Pancreatic Cancer

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Objectives

Pancreatic cancer:

- epidemiology
- diagnosis
- treatments

Pancreatic Cancer

- Projected 57,600 new cases of pancreatic cancer in US with 47,000 deaths in 2020
- 5-yr OS 9%
- 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)

Siegel RL, et al. Cancer Statistics 2020

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 1st 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

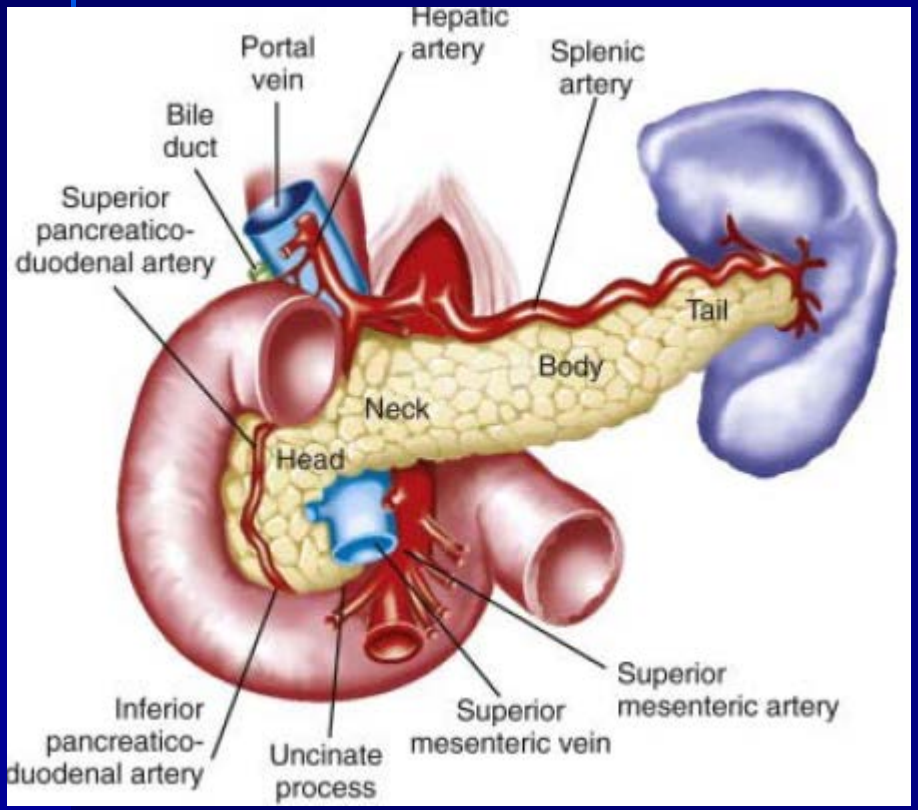
Klein AP et al. Cancer Research 2004; 64; 2634-2638

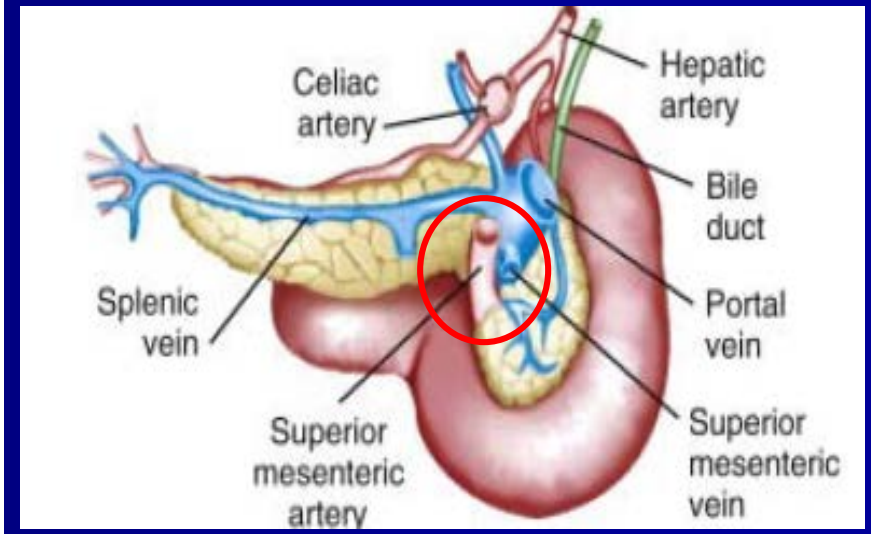
Risk Factor: Genetics

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

Summarized in: Syngal et al. American Journal Gastroenterology 2015
Screening recommendations: Syngal et al. American Journal Gastroenterology 2015, Canto et al. Gut 2012.

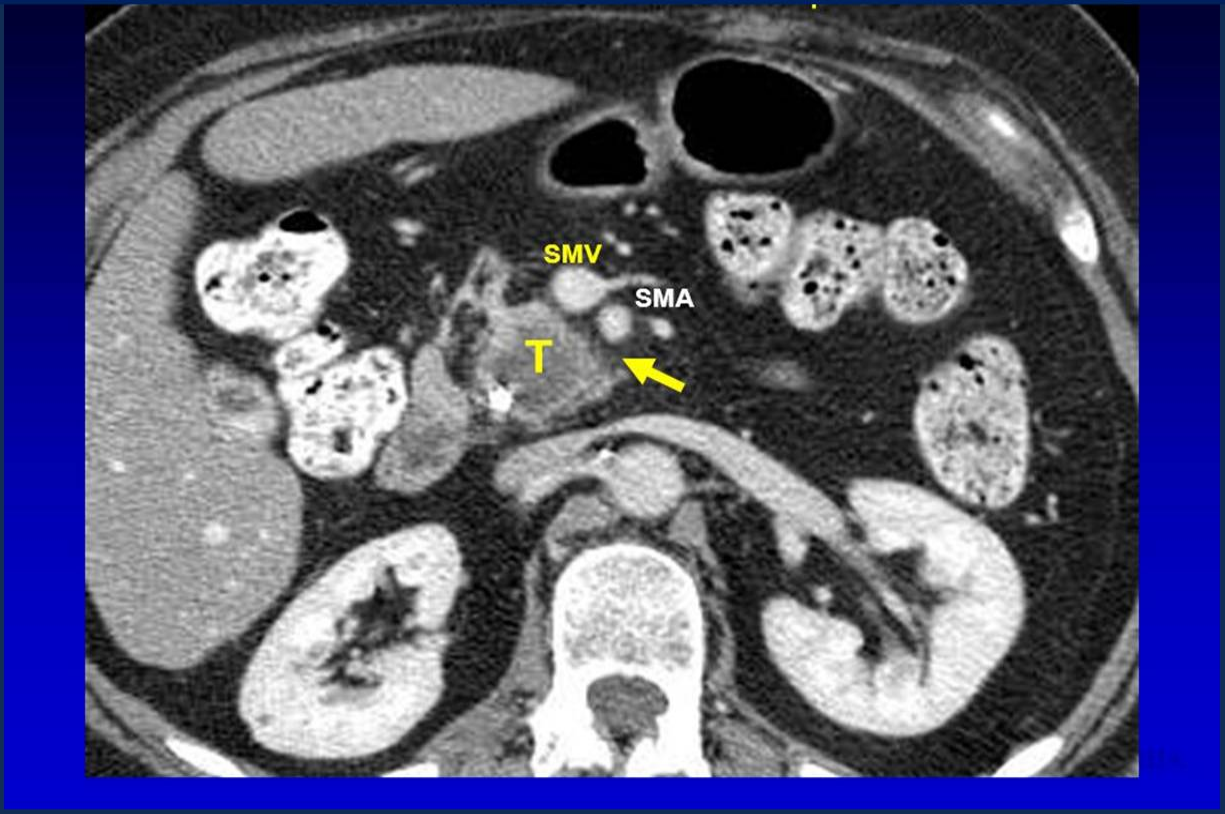
Defining Resectability





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

Resectable Pancreatic Adenocarcinoma



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

55 yo woman underwent R0 resection for pT3N2 pancreatic adenocarcinoma. She recovered well after surgery with no post-operative complications.

CA19-9 after surgery is 19 (normal 0-54)

CT scans show no evidence of metastatic disease.

She has a history of hypertension.

