

Pancreatic Cancer 2021

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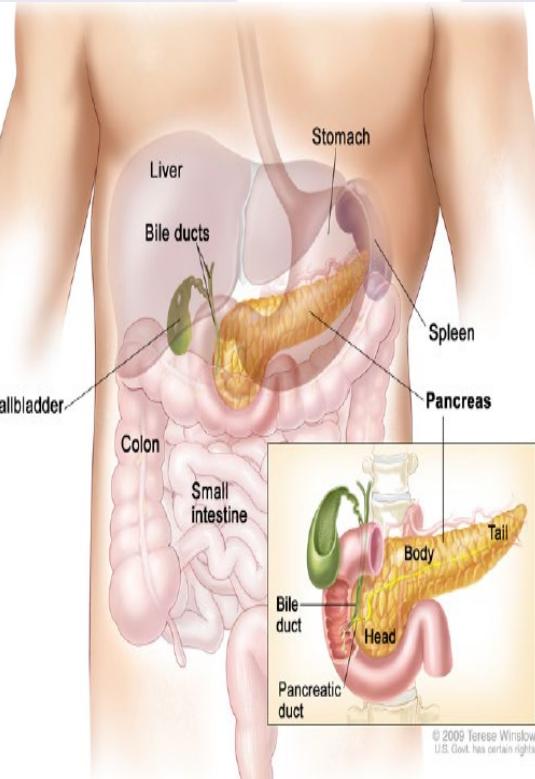
Objectives

- Overview of pancreatic cancer risk factors
- Stages and multi-D treatment guidelines
- Standard treatments
- Molecular targets and novel therapies

Pancreatic Cancer: the Problem

The pancreas

The pancreas is located behind the stomach and next to the spleen. The small intestine wraps around the wide end of the pancreas. The liver and gallbladder are found nearby.



- Projected 60,430 new cases of pancreatic cancer in US with 48,220 deaths in 2021
- 5-yr OS 10%
- Stage for stage, it is associated with the lowest survival rates of any major cancer type
- By 2030 it is expected to rise to the 2nd leading cause of cancer death in the US (behind lung cancer)

Risk Factors

- Age
- Gender (men slightly higher than women)
- Race
- Smoking
- Obesity
- Diet
- Chronic pancreatitis
- Exposures (pesticides, benzene, dyes, petrochemicals)
- Family history / genetic mutations

Number of 1 st Degree Relatives	Standardized Incidence Ratio (95% CI)	Incidence (per 100,000 in U.S. population)
General U.S. Population	-	9
1	4.5 (0.54 - 16.3)	41
2	6.4 (1.8 – 16.4)	58
3 or more	32 (10.4 – 74.7)	288

Genetic Predisposition to Pancreatic Cancer

Syndrome	Mutation	Relative Risk of Pancreatic Cancer	Other Malignancies
Hereditary Breast and Ovarian Cancer (HBOC)	<i>BRCA1, BRCA2</i>	2-9	Ovary, prostate, melanoma
	<i>PALB2</i>	Increased	Breast, ovarian, prostate
Ataxia Telangiectasia	<i>ATM</i>	3	Breast
Familial Atypical Multiple Mole Melanoma (FAMMM)	<i>CDKN2A/P16</i>	13-39	Multiple nevi, dysplastic nevi, melanomas
Peutz-Jeghers Syndrome	<i>STK11</i>	132	Hamartomatous polyps, breast, colon, small intestine, ovarian
Lynch Syndrome	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	9-11	Colon, endometrial, ovary, gastric, small bowel, renal pelvis, brain, sebaceous
Hereditary Pancreatitis	<i>PRSS1</i>	53	
Familial Polyposis	<i>APC</i>	5	Colon, small bowel, fundic gland polyps, desmoid, thyroid, hepatoblastoma, brain

First Steps after Suspicion of Pancreas Cancer

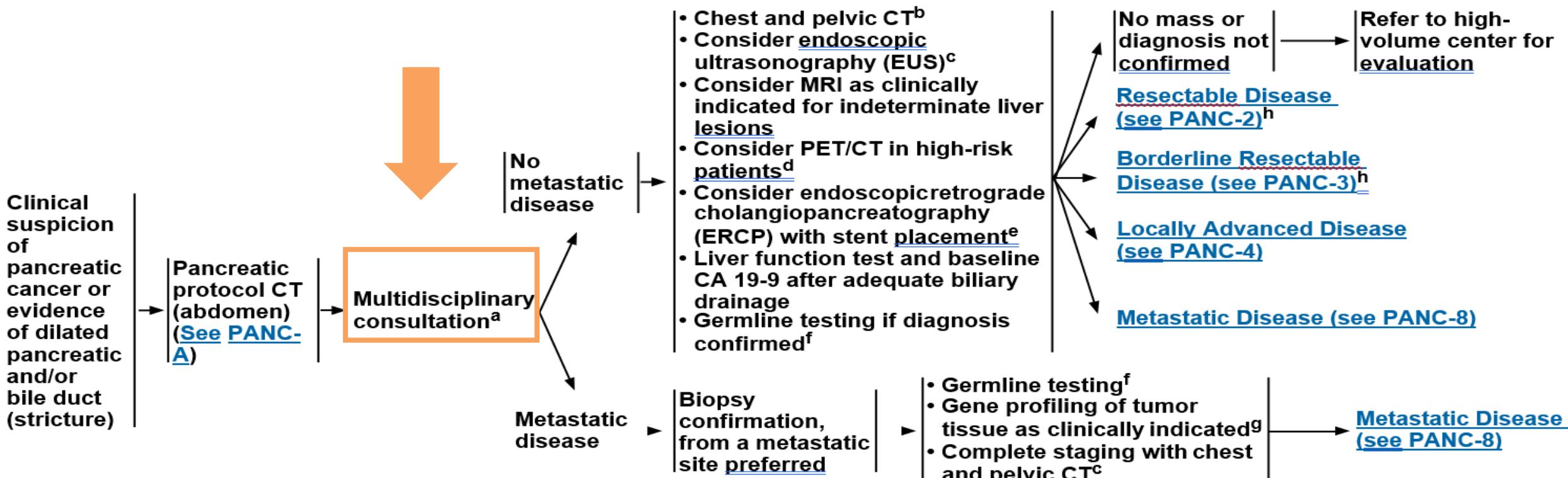
NCCN

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NCCN Guidelines Version 1.2021 Pancreatic Adenocarcinoma

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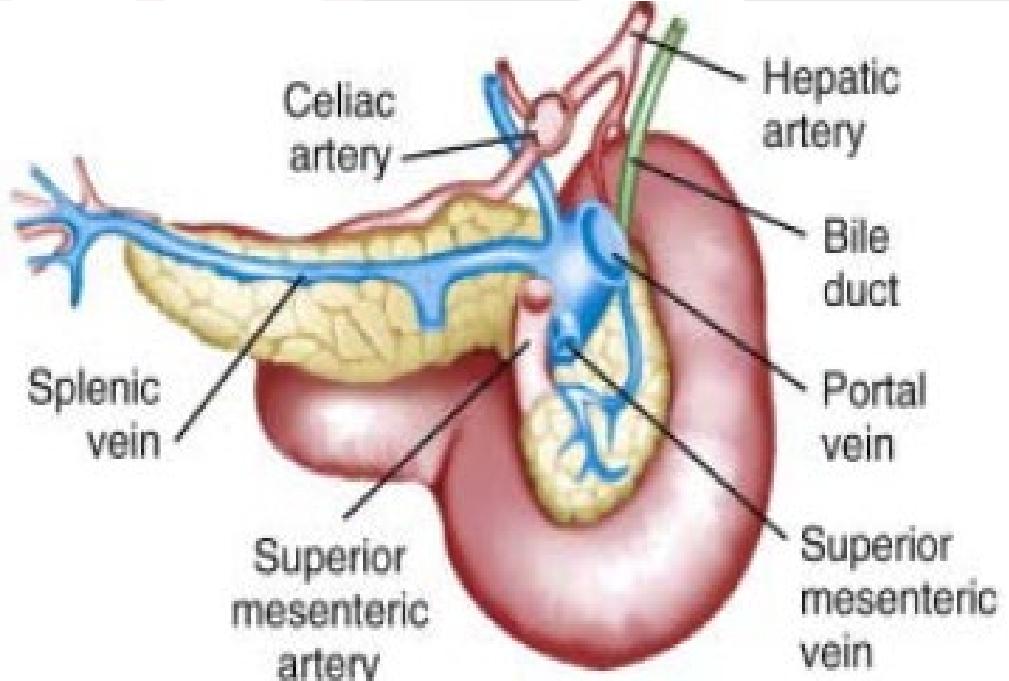
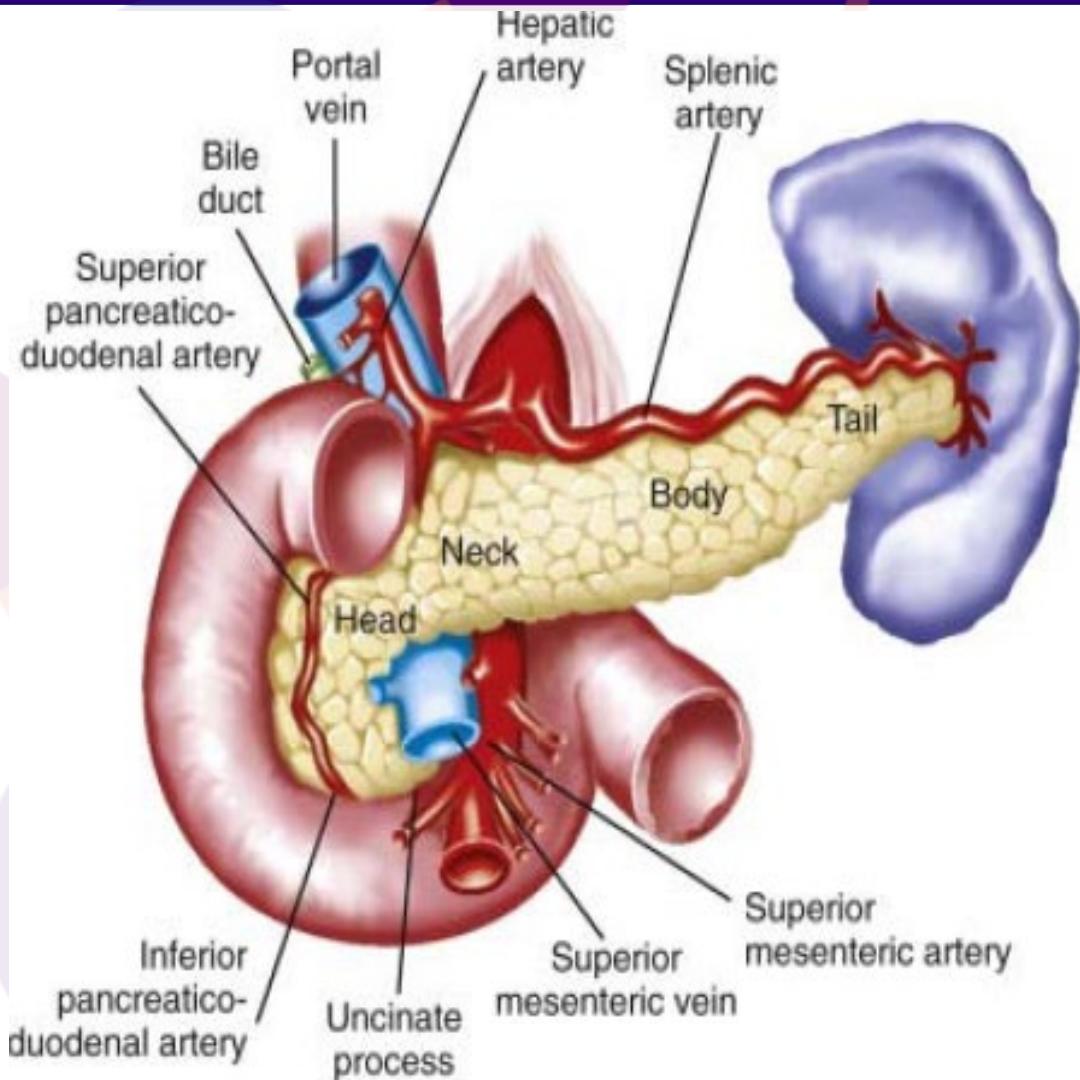
CLINICAL PRESENTATION AND WORKUP



^a Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, and palliative care ([see Principles of Palliation and Supportive Care \[PANC-H\]](#)). Consider consultation with a registered dietitian. See

^b Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status.

Defining Resectability



Sleisinger and Fordtran's Gastrointestinal and Liver Disease, 9th edition

Resectable Pancreatic Adenocarcinoma



PRESENTED AT: ASCO ANNUAL MEETING '16

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Presented by: E. Gabriela Chiorean

Case 1: What is the standard of care after surgery?

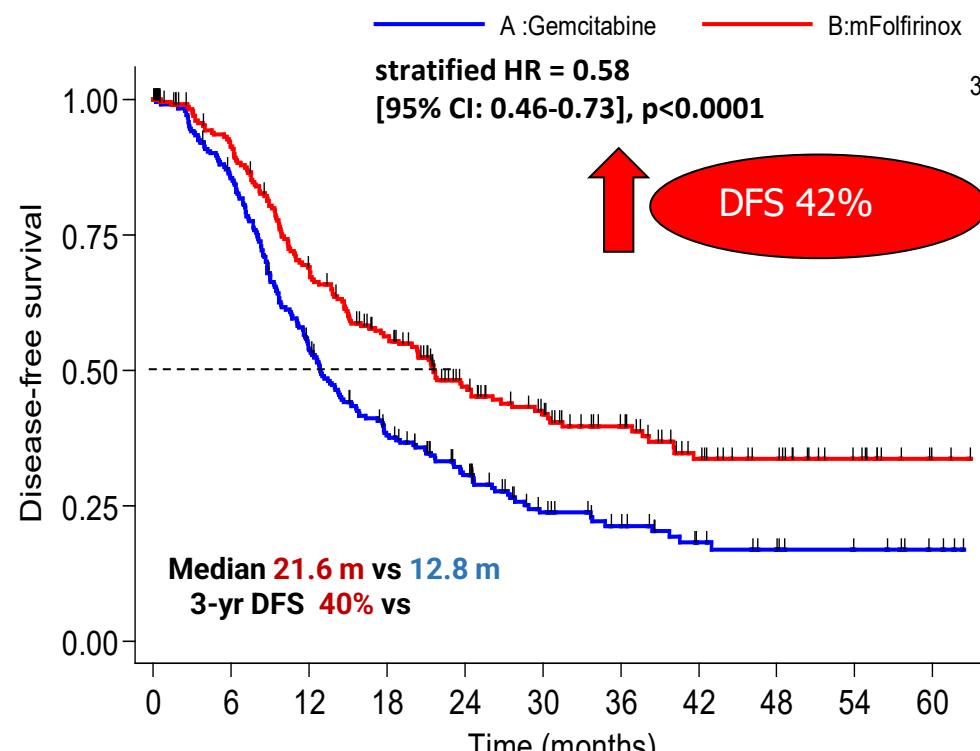
55 yo woman underwent surgery for a 3 cm pancreatic cancer. She recovered well after surgery. CT scans show no evidence of metastatic disease.

Which of the following would you consider the most appropriate adjuvant treatment?

