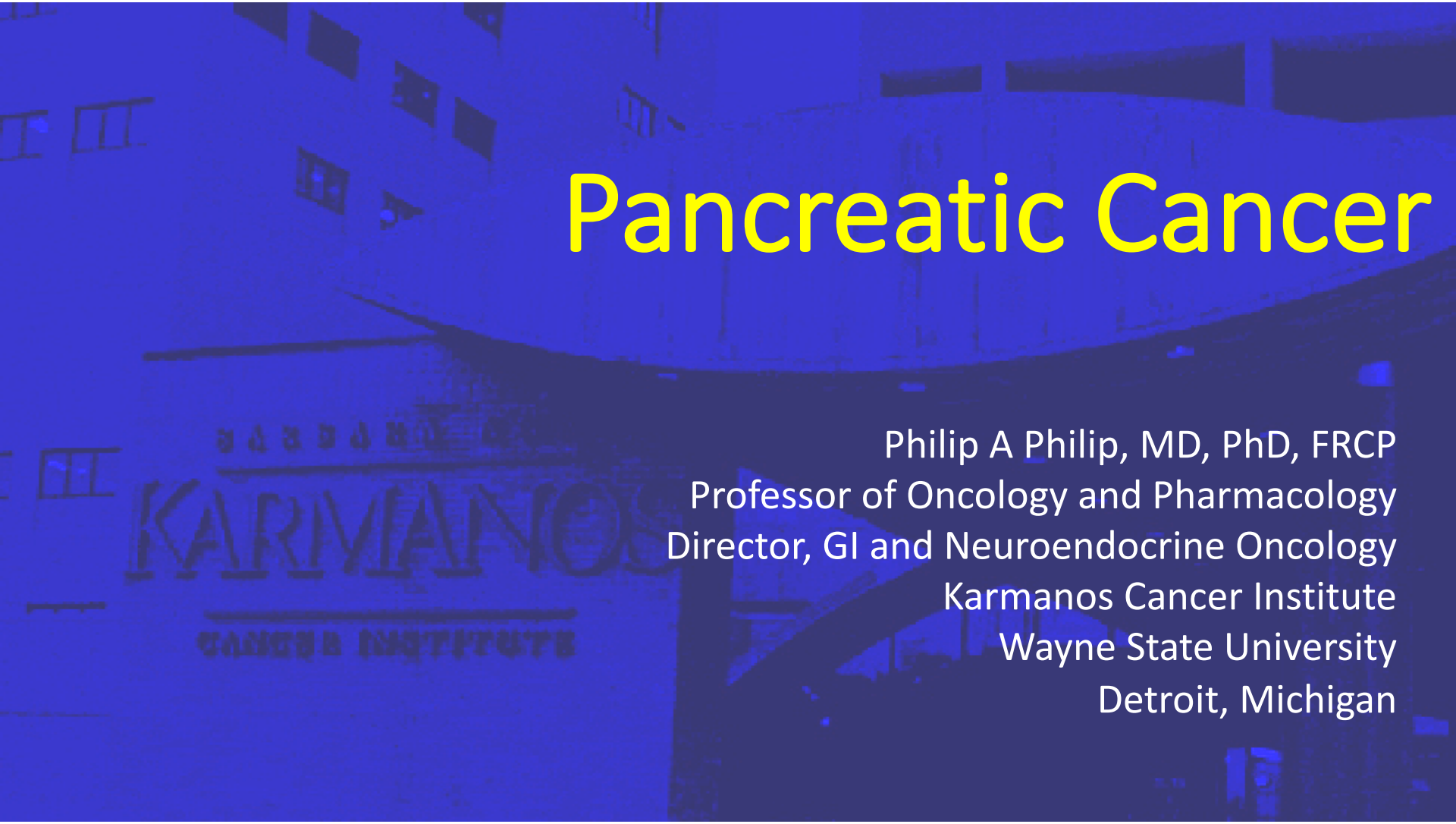



# Pancreatic Cancer

Philip A Philip, MD, PhD, FRCP
Professor of Oncology and Pharmacology
Director, GI and Neuroendocrine Oncology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

