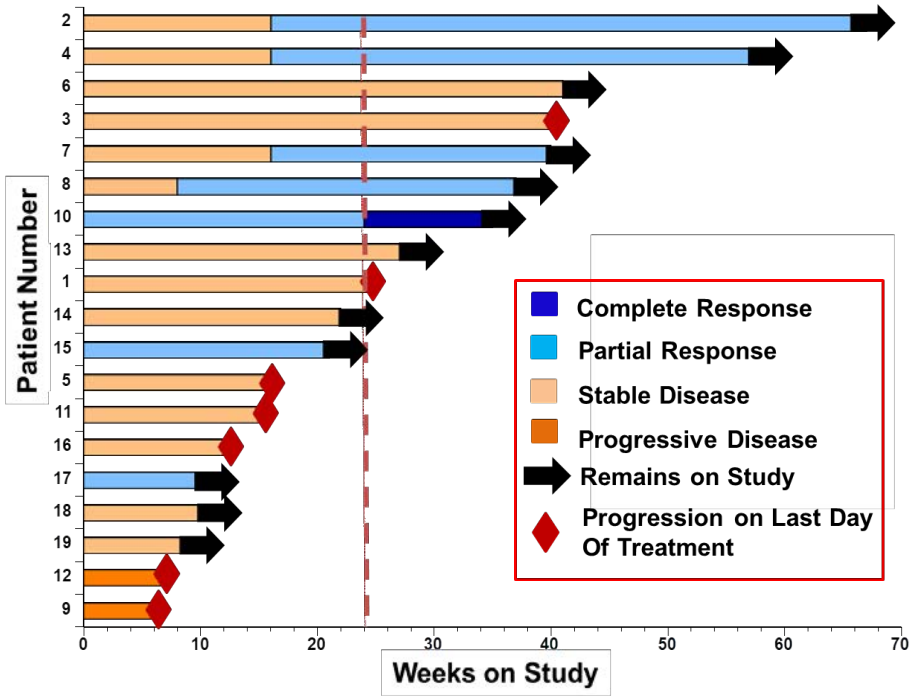
Kindler HL et al. ESMO GI 2020

Courtesy of Tanios Bekaii-Saab, MD

Maintenance Rucaparib Treatment in BRCA- or PALB2-Mutated PDAC (including Somatic Alterations)



ORR all patients	37.8%
ORR evaluable patients	41.1%
DCR at 8 weeks	89.5%



Binder KAR et al. *Cancer Res.* 2019;79(13_suppl): Abstract CT234.

