Updates in Pancreatic And Biliary Cancers

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NCI Designated Comprehensive Cancer Center

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- Ad-hoc SAB: Taiho, Ignyta, Glycyx, Array

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Outline

- Adjuvant treatment of PDAC
  - APACT vs PRODIGE vs ESPAC-4 trial
- Maintenance treatment for BRCA+ PDAC
  - POLO trial
- New standard 2nd line for advanced biliary cancers
  - ABC-06 trial

PDAC = Pancreatic ductal adenocarcinoma

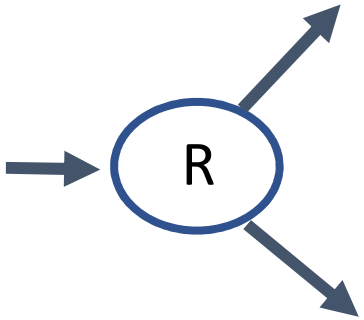
State of the art for PDAC

- Early stage:
  - Adjuvant vs. neoadjuvant
  - Role of radiation: GITSG 1985?
- Locally advanced disease: Chemo +/- radiation
- Metastatic disease:
  - 1L: Folfirinox or Nab-paclitaxel + Gem > Gem
  - 2L: MM-398/5FU, fluoropyrimidines + oxaliplatin
  - Genetic testing in **every patient**: dMMR, *NTRK, BRCA*

PDAC = Pancreatic ductal adenocarcinoma

ESPAC-4: GEMCAP > GEM

POPULATION N=732
PDAC < 12 w
Age > 18yo, PS 0-2*
Ca19.9 no limit
No mandatory postop CT scan
92 centers (>UK)
R0/R1
1º Endpoint OS
STRATIFICATION
Country



Gem 1000mg/m2 d1, 8 & 15 x 6 m

Gem 1000mg/m2
Cape 1660mg/m2 d 1-21 x 6 m

*98% PS 0-1, 2% PS 2
High risk population: R1 60%, LN+ 80%, No limit Ca19.9
OS = overall survival

Neoptolemos Lancet 2017

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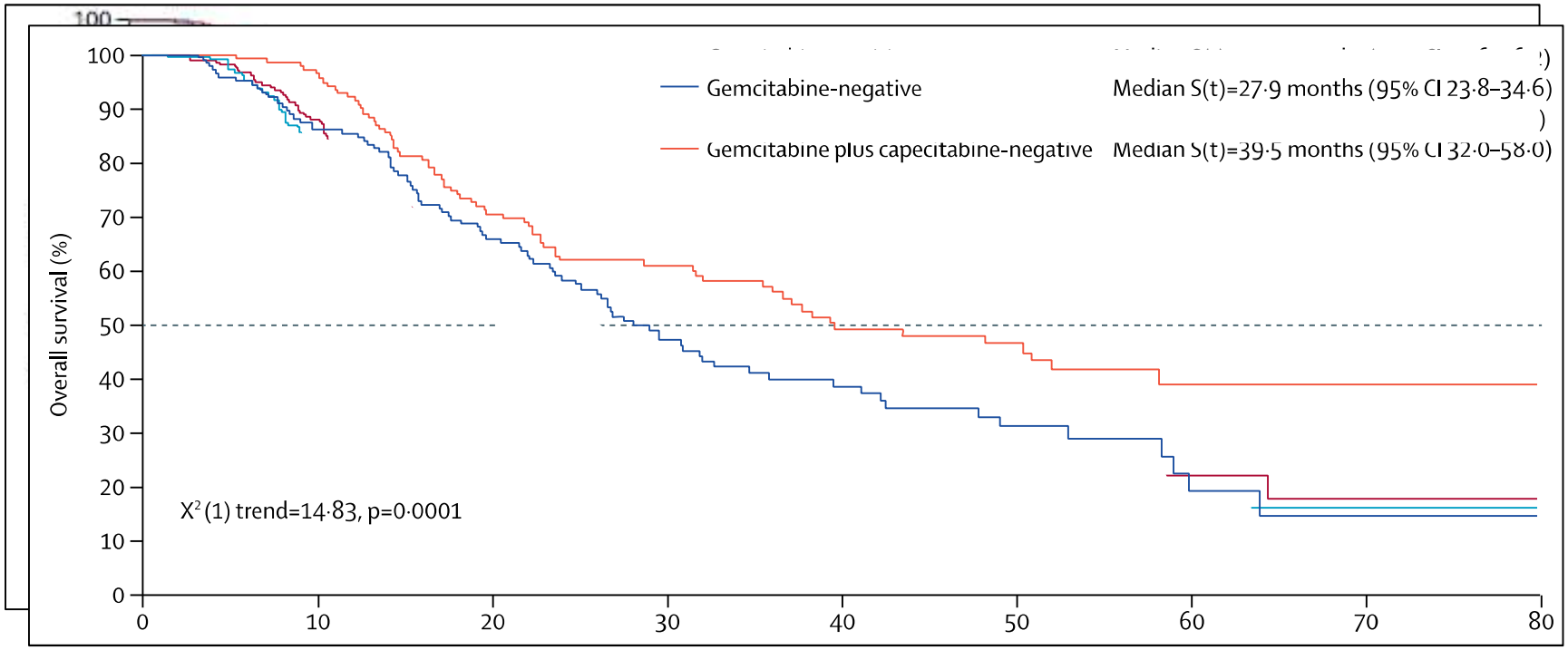
GemCap improved OS

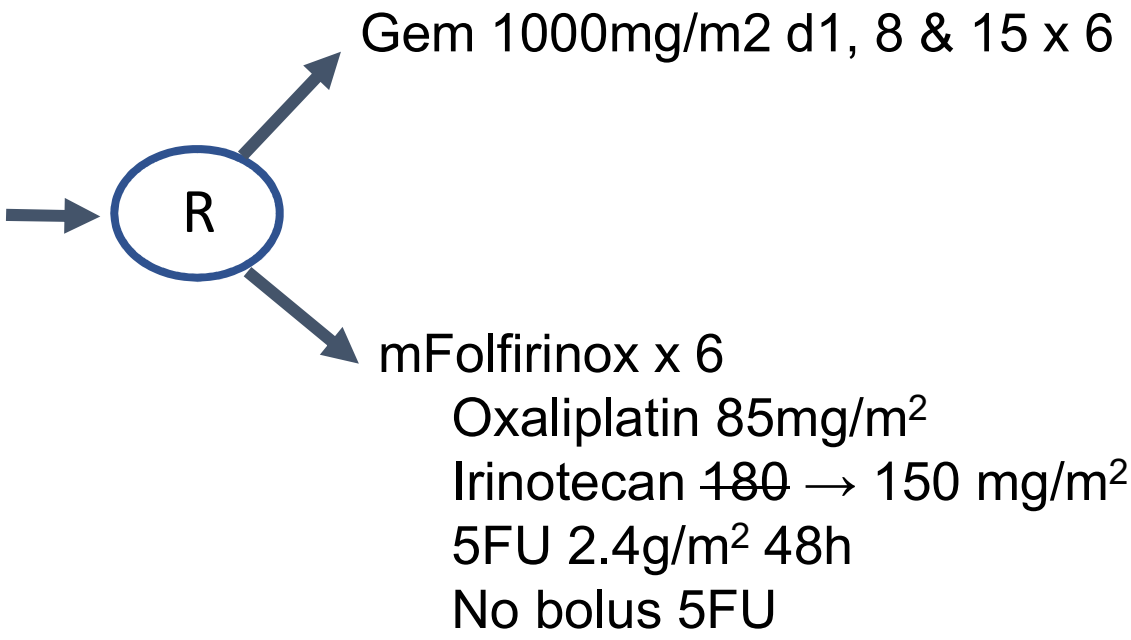


Resection margin			
Negative	90/147	70/143	0·68 (0·49–0·93)
Positive	149/219	149/221	0·90 (0·72–1·13)

Neoptolemos Lancet 2017

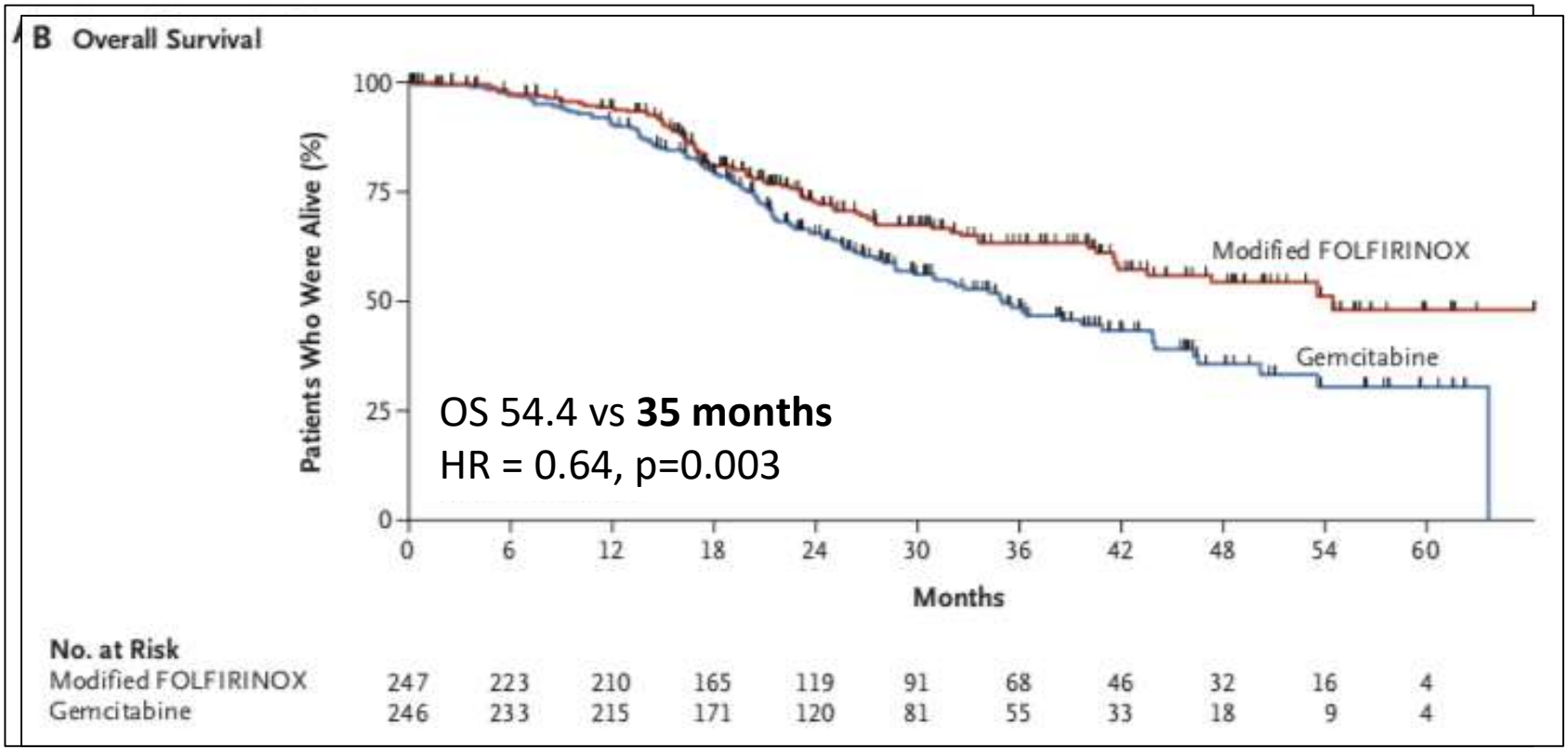
PRODIGE-24: FFNOX > GEM

POPULATION N=493
PDAC < 12 w
Age > 18-79yo
Ca19.9 <180
Postop CT scan NED
58 centers (>France)
R0/R1
1º Endpoint DFS
STRATIFICATION
R0/R1, Ca19.9, N0 vs N1, Center



