Management of Relapsed Pancreatic Cancer

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Disclosure

Research funding: Taiho Oncology, Ipsen Pharmaceuticals, GSK, Bristol Myers Squibb, PCI Biotech AS, ASCO, Calithera Biosciences, Inc., SynCore Biotechnology Co., Ltd., Mabspace Biosciences, Corcept Therapeutics Inc., Hutchison MediPharma

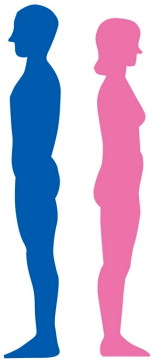
Consulting/Advisory Role: Taiho, Pfizer, QED Therapeutics

Epidemiology

- Pancreatic cancer: about 3% of all cancers in the US, and about 8% of all cancer deaths
- Estimated 62,210 new diagnoses in 2022 - 32,970 men and 29,240 women
- 49,830 deaths (25,970 men and 23,860 women
- For all stages combined, pancreatic cancer has the lowest 5-year relative survival rate - 11%

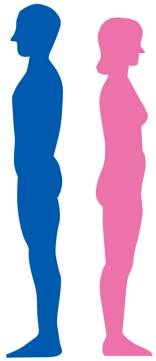
Estimated New Cases

Males			Females		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**



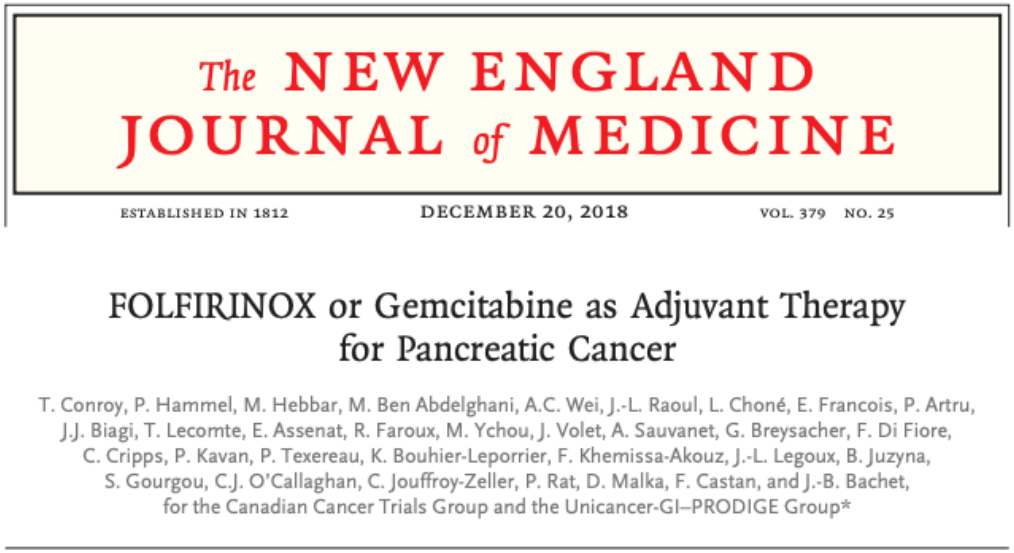
Estimated Deaths

Males			Females		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**



American Cancer Society, Petrick JL et al. Int J Cancer. 2016;139(7):1534-1545, Okuda K et al. J Gastroenterol Hepatol. 2002;17:1049-1055, Bertuccio P et al. Ann Oncol. 2013;24(6):1667-1674.

PRODIGE 24–ACCORD



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 20, 2018 VOL. 379 NO. 25

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

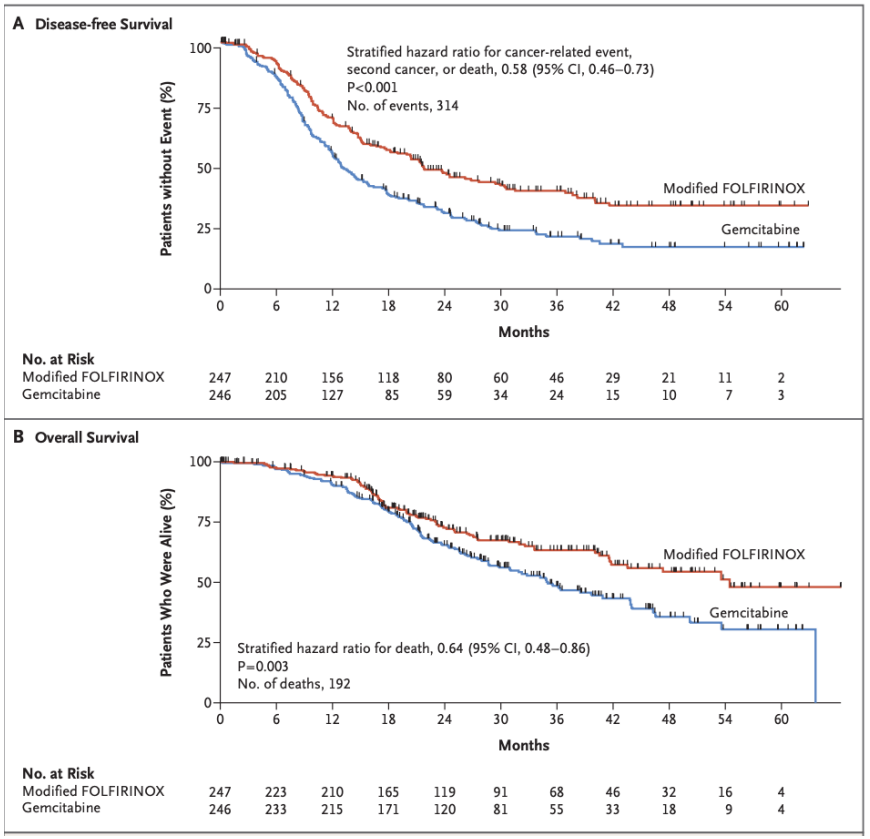
- Multicenter, randomized, open-label, phase 3 trial conducted at 77 hospitals in France and Canada
- 493 patients with resected PDAC randomized to mFOLFIRINOX or weekly gemcitabine for 24 weeks
- Primary end point – DFS
- Secondary end points – OS, safety

Conroy T, et al. N Engl J Med. 2018 Dec 20;379(25):2395-2406.

PRODIGE 24–ACCORD

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)
Age		
Median (range) — yr	63 (30–79)	64 (30–81)
≥70 yr — no. (%)	47 (19.0)	54 (22.0)
Male sex — no. (%)	142 (57.5)	135 (54.9)
WHO performance-status score — no./total no. (%)†		
0	122/245 (49.8)	127/242 (52.5)
1	123/245 (50.2)	115/242 (47.5)
Status of surgical margins — no. (%)‡		
R0	148 (59.9)	134 (54.5)
R1	99 (40.1)	112 (45.5)
Tumor histologic findings — no./total no. (%)		
Ductal adenocarcinoma	244/247 (98.8)	242/245 (98.8)
Nonductal carcinoma	3/247 (1.2)	3/245 (1.2)
Tumor stage — no. (%)§		
I	12 (4.9)	14 (5.7)
IIA	43 (17.4)	47 (19.1)
IIB	183 (74.1)	179 (72.8)
III	1 (0.4)	1 (0.4)
IV	8 (3.2)	5 (2.0)
Lymphovascular invasion — no./total no. (%)	154/209 (73.7)	135/214 (63.1)
Perineural invasion — no. (%)	205/221 (92.8)	207/231 (89.6)
Surgery		
Venous resection — no./total no. (%)	53/245 (21.6)	69/245 (28.2)
Portal-vein resection — no. (%)	32 (13.0)	42 (17.1)
Superior-mesenteric-vein resection — no. (%)	19 (7.7)	25 (10.2)
Arterial resection — no./total no. (%)	8/247 (3.2)	7/245 (2.9)



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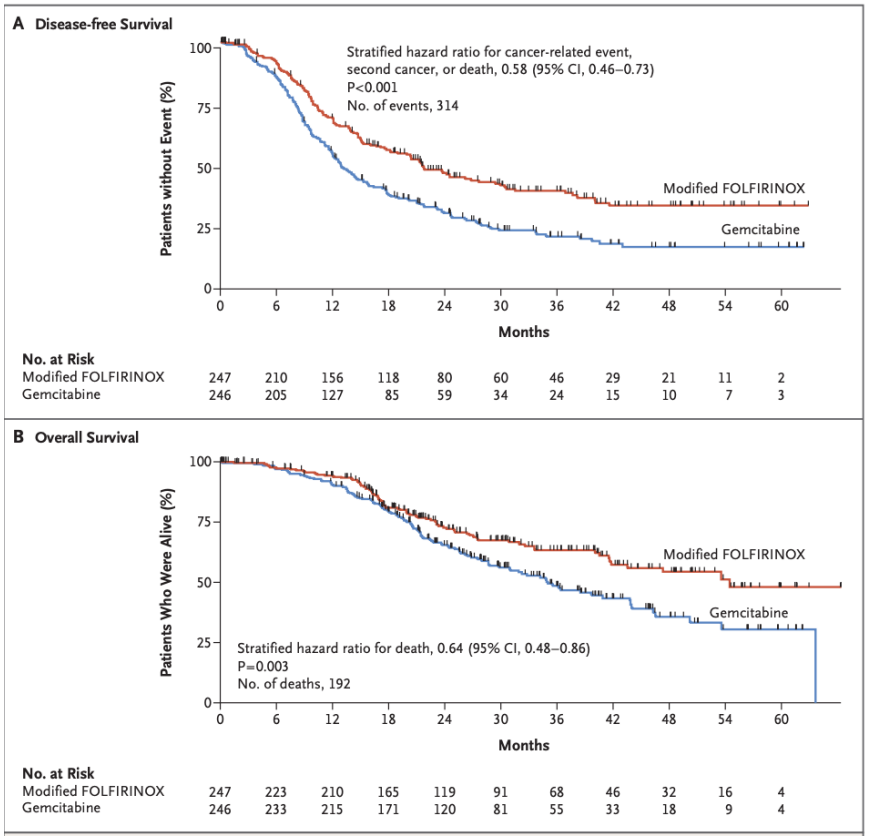

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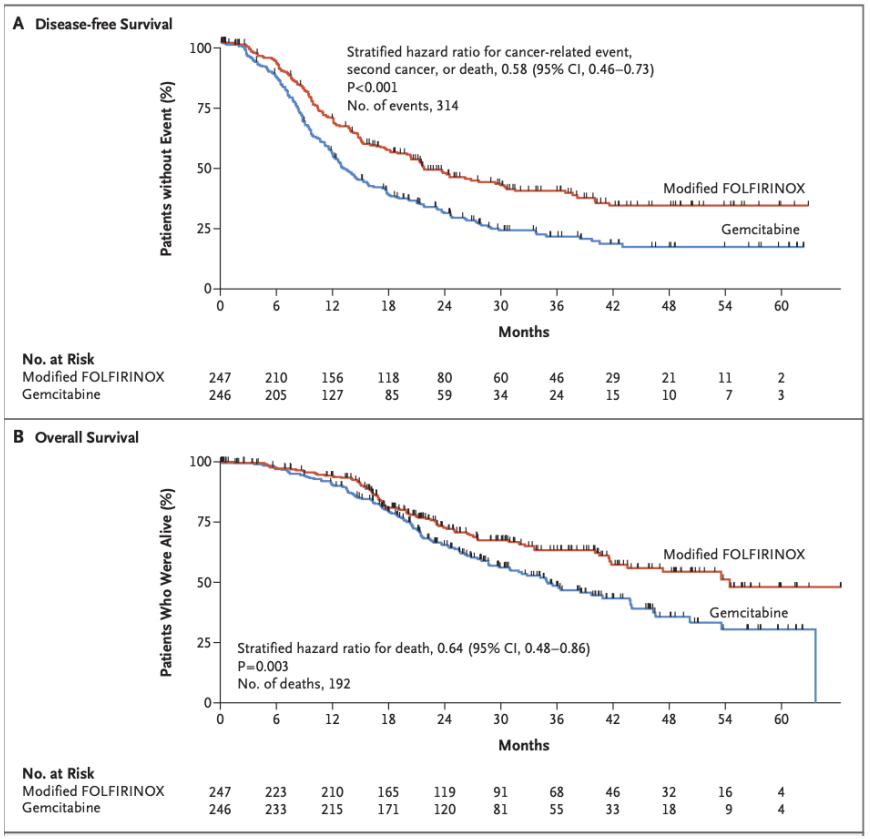
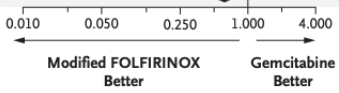


- mOS: 54.4 mos vs. 35.0 mos (HR 0.64; 0.48 - 0.86; P=0.003)
- OS rate at 3 years: 63.4% vs. 48.6%

Conroy T, et al. N Engl J Med. 2018 Dec 20;379(25):2395-2406.