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

A. Gemcitabine

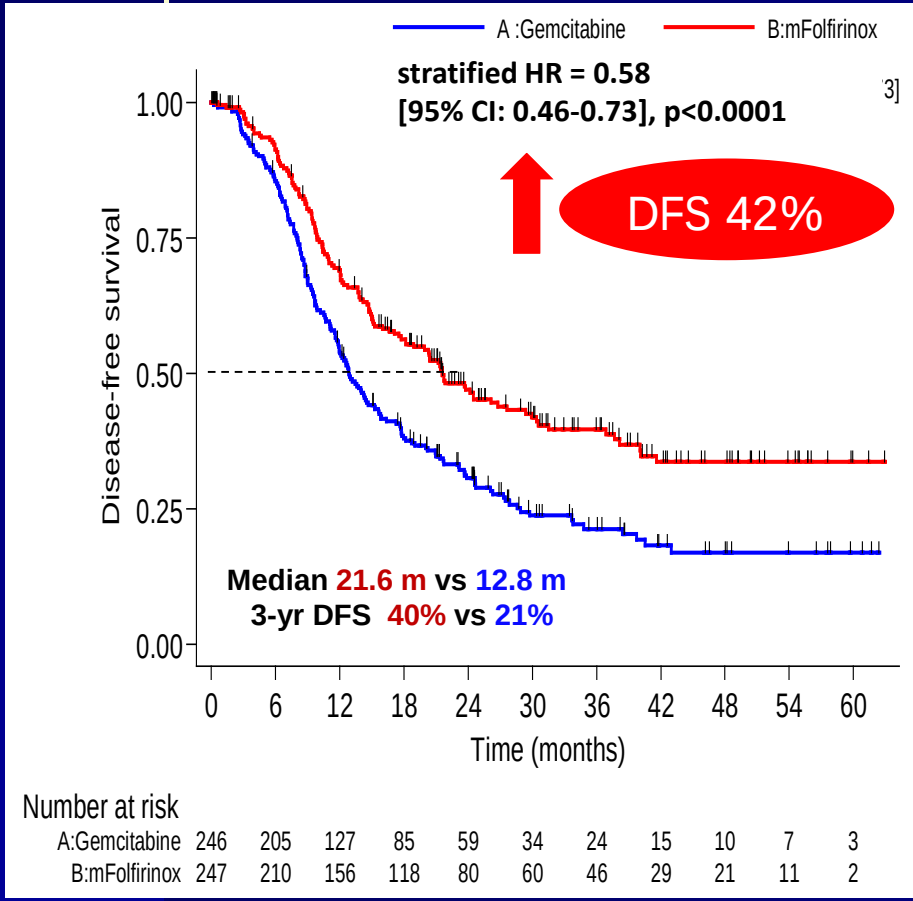
B. Gemcitabine + capecitabine

C. modified FOLFIRINOX

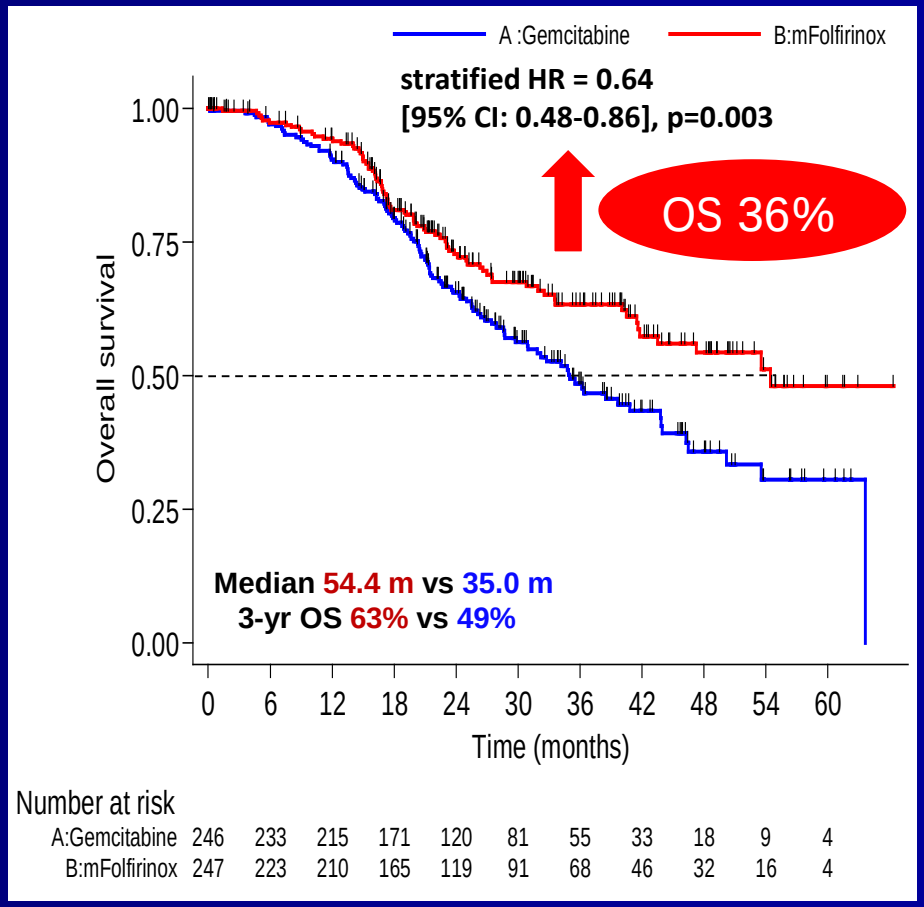
D. Gemcitabine/*nab*-paclitaxel

PRODIGE 24: mFOLFIRINOX vs Gemcitabine

DFS



OS



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

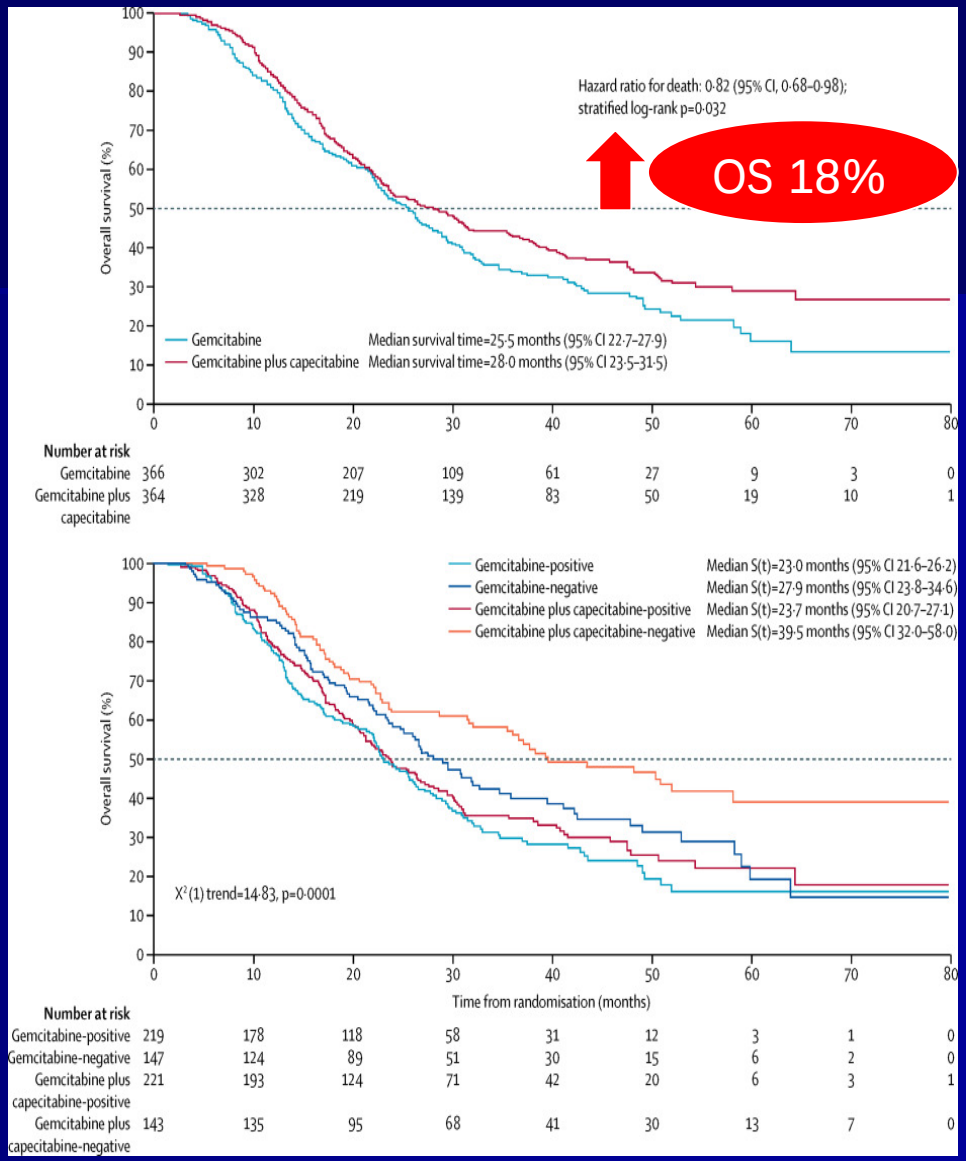
ESPAC 4

Gemcitabine + Capecitabine vs Gemcitabine

OS: 28 vs 25.5 mos

RFS: 13.9 vs 13 mos

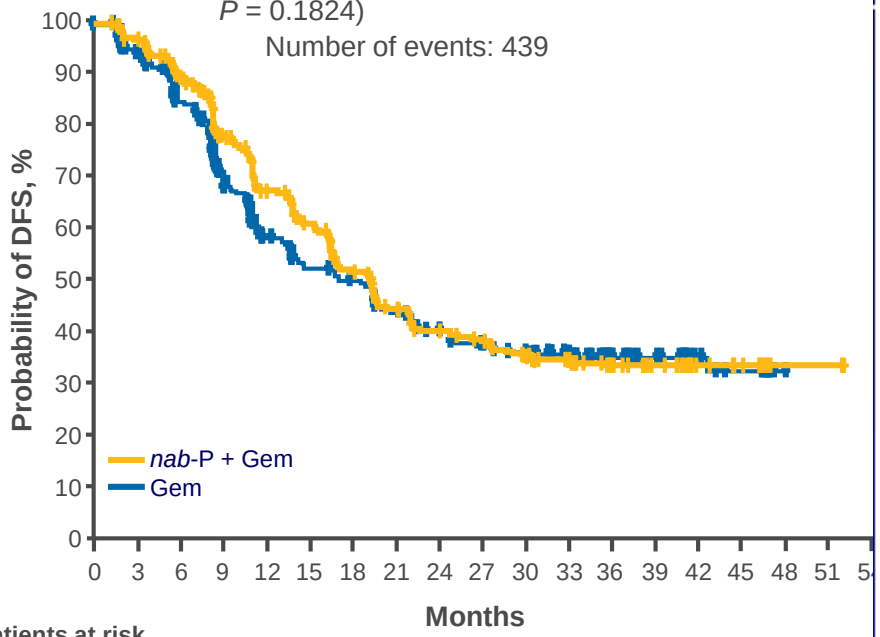
3-year RFS: 24% vs 21%



Neoptolemos JP, et al Lancet 2017 389:1011

APACT: Gemcitabine / nab-Paclitaxel

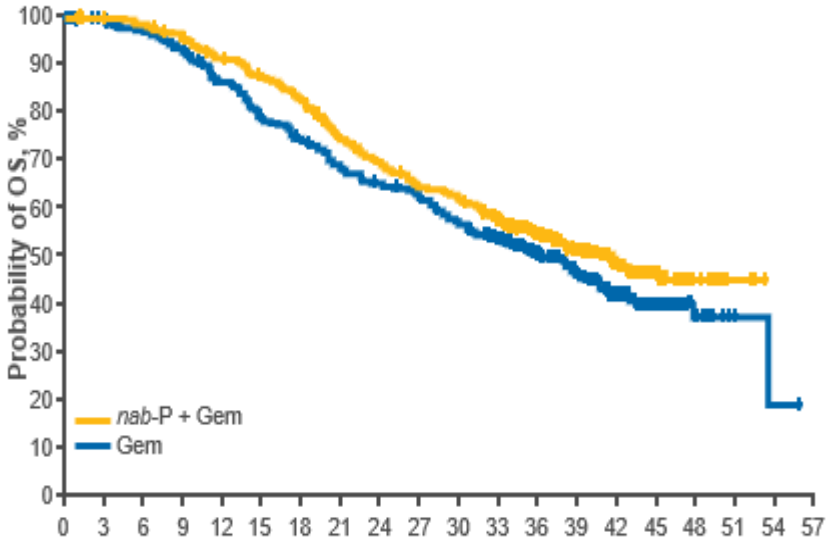
Median independently assessed DFS
nab-P + Gem: **19.4** months
Gem: **18.8** months
(HR 0.88; 95% CI, 0.729 - 1.063; stratified log-rank *P* = 0.1824)
Number of events: 439



Patients at risk

nab-P + Gem	432	391	338	279	236	204	167	138	121	112	99	88	54	43	20	14	2	2
Gem	434	368	309	235	183	157	147	127	116	105	98	88	59	42	15	10	1	

Median interim OS (68% mature)
nab-P + Gem: **40.5 mo**
Gem: **36.2 mo**
(HR 0.82; 95% CI, 0.680 - 0.996; nominal *P* = 0.045)
Number of events: 427; Median follow-up, 38.5 months



Patients at risk

nab-P + Gem	432	427	420	406	385	366	344	307	284	264	252	219	162	113	73	40	12	3
Gem	434	415	404	384	354	320	301	275	262	249	228	198	153	101	64	29	12	2	1

Tempero M et al ASCO 2019

Case 1: What is the standard of care after surgery for pancreatic cancer in fit patients?

55 yo woman underwent R0 resection for pT3N2 pancreatic adenocarcinoma. She recovered well after surgery with no post-operative complications.

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

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C. modified FOLFIRINOX

D. Gemcitabine/*nab*-paclitaxel

Neoadjuvant / Perioperative Chemotherapy

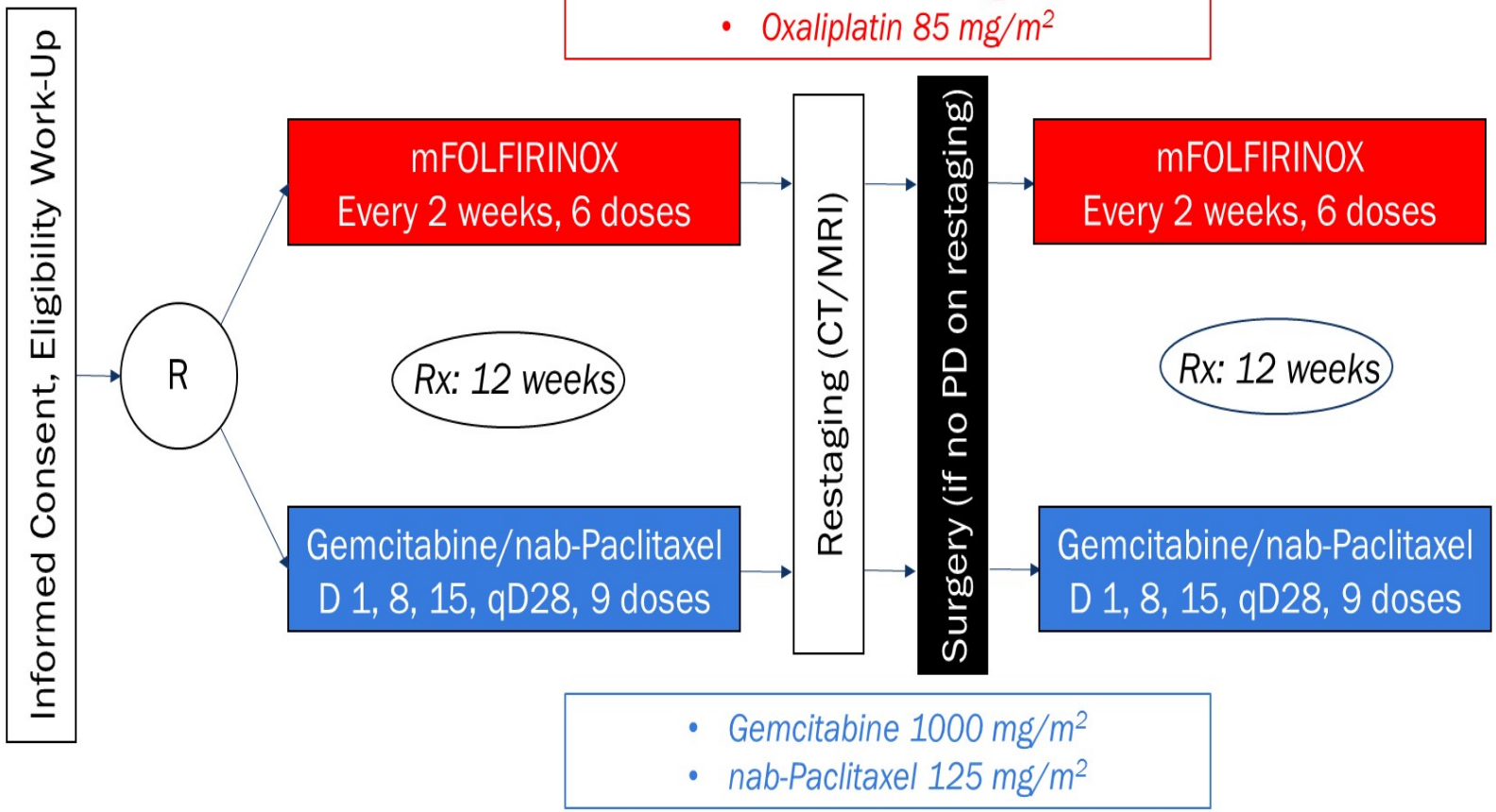
SWOG S1505: Results of Perioperative Chemotherapy with mFOLFIRINOX vs Gemcitabine/nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma

Davendra P. S. Sohal, Mai Duong, Syed A. Ahmad, Namita S. Gandhi, M. Shaalan Beg, Andrea Wang-Gillam, James L. Wade III, E. Gabriela Chiorean, Katherine A. Guthrie, Andrew M. Lowy, Philip A. Philip, Howard S. Hochster

Presented By: Davendra Sohal, MD, MPH
Associate Professor of Medicine
Director of Experimental Therapeutics, Clinic Medical Director
Hematology and Oncology, University of Cincinnati

Study Schema

- *5-Fluorouracil 2400 mg/m^2, over 46 hrs*
- *Irinotecan 180 mg/m^2*
- *Oxaliplatin 85 mg/m^2*

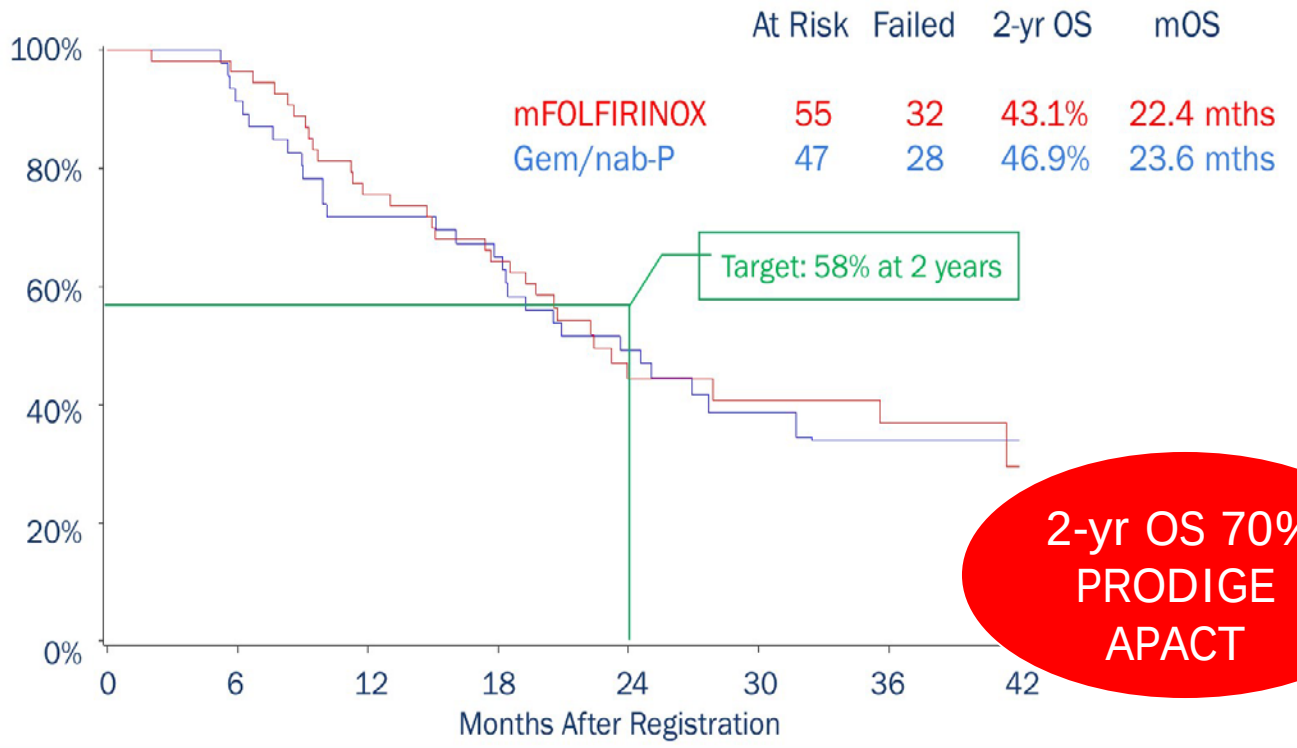


- *Gemcitabine 1000 mg/m^2*
- *nab-Paclitaxel 125 mg/m^2*

Both Regimens were Similar and Did Not Reach 58% 2-Yr OS

Patients who qualify for adjuvant chemotherapy trials are very selected

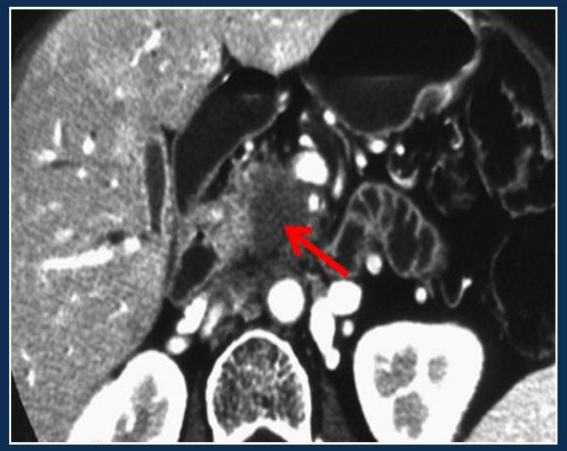
Primary Endpoint: Two-year OS

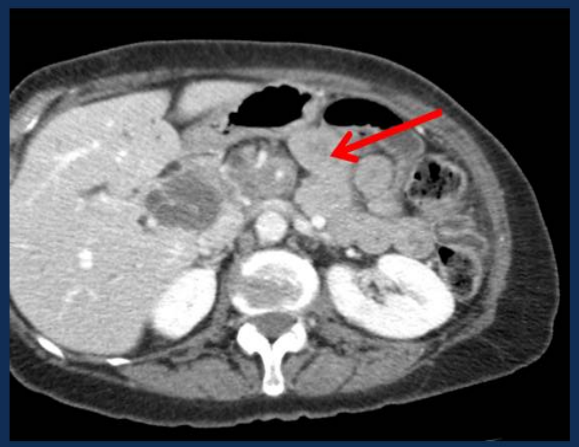


2-yr OS 70%
PRODIGE
APACT

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

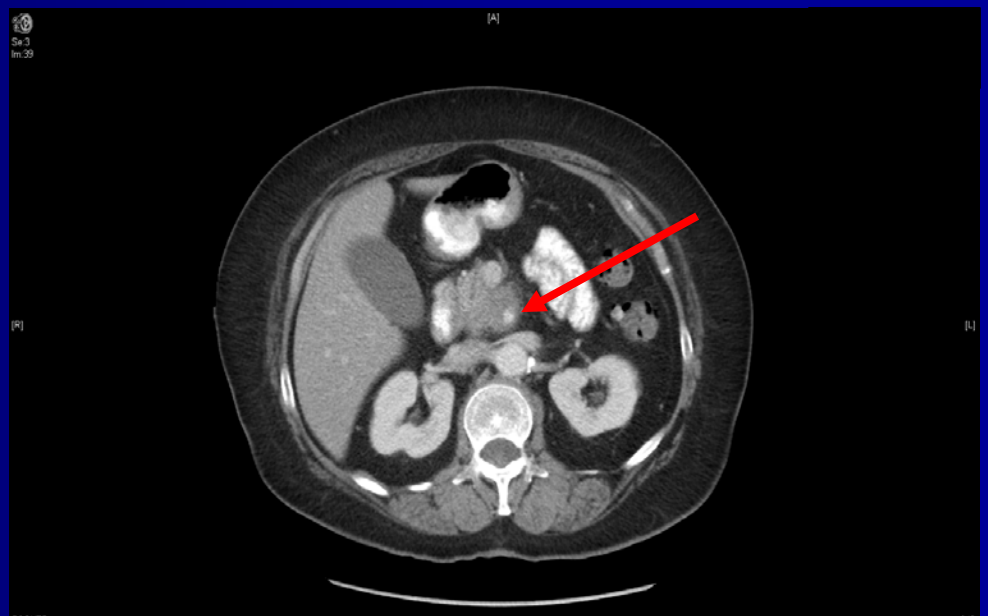
Case 2: Management of LAPC

- 64 y/o woman presents with dull LLQ pain and fatigue x 1 month
- Refractory to metamucil and proton pump inhibitor

- CT scan shows a 3.5cm pancreatic mass in uncinate process encasing SMA
- PMH: small fiber idiopathic peripheral neuropathy; diabetes, GERD
- FH: maternal aunts breast cancer x2 (50, 60), maternal cousin breast cancer at 64

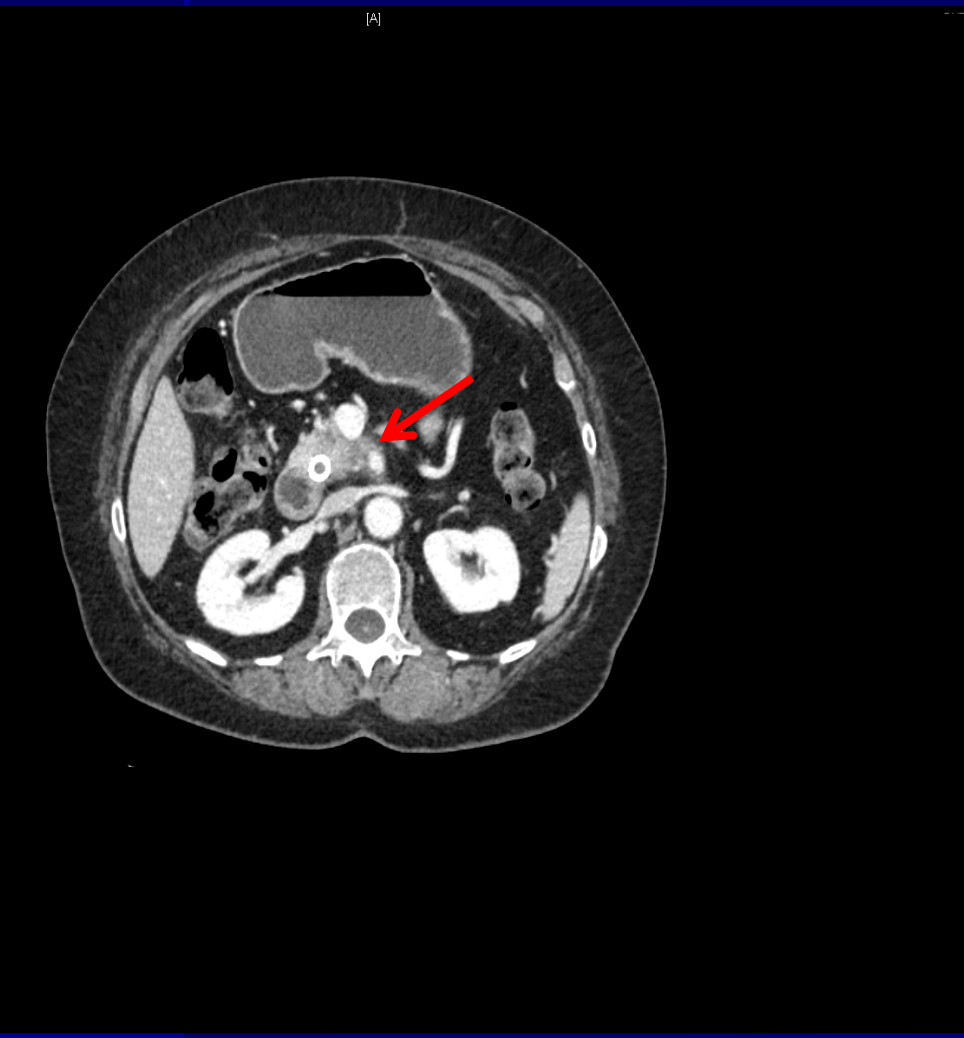
- ECOG PS 1
- CA19-9 = 87 U/mL (0-54)
- Genetics:

  germline no pathogenic mutations

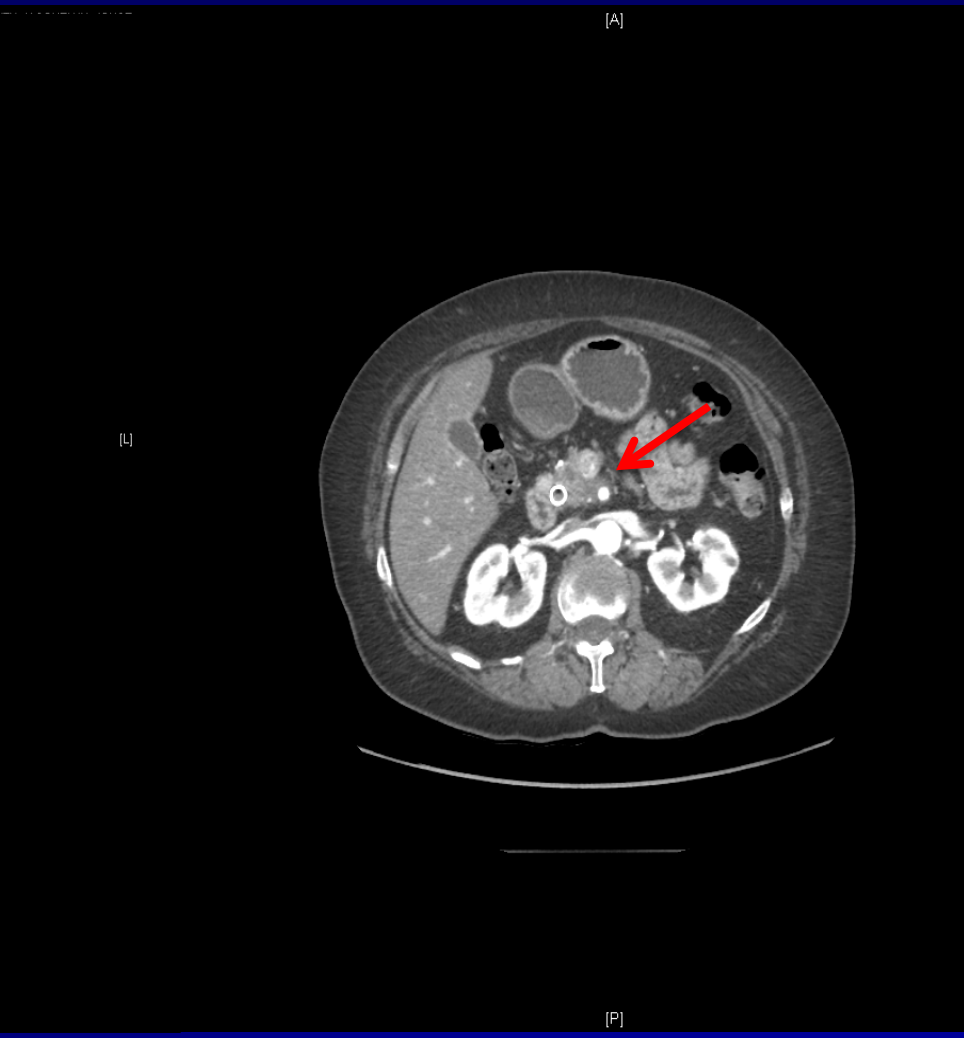


Presented by: E. Gabriela Chiorean at ASCO 2017 meeting

Post 2 months of mFOLFIRINOX:
- continued SMA encasement
- decreased tumor size



Post 4 months of mFOLFIRINOX:
- decreased SMA encasement
- decreased tumor size



- Grade 4 N/V/D after Cycle 1
- C Diff colitis after Cycle 2

20% 5FU and oxaliplatin dose reduction
40% irinotecan reduction

Next Steps

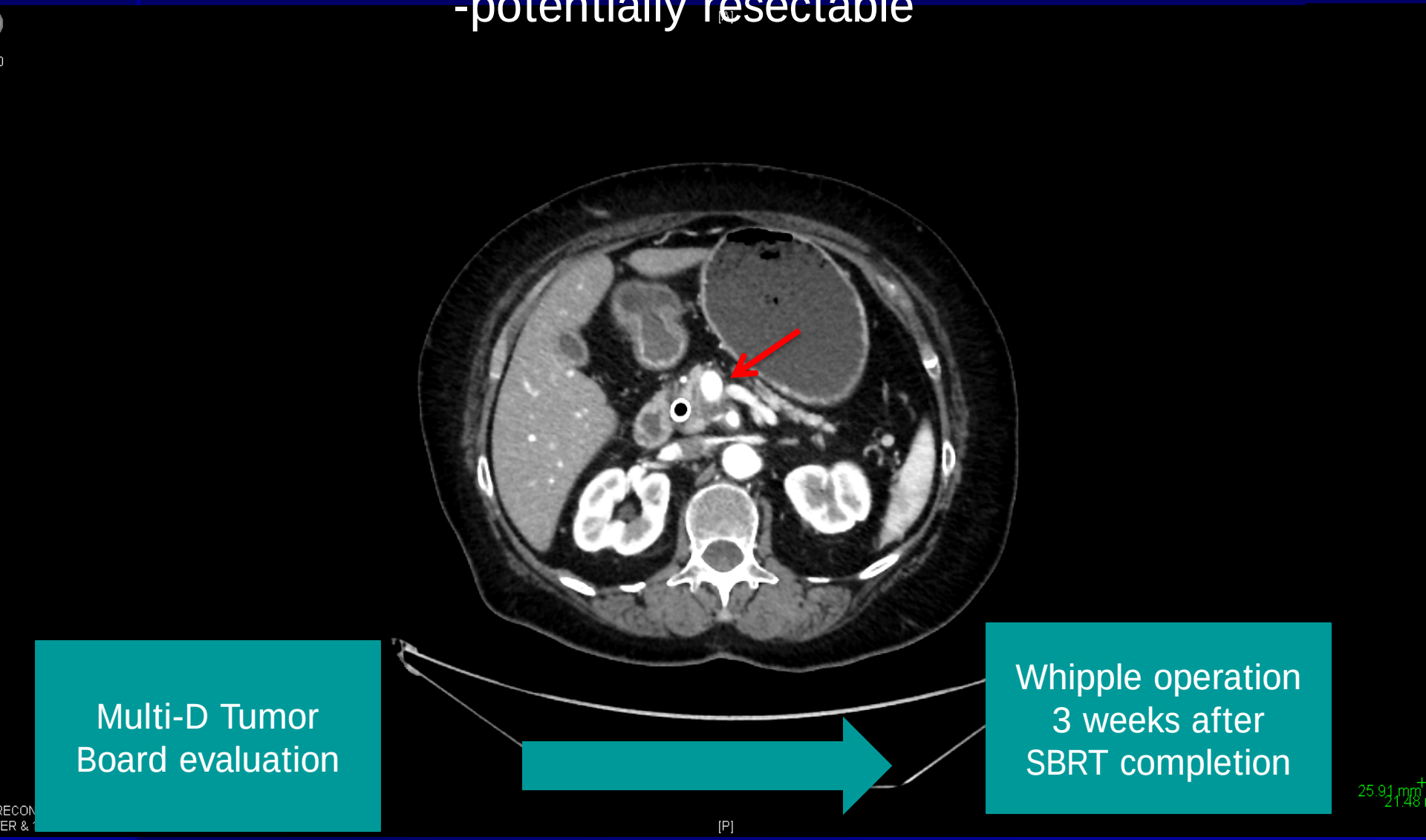
Would you recommend:

a. continue mFOLFIRINOX

b. chemoradiotherapy or SBRT

c. surgical exploration

Post SBRT
-more tumor shrinkage
-potentially resectable



Multi-D Tumor Board evaluation

Whipple operation 3 weeks after SBRT completion

Pathology

- Grade 1 well differentiated 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)
- PanIN-3 present

Sequencing of Chemotherapy and RT

Table 4 Recommendations for sequencing of chemotherapy and RT in patients receiving RT

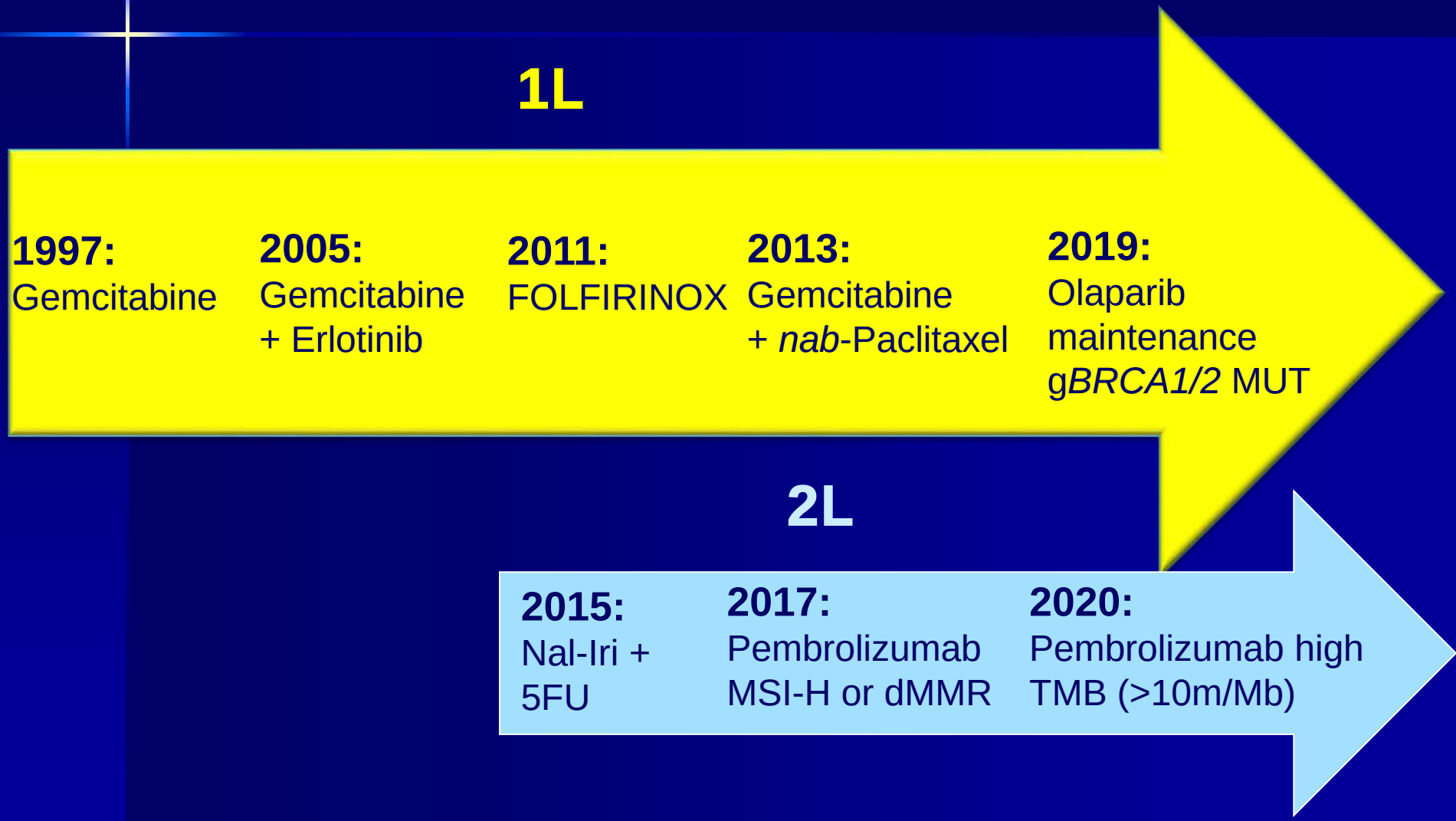
KQ 3 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	92%*
2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	92%*
3. For patients with unresectable or locally advanced pancreatic cancer without systemic progressionfollowing 4-6+ months of chemotherapy, definitive RT is recommended.	**Strong**	**Moderate**	85%*

Abbreviations: KQ = key question; RT = radiation therapy.