# Disclosures relevant to this presentation

- Research Grants:
  - Celgene, Halozyme
- Speaker:
  - Celgene, Merrimack
- Consultancy and Ad boards:
  - Merrimack, Halozyme, Celgene
- Stocks:
  - None

# Definitions of resectability of pancreatic cancer

| Category | Criteria |
|---|---|
| Resectable | Clear fat plane around celiac axis, hepatic artery, and SMA<br>No radiologic evidence of SMV or PV distortion |
| Borderline resectable | |
| Venous Involvement | SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal or distal, allowing for safe resection and replacement |
| Arterial Involvement | Encasement of short segment of hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the SMA involving $\leq 180^{\circ}$ of the artery circumference |
| Unresectable | |
| Venous Involvement | Major venous thrombosis of the PV or SMV extending for several centimeters |
| Arterial Involvement | Circumferential encasement of the SMA, celiac axis, or proximal hepatic artery |

PV = portal vein, SMA = superior mesenteric artery, SMV = superior mesenteric vein. Adapted from the National Comprehensive Cancer Network Guidelines.

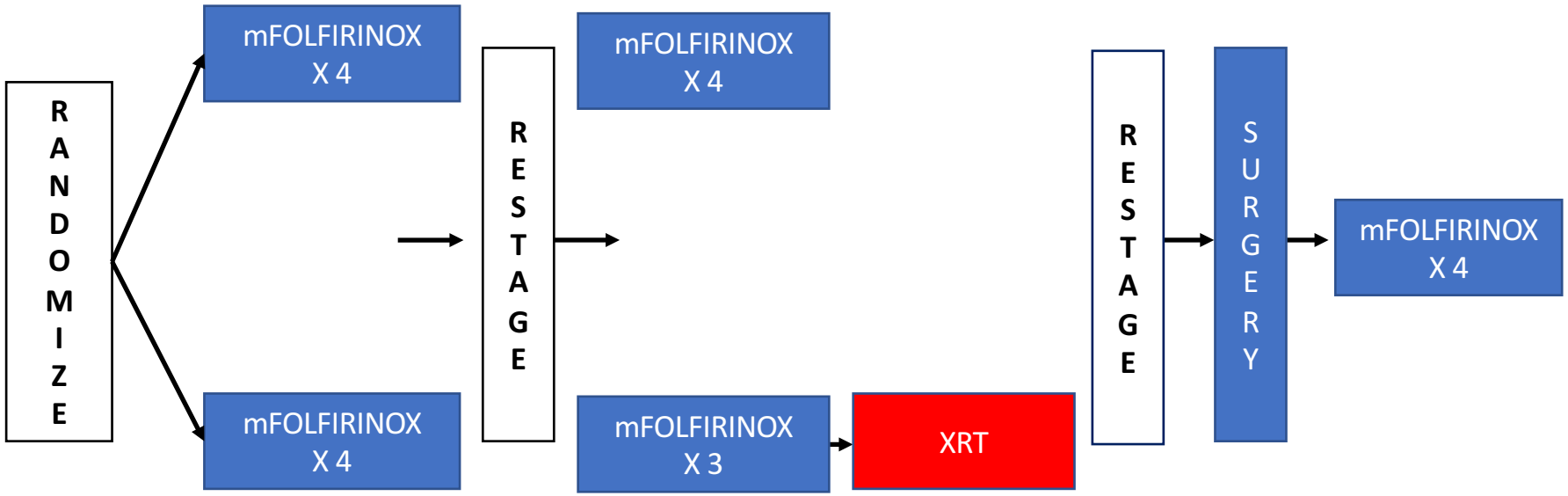
# Neoadjuvant FOLFIRINOX in localized pancreatic cancer

| Study | N | Stage | Resection Rate % | Path CR % | R0 resection % |
|---|---|---|---|---|---|
| **Katz et al*** | **22** | **Borderline** | **68%** | **13** | **93** |
| Blazer et al | 43 | Borderline/ Locally advanced | 51 | - | 85.7 |
| Hackert et al | 575 | Locally advanced | 61 | 5.3 | 41 |
| Kushman et al | 51 | Borderline/ Locally advanced | 25 | 2 | 70 |
| Petrelli et al | 253 | Borderline resectable/Locally advanced | 43 | - | 85 |
| Suker et al | 325 | Locally advanced | 25.9 | - | 74 |