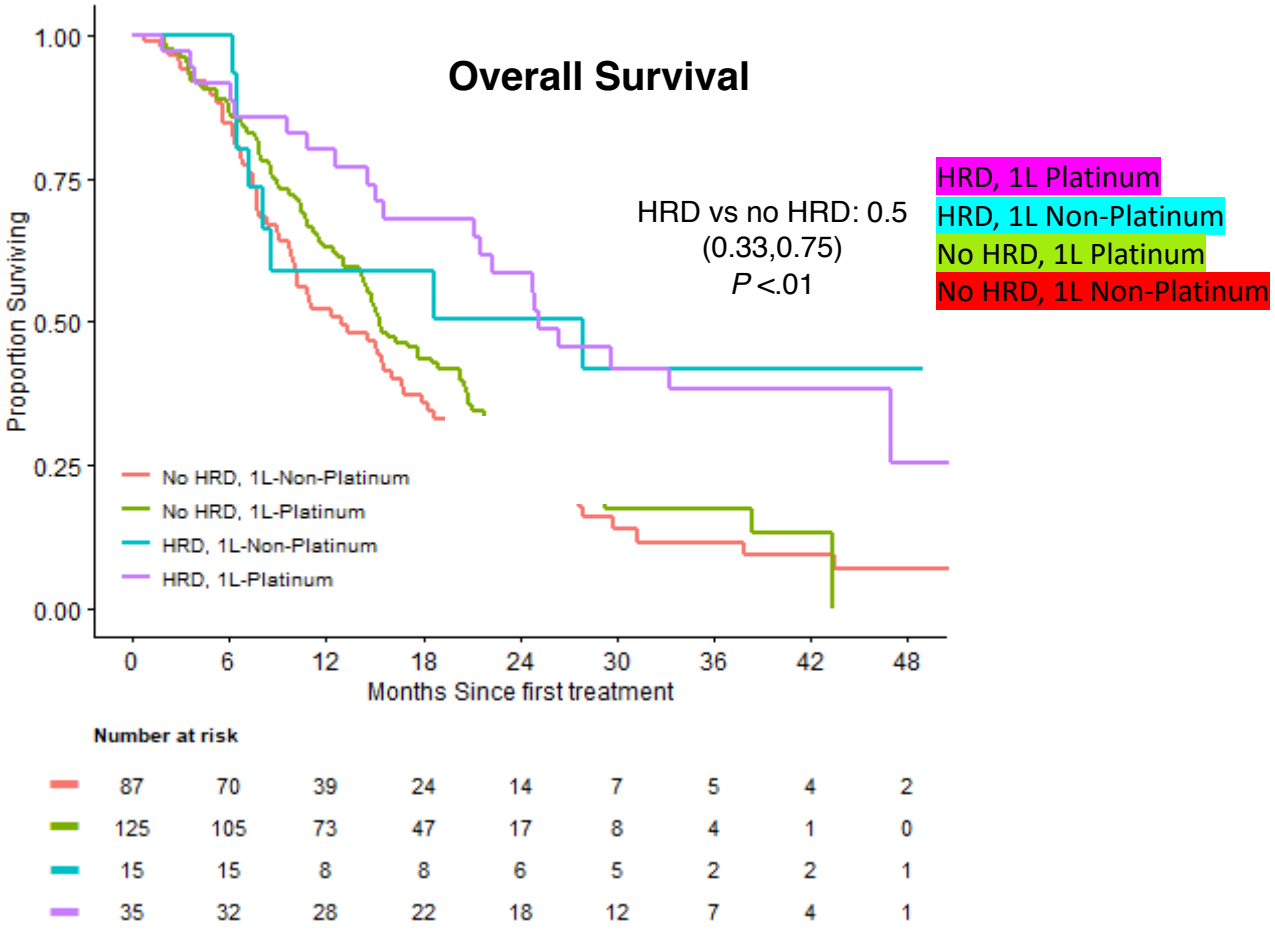
Courtesy of Tanios Bekaii-Saab, MD

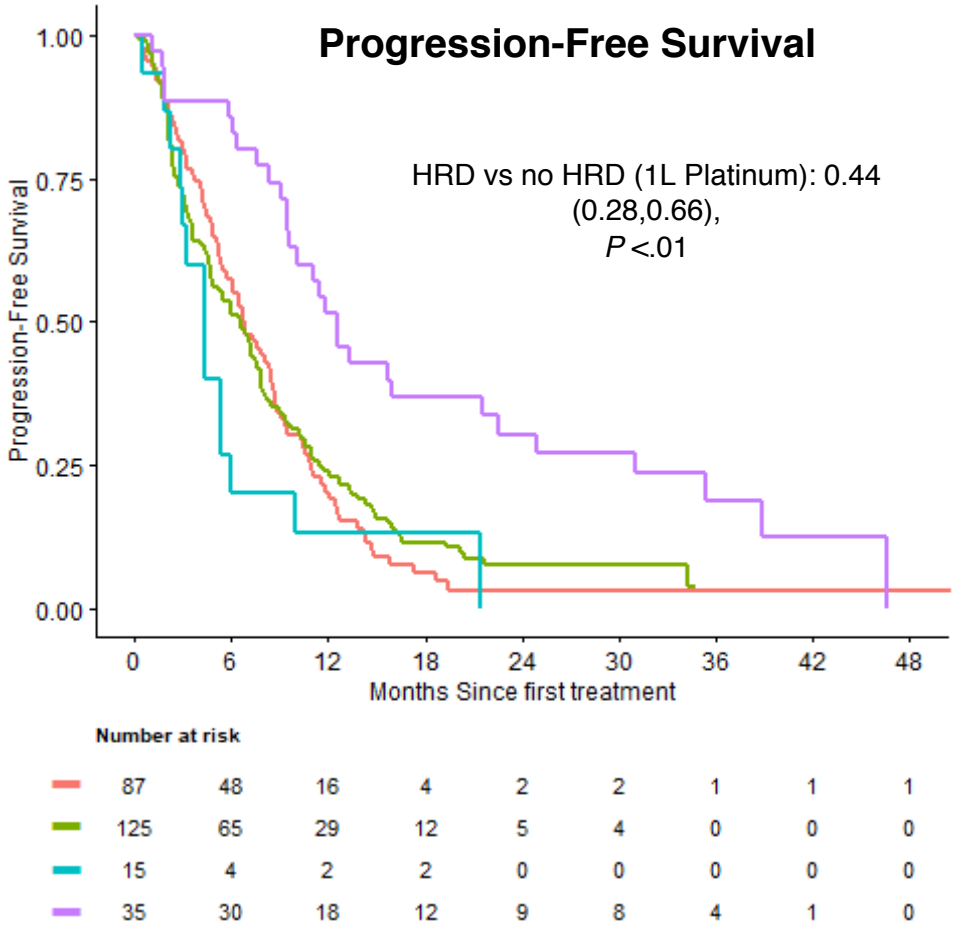
Conclusions

- Clinical Implications
  - ❑ Olaparib improves PFS but not OS as maintenance (**switch**) therapy for patients with advanced PDAC in the presence of germline *BRCA1/2* mutations, and can be considered as an option following disease control on at ≥4 months of up-front platinum-based chemotherapy
  - ❑ Side effects are predictable and appear to be consistent regardless of age
  - ❑ Data with rucaparib appears to suggest benefits in the presence of somatic *BRCA1/2* and germline and *PALB2* mutations
  - ❑ All patients with a diagnosis of pancreatic cancer should be offered germline testing and somatic tumor profiling
- Future Directions
  - ❑ Strategies aiming to maximize therapeutic index with sequential dosing Rucaparib combined with Liposomal Irinotecan are ongoing (NCT03337087)