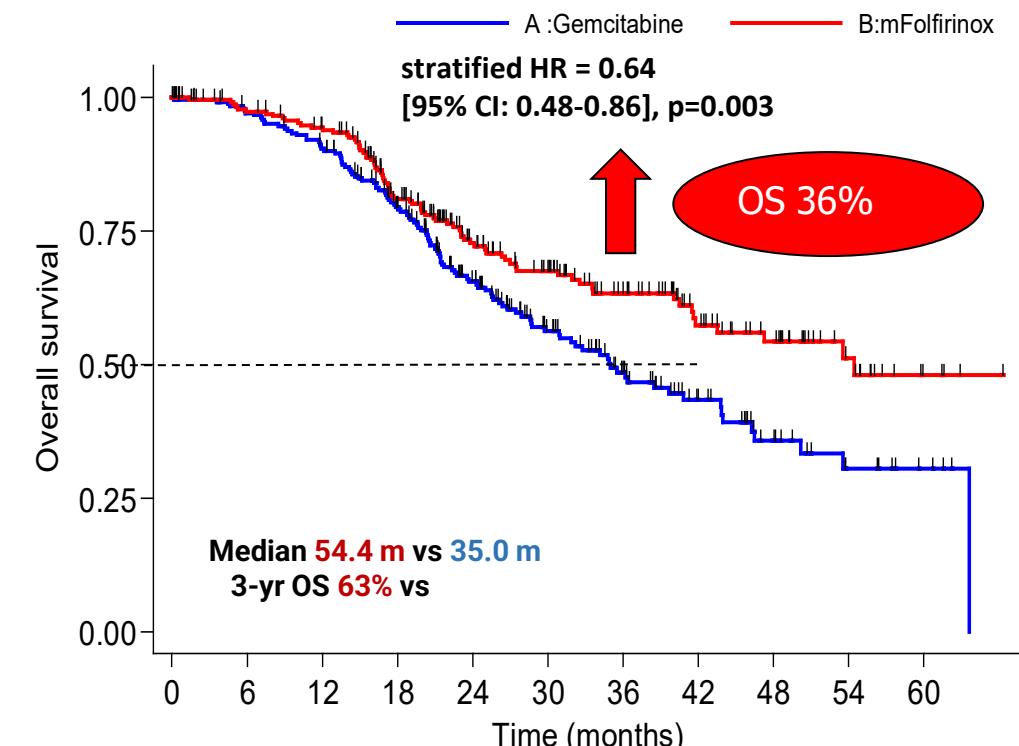
- A. Gemcitabine
- B. Gemcitabine + capecitabine
- C. modified FOLFIRINOX
- D. Gemcitabine/nab-paclitaxel

mFOLFIRINOX vs Gemcitabine

Disease Free Survival



Overall Survival



Number at risk

A:Gemcitabine	246	205	127	85	59	34	24	15	10	7	3
B:mFOLFIRINOX	247	210	156	118	80	60	46	29	21	11	2

Number at risk

A:Gemcitabine	246	233	215	171	120	81	55	33	18	9	4
B:mFOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4

DFS = first occurrence of any tumor recurrence or metastases, second cancer or death from any cause

Conroy T, et al N Engl J Med 2018

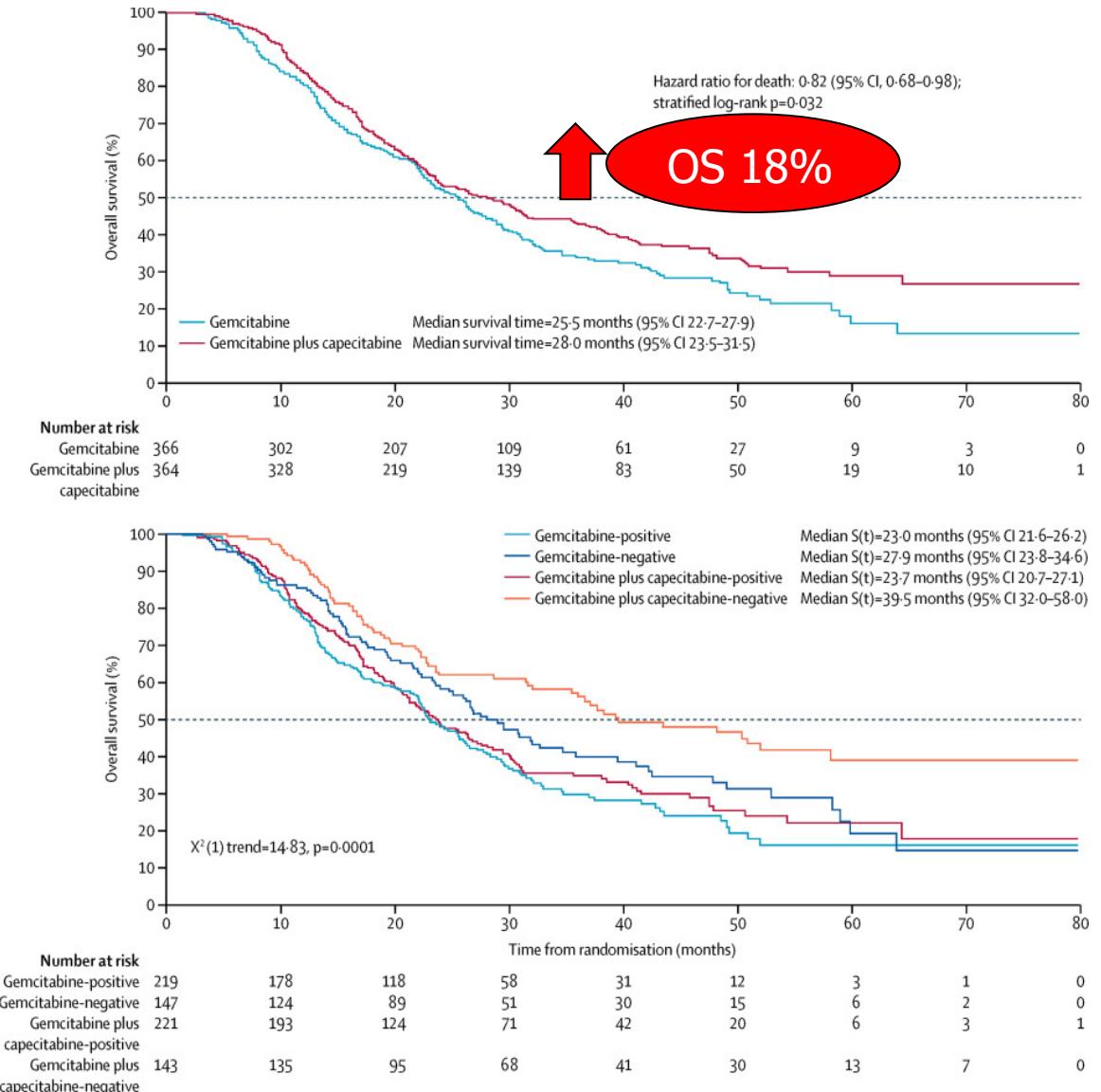
ESPAC 4

Gemcitabine + Capecitabine vs Gemcitabine

OS: 28 vs 25.5 mos

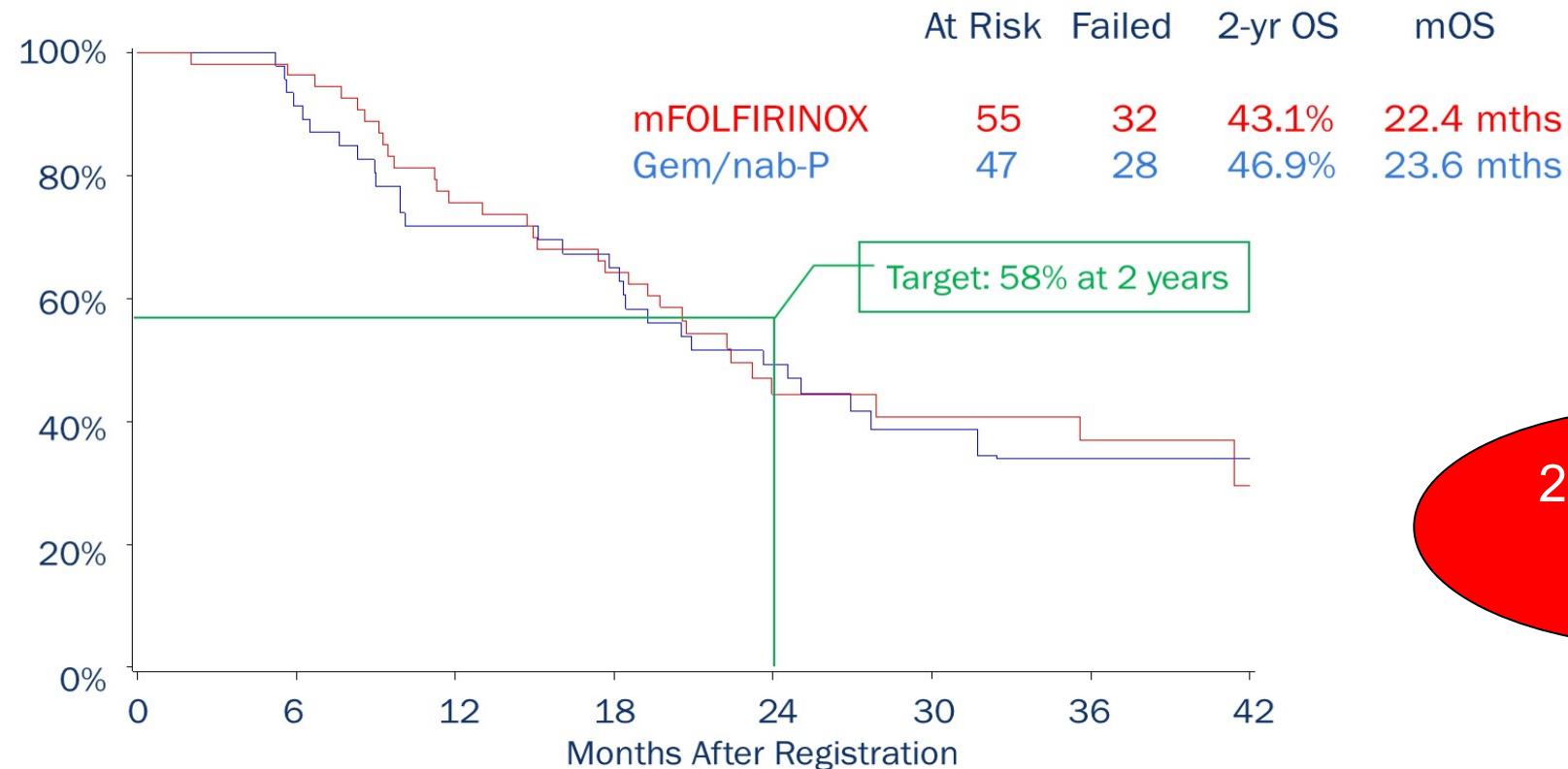
RFS: 13.9 vs 13 mos

3-year RFS: 24% vs 21%



Perioperative FOLFIRINOX vs Gemcitabine + nab-Paclitaxel in Resectable PDA

Primary Endpoint: Two-year OS



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2020 ASCO®
ANNUAL MEETING

#ASCO20
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PRESENTED BY: Davendra Sohal, MD, MPH



CANCER
RESEARCH
NETWORK
NCI National Clinical Trials Network
a National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute
of the National Institutes of Health

Case 1: What is the standard of care after surgery?

55 yo woman underwent surgery for a 3 cm pancreatic cancer. She recovered well after surgery. CT scans show no evidence of metastatic disease.

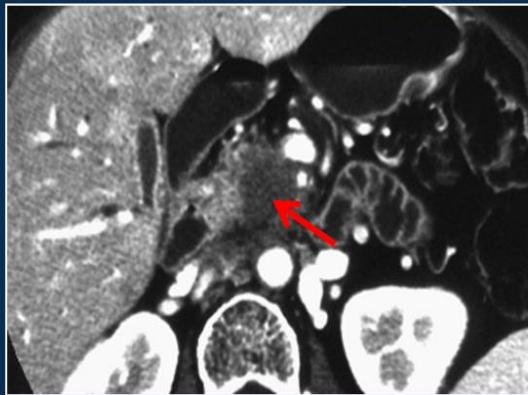
Which of the following would you consider the most appropriate adjuvant treatment?

- A. Gemcitabine
- B. Gemcitabine + capecitabine
- C. modified FOLFIRINOX**
- D. Gemcitabine/nab-paclitaxel

Borderline Resectable vs Locally Advanced

BRPC and LAUPC

<180°



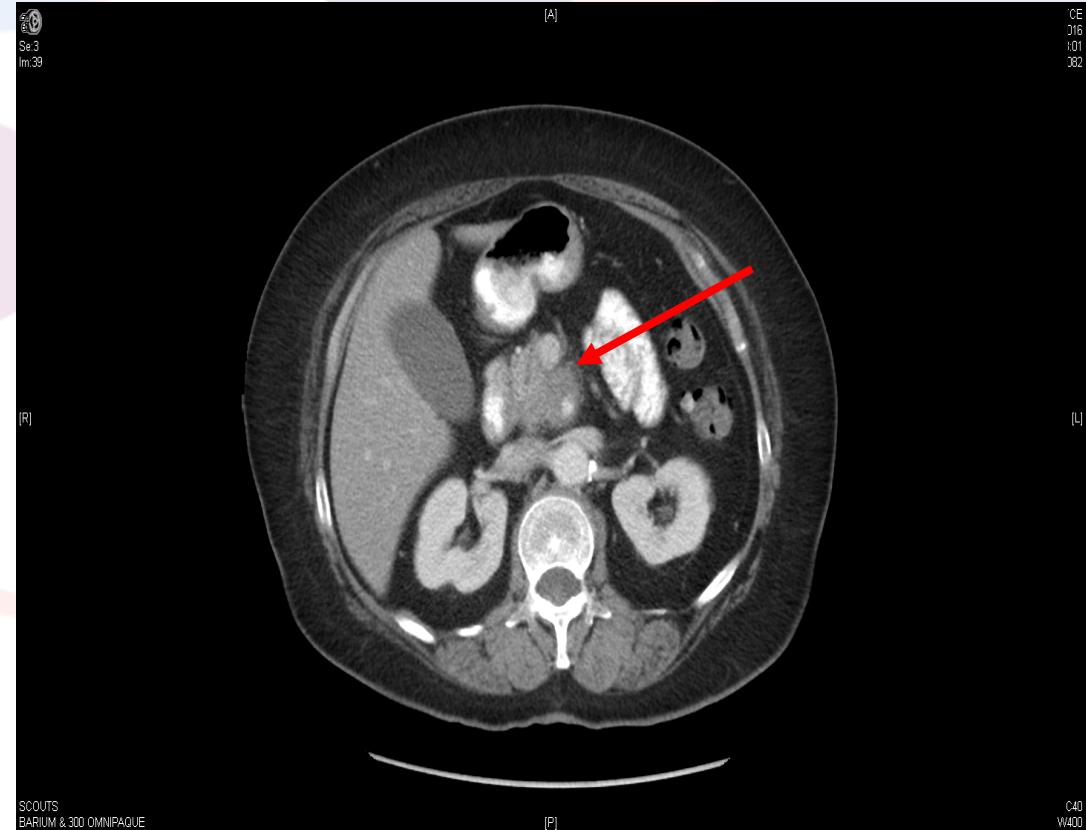
≥180°



- Locally advanced pancreatic cancer: involvement of a major arterial axis (superior mesenteric artery, celiac trunk)
- LAUPC = stage 3 (T4NxM0)
- Treatment of BRPC/LAUPC: like metastatic disease +/- CRT

Case 2: Management of Locally Advanced PDA

- 64 y/o woman presents with dull abdominal pain and fatigue x 1 month
- Refractory to metamucil and antacids
- CT scan shows a 3.5cm pancreatic mass encasing SMA
- Family History: maternal aunts breast cancer x2 (50, 60), maternal cousin breast cancer at 64
- ECOG PS 1 (activity level is good)
- CA19-9 = 87 U/mL (0-54)
- Genetics: germline negative



6 months of Chemotherapy Followed by Radiation Therapy



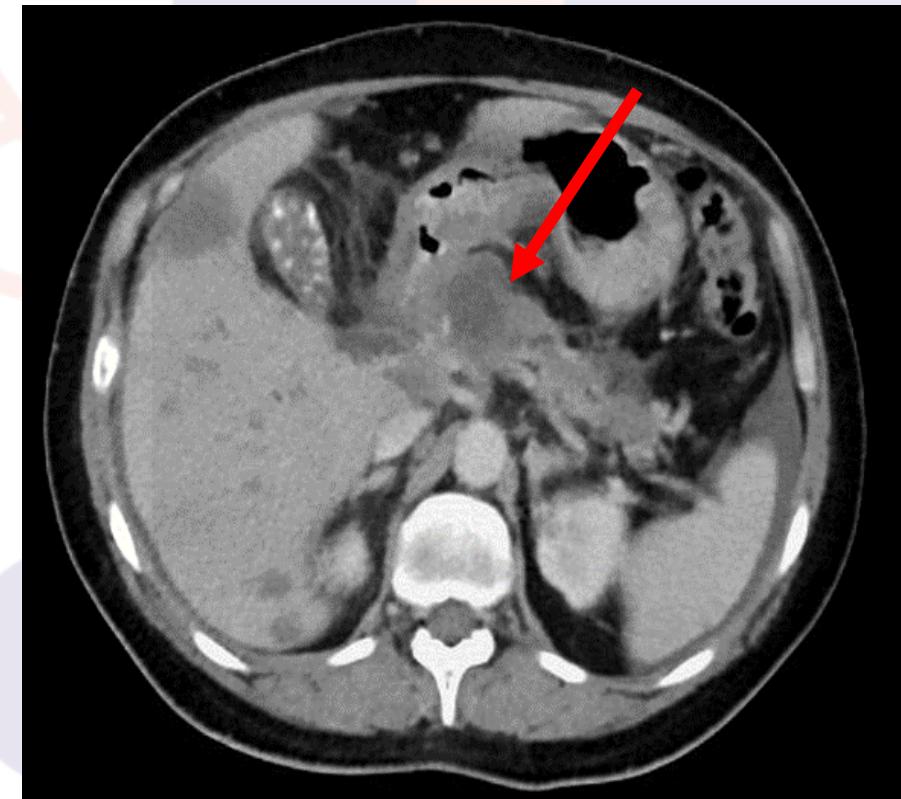
Pathology

- Grade 1 well differentiated (slow growing) ductal adenocarcinoma
- 5.5 cm mass with chronic pancreatitis
- **few small foci of residual adenocarcinoma largest <0.1cm**
- **viable adenocarcinoma <5% of mass**
- 16 lymph nodes negative for metastatic carcinoma
- No lympho-vascular invasion
- Margins negative (R0)

Alive
Cancer Free
After 6 years

Case 3: Management of Metastatic Disease

- 66-yr-old man with 2 mos of epigastric pain, 15-lb weight loss, and gradual jaundice and clay-colored stools
- CT: mass in the head of pancreas and multiple liver metastases
- ERCP: metallic biliary stent through a malignant stricture
- Liver biopsy: adenocarcinoma CK7+, CDX2+, CK20-
- No family history of pancreatic or other cancers
- ECOG PS 1



What is the optimal 1L treatment option?