PRODIGE 24–ACCORD

Subgroup	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)	Unstratified Hazard Ratio (95% CI)	P Value
	no. of events/total no. of patients			
Sex				0.42
Male	78/142	96/135	0.68 (0.50–0.92)	
Female	56/105	84/111	0.56 (0.40–0.78)	
Age				0.88
<65 yr	83/152	103/140	0.61 (0.46–0.82)	
≥65 yr	51/95	77/106	0.63 (0.44–0.90)	
WHO performance-status score				0.10
0	61/122	96/127	0.51 (0.37–0.71)	
1	73/123	80/115	0.77 (0.56–1.06)	
Diabetes				0.59
No	100/183	123/177	0.66 (0.50–0.86)	
Yes	33/62	52/64	0.55 (0.35–0.85)	
Tumor location				0.89
Head	105/193	129/175	0.62 (0.48–0.80)	
Other	28/53	47/67	0.62 (0.39–0.98)	
Tumor grade				0.69
Well differentiated	32/70	58/79	0.52 (0.34–0.81)	
Moderately differentiated	75/124	91/125	0.69 (0.51–0.93)	
Poorly differentiated or undifferentiated	21/35	23/29	0.62 (0.34–1.13)	
Primary tumor status				0.82
pT1 or pT2	16/31	16/25	0.67 (0.34–1.34)	
pT3 or pT4	118/216	164/221	0.62 (0.49–0.79)	
Nodal status				0.10
pN0	25/55	33/61	0.89 (0.53–1.49)	
pN1	109/192	147/185	0.54 (0.42–0.69)	
Tumor stage				0.31
IA or IB	3/12	8/14	0.36 (0.10–1.38)	
IIA or IIB	127/226	167/226	0.64 (0.50–0.80)	
III or IV	4/9	5/6	0.07 (0.01–0.61)	
Status of surgical margins				0.15
R0	73/148	88/134	0.72 (0.53–0.98)	
R1	61/99	92/112	0.52 (0.37–0.72)	
Superior-mesenteric-vein resection				0.29
No	122/228	161/221	0.61 (0.48–0.77)	
Yes	12/19	19/25	0.92 (0.44–1.91)	
Portal-vein resection				0.86
No	112/215	145/204	0.62 (0.49–0.80)	
Yes	22/32	35/42	0.64 (0.37–1.11)	
Postoperative CA 19-9 level				0.85
≤90 U/ml	123/231	166/226	0.61 (0.48–0.77)	
>90 U/ml	11/16	14/20	0.74 (0.33–1.64)	
Early stopping of treatment				0.49
No	83/158	137/192	0.56 (0.42–0.73)	
Yes	51/80	42/51	0.53 (0.35–0.81)	
Overall	134/247	180/246	0.62 (0.49–0.77)	



Conroy T, et al. N Engl J Med. 2018 Dec 20;379(25):2395-2406.

- Relapsed disease

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Pancreatic Adenocarcinoma

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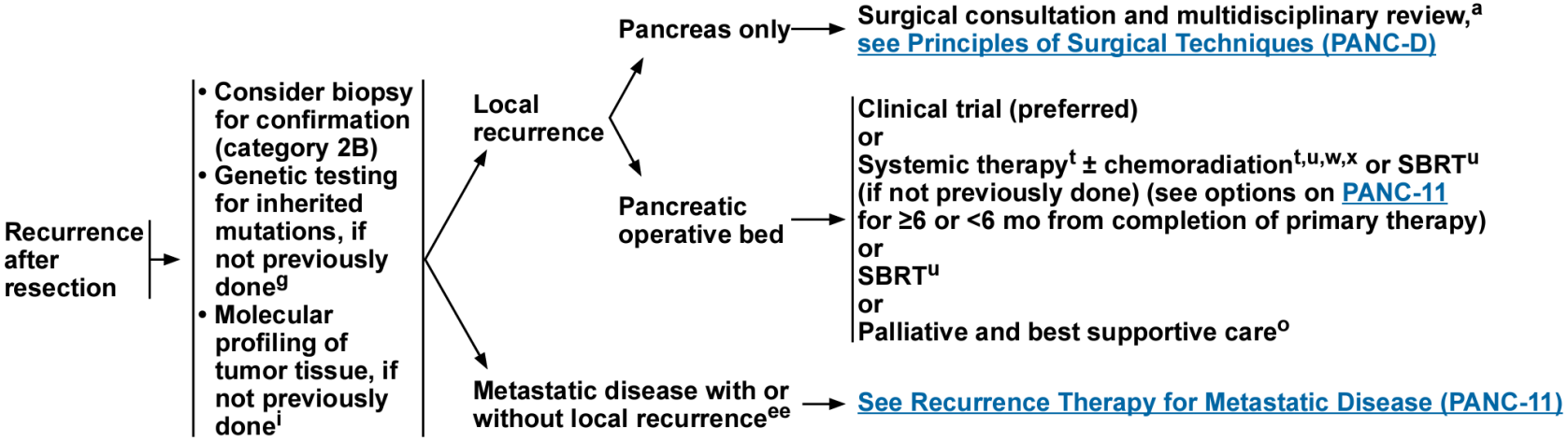
RECURRENCE AFTER RESECTION

RECURRENCE THERAPY[dd]



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Pancreatic Adenocarcinoma

NCCN Guidelines Index
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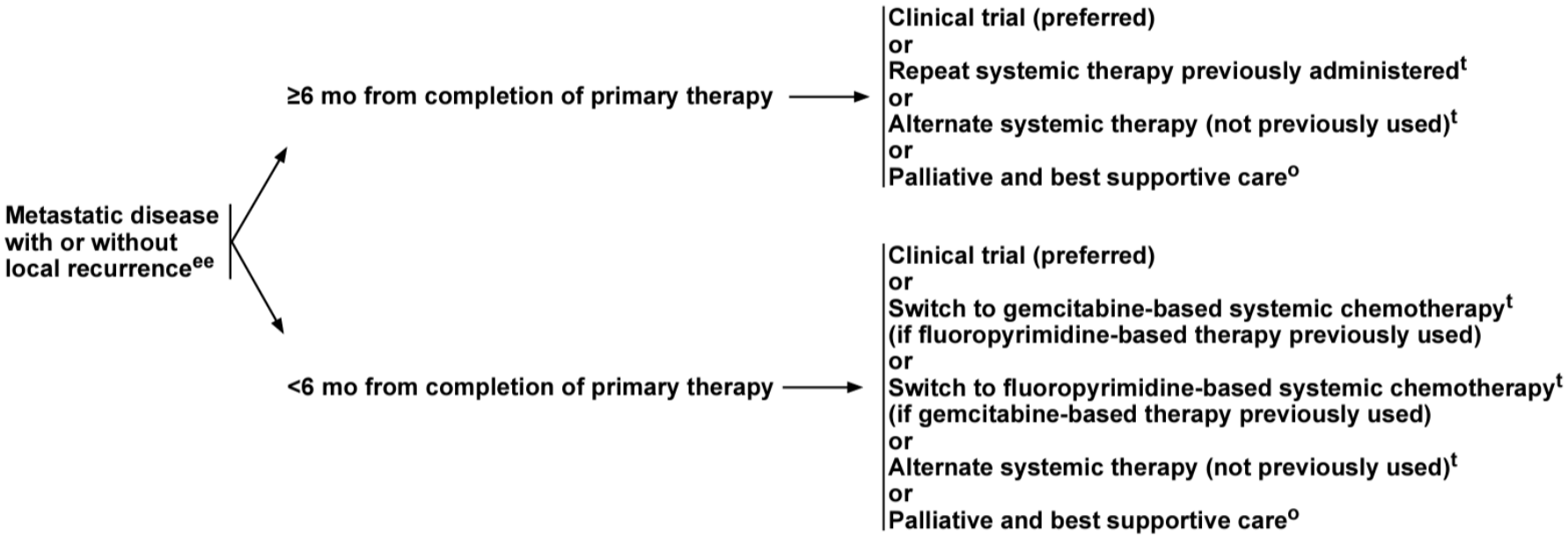
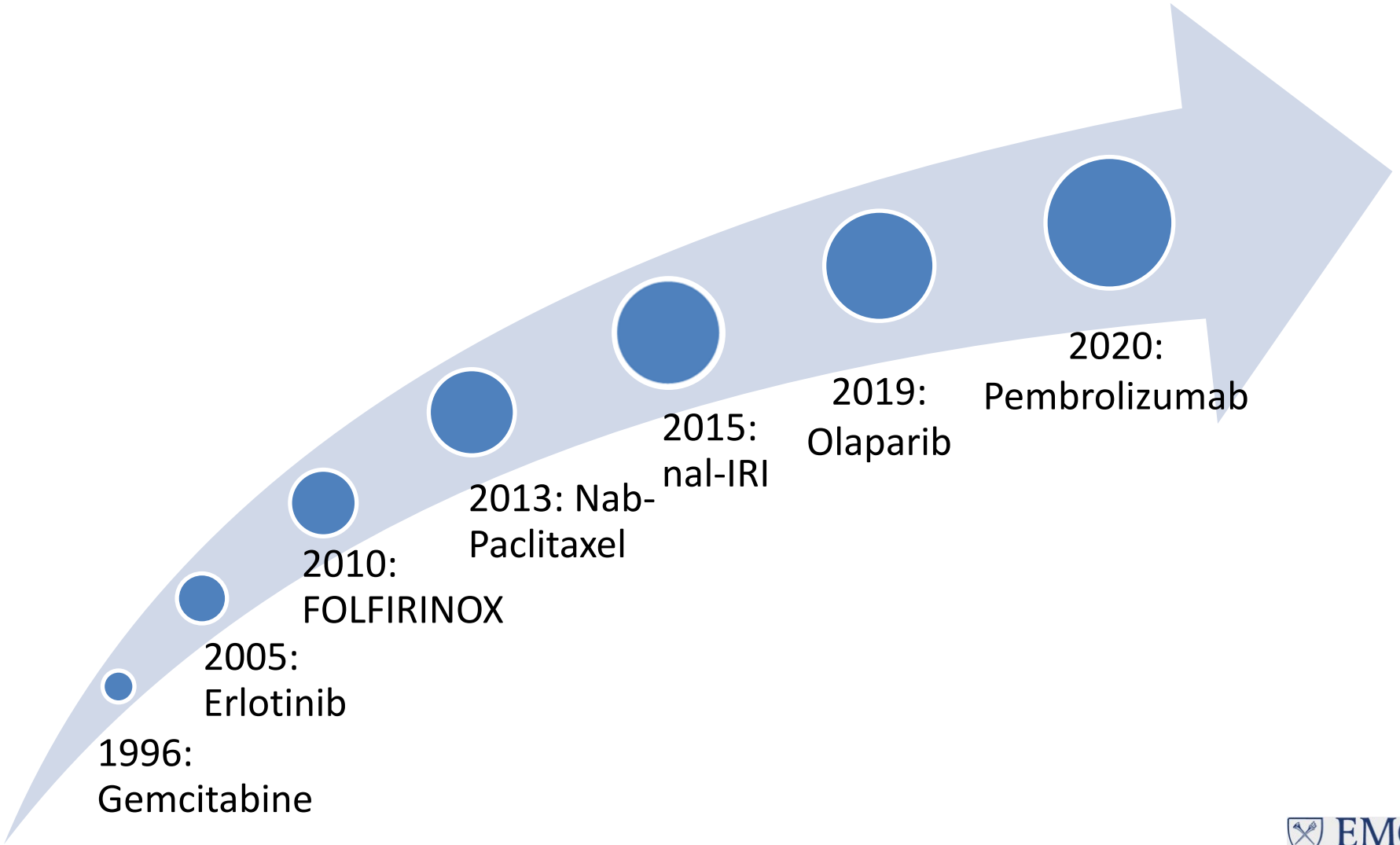
Discussion