  - ❑ Ongoing trials combining PARPi with PD-1i , MAPKi and other rational targets are underway
  - ❑ Expanding potential benefit to all HRR under study

Courtesy of Tanios Bekaii-Saab, MD

HR Deficiency and PDAC Outcome (N = 262)





Park W et al. *Clin Cancer Res.* 2020;26(13):3239-3247.

Courtesy of Tanios Bekaii-Saab, MD

Randomized Phase II Trial of Gemcitabine and Cisplatin +/- Veliparib in Patients With PDAC and Germline *BRCA/PALB2* Mutation

TABLE 2. Best Response to Treatment

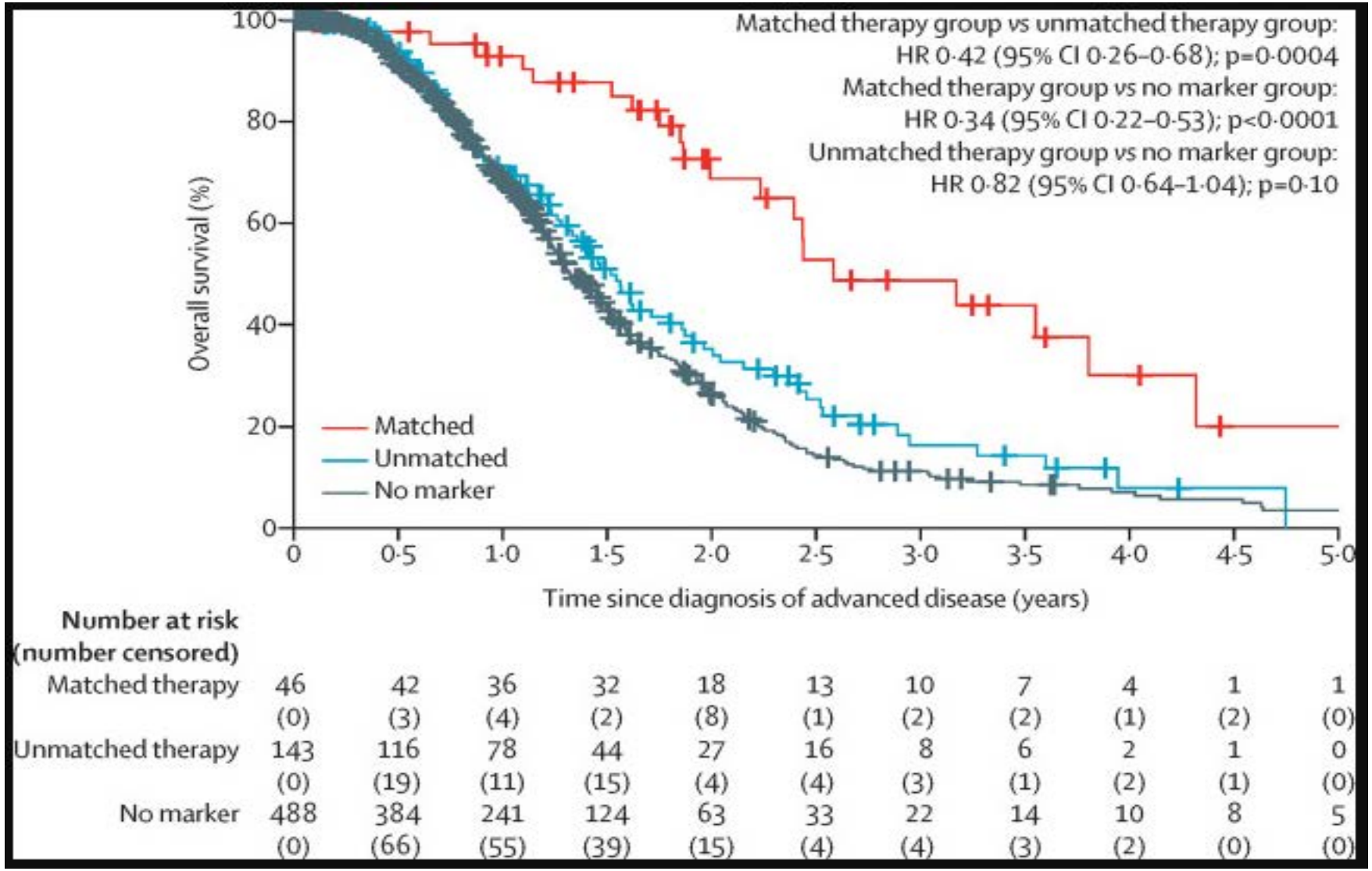
	Arm A (gemcitabine, cisplatin, veliparib) (n = 27)				Arm B (gemcitabine, cisplatin) (n = 23)				
Response	**No.**	**%**	**Median (months)**	**95% CI**	**No.**	**%**	**Median (months)**	**95% CI**	***P***
Response rate	20	74.1			15	65.2			.55
Disease control rate (CR + PR + SD)	27	100			18	78.3			.02
PFS			10.1	6.7 to 11.5			9.7	4.2 to 13.6	.73
OS			15.5	12.2 to 24.3			16.4	11.7 to 23.4	.6