Conroy NEJM 2018

mFolfirinox improved DFS/OS



Status of surgical margins				
R0	73/148	88/134		0.72 (0.53–0.98)
R1	61/99	92/112		0.52 (0.37–0.72)

Grade 3-4 diarrea 20%

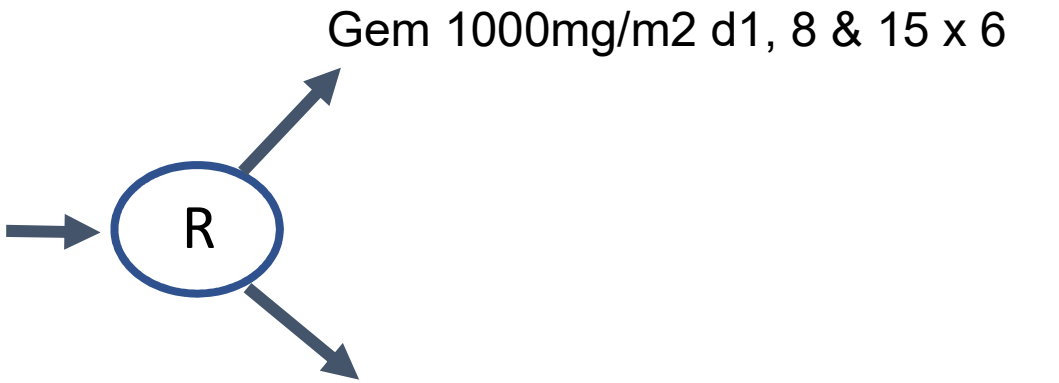
Conroy NEJM 2018

Different populations?

	PRODIGE-24 mFOLFIRINOX	ESPAC-4 GEMCAP
Age/Male/PS0-1	63/57%/99%	65/57%/97%
Ca19.9	<180 <90	No limit (0.6-8,112) Only 17% Ca 19.9 > 92
N0/N1	22.3/77.7%	21/79%
R0/R1	60/40%	61/39%
Vein resection	21%	11%
CT scan	Postop CT	Pre or postop (<3m randomizat)
Median dose intensity	70%	78%
Salvage chemo	63%	33%
DFS (months)	**21.6 vs 12.8, HR=0.58, p<0.0001**	13.9 vs 13.1, HR=0.86, p=0.082
OS (months)	54.4 vs 35.5, HR=0.64, p=0.003	**28 vs 25.5**, HR=0.82, p=0.032

APACT: Nab-P + GEM vs GEM

POPULATION N=866
PDAC < 12 w
Age > 18yo
Ca19.9 <100
Postop CT scan NED
179 centers
R0/R1
1º Endpoint DFS (Central)
STRATIFICATION
R0/R1, Ca19.9, N0 vs N1, Geographic region



Conroy NEJM 2018

PRODIGE-24 vs. APACT

	PRODIGE-24 mFOLFIRINOX (N=493)	APACT ABI/Gem (N=866)
Age/Male/PS0-1	63/57%/99%	64/56%/100%
Ca19.9	<180 <90	Only <100 eligible
N0/N1	22.3/77.7%	28/72%
R0/R1	60/40%	76/24%
Vein resection	21%	NR?
CT scan	Postop CT	Postop CT
Dose intensity	R 70% (66% completed C6)	75/80% (69% pts completed C6)
Salvage chemo	63%	NR?
DFS	**21.6 vs 12.8, HR=0.58, p<0.0001**	19.4 vs 18.8, HR=0.88 p=0.18
OS	54.4 vs 35.5, HR=0.64, p=0.003	40 vs 36.2, HR=0.82 p=0.045

NR = Not reported

Nab-P + Gem well tolerated

SAFETY (TREATED POPULATION)

apact

Event, n (%)	*nab*-P + Gem	Gem
Safety summary	**(n = 429)**	**(n = 423)**
Patients with ≥ 1 grade ≥ 3 TEAE	371 (86)	286 (68)
Patients with ≥ 1 serious TEAE	176 (41)	96 (23)
Grade ≥ 3 hematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Any hematologic TEAEs	250 (58)	204 (48)
Neutropenia	212 (49)	184 (43)
Anemia	63 (15)	33 (8)
Leukopenia	36 (8)	20 (5)
Febrile neutropenia	21 (5)	4 (1)
Grade ≥ 3 nonhematologic TEAEs (occurring in ≥ 5% of patients in either treatment arm)		
Peripheral neuropathy (SMQ)[a]	64 (15)	0
Fatigue	43 (10)	13 (3)
Diarrhea	22 (5)	4 (1)
Asthenia	21 (5)	8 (2)
Hypertension	17 (4)	27 (6)

- TEAEs led to death in 2 patients in each arm
- Ten patients (16%) with grade ≥ 3 peripheral neuropathy improved to grade ≤ 1
- The incidence of TEAEs of special interest—gastrointestinal events, hepatic toxicity, and sepsis—was generally low in both arms

% use of G-CSF?

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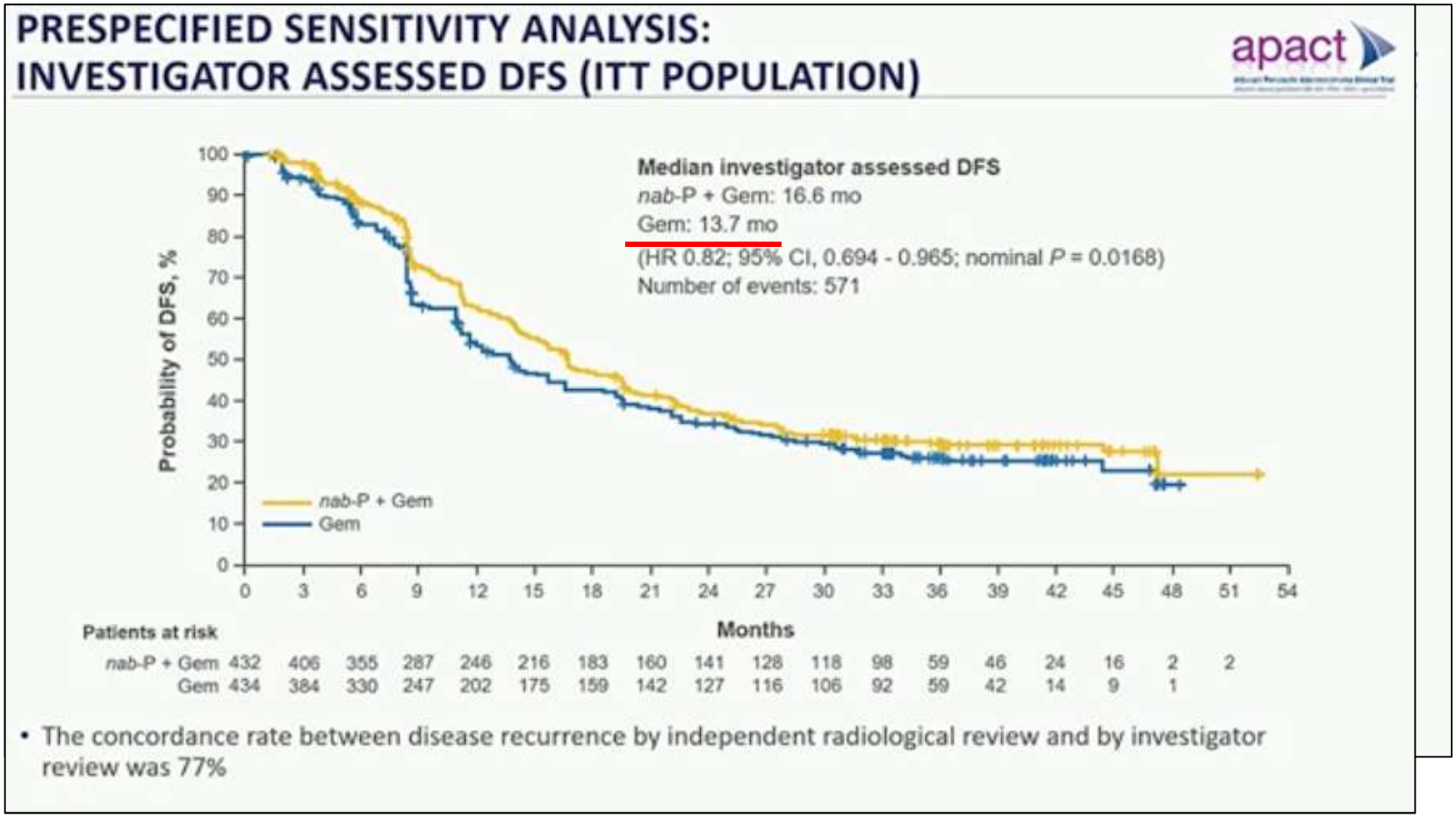
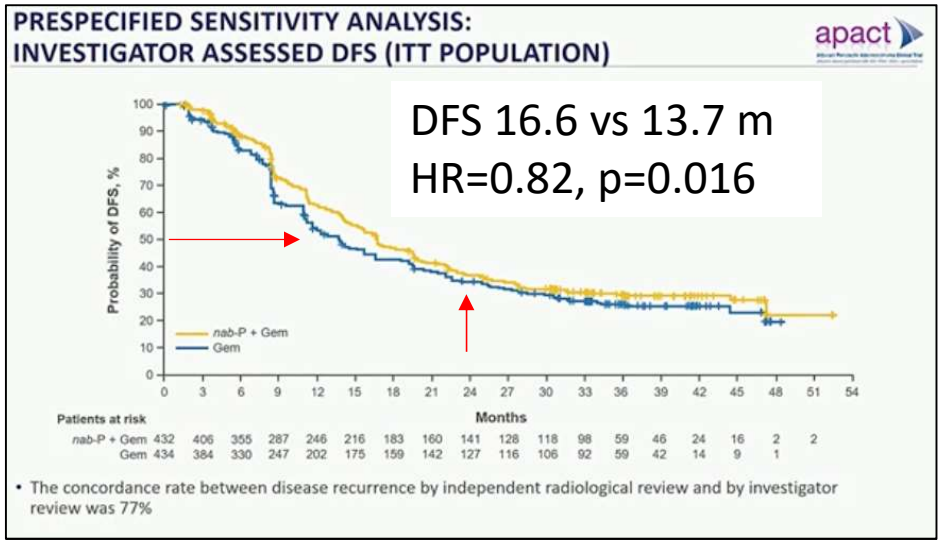
DFS central review vs. investigator

