PANCREATIC CANCER: ARE WE FINALLY MAKING PROGRESS?

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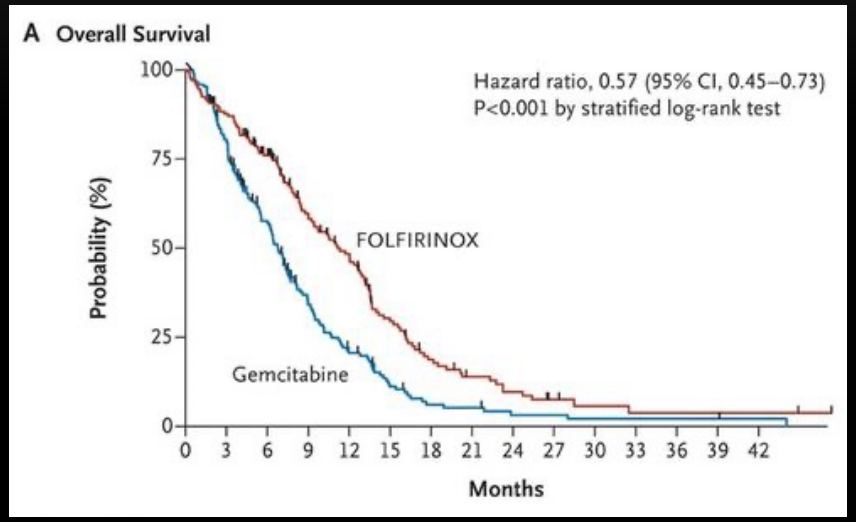
CHEMOTHERAPY REMAINS THE MAINSTAY OF TREATMENT FOR ADVANCED/METASTATIC PANCREATIC CANCER, BUT SURVIVAL REMAINS POOR



FOLFIRINOX vs gemcitabine

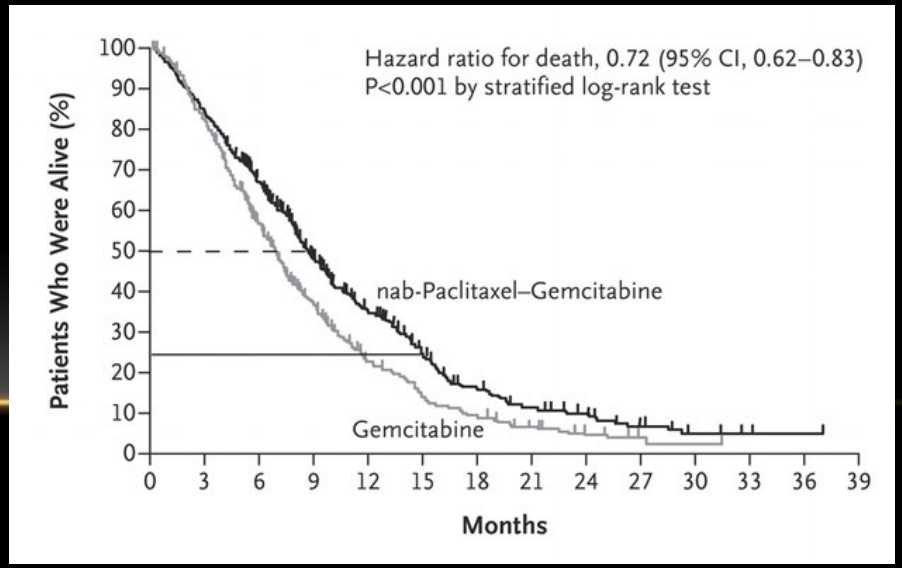
(Conroy et al, *N Eng J Med* 2011; 364:1817-25)

Median OS, 11.1 vs 6.8 months (HR 0.57)
1-year OS, 48.4% vs 20.6%

Gemcitabine/nab-paclitaxel vs gemcitabine

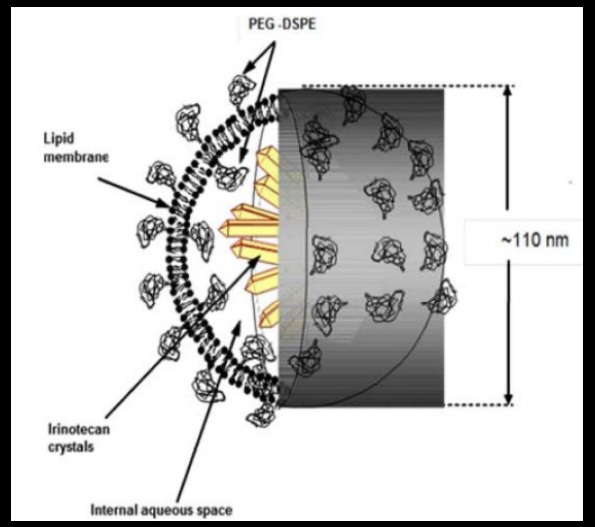
(von Hoff et al, *N Eng J Med* 2013; 369:1691-703).

Median OS, 8.5 vs 6.7 months (HR 0.72)
1-year OS, 35% vs 22%



A NEW 1L STANDARD FOR METASTATIC PANCREATIC CANCER?: THE PHASE III **NAPOLI-3** TRIAL

- **Nanoliposomal irinotecan** = currently approved for use in 2L setting (following gemcitabine-based rx)
- Prior phase I/II study defined the MTD when incorporating this agent into FOLFIRINOX regimen ("NALIRIFOX")
- Basis for international NAPOLI-3 trial



N = 770
Key inclusion criteria

- Confirmed PDAC not previously treated in the metastatic setting
- Metastatic disease diagnosed ≤6 weeks prior to screening
- RECIST measurable disease
- ECOG PS of 0 or 1

R1:1

Stratification
- ECOG PS 0/1
- Region
- Liver metastases

NALIRIFOX

Liposomal irinotecan 50 mg/m^2
+ **5-FU** 2400 mg/m^2
+ **LV** 400 mg/m^2
+ **oxaliplatin** 60 mg/m^2
Days 1 and 15 of a 28-day cycle

Gem+NabP

Gem 1000 mg/m^2
+ NabP 125 mg/m^2
Days 1, 8 and 15 of a 28-day cycle

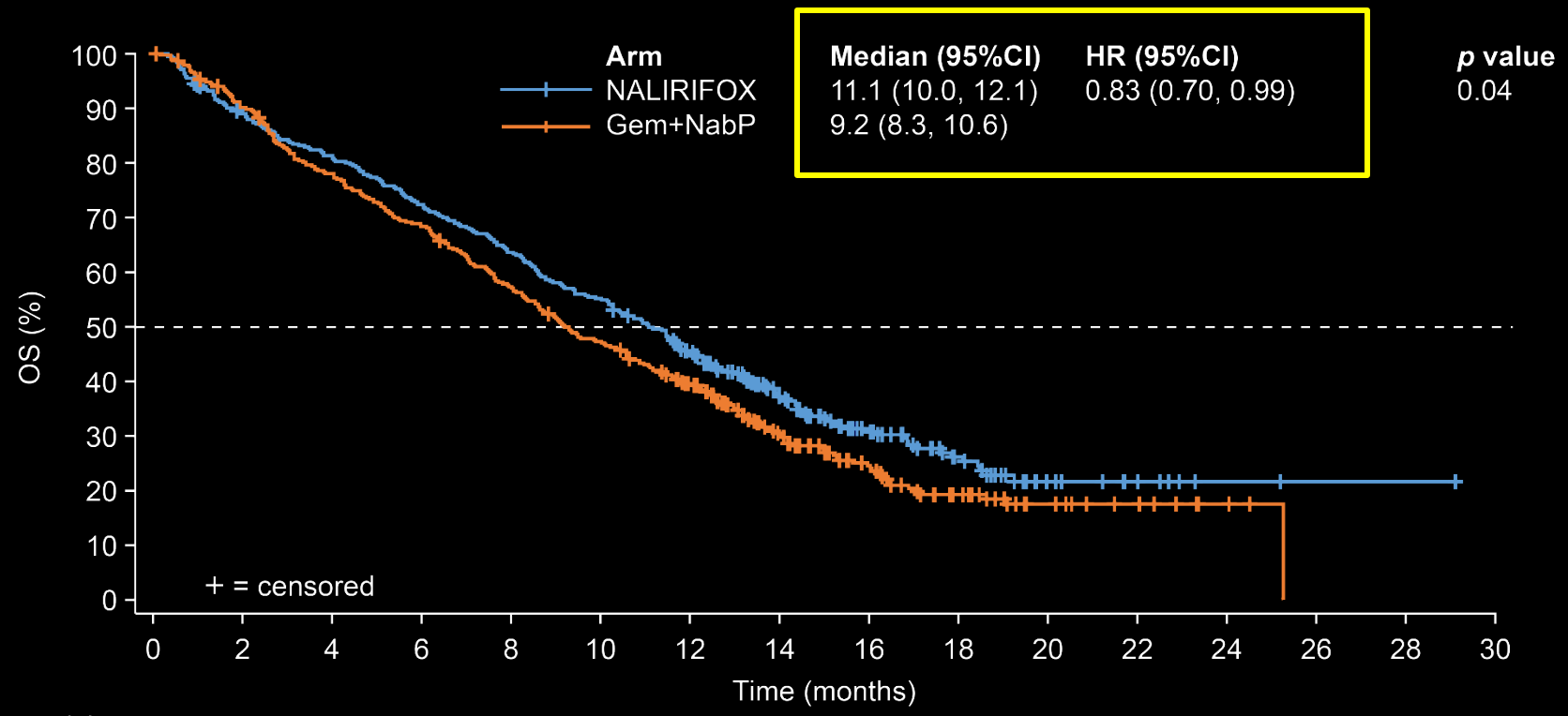
Tumor assessment every 8 weeks per RECIST v1.1[a]