- a. Gemcitabine alone
- b. Gemcitabine + nab-paclitaxel
- c. FOLFOX
- d. FOLFIRINOX
- e. Either b or d are preferred 1st line options

Treatment of Metastatic Disease

1L

1997:
Gemcitabine

2005:
Gemcitabine
+ Erlotinib

2011:
FOLFIRINOX

2013:
Gemcitabine
+ *nab*-Paclitaxel

2019:
Olaparib
maintenance
gBRCA1/2 MUT

2L+

2015:
Nal-Iri +
5FU

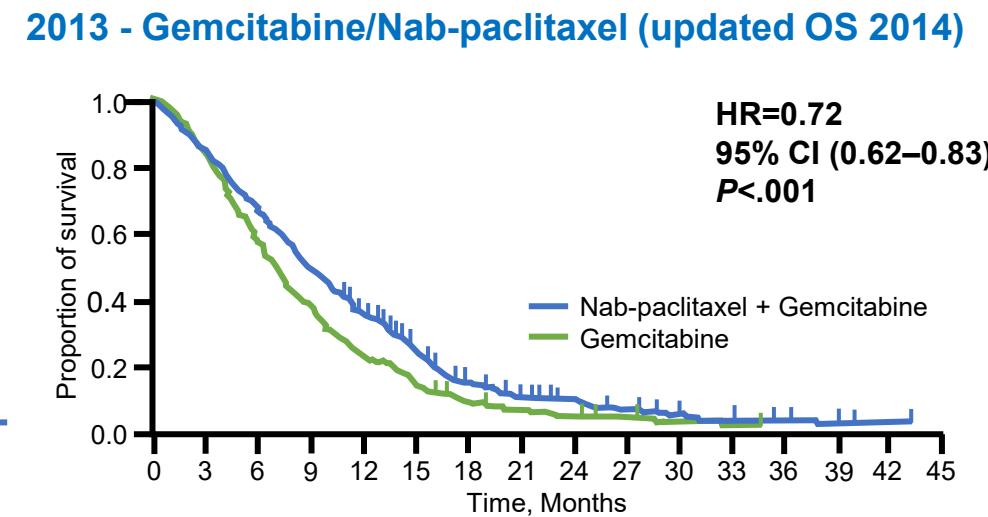
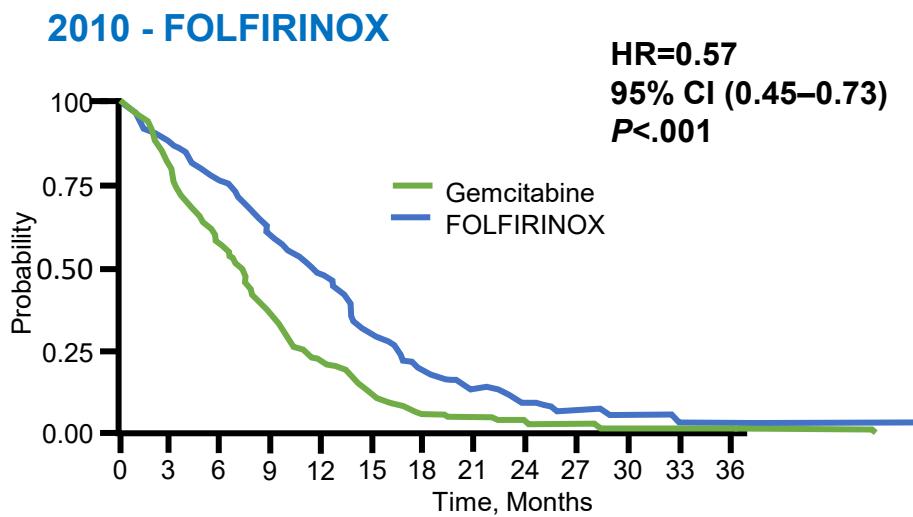
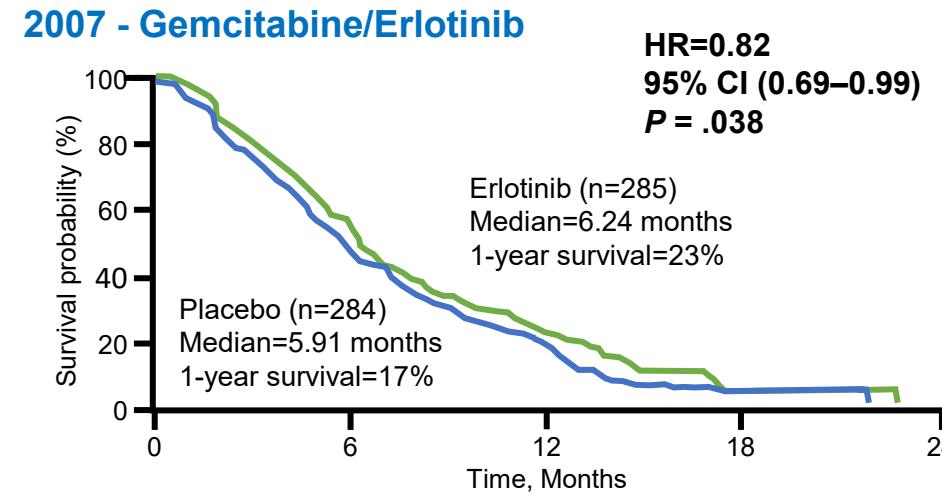
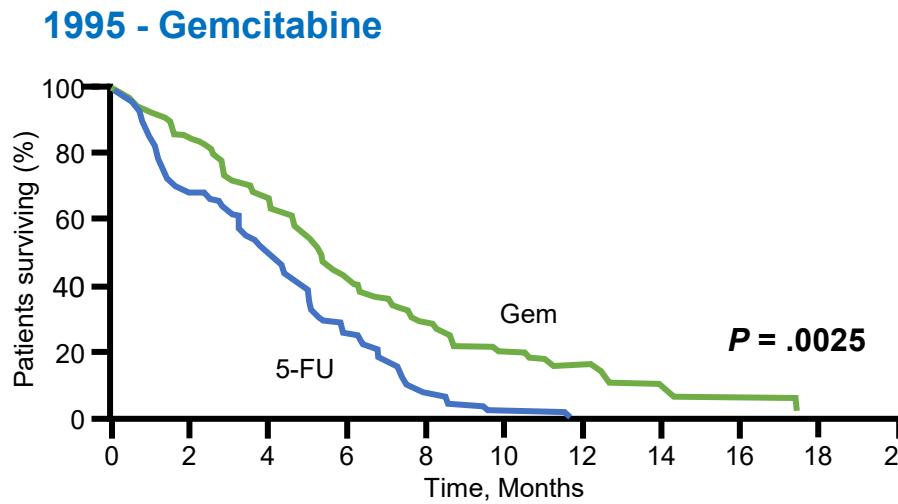
2017:
Pembrolizumab
MSI-H or dMMR

2018:
Larotrectinib
NTRK fusion

2019:
Entrectinib
NTRK fusions

2020:
Pembrolizumab
TMB high

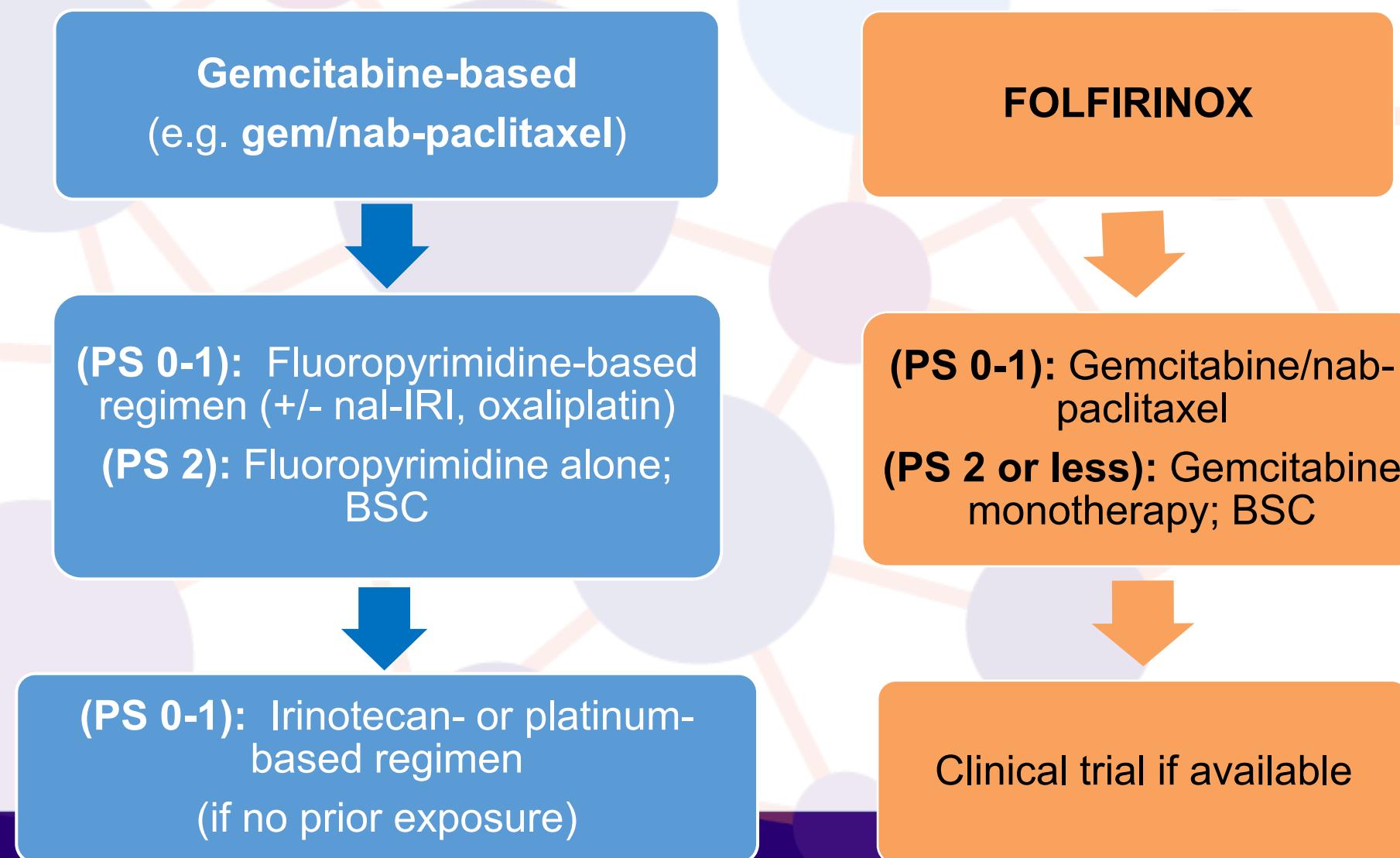
Efficacy of First-Line Treatments mPDA



MPDAC, metastatic pancreatic adenocarcinoma

Burris HA 3rd, et al. *J Clin Oncol*. 1997;15(6):2403-2413. Moore MJ, et al. *J Clin Oncol*. 2007;25(15):1960-1966. Conroy T, et al. *N Engl J Med*. 2011;364(19):1817-1825. Goldstein D, et al. *J Natl Cancer Inst*. 2015;107(2):dju413.

Treatment Sequencing for Metastatic Pancreatic Cancer



What is the optimal 1L treatment option?

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- c. FOLFOX
- d. FOLFIRINOX
- e. **Either b or d are preferred 1st line options**

Germline and Somatic Genomic Testing

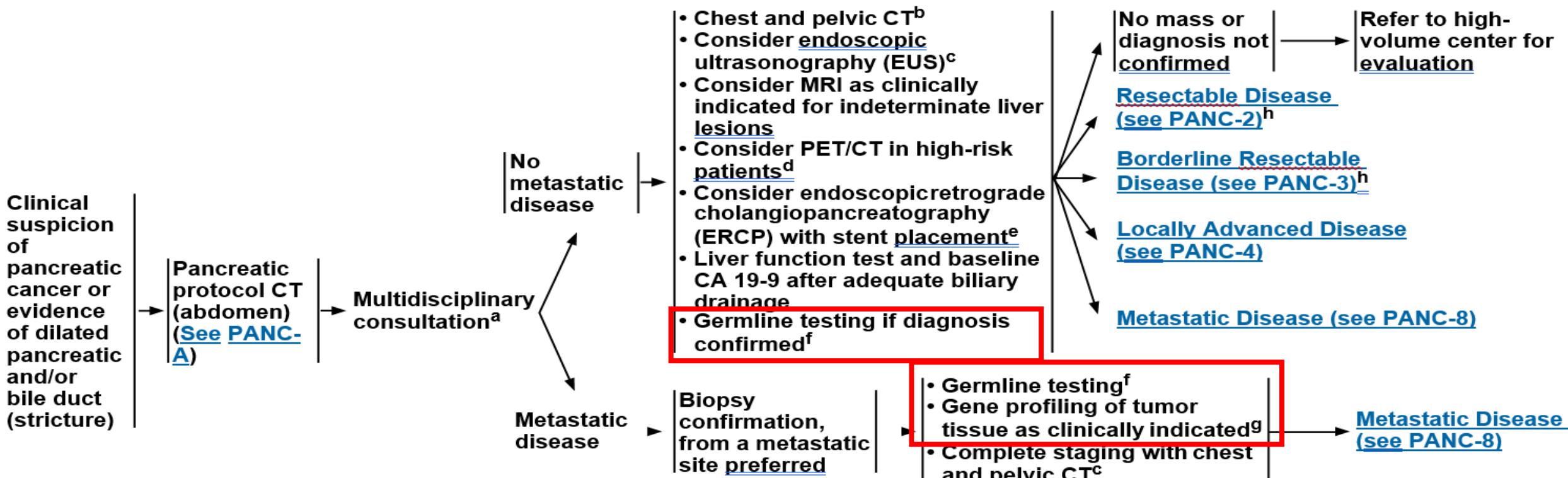
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NCCN Guidelines Version 1.2021 Pancreatic Adenocarcinoma