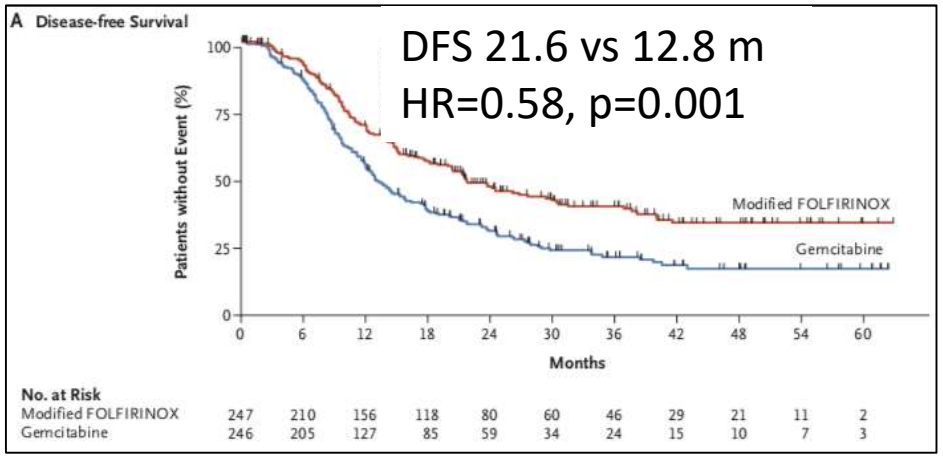


Tempero et al ASCO 2019

APACT: is the discussion about central review even worthy?

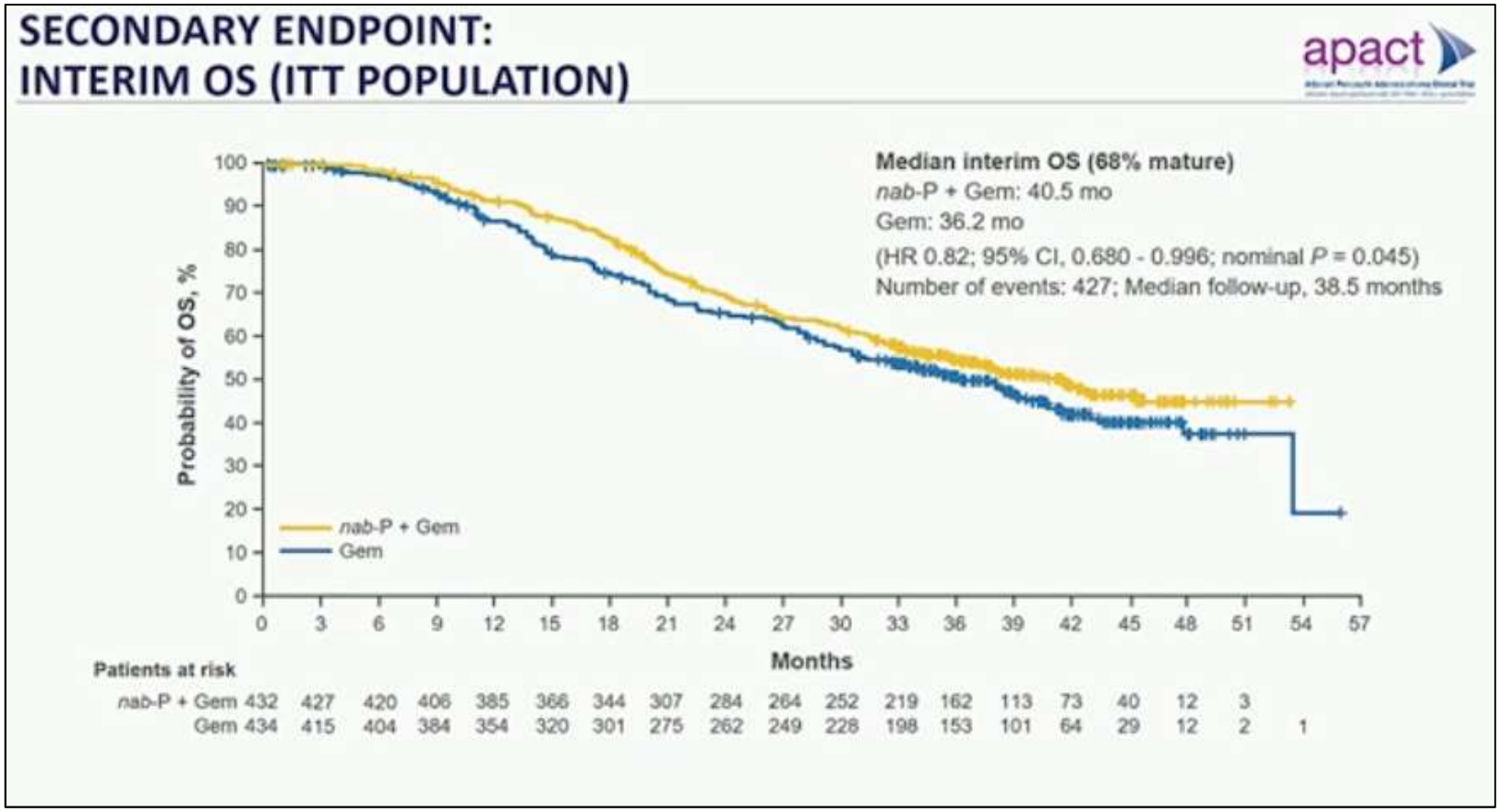


APACT



PRODIGE-24

Need to wait mature OS data



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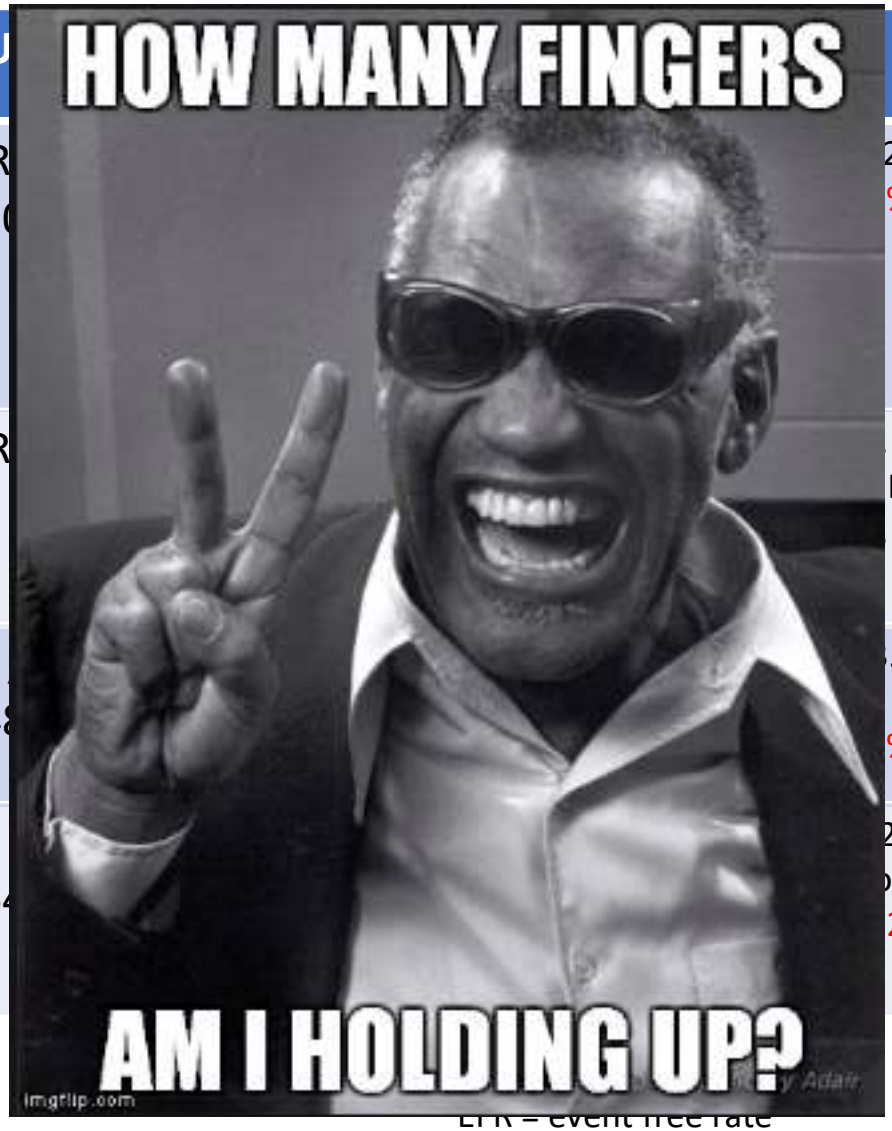
Neoadjuvant = downstaging