METASTATIC DISEASE FOLLOWING SURGERY

RECURRENCE THERAPY[dd]

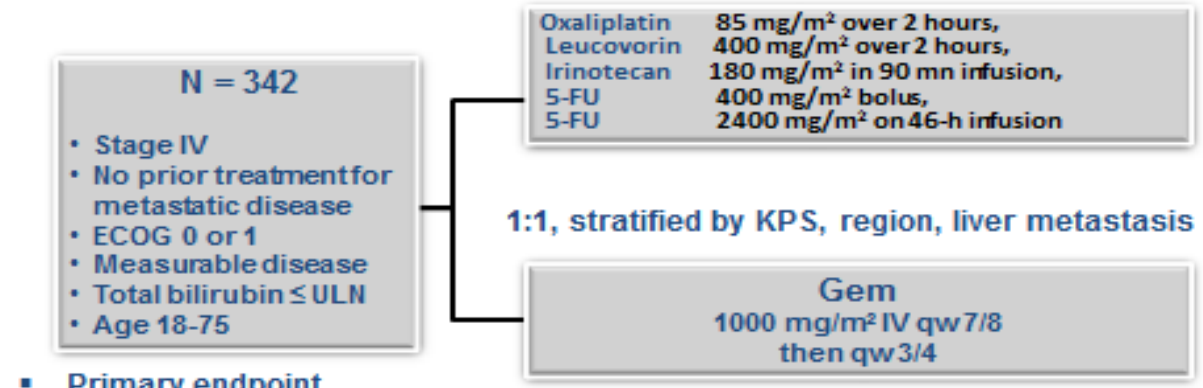


Milestones in systemic therapy for advanced pancreatic cancer



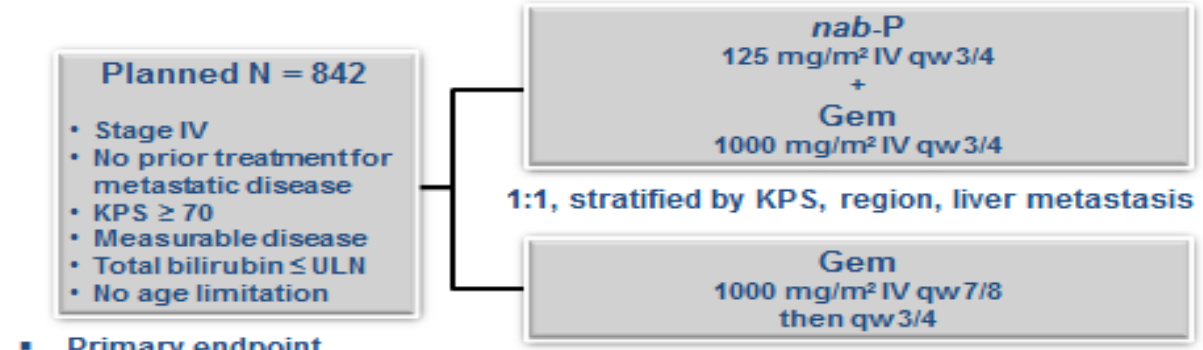
Frontline therapies

Study Design -Prodige 4 - ACCORD 11



- Primary endpoint
  - OS

Study Design -IMPACT



- Primary endpoint
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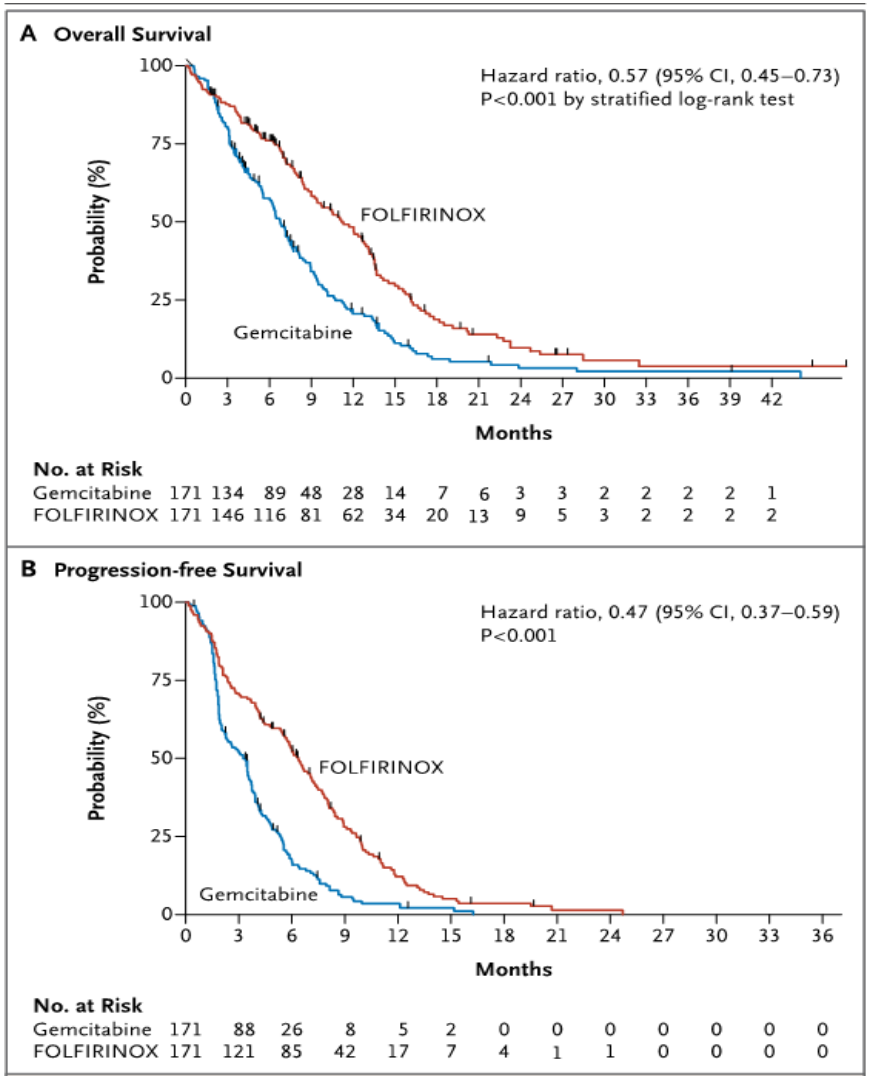
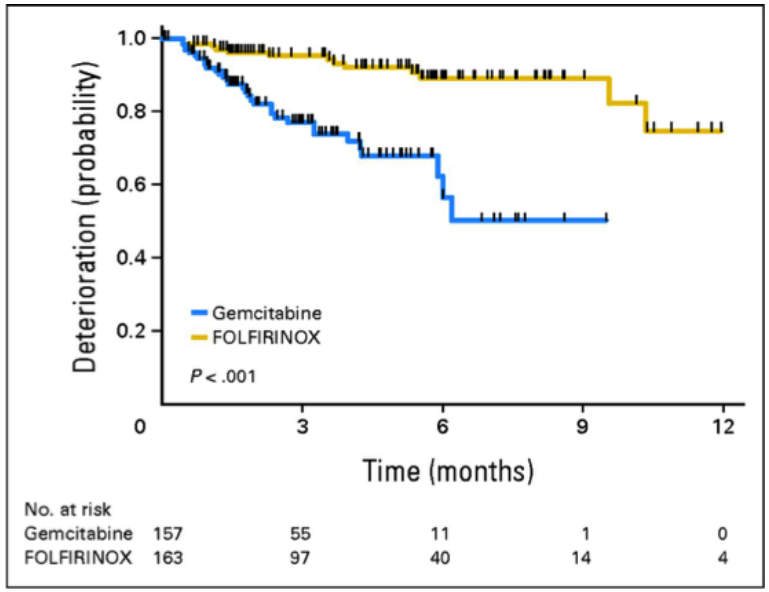
PRODIGE 4/ACCORD 11