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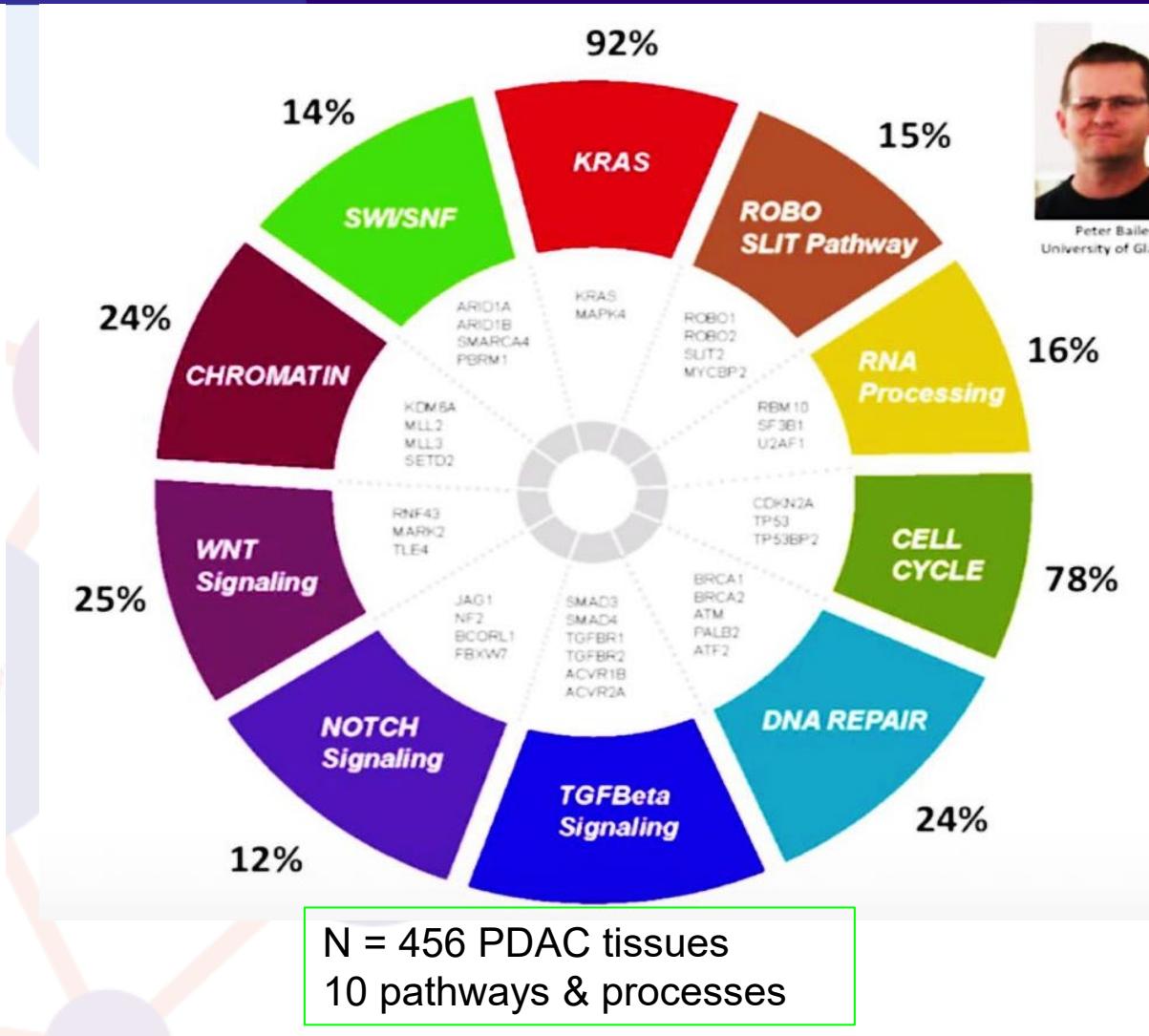
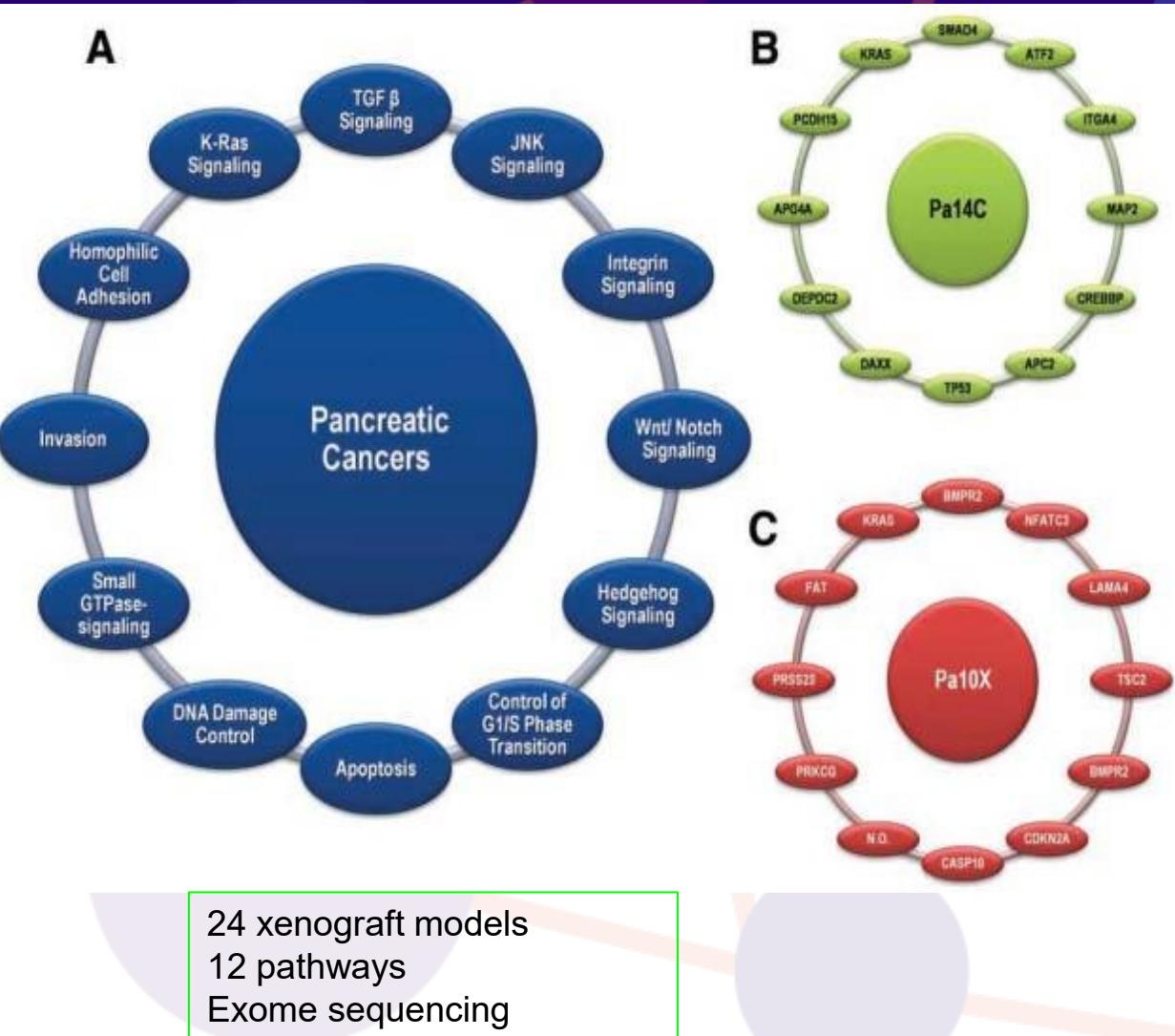
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Genomic Sequencing in Pancreatic Cancers



gBRCA1/2+ Pancreatic Cancer Without Progression on Platinum Chemotherapy: Phase III POLO trial



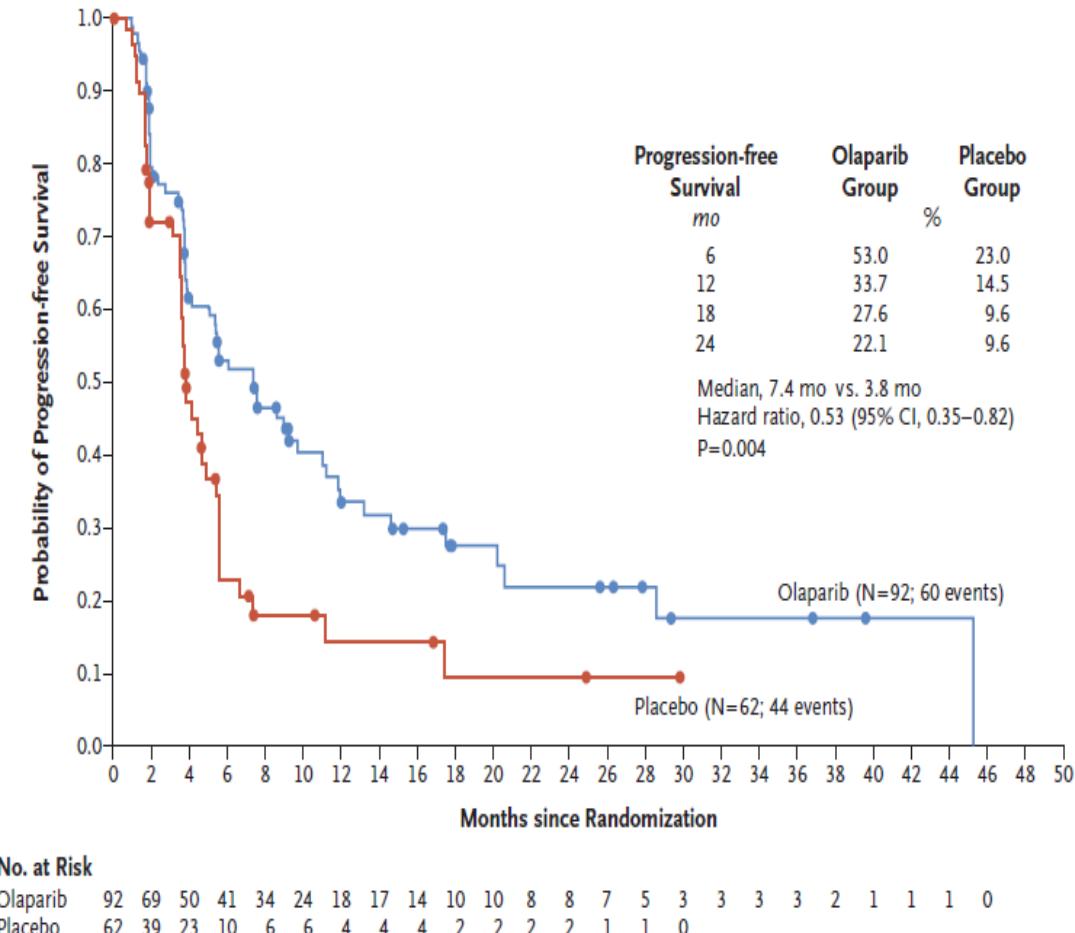
The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

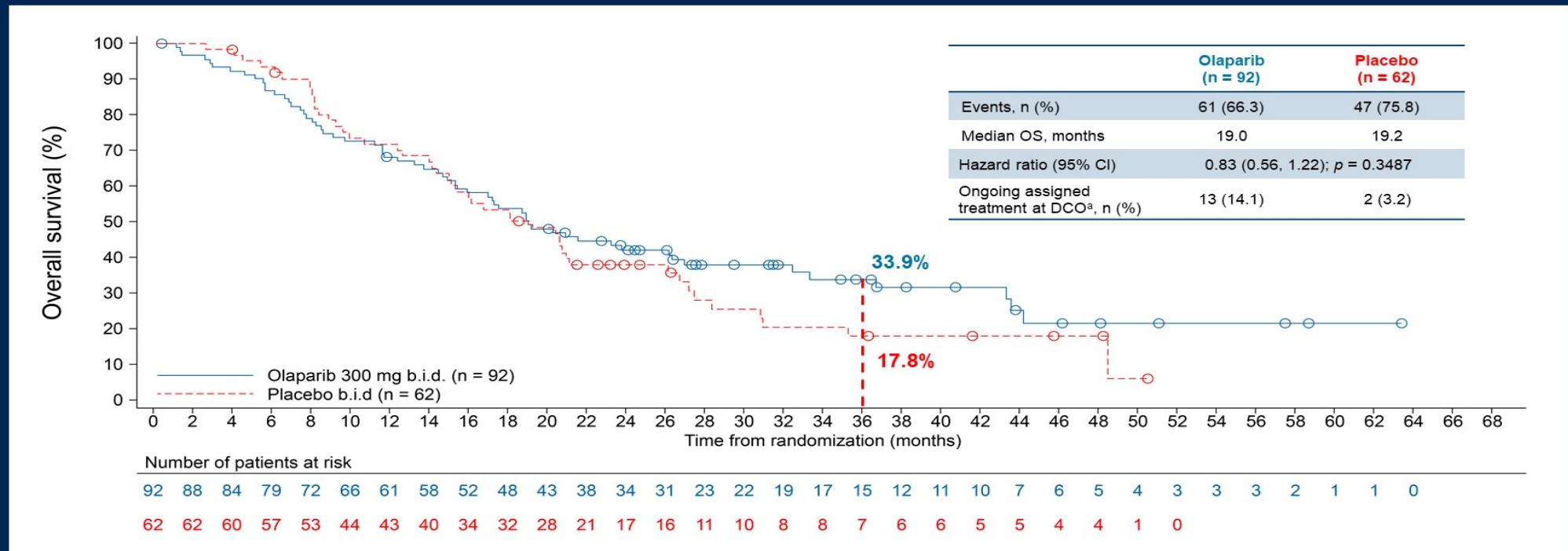
Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D.,
Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D.,
Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D.,
Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D.,
Anke Reinacher-Schick, M.D., Ph.D., Giampaolo 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.

A Progression-free Survival



Maintenance Olaparib vs Placebo: Survival Analysis

POLO: final OS analysis



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Gastrointestinal
Cancers Symposium

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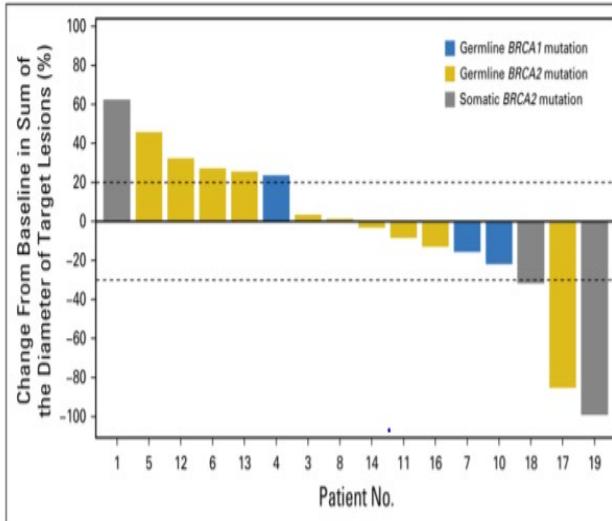
PRESENTED BY: Dr. Talia Golan

#GI21

Golan T, et al ASCO GI 2021

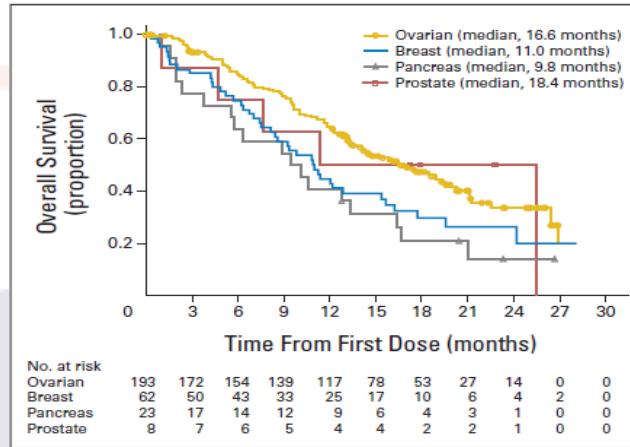
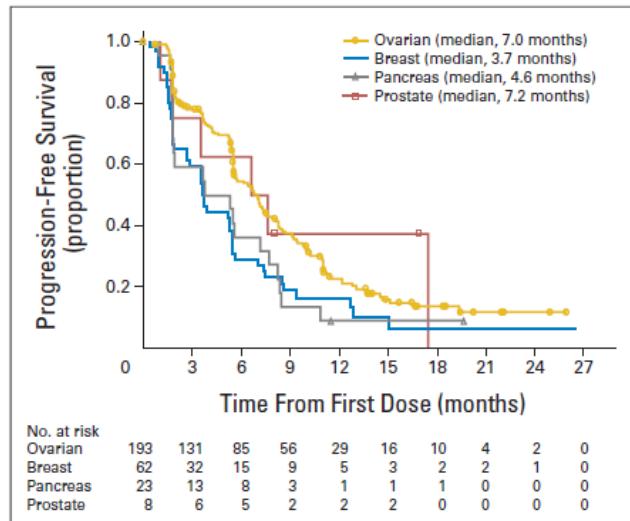
PARP Inhibitors Have Modest Efficacy in gBRCA1/2+ PDA

