City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

HEPATIC PANCREATIC BILIARY (HPB)

Systemic Therapy Consideration in PDAC Peritoneal Metastases

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City of Hope

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- On the Speakers Bureau for AstraZeneca, and Ipsen.
- Consultant for Pfizer.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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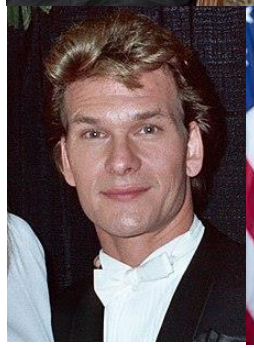
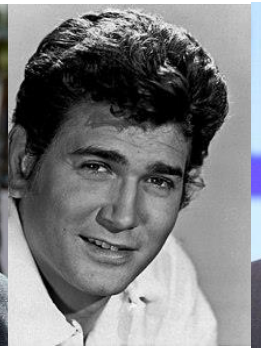
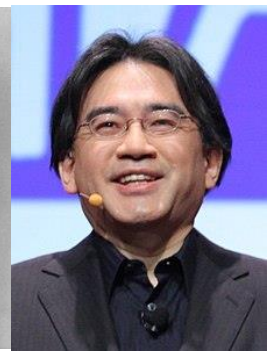
Scope of the Problem

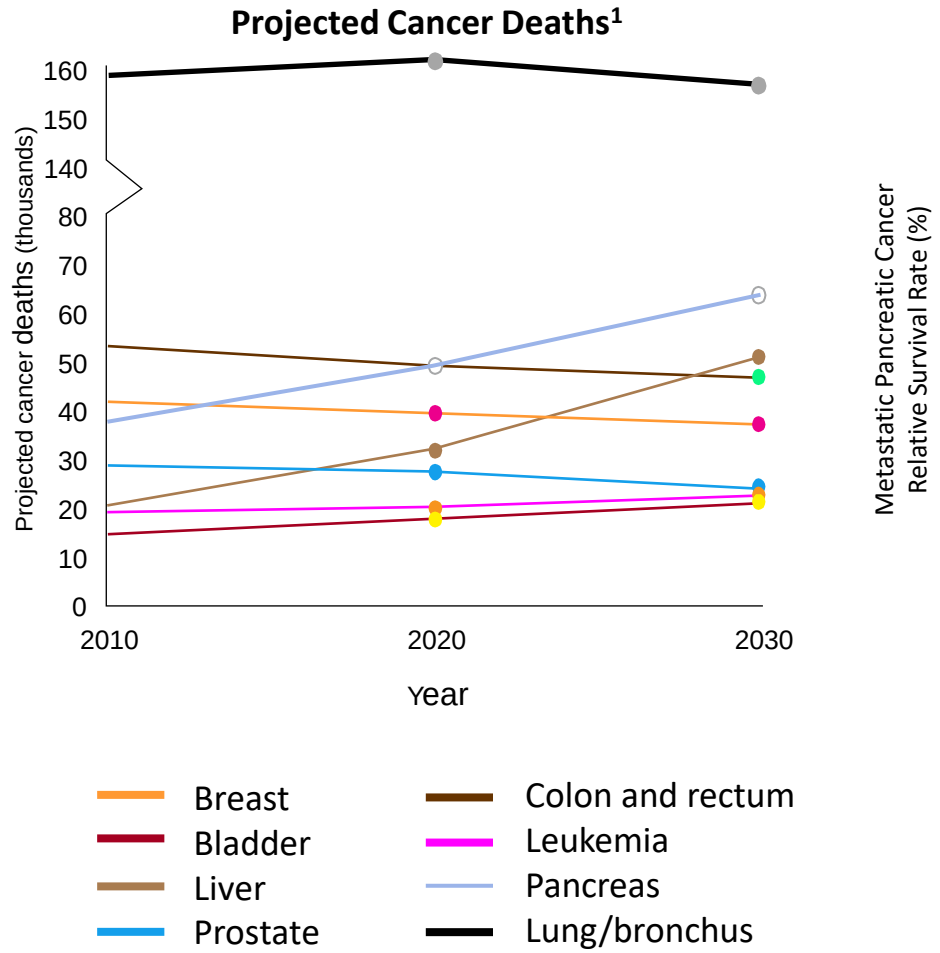






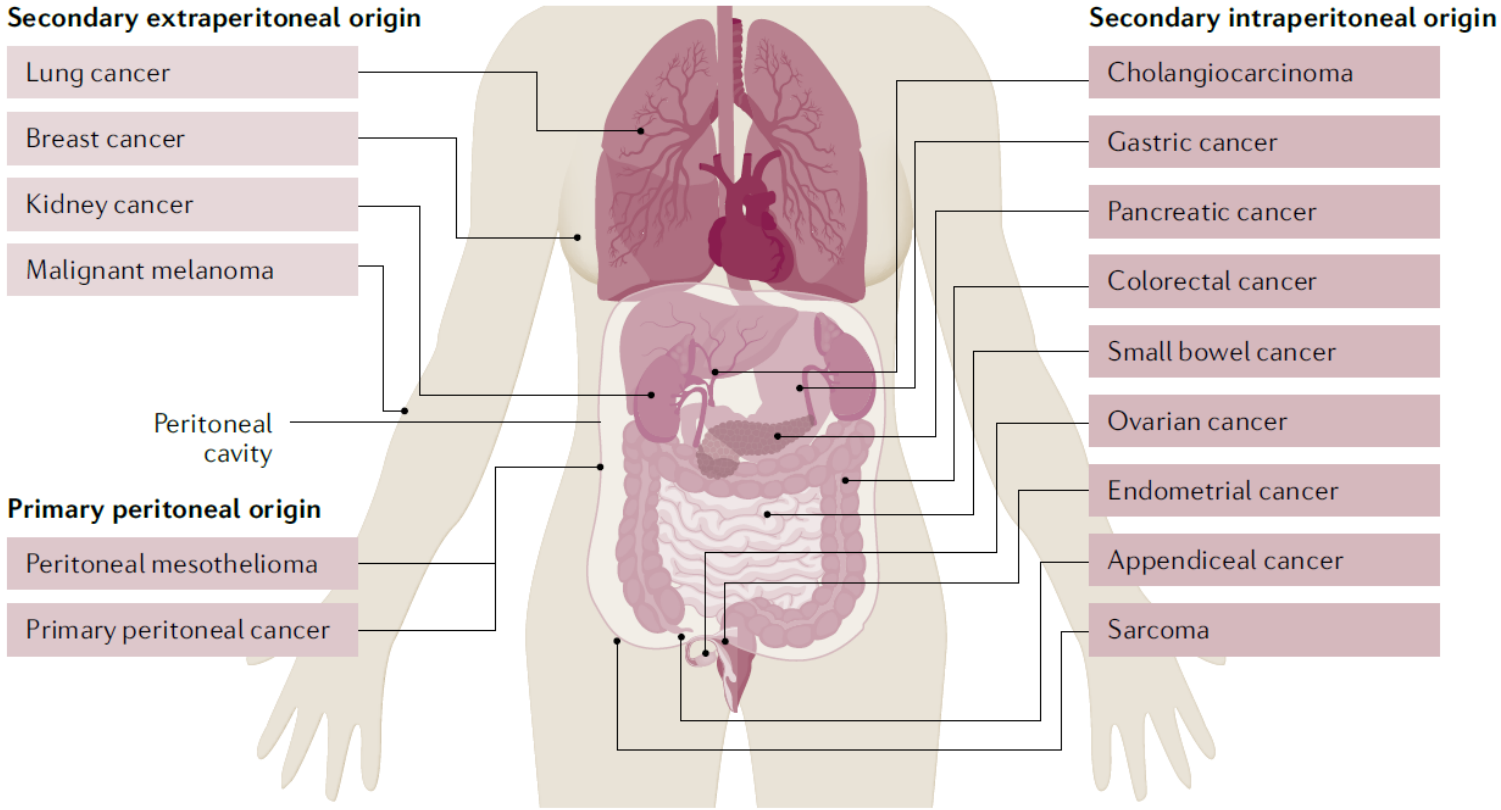
- Worst survival of any
- solid tumor
- 2022 US estimation
  - 62,210 new cases
  - 49,830 deaths

National Cancer Institute.
SEER Stat Fact Sheets: Pancreas.



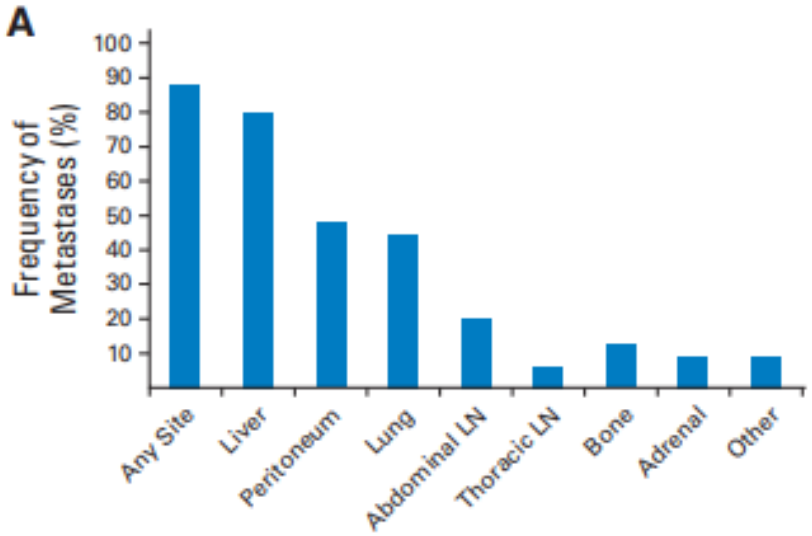
Rahib L, *et al. Cancer Res*. 2014;74(11):2913-2921.

Tumors causing peritoneal surface malignancies



- Transcoelomic dissemination
- Passive peritoneal dissemination

Rapid autopsy series)



Cortes-guiral D, et al. Nature Reviews Disease Primer 7:91. 2021
Iacobuzio-Donahue CA, et al. J Clin Oncol 27:1806-1813. 2009