*Prospective study

Katz et al, JAMA Surg, 2016; Hackert et al, Ann Surg 2016;264:457–463; Blazer et al, JCO 32 suppl 3, #274; Kushman et al, Pancreatology 15 (2015) 667e673, Pancreatology, 2015, 667-673; Nanda et al, J. Surg. Oncol. 111 (8) (2015) 1028–1034; Suker M et al, Lancet Oncol 2016; 17: 801–10; Petrelli Pancreas 2015;44: 515–521

# Alliance 021501: Preoperative chemotherapy and chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas



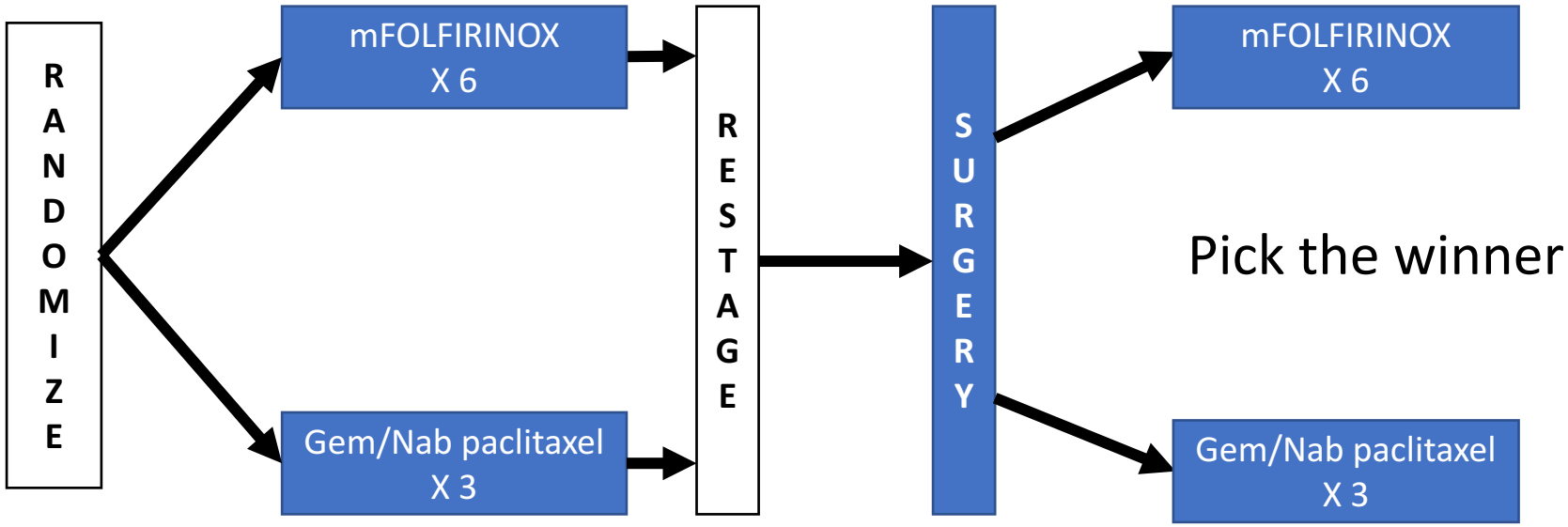

PI; Matthew Katz

# Neoadjuvant gemcitabine plus nab-paclitaxel in localized pancreatic cancer

| Study | N | Stage | RECIST response % | Resection Rate % | R0 resection % |
|---|---|---|---|---|---|
| Ielpo et al | 25 | Resectable/ borderline Resectable | 30 | 68 | 100 |
| Van Laethem et al | 23 | Borderline resectable/ Locally advanced | 35 | 56 | 50 |
| Barbour et al | 41 | Resectable | 26 | 73 | 52 |