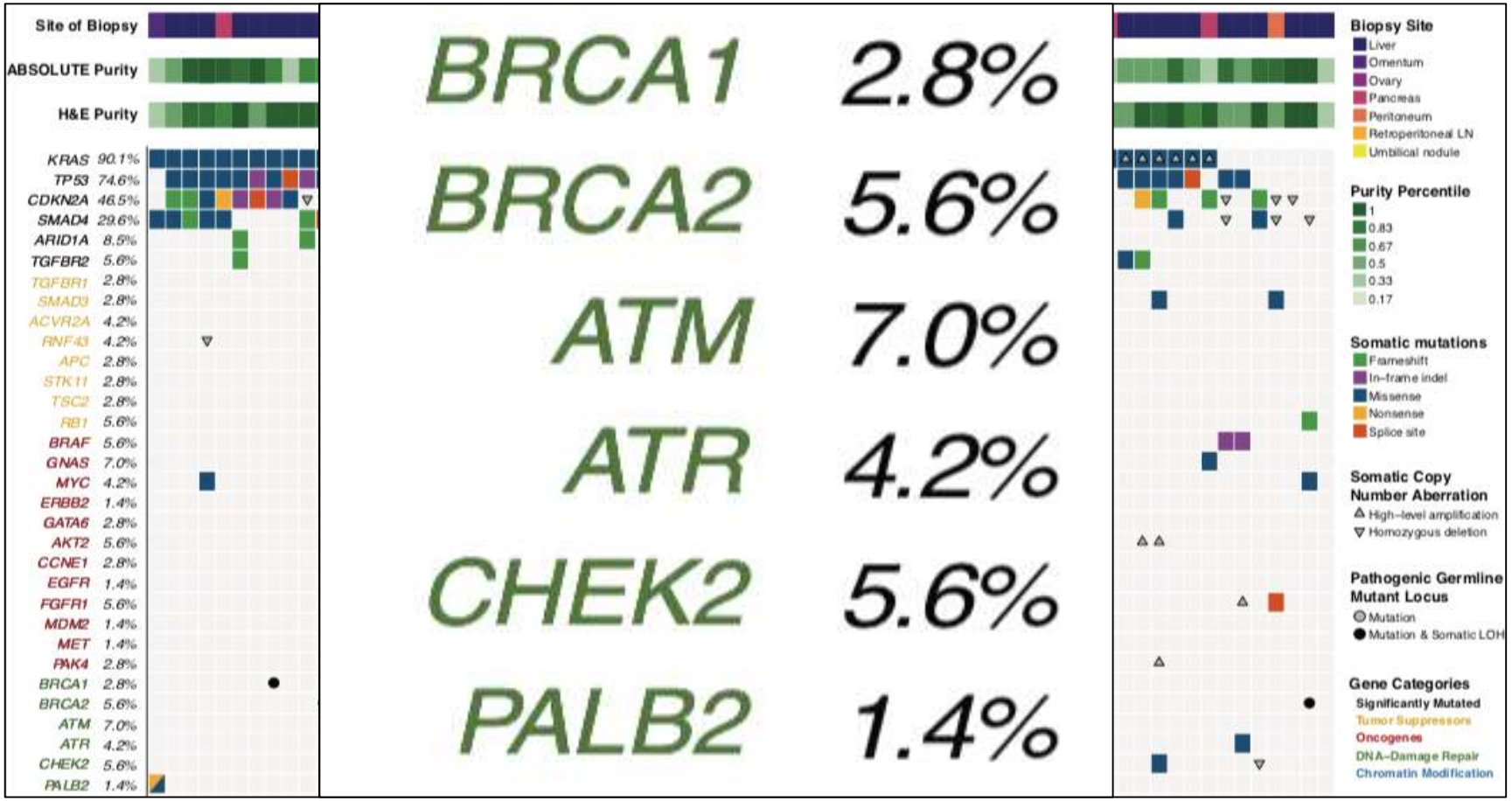
STUDY	POPU	
Jang Ann Surg 2018	BR ; R N=11(	26% (p=0.03) % (p=0.004)
Reni PACT-15 Lancet GH 2018	BR ; R N=93	R0 27% R0 37% R0 63%
PREOPANC	R/BR N=24	.7 m (HR=0.74, p=0.074) %
JSAP-05	R N=364	26.6 (HR=0.72, P=0.015) orted 2%



R=Resectable
BR= Borderline resectable

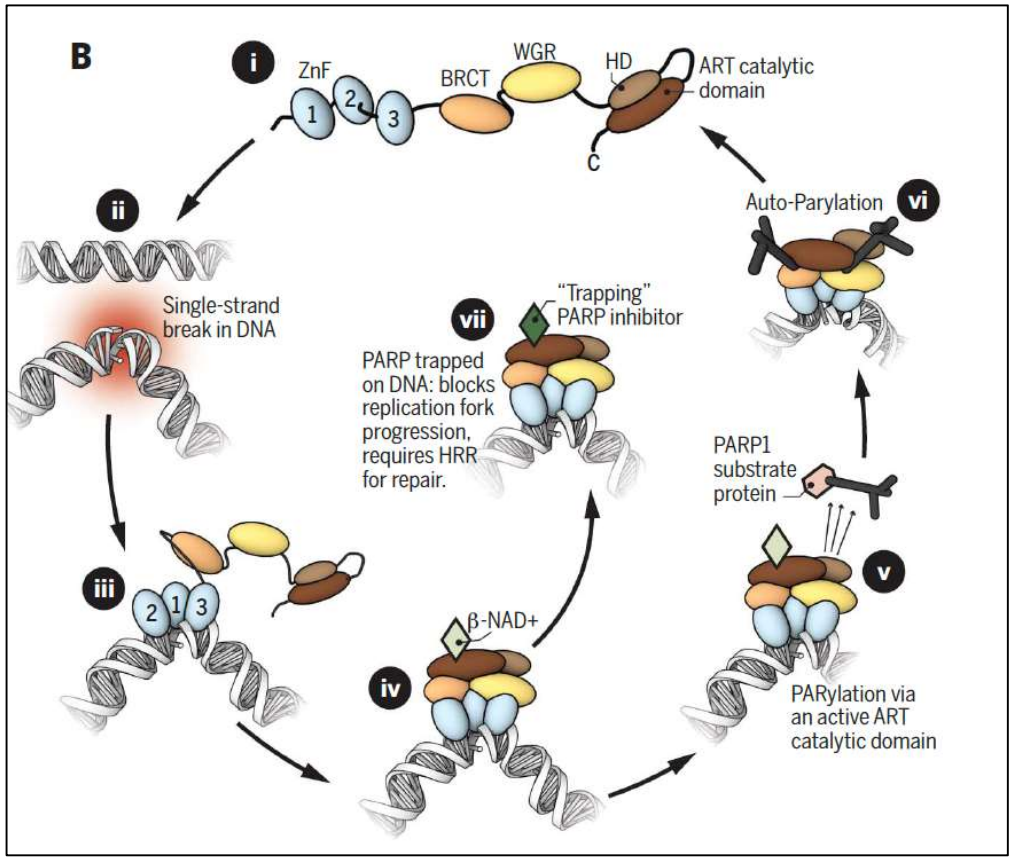
EFR = event free rate

20-30% PDAC samples harbor mutations in DNA repair pathway



Aguirre et al. Can Dis 2018

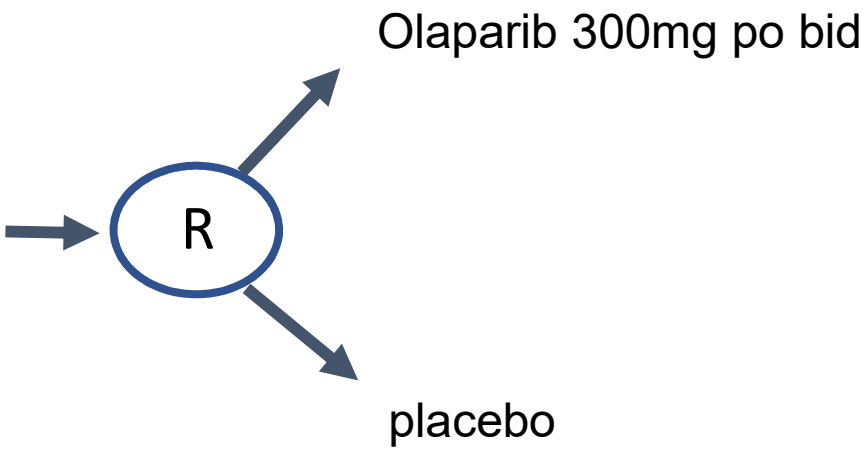
PARP inhibitors impair DNA damage response



Lord & Ashworth, Science 2017

POLO trial: olaparib vs placebo

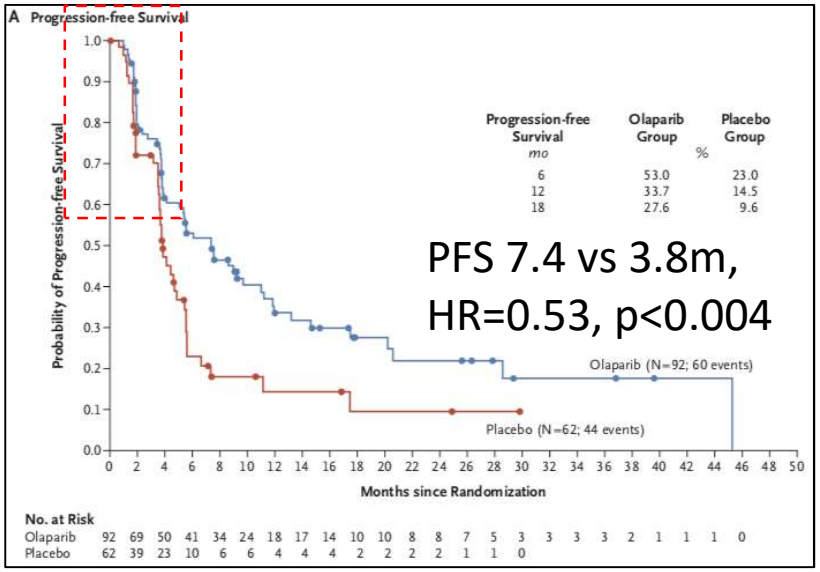
POPULATION (Screen/R) 3315/154 (<5%)
No POD ≥ 16w platinum
Start <4-8w last platinum
gBRCA 1/2 (central)
119 centers
No cross over
1º Endpoint PFS (Central)
No stratification

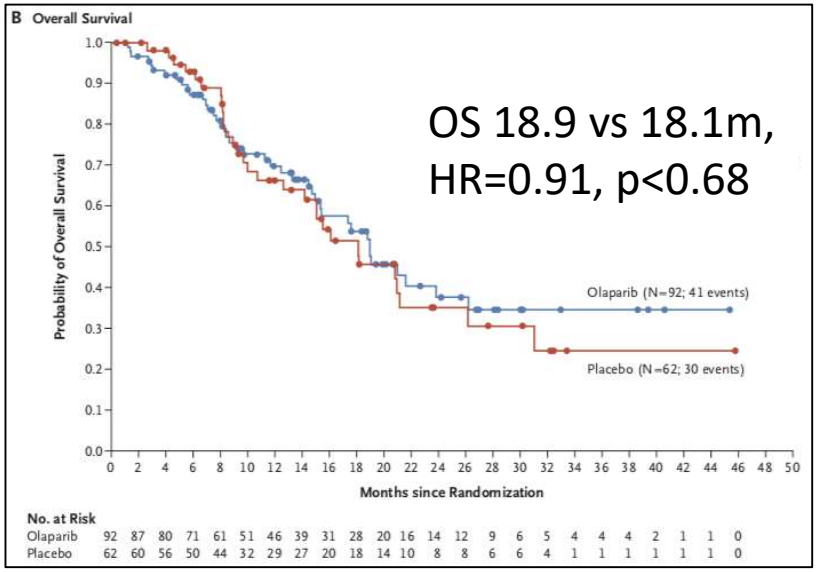


Patient characteristics well balanced in each arm?
Liver mets: 66% (olaparib) vs 77% (placebo)