FOLFIRINOX vs. gemcitabine



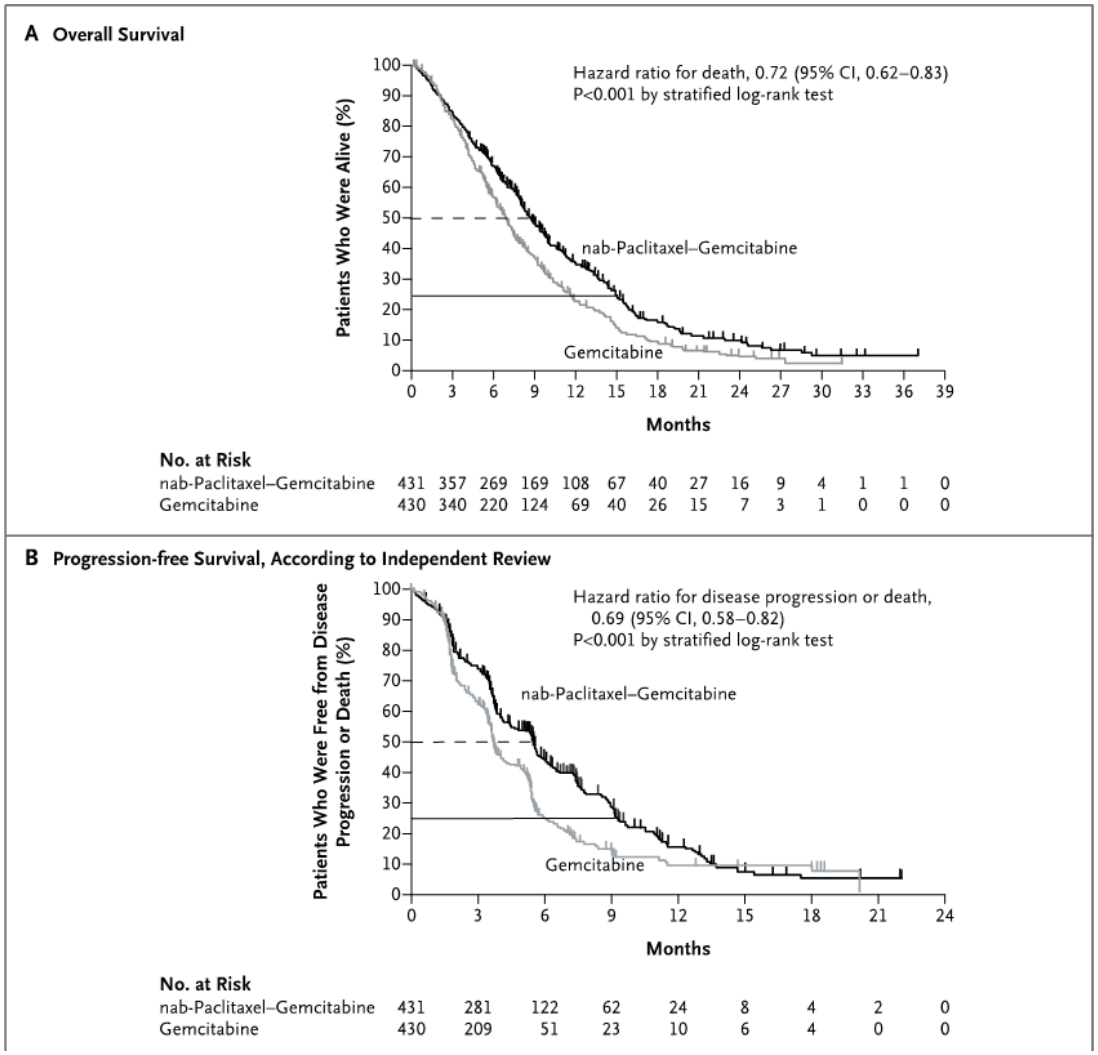


Time until definitive deterioration more than 20 points for EORTC QoL Questionnaire C30 global health status/quality of life.

Conroy T et al. N Engl J Med 2011;364:1817-1825.

Sophie Gourgou-Bourgade et al. JCO 2013;31:23-29

Gemcitabine +/- nab-Paclitaxel



Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

NAPOLI-1

Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial

Andrea Wang-Gillam*, Chung-Pin Li, György Bodoky, Andrew Dean, Yan-Shen Shan, Gayle Jameson, Teresa Macarulla, Kyung-Hun Lee, David Cunningham, Jean F Blanc, Richard A Hubner, Chang-Fang Chiu, Gilberto Schwartsmann, Jens T Siveke, Fadi Braiteh, Victor Moyo, Bruce Belanger, Navreet Dhindsa, Eliel Bayever, Daniel D Von Hoff*, Li-Tzong Chen*, for the NAPOLI-1 Study Group†

- Global, phase 3, randomised, open-label trial
- Patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy
- Randomly assigned (1:1) to 5FU/LV +/- nanoliposomal irinotecan
    - Primary endpoint was overall survival (ITT)

Wang-Gillam A, et al. Lancet. 2016 Feb 6;387(10018):545-557.

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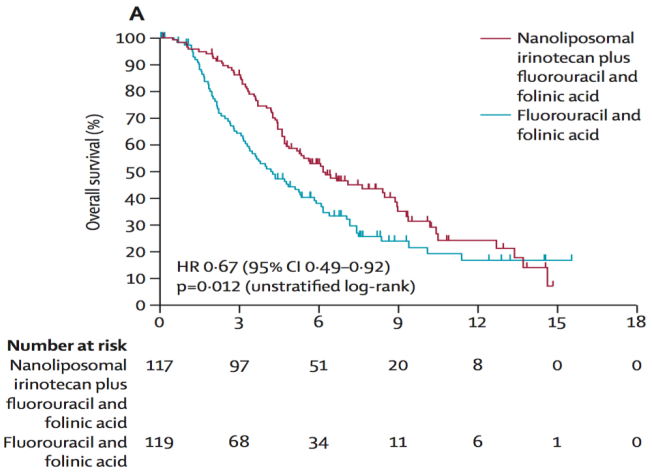
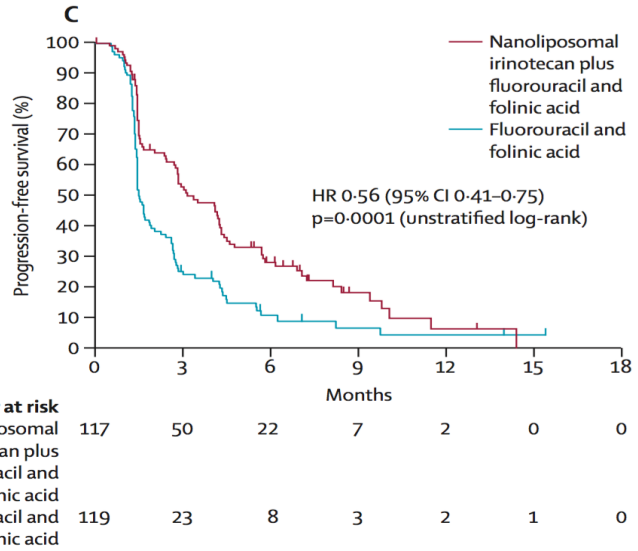
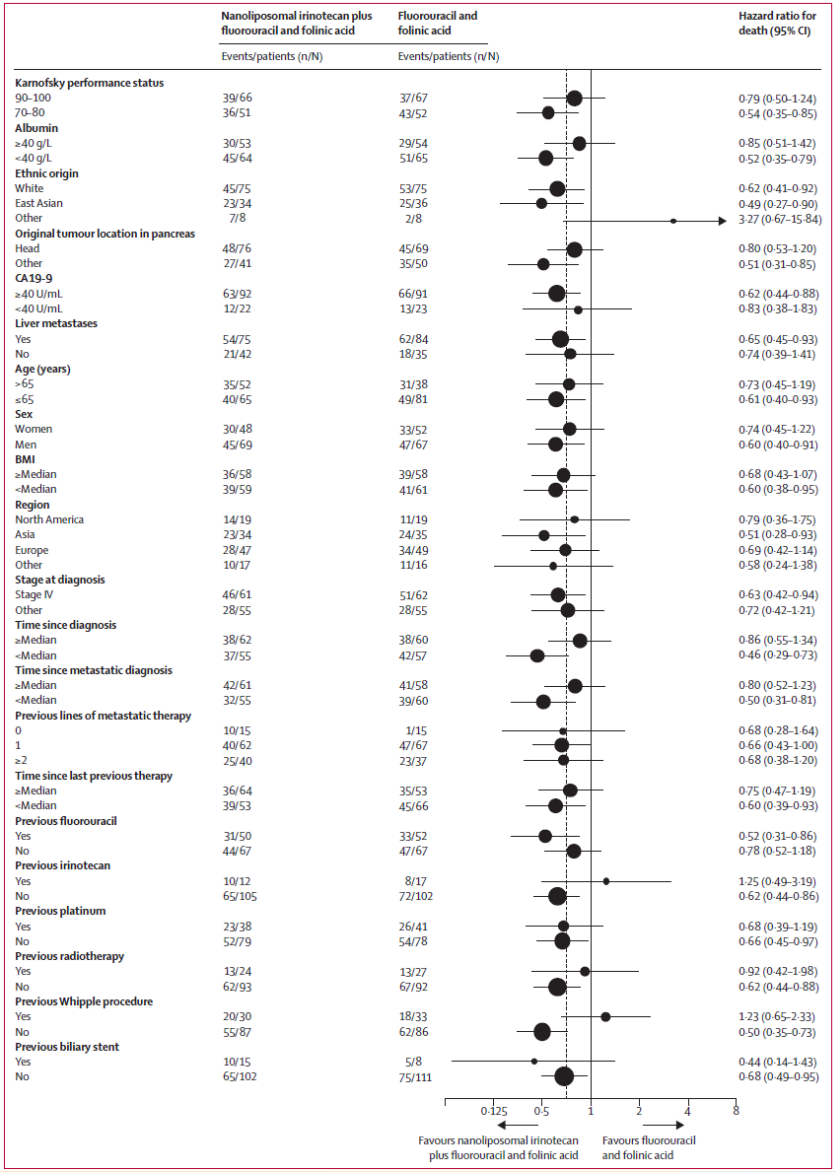
NAPOLI-1







Andrea Wang-Gillam, et al. Lancet, Volume 387, Issue 10018, 545 - 557

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Mutations Associated with Pancreatic Cancer

	Incidence (%)
KRAS Mutation	90%
CDKN2A	90%
p53	70%
SMAD4	55%
chromatin	20%
DNA repair	17%
germline BRCA	4 - 7%
cell-cycle regulators	15%
WNT	10%
Robo/slit pathway	5%
Notch signaling	5%

Lai, E., Ziranu, P., Spanu, D. et al. BRCA-mutant pancreatic ductal adenocarcinoma. Br J Cancer 125, 1321–1332 (2021).

Gemcitabine/Cisplatin

rapid communications

Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline *BRCA/PALB2* Mutation

Eileen M. O'Reilly, MD[1]; Jonathan W. Lee, MSc[1]; Mark Zalupski, MD[2]; Marinela Capanu[1]; Jennifer Park, BS[1]; Talia Golan, MD[3]; Esther Tahover, MD[4]; Maeve A. Lowery, MD[5]; Joanne F. Chou, MPH[1]; Vaibhav Sahai, MBBS, MS[2]; Robin Brenner, RN, BSN[1]; Hedy L. Kindler, MD[6]; Kenneth H. Yu, MD[1]; Alice Zervoudakis, MD[1]; Shreya Vemuri, BS[1]; Zsofia K. Stadler, MD[1]; Richard K. G. Do, MD, PhD[1]; Neesha Dhani, MD, PhD[7]; Alice P. Chen, MD[8]; and David P. Kelsen, MD[1]

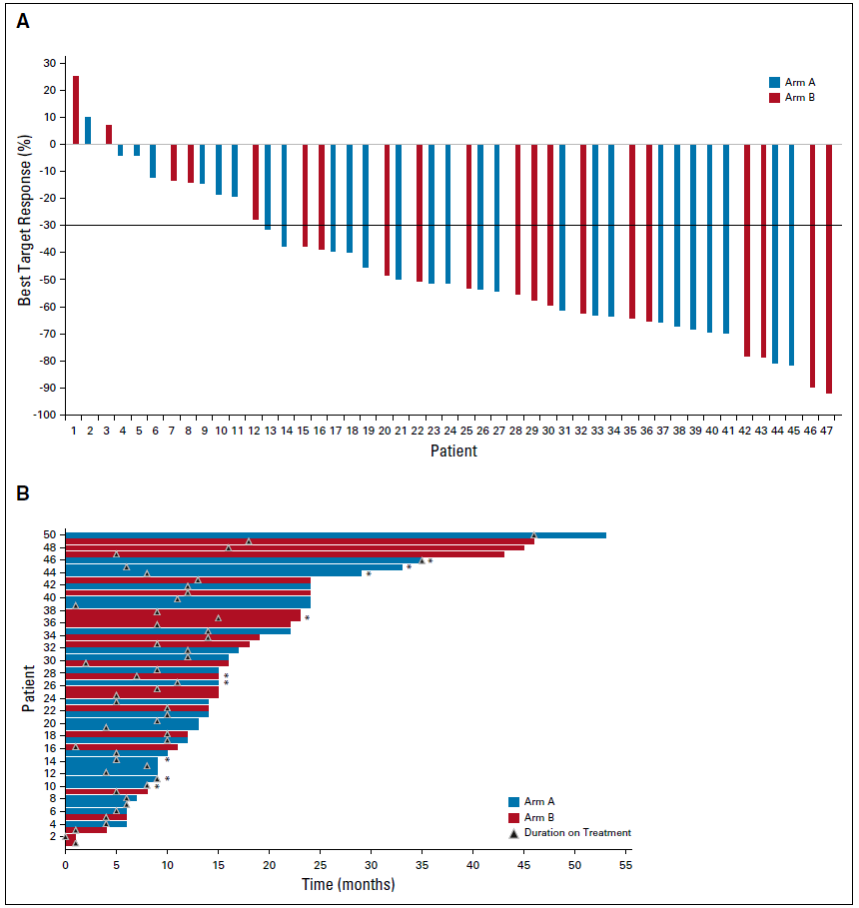
- Open-label, randomized, multicenter, two-arm phase II trial
- Patients with untreated gBRCA/PALB2+ stage III to IV PDAC
- Cisplatin 25 mg/m2 + Gemcitabine 600 mg/m2 on D3 and D10
- +/- Veliparib 80 mg bid D1 to 12 q3 weeks
  - Primary end point - RRs evaluated separately using a Simon two-stage design
  - Secondary end points PFS, DCR, OS, safety, and correlative analyses.