* The medical physics representative abstained from rating these recommendations.

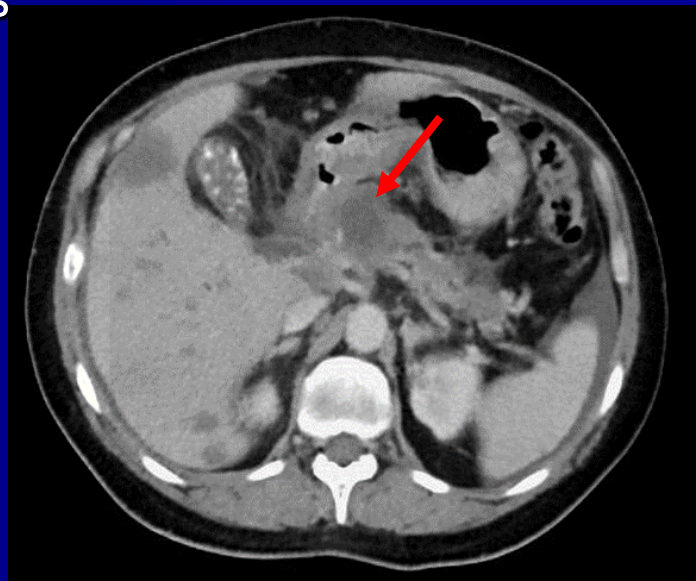
Palta M et al Practical Rad Oncol 2019
ASTRO guidelines

Metastatic Pancreatic Cancer



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
  - total bilirubin 4.5 mg/dL, ALK 273, AST/ALT 85/90
- CT: mass in the head of pancreas and multiple liver metastases
- ERCP: metallic biliary stent through a malignant common bile duct stricture
- Liver biopsy: adenocarcinoma CK7+, CDX2+, CK20-
- Bilirubin 10 days later: 0.8 mg/dL
- No family history of pancreatic or other cancers
- ECOG PS 1



Question: What would you choose as the optimal 1L treatment option for this patient?

a. Gemcitabine alone

b. Gemcitabine + nab-paclitaxel

c. FOLFOX

d. FOLFIRINOX

e. Either b or d are preferred 1st line options

What genetic and molecular markers would you order to help with treatment decisions?

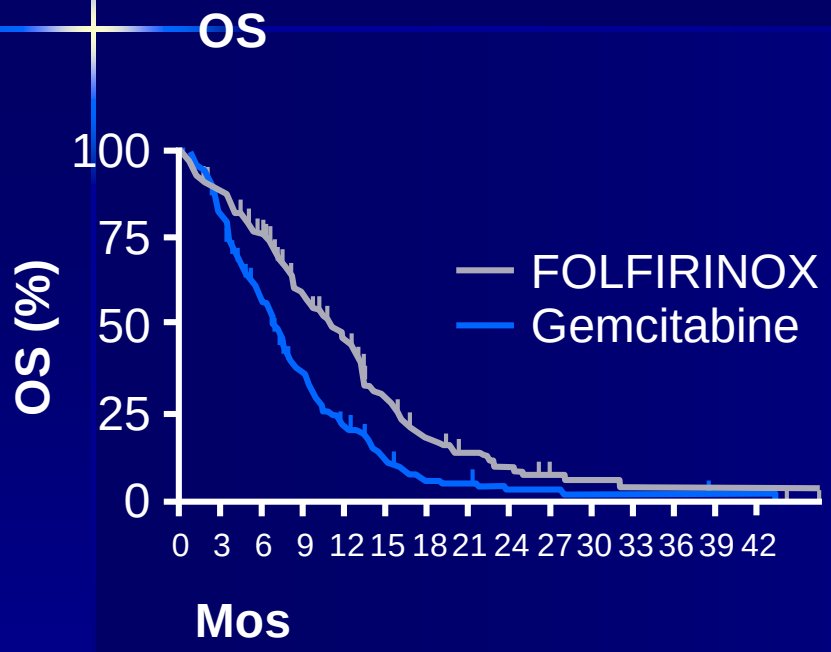
a. Microsatellite instability (MSI) germline (blood) test

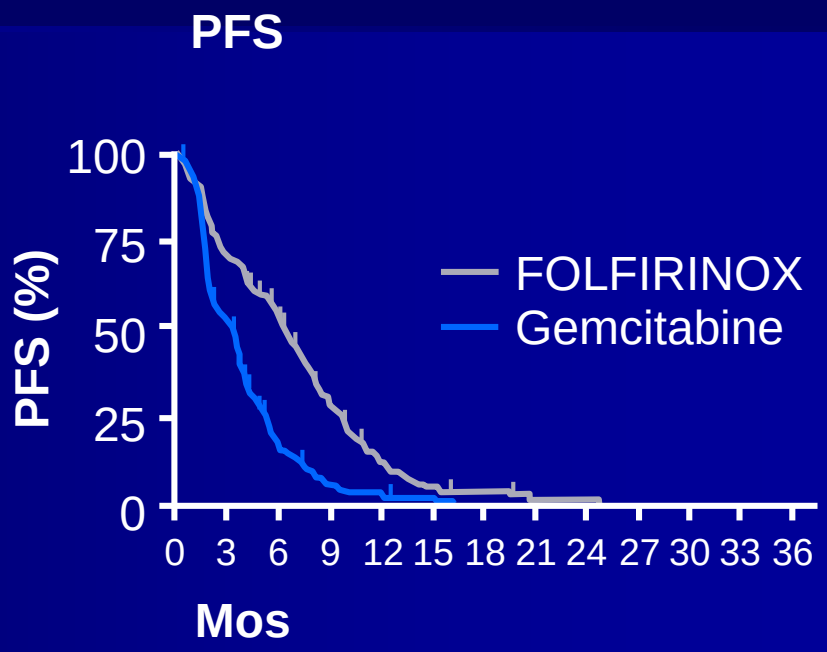
b. BRCA1, BRCA2 germline testing

c. Comprehensive somatic (tumor) gene profiling

d. a, b and c

FOLFIRINOX vs Gemcitabine: OS and PFS



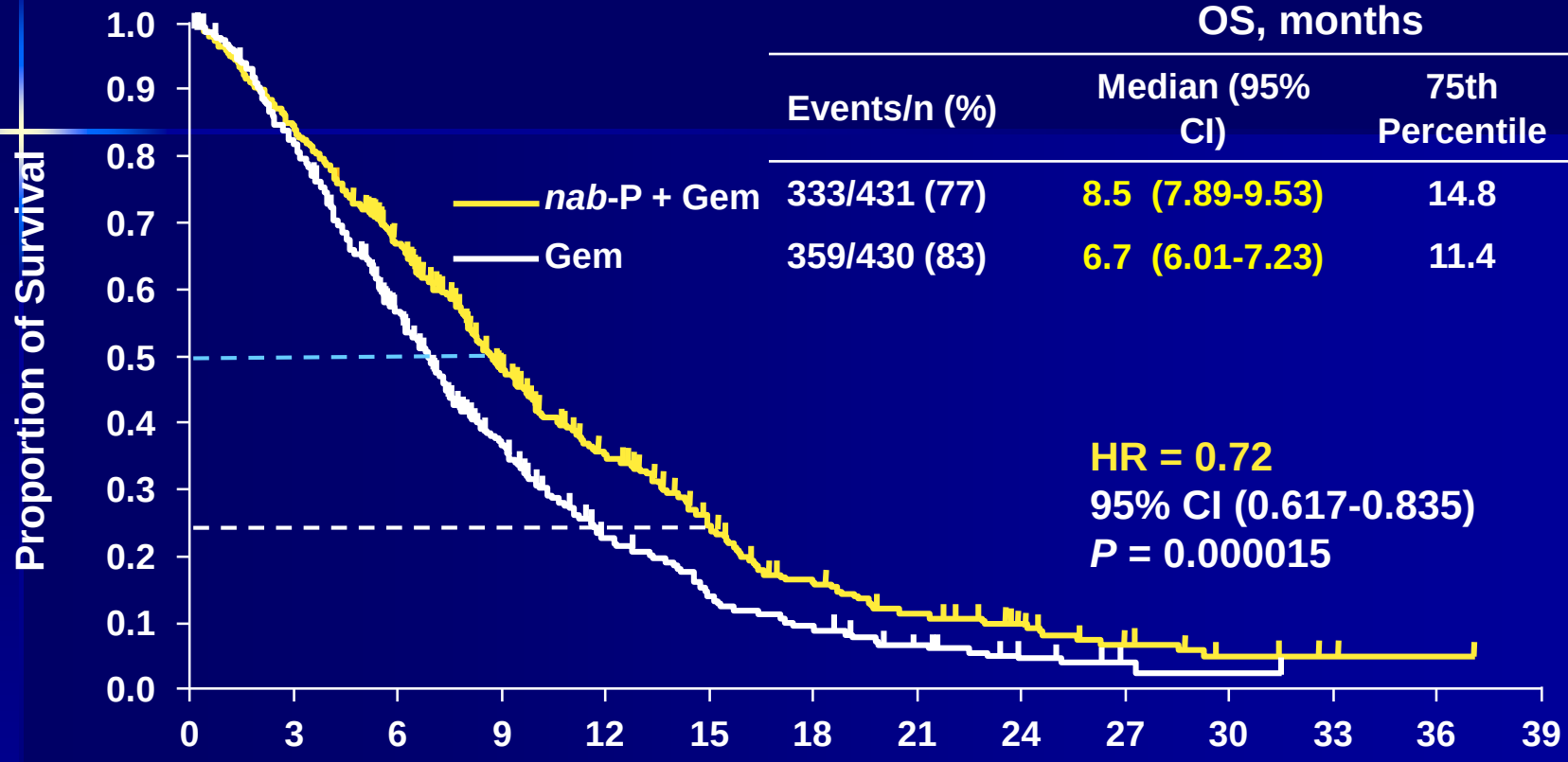


Median OS: 11.1 vs 6.8 mos
HR: 0.57 (95% CI: 0.45-0.73; *P* < .001)

Median PFS: 6.4 vs 3.3 mos
HR: 0.47 (95% CI: 0.37-0.59; *P* < .001)

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

Gemcitabine/*nab*-Paclitaxel vs Gemcitabine



	OS, months	
Events/n (%)	Median (95% CI)	75th Percentile
333/431 (77)	8.5 (7.89-9.53)	14.8
359/430 (83)	6.7 (6.01-7.23)	11.4

HR = 0.72
95% CI (0.617-0.835)
P = 0.000015

Pts at risk

nab-P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Von Hoff et al. NEJM 2013