Treatment until disease progression, unacceptable toxicity or study withdrawal[b]

Follow-up every 8 weeks until death or study end[c]

Wainberg et al, ASCO GI Symposium 2023, LBA 661.

NAPOLI-3: OVERALL SURVIVAL RESULTS



- **Median PFS, 7.4 vs 5.6 months (HR 0.69, p<0.0001)**
- **ORR 41.8 vs 36.2%**

Wainberg et al, ASCO GI Symposium 2023, LBA 661.

NAPOLI 3: SELECTED ANY-CAUSE TREATMENT-EMERGENT ADVERSE EVENTS IN ≥10% OF PATIENTS

Any-cause TEAEs in ≥10% of patients, %[a]	NALIRIFOX (N = 370)		Gem+NabP (N = 379)	
	Any grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Hematologic				
Neutropenia / neutrophil count decr / febrile neutropenia	29.5 / 20.5 / 2.4	14.1 / 9.7 / 2.4	31.9 / 18.7 / 2.6	24.5 / 13.5 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia / plt count decr	13.5 / 10.5	0.8 / 0.8	22.7 / 17.9	3.7 / 2.4
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy	17.8	3.2	17.4	5.8
Peripheral sensory neuropathy	15.1	3.5	13.5	2.9
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

Wainberg et al, ASCO GI Symposium 2023, LBA 661.

NAPOLI-3: IMPLICATIONS FOR PRACTICE AND FUTURE CLINICAL TRIAL DESIGN?

- Finally provides level 1 evidence, in a head-to-head comparison, that a triplet regimen is significantly better than doublet for the 1L treatment of metastatic pancreatic cancer
- But –
  - How excited should we be about a HR for OS of 0.83?
  - And, does NALIRIFOX represent a substantial advance over FOLFIRINOX?

	NALIRIFOX (n=370)	**FOLFIRINOX (n=171)**
Median OS	**11.1 months**	**11.1 months**
1-yr OS	NR (approx. the same)	48.4%
Median PFS	7.4 months	6.4 months
ORR	41.8%	31.6 %
Grade 3/4 AEs	Neutropenia 23.8% / F&N 2.4% Diarrhea 20.3%, PSN (3.2 + 3.5% + 0.3%)	Neutropenia 45.7% / F&N 5.4% Diarrhea 12.7%, PSN 9.0%

HOW MUCH "PRECISION ONCOLOGY" DO WE PRACTICE IN PANCREATIC CANCER TREATMENT?

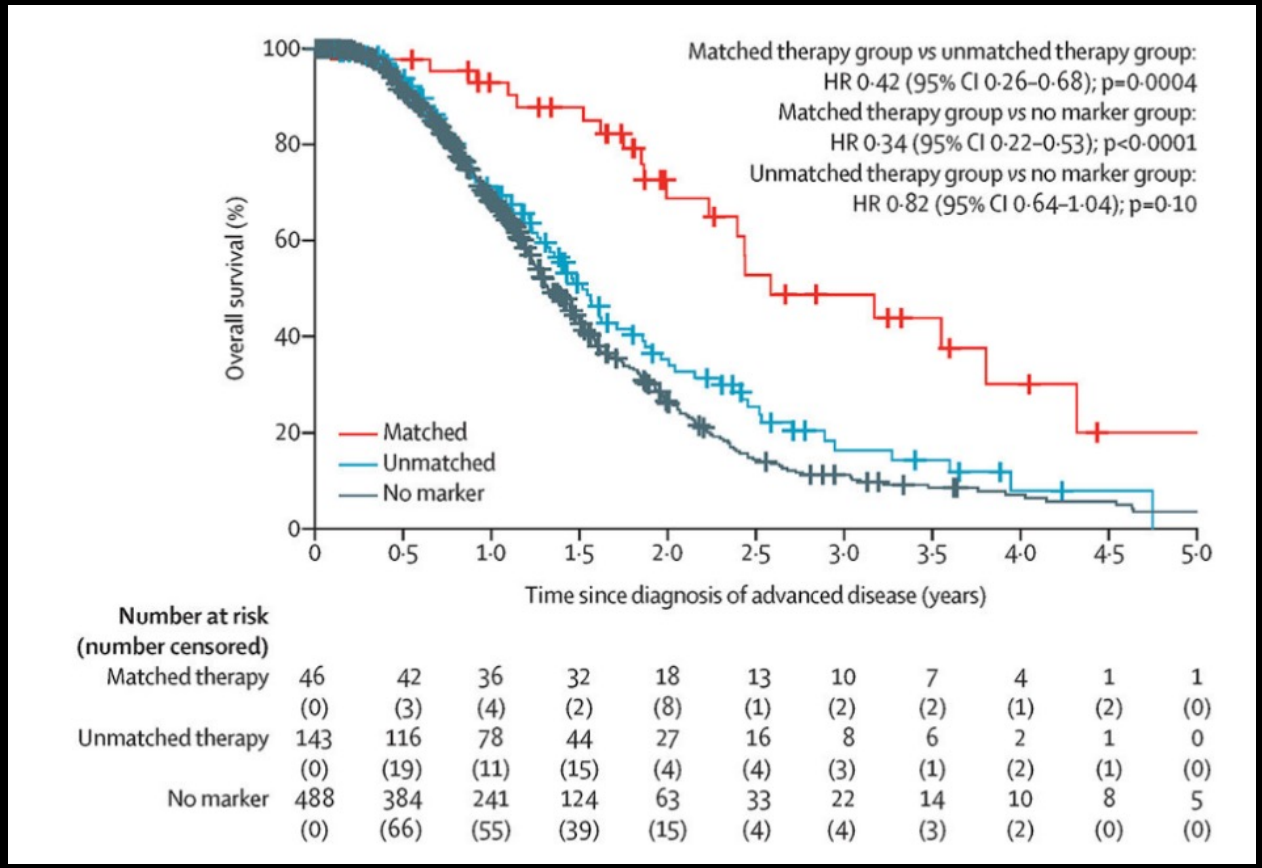
- National guidelines now recommend germline (inherited gene) testing for ALL patients diagnosed with pancreatic cancer, regardless of family history
  - JHH cohort: 3.9% of patients found to have pathogenic germline mutation, inc many apparently 'sporadic cases' w/o provocative FHx

- Somatic (tumor tissue) should be considered for *all* patients with locally advanced or metastatic pancreatic cancer who are candidates for treatment
  - Challenge: pancreatic tumor samples often lack adequate cellularity for full NGS testing

Shindo et al, *J Clin Oncol* 2017; 25:3382-90.

KNOW YOUR TUMOR: MATCHED THERAPY *CAN* IMPROVE SURVIVAL

- **1028 pancreatic cancer patients: all underwent molecular profiling with NGS**
  - 677 patients with outcome information
    - 189 with actionable findings
    - 46 received molecularly matched therapy
    - 143 received "unmatched" therapy
  - 488 with no actionable findings
- **Overall survival**
  - **Matched 1 y > unmatched**
  - **Matched 1.3 y > no actionable marker**



Pishvaian M, et al. *Lancet Oncol*. 2020; 21:508.