O'Reilly EM, et al. J Clin Oncol. 2020 May 1;38(13):1378-1388.

Gemcitabine/Cisplatin

TABLE 1. Baseline Patient Characteristics

	Arm A		Arm B		Combined Arms	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total patients	27	54	23	46	50	100
Median age, years (range)	64 (48-82)		63 (37-81)		63.5 (37-82)	
Sex						
Male	12	44	10	43	22	44
Female	15	56	13	57	28	56
AJCC stage						
III (locally advanced)	5	19	3	13	8	16
IV (metastatic)	22	81	20	87	42	84
ECOG PS						
0	15	56	8	35	23	46
1	12	44	15	65	27	54
Race						
White	25	92	21	91	46	92
Black	1	4	1	4	2	4
Asian	1	4	—		1	2
Unknown	—		1	4	1	2
Ashkenazi Jewish descent	19	70	11	48	30	60
Germline *BRCA* mutation						
BRCA1	7	26	5	22	12	24
BRCA2	19	70	16	70	35	70
PALB2	1	4	2	9	3	6
BRCA Ashkenazi founder mutations (n = 28; 56%)						
BRCA1 187delAG	2	7	1	4	3	6
BRCA1 5385insC	2	7	2	9	4	8
BRCA2 6174delT	13	48	8	35	21	42
Pancreatic primary location						
Head	11	41	9	39	20	40
Body	12	44	5	22	17	34
Tail	4	15	9	39	13	26
Site of metastases						
Liver	20	74	17	74	37	74
Lung	7	26	7	30	14	28
Lymph nodes	10	37	8	35	18	36
Peritoneum	3	11	4	17	7	14
Other sites	1	4	2	9	3	6
Previous surgery	5	19	2	9	7	14



O'Reilly EM, et al. J Clin Oncol. 2020 May 1;38(13):1378-1388.

Gemcitabine/Cisplatin

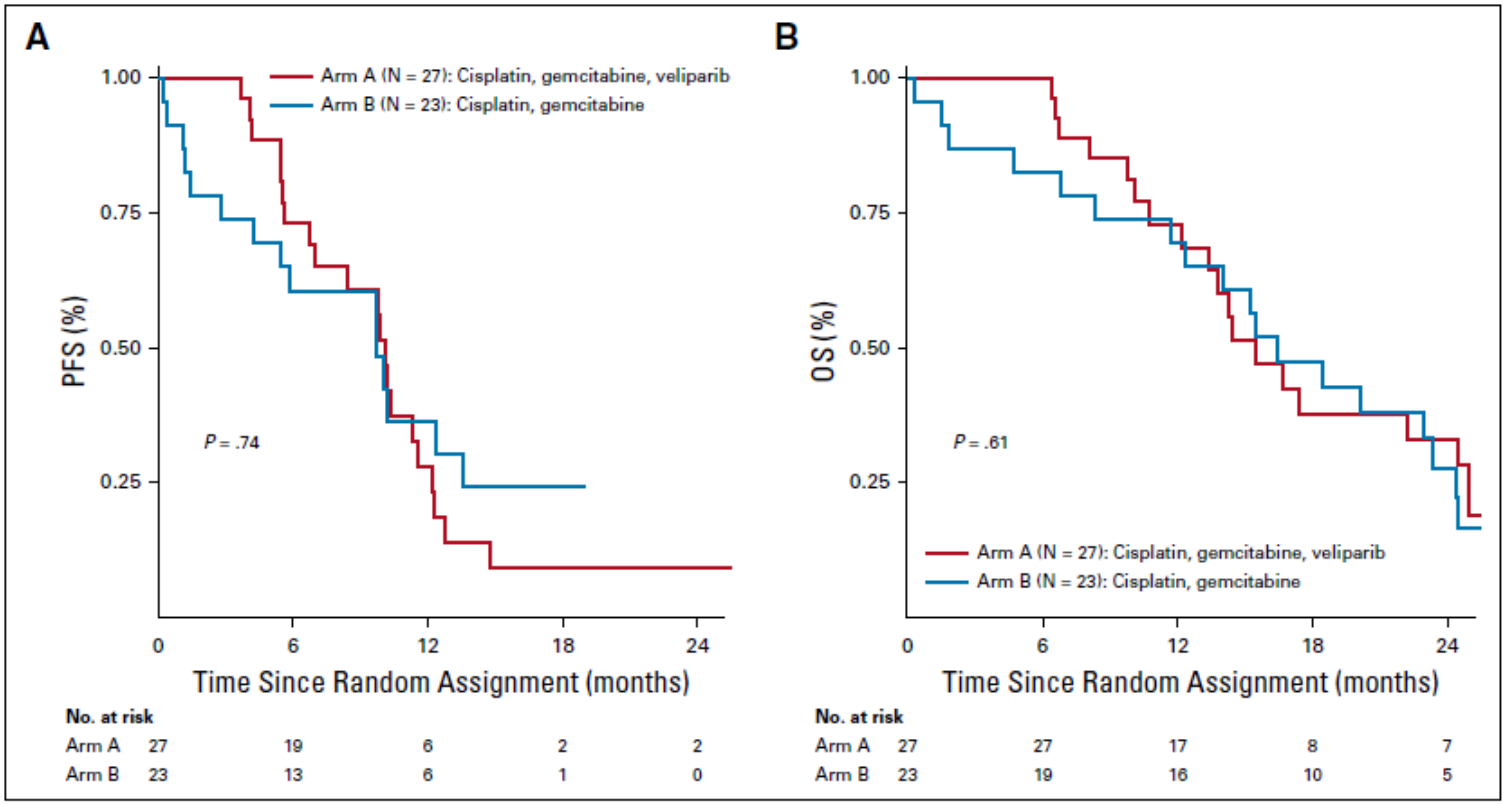


FIG 3. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS).

O'Reilly EM, et al. J Clin Oncol. 2020 May 1;38(13):1378-1388.

POLO: Olaparib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

- Randomized, double-blind, placebo-controlled, phase 3 trial
- Patients with germline *BRCA1* or *BRCA2* mutation and metastatic pancreatic cancer
- Must not have progressed during first-line platinum-based chemotherapy
- Randomly assigned 3:2 to maintenance olaparib tablets (300 mg bid) or placebo
  - Primary end point - PFS by blinded independent central review.

Golan T, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317-327.

POLO: Olaparib

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib (N=92)	Placebo (N=62)
Age at randomization — yr		
Median	57	57
Range	37–84	36–75
Age ≥65 yr at randomization — no. (%)	28 (30)	13 (21)
Male sex — no. (%)	53 (58)	31 (50)
ECOG performance status — no. (%)		
0, normal activity	65 (71)	38 (61)
1, restricted activity	25 (27)	23 (37)
Missing data	2 (2)	1 (2)
Germline *BRCA* mutation — no. (%)†		
BRCA1	29 (32)	16 (26)
BRCA2	62 (67)	46 (74)
Both *BRCA1* and *BRCA2*	1 (1)	0
Time from diagnosis to randomization — mo		
Median	6.9	7.0
Range	3.6–38.4	4.1–30.2
First-line platinum-based chemotherapy — no. (%)‡		
FOLFIRINOX variants	79 (86)	50 (81)
Gemcitabine–cisplatin	2 (2)	3 (5)
Other platinum-based treatments	10 (11)	8 (13)
Missing data	1 (1)	1 (2)
Duration of first-line chemotherapy before randomization		
Median — mo	5.0	5.1
Range — mo	2.5–35.2	3.4–20.4
16 wk–6 mo — no. (%)	61 (66)	40 (65)
>6 mo — no. (%)	30 (33)	21 (34)
Missing data — no. (%)	1 (1)	1 (2)
Best response with first-line chemotherapy — no. (%)		
Complete or partial response	46 (50)	30 (48)
Stable disease	45 (49)	31 (50)
Missing data	1 (1)	1 (2)

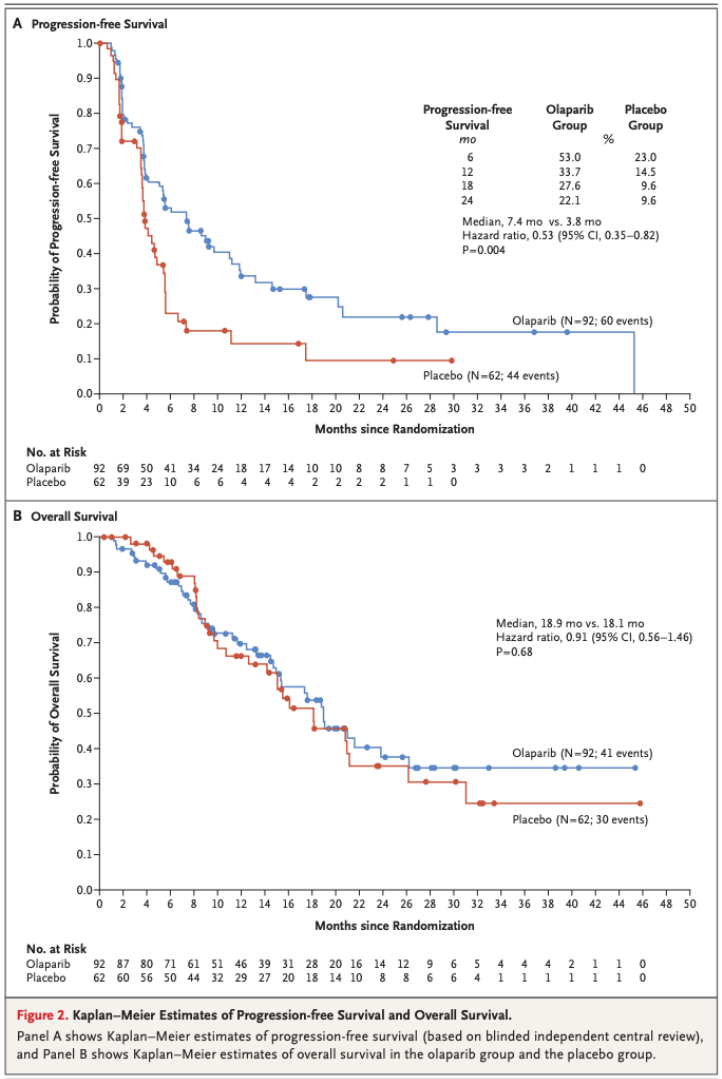


Figure 2. Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.
Panel A shows Kaplan–Meier estimates of progression-free survival (based on blinded independent central review), and Panel B shows Kaplan–Meier estimates of overall survival in the olaparib group and the placebo group.

