City of Hope

Advances in Pancreatic Cancer


Vincent Chung, MD, FACP

18th Annual California Cancer Consortium

The Langham Hotel, Pasadena, CA

August 20, 2022

Overview

Scope of the problem

Progress in the treatment of pancreatic cancer

Targeted therapies

Future therapies

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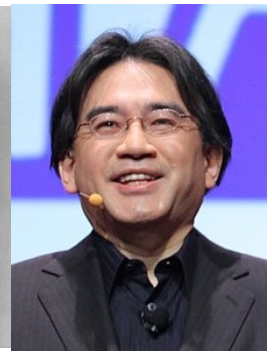
Scope of the Problem



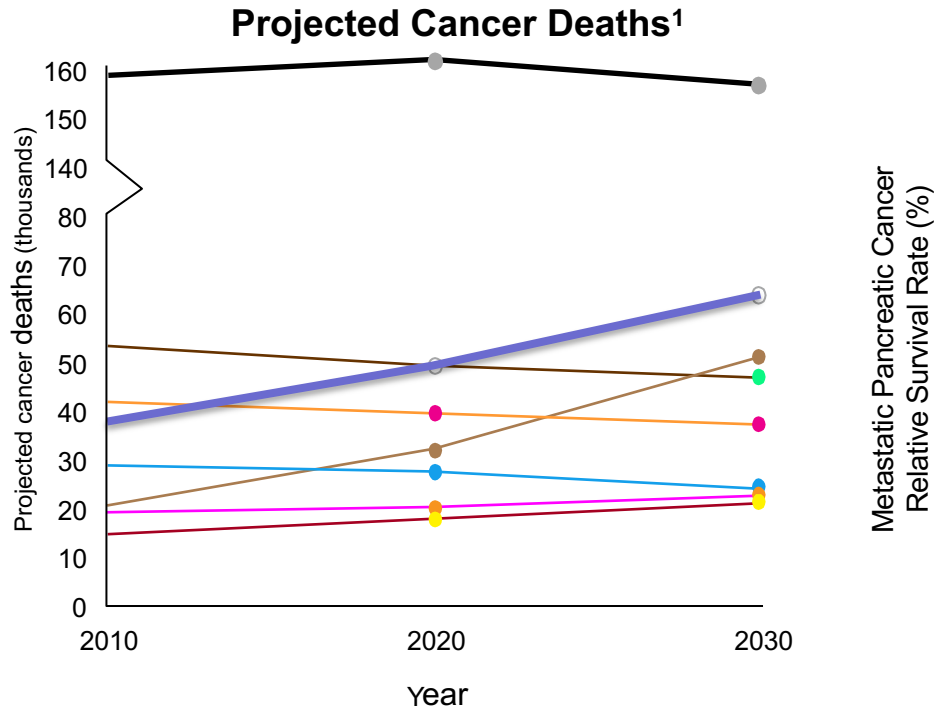
Worst survival of any

solid tumor

2022 US estimation

- 62,210 new cases
- 49,830 deaths

National Cancer Institute.
SEER Stat Fact Sheets: Pancreas.



Rahib L, *et al. Cancer Res*. 2014;74(11):2913-2921.

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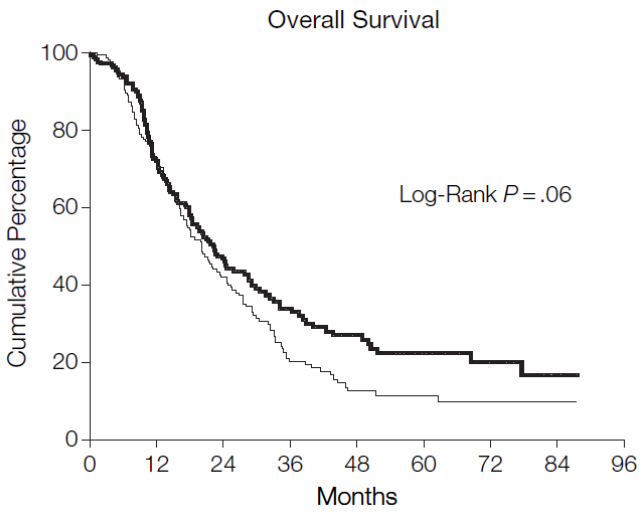
Adjuvant Therapy for Pancreatic Cancer

CONKO-01

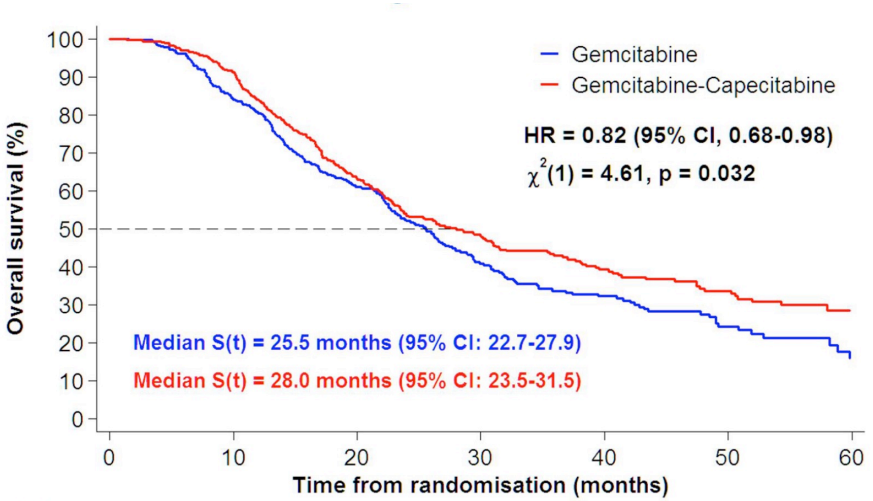
Gemcitabine



Median OS 20.2 vs 22.1 mo

ESPAC4

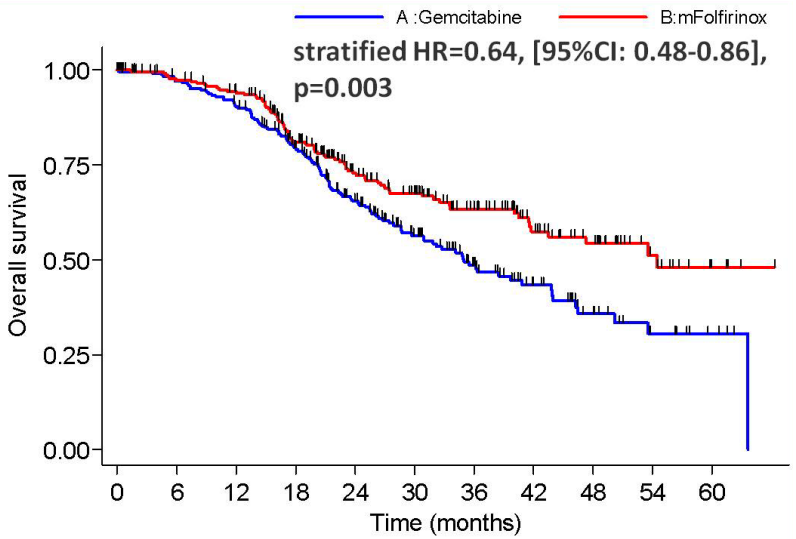
Gemcitabine + Capecitabine



Median OS 25.5 vs 28 mo

PRODIGE 24

FOLFIRINOX



Median OS 35 vs 54.4 mo

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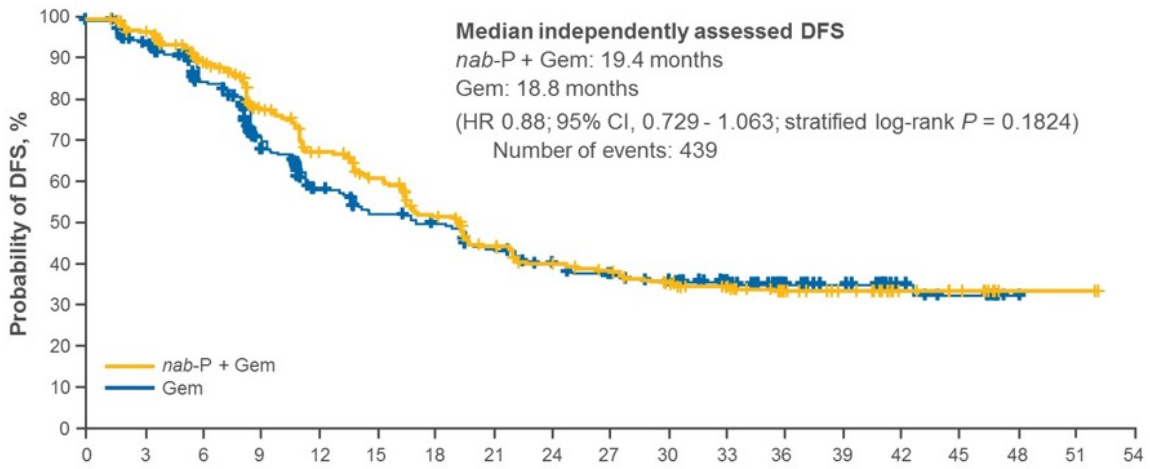
APACT: Phase 3 Trial Adjuvant Nab-paclitaxel plus Gemcitabine versus Gemcitabine Alone in pts with Surgically Resected Pancreatic Cancer