Cytoreduction and HIPEC for peritoneal carcinomatosis of pancreatic cancer

Patients	*PCI*	*CC*	*HIPEC*	*Site of failure*	*Overall survival*	*Neo-adjuvant chemotherapy*
Female, 59y	23	CC-1	Cis-platin+Mit-C	Liver	36	No
Male, 59y	14	CC-0	gemcitabine	Head of the pancreas	12	Yes
Male, 59y	3	CC-0	gemcitabine	-	Hospital death	No
Male, 54y	16	CC-0	gemcitabine	Liver, peritoneum	4	Yes
Male, 54y	22	CC-3	-		1	No
Female, 28y	9	CC-0	gemcitabine	Liver	12	No
Female, 35y	3	CC-0	Cis-platin+Mit-C	NED	12	No
Female, 69y	13	CC-0	Cis-platin+Mit-C	-	4 months	No

NED: no evidence of disease. For other abbreviations see text

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*

- Oxaliplatin 85 mg/m^2
- Irinotecan 180 mg/m^2 (150)
- Leucovorin 400 mg/m^2
- Fluorouracil bolus 400 mg/m^2 (remove)
- Fluorouracil CIV 2400 mg/m^2 (46 hrs)
    - Every 2 weeks

Median OS 11.1 mos vs 6.8 mos p<0.001
Response rate 32%

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

No. of measurable metastatic sites — no. of patients/total no. (%)		
Liver	149/170 (87.6)	150/171 (87.7)
Pancreas	90/170 (52.9)	91/171 (53.2)
Lymph node	49/170 (28.8)	39/171 (22.8)
Lung	33/170 (19.4)	49/171 (28.7)
Peritoneal	33/170 (19.4)	32/171 (18.7)
Other	18/170 (10.6)	29/171 (17.0)

NEJM 2011;364:1817-1825.

ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

- Gemcitabine 1000 mg/m^2
- Nab-Paclitaxel 125 mg/m^2
  - Days 1, 8, 15 every 28 days

Median OS 8.5 mos vs 6.7 mos p<0.001
Response rate 24%

Common Adverse Events Grade 3 or higher

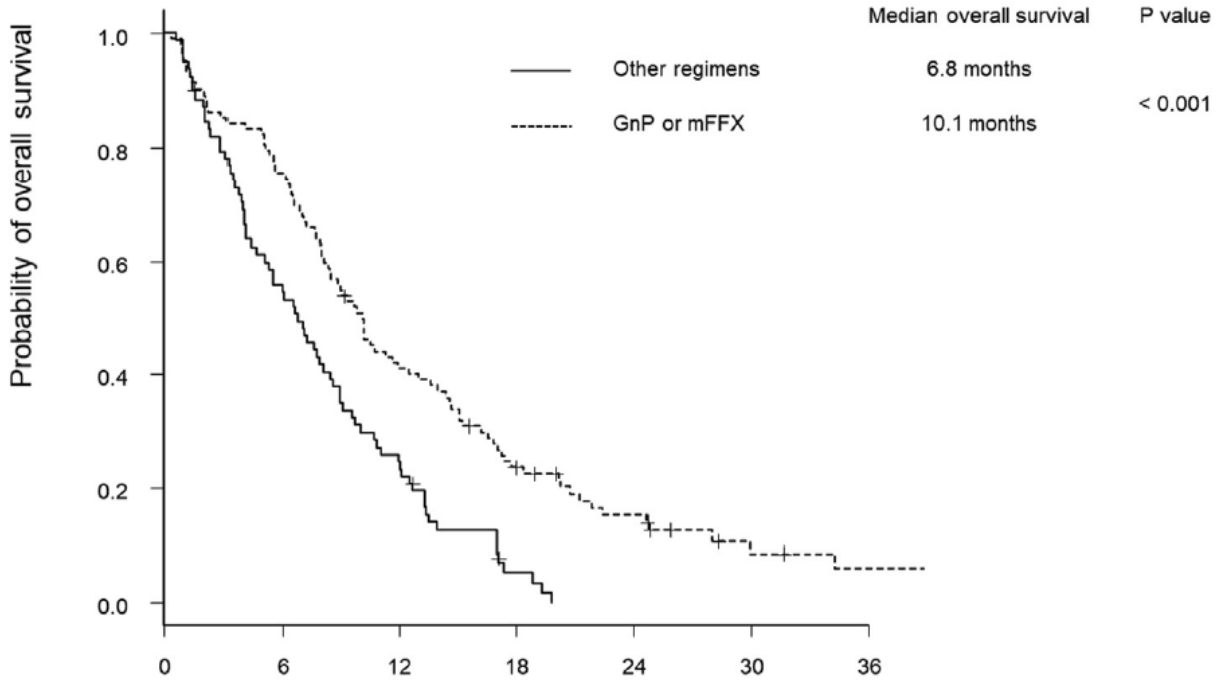
Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

Site of metastatic disease — no. (%)			
Liver	365 (85)	360 (84)	725 (84)
Lung	153 (35)	184 (43)	337 (39)
Peritoneum	19 (4)	10 (2)	29 (3)

NEJM 2013;369:1671-1703.

Modern chemotherapy has helped improve survival in pancreatic cancer (PC) patients with peritoneal carcinomatosis

- Retrospective review in Japan
- Synchronous peritoneal metastases (PM) has a very poor prognosis OS 3-6 months
- 180 PC patients with synchronous PM (88 GnP and 14 mFFX)
  - 89 peritoneal alone
  - 91 other distant sites