Golan T, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317-327.

POLO: Olaparib

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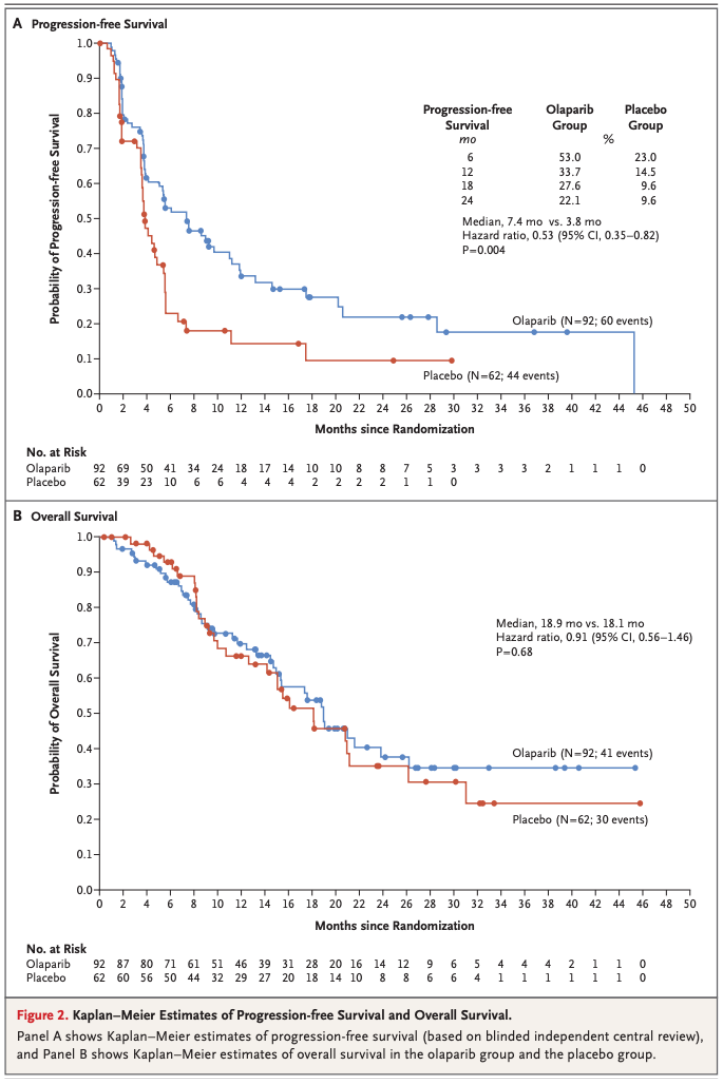

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Golan T, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317-327.

POLO: Olaparib

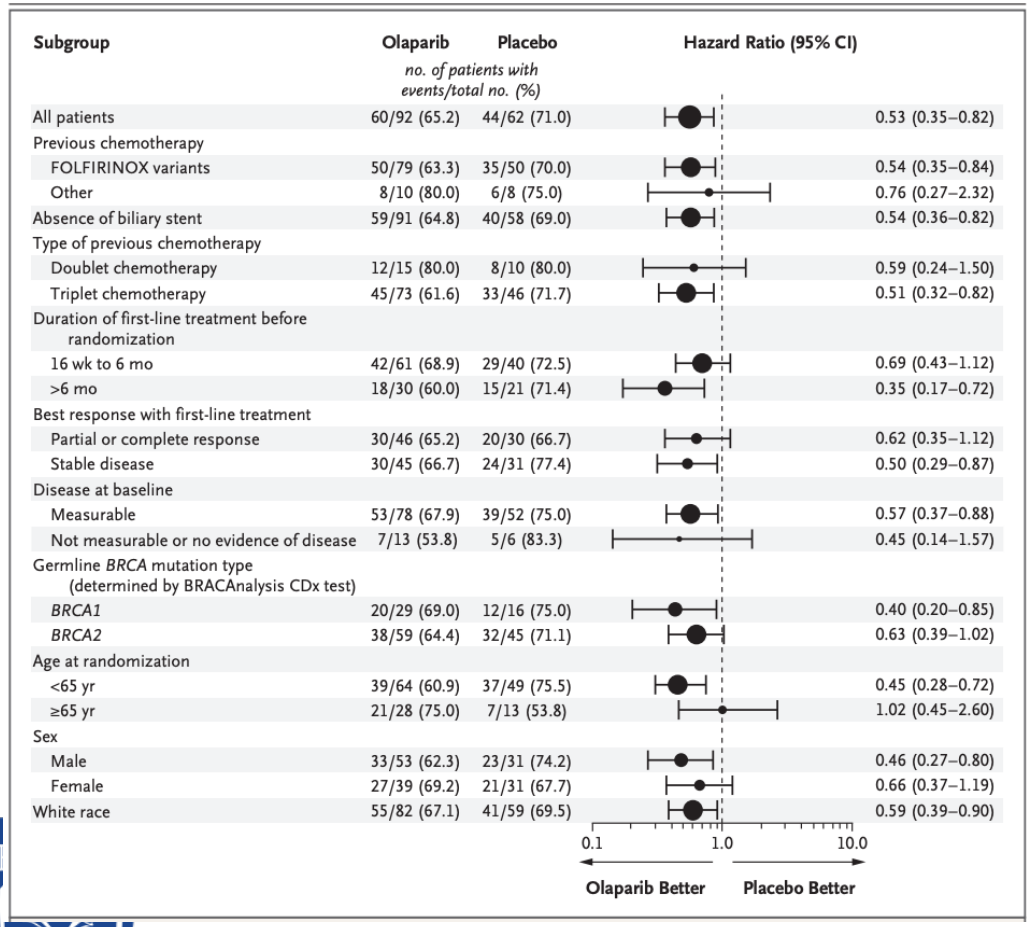


Table S4. First-Line Platinum-Based Chemotherapy Received by Patients Immediately Prior to Randomization in POLO

Prior chemotherapy — no. (%)	Olaparib (N = 92)	Placebo (N = 62)
FOLFIRINOX	73 (79.3)	44 (71.0)
FOLFOX	4 (4.3)	5 (8.1)
GEMOX	5 (5.4)	1 (1.6)
Gemcitabine/cisplatin	2 (2.2)	3 (4.8)
Gemcitabine/nab-paclitaxel/capecitabine/cisplatin	2 (2.2)	2 (3.2)
XELOX	2 (2.2)	1 (1.6)
Oxaliplatin	1 (1.1)	1 (1.6)
Gemcitabine/epirubicin/capecitabine/cisplatin	0	2 (3.2)
FOLFIRI/cisplatin	0	1 (1.6)
FOLFOX/nab-paclitaxel	0	1 (1.6)
5-fluorouracil/carboplatin	1 (1.1)	0
FOLF/cisplatin	1 (1.1)	0

Golan T, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019 Jul 25;381(4):317-327.

CPI in dMMR PDAC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

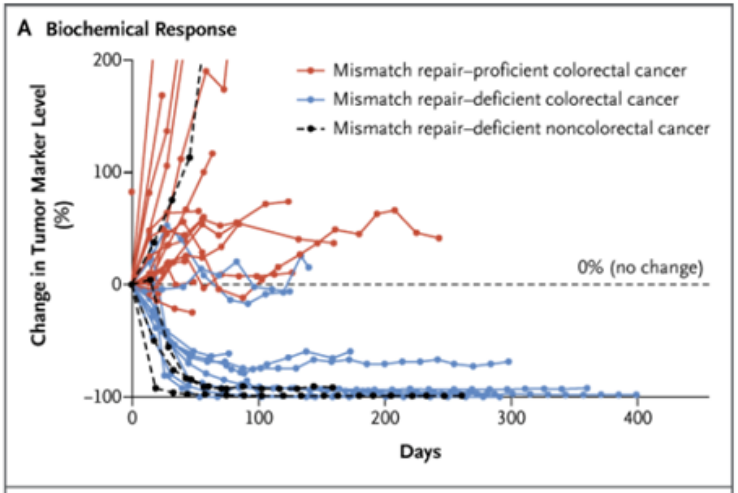
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

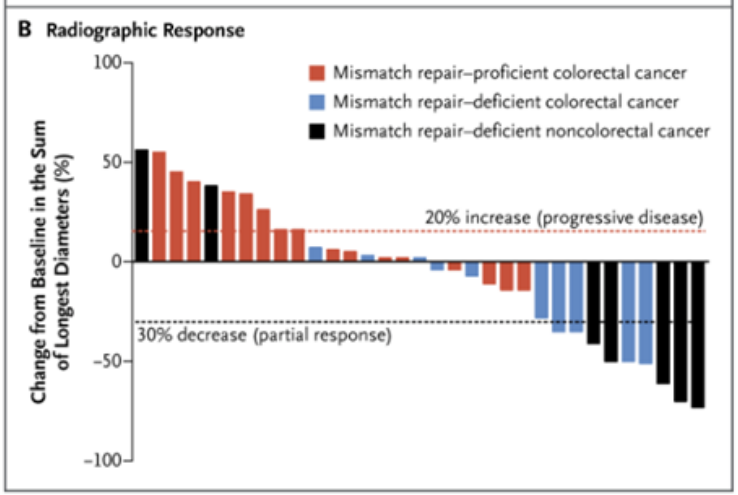
D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

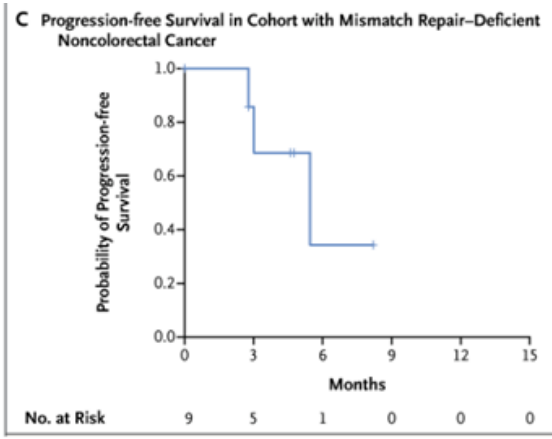
Demographic and Baseline Characteristics of the Patients.*