Golan NEJM 2019

Olaparib improves PFS



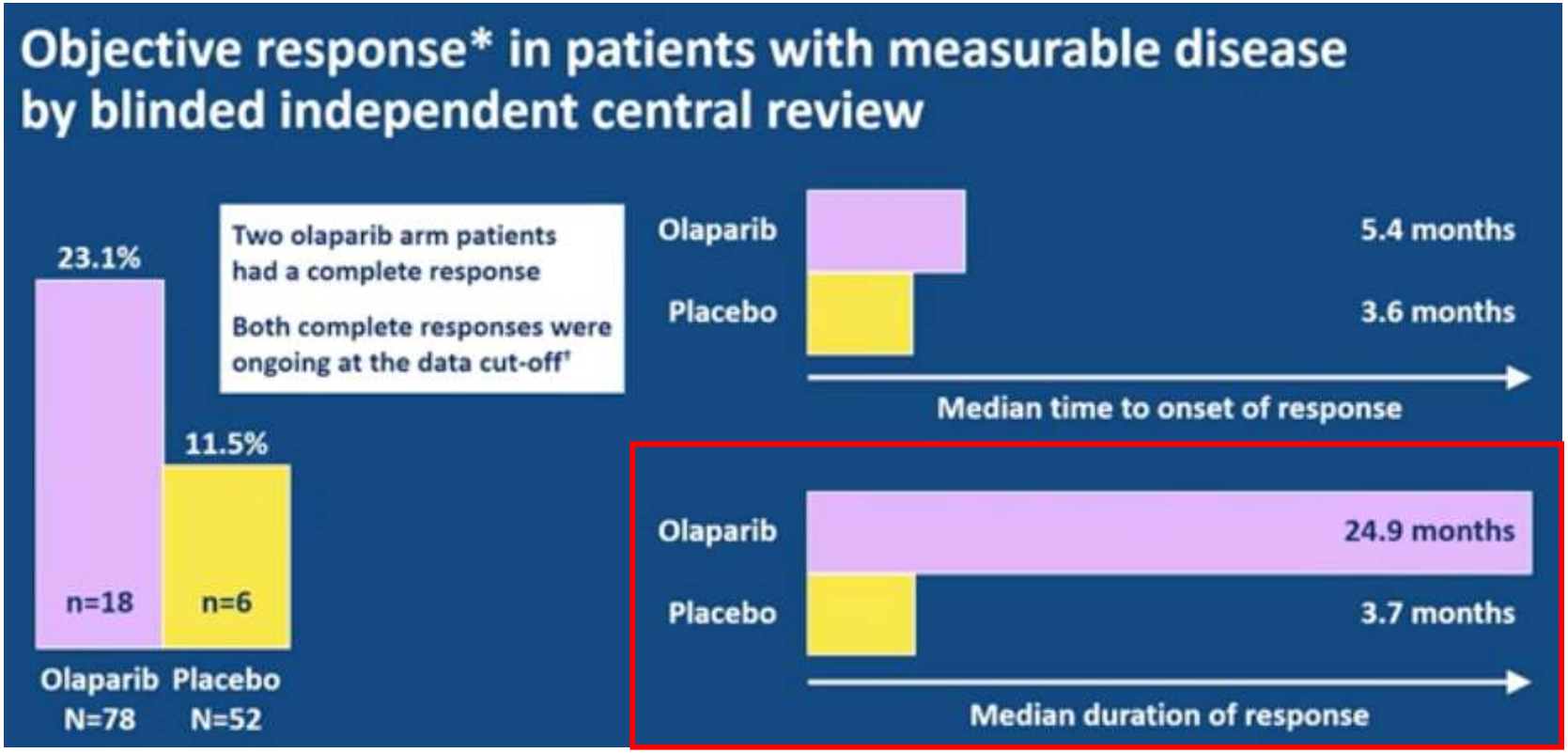


Data maturity only 46%
2L Ola vs Placebo 49 vs 74%

PFS = Progression Free Survival

Golan NEJM 2019

Prolonged responses with olaparib



DOR = Duration of response

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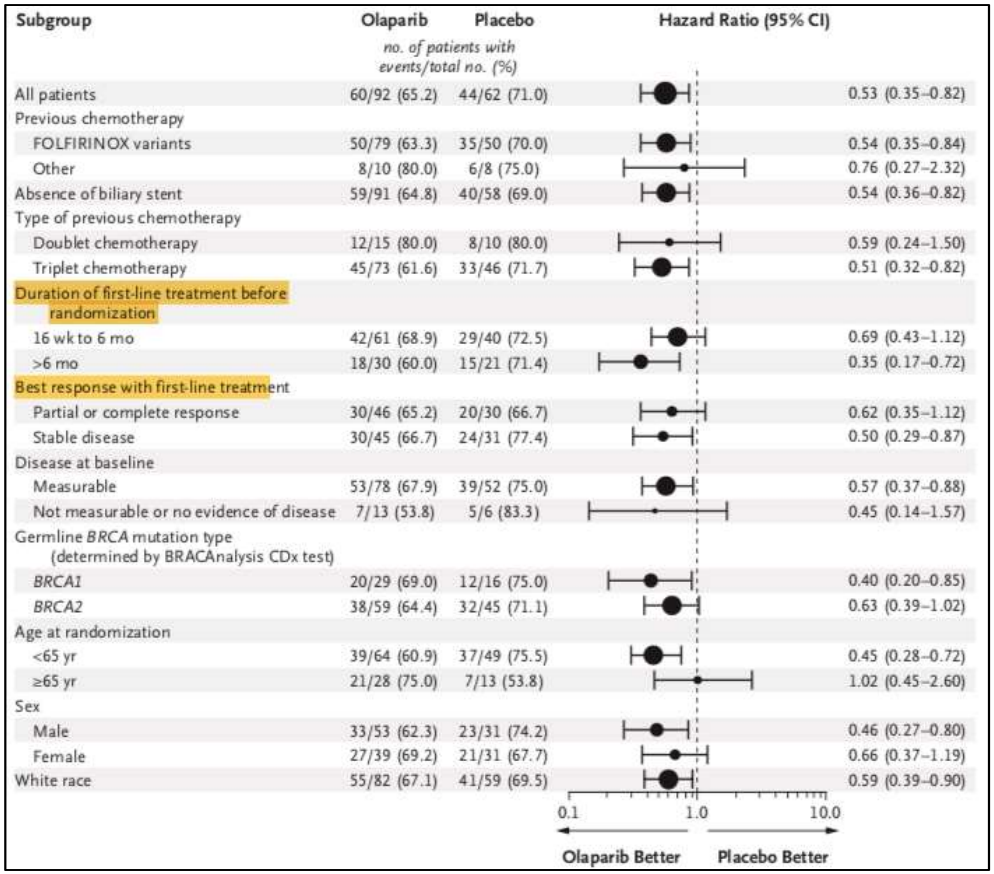
PFS benefit across all subgroups…



Subgroup	Olaparib	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no. (%)		
All patients	60/92 (65.2)	44/62 (71.0)	0.53 (0.35–0.82)
Previous chemotherapy			
FOLFIRINOX variants	50/79 (63.3)	35/50 (70.0)	0.54 (0.35–0.84)
Other	8/10 (80.0)	6/8 (75.0)	0.76 (0.27–2.32)
Absence of biliary stent	59/91 (64.8)	40/58 (69.0)	0.54 (0.36–0.82)
Type of previous chemotherapy			
Doublet chemotherapy	12/15 (80.0)	8/10 (80.0)	0.59 (0.24–1.50)
Triplet chemotherapy	45/73 (61.6)	33/46 (71.7)	0.51 (0.32–0.82)
Duration of first-line treatment before randomization			
16 wk to 6 mo	42/61 (68.9)	29/40 (72.5)	0.69 (0.43–1.12)
>6 mo	18/30 (60.0)	15/21 (71.4)	0.35 (0.17–0.72)
Best response with first-line treatment			
Partial or complete response	30/46 (65.2)	20/30 (66.7)	0.62 (0.35–1.12)
Stable disease	30/45 (66.7)	24/31 (77.4)	0.50 (0.29–0.87)
Disease at baseline			
Measurable	53/78 (67.9)	39/52 (75.0)	0.57 (0.37–0.88)
Not measurable or no evidence of disease	7/13 (53.8)	5/6 (83.3)	0.45 (0.14–1.57)
Germline *BRCA* mutation type (determined by BRACAnalysis CDx test)			
BRCA1	20/29 (69.0)	12/16 (75.0)	0.40 (0.20–0.85)
BRCA2	38/59 (64.4)	32/45 (71.1)	0.63 (0.39–1.02)
Age at randomization			
<65 yr	39/64 (60.9)	37/49 (75.5)	0.45 (0.28–0.72)
≥65 yr	21/28 (75.0)	7/13 (53.8)	1.02 (0.45–2.60)
Sex			
Male	33/53 (62.3)	23/31 (74.2)	0.46 (0.27–0.80)
Female	27/39 (69.2)	21/31 (67.7)	0.66 (0.37–1.19)
White race	55/82 (67.1)	41/59 (69.5)	0.59 (0.39–0.90)

…regardless of response to Folfirinox, type of *BRCA* mut,…

Golan NEJM 2019

Olaparib was well tolerated

Variable	Olaparib (N=91)		Placebo (N=60)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	87 (96)	36 (40)	56 (93)	14 (23)
Fatigue or asthenia	55 (60)	5 (5)	21 (35)	1 (2)
Nausea	41 (45)	0	14 (23)	1 (2)
Anemia†	25 (27)	10 (11)	10 (17)	2 (3)
Abdominal pain	26 (29)	2 (2)	15 (25)	1 (2)
Diarrhea	26 (29)	0	9 (15)	0
Decreased appetite	23 (25)	3 (3)	4 (7)	0
Constipation	21 (23)	0	6 (10)	0
Vomiting	18 (20)	1 (1)	9 (15)	1 (2)
Back pain	17 (19)	0	10 (17)	1 (2)
Arthralgia	14 (15)	1 (1)	6 (10)	0
Interruption of intervention owing to adverse event	32 (35)	NA	3 (5)	NA
Dose reduction owing to adverse event	15 (16)	NA	2 (3)	NA
Discontinuation of intervention owing to adverse event	5 (5)	NA	1 (2)	NA