- 866 patients accrued
- Primary endpoint – independently assessed DFS
- Never used in an adjuvant pancreas trial
- Negative trial due to not meeting primary endpoint
- Clinical progression (symptoms, CA19-9, etc) may occur without RECIST progression on imaging



- Updated results at 2021 ESMO GI meeting
- Median OS 41.8 mos Gem Nab vs 37.7 mos Gem alone (HR 0.80, p=0.009)
- 5 yr OS 38% vs 31%

Tempero M, et al. 2021 ESMO World Congress on GI

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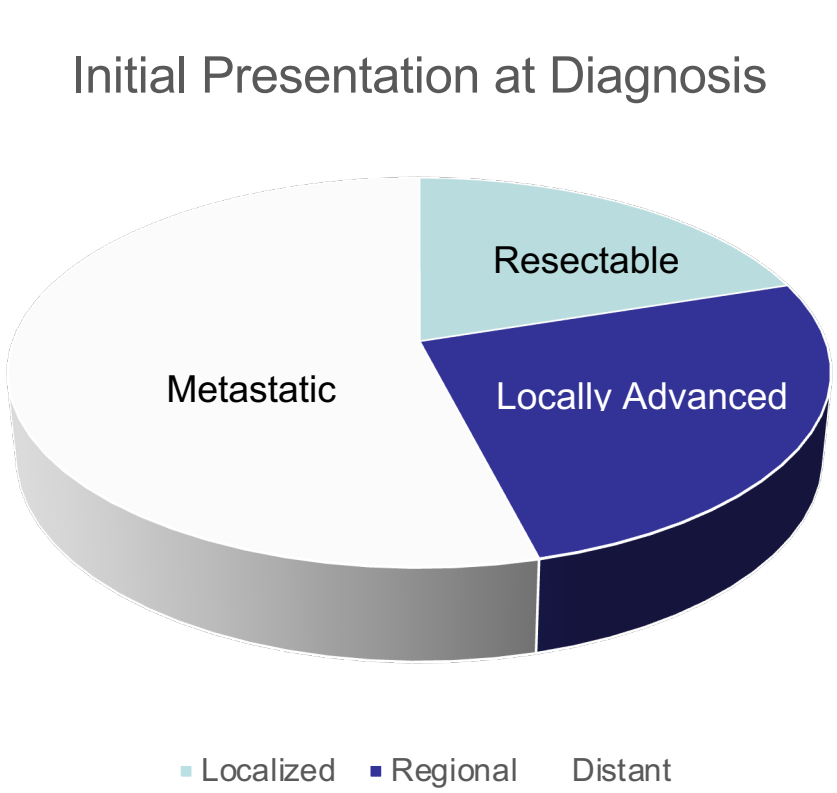
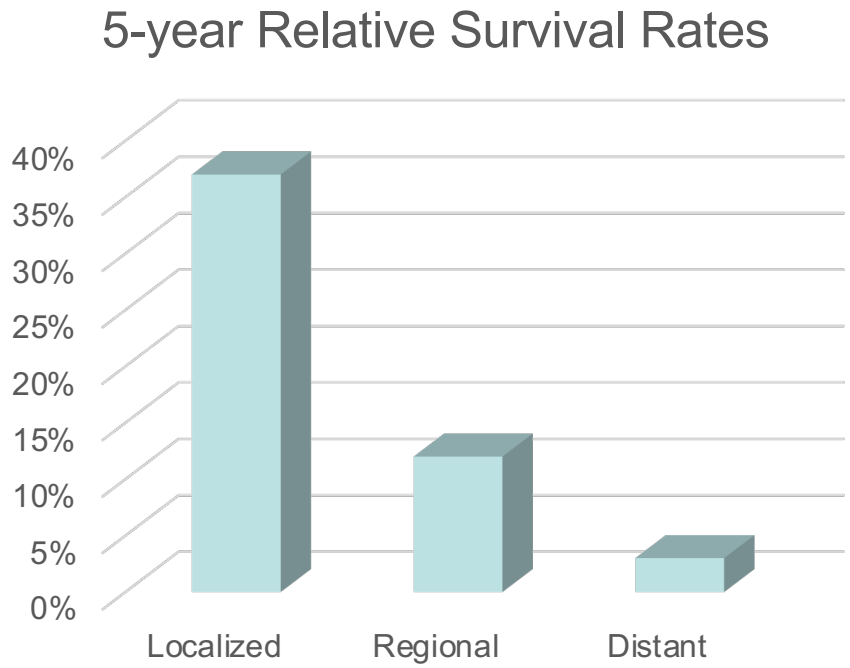
Diagnosis of Pancreatic Cancer is Usually Late





Based on people diagnosed with pancreatic cancer between 2009 and 2015
Data from American Cancer Society

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Rationale for Neoadjuvant Treatment

- Pancreas cancer is aggressive with most patients having recurrent disease
- Patients have difficulty tolerating chemotherapy after surgery
- Provides early treatment of micrometastatic disease
- Primary tumor is intact and relatively well-perfused
- Avoids surgery in patients with rapidly progressive disease

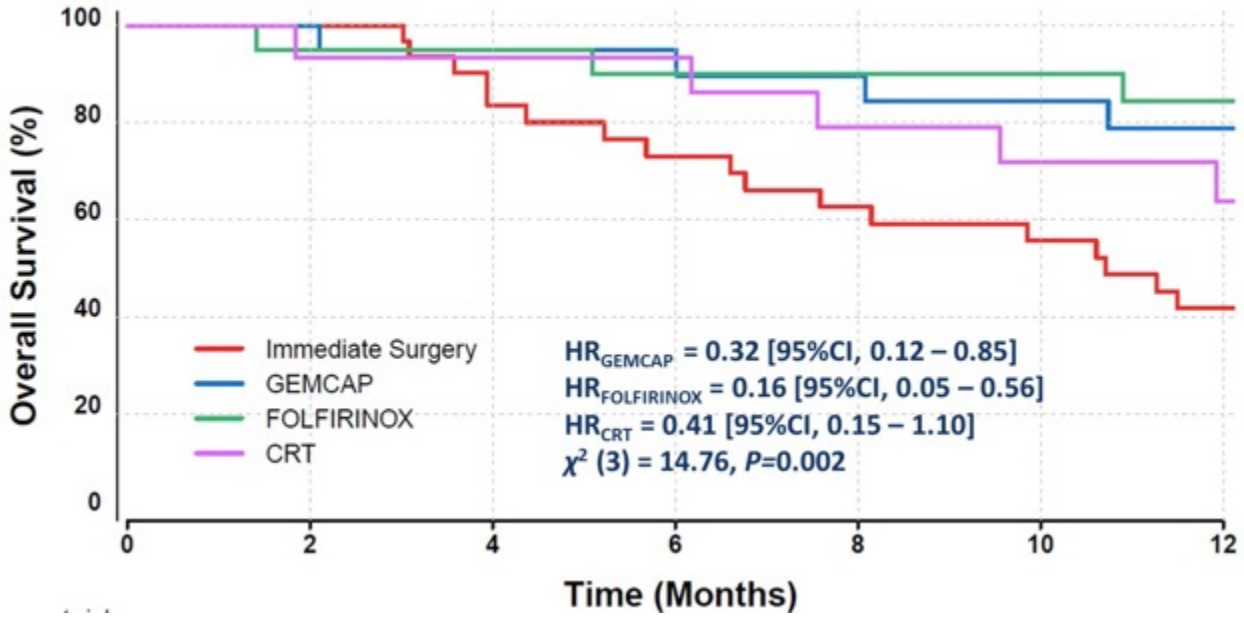
Total Neoadjuvant Therapy for Operable Pancreatic Cancer

Rebecca Y. Kim, MD, MPH[1], Kathleen K. Christians, MD[1], Mohammed Aldakkak, MD[1], Callisia N. Clarke, MD[1], Ben George, MD[2], Mandana Kamgar, MD, MPH[2], Abdul H. Khan, MD[3], Naveen Kulkarni, MD[4], William A. Hall, MD[5], Beth A. Erickson, MD[5], Douglas B. Evans, MD[1], and Susan Tsai, MD, MHS[1]

- Retrospective review 541 patients from 2009-2019
- Total neoadjuvant (TNT) – 89 (16%)
- Short neoadjuvant (SNT) – 452 (84%)
- More patients are able to complete chemotherapy
- Higher CR rate with TNT

Ann Surg Oncol (2021) 28:2246–2256

ESPAC -5F Phase 2 Trial of Immediate Surgery vs Neoadjuvant Chemotherapy or Chemoradiation in Borderline Resectable Pancreas Cancer



12-months survival estimate (95% CI)	
Immediate Surgery	42% (27% , 64%)
GEMCAP	79% (62% , 100%)
FOLFIRINOX	84% (70% , 100%)
CRT	64% (43% , 95%)

- Neoadjuvant FOLFIRINOX demonstrated the best survival at 1 yr but was also associated with more toxicity

- No difference in resection rates
- Significant survival advantage at 1 year for neoadjuvant therapy compared to immediate surgery 77% vs 42%

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Paula Ghaneh, et al. ASCO 2020

JAMA Oncology | Original Investigation

JAMA Oncol. 2021;7(3):421-427

Efficacy of Perioperative Chemotherapy for Resectable Pancreatic Adenocarcinoma

A Phase 2 Randomized Clinical Trial

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

- The primary outcome was 2-year overall survival (OS), using a pick-the-winner design
- 12 weeks preoperative, 12 weeks postoperative
- Median OS 23.6 mos GemNab vs 23.2 mos mFOLFIRINOX

Characteristic	No. (%) mFOLFIRINOX (n = 40)	Gem/nab-P (n = 33)	*P* value (2-sided)
R0 resection	34 (85)	28 (85)	>.99
Pathologic response			
Complete	1 (3)	3 (10)	.32
Moderate	9 (22)	10 (30)	.59
Minimal	12 (30)	10 (30)	>.99
Poor or none	18 (45)	10 (30)	.23
Total nodes resected, median (range)	19 (1-56)	18 (3-45)	.64
Node-negative resection	16 (40)	15 (45)	.81
Median disease-free survival after resection, mo	10.9	14.2	.86

Abbreviations: Gem/nab-P, gemcitabine/nab-paclitaxel; mFOLFIRINOX, modified FOLFIRINOX, treatment with fluorouracil, irinotecan, and oxaliplatin.