Ielpo et al, EJSO, 42;1394-1400, 2016; Van Laethem et al, ASCO 2016, 4116; Barbour et al, JCO 34, 2016 (suppl; abstr 4105)

# SWOG-S1505: Randomized Phase II Study of Perioperative mFOLFIRINOX vs. Gemcitabine/nab-Paclitaxel in Resectable Pancreatic Cancer




PI; Matthew Katz

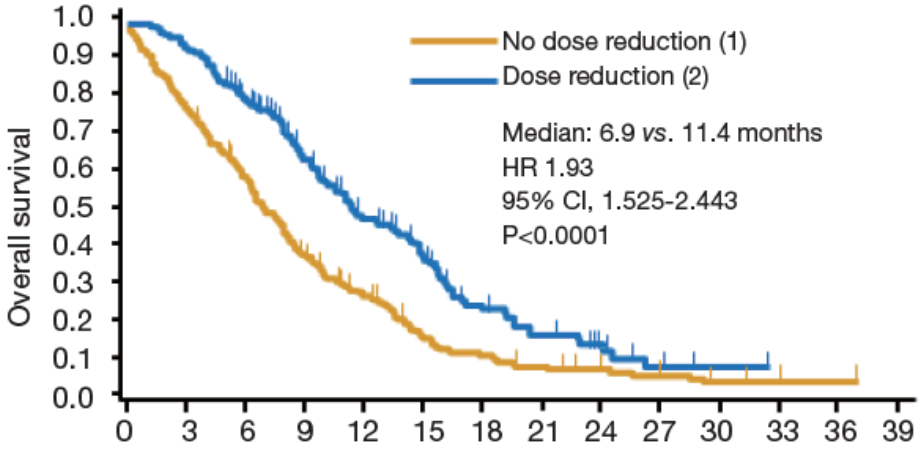
# Dose modifications of FOLFIRINOX regimen

| Study | N | Modifications | | Fatigue Gr 3 or 4 (%) | Diarrhea Gr 3 or 4 (%) | RR (%) | mPFS (months) |
|---|---|---|---|---|---|---|---|
| | | IRI | Bolus FU | | | | |
| Ueno | 69 | 150 mg/m$^2$ | Removed | <5 | 10.1 | 47.8 | 5.5 |
| Stein* | 74 | Reduce by 25% | Reduced by 25% | 2.7 | 16.2 | 35.1 | 6.1 |
| Mahaseth | 60 | Full dose | Removed | 13 | 13 | 30 | 8.5 |

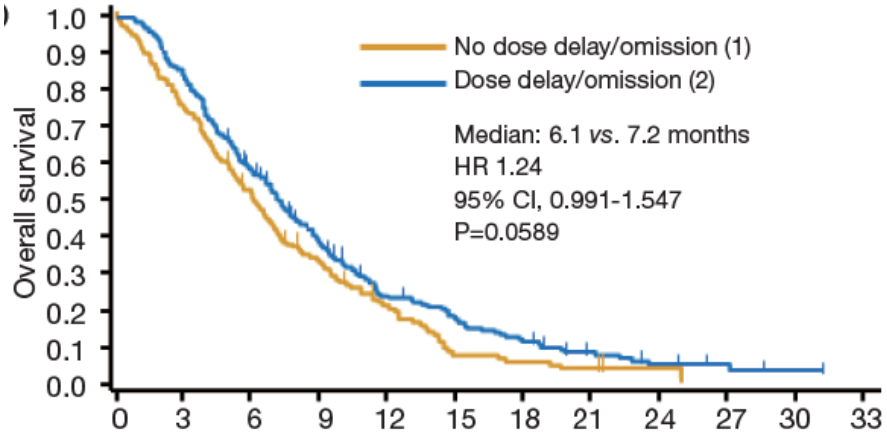
*Prospective

Ueno M et al, Proc ASCO 2016;Abstract 4111; Stein et al, BJC, 2016, 114:737-43; Mahaseth H et al, Pancreas 2013;42(8):1311-5.