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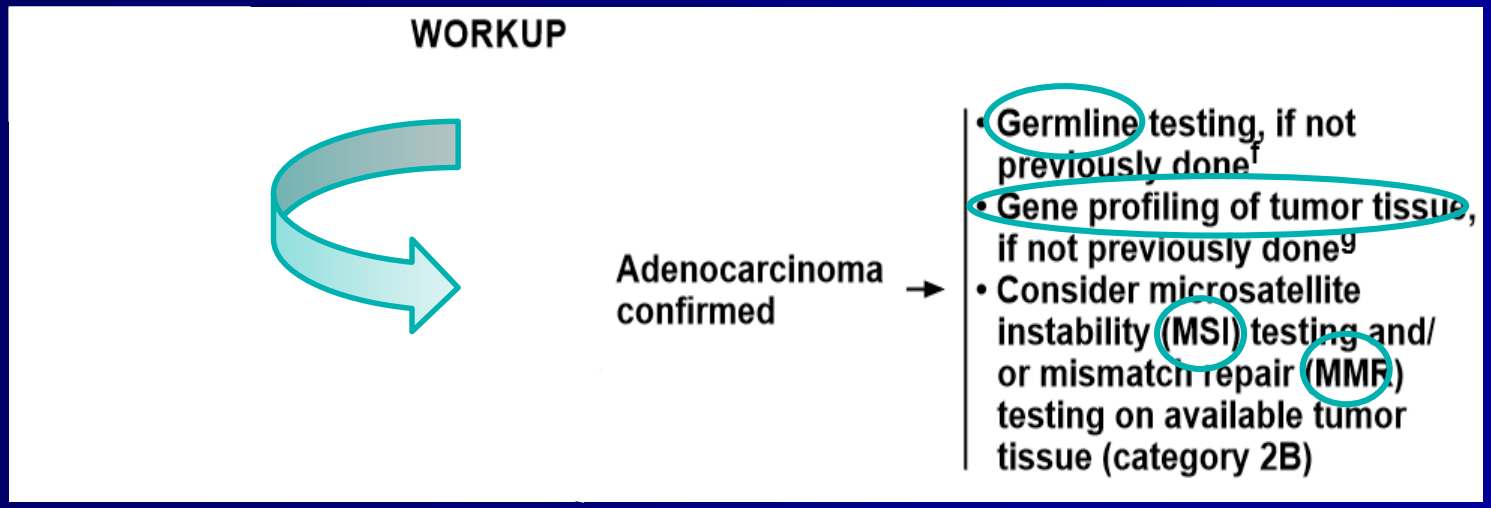
Genetic Testing for Pancreatic Cancer



Tempero, M, Malafa MP, Chiorean EG, NCCN Guidelines 2019, JNCCN 2019

What genetic markers would you order to help with treatment decisions?

a. Microsatellite instability (MSI) germline (blood) test

b. BRCA1, BRCA2 germline testing

c. Comprehensive somatic (tumor) gene profiling

d. a, b and c

Case 4: 2L Treatment for metastatic disease

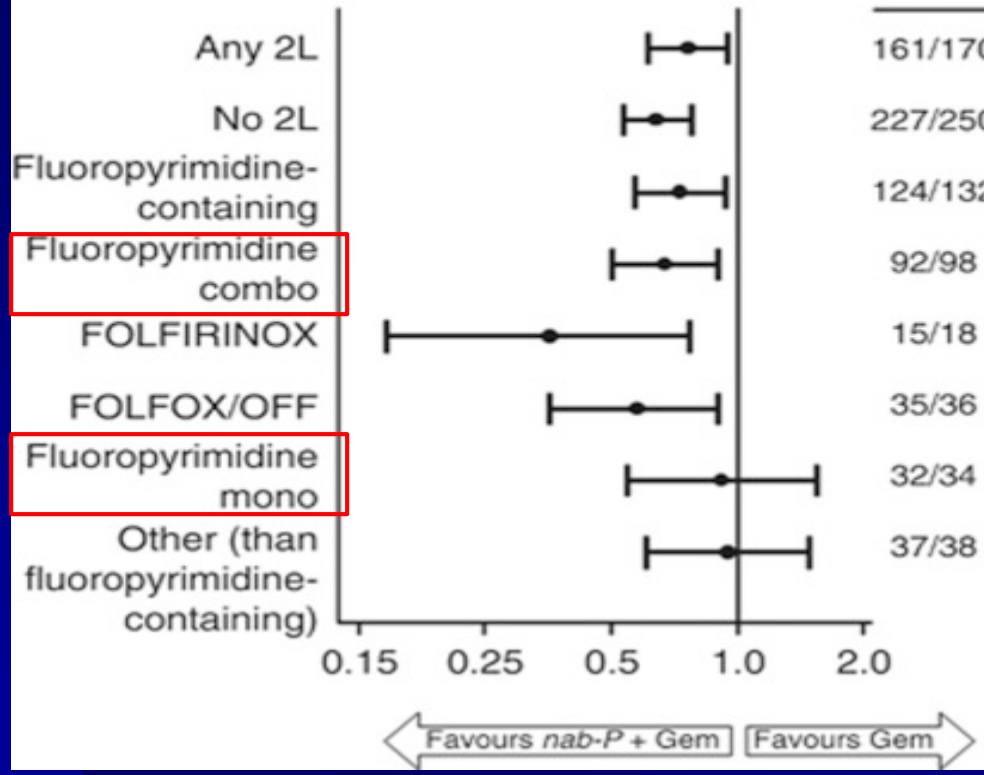
- 69-yr-old female with metastatic pancreatic adenocarcinoma to the liver
- Initial treatment consisted of gemcitabine and *nab*-paclitaxel
  - Achieved a PR lasting for 8 mos

- CT scan at 8 mos shows new peritoneal nodules
- ECOG PS at 1
- She has persistent mild peripheral sensory neuropathy (gr 2)

Question: What would you choose as the best treatment option for this patient?

a. 5-FU/LV
b. FOLFOX
c. FOLFIRINOX
d. 5-FU/LV + nanoliposomal irinotecan

OS after Gem / nab-Paclitaxel Depending on 2nd line Therapy



	nab-P + Gem		Gem		HR	*P*-value
	Events/ *n*	Median OS, months	Events/ n	Median OS, months		
Any 2L	161/170	12.8	166/177	9.9	0.76	0.015
No 2L	227/250	6.3	218/226	4.3	0.64	< 0.001
Fluoropyrimidine-containing	124/132	13.5	124/135	9.5	0.73	0.012
Fluoropyrimidine combo	92/98	14.0	99/107	9.5	0.67	0.006
FOLFIRINOX	15/18	15.7	15/17	7.2	0.36	0.007
FOLFOX/OFF	35/36	13.7	46/49	9.8	0.57	0.015
Fluoropyrimidine mono	32/34	11.9	25/28	9.4	0.92	0.746
Other (than fluoropyrimidine-containing)	37/38	10.9	42/42	11.3	0.95	0.806

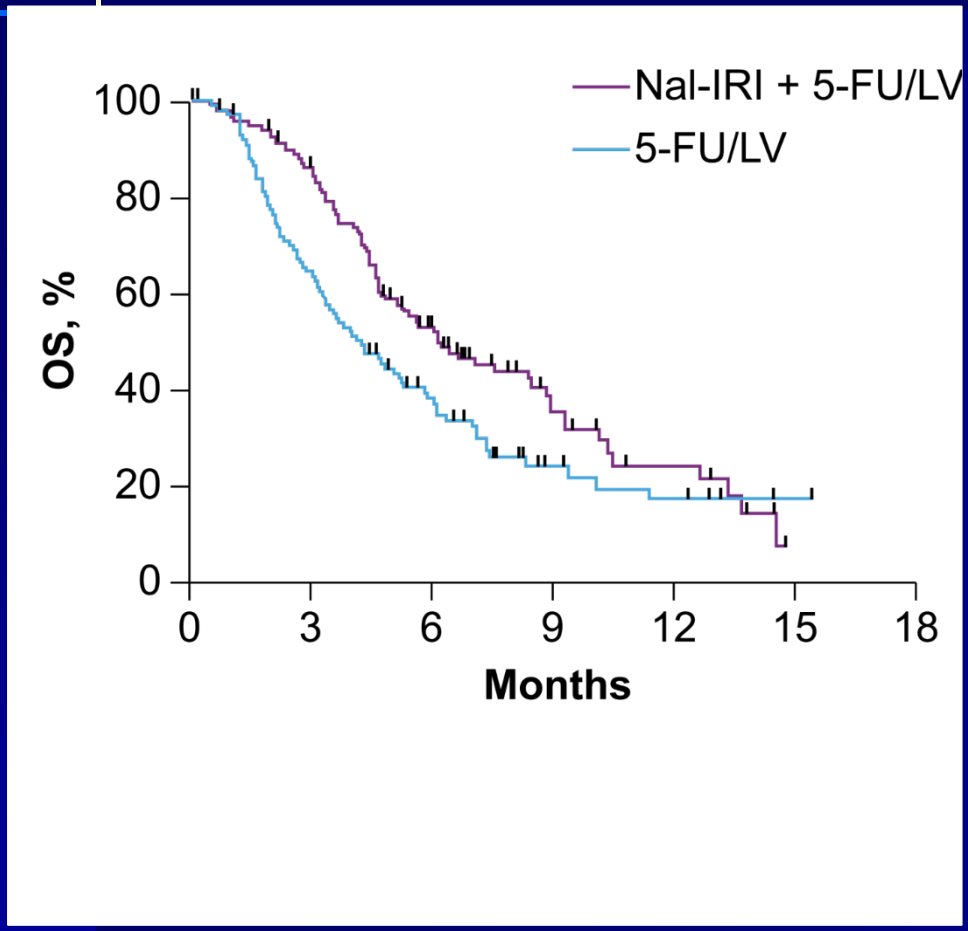
Chiorean EG, et al *Br J Cancer* 2016

Comparison of 2nd Line Studies with Oxaliplatin-Based Chemo

	CONKO-003 (OFF vs. 5-FU/FA)	PANCREOX (mFOLFOX-6 vs. 5-FU/LV)
Sample size	160	108
Median survival	**5.9 vs. 3.3 months** (HR 0.66)	**6.1 vs. 9.9 months** (HR 1.78)
Median PFS	2.9 vs. 2.0 months (HR 0.68)	3.1 vs. 2.9 months (HR 1.0)
Objective response rate	N/A	13.2 vs. 8.5%
Grade 3/4 AEs (for experimental arm)	Pain (32%) Paresthesias (4%) Anemia (4%)	Neutropenia (33%) Fatigue (14%) Thrombocytopenia (8%) Dehydration (8%)

Oettle H et al, *J Clin Oncol* 2014 Aug, 32:2423-9; Gill S et al, *J Clin Oncol* 2016 Nov, 34:3914-3920.