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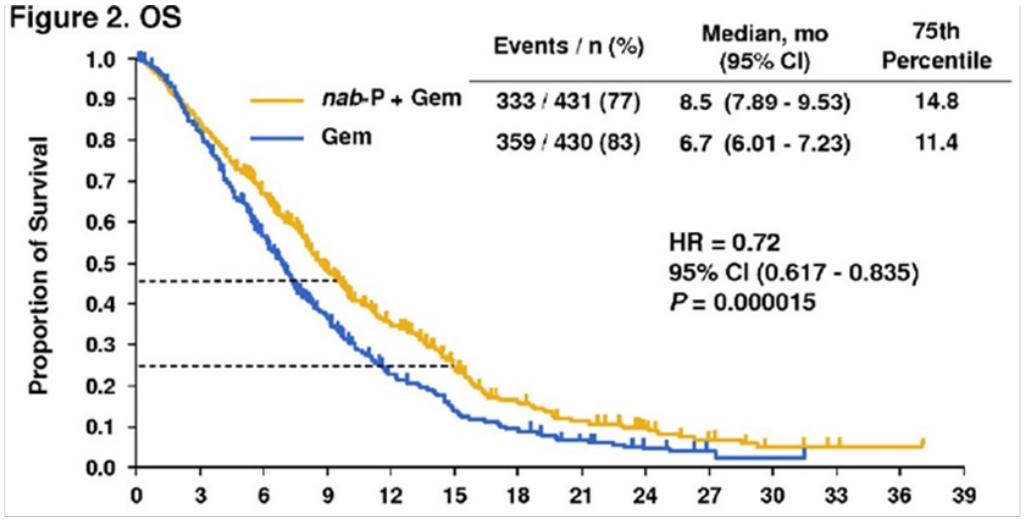
Management of Advanced Pancreatic Cancer

MPACT

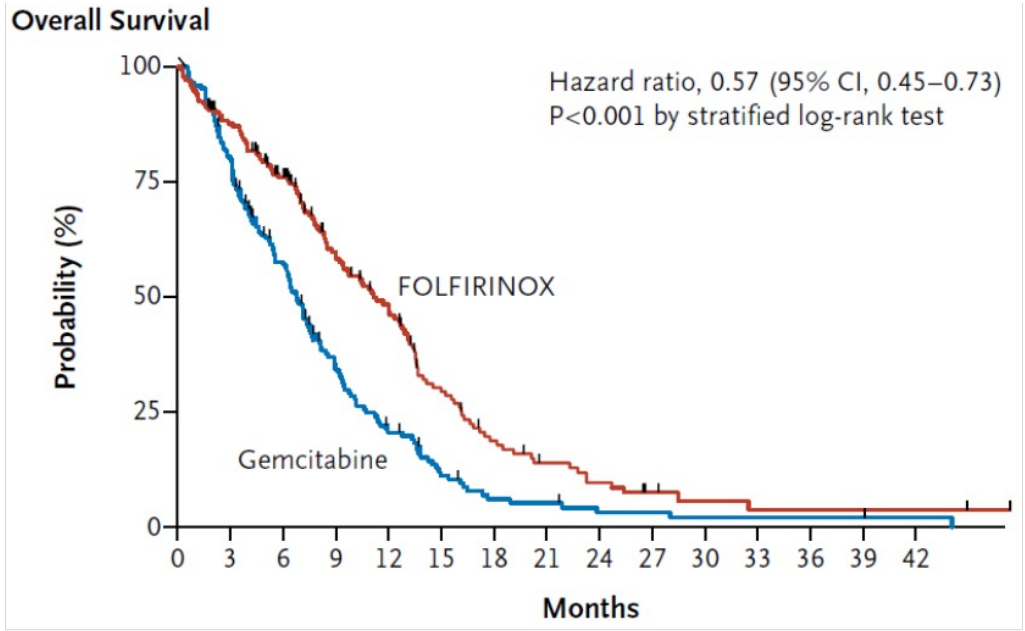
Gemcitabine and nab-paclitaxel



Median OS 8.5 vs 6.7 mo HR 0.72 p=0.000015
Median PFS 5.5 vs 3.7 mo HR 0.69 p=0.000024

PRODIGE 4 / ACCORD 11

FOLFIRINOX



Median OS 11.1 vs 6.8 mo HR 0.57 p<0.001
Median PFS 6.4 vs 3.3 mo HR 0.47 p<0.001

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Conroy T, et al. NEJM 2011.
Von Hoff D, et al. NEJM 2013.

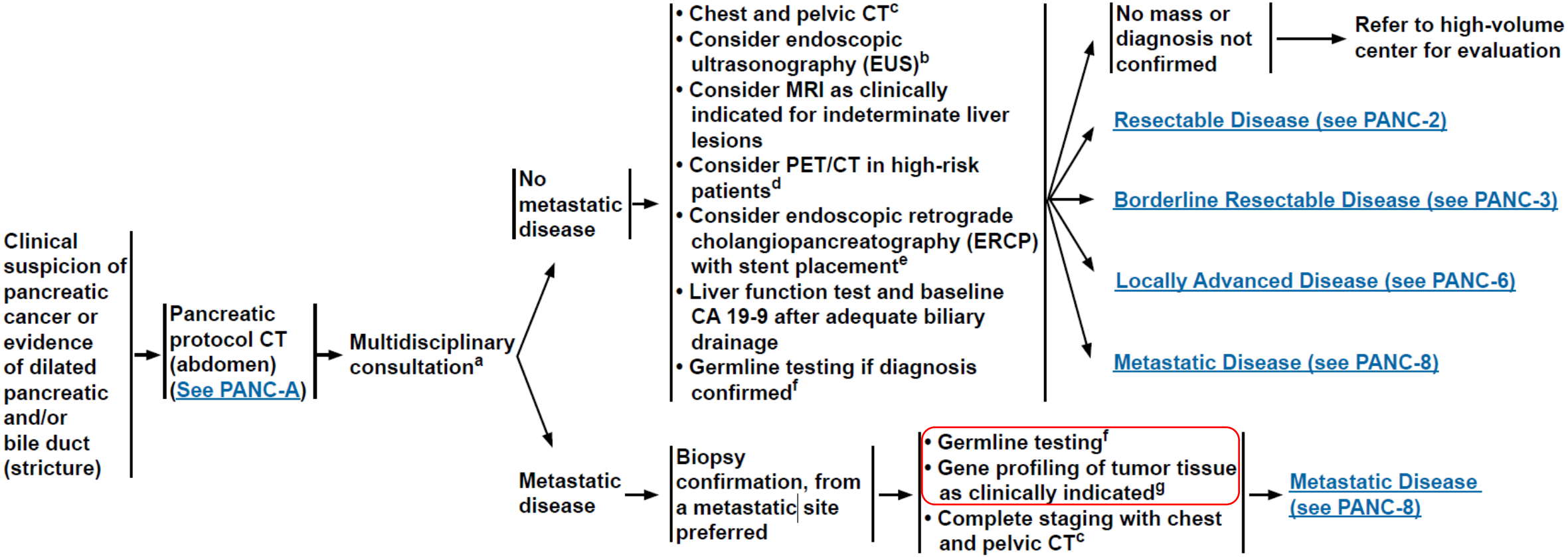
PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy)

- Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• If previous platinum-based chemotherapy: ▸ Olaparib (only for germline *BRCA1/2* mutations)	• Clinical trial or • If previous first-line FOLFIRINOX: ▸ Capecitabine or • If previous first-line gemcitabine + nab-paclitaxel: ▸ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ▸ Gemcitabine single agent (category 2B)	• If previous first-line FOLFIRINOX: ▸ 5-FU ± irinotecan[k] ▸ FOLFOX[l] (category 2B)