THE PROBLEM IN PANCREATIC CANCER

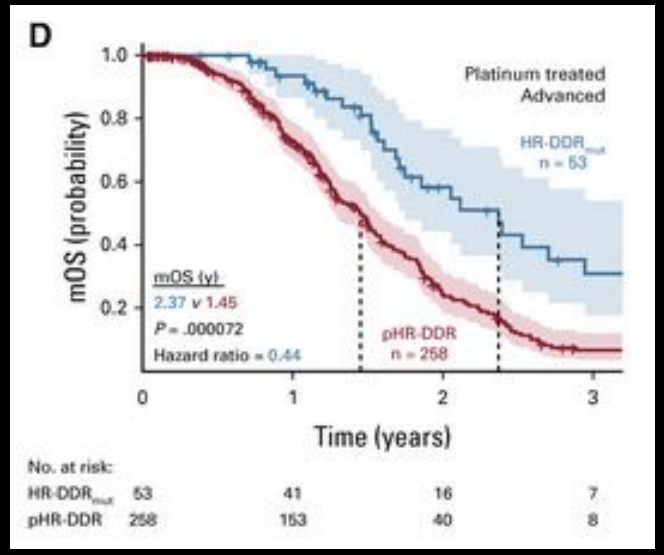
- The therapeutic “actionability” of many putative predictive biomarkers is… questionable
- The presence of biomarkers with true (and robust) clinical actionability are uncommon, sometimes exceedingly rare
  - *For clinical trial design, this presents the usual “screen 50 to identify 1 eligible patient” dilemma!*
- Pancreatic cancer patients oftentimes cannot afford to wait very long for readouts

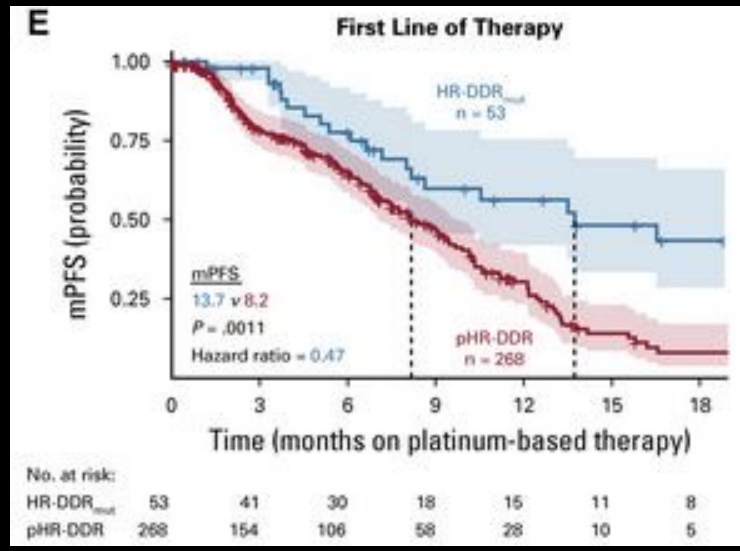
MOST "ACTIONABLE" FINDING IN PANCREATIC CANCER: **HRD** (HOMOLOGOUS RECOMBINATION DEFICIENCY)-ASSOCIATED

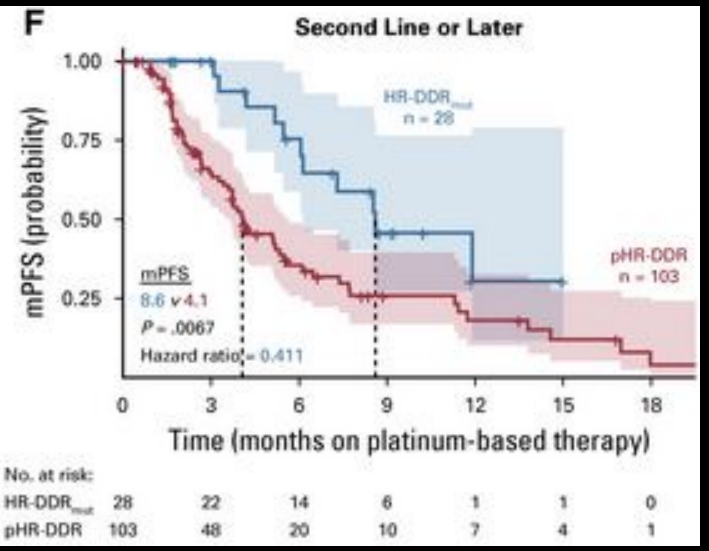
- Core HRD-assoc genes (BRCA1/2, PALB2) vs other (ATM/ATR, RAD51, CHEK2, etc)
- Present in ~10-15% of all pancreatic cancers
- Therapeutic relevance re:
  - Sensitivity to platinum analogues
  - Application of PARP inhibitors
- Intense interest in developing clinical trials specifically for this subgroup

MULTIPLE LINES OF EVIDENCE SUPPORT **PLATINUM-BASED** THERAPIES IN PATIENTS WITH HR-DEFICIENT PDAC (IMPROVED ORR, PFS, AND/OR OS)

HR-DDR Deficient v HR-DDR Proficient







OS

PFS (1L and 2L+)

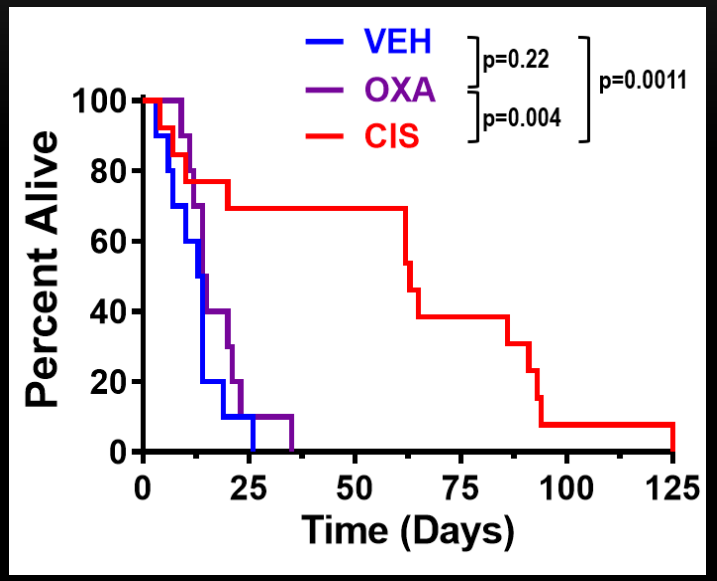
HRD = pathogenic mutations of somatic or germline origin in BRCA1/2 or PALB2 (group 1); ATM/ATR/ATRX (group 2); or BAP1, BARD1, BRIP1, CHEK1/2, RAD50/51/51B, or FANCA/C/D2/E/F/G/L

Golan et *al*, Br J Cancer 2014; **Pishvaian et *al*. JCO Precision Onc 2019**; Wattenberg et *al*., Br J Cancer 2020; Park et *al*. Clin Cancer Res 2020

ANY DIFFERENCES BETWEEN CISPLATIN AND OXALIPLATIN?

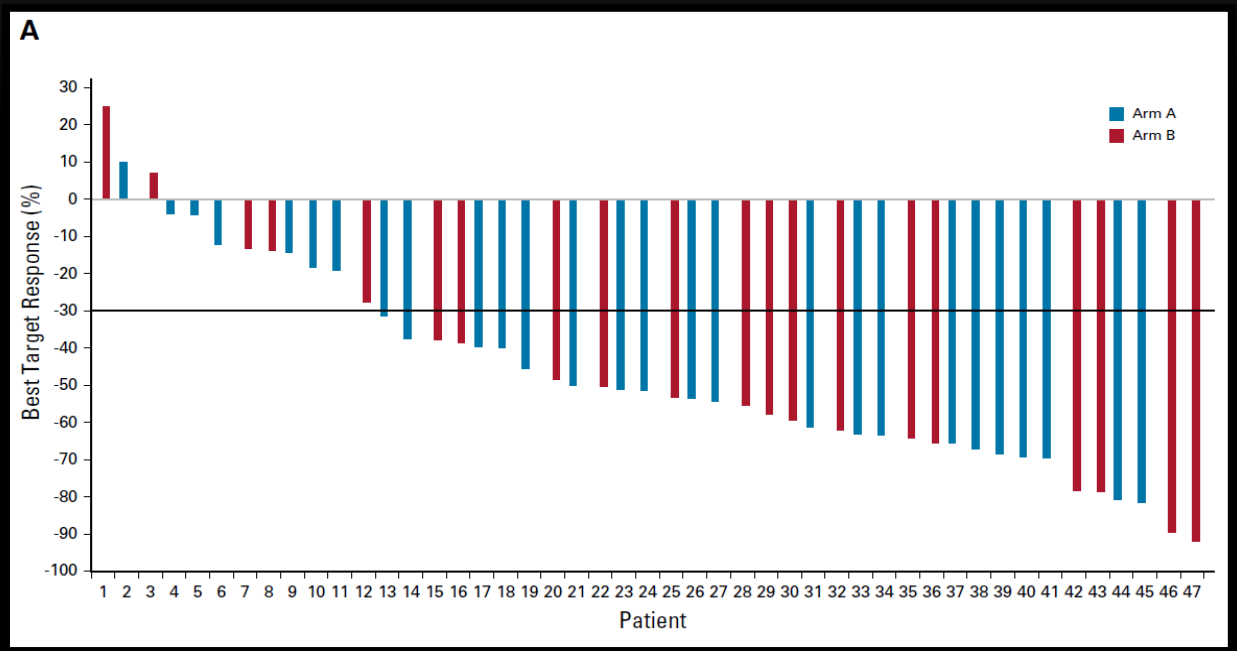
- BRCA null KPC mice: Response to cisplatin monotherapy >> oxaliplatin (even at double the molar dose as cisplatin) (Ken Olive, Columbia Univ, personal correspondence)
  - Molecular mechanism of cisplatin: induction of tumor-cell specific endoreplication specifically in *Brca2* null pancreatic tumor cells → giant cell formation and mitotic catastrophe (not observed with oxaliplatin)