NAPOLI-1 Trial
5FU +/- Nanoliposomal Irinotecan



- **Median OS: 6.1 vs 4.2 months**
  HR = 0.67, p = .012
- Median PFS 3.1 vs 1.5 months
- ORR 16% vs 1%

Wang-Gillam A et al, Lancet 2015

Treatment Sequencing for Metastatic Pancreatic Cancer

Gemcitabine-based

(e.g. gemcitabine, **gem/nab-paclitaxel**, gemcitabine /erlotinib)

(PS 0-1): Fluoropyrimidine-based regimen (+/- nal-IRI, oxaliplatin)

(PS 2): Fluoropyrimidine alone; BSC

(PS 0-1): Irinotecan- or platinum-based regimen

(if no prior exposure)

FOLFIRINOX

(PS 0-1): Gemcitabine/nab-paclitaxel

(PS 2 or less): Gemcitabine monotherapy; BSC

Clinical trial if available

Question: What would you choose as the best treatment option for a patient who progressed after gemcitabine/nab-paclitaxel and has grade 2 neuropathy?

a. 5-FU/LV

b. FOLFOX

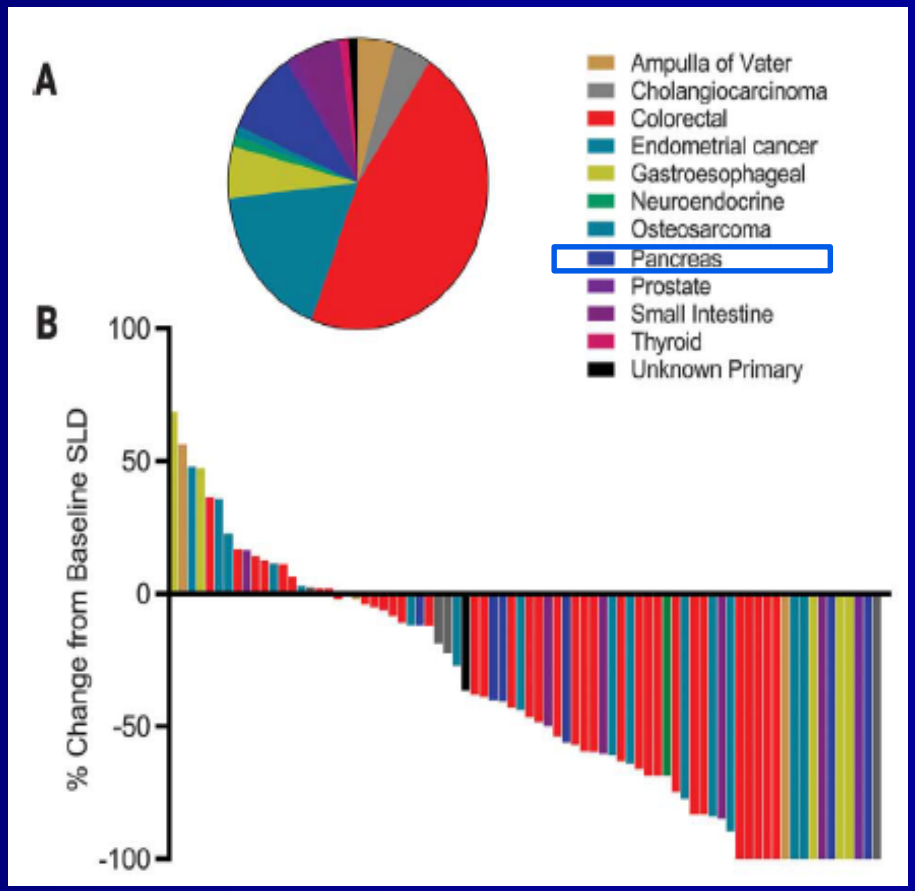
c. FOLFIRINOX

d. 5-FU/LV + nanoliposomal irinotecan

Treatment for Specific Patient Subgroups: MSI-High

- **<1%** of pancreatic cancers are associated with defective mismatch repair (dMMR/MSI-high)

- Immune checkpoint inhibitors (anti-PD1 mAbs, e.g., pembrolizumab) now approved for this indication (disease-agnostic)



Le DT et al. *Science* 2017 Jul ; 357(6349):409-413.

Olaparib maintenance following 1st -line platinum-based chemotherapy in mPC patients with a gBRCA mutation: Phase III POLO trial

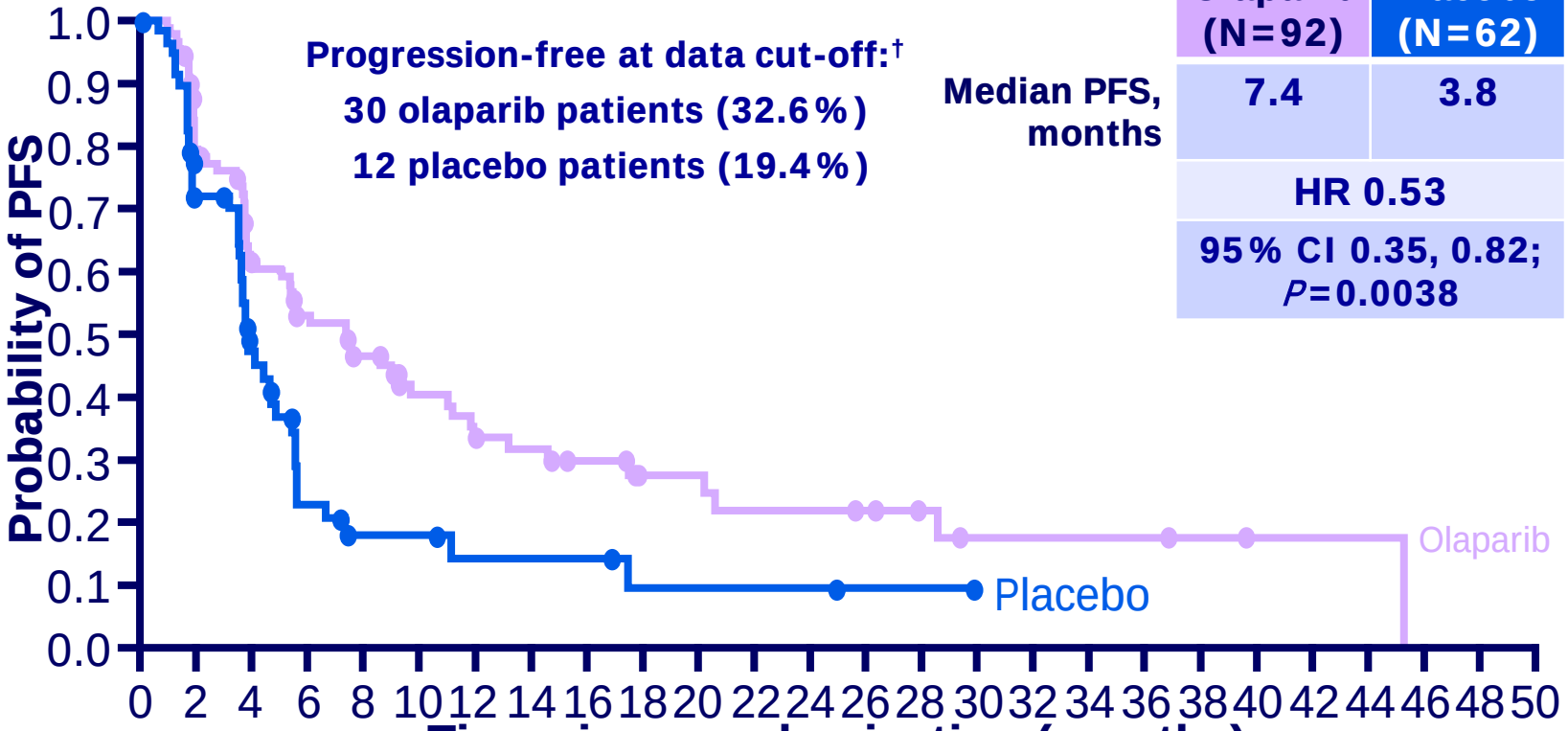
The NEW ENGLAND JOURNAL of MEDICINE

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.

Primary endpoint: PFS by blinded independent central review*



*Dots indicate censorship. †January 15, 2019. CI, confidence interval

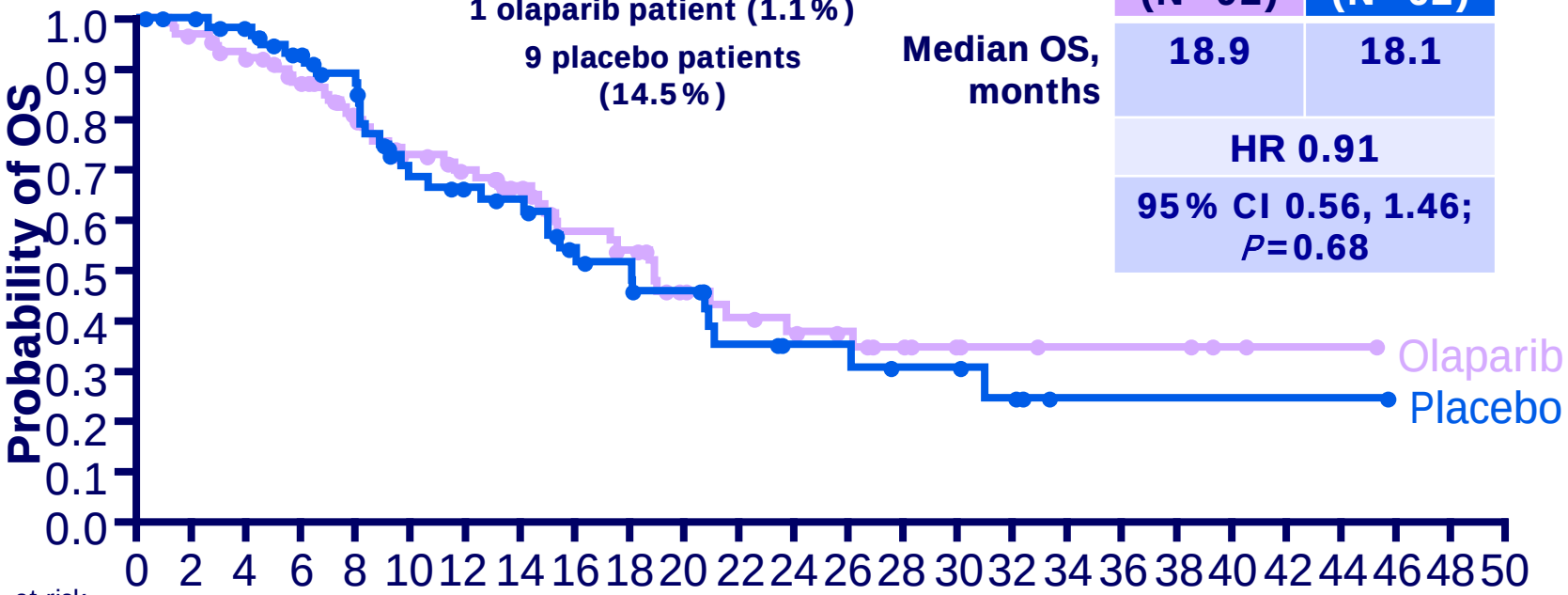
OS: interim analysis, 46% maturity*

Subsequent treatment with a PARP inhibitor:†

1 olaparib patient (1.1%)

9 placebo patients (14.5%)

	Olaparib (N=92)	Placebo (N=62)
Median OS, months	18.9	18.1
HR 0.91		
95% CI 0.56, 1.46; *P*=0.68		



No. at risk

Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

*Dots indicate censorship. †Crossover to olaparib was not permitted during this study; subsequent therapies were given at the investigators' discretion

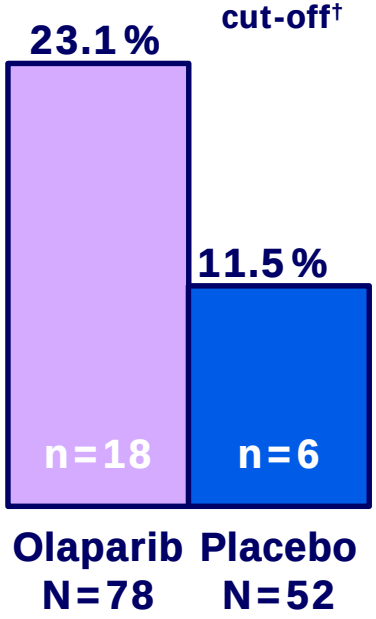
Time since randomization (months)