CLINICAL PRESENTATION AND WORKUP



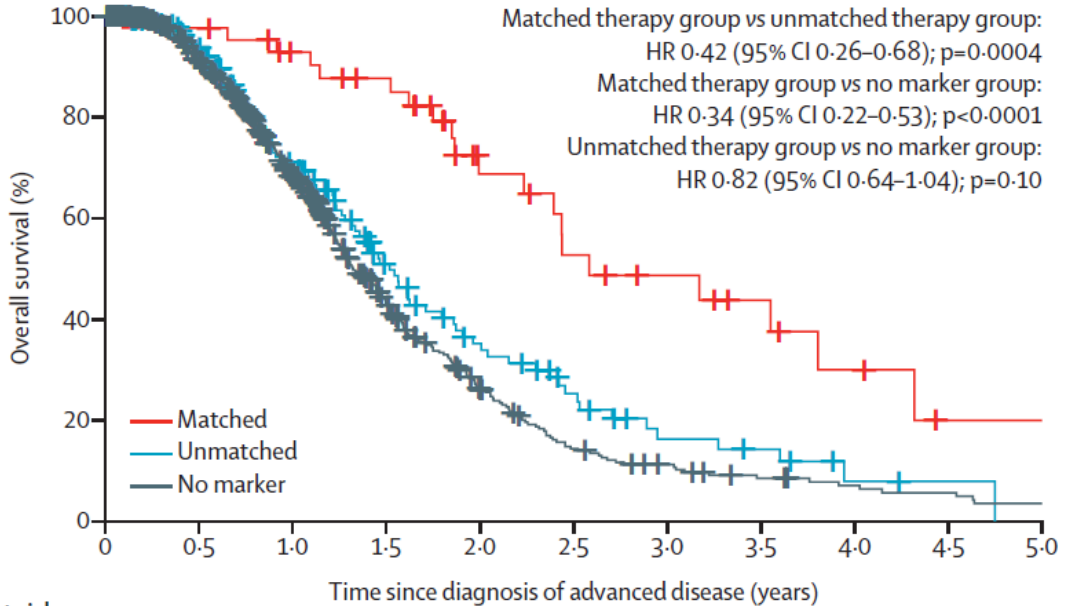
2019 Molecular profiling added to the NCCN guidelines

THE LANCET Oncology

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial

Michael J Pishvaian, Edik M Blais*, Jonathan R Brody, Emily Lyons, Patricia DeArbeloa, Andrew Hendifar, Sam Mikhail, Vincent Chung, Vaibhav Sahai, Davendra P S Sohal, Sara Bellakbira, Dzung Thach, Lola Rahib, Subha Madhavan, Lynn M Matrisian, Emanuel F Petricoin III*

- 1856 patients referred to KYT between June 2014 and March 2019
- About 25% of pancreatic cancer harbor actionable molecular alterations
- Patients receiving matched therapy had significantly longer median overall survival compared to patients receiving unmatched therapies.



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Lancet Oncology 2020; 21:508-18.

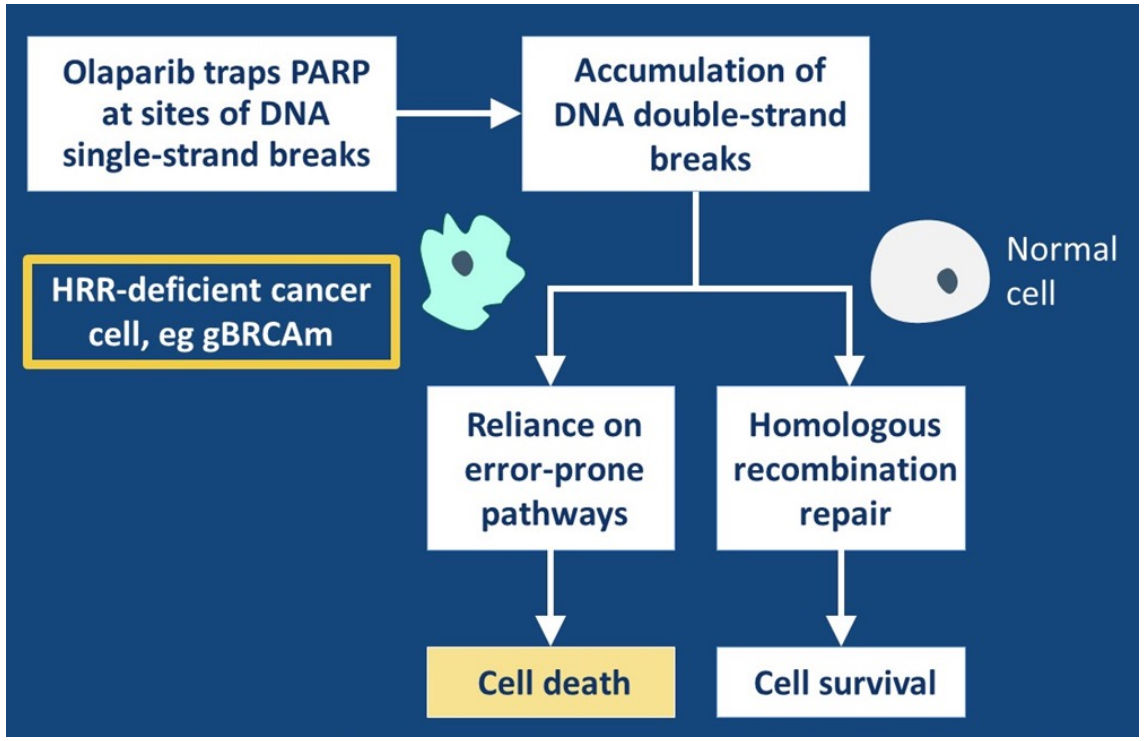
Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

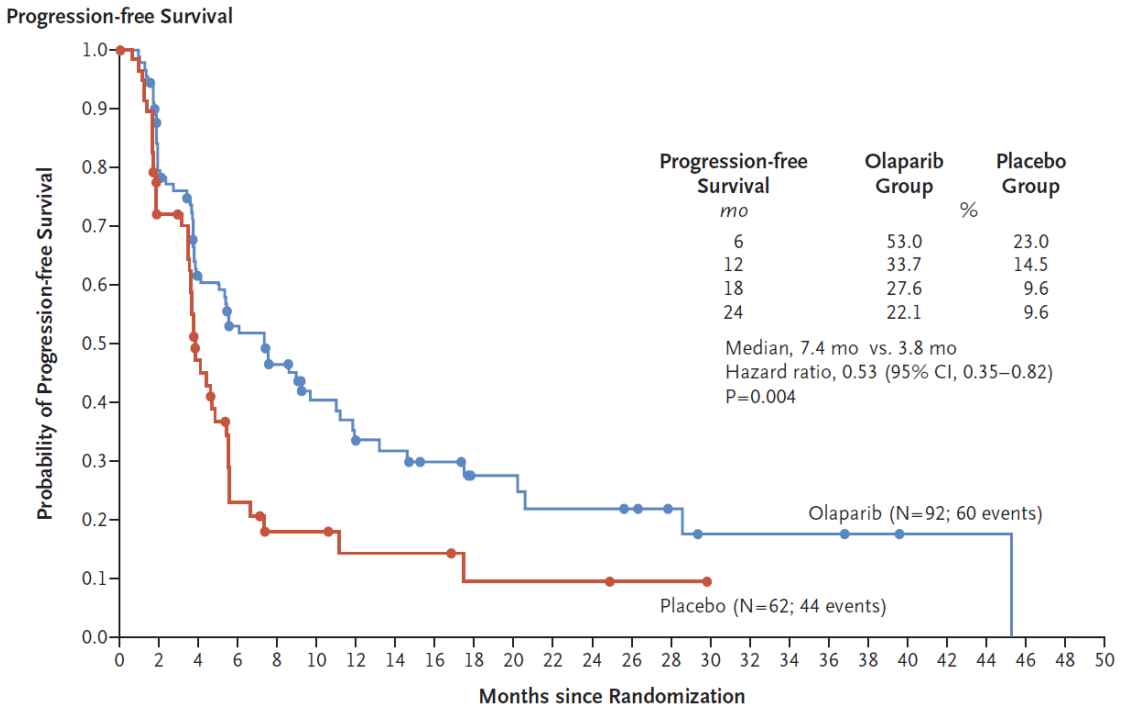
The NEW ENGLAND JOURNAL of MEDICINE

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.

Germline BRCA 1/2 - only 7%

3315 pts screened to enroll 154





NEJM 2019;381:317-327.