Abbreviations: CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Eileen M. O'Reilly et al *Journal of Clinical Oncology* 2020 381378-1388.

Courtesy of Tanios Bekaii-Saab, MD

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial



Pishvaian M et al Lancet Oncology , 2020.

Courtesy of Tanios Bekaii-Saab, MD

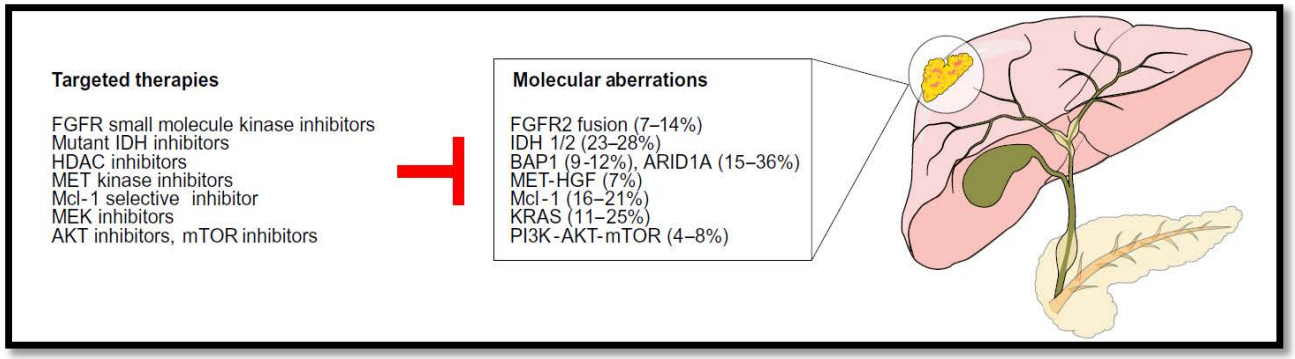
Conclusions

- Clinical Implications
  - ❑ Low dose Cisplatin + gemcitabine may be preferable over FOLFIRINOX in patients with *BRCA/PALB* mutations. Consider every other week schedule
- Future Directions
  - ❑Novel therapeutics under investigation may one day complement, but are unlikely to replace, standard cytotoxic agents
    - Include stromal-depleting agents, immunotherapies, and signal transduction inhibitors

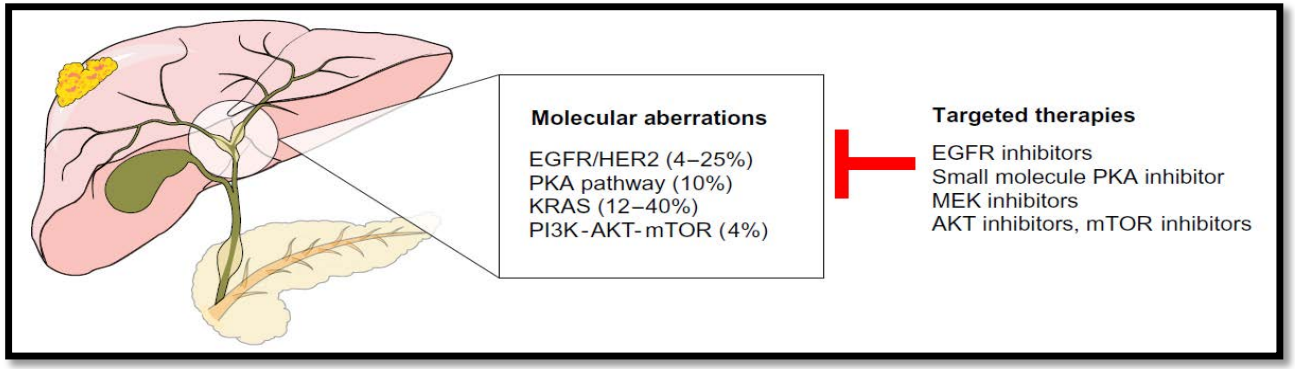
Courtesy of Tanios Bekaii-Saab, MD

Biliary Tract Cancers (BTC) : A Complex Landscape

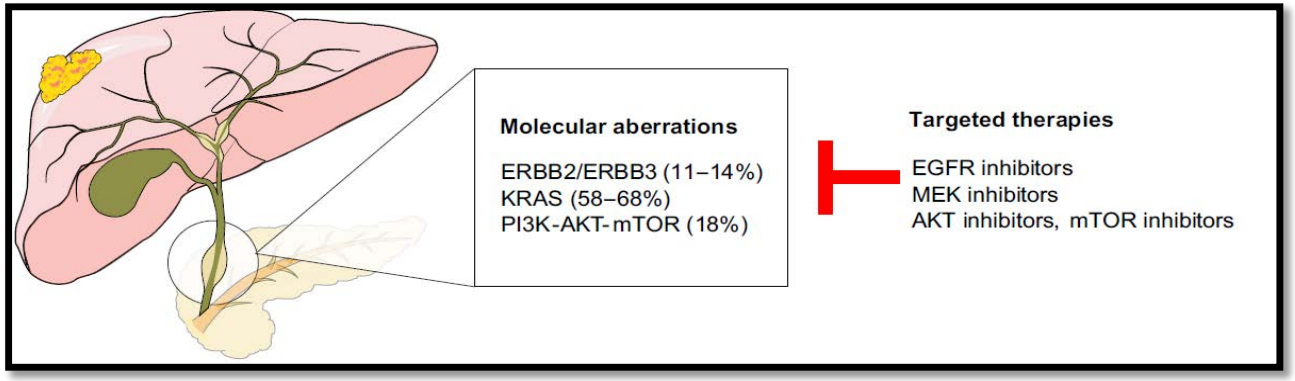
Anatomic and Genetic Diversity → Targets Galore