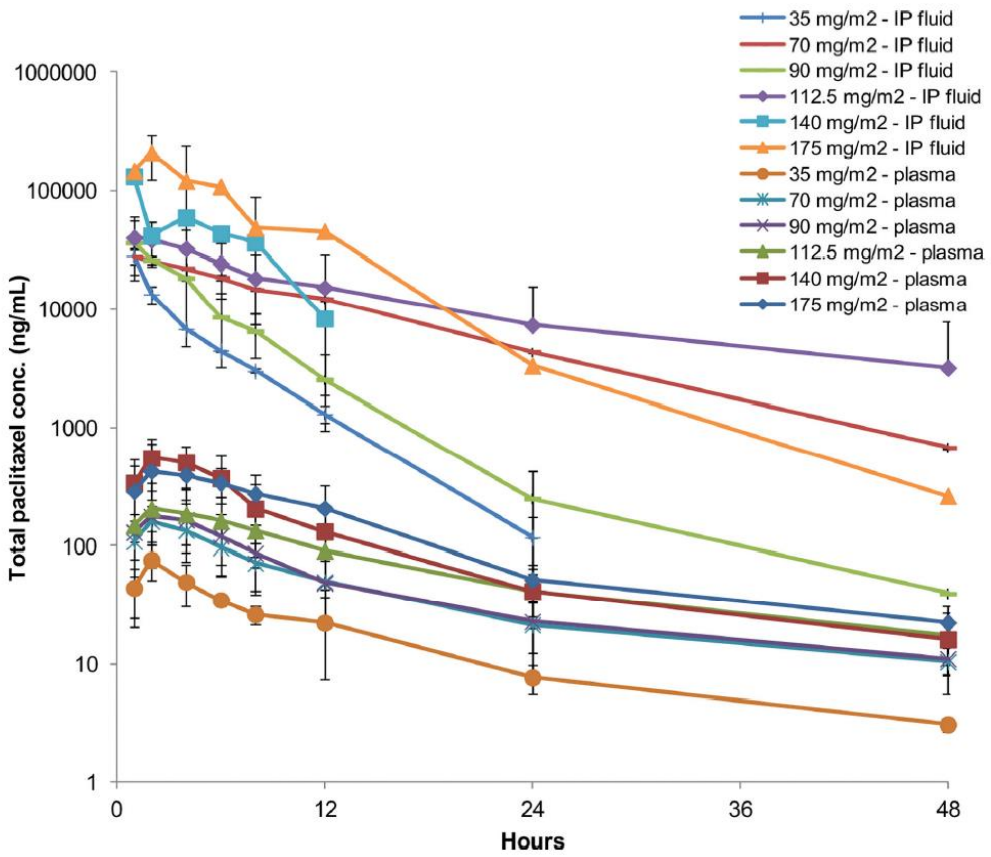


Objective response rate (28% vs. 5%, p < 0.001)
Disease control rate (73% vs. 47%, p < 0.001)

Pancreas Cancer has the Most Number of Negative 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)

A Phase I trial of intraperitoneal nab-paclitaxel in the treatment of advanced malignancies primarily confined to the peritoneal cavity



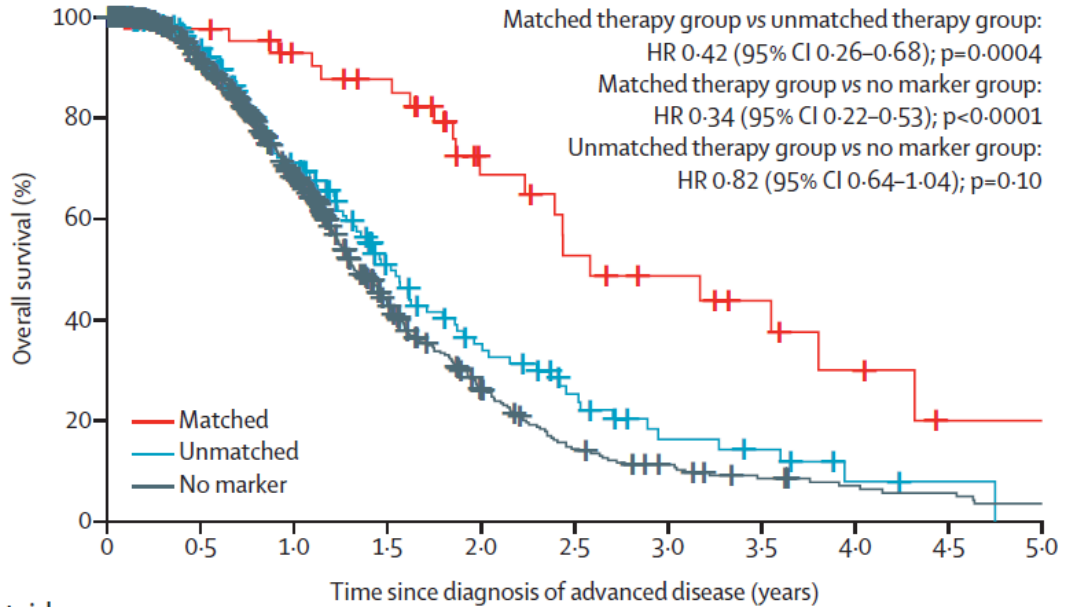
- Maximum tolerated dose (MTD) and pharmacokinetics (PK) of IP nab-paclitaxel
- MTD of IP nab-paclitaxel was established at 140mg/m2 on days 1, 8, and 15 of a 28-day cycle
- PK advantage of 147 fold
- Comparable to plasma concentrations of weekly IV administration of nab-paclitaxel at 100–130 mg/m2

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.

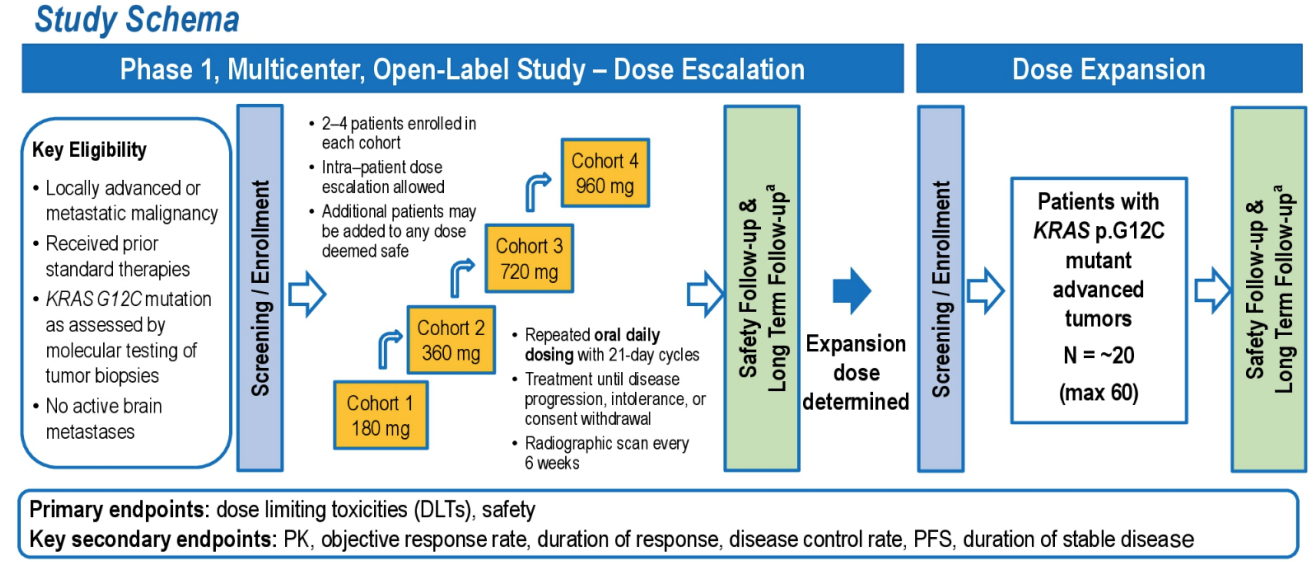


Lancet Oncology 2020; 21:508-18.