- Other observed differences in drug mechanism between different platinum analogues (Bruno, *Nat Medicine* 2017)
  - Cisplatin, carboplatin: DNA-damage response
  - Oxaliplatin: induction of ribosome biogenesis stress



Preclinical effects of platinum analogs in a PDAC mouse model. Survival plot of $Kras^{LSL.G12D/+}$; $p53^{R27H/+}$; $Pdx1Cre^{tg/+}$; $Brca2^{Fl/Fl}$ mice following enrollment with 6-9mm diameter autochthonous tumors and treatment with vehicle (VEH), oxaliplatin (OXA), or cisplatin (CIS). Kaplan-Meyer survival statistic shown for each comparison. (Courtesy of K. Olive)

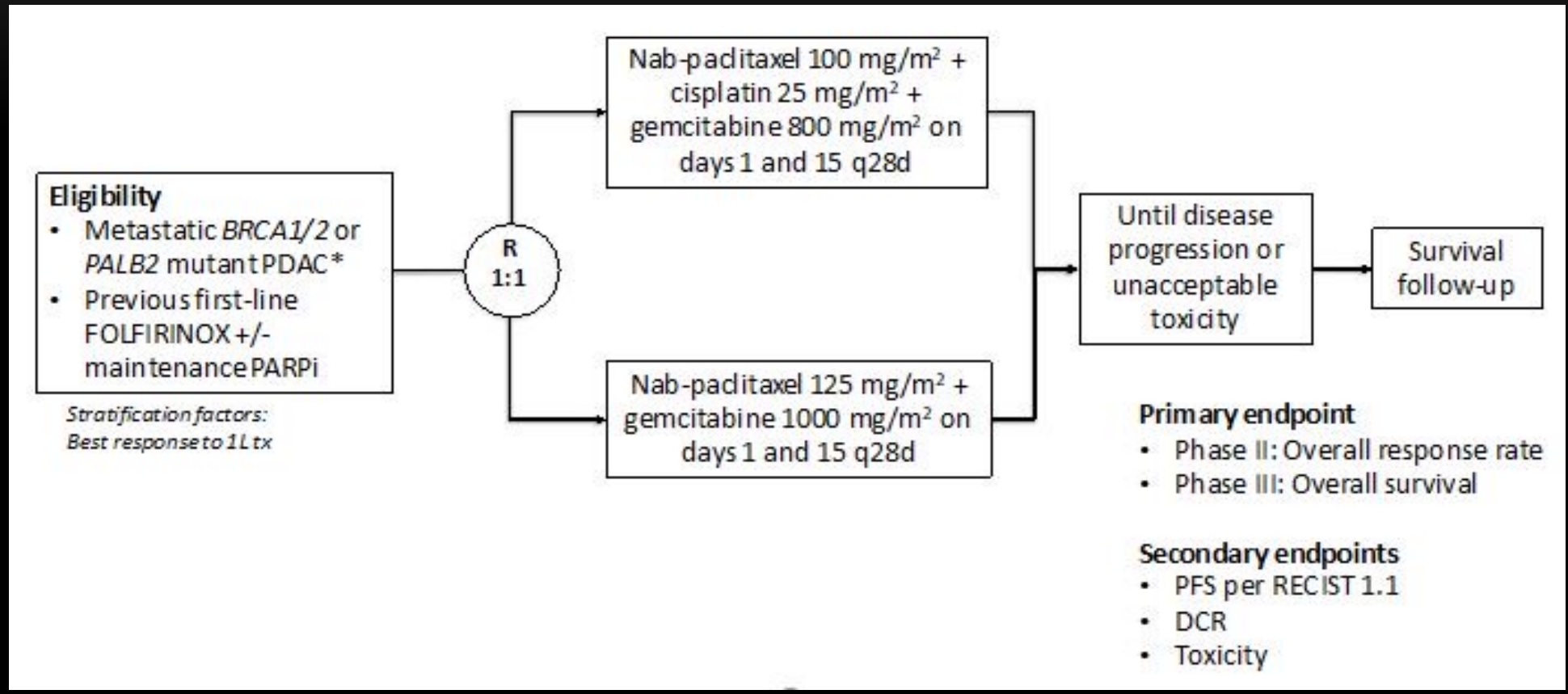
RANDOMIZED PHASE II TRIAL OF GEMCITABINE/CISPLATIN +/- VELIPARIB IN PDAC PATIENTS WITH g*BRCA/PALB2* MUTATION



	Arm A (gem/cisplat + PARPi)	Arm B (gem/cisplat)
ORR	**74.1%**	**65.2%**
PFS	10.1 months	9.7 months
OS	15.5 months	16.4 months

O'Reilly et *al*. *J Clin Oncol* 2020;38:1378-88.

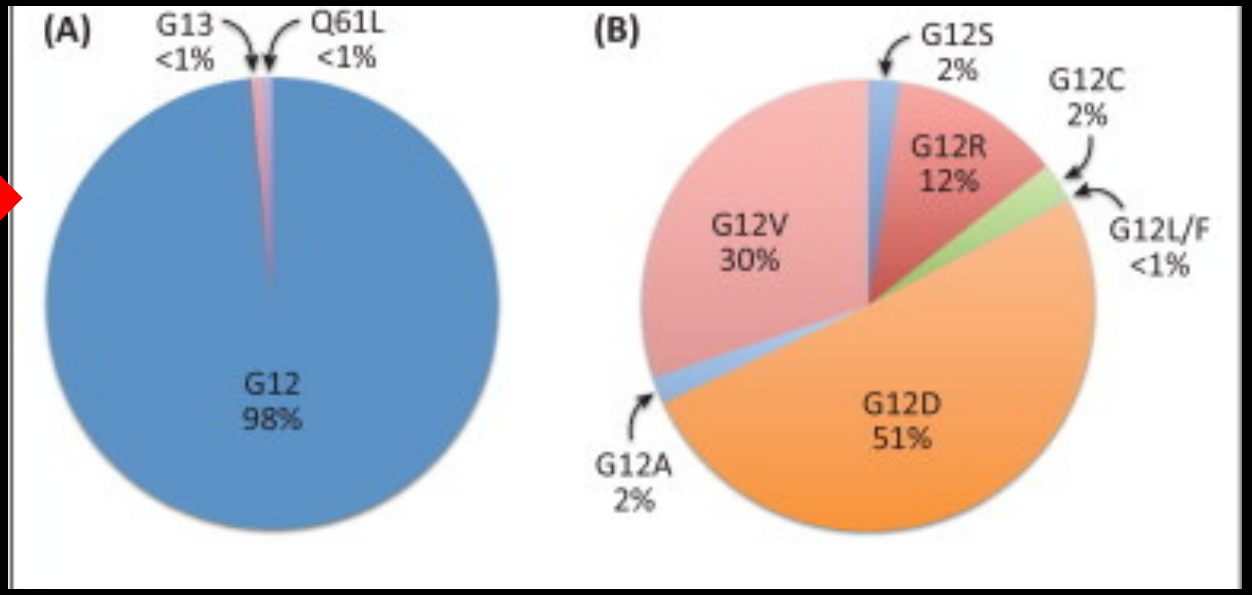
PHASE II/III SECOND-LINE NABPLAGEM VS. NAB-PACLITAXEL/GEMCITABINE IN HR-DEFICIENT PDAC