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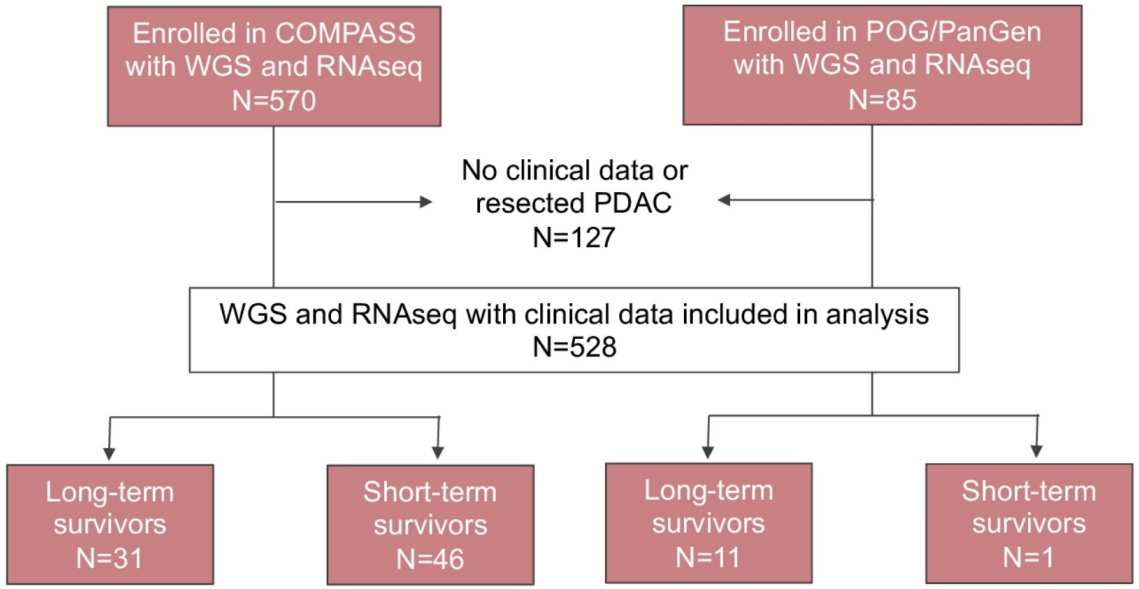
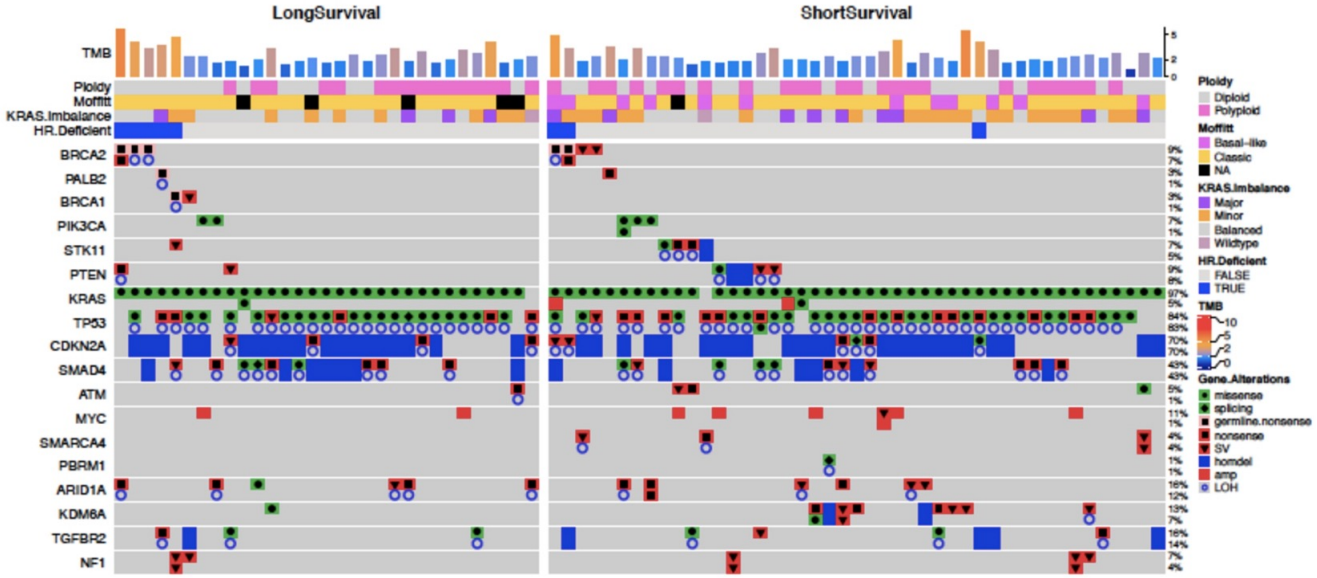
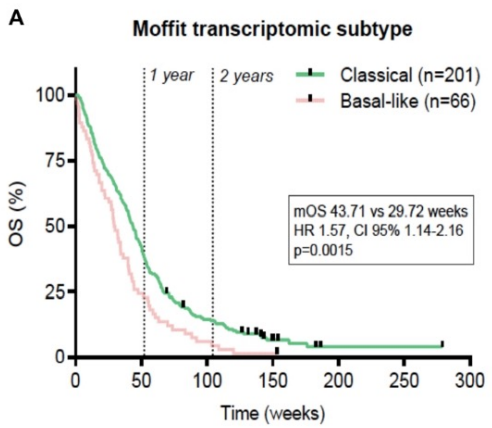
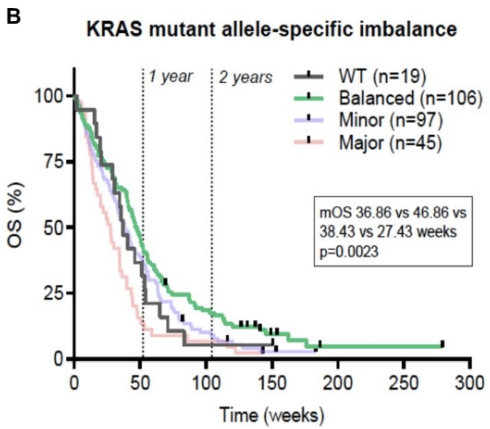
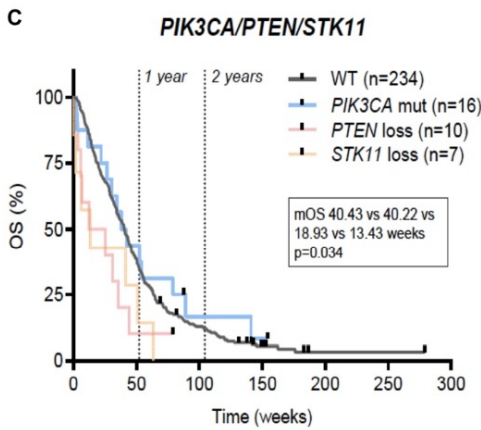
COMPASS











Survival ≤3 mo

- Enhanced RAS signaling
- Deregulation of the PI3K/AKT/mTOR pathway
- Basal-like transcriptomic subtype.

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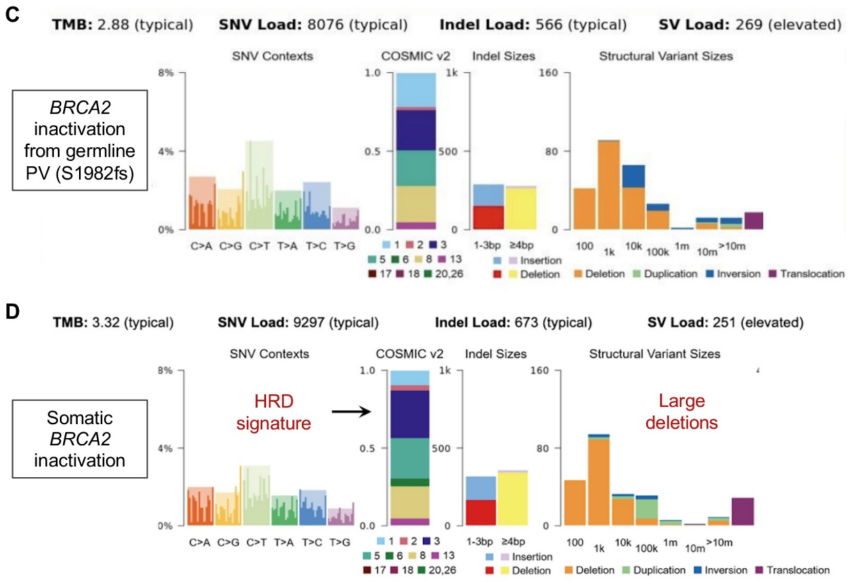
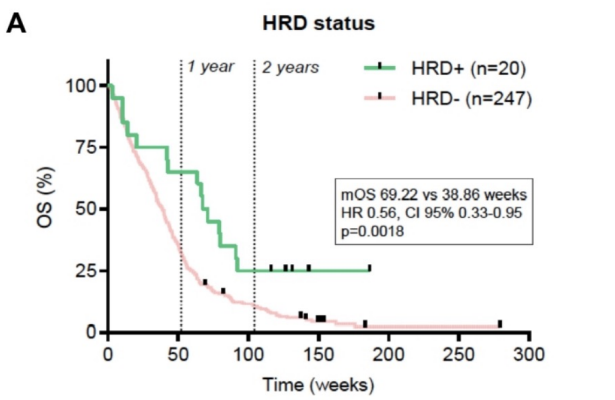
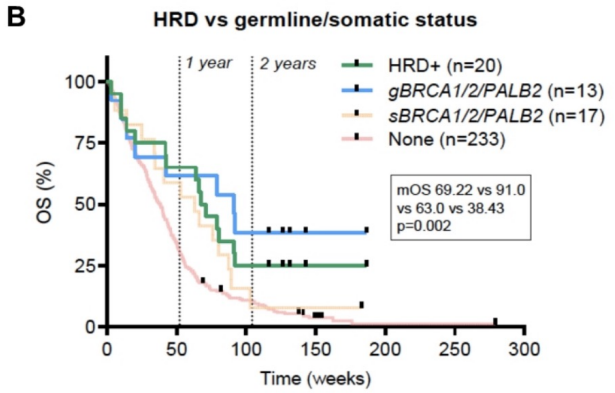
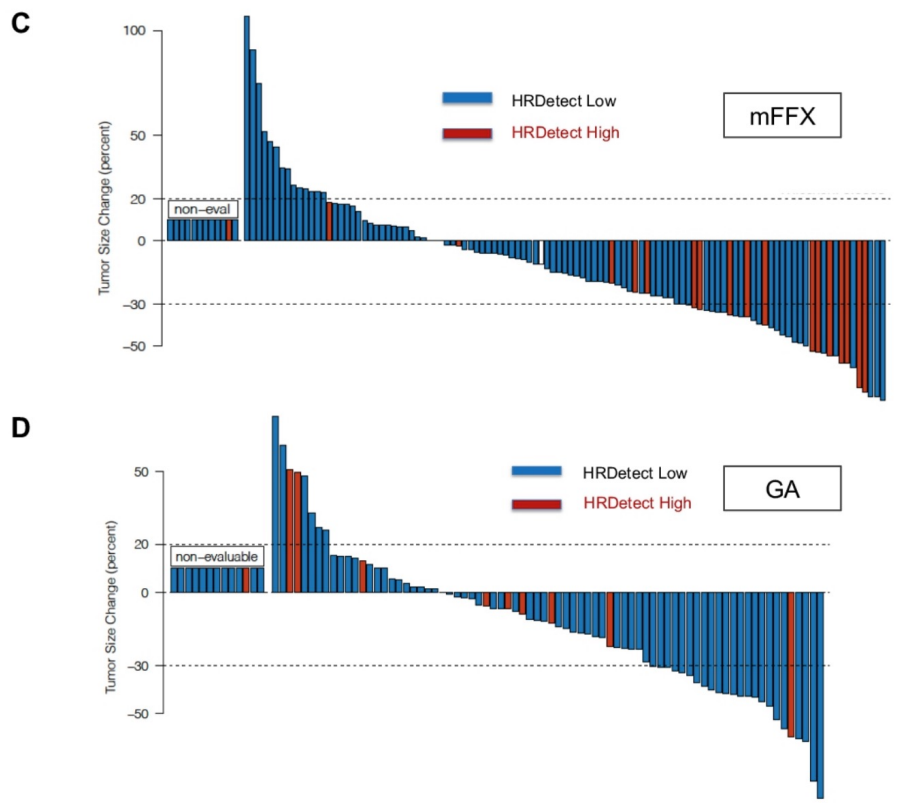
Antras JF, et. J Clin Oncol 40, 2022 (suppl 16; abstr 4024)