Characteristic	Mismatch Repair–Deficient Colorectal Cancer (N = 11)	Mismatch Repair–Proficient Colorectal Cancer (N = 21)	Mismatch Repair–Deficient Noncolorectal Cancer (N = 9)	P Value†
Median age (range) — yr	46 (24–65)	61 (32–79)	57 (34–92)	0.02
Sex — no. (%)				0.72
Female	5 (45)	8 (38)	4 (44)	
Male	6 (55)	13 (62)	5 (56)	
Race — no. (%)‡				0.66
White	8 (73)	17 (81)	8 (89)	
Black	1 (9)	3 (14)	0	
Other	2 (18)	1 (5)	1 (11)	
ECOG performance status — no. (%)§				0.07
0	0	6 (29)	2 (22)	
1	11 (100)	15 (71)	7 (78)	
Cancer type — no. (%)				>0.99
Colon	9 (82)	18 (86)	0	
Rectal	2 (18)	3 (14)	0	
Ampullary or cholangiocarcinoma	0	NA	4 (44)	
Endometrial	0	NA	2 (22)	
Small bowel	0	NA	2 (22)	
Gastric	0	NA	1 (11)	
Histologic grade — no. (%)				0.20
Well or moderately differentiated	7 (64)	18 (86)	4 (44)	
Poorly differentiated	4 (36)	3 (14)	3 (33)	
Other	0	0	2 (22)	
Stage IV cancer — no. (%)	11(100)	21 (100)	9 (100)	>0.99

CPI in dMMR PDAC







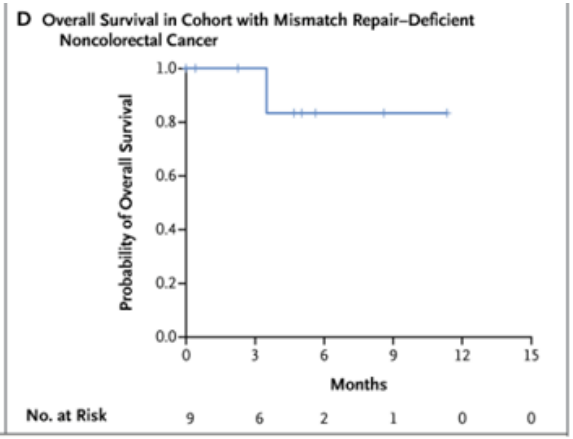


Table 2

Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N = 10)	Mismatch Repair–Proficient Colorectal Cancer (N = 18)	Mismatch Repair–Deficient Noncolorectal Cancer (N = 7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

CPI in dMMR PDAC

rapid communications

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron R. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18]; and Luis A. Diaz Jr, MD[19]

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

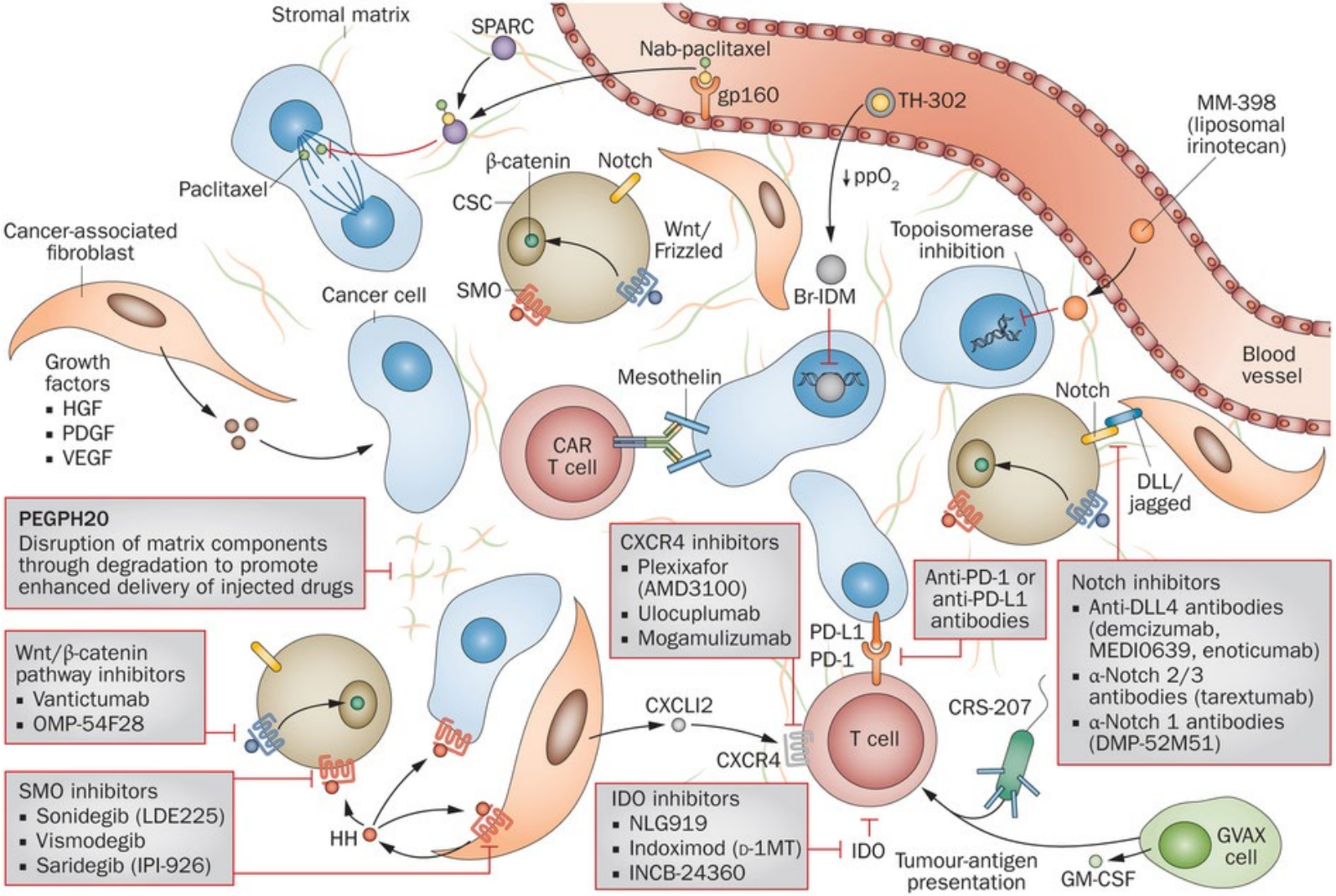
Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

- 233 patients with multiple tumor types: median follow up = 13.4 mo
- ORR = 34.3%, PFS 4.1 mo mOS 23.5 mo

Pancreatic cancer n=22, ORR 18.2%, PFS 2.1m, mOS 4m

JCO Volume 38, Issue 1 (January 01, 2020) 1-10. Published online November 04, 2019.

Pancreatic cancer therapies

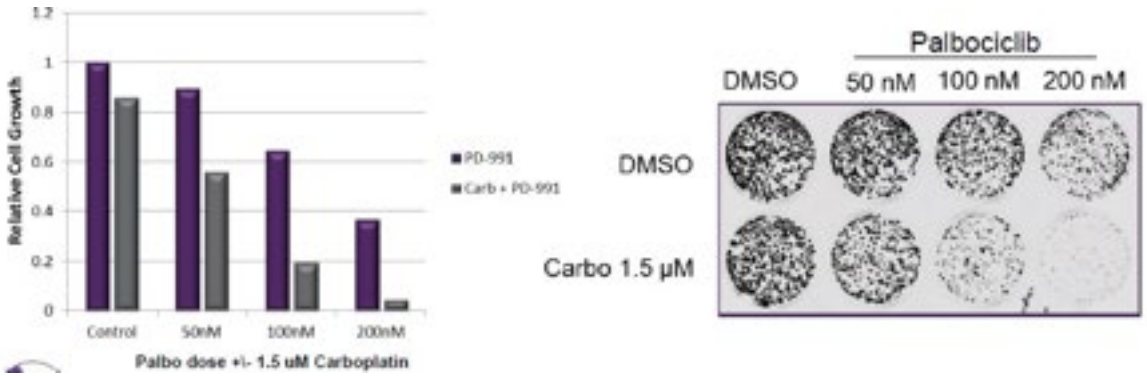


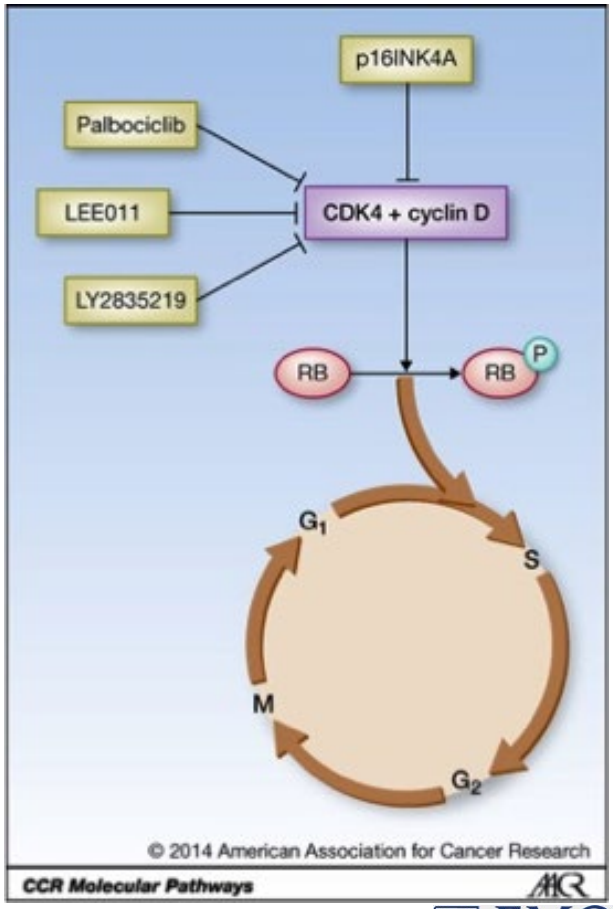
Nature Reviews | Clinical Oncology

Winship3263

Phase 1 study of palbociclib in combination with cisplatin or carboplatin in advanced solid malignancies

- Cycling dependent kinases (CDK) regulate the orderly progression of dividing cells through various stages of the cell cycle
- Alterations in this family of kinases are frequently described in solid malignancies leading to the recognition of CDKs as valid targets of anticancer therapy





palbociclib (PD-991) + carboplatin (Carbo) was synergetic against NCI-H520 cell line

Malumbres M, Barbacid M: Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer 2009, 9:153-166.

Winship3263

Primary Objectives

- Safety and tolerability of palbociclib + cis or carbo
- RP2D of the tested combinations

Secondary Objectives

- Characterize PK profiles
- Preliminary anti-tumor efficacy
- PK/PD correlative analyses (palbociclib trough conc. and CDK4 inhibition read-outs in tumor and surrogate samples - C1D22)
- Assess potential association between tissue-based biomarkers and efficacy

Expansion cohorts: NSCLC, pancreatico-biliary cancers.