Current Alliance concept (under review at NCI)
P.I.s, A.Ko and E. Tsang

KRAS AND OTHER COMMON MUTATIONS IN PANCREATIC CANCER

Gene	Frequency
KRAS	70%–95%
TP53	20%–76%
CDKN2A	49%–98%
SMAD4	19%–50%

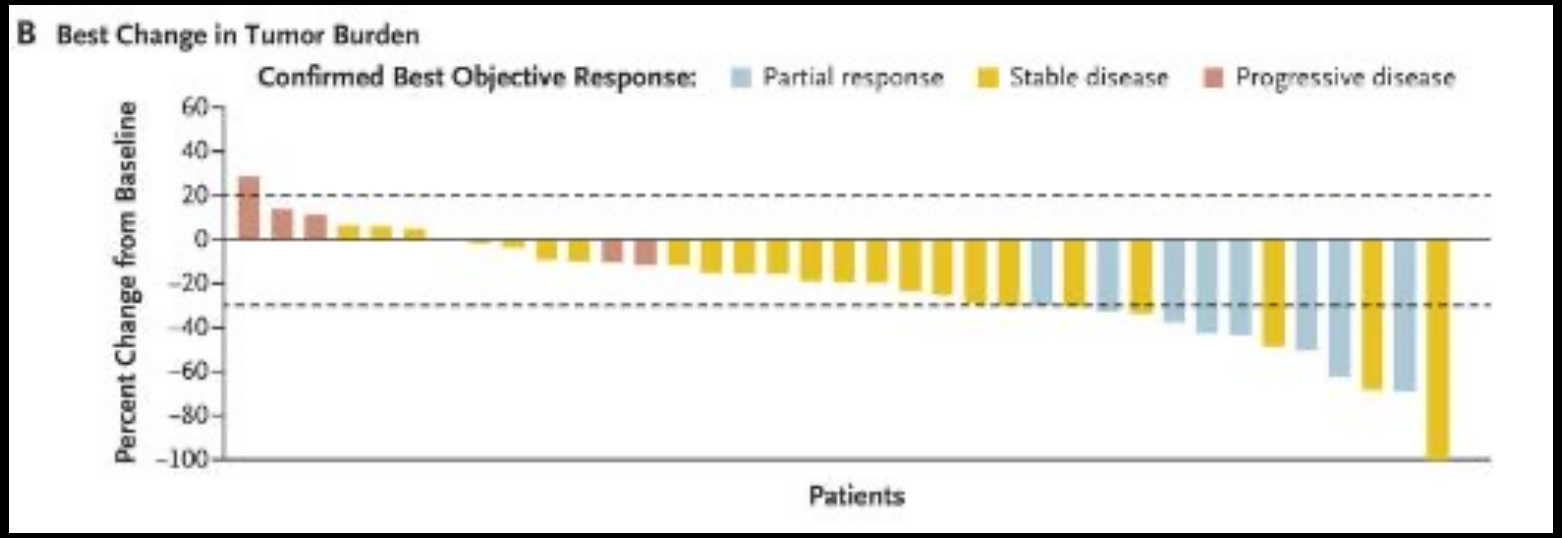


Bryant et al, *Trends in Biochem Sci* 2014, 39:91-100.
Cicenas et al, *Cancers* (Basel) 2017 Apr 28;9(5).

Example #1: DIRECT KRAS G12C INHIBITORS

Incidence in PDAC ~2%

Phase I/II TRIAL OF SOTARASIB (n=38)



- ORR 21% (8/38), DCR 84%
- Median PFS: 4.0 months, Median OS: 6.9 months (95% CI: 5.0, 9.1)
- Common AEs: diarrhea and fatigue

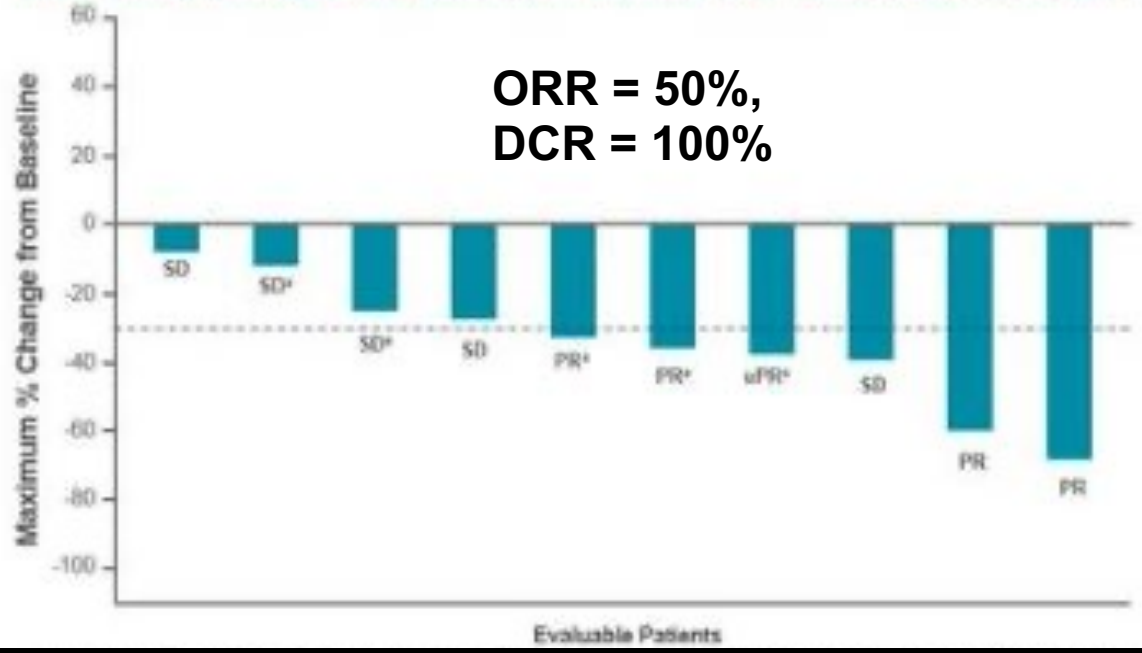
Strickler JH, et al. N Eng J Med. 2023;388:33-43.

Example #1: DIRECT KRAS G12C INHIBITORS

Incidence in PDAC ~2%

Phase I/II KRYSTAL-1 TRIAL of ADAGRASIB (n=10)

Best Tumor Change From Baseline in Patients With Pancreatic Cancer (n=10)



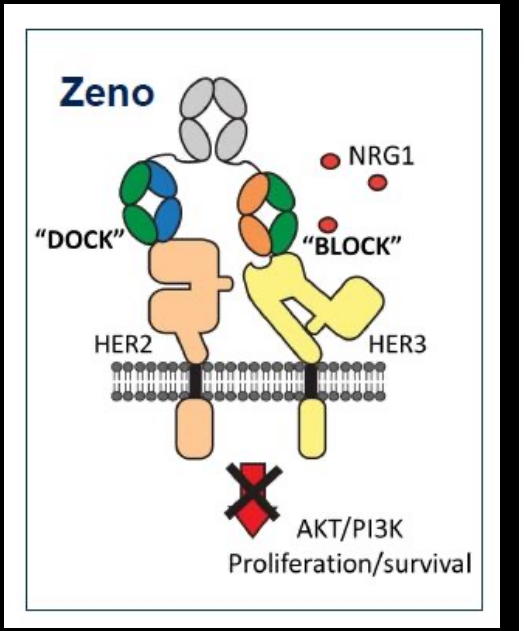
Selected Patient Demographics

	Pancreatic Cancer (n=12)
Median age, y (range)	67 (40-80)
Female, n (%)	4 (33%)
ECOG PS, n (%)	
0	0 (0%)
1	12 (100%)
Prior lines of systemic therapy, median (range)	3 (1-4)
Prior lines of systemic therapy, %	
1	8%
2	42%
3	33%
≥4	17%