COMPASS Trail









Molecular signature for germline and somatic BRCA2 mutations are similar

HRD+ associated with improved survival

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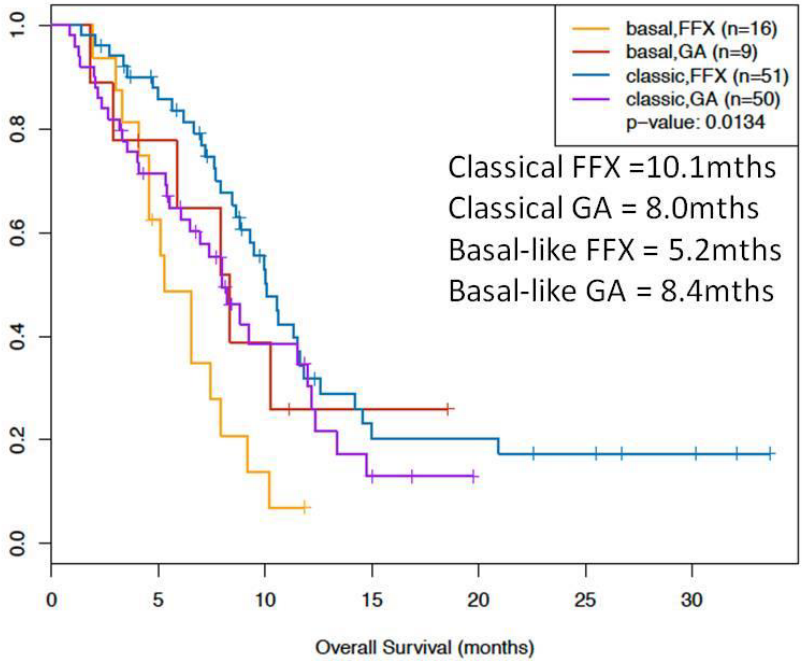
Antras JF, et. J Clin Oncol 40, 2022 (suppl 16; abstr 4024)

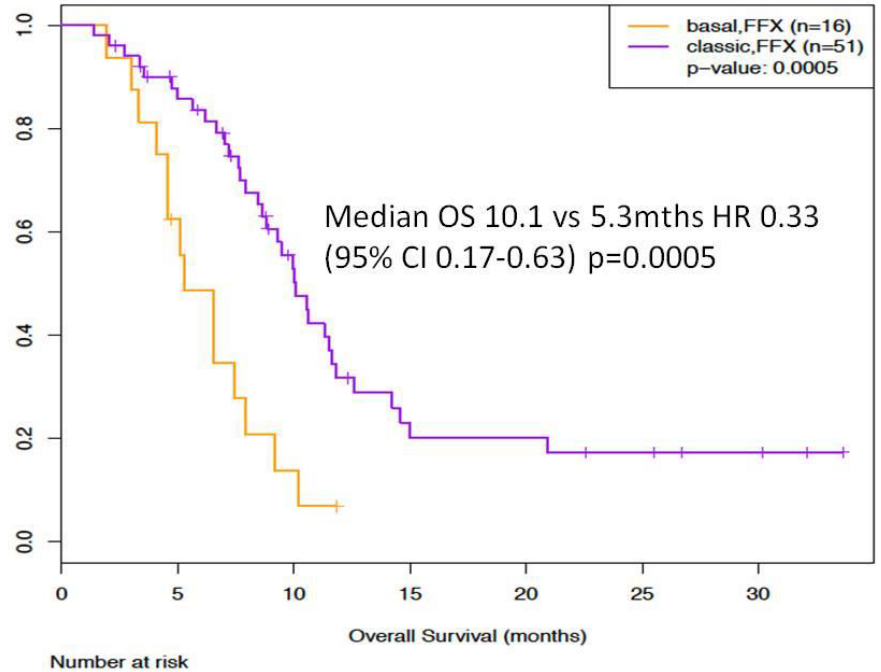
COMPASS Results: Overall Survival by Chemotherapy

All patients≥ 1 dose chemo n=126



Number at risk							
basal,FFX	16	9	2				
basal,GA	9	6	3	1			
classic,FFX	51	40	19	7	7	5	3
classic,GA	50	33	10	3			

OS mFFX only n=67



Number at risk							
basal,FFX	16	9	2				
classic,FFX	51	40	19	7	7	5	3

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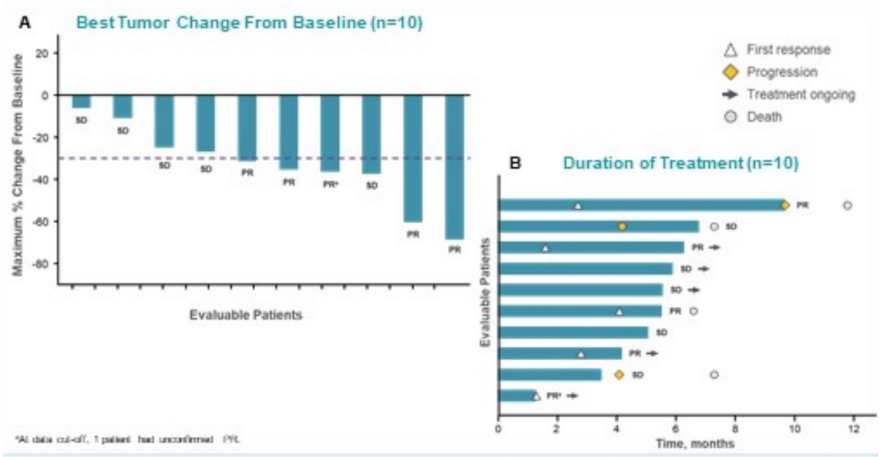
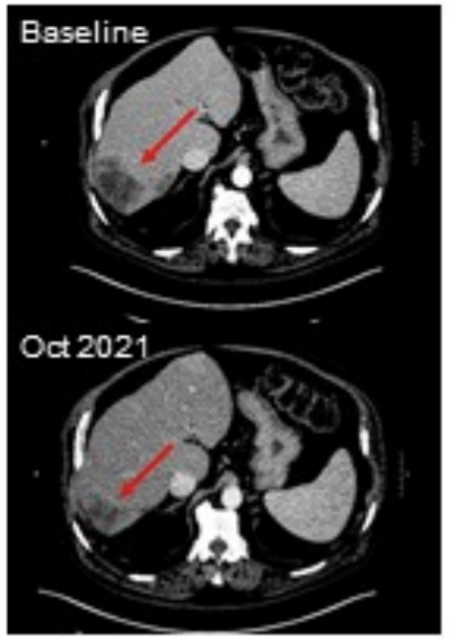
KRYSTAL-1: adagrasib (MRTX849) in patients with pancreatic cancer and other GI tumors harboring a KRAS G12C mutation