Intrahepatic Cholangiocarcinoma (IHCC)



Perihilar Cholangiocarcinoma

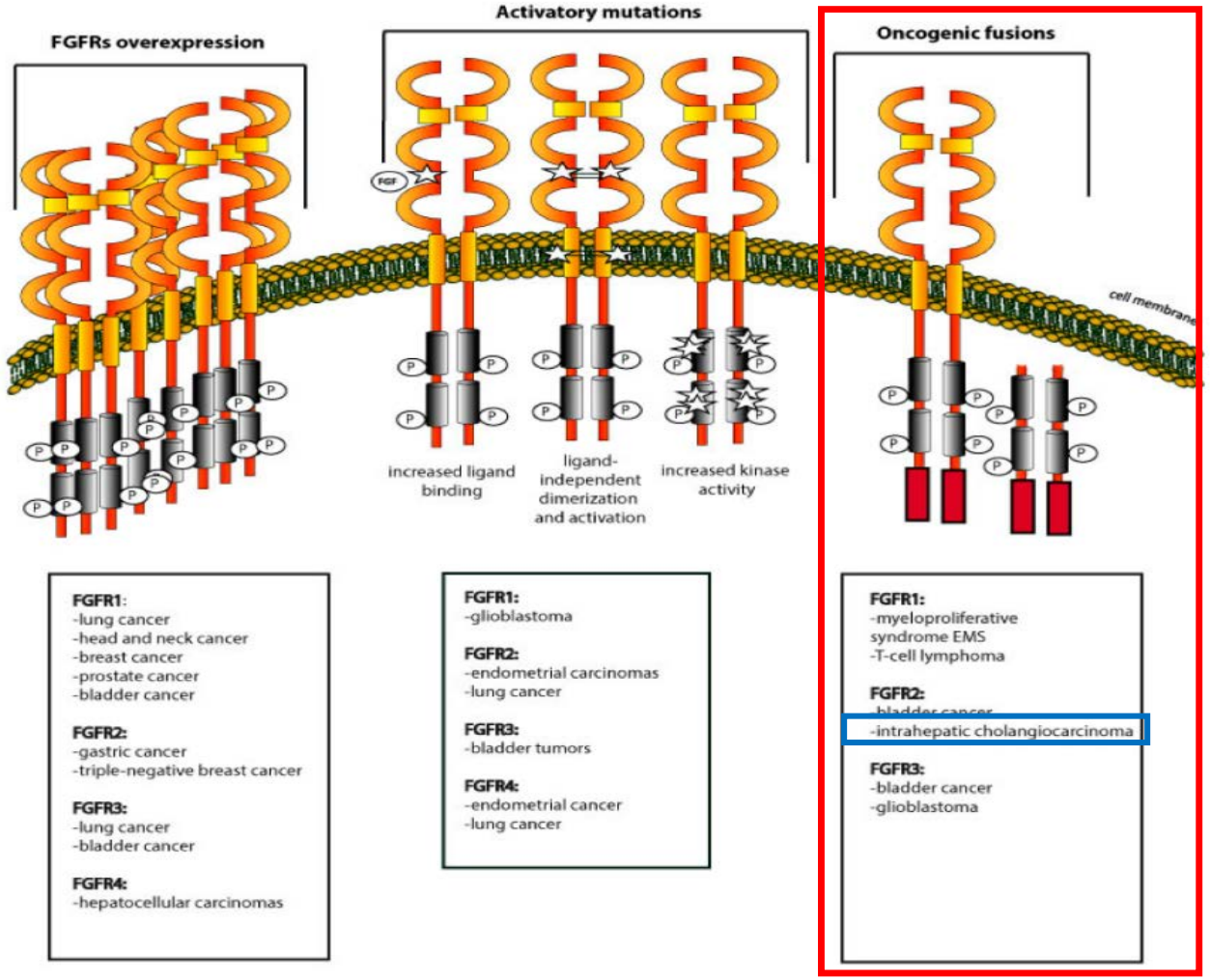


Distal Cholangiocarcinoma + Gallbladder Cancer

Valle J et al. Cancer Discov 2017;7:943-962

Courtesy of Tanios Bekaii-Saab, MD

Targeting Dysregulation of FGFR in BTC



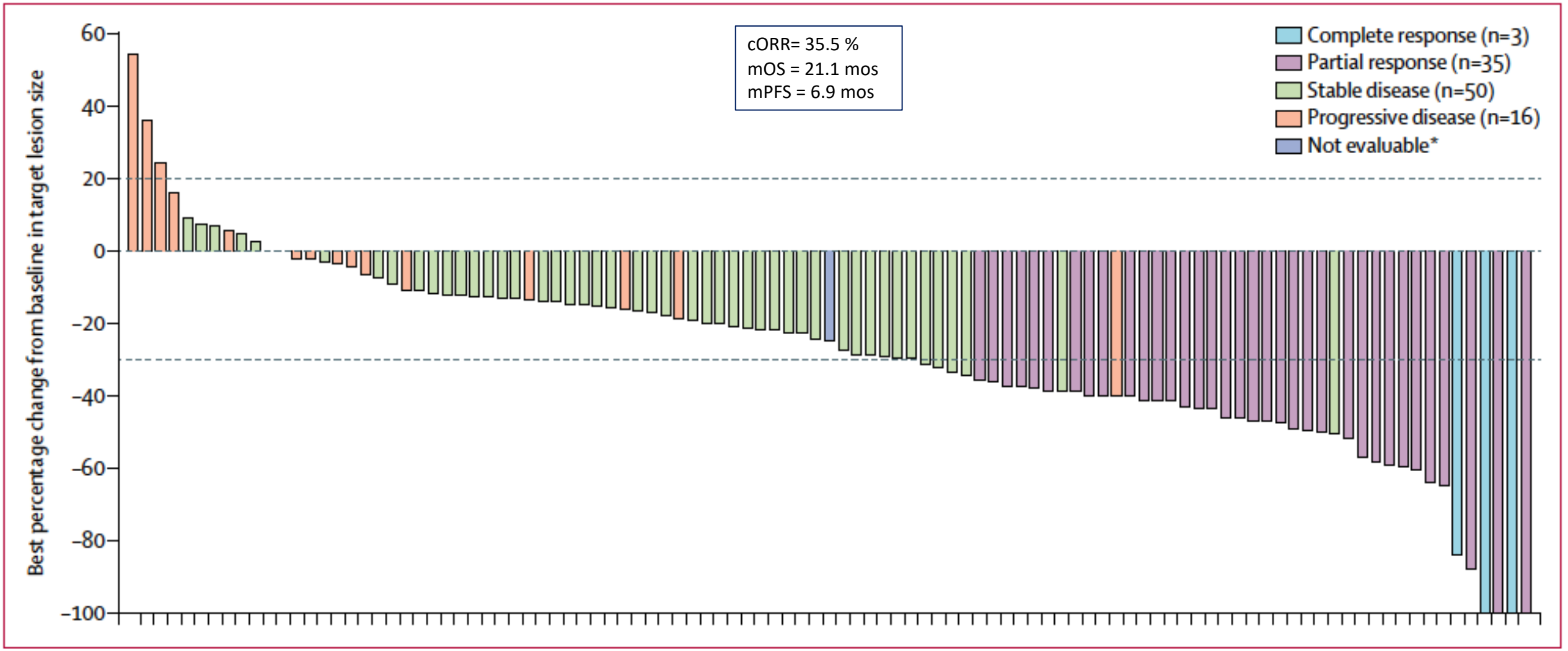
Agents in Development:

- Pemigatinib
- Infigratinib
- Futibatinib
- Derazantinib
- And others

Borad M et al. Current Opinion in Gastroenterology. May 2015

Courtesy of Tanios Bekaii-Saab, MD

FIGHT-202 (Pemigatinib)
Waterfall Plot results for individual patients with *FGFR2* fusions or rearrangements



Abou-Alfa G et al. Lancet Oncology . March 20 , 2020

Courtesy of Tanios Bekaii-Saab, MD

Pemigatinib: Common AEs

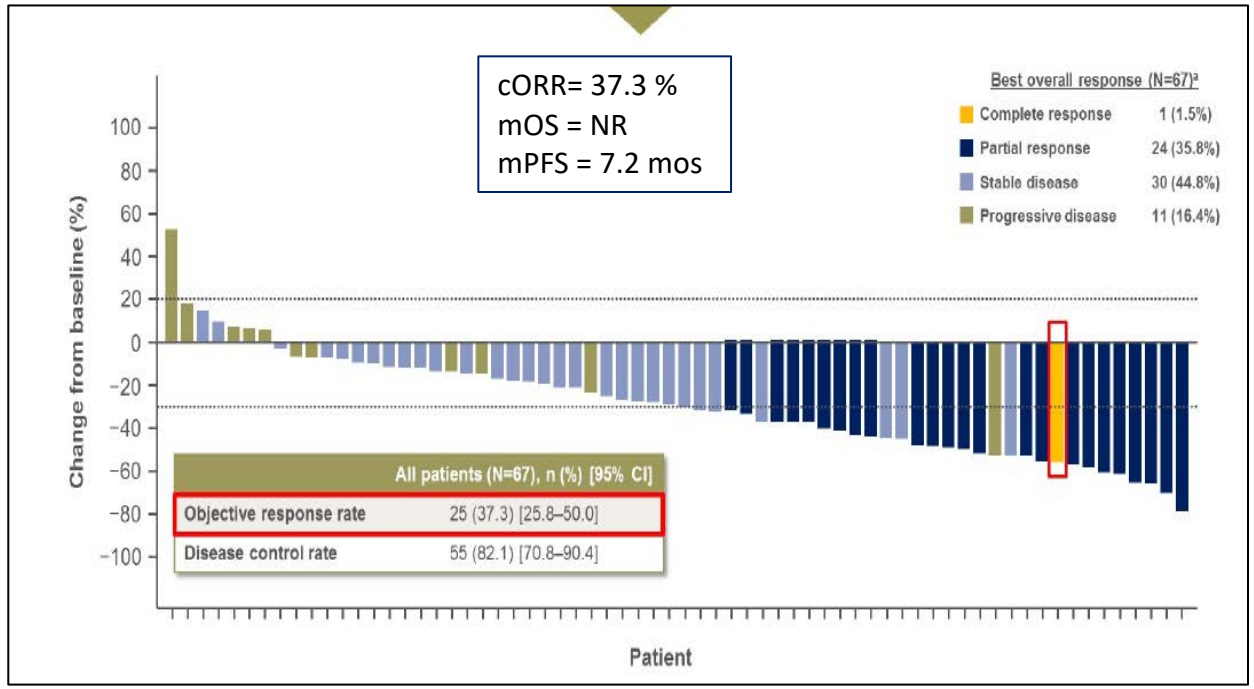
	Grade 1–2	Grade 3	Grade 4
Paronychia	81 (55%)	0	0
Alopecia	67 (46%)	0	0
Dysgeusia	55 (38%)	0	0
Diarrhoea	49 (34%)	4 (3%)	0
Fatigue	45 (31%)	2 (1%)	0
Stomatitis	39 (27%)	8 (5%)	0
Dry mouth	42 (29%)	0	0
Nausea	34 (23%)	2 (1%)	0
Decreased appetite	34 (23%)	1 (1%)	0
Dry eye	30 (21%)	1 (1%)	0
Dry skin	22 (15%)	1 (1%)	0
Arthralgia	16 (11%)	6 (4%)	0
Palmar-plantar erythrodysaesthesia	16 (11%)	6 (4%)	0
Constipation	20 (14%)	0	0
Hypophosphataemia*	8 (5%)	10 (7%)	0
Pain in extremity	15 (10%)	0	0
Vomiting	13 (9%)	1 (1%)	0
Weight decreased	13 (9%)	1 (1%)	0
Myalgia	10 (7%)	1 (1%)	0
Nail discolouration	10 (7%)	1 (1%)	0
Abdominal pain	8 (5%)	1 (1%)	0
Anaemia	8 (5%)	1 (1%)	0
Onychoclasis	8 (5%)	1 (1%)	0
Paronychia	8 (5%)	1 (1%)	0