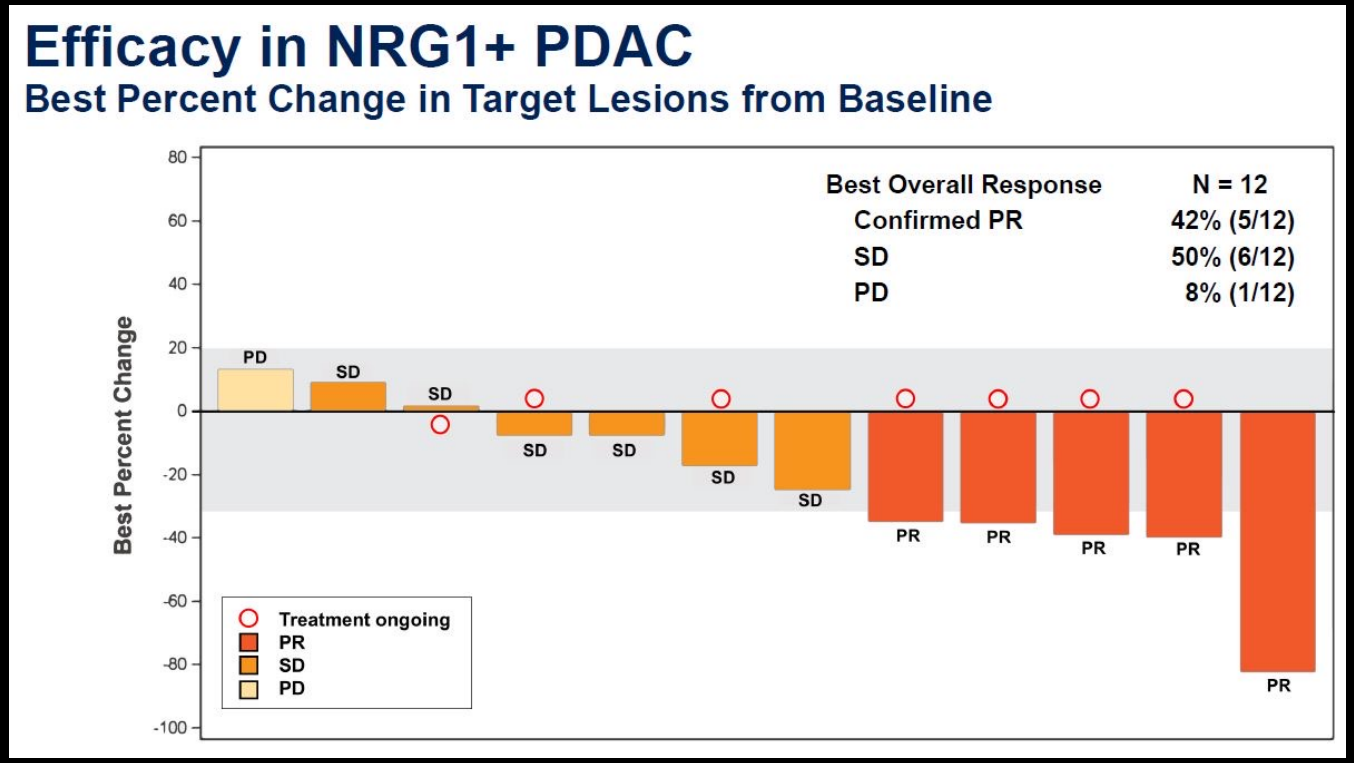
Bekaii-Saab et al, ASCO Gastrointestinal Cancers Symposium, abstract 519.

Example #2: TARGETING NRG-1 FUSIONS: ZENOCUTUZUMAB

Incidence in pancreatic cancer ~0.5%



Bispecific HER2-HER3 Antibody – blocks NRG1 Interaction with HER3



Schram et al, *J Clin Oncol* 2021, 39, no. 15_suppl, abstr 3003.

Example #3: IMMUNE CHECKPOINT INHIBITION FOR MSI-HIGH SUBGROUP

Incidence in pancreatic cancer ~1%

Tumor Type	CR/PR, n	ORR, %	Median PFS, mo	Median OS, mo	Median DOR, mo
Endometrial (n = 49)	8/20	57.1	25.7	NR	NR
Gastric (n = 24)	4/7	45.8	11.0	NR	NR
Cholangiocarcinoma (n = 22)	2/7	40.9	4.2	24.3	NR
Pancreatic (n = 22)	**1/3**	**18.2**	**2.1**	**4.0**	**13.4**
Small intestine (n = 19)	3/5	42.1	9.2	NR	NR
Ovarian (n = 15)	3/2	33.3	2.3	NR	NR
Brain (n = 13)	0/0	0	1.1	5.6	--

KEYNOTE-158: Pembrolizumab in MSI-H or dMMR Solid Tumors (Noncolorectal)

Hu et al, *Clin Cancer Res*. 2018; 24(6):1326-1336.
Marabelle et al, *J Clin Oncol*. 2020 Jan 1;38(1):1-10

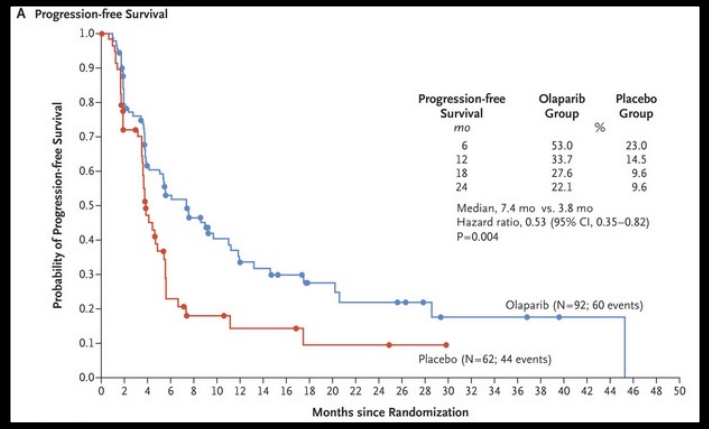
INCREASED CLINICAL OPPORTUNITIES IN THE "MAINTENANCE" SETTING

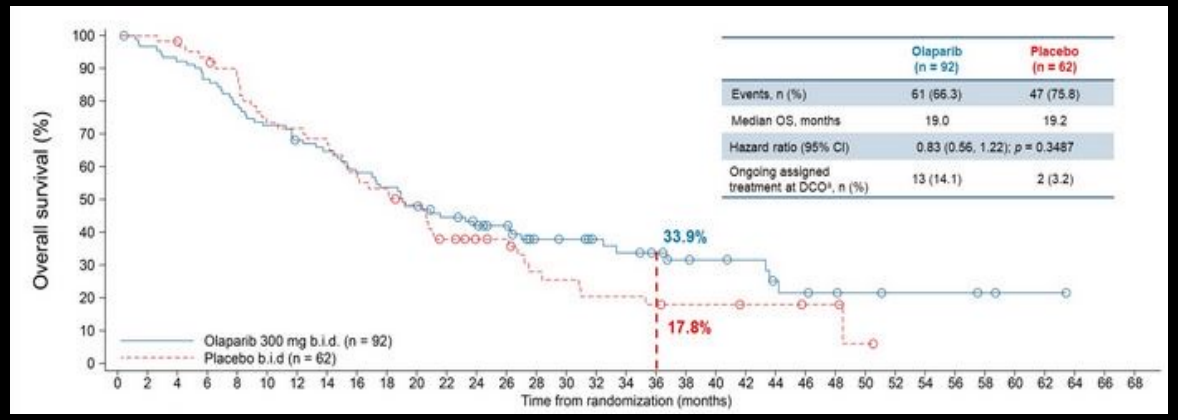
- In current era of more effective systemic regimens, patients with advanced disease may reach dose-limiting cumulative toxicities and/or a plateau in response rather than demonstrating disease progression… what comes next?

- Key considerations for maintenance rx:
  - Well-tolerated/minimal cumulative side fx
  - Convenience and ease of administration

MAINTENANCE PARP INHIBITION FOR gBRCA-ASSOCIATED PDAC: POLO-1 TRIAL

3315 patients screened to identify 154 eligible patients





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

Time to first subseq rx:
9.0 vs 5.4 mos (HR 0.44, p<0.001)