- KRAS mutations occur in approximately 90% of pancreatic cancer, and approximately 2% of these are KRAS G12C mutations.
- Adagrasib irreversibly and selectively binds KRAS G12C
- 12 pts with PDAC (median 3 prior lines of therapy), 10 were evaluable for clinical activity
  - PRs were seen in 50% (5/10)
  - DCR was 100% (10/10)



Patient Case: Response in PDAC Harboring a KRAS^{G12C} Mutation

- 76-year-old female with locally advanced adenocarcinoma of the pancreas
- Diagnosis January 2020
- Treatment history and best overall response:
  - gemcitabine, abraxane (January–July 2020): SD;
  - pembrolizumab, GVAX pancreas vaccine, CSF1R inhibitor (August 2020 – January 2021): SD
- Disease progression February 2021
- Adagrasib 600 mg BID started March 2021
  - September 2021 (cycle 8), SD (-25%)
  - October 2021, PR (-38%) after data cut-off
  - December 2021, confirmed PR (-38%) after data cut-off
- No treatment-related adverse events (TRAEs)
- Patient remains on study



TS Bekaii-Saab, et al. ASCO GI 2022

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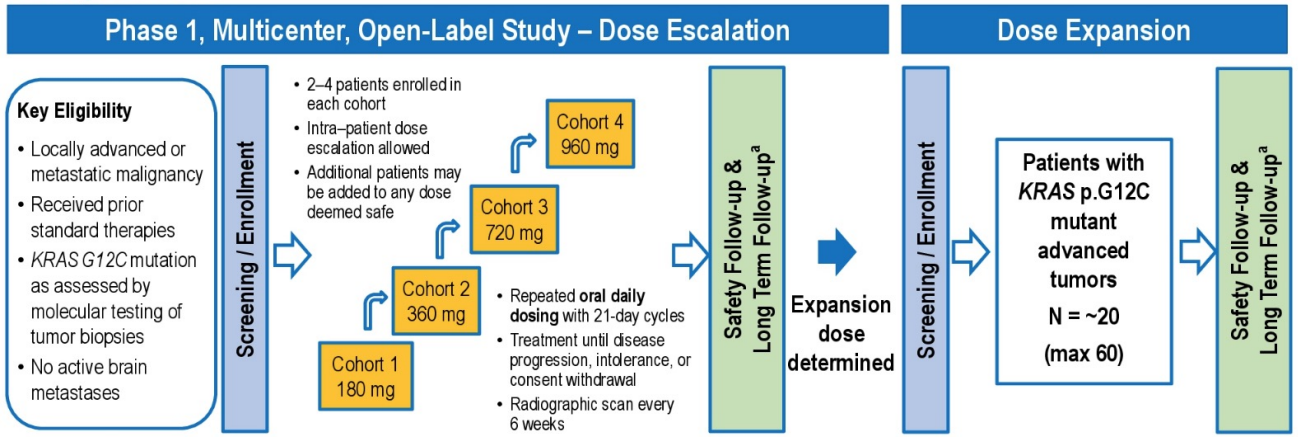
CodeBreak 100: Phase I study of AMG 510, sotorasib, in patients with advanced solid tumors (ASCO 2022 Strickler)

Sotorasib is a small molecule that specifically and irreversibly inhibits KRASG12C by covalently binding to a pocket of the switch II region that is present only in the inactive GDP-bound conformation

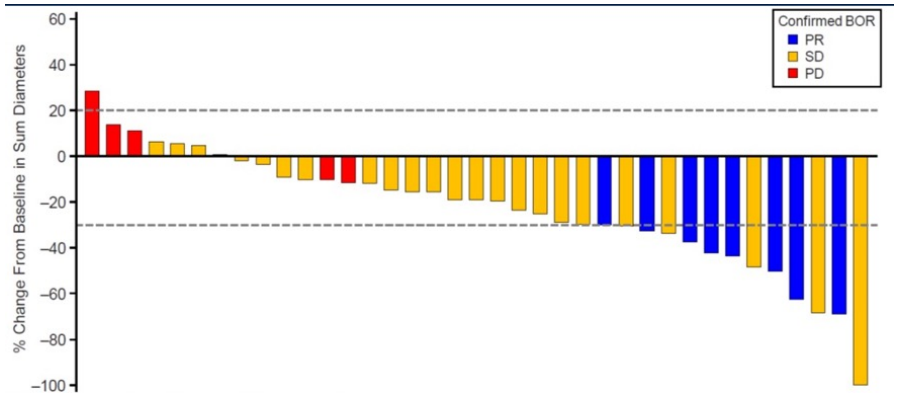
Stable disease seen in 6 of 8 pancreatic cancer patients

Study Schema



[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

	All treatment-related AEs (TRAEs) N=38, n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	16 (42.1) 12 (31.6) 6 (15.8) 0 (0.0)
AEs leading to reduction or interruption of sotorasib	5 (13.2)
Serious AEs	3 (7.9)
Fatal AEs	0 (0.0)
AEs leading to sotorasib discontinuation	0 (0.0)



	N	ORR (%), 95% CI	DCR (%), 95% CI	PFS (months), 95% CI
NSCLC[1]	172	41 (33.3-48.4)	84 (77.3-88.9)	6.3 (5.3-8.2)
Pancreatic cancer	38	21 (9.6-37.3)	84 (68.8-94.0)	4.0 (2.8-5.6)
Colorectal cancer[2]	62	10 (3.6-19.9)	82 (70.5-90.8)	4.0 (2.8-4.2)

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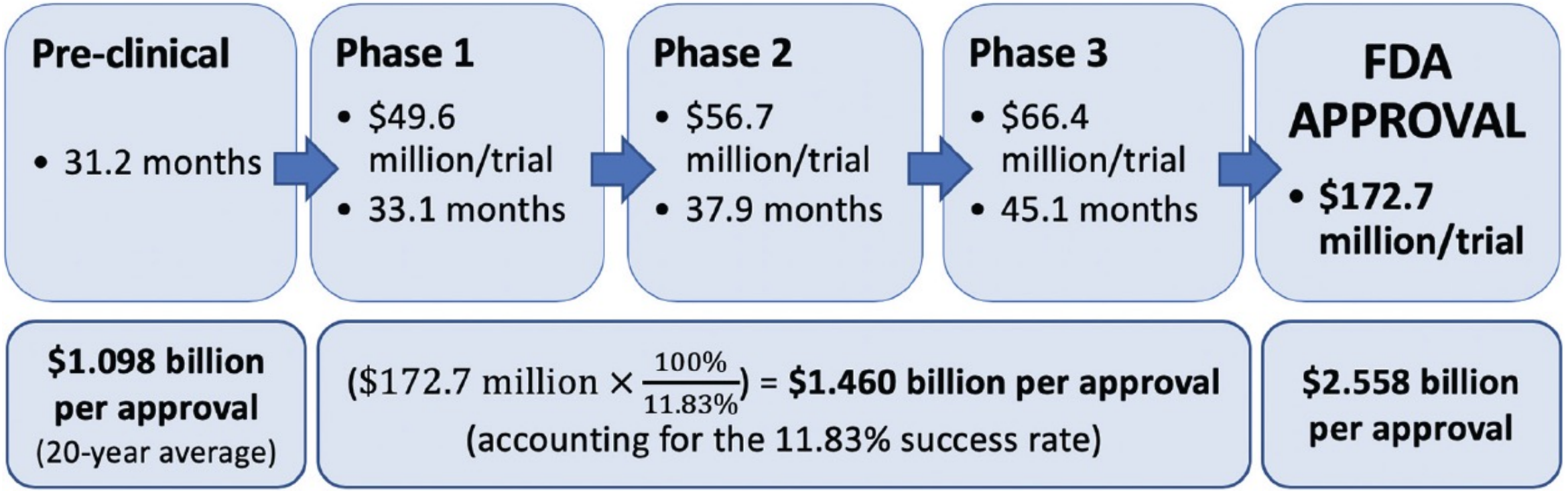
Phase 3 Clinical Trials

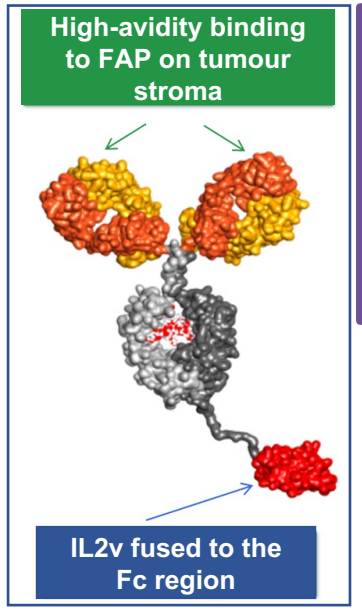
Reference	Clinical Trial	Results
NCT02715804(JCO 2020)	HALO 109-301 (Gem/Nab +/- PEGPH20) N=494	OS 11.2 (PEG) vs 11.5 mo (HR 1, p=0.97)
NCT02993731 (ESMO 2021)	CanStem111P (Gem/Nab +/- napabucasin) n=1134	OS 11.73 (nap) vs 11.43 mo
NCT03504423 (ASCO 2022)	Avenger 500 (FOLFIRINOX +/- CPI-613) n=528	OS 11.1 (CPI) vs 11.7 mo (HR 0.95, p=0.655)
NCT03665441(ASCO Gi 2022)	Trybeca-1 (2nd line chemo + Eryaspase)	OS 7.5 (Ery) vc 6.7 mo (HR 0.92, p=0.375)