Clinical trial information: NCT02897375

Sponsor: Pfizer

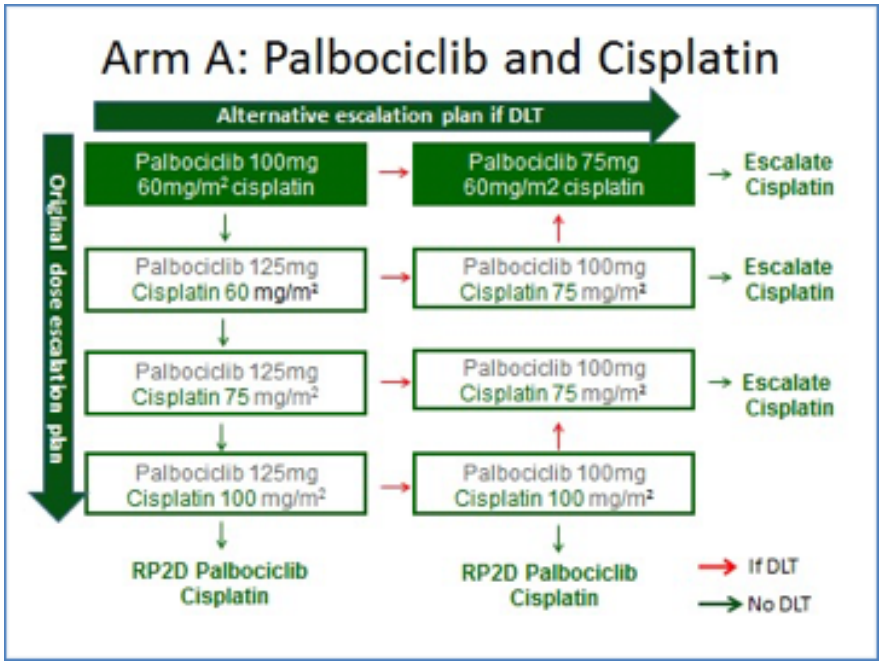
Combined Chemo (concurrent)	SKMES-1	H226	H520
Docetaxel	Additive	Additive	Additive
Paclitaxel	ND*	ND	Additive
Cisplatin	Not detected	Additive	Additive/Synergistic
Carboplatin	Additive	Additive	Additive/Synergistic
Gemcitabine	Not detected	Not detected	Not detected
Pemetrexed	ND	ND	Slight Additive
Pac + Cis	ND	ND	Additive/Synergistic
Pem + Carbo	ND	ND	ND
Pem + Cis	ND	ND	ND
Gem + Cis	ND	ND	ND
Carbo + Doce***	Additive	ND	Synergistic
Carbo + Cis***	Additive/Synergistic	Additive	Additive/Synergistic
Carbo + Gem***	Not detected	Additive	Additive/Synergistic

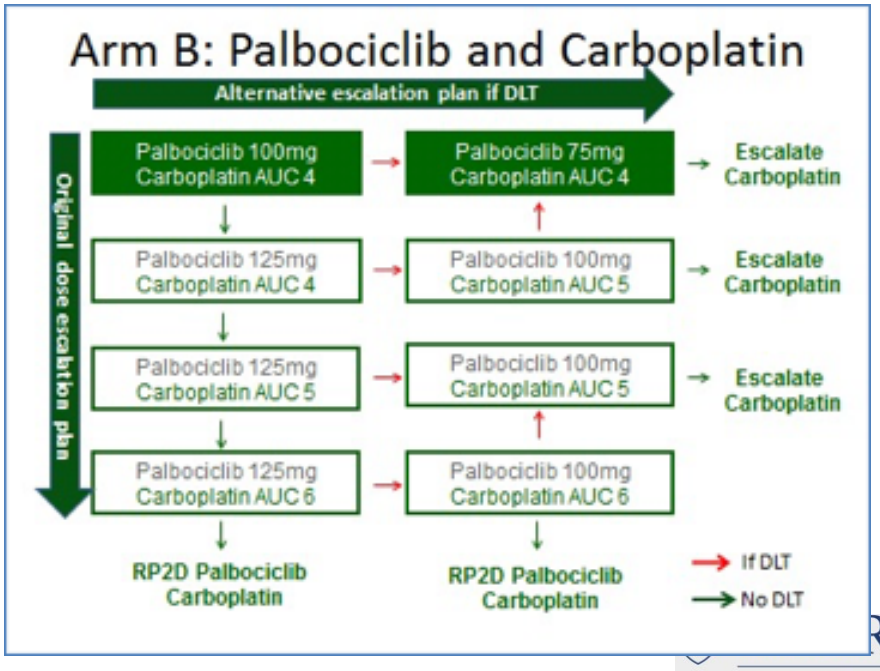
Synergy, additivity and antagonism of palbociclib in combination with cytotoxic agents commonly employed for the treatment of squamous and non squamous NSCLC

Winship3263

Stage	Dose level	Palbociclib (mg once daily)	Cisplatin (mg/m²) IV
Stage I	-1	75	60
	1: Starting dose level	100	60
Stage II	2	125	60
	3	125	75
Expansion	RP2D	TBD	TBD

Stage	Dose level	Palbociclib (mg once daily)	Carboplatin (AUC) IV
Stage I	-1	75	4
	1: Starting dose level	100	4
Stage II	2	125	4
	3	125	5
	4	125	6
Expansion	RP2D	TBD	TBD





#2085; A Phase 1 Study of Palbociclib in Combination with Cisplatin or Carboplatin in Advanced Solid Malignancies

9-13 September 2022

Correlatives/Exploratory Endpoints

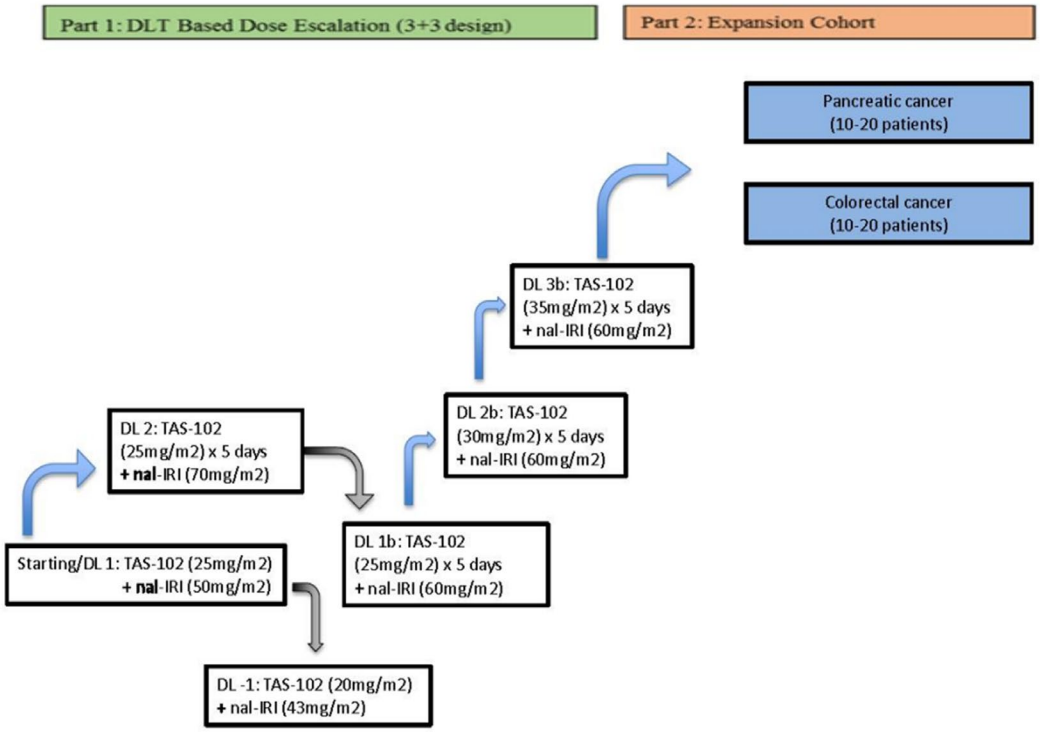
- PK Assessments:
  - Cisplatin and carboplatin using peripheral blood samples on C1D1 and C2D1
  - Trough samples for palbociclib will be determined on C1D15 and C1D22
- PD Assessments
  - Protein expression by IHC - CDK4 inhibition using surrogate skin biopsy samples
  - pRB, Ki67 and CDK4 expression
- Gene expression and somatic mutations by NextGen platform
  - LKB1, RB1, Cyclin D, CDK4, CDK6 and KRAS

Biomarker assay and sample type	Baseline	C1D1	C1D15	C1D22	C2D1	Progression
Platinum PK Samples		X			X	
Palbociclib trough PK sample			X	X		
Tumor biopsy*	X			X		X
Skin Biopsy	X	X		X		X
PBMC/Serum or Plasma	X	X		X		X

Winship 4146: OniLon

Phase I/II Study of Trifluridine/Tipiracil (TAS102) in Combination with Nanoliposomal Irinotecan (NAL-IRI) in Advanced GI Cancers

- Stage IV or locally advanced unresectable GI adenocarcinomas (Gastric, Esophageal [EA], Pancreatic [PDAC], biliary tract cancer [BTC], CRC)
- Progression of disease after at least 1 prior line of therapy (including Irinotecan).
- Exclusion criteria included patients homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) or heterozygotes for UGT1A1*28 (UGT1A11 7/6 genotype)
- Trial design - standard 3+3



Primary objective - RP2D of the combination therapy

Drug	Frequency	Route	Treatment Period
NAL-IRI	Day 1	IV infusion	Cycle is 14-days
TAS-102	BID, Days 1-5	Oral	

Clinical trial information: NCT03368963

Sponsors: Taiho Oncology, Ipsen Biopharmaceuticals

Winship 4146: OniLon

2021 ESMO World Congress on GI Cancer

- 46 patients screened; 24 patients enrolled.
- Screen failures were due to homozygous UGT1A1 enzyme status that could only have been determined after screening.
- All the patients were treatment refractory; median age 66.5 years.
- 18 CRC, 4 PDAC, 1 BTC, and 1 EA
- MTD = RP2D

- TAS-102: 35mg/m2 bid on days 1-5
- Nal-IRI: 60mg/m2 IV on day 1

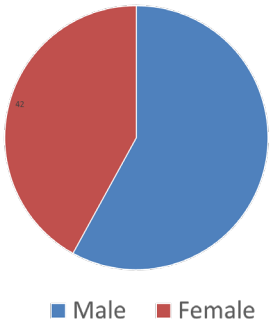


Figure 2: Gender distribution

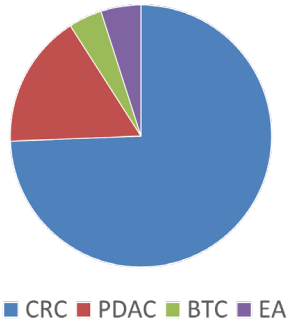


Figure 3: Distribution of diagnoses

AE Counts by Attribution	Any grade	Grade 3/4
Definite		
Neutropenia	4	0
Neutropenic fever	1	1
Altered mentation (steroid induced)	1	1
Diarrhea	3	1
Nausea	2	1
Thrombocytopenia	1	0
Vomiting	2	2
Probable		
Dehydration	1	0
Diarrhea	3	0
Fatigue	3	0
Hypomagnesemia	1	0
Loss of appetite/anorexia	2	2
Nausea	4	1
Non-neutropenic fever	1	0
Dry heaves	1	0
Vomiting	3	0
Weight loss	1	0

Most common tx related toxicities: neutropenia, nausea, fatigue, diarrhea, vomiting and anorexia.

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- Disease control rate was 62.5%.
- One CRC patient who had had progression of disease after 4 lines of therapy, achieved and maintained partial response (55% reduction in tumor volume) for 12 months on the study.
- Fourteen additional patients (EA=1, BTC=1, CRC=10 and PDAC=2) had stable disease as best response.
- A dose expansion phase II of this study is currently enrolling PDAC patients.

Olatunji B. Alese, Walid L. Shaib, Mehmet Akce et. al…Annals of Oncology 32, S200

Conclusion

- Adjuvant chemotherapy is very important in reducing risk of recurrence following resection of PDAC
- Treatment options for relapsed pancreatic cancers are expanding, mostly due to novel molecular targets
- Additional efforts are ongoing in the discovery of predictive biomarkers

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