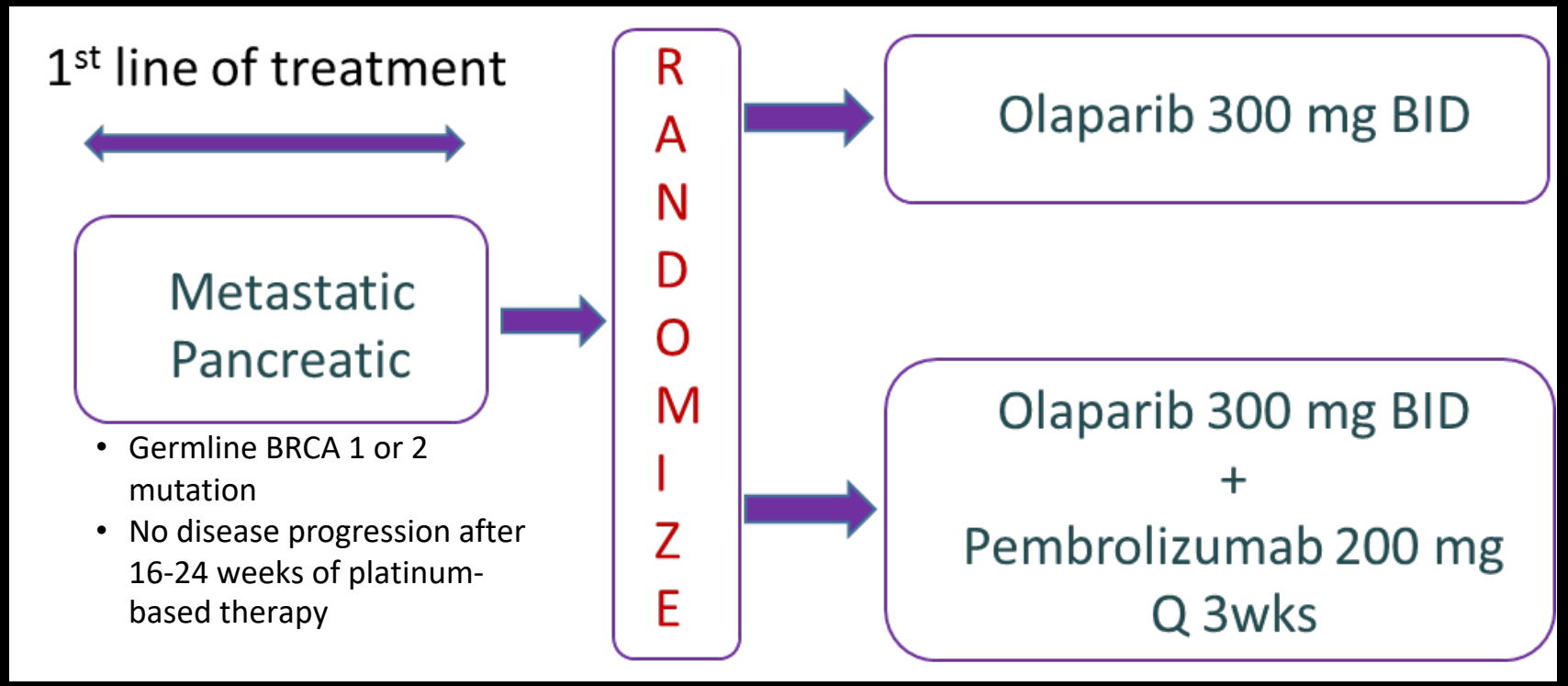
Median OS: 19.0 vs 19.2 months
HR: 0.83 (*P* = 0.35)

2-yr survival rate: 37% vs 27%

Golan et al. *N Engl J Med* 2019;381(4):317-327.
Golan et al. *J Clin Oncol* 39, no. 3_suppl (January 20, 2021) 378.

ROLE FOR COMBINING PARP PLUS IMMUNE CHECKPOINT INHIBITION?

SWOG S2001: Randomized Phase II Clinical Trial of Olaparib +/- Pembrolizumab vs. Olaparib as Maintenance Therapy in gBRCA-assoc Metastatic Pancreatic Cancer

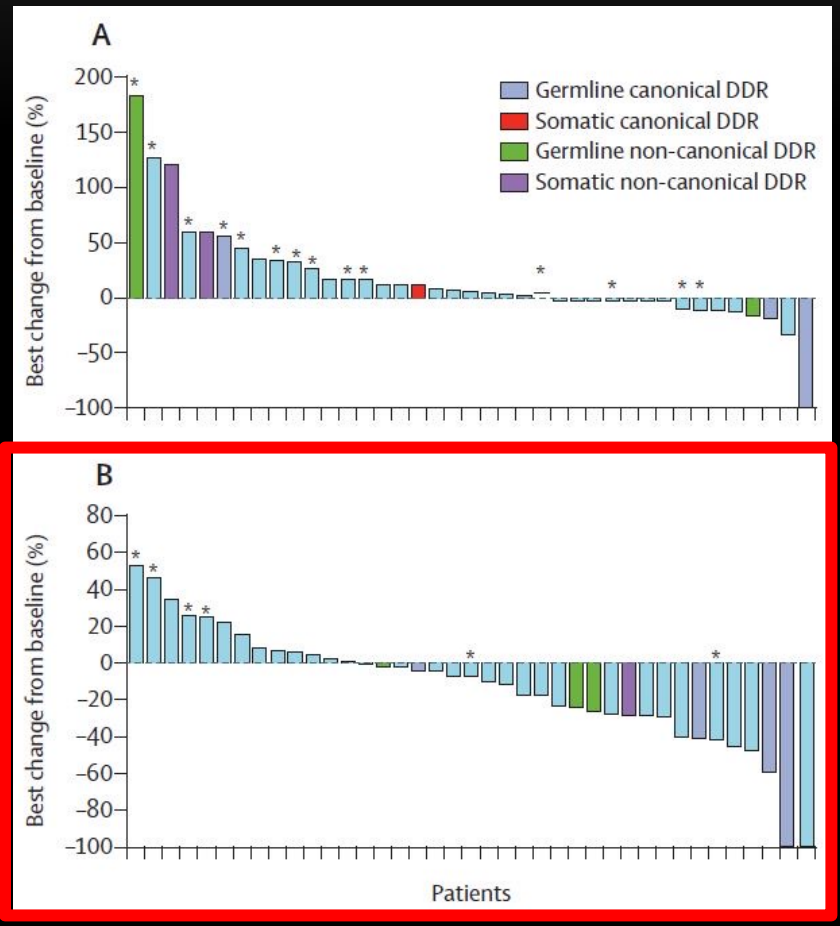


Clinicaltrials.gov NCT04548752.

PARP + CTLA-4 INHIBITION IN THE MAINTENANCE SETTING

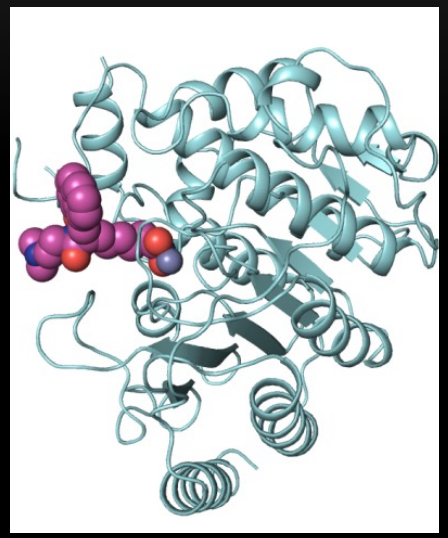
	Primary efficacy population			
	6-month progression-free survival	Objective response rate*	Median progression-free survival, months	Median overall survival, months
Niraparib plus nivolumab				
Patients	44	39	44	44
Outcome	20·6% (8·3–32·9); p=0·0002 *vs* 44%	7·7% (1·5–19·5)	1·9 (1·4–2·3)	13·2 (8·1–16·7)
Niraparib plus ipilimumab				
Patients	40	39	40	40
Outcome	59·6% (44·3–74·9); p=0·045 *vs* 44%	15·4% (5·9–30·5)	8·1 (5·5–10·6)	17·3 (12·8–21·9)

74% of subjects with no known HRD mutation



Reiss et al, *Lancet Oncol* 2022; 23:1009-20.