Rucaparib : ORR 16%



Patient No.	BRCA Mutation	No. of Prior Regimens	Prior Platinum	Prior Refractory	Rucaparib treatment	Response	Progressive disease reported on last day of treatment
1	BRCA2 Somatic	2	Yes	Yes	Yes	PR	-
2	BRCA1 Germline	1	Yes	No ^a	Yes	PR	-
3	BRCA2 Germline	1	Yes	No	Yes	SD	-
4	BRCA1 Germline	1	Yes	No	Yes	SD	-
5	BRCA2 Germline	2	Yes	No ^a	Yes	SD	-
6	BRCA2 Germline	2	Yes	Yes	Yes	SD	-
7	BRCA1 Germline	2	Yes	Yes	Yes	SD	PR
8	BRCA2 Germline	2	Yes	No ^a	Yes	SD	SD 72 weeks
9	BRCA2 Germline	1	No	NA	-	-	-
10	BRCA1 Germline	2	Yes	Yes	Yes	SD	SD 20 weeks
11	BRCA2 Germline	2	Yes	No	Yes	SD	SD 5 weeks
12	BRCA2 Germline ^b	2	Yes	Yes	Yes	SD	SD 5 weeks
13	BRCA2 Germline	1	No	NA	-	-	-
14	BRCA2 Germline	3	Yes	Yes	Yes	SD	SD 36 weeks
15	BRCA2 Germline	2	Yes	Yes	Yes	SD	SD 24 weeks
16	BRCA2 Germline	1	No	NA	Yes	SD	SD 5 weeks
17	BRCA2 Germline	1	No	NA	Yes	SD	SD 5 weeks
18	BRCA2 Somatic	1	Yes	No	Yes	SD	SD 25 weeks
19	BRCA2 Somatic	1	Yes	-	Yes	SD	SD 19 weeks

Olaparib: ORR 20%



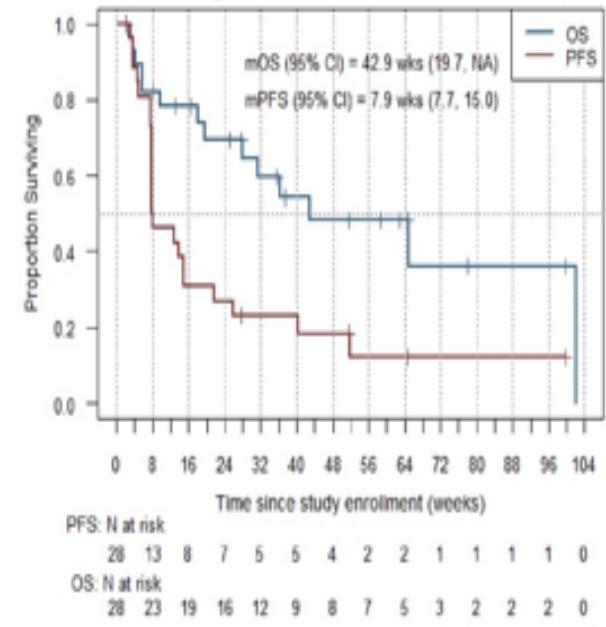
Olaparib ORR 7%

Table 1: Efficacy Outcomes (N=28)¹

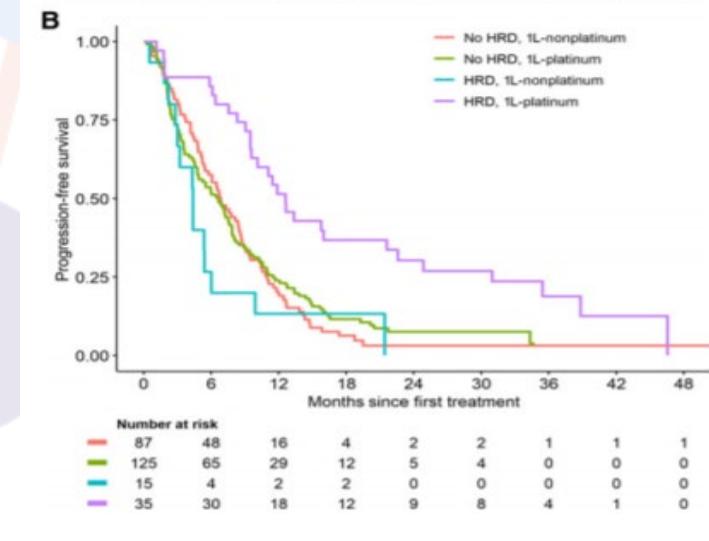
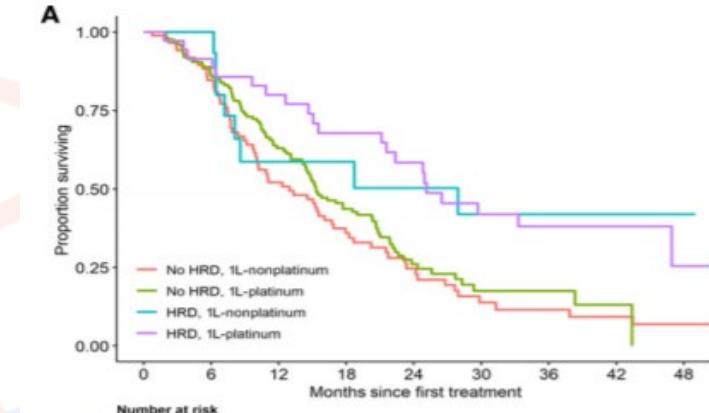
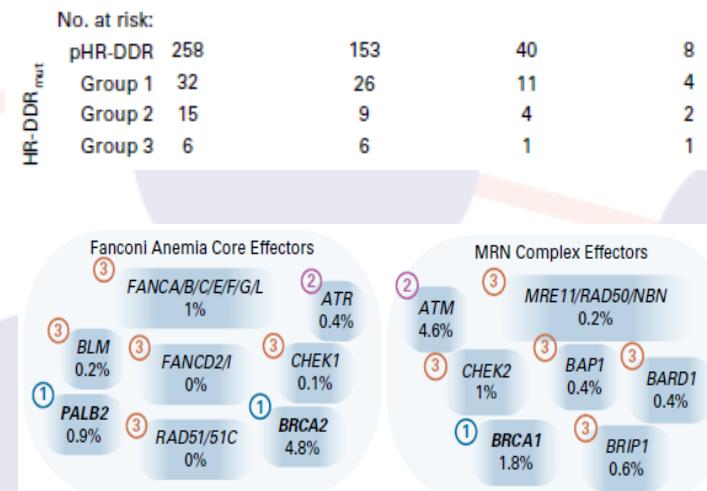
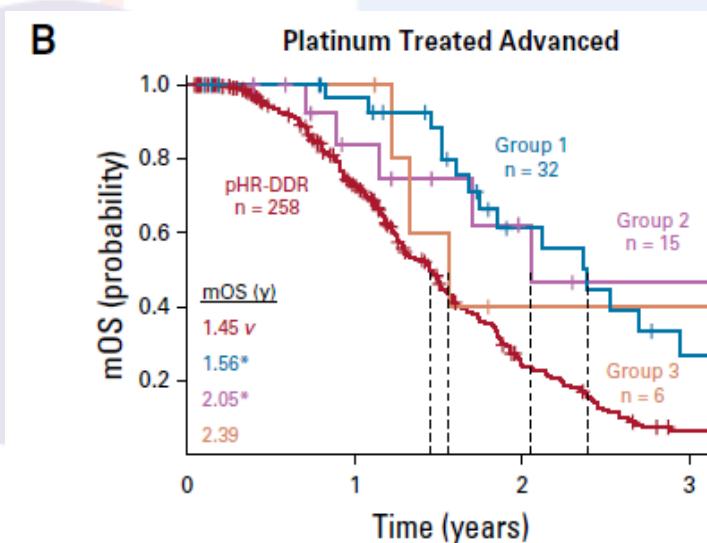
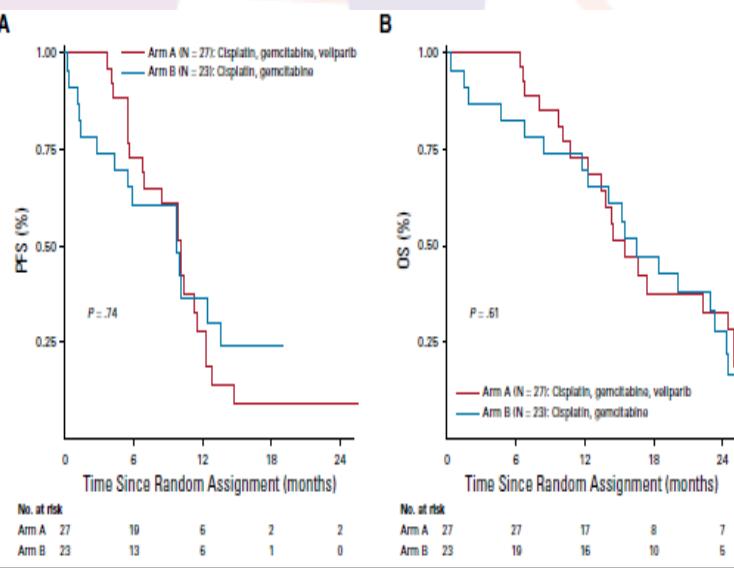
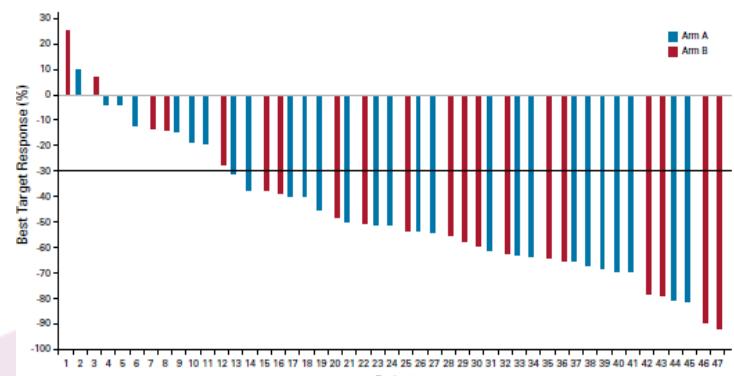
DC rate, % (90% CI)	31 (18, 40)
OR rate, % (95% CI)	7 (0, 24)
1 year OS, % (95% CI)	48.2 (26.0, 67.3)

¹2 enrolled pts were not evaluable and are excluded from efficacy analyses

Figure 1: OS and PFS in Pts with Advanced PC with BRCA1/2 Inactivating Mutations Treated with O (N=28)