<5% discontinue treatment due to AEs
Median dose intensity 99%

Golan NEJM 2019

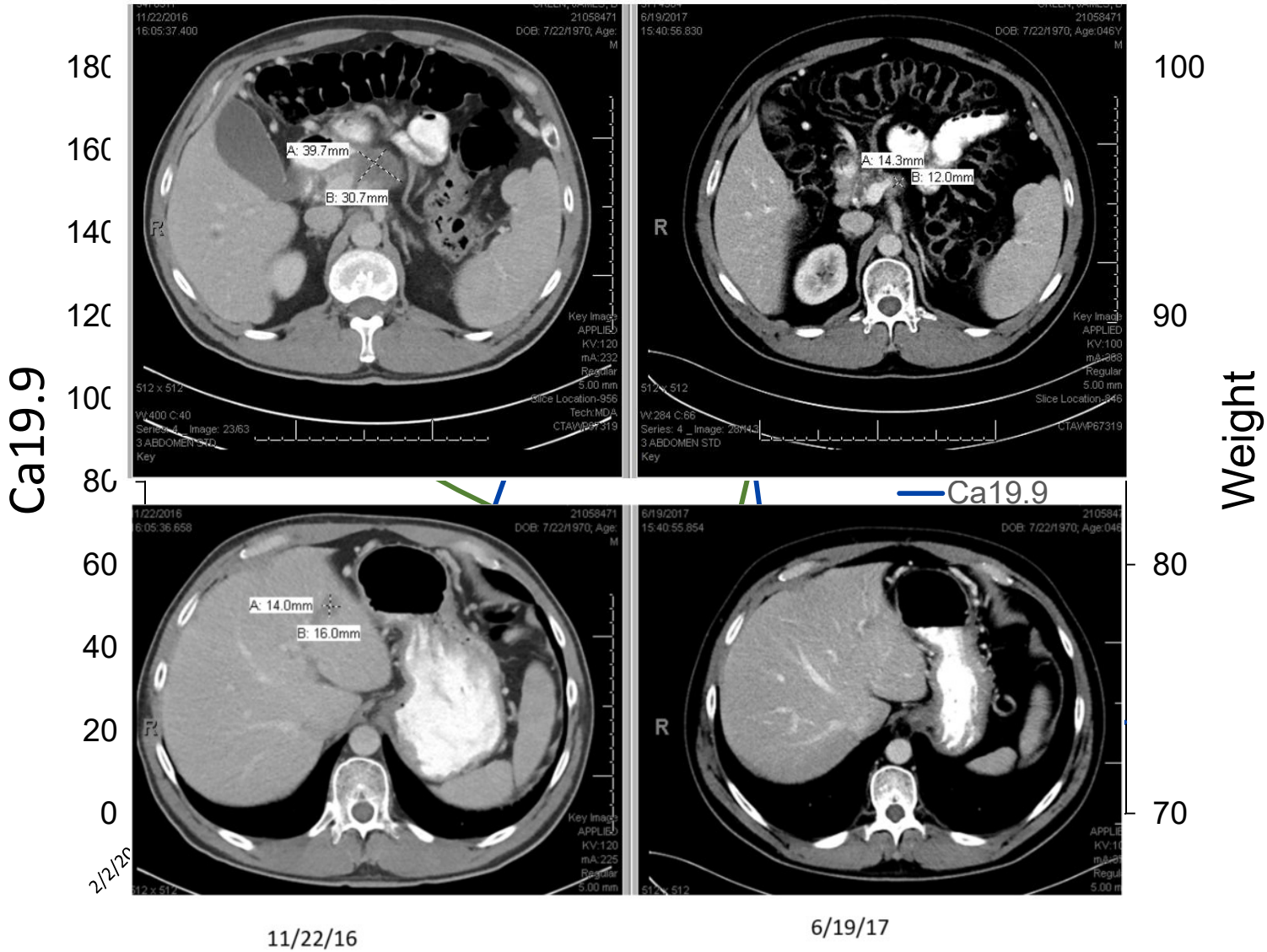
Second hits not likely in non-BRCA DDR genes

Case	Germline mutation	Somatic event	Family history of cancer	Age at Dx (y)
0400094_T2	*ATM* (p.D1013fs) *CDKN2A* (p.G101W)	Nonsense mutation None	Mother: breast cancer Father: melanoma	51
0400209_T1	*ATM* (splice site)	None	No family history	61
0400235_T1	*ATM* (p.E1978*)	None	Mother: breast cancer Maternal uncle: melanoma	65
0400027_T1	*BRCA2* (p.S1982fs)	LOH	Sister: breast cancer	64
0400067_T1	*BRCA2* (p.S1982fs)	LOH	Maternal half-brother: melanoma Maternal half-sister: colon cancer Paternal grandfather: unknown primary cancer	59
0400078_T1	*BRCA2* (p.W1692Mfs*3)	LOH	Father: melanoma and prostate cancer Paternal aunt 1: breast cancer Paternal aunt 2: brain cancer Paternal grandmother: lung cancer	39
0400075_T1	*BRCA1* (p.Q1756fs)	LOH	Mother: ovarian cancer Maternal grandmother: ovarian cancer	58
0400242_T1	*BRCA1* (p.T276Afs*14)	LOH	Mother: breast cancer Brother: pancreatic cancer	63
0400124_T1	*CHEK2* (Ex2_3del)	LOH	Mother: breast cancer Father: prostate cancer Brother: prostate cancer Paternal grandfather: colon cancer Maternal grandmother: intra-abdominal/ pelvic cancer	73
0400215_T1	*BLM* (p.P1320fs)	None	Brother: glioblastoma Father: lung cancer Maternal grandmother: brain cancer	53
0400214_T1	*FANCA* (p.Q343*)	None	Sister: ovarian cancer	59
0400164_T1	*FANCL* (p.T367fs)	None	No family history	70
0400192_T1	*RAD50* (p.S653*)	None	Daughter: lung cancer	67

Is germline status sufficient to determine response to PARPi in DDR mut-non BRCA PDAC?