Courtesy of Tanios Bekaii-Saab, MD

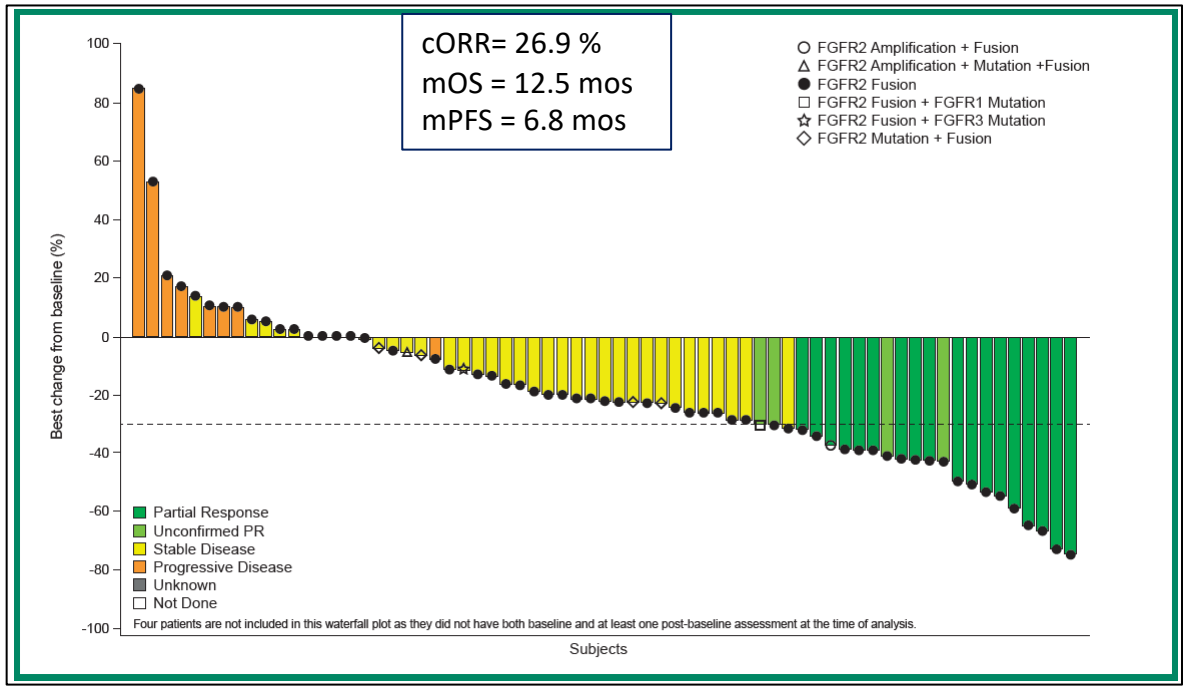
Abou-Alfa G et al. Lancet Oncology . March 20 , 2020

Other FGFR inhibitors in patients with FGFR2 fusions and IHCC

FUTIBATINIB (FOENIX-CCA2 Phase II Trial)[1]



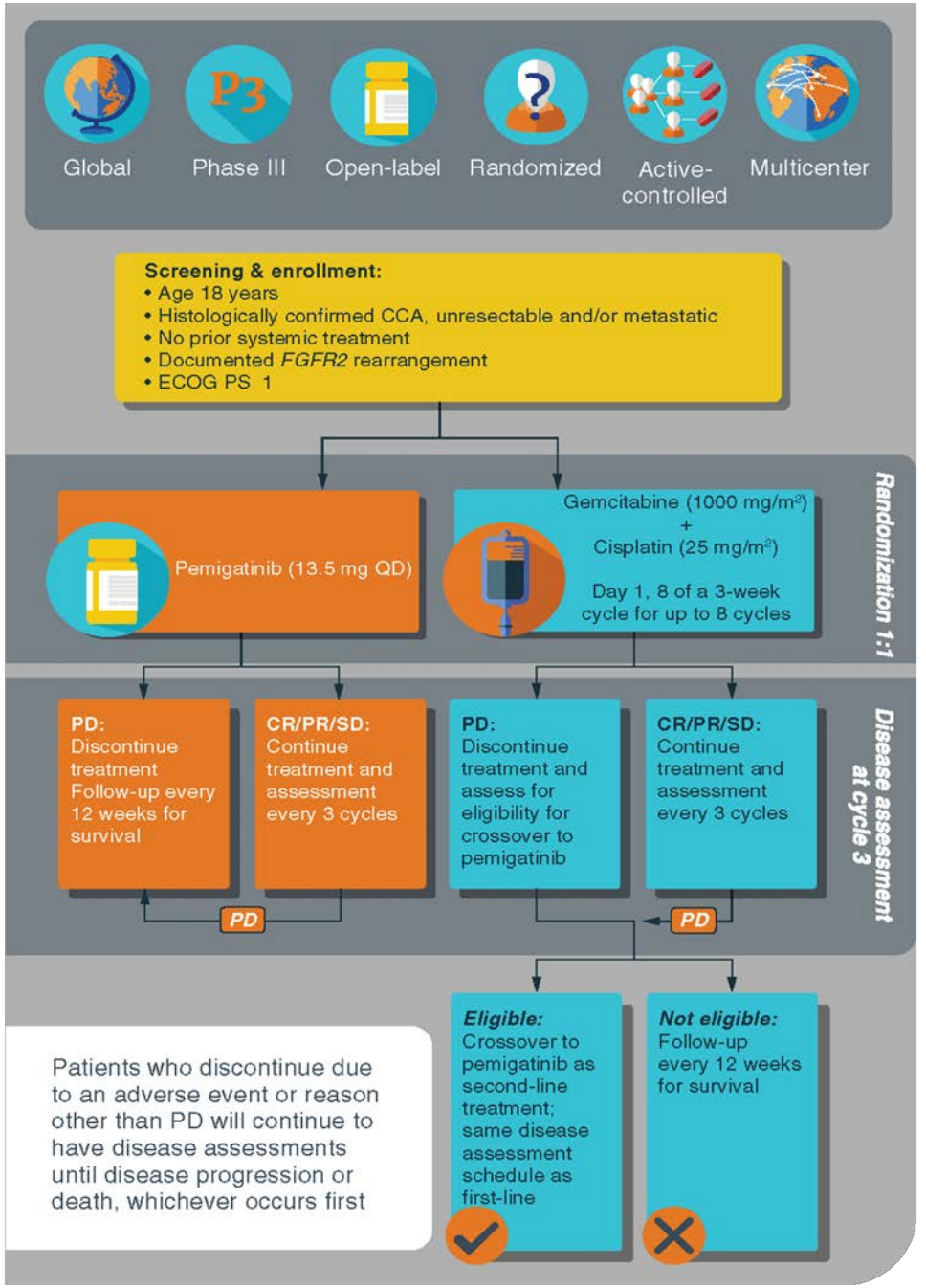
INFIGRATINIB (Phase II Trial)[2]



1-Goyal L et al ASCO 2020; 2- Javle M et al ESMO 2018

Courtesy of Tanios Bekaii-Saab, MD

FIGHT-302: 1L Pemigatinib vs gemcitabine plus cisplatin for advanced IHCA with *FGFR2* rearrangements



Bekaii-Saab T et al. *Future Oncology* 2020.