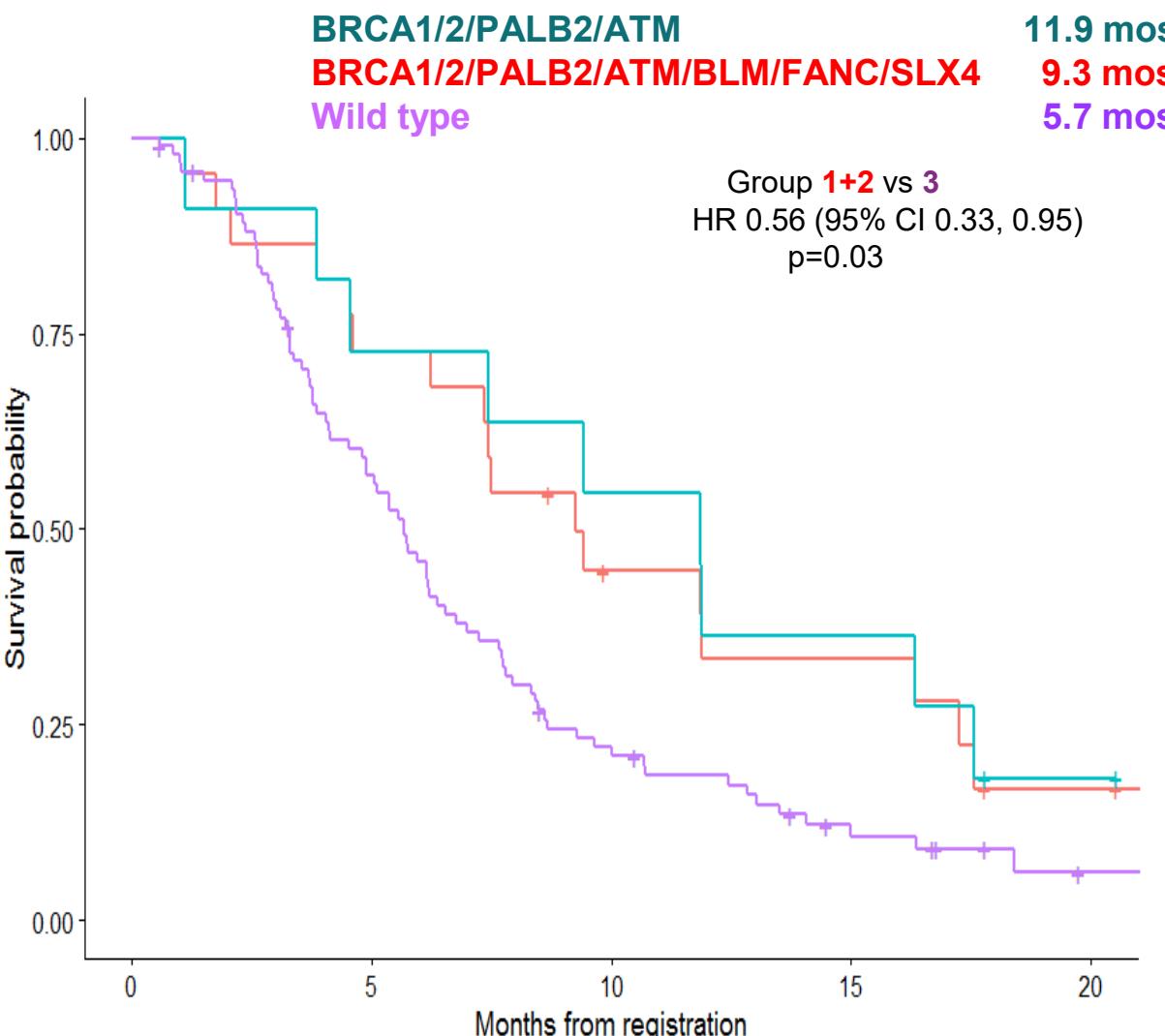


Platinum Chemotherapy is Effective for gBRCA1/2+ and HRD

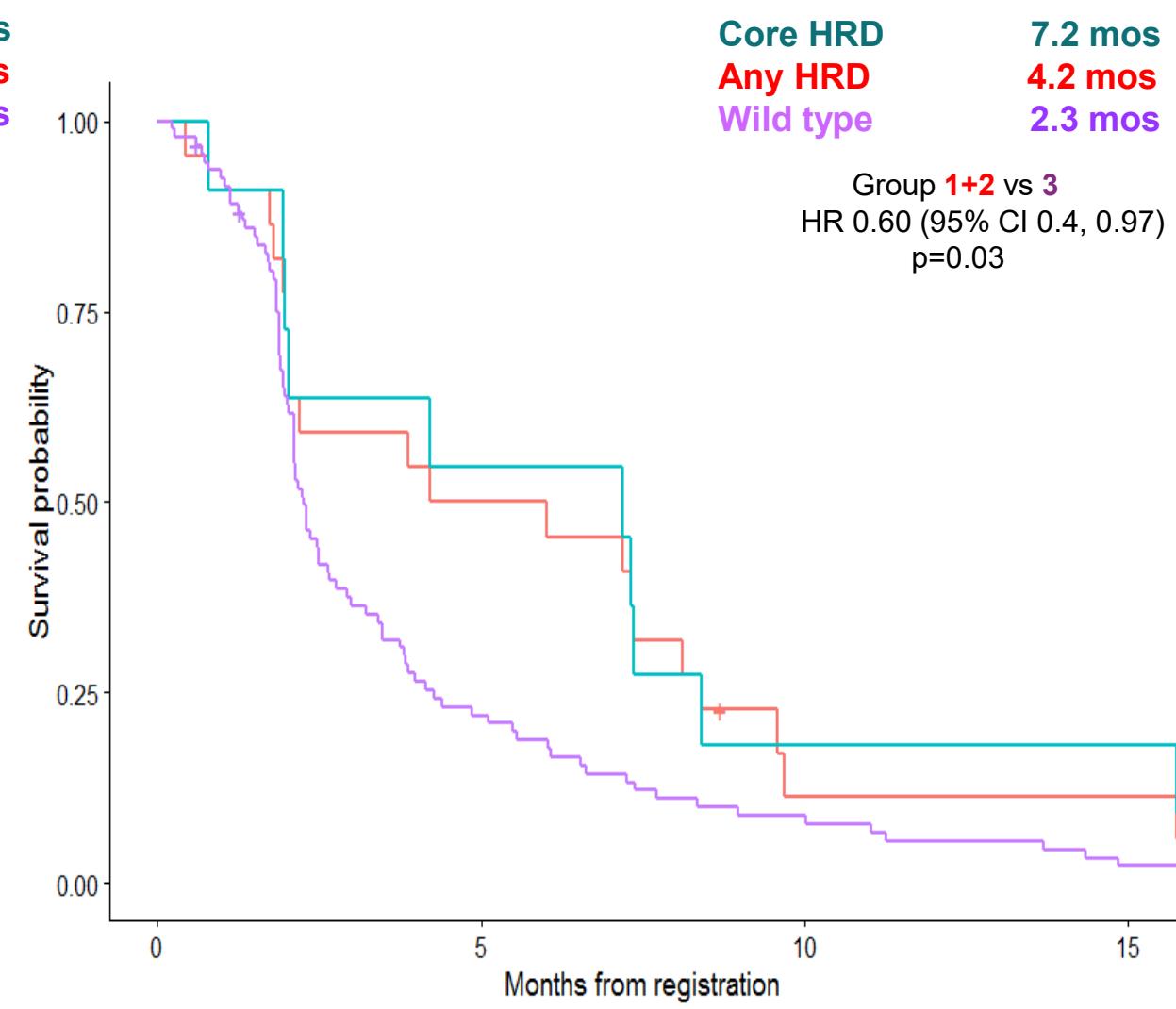


SWOG S1513: FOLFIRI +/- PARP Inhibitor in 2nd line PDA

OS by HRD Status



PFS by HRD Status



HRD = homologous recombination repair deficiency

New Research with PARP Inhibitors in BRCA1/2/PALB2+ Pancreatic Cancers

SWOG S2001: Olaparib +/- Pembrolizumab Maintenance Trial

Ongoing

Metastatic
PDAC
gBRCA1/2

Platinum SD,
PR or CR

ECOG 0-1

Olaparib 300 mg BID

Olaparib 300 mg BID +
Pembrolizumab 200 mg IV q 3 weeks

Primary endpoint: PFS (HR 0.6; 7→ 11.7 m)

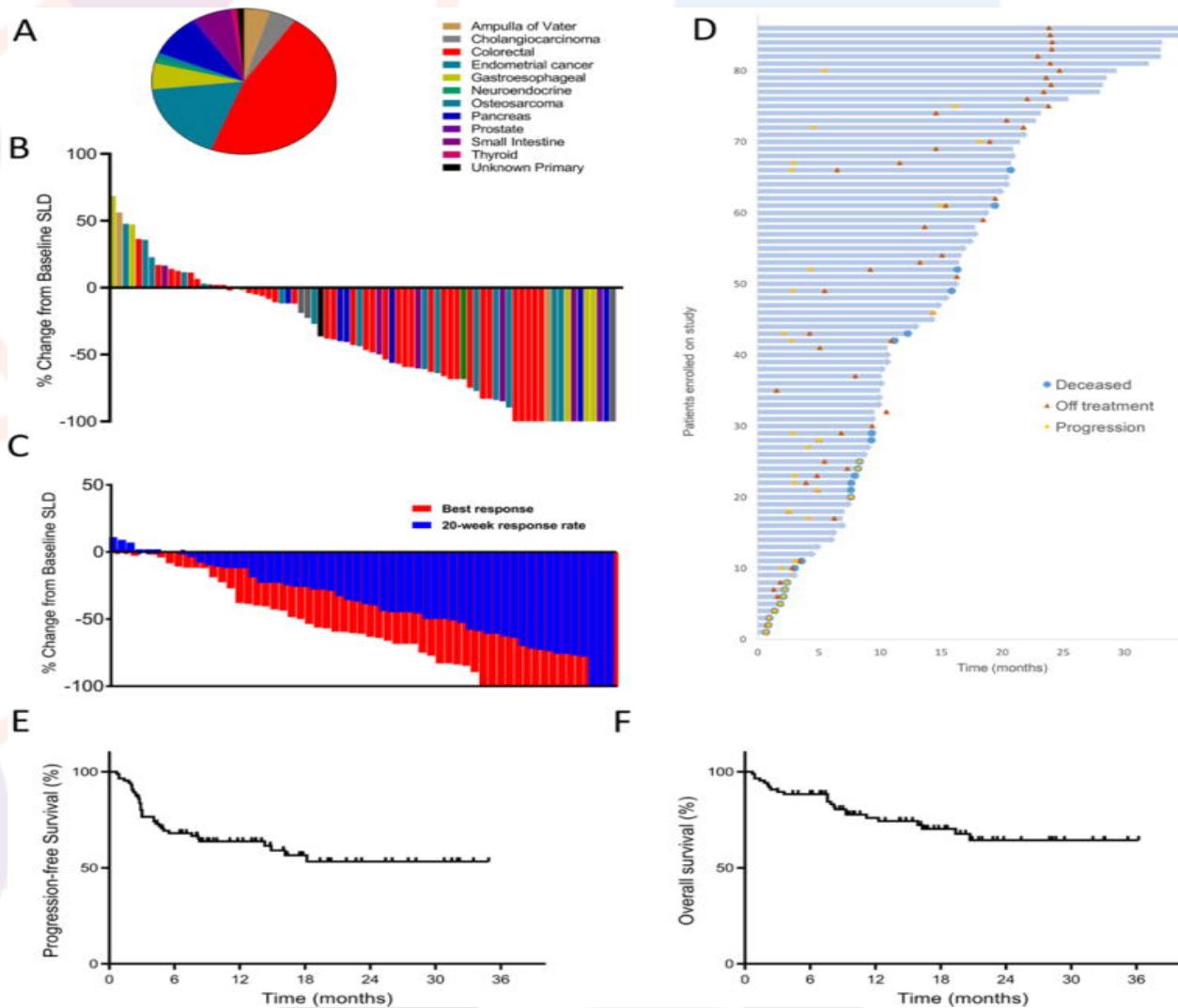
APOLLO: Olaparib vs Placebo Maintenance for Resected PDA after Neo/Adjuvant Chemotherapy

Resected PDA
germline/somatic
BRCA1/2/PALB2

Olaparib 300 mg BID

Placebo

Pembrolizumab in MSI-H non-CRC Cancers: KN-16



N=8
ORR 5/8 (62%)

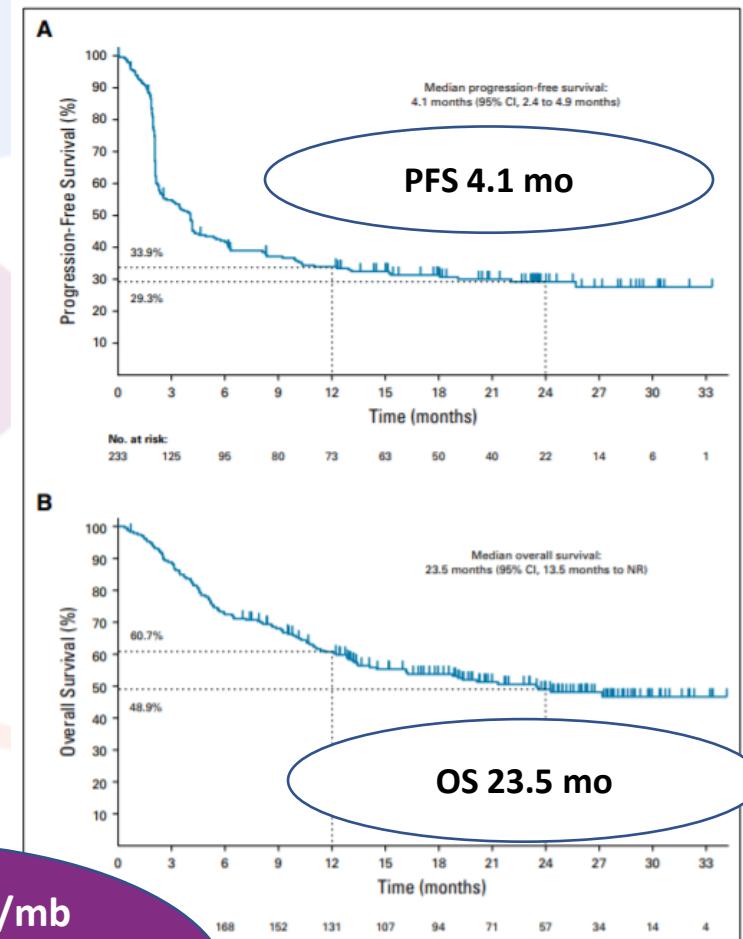
Pembrolizumab in MSI-High and TMB-High Cancers: KN-158

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	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)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 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)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)
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)

N=22
ORR 4/22 (18%)
PFS 2.1 mo
OS 4 mo

TMB-High ≥ 10 m/m^b
N=105 solid tumors
(no PDA)
ORR 29% vs 6% (TMB-L)



Pancreatic Cancer: Is KRAS the Biggest Problem?