# MPACT trial: no deleterious effects of dose reductions/delays on overall survival




Gemcitabine and nab paclitaxel arm




Gemcitabine arm

Nab paclitaxel dosing

- Dose reductions in 41%
- Dose delays in 71%
- Increased cumulative dosing with dose modification

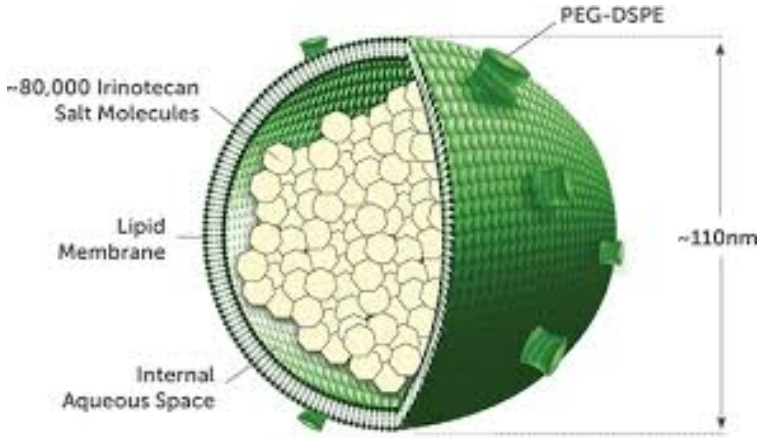
Scheithauer W et al, J Gastrointest Oncol 2016;7(3):469-478

# Modification of gemcitabine and nab paclitaxel regimen: an every other week schedule

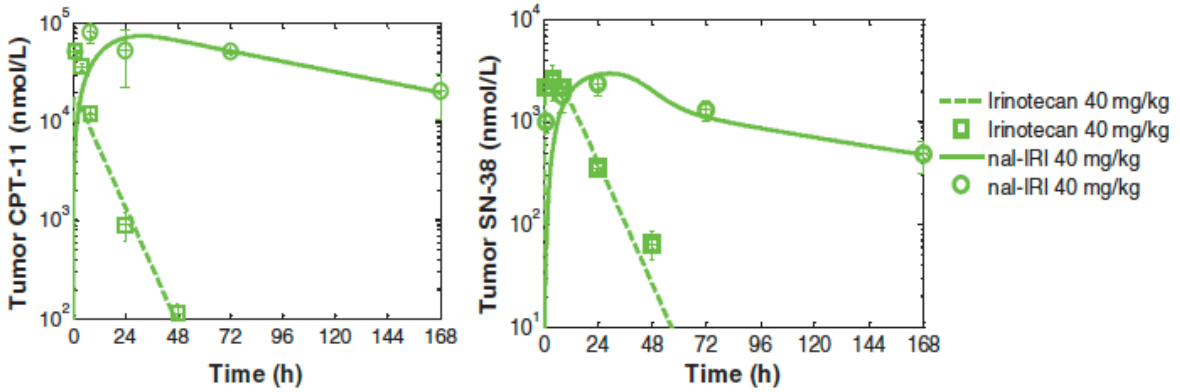
| | Krishna et al[1] | MPACT[2] |
|---|---|---|
| N | 49 | 421 |
| Median age | 65 | 62 |
| Median PFS in months | 4.8 | 5.5 |
| Median OS in months | 11.1 | 8.5 |
| Growth factor use, % | 6 | 26 |
| Neutropenic fever, % | 2.1 | 3 |
| Fatigue (Gr 3 or 4), % | 6 | 17 |
| Thrombocytopenia (Gr 3 or 4), % | 4 | 13 |

[1] Krishna K et al. Gastrointestinal Cancers Sympsium 2015;Abstract 366.
[2] Von Hoff DD et al. *N Engl J Med* 2013;369:1691-703.

# Nano-liposomal packaging of irinotecan