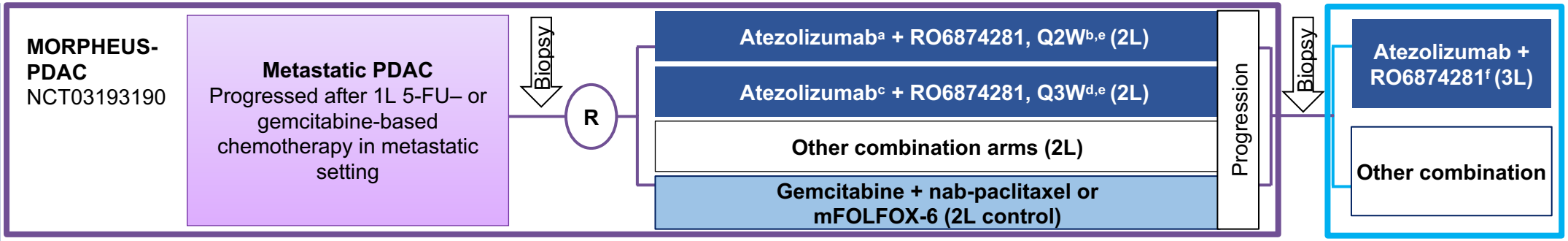
Phase 3 Clinical Trials



Data from DiMasi et al. (2016)

Phase Ib/II, open-label, randomised evaluation of atezolizumab plus RO6874281 vs control in MORPHEUS–pancreatic ductal adenocarcinoma (PDAC)





- RO6874281 (also called FAP-IL2v) is a novel, monomeric, tumour-targeted IL2v that comprises a fusion of a single IL2v moiety to a human IgG1 antibody against fibroblast activation protein-α (FAP), which is highly expressed in PDAC[1]
- IL2v preferentially expands and activates CD8 T and NK cells in the periphery and tumours but not Treg cells
- RO6874281 was developed to overcome limitations of wild-type IL-2 by activating immune effector cells and selectively promoting immune responses in the microenvironment of the tumors that overexpress FAP

[a]Atezolizumab 840 mg IV Q2W in a 28-day cycle. [b]RO6874281 10 mg IV Day 1 and 15 mg IV on Days 8, 15 and 22 of Cycle 1, and 15 mg on Days 1 and 15 of each subsequent cycle in a 28-day cycle. [c]Atezolizumab 1200 mg IV Q3W in a 21-day cycle. [d]RO6874281 10 mg IV Q3W in a 21-day cycle. [e]Patients not eligible for 3L atezolizumab + RO6874281 arms. [f]Majority of the patients received Q3W regimen, and 1 patient received Q2W regimen. [1]Shi M. *World J Gastroenterol*. 2012.

Dr. Vincent Chung
MORPHEUS-PDAC
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PRECISION PROMISE^{SM} (PRP): AN ADAPTIVE, MULTI-ARM REGISTRATION TRIAL IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

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Abstract # 159a
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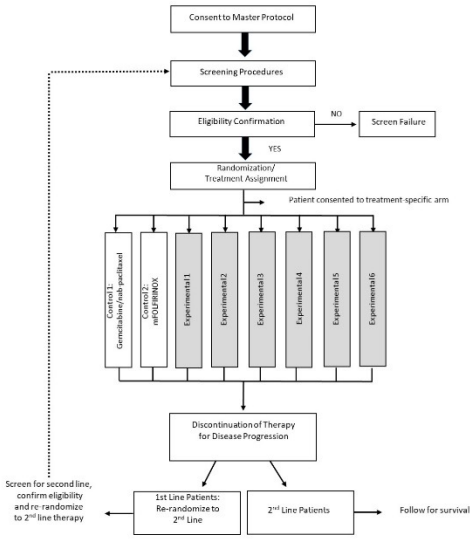
Background

Currently, the success rate of drug development in Pancreatic Ductal Adenocarcinoma (PDAC) is disappointingly low. Precision Promise (PrP) is a transformative, adaptive platform clinical trial designed to continuously evaluate many novel therapeutic options while increasing the probability that patients (pts) are randomized to effective experimental therapies. The study cultivates enhanced cooperation among groups representing patient advocacy, pharmaceutical companies, academia, and the FDA. This patient-centric study aims to become the largest Phase 3 registrational study in PDAC and represents a fundamental shift in drug development for PDAC in the United States (US).



Methods

- PrP (NCT04229004) is a platform clinical trial sponsored by Pancreatic Cancer Action Network (PanCAN).
- Developed based on FDA 2020 "Complex Innovative Designs" guidance document. https://www.fda.gov/media/130897/download.
- It utilizes adaptive randomization and other Bayesian statistical innovations provided by Berry Consultants LLC, including the "time machine," which uses previously randomized controls for each arm, suitably adjusted for line therapy and the time period of each arm.
- Focuses on 1st and 2nd line treatment of mPDAC, and patients are randomized to one of 2 control arms (gemcitabine + nab-paclitaxel or mFOLFIRINOX – 30%) or experimental therapy (70% of patients).
- Experimental arm candidates are reviewed by an Arm Selection Committee based on validity of the treatment and strength of the pre-clinical / clinical data.
- Primary endpoint is overall survival (OS).
- Includes molecular testing.
- PrP contains 3 sub-protocols evaluating quality of life, sarcopenia, and actigraphy.

Standard Clinical Trials	PanCAN's Precision Promise
500+ patients	**175 patients on experimental therapy**
Test one drug at a time	**Test multiple drugs simultaneously**
Up to 7 years to complete	**As little as 3.5 years to complete**
Learn at the end	**Learn as you go (continuous learning)**
$100M +	**¼ the cost or less**
12-18 months planning for industry	**Plug and play infrastructure for industry**

Current Directions

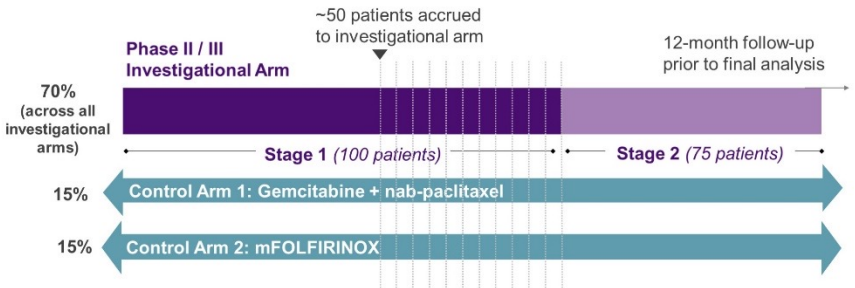
- Precision Promise launched in 2020
- Enrolled more than 182 patients
- 30 US sites selected with 20 sites active
- Three investigational arms to date

Future Directions

- Continue to engage with companies to continually bring potential new treatments
- Continue enrollment across all sites
- Add additional sites with a focus on diverse communities

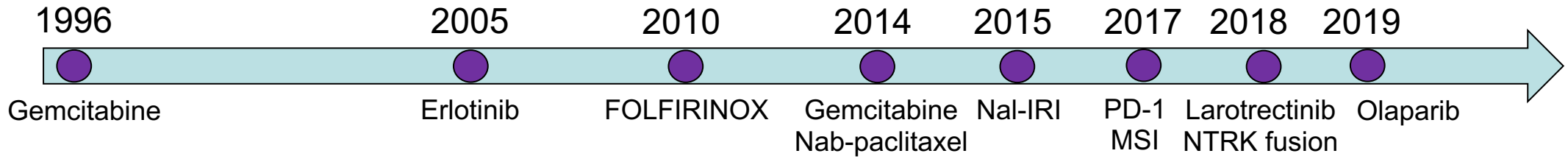
Randomization

- Randomization probabilities are updated monthly based on available outcome data, and randomization probabilities for control arms remained fixed.
- Randomization is in the first line and second line
  - Stage 1 reaches a sample size of approximately 100 patients randomized and initiated treatment, and if this arm reaches the threshold to graduate to stage 2, enrollment proceeds automatically (does not change treatment for subjects currently being treated in Stage 1)
  - Stage 2 reaches a maximum sample size of an additional 75 patients randomized and initiated treatment
- A therapy's first futility analysis will be conducted at the next monthly analyses after its 50th patient was randomized and initiated treatment.



- Indication: L1 and L2 patients with metastatic pancreatic cancer; if the treatment assigned in L1 fails, the patient can be re-randomized to a L2 treatment.
- Patient assignment is stratified by line of therapy, so the 3 possible graduating signatures are L1, L2, L1+L2.

Final Thoughts



- Accelerating progress in pancreatic cancer research
- Pancreatic cancer can be divided into molecular subtypes
- Targeted treatments improve overall survival
- Novel trial designs will help accelerate drug development in pancreatic cancer