A PHASE IB/II RANDOMIZED STUDY OF CAPECITABINE +/- IVALTINOSTAT AS MAINTENANCE RX POST-FOLFIRINOX



Ivaltinostat

- Pan-HDAC inhibitor
- Antitumor activity when combined with capecitabine in syngeneic PDAC mouse models

Met PDAC (n=52)

- Stable or responding disease after 16+ weeks of 1L FOLFIRINOX
- No known gBRCA/PALB2 mutation

1:1 randomization

Capecitabine	Ivaltinostat (RP2D days 1,8 q21 days) plus Capecitabine
1,000 mg/m2 BID Days 1-14 q21 days	

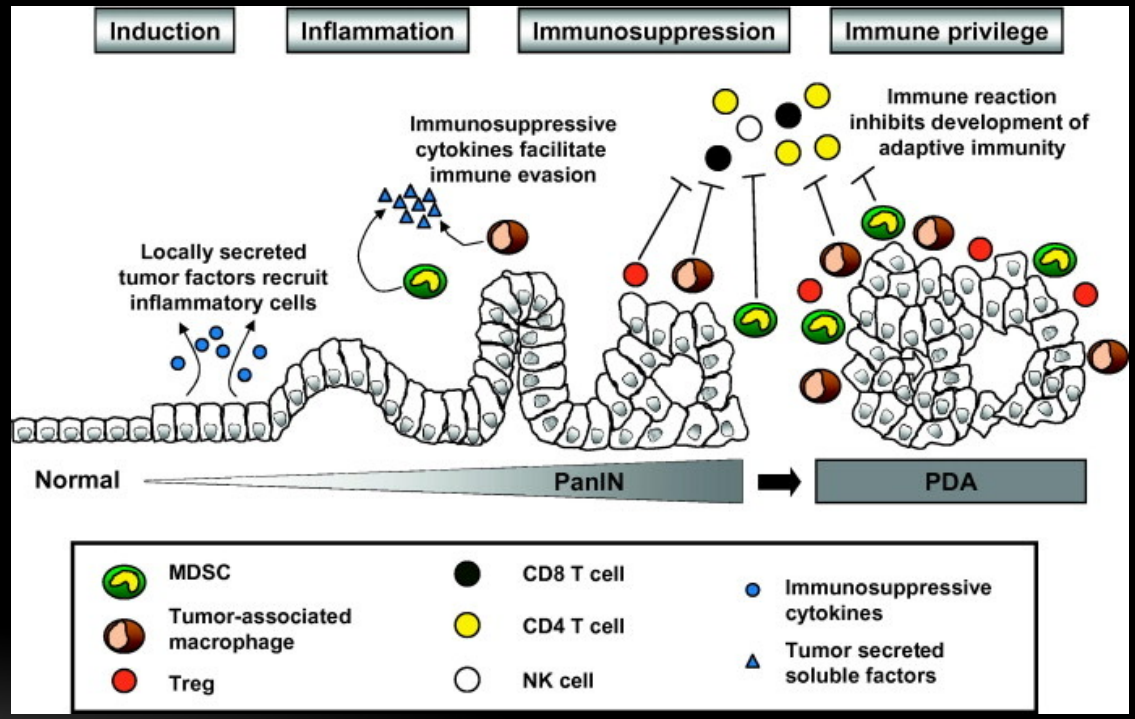
1o = PFS (investigator-adjudicated)

Walker and Ko, *J Clin Oncol* 2022; 40:TPS4181.
Clinicaltrials.gov NCT05249101

CAN IMMUNOTHERAPY TRANSFORM PANCREATIC CANCER IN THE SAME WAY IT HAS OTHER MALIGNANCIES?

WHY IMMUNOTHERAPY HAS LIMITED EFFICACY IN PANCREATIC CANCER

- Genetically engineered mouse models: pancreatic cancer development a/w progressive infiltration of leukocytes dominated by immune-suppressive cells that suppress the development of an adaptive immune response
  - *Tumor-associated macrophages (TAMs)*
  - *Myeloid-derived suppressor cells (MDSCs)*
  - *Regulatory T cells (Tregs)*
- Conversely, striking **paucity** of activated cytotoxic (effector) CD8+ T cells or NK cells
- Also on the lower end of the mutational burden spectrum compared to other solid tumors



Clark, *Cancer Res* 2007;67:9518-27

IMMUNOTHERAPIES CURRENTLY UNDER INVESTIGATION IN PANCREATIC CANCER

Category	Description/Examples
Immune checkpoint inhibitors	• Anti-PD-1 / PD-L1 and CTLA-4 mAbs
CD40 agonist mAbs	• Selicrelumab, APX-005M
CCR2 and CXCR4 antagonists	• PF-04136309, CCX872; BL-8040
CSF-1R antagonists	• Cabiralizumab, emactuzumab
Vaccines	• Adenovirus, dendritic cell, peptide-based vaccines (vs KRAS, multiple other antigens)
CAR-T cell therapy	• Targets: CEA, mesothelin

PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

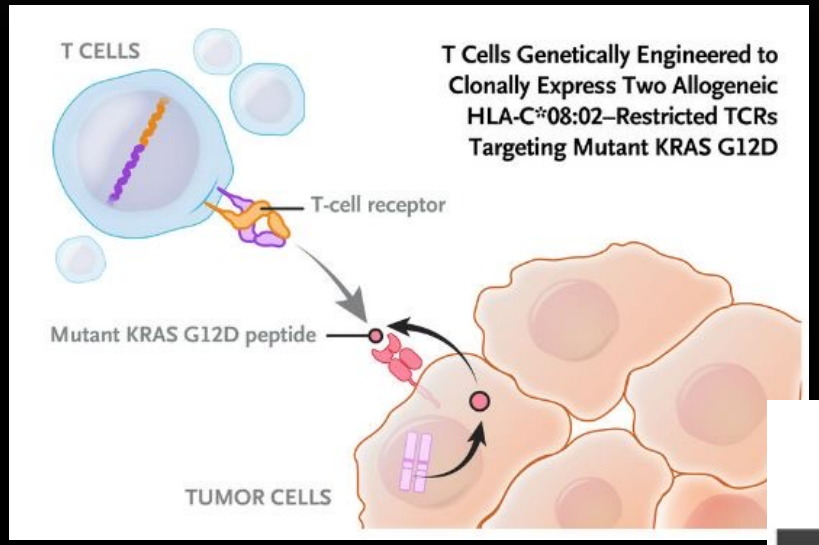
- Participating sites: Penn, MSKCC, Farber, UCSF, UCLA, MD Anderson, Stanford
- Focus: Evaluation of multiple novel chemotherapy + immunotherapy regimens
- Extensive tissue- and blood-based biomarker and immune analyses
- Initial study: Randomized phase Ib/II **PRINCE** trial
  - Gemcitabine/nab-paclitaxel + nivolumab +/- sotigalimab (agnostic CD40 mAb) (O'Hara et al, *Lancet Oncol* 2021; Padron et al, *Nat Med* 2022)
- Ongoing study: **REVOLUTION** platform trial design
  - Gemcitabine/nab-paclitaxel in combination with:
    - Cohort A: chemo + ipiliumumab/nivolumab
    - Cohort B: chemo + ipilimumab/hydroxychloroquine
    - Cohort C: chemo + ipilimumab/NG-350A (oncolytic CD-40 mAb-expressing adenoviral vector)
    - …more arms planned!

Clinicaltrials.gov NCT04787991.

RESEARCH SUMMARY

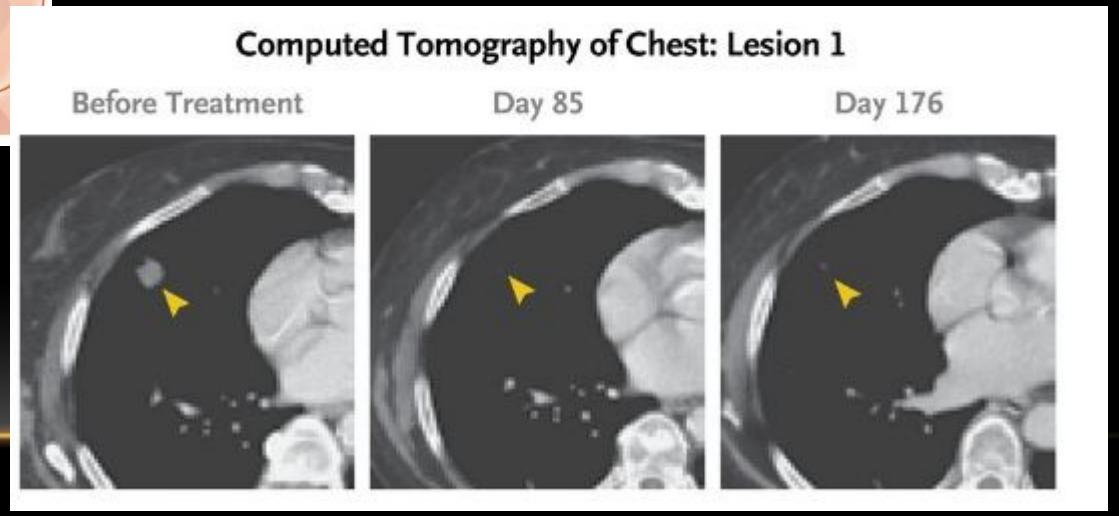
Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Leidner R et al. DOI: 10.1056/NEJMoa2119662



- 71 yof s/p Whipple resection, adjuvant FOLFIRINOX
- and chemoRT
- Subseq pulm recurrence, continued to progress on separate IO trial
- Single-patient IND for KRAS-targeting CART cell rx

Ongoing response (RECIST 72%) at 6 months post-rx!



R Leidner et al. *N Engl J Med* 2022;386:2112-2119.


THANK YOU