Aguirre et al. Can Dis 2018

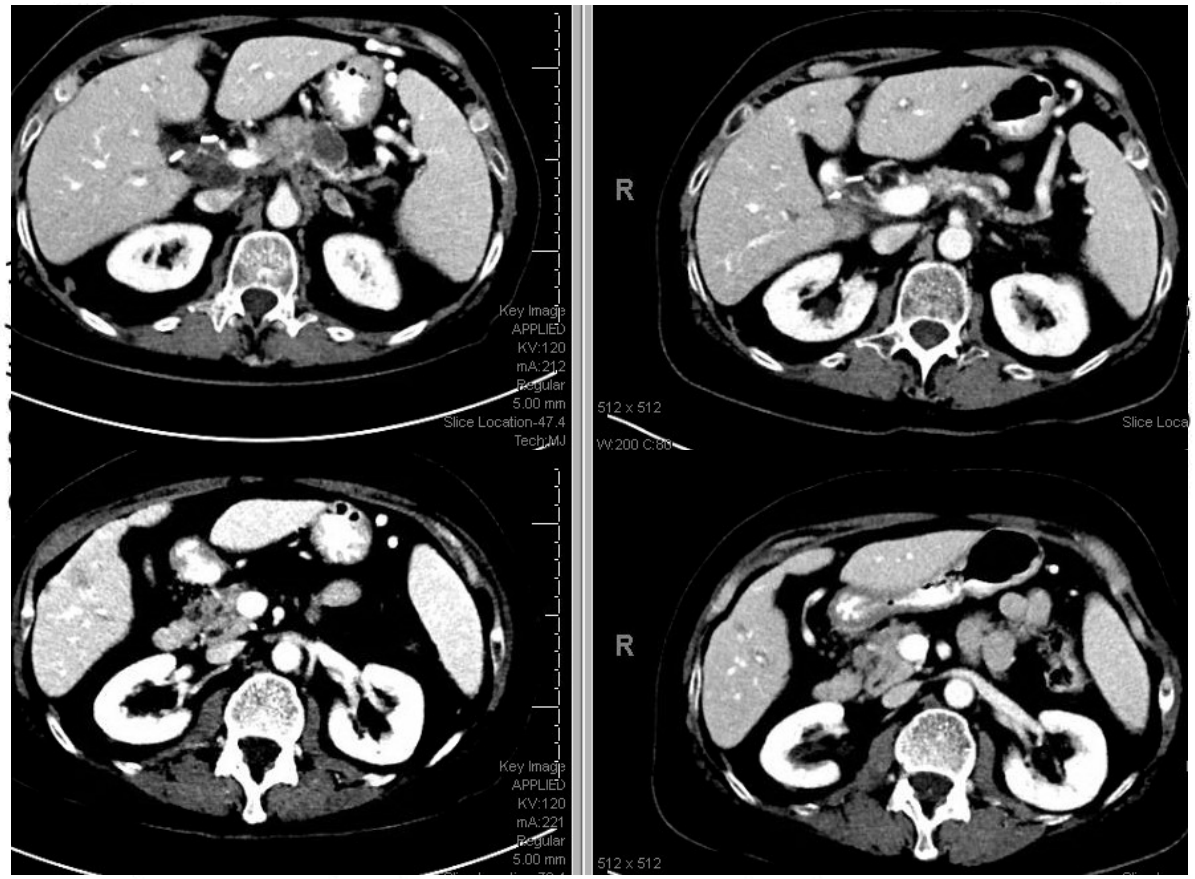
TPR-NTRK1 fusion in PDAC



Pishvaian, Garrido-Laguna. JCO PO 2018

Partial response in PDAC with Lynch Syndrome

ABI/Gem Folfox + Pembro Pembro



del exons 1-6 *MSH2*

Stenehjem,… & Garrido-Laguna et al. JIPO 2018

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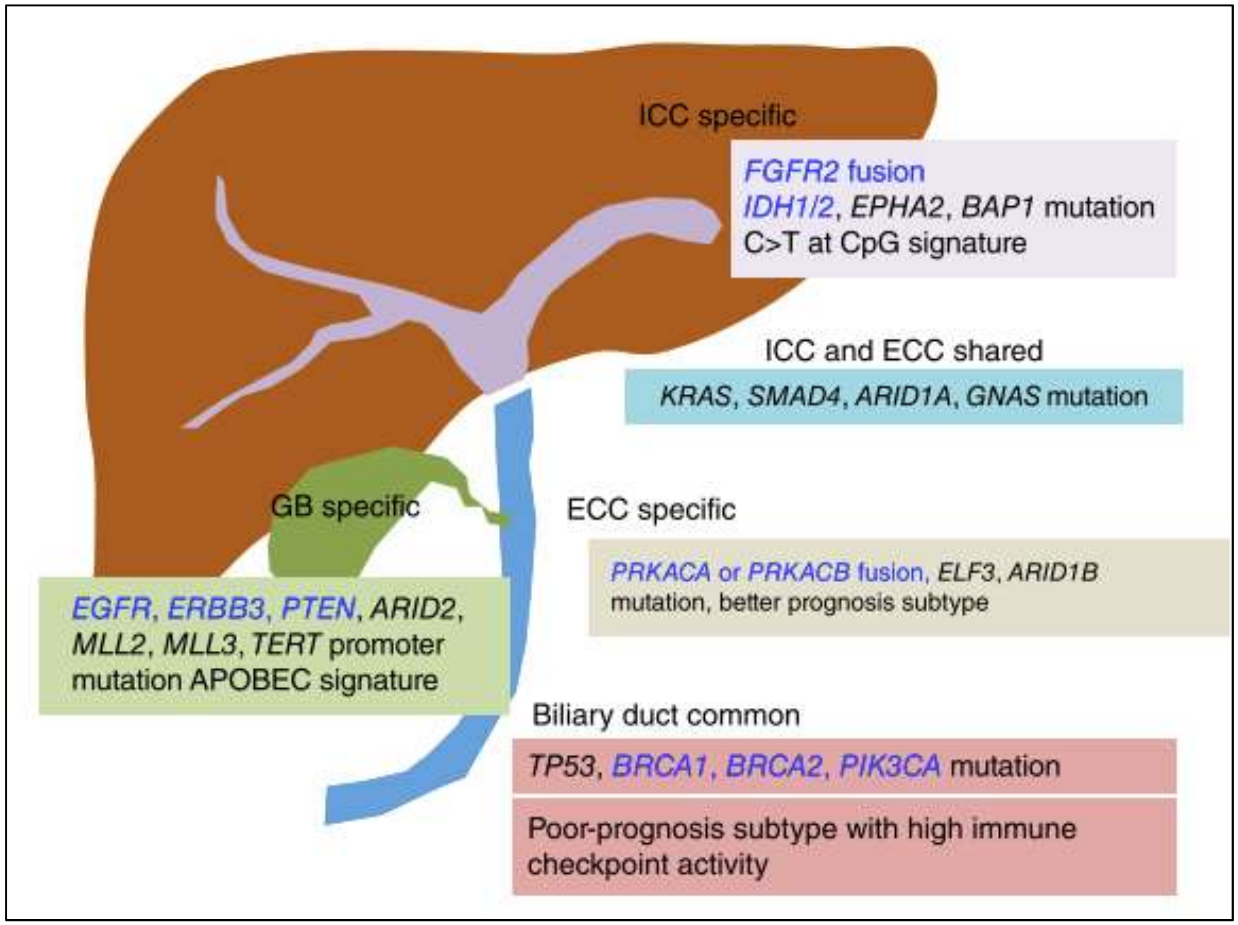
Biliary cancers: Genetic Heterogeneity



Nakamura Nat Genetics 2015

State of the art for biliary cancer

- Early stage:
  - BILCAP trial: Capecitabine x 6m ↑ OS
    - Negative: PRODIGE-12 (~~GEMOX~~), BCAT ~~(Gemcitabine)~~
  - Role of chemo/XRT? GemCap → Cape/XRT (SWOG-0809)
- Metastatic disease:
  - 1L: ABC-02 trial Cisplatin + Gem
    - SWOG1815: Cis + Gem +/- nab-paclitaxel
  - 2L: ABC-06 Folfox vs ASC
- Targeted therapies: FGFR, IDH, BRCA,…

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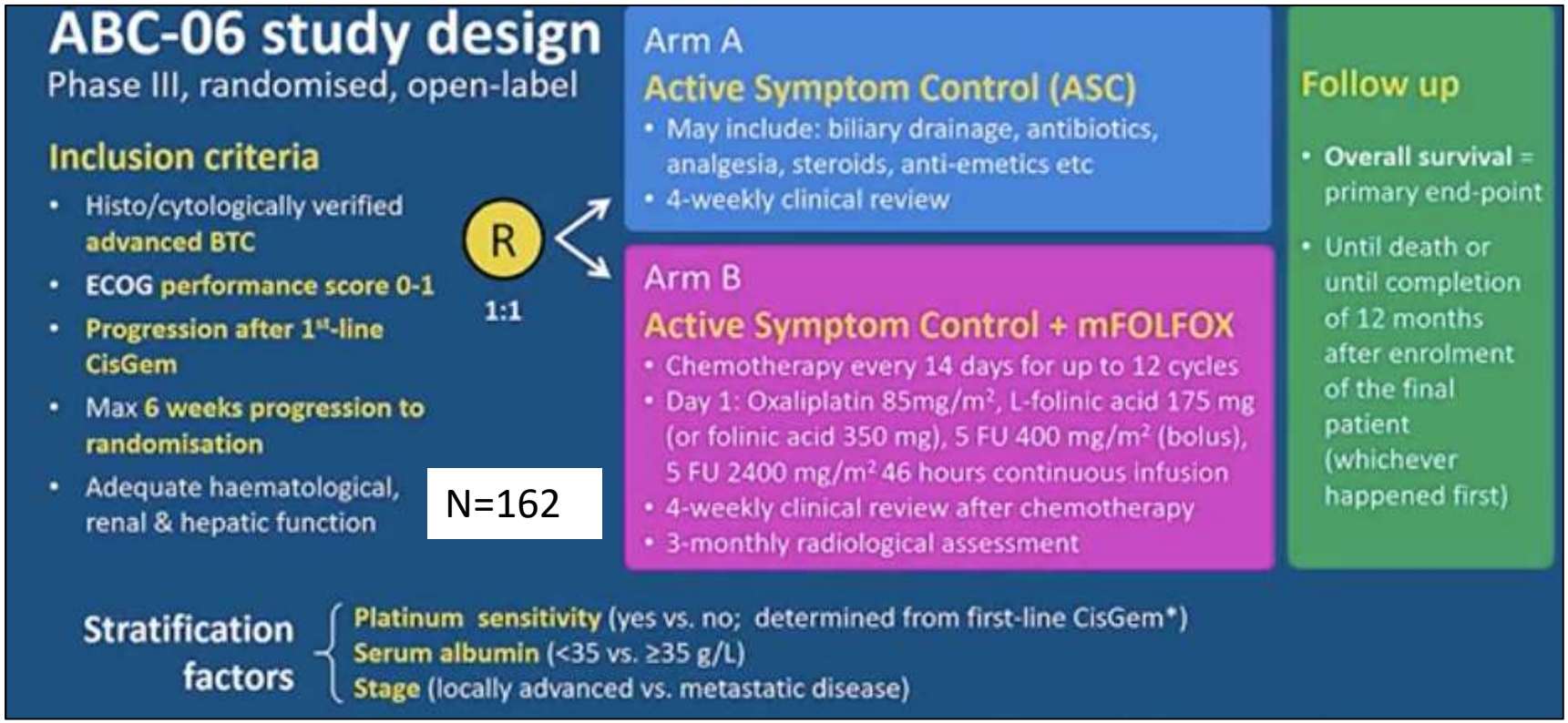
ABC-06 trial: 2nd line Folfox



Lamarca ASCO 2019

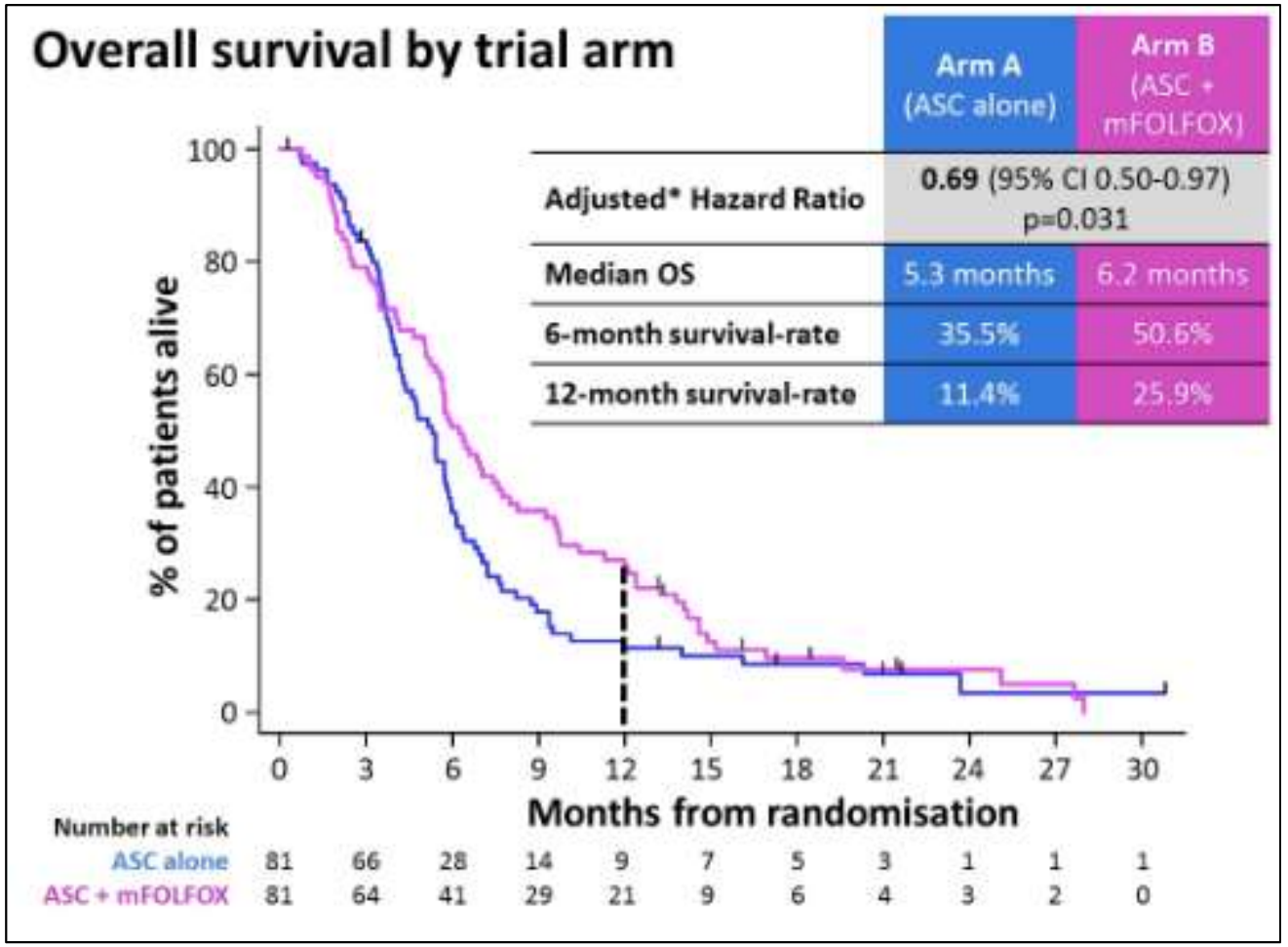
Treatment arms well balanced

		Arm A (ASC alone) n=81 pts		Arm B (ASC + mFOLFOX) n=81 pts	
		n	%	n	%
Gender	Male/female	37/44	46%/54%	43/38	53%/47%
Age (years)	Median (range)	65 (26-81)		65 (26-84)	
Platinum sensitivity*	Resistant/refractory	47	58%	54	67%
	Sensitive	34	42%	27	33%
Albumin*	<35 g/L	21	26%	19	23%
	≥35 g/L	60	74%	62	77%
Disease stage*	Locally advanced	15	19%	14	17%
	Metastatic	66	81%	67	83%
Tumour site	Intrahepatic	38	47%	34	42%
	Extrahepatic	19	23%	26	32%
	Gallbladder	17	21%	17	21%
	Ampulla	7	9%	4	5%
Histology	Adenocarcinoma	74	91%	73	90%
	Others**	7	9%	8	10%
Grade of differentiation	Well	5	6%	9	11%
	Moderate	41	51%	37	46%
	Poorly	11	14%	9	11%
	Not specified/missing	23/1	28%/1%	26/0	32%/0%