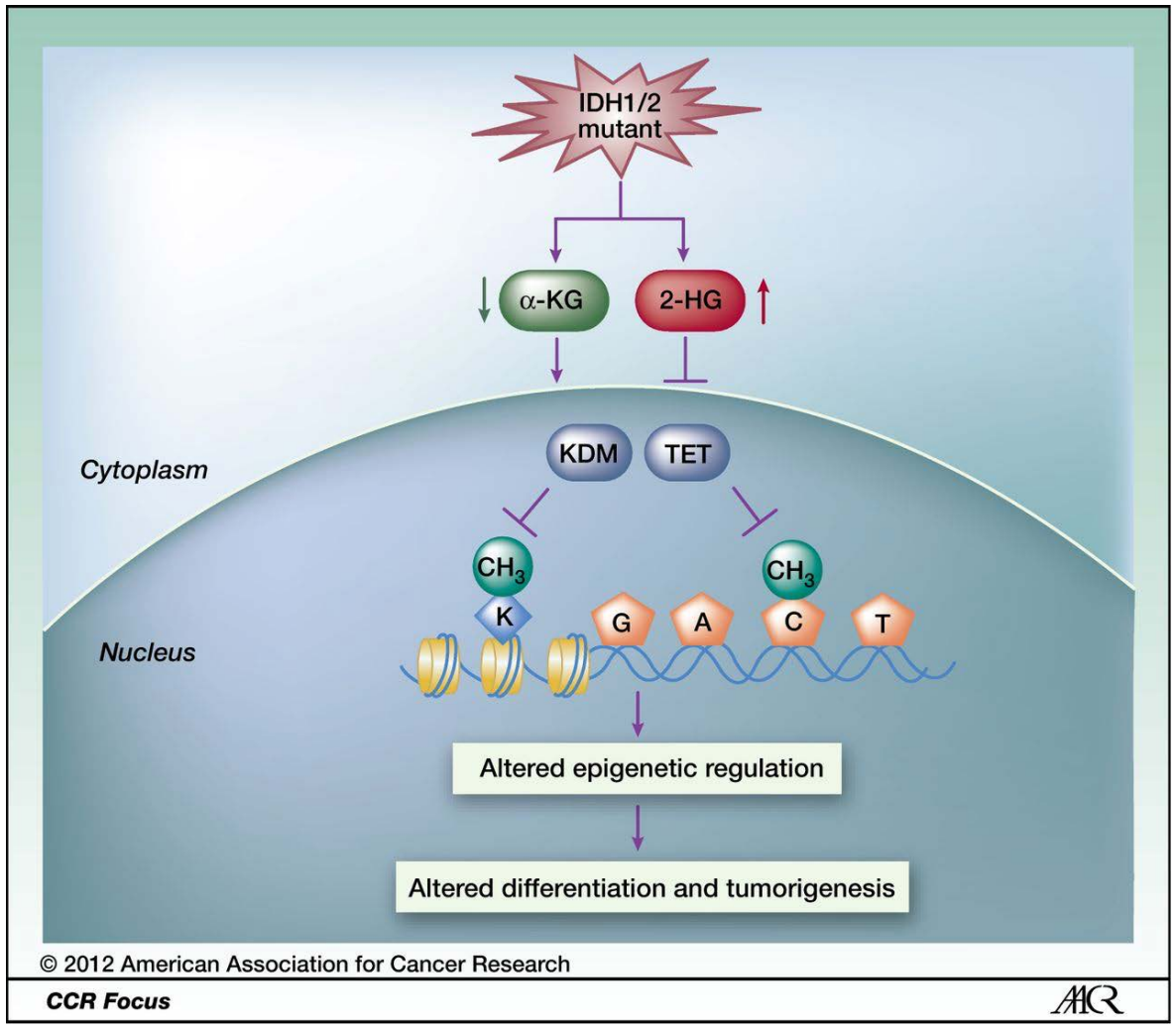
Courtesy of Tanios Bekaii-Saab, MD

Conclusions

- Clinical Implications
  - ❑Targeting FGFR2 fusions has been validated consistently with multiple agents in development
  - ❑Pemigatinib has recently been approved by FDA for clinical use in refractory IHCA with FGFR2 fusions
  - ❑Side effects: Hyperphosphatemia, skin/nail toxicities, mucosal toxicities…
- Future Directions
  - ❑Ongoing trials with first line strategies in IHCA and FGFR2 fusions vs. standard gemcitabine/cisplatin
  - ❑ Better understanding mechanisms of resistance
  - ❑Potential activity in other FGFR alterations (less interesting)

Courtesy of Tanios Bekaii-Saab, MD

IDH1/2 mutations inhibit both histone and DNA demethylation and alter epigenetic regulation.