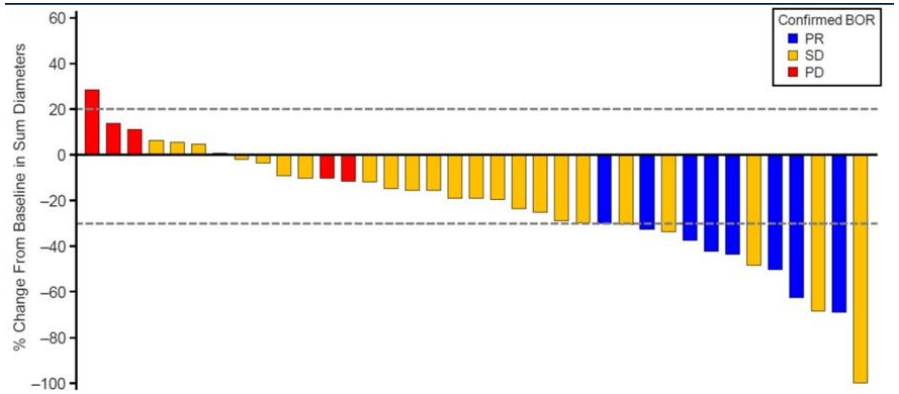
CodeBreak 100: Phase I study of AMG 510, sotorasib, in patients with advanced solid tumors (ASCO 2022 Strickler)

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

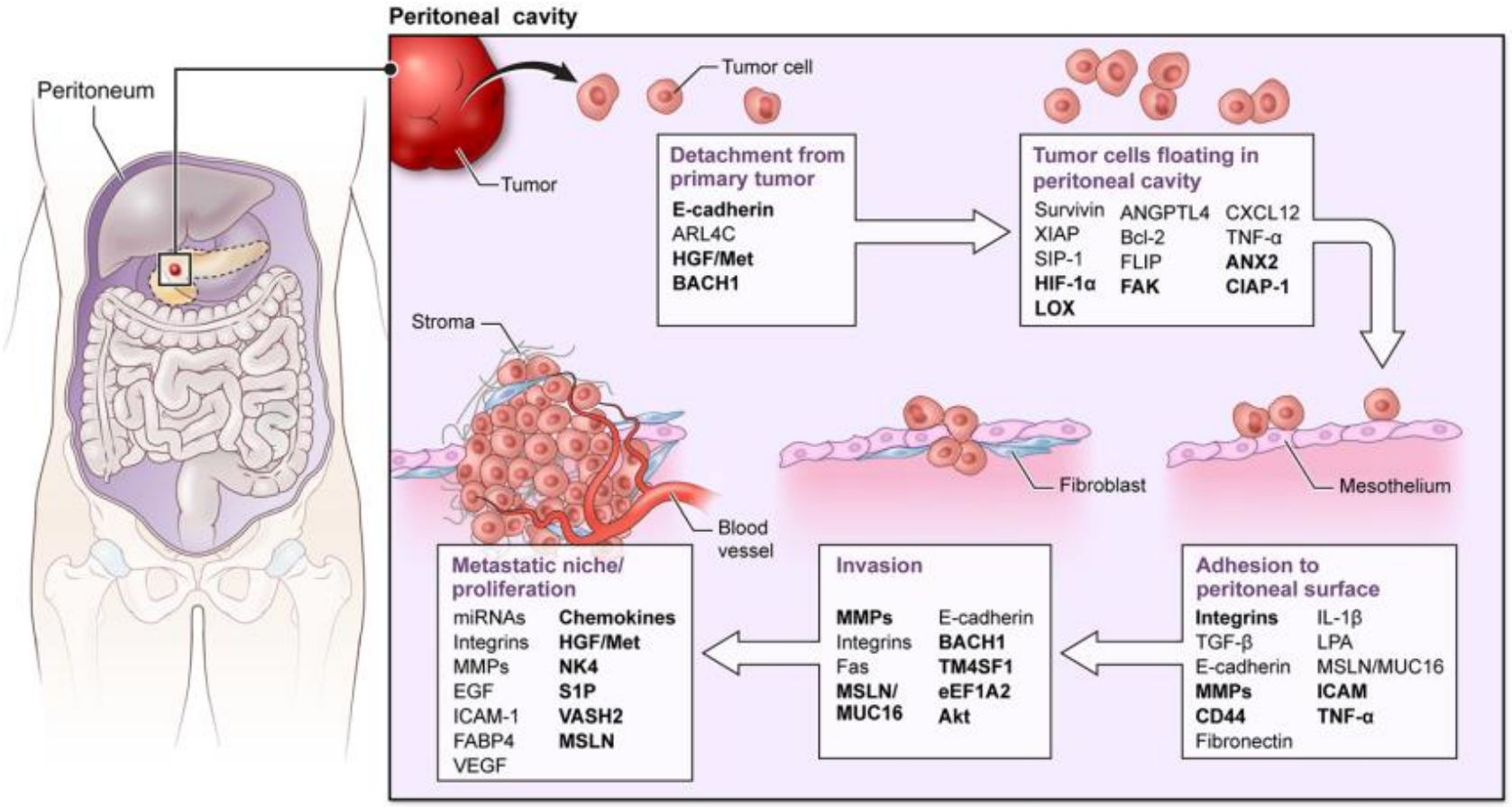


	All treatment-related AEs (TRAEs) N=38, n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	16 (42.1) 12 (31.6) 6 (15.8) 0 (0.0)
AEs leading to reduction or interruption of sotorasib	5 (13.2)
Serious AEs	3 (7.9)
Fatal AEs	0 (0.0)
AEs leading to sotorasib discontinuation	0 (0.0)