High prevalence: *KRAS*, *TP53*, *CDKN2A*, & *SMAD4*

Other mutations: High variability and low prevalence

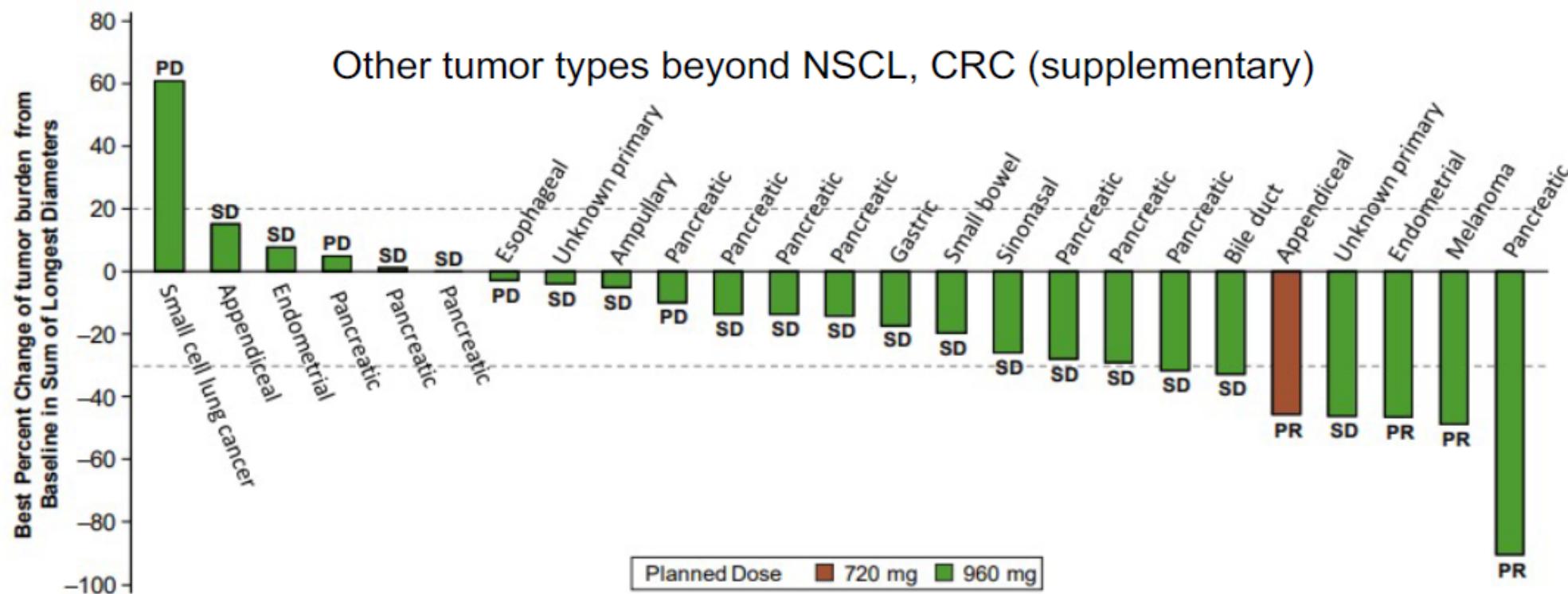


Targeting KRAS Variants

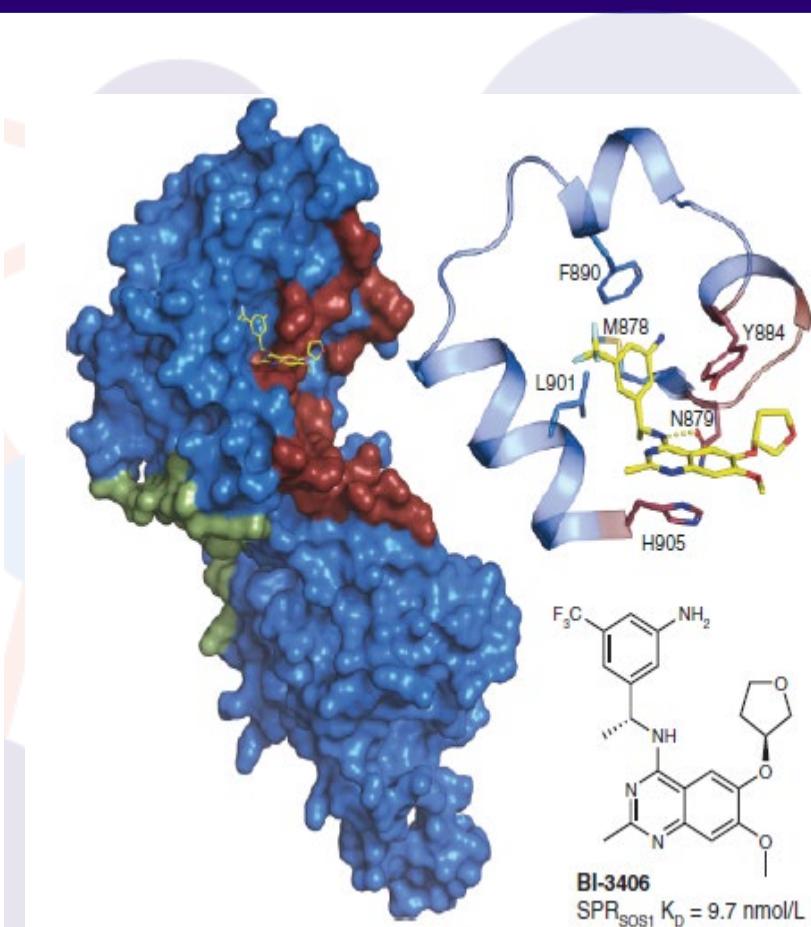
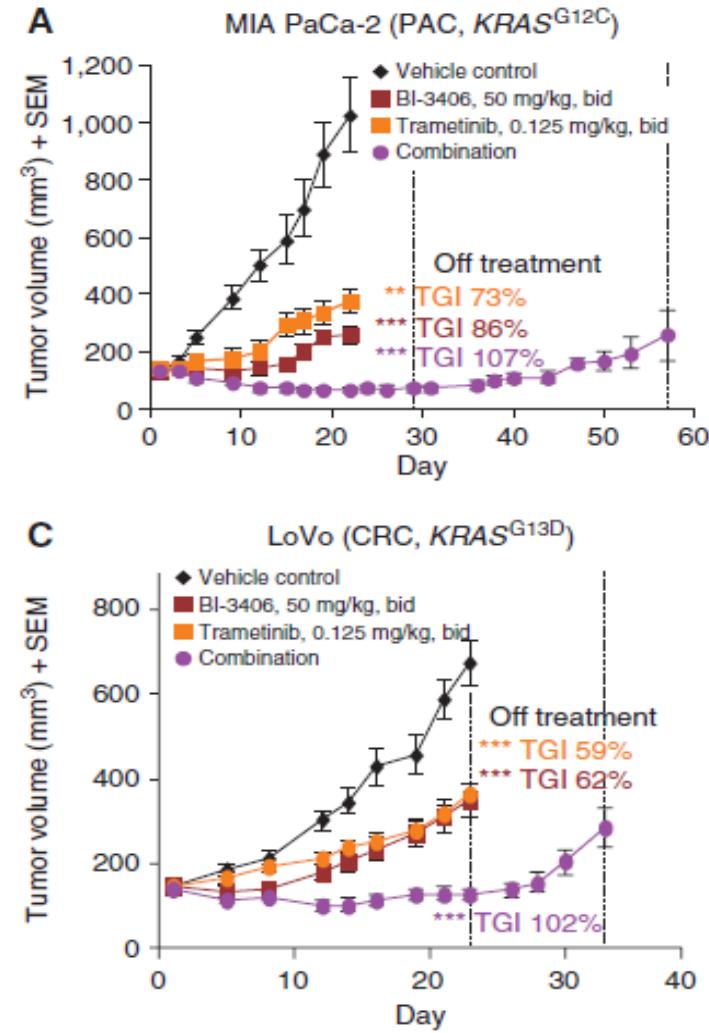
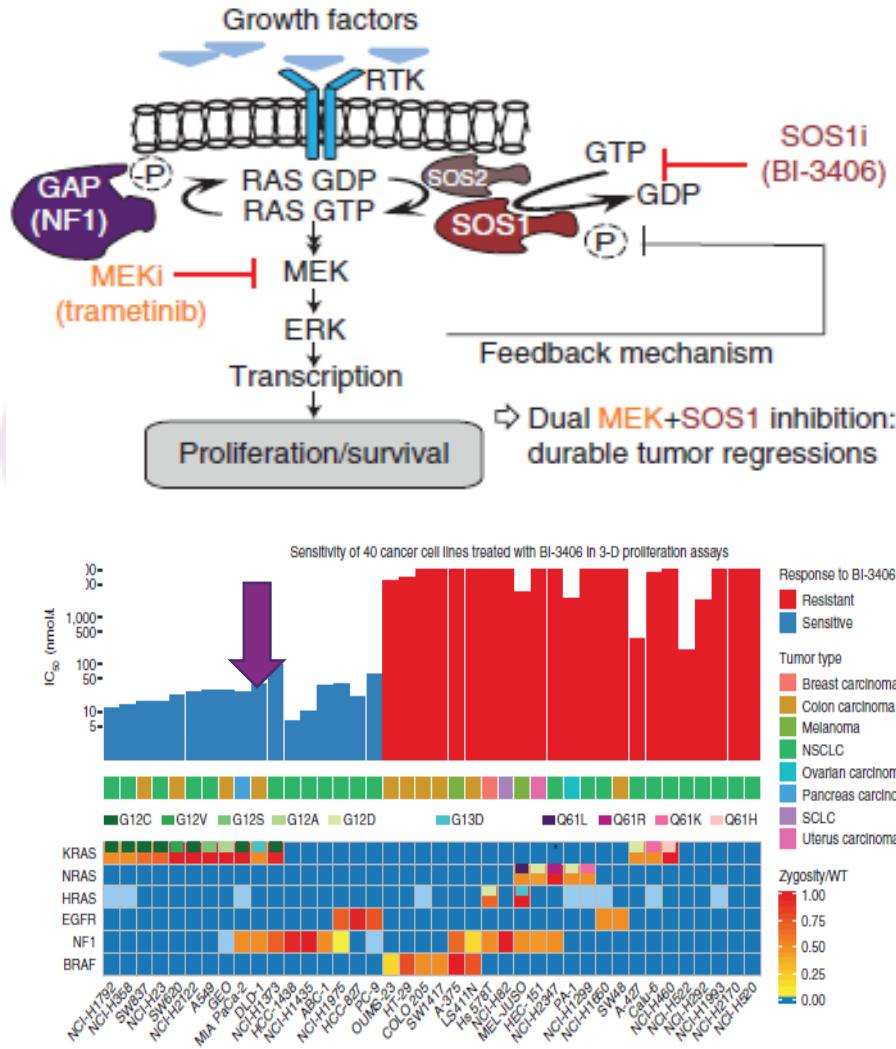
KRAS-mutant G12C 1-2% PDAC

Sotorasib (AMG510), MRTX-849, JNJ-74699157 (allele inhibitors)

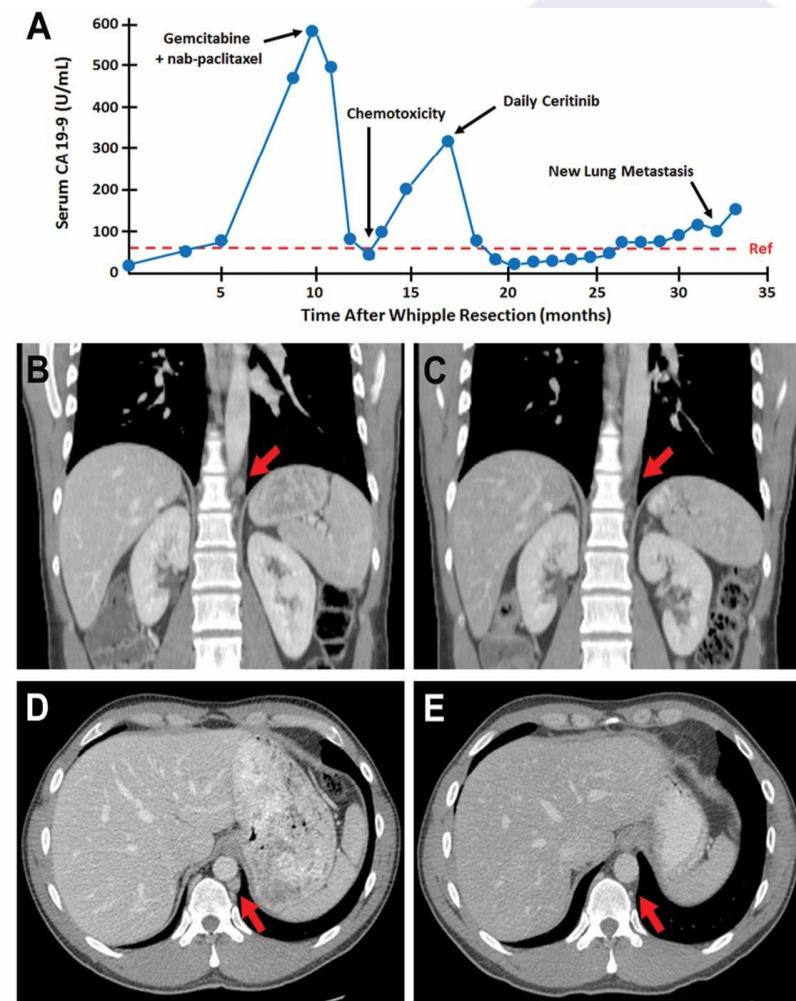
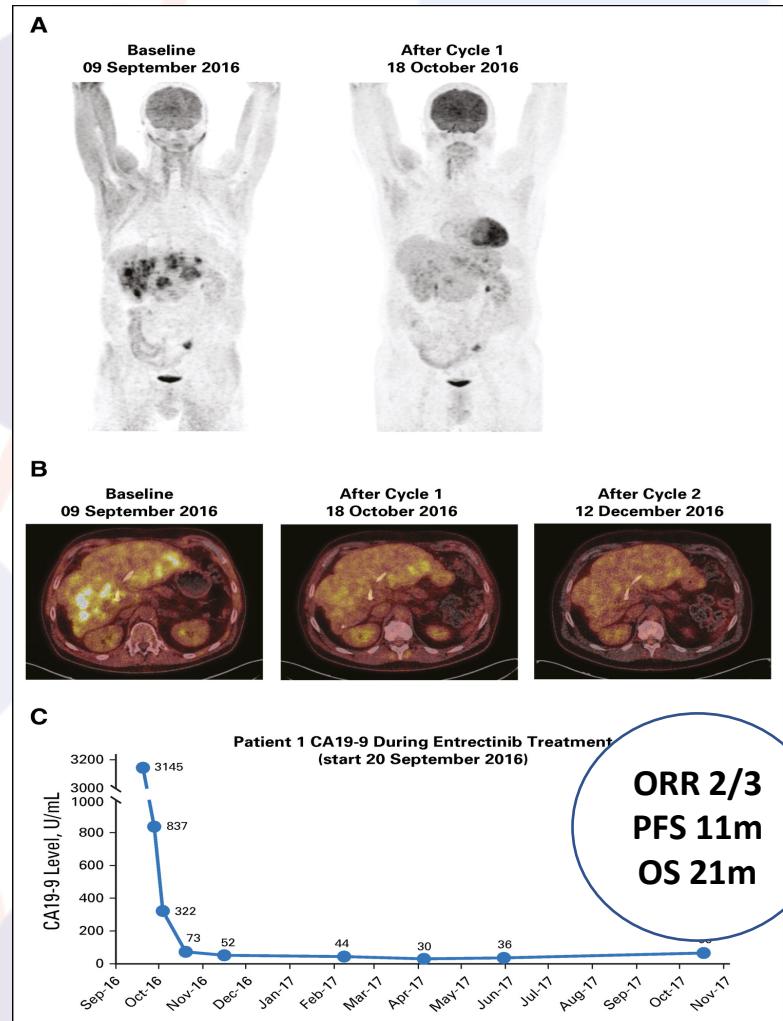
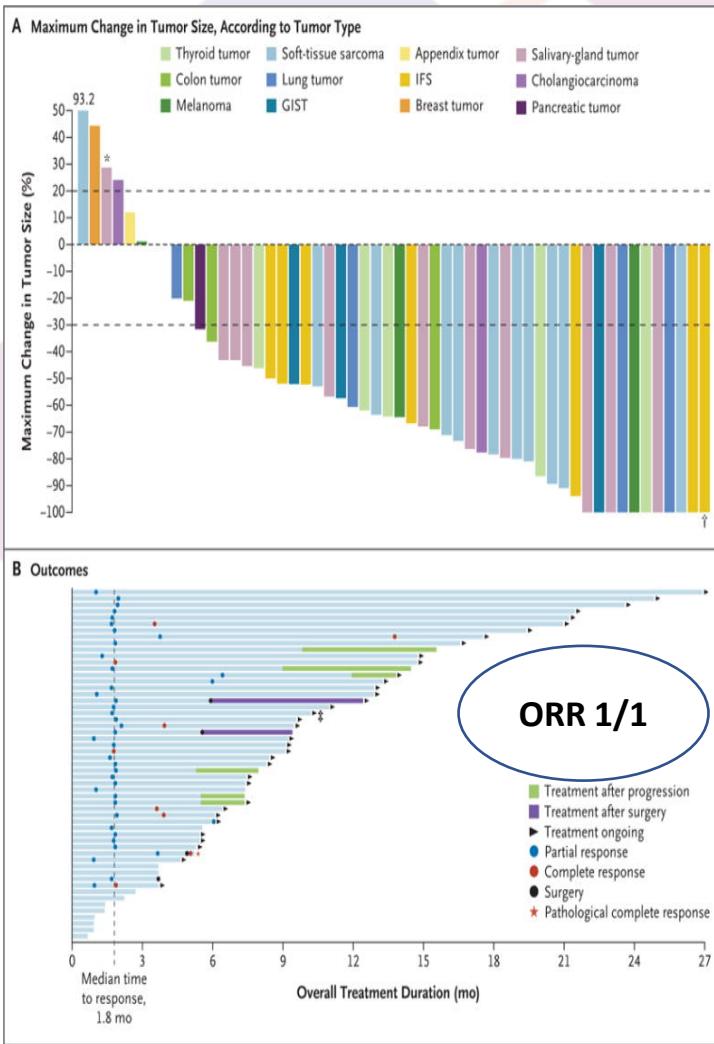
N= 12 PDAC: 1 PR, 9 SD



Blocking KRAS-SOS1 Interaction with BI-3406



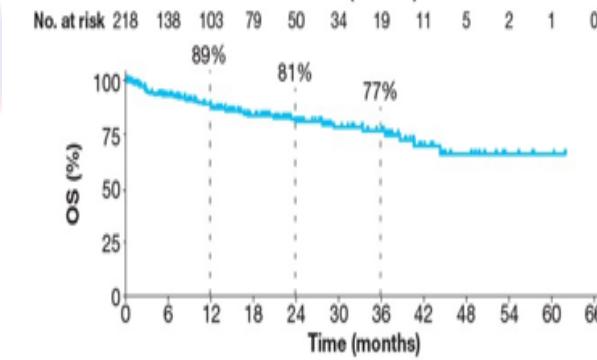
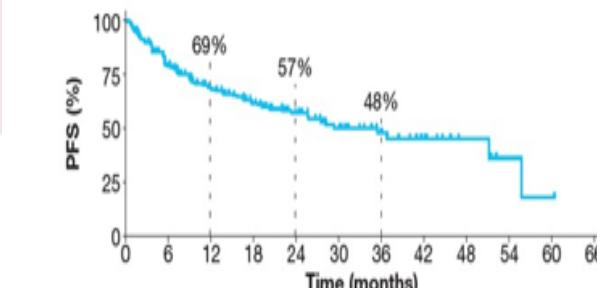
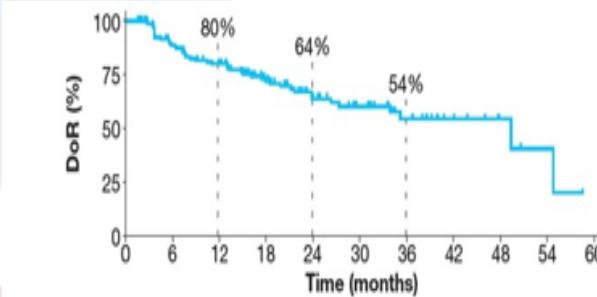
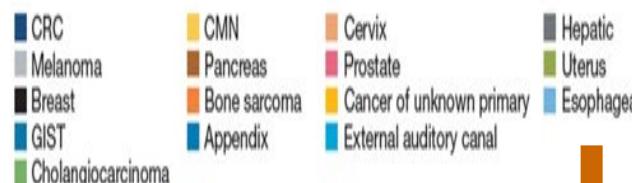
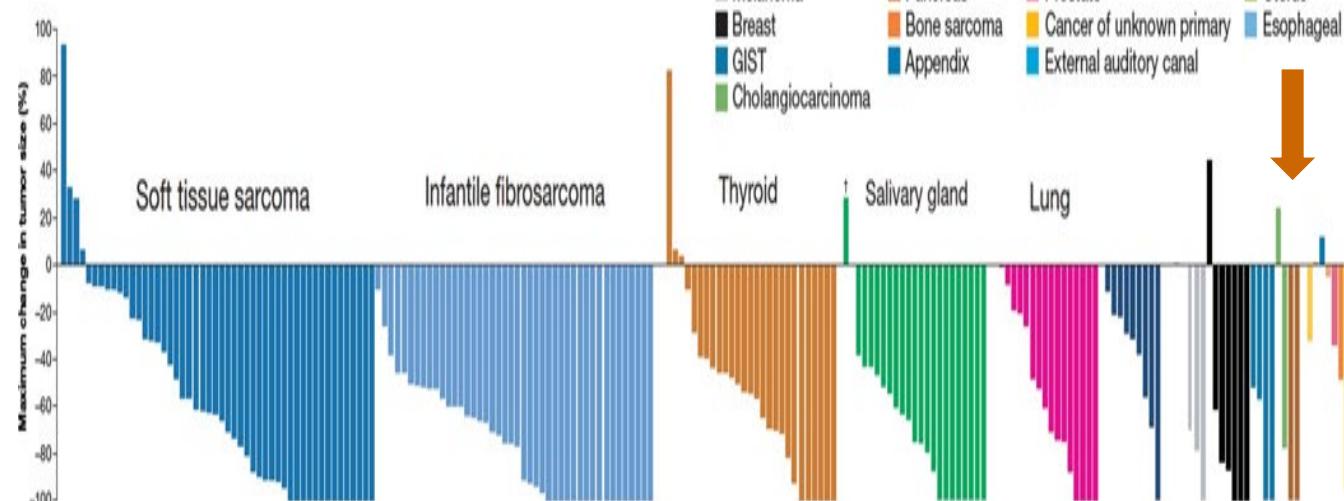
KRAS Wild Type: *NTRK*, *ROS1* and *ALK*