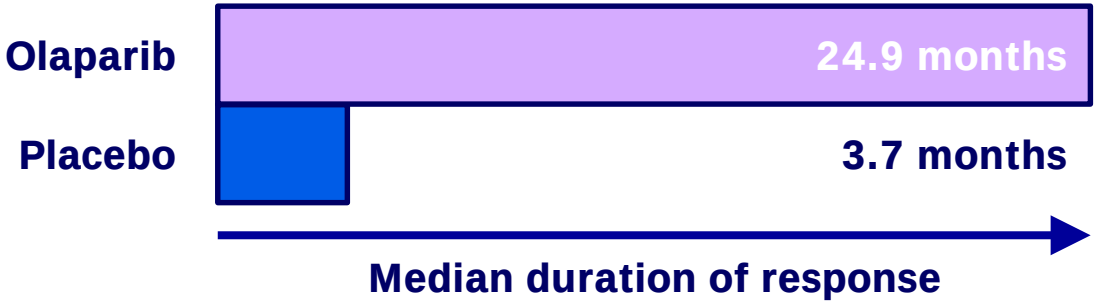
Final OS analysis planned at 106 events

Objective response* in patients with measurable disease

Two olaparib arm patients had a complete response

Both complete responses were ongoing at the data cut-off†

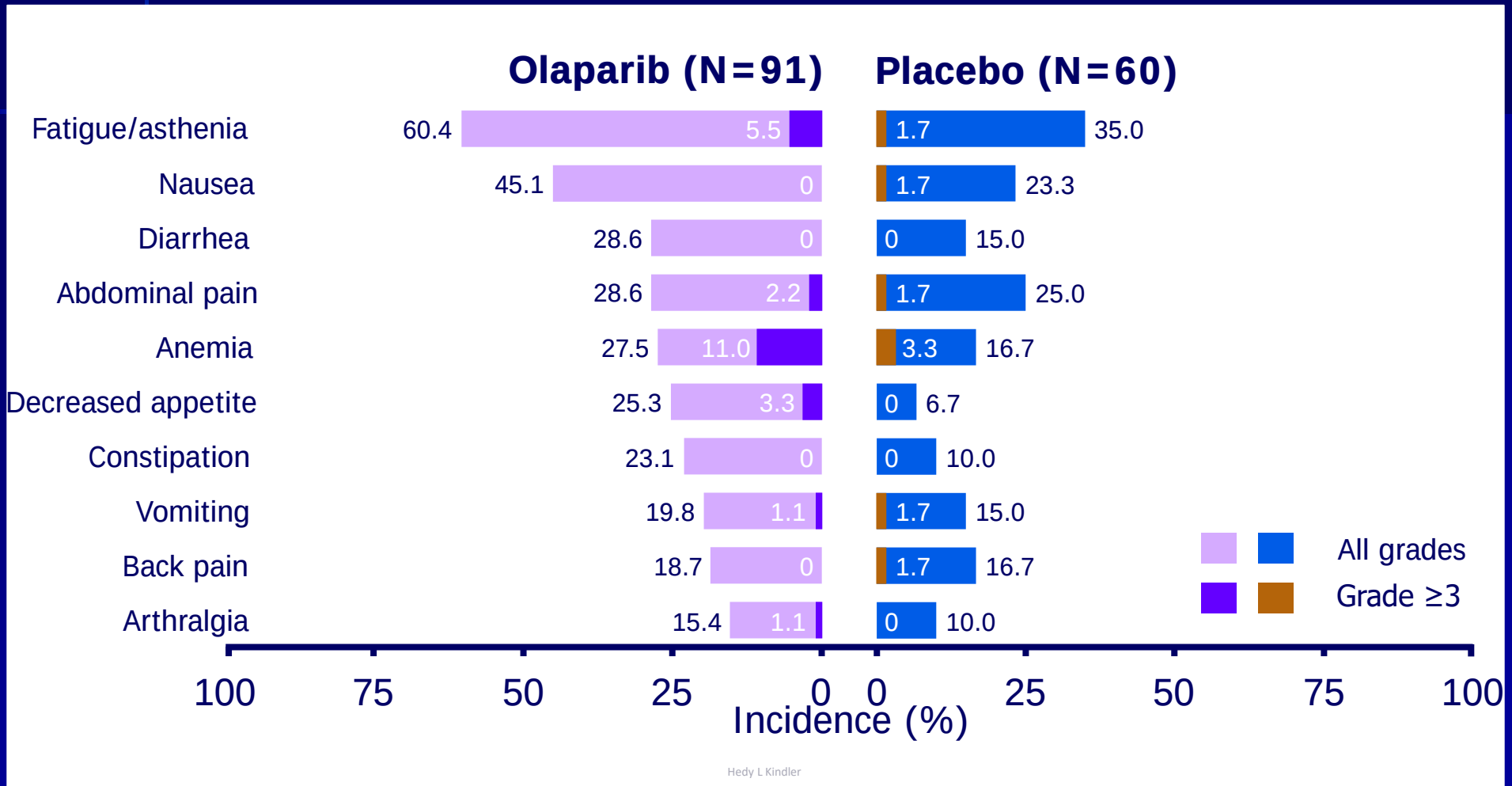




*By modified RECIST v1.1. †January 15, 2019

Hedy L Kindler

Most common AEs



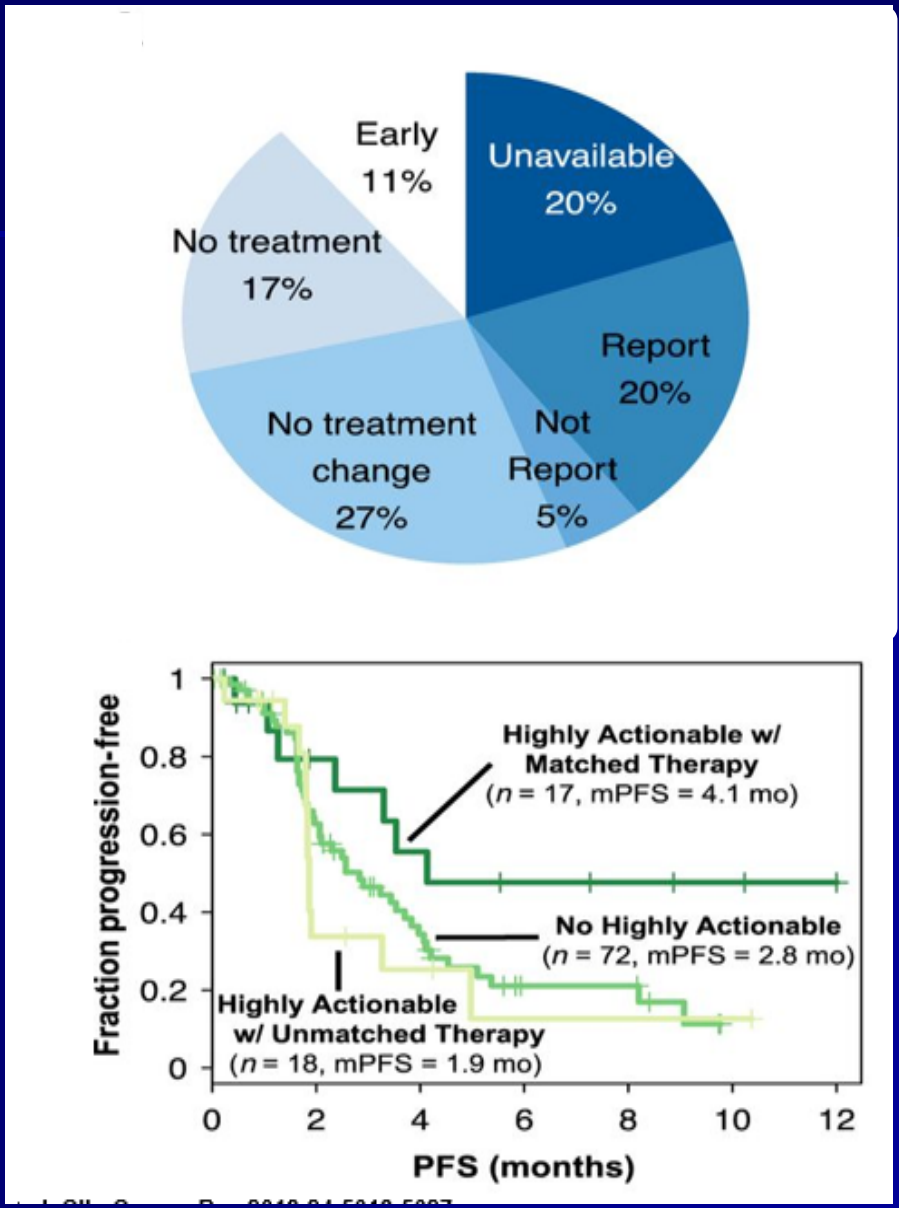
PanCan Know Your Tumor Project Genomics

N=640
had Know Your Tumor NGS

N=126
utilized a report-listed therapy

N=35 (5%)
had highly actionable mutations

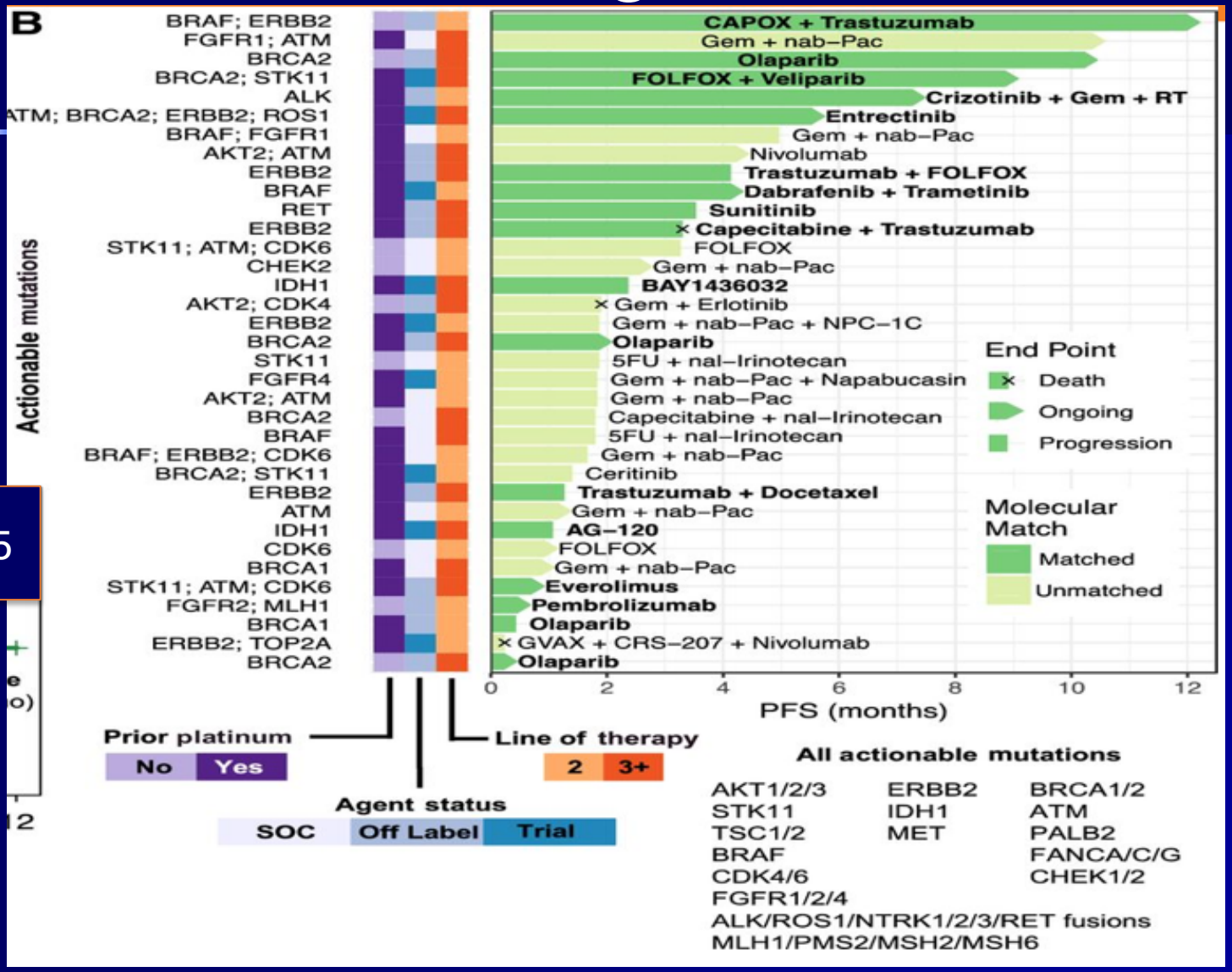
N=17 (2.6%)
utilized molecularly targeted therapies



Pishvaian MJ et al. Clin Cancer Res 2018;24:5018-5027

Outcomes in Patients with Actionable Targets

N=35



Pishvaian MJ et al. Clin Cancer Res 2018;24:5018-5027

Case 5: 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**: remains standard of care after surgery for good PS patients
- Chemotherapy alone is standard for localized unresectable PC, but CRT remains an option for select patients after 4-6 mos of induction chemo
- FOLFIRINOX and Gemcitabine-nab/paclitaxel are 1st line options for mPC
- 2nd line therapy: nanoliposomal irinotecan +5FU (~ FOLFIRI)
- Pembrolizumab for MSI-H/dMMR pancreatic cancer (<1%)
- Maintenance Olaparib for germline BRCA1/2 MUT
- Germline testing for all PC patients
- Somatic genomic testing: for LAPC and Metastatic
- Palliative Care: essential