	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)

Molecular Alterations with Peritoneal Carcinomatosis

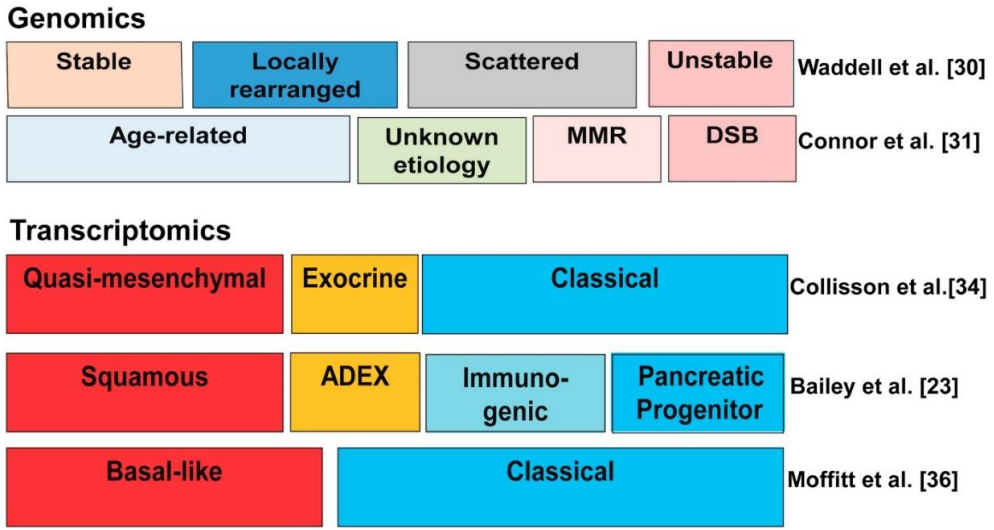


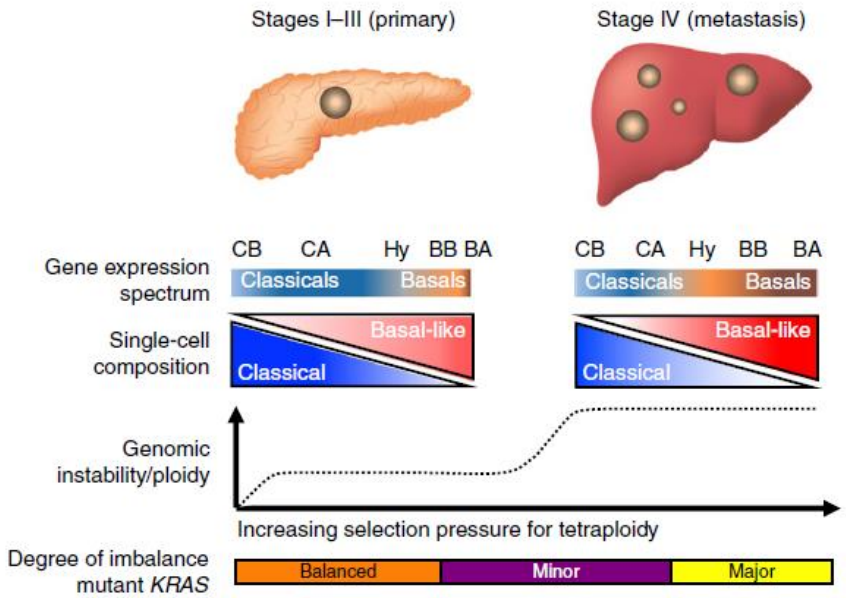
Cancer Metastasis Rev (2020) 39:1223–1243

- The classes of proteins important for peritoneal metastasis seem to be conserved across the different tumor types.
  - Cell adhesion
  - EMT
  - Apoptosis
  - Tumor suppression

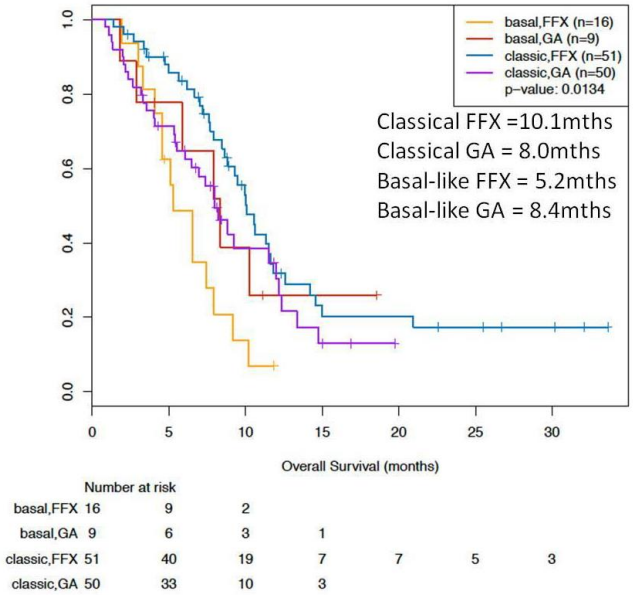
Pancreatic cancer is no longer one disease