Hui Yang et al. Clin Cancer Res 2012;18:5562-5571

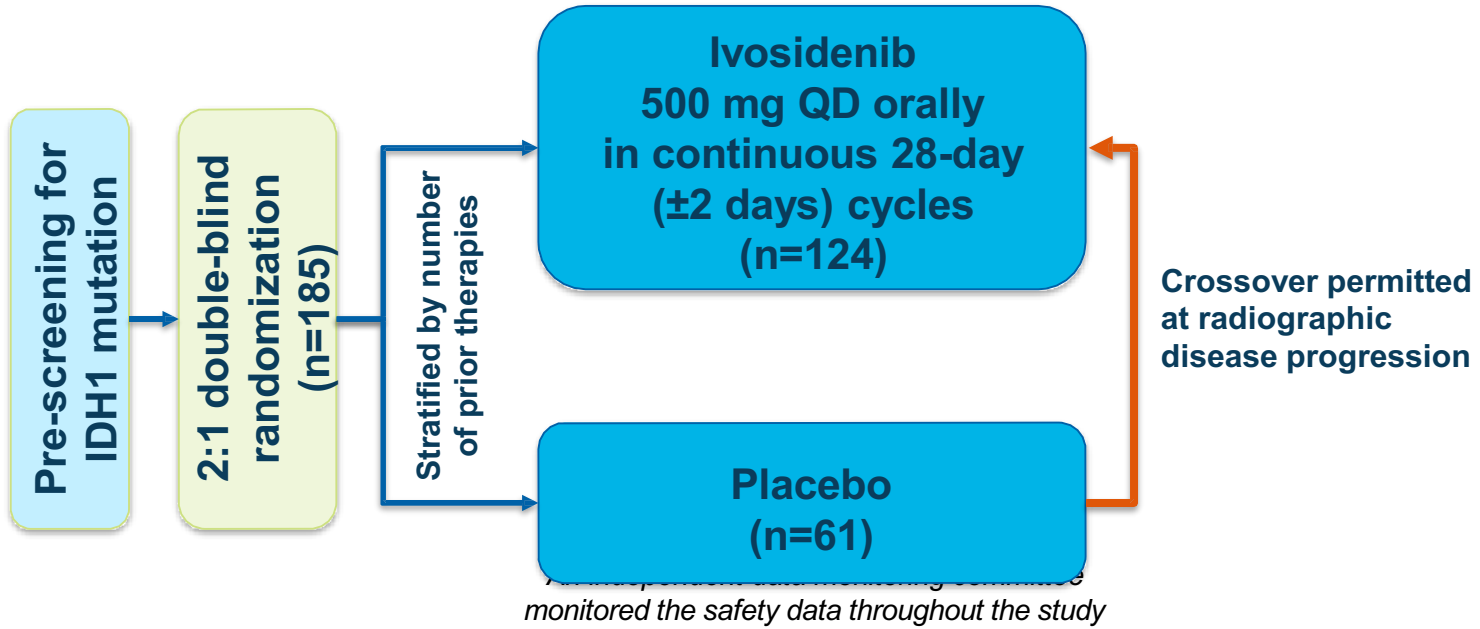
Courtesy of Tanios Bekaii-Saab, MD

ClarIDHy

Key eligibility criteria

- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- 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

NCT02989857



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

*IDH1 mutation status prospectively confirmed by NGS-based Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments-certified laboratory.

†Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions.

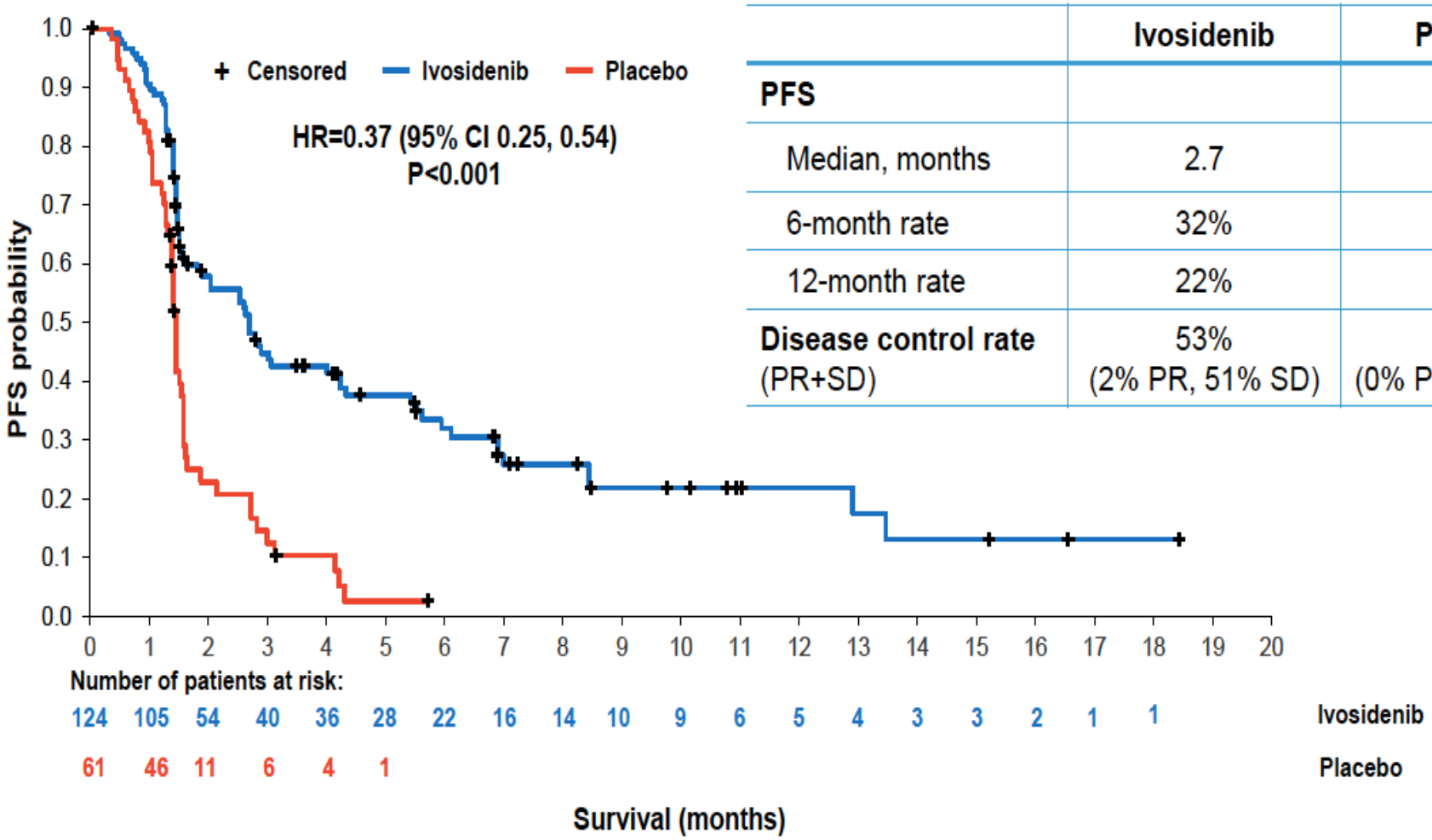
ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=5-level EuroQoL-5 Dimension questionnaire; FU=fluorouracil; NGS=next-generation sequencing; PGI=Patient Global Impression; QD=once daily; QLQ-BIL21=Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30=Quality of Life Questionnaire Core 30;

RECIST=Response Evaluation Criteria in Solid Tumors.

Courtesy of Tanios Bekaii-Saab, MD

Abou Alfa et al ESMO 2019

Targeting IDH1 in IHCC: Ivosidenib vs. Placebo



	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)

Abou-Alfa GK et al. *Lancet Oncol* 2020;32(6):796-807; Abou-Alfa G et al. ESMO 2019

Courtesy of Tanios Bekaii-Saab, MD

Conclusions

- Clinical Implications
  - ❑Ivosidenib achieved its primary endpoint of PFS in IDH1 MT IHCA without improving OS
    - ❑Currently under review at FDA
- Future Directions
  - ❑Combining IDH1 inhibitors with chemotherapy and moving to 1L
  - ❑There are ongoing efforts to expand the role of targeted therapies to IDH2, BRAF V600E, HER2 amplifications and others.

Courtesy of Tanios Bekaii-Saab, MD