Targeting *NTRK* Gene Fusions In Solid Tumors and PDA

Response	Integrated dataset (N=218)	CNS metastases at baseline (N=19)
Evaluable patients, n	206	15
ORR, % (95% CI)	75 (68–81)	73 (45–92)
Best overall response, n (%)		
Complete response	45 (22)	0
Partial response	109 (53)	11 (73)
Stable disease	33 (16)	2 (13)
Progressive disease	13 (6)	2 (13)
Not determined	6 (3)	0

Larotrectinib



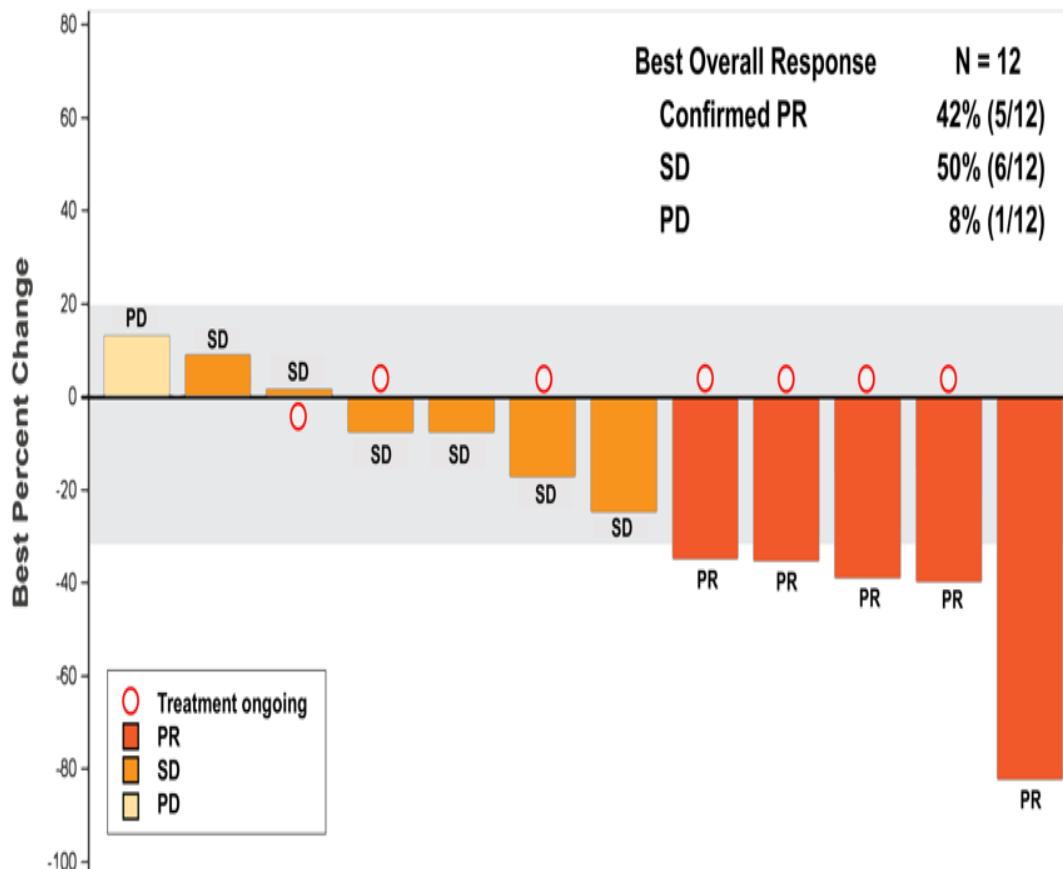
- Median DoR: 49.3 months (95% CI 27.3–NE)
 - Median follow-up: 22.3 months

- Median PFS: 35.4 months (95% CI 23.4–55.7)
 - Median follow-up: 20.3 months

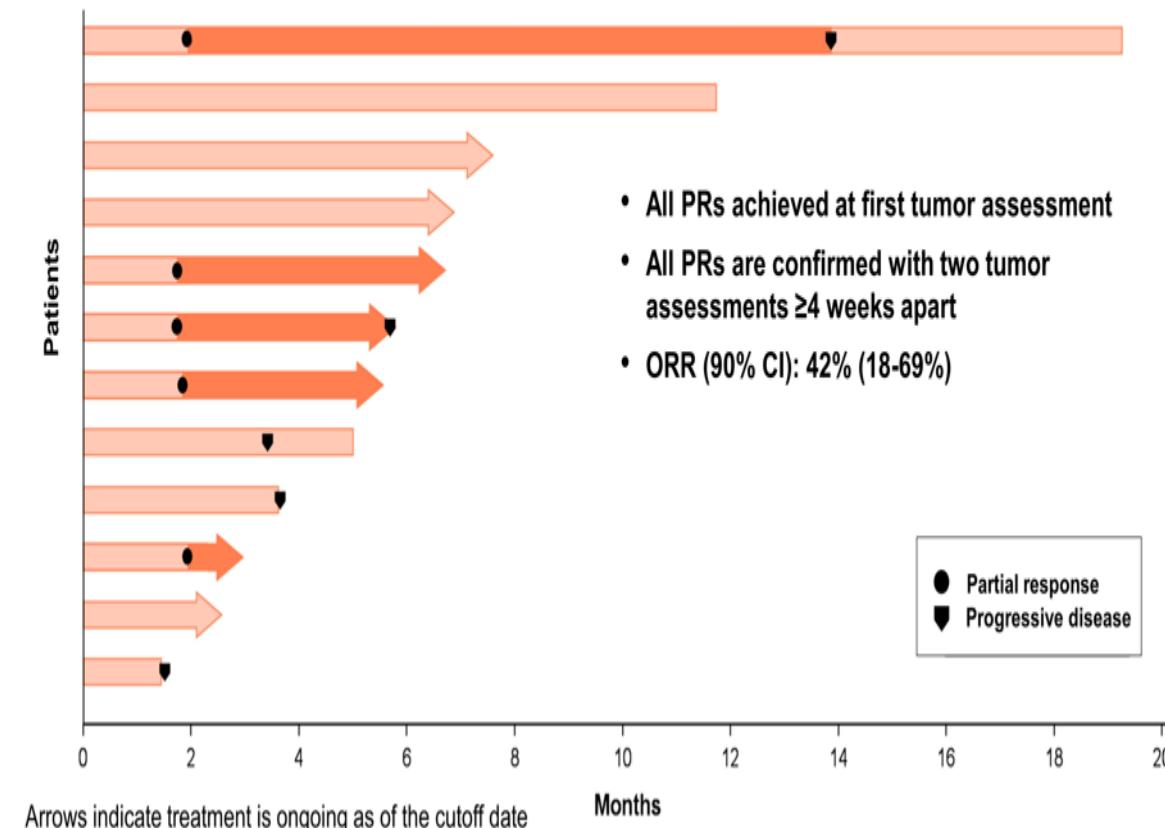
- Median OS: not reached (95% CI NE–NE)
 - Median follow-up: 22.3 months

NRG1 Fusions Bispecific HER2/HER3 Ab Zenocutuzumab (MCLA-128)

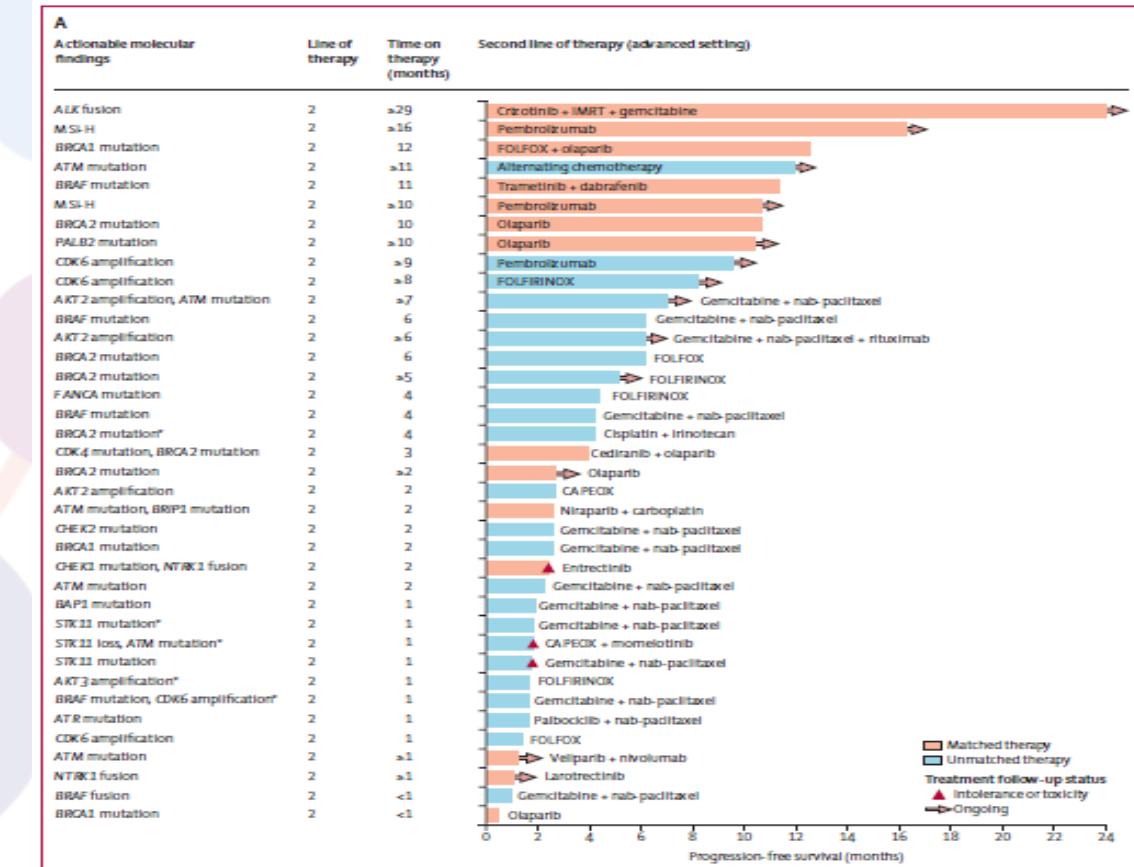
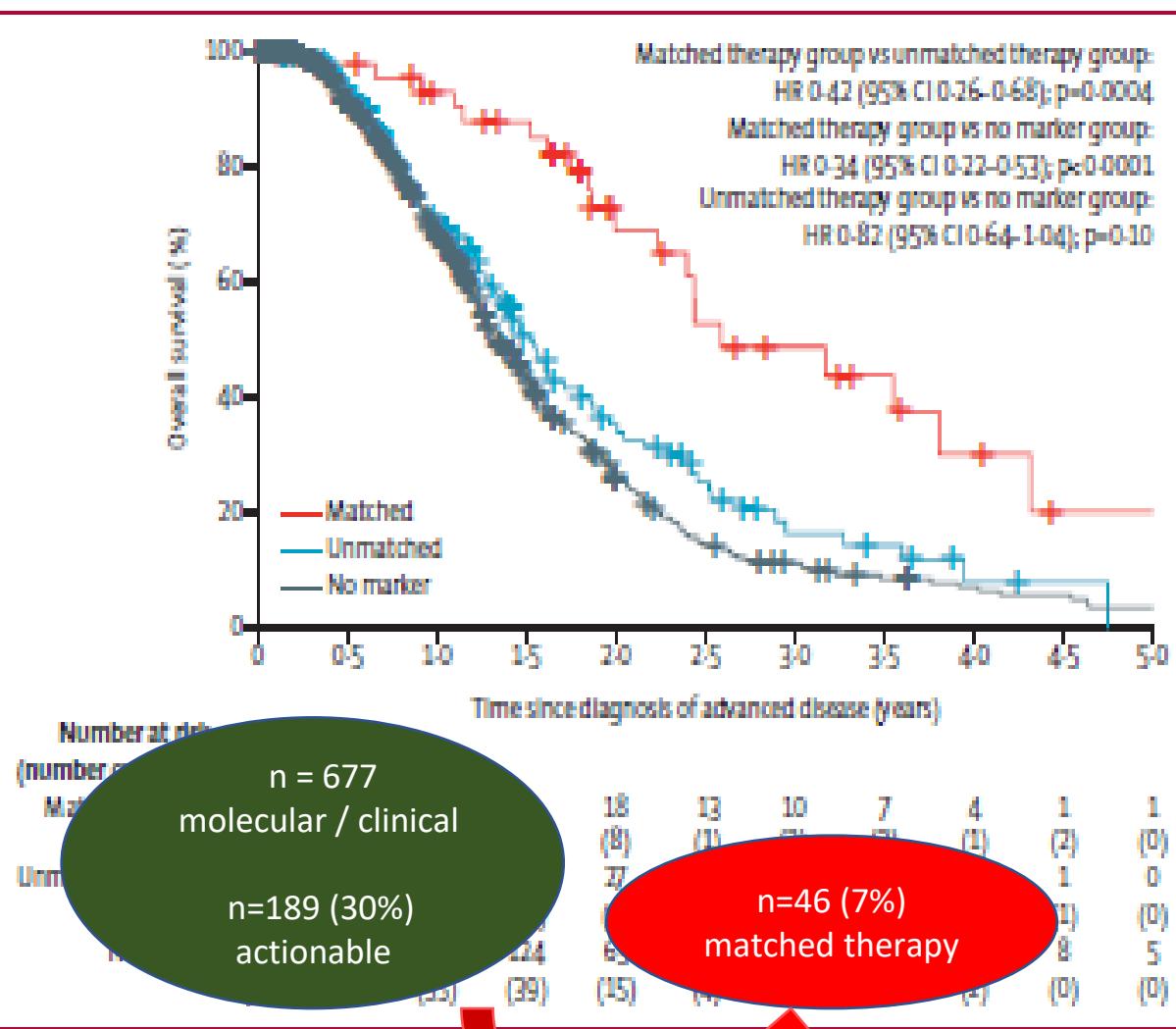
Best % Change in Target Lesions from Baseline



Time to Response & Duration of Exposure Patients with NRG1+ PDAC



Pancreatic Cancer Action Network Registry Matched Therapy: DDR, MSI, NTRK, ALK, BRAF



DOUBLE SURVIVAL

Case for Palliative Care

A 45-year-old male recently diagnosed with metastatic pancreatic cancer is going to initiate first-line palliative chemotherapy and reports mild, vague abdominal pain. When should this patient be referred to palliative care?

- A. When his symptoms become intolerable
- B. When all cancer-directed therapies have been exhausted
- C. There is no role for palliative care in this setting
- D. As soon as possible
- E. When he decides he is ready for hospice care

Pancreas Cancer: Palliative Care

- Biliary obstruction (70-85% patients present with pancreatic head tumors): in unresectable patients, metal stent preferred (covered or uncovered)
- Pancreatic insufficiency: Pancreatic enzyme supplementation (Creon)
- Diabetes: Insulin
- Nutrition: appetite stimulants, dietary counseling
- Abdominal pain: Narcotics, celiac plexus neurolysis –
 - 60-80% of pancreas cancer patients report some degree of pain relief with celiac block

Summary

- **mFOLFIRINOX**: standard of care after surgery for patients with good performance status
- Chemotherapy alone is standard for borderline resectable and locally advanced PDA; radiation on a case by case basis
- **FOLFIRINOX** and **Gemcitabine-nab/paclitaxel** are 1st line options for metastatic pancreatic cancer
- 2nd line therapy: nano-liposomal irinotecan +5FU (~ FOLFIRI); FOLFOX, Gem/nab-P
- **Pembrolizumab** for MSI-H/dMMR (<1%) or TMB-High
- Maintenance **Olaparib** for germline BRCA1/2 MUT after response to platinum
- **Larotrectinib** or **entrectinib** for NTRK fusion+
- Germline (blood test for hereditary genes) testing for all stages
- Tumor molecular profiling (genomic, RNA, proteins): Locally Advanced and Metastatic
- **Palliative Care**: essential

Clinical Trials Every Step
of the Way