Classifications of Pancreatic Cancer

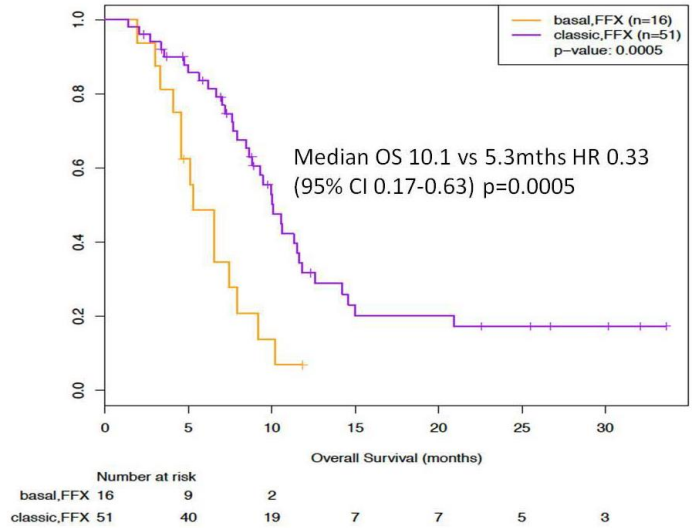




All patients≥ 1 dose chemo n=126



OS mFFX only n=67



- Classical subtype responded better to FOLFIRINOX chemotherapy

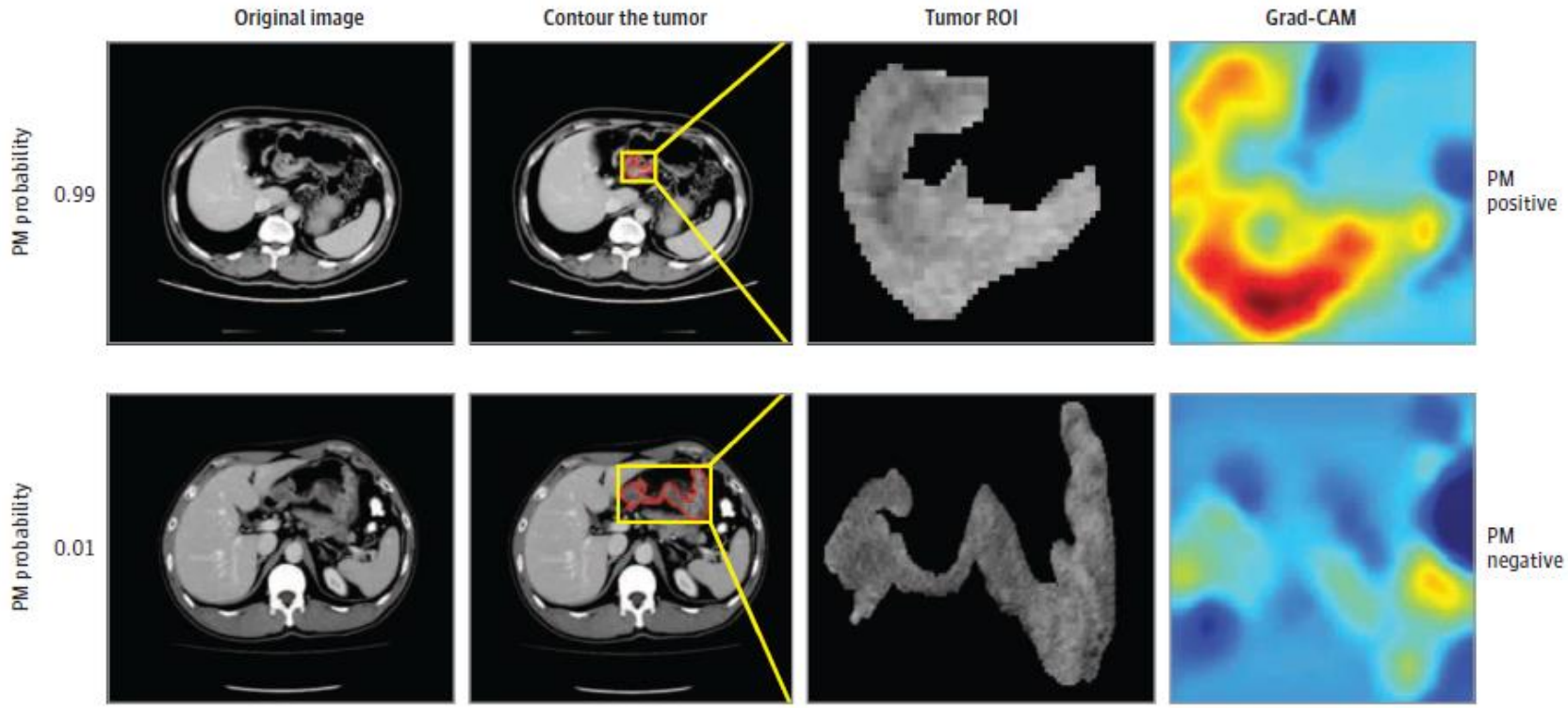
Le Large, et al. Seminars in Cancer Biology 2017.
Chan-Seng-Yue M, et al. Nature Genetics 2020.