ASC = Active symptom control

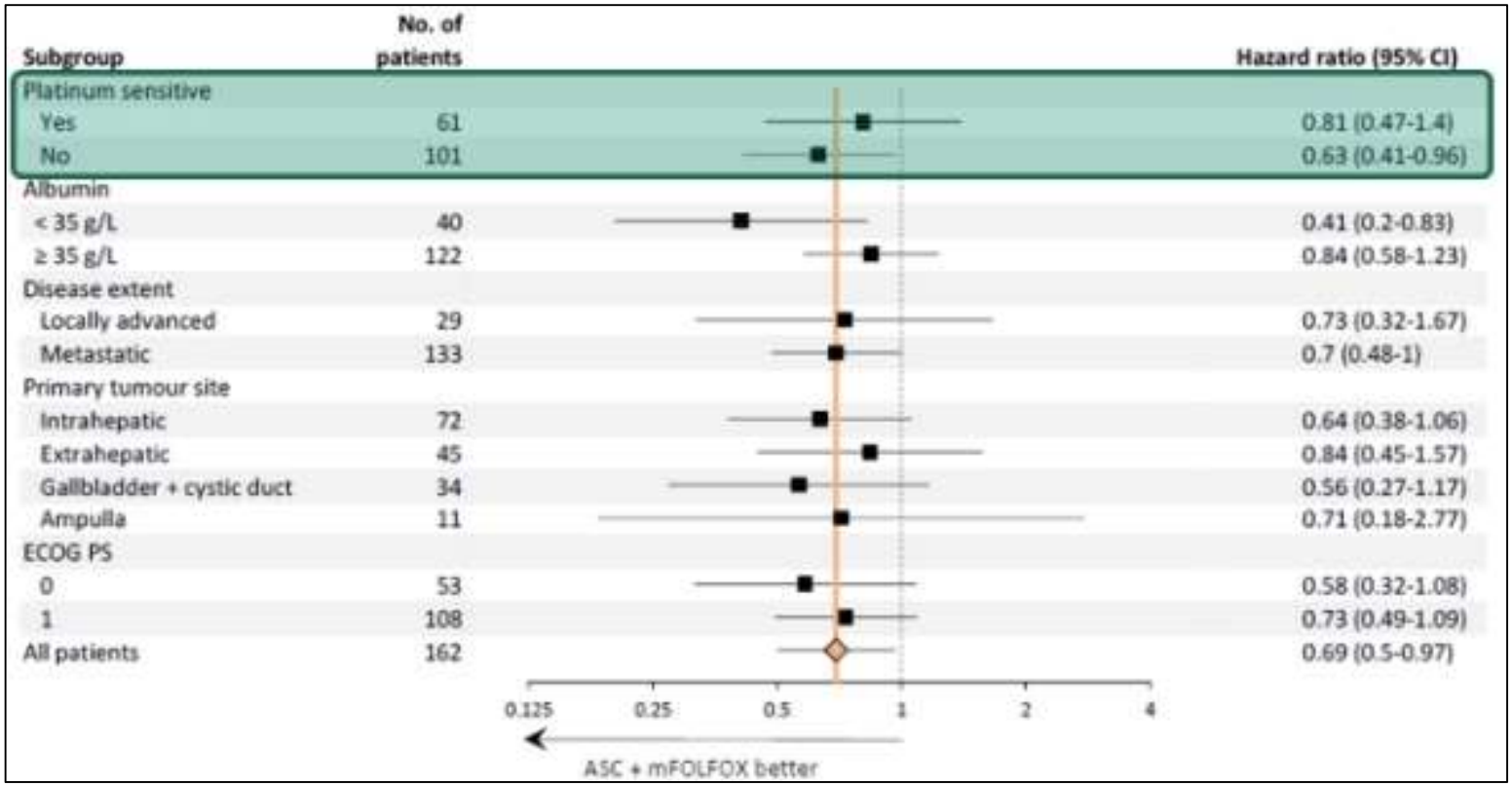
Lamarca ASCO 2019

Modest improvement in survival



Postprogression treatment (15%). Well balanced.

Benefit seen across all subgroups

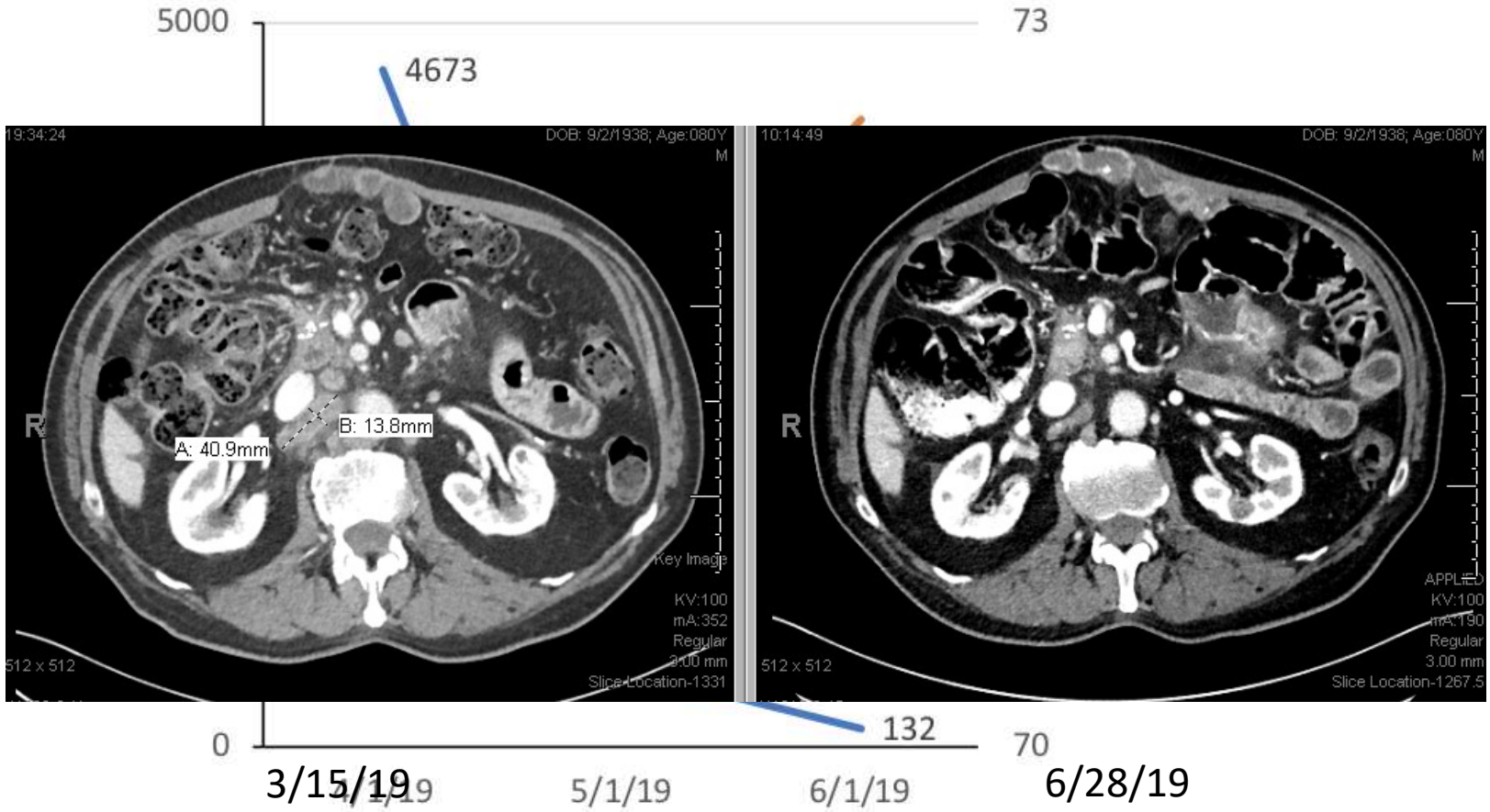


Ongoing randomized trials in molecularly defined subsets

Line	Study	Phase (N)	Subset	ARMS	1º Endpoint
First	PROOF	RP3 (N=350)	FGFR2 fusion	Cis + Gem vs BGJ-398 (Infigratinib)	PFS
	FIGHT-302	RP3 (n=432)	FGFR2 fusion	Cis + Gem vs Pemigatinib	PFS
2nd 3rd	ClarIDHy	RP3 (N=186)	IDH1	AG-120 (ivosidenib)	PFS

ClarIDHy trial to be presented at ESMO 2019 (press release ↑ PFS)

Response to PARPi in dEHCC with *BRCA1* loss



Conclusions

- Adjuvant treatment for PDAC:
  - Fit patients = mFolfirinox
  - Unfit for Folfirinox/neuropathy: GemCap (R1?)
  - Can't support nab-paclitaxel + Gem: mature data on OS? (2^o endpoint)
- gBRCA+ PDAC: Olaparib increases PFS (OS?)
  - Role in platinum refractory?
  - Role in other DDR?
- Biliary cancers:
  - Folfox modest benefit in 2L (↑ OS by 1 month)
  - Exciting! = Molecular subsets: *IDHi, FGFRi, BRCA,BRAF,…*

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Thanks NOSCM!

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