Original Investigation | Imaging

Noninvasive Prediction of Occult Peritoneal Metastasis in Gastric Cancer Using Deep Learning

Yuming Jiang, MD, PhD; Xiaokun Liang, PhD; Wei Wang, MD; Chuanli Chen, MD; Qingyu Yuan, MD; Xiaodong Zhang, MD, PhD; Na Li, PhD; Hao Chen, MD; Jiang Yu, MD; Yaoqin Xie, PhD; Yikai Xu, MD, PhD; Zhiwei Zhou, MD, PhD; Guoxin Li, MD, PhD; Ruijiang Li, PhD

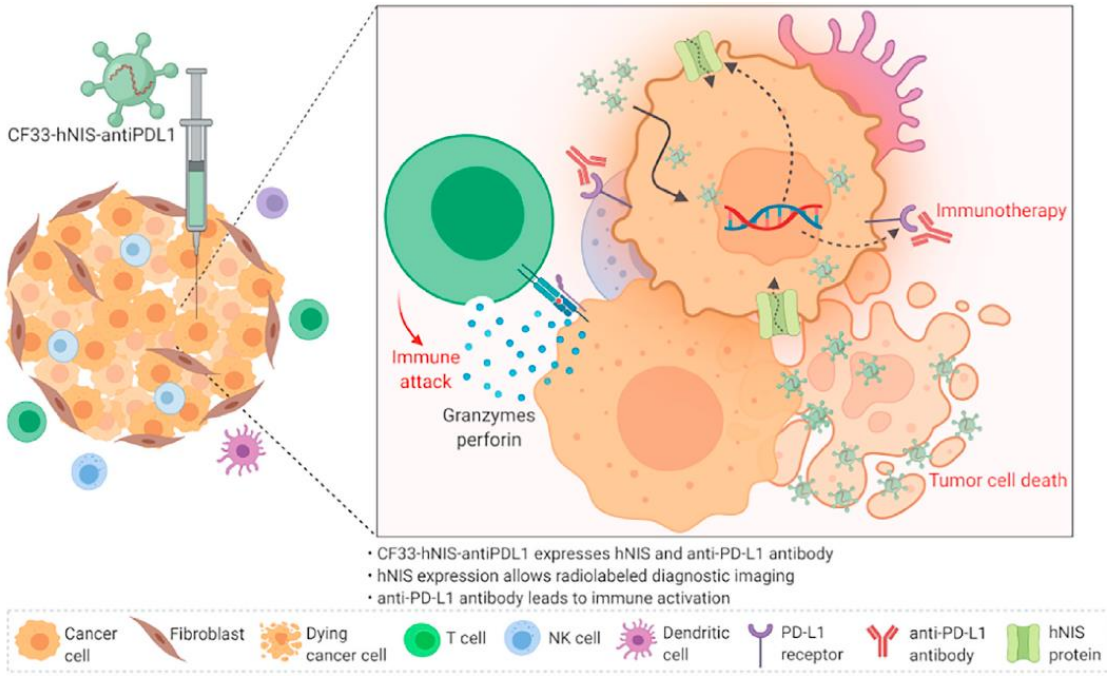
1. Two Representative Computed Tomography (CT) Images and the Corresponding Output From the Deep Learning Model

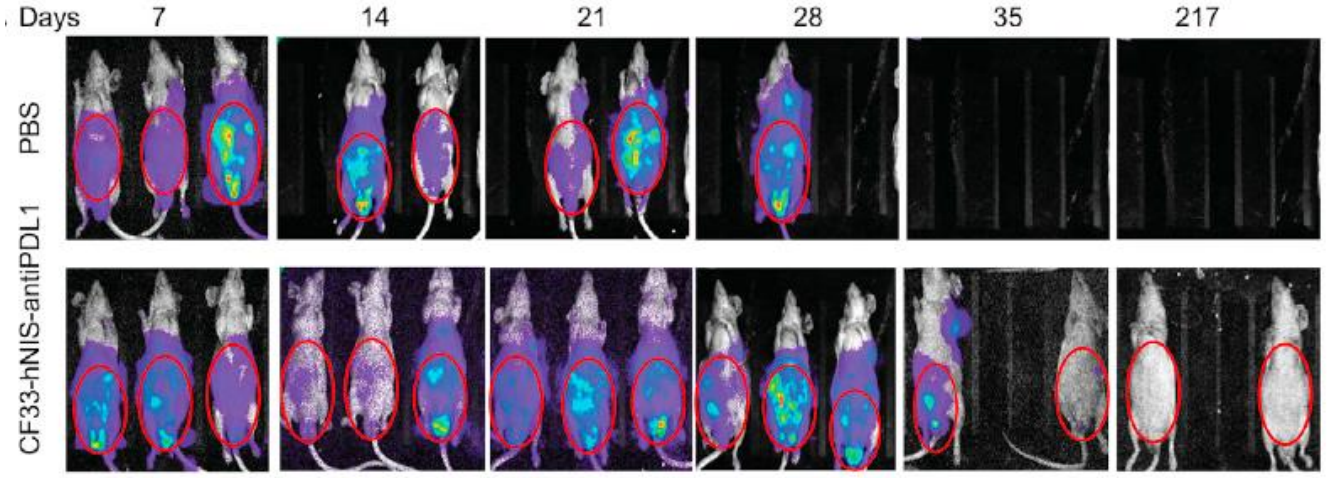


Model to predict peritoneal metastases prior to surgical resection

Sensitivity of 75.4%
Specificity of 92.9%

CF33-hNIS-antiPDL1 for pancreatic cancer with peritoneal carcinomatosis





- CF33 engineered chimeric orthopoxvirus with hNIS (sodium iodide transporter) and anti-PD-L1

Serial bioluminescence of CF33-hNIS-antiPDL1 treatment
By day 14, the CF33-hNIS-antiPDL1-treated group showed significantly lower s.c. tumor burden compared to the control group

Phase 1 clinical trial is currently on-going
ClinicalTrials.gov Identifier: NCT05346484

Zhang Z, et al. Molecular Therapy: Oncolytics Vol. 24 March 2022

Conclusions

- Pancreatic cancer is a systemic disease best controlled with chemotherapy
- Selection of patients is critical when considering local therapy
- Predictive models are needed to better define patients with peritoneal only disease
- Future is bright for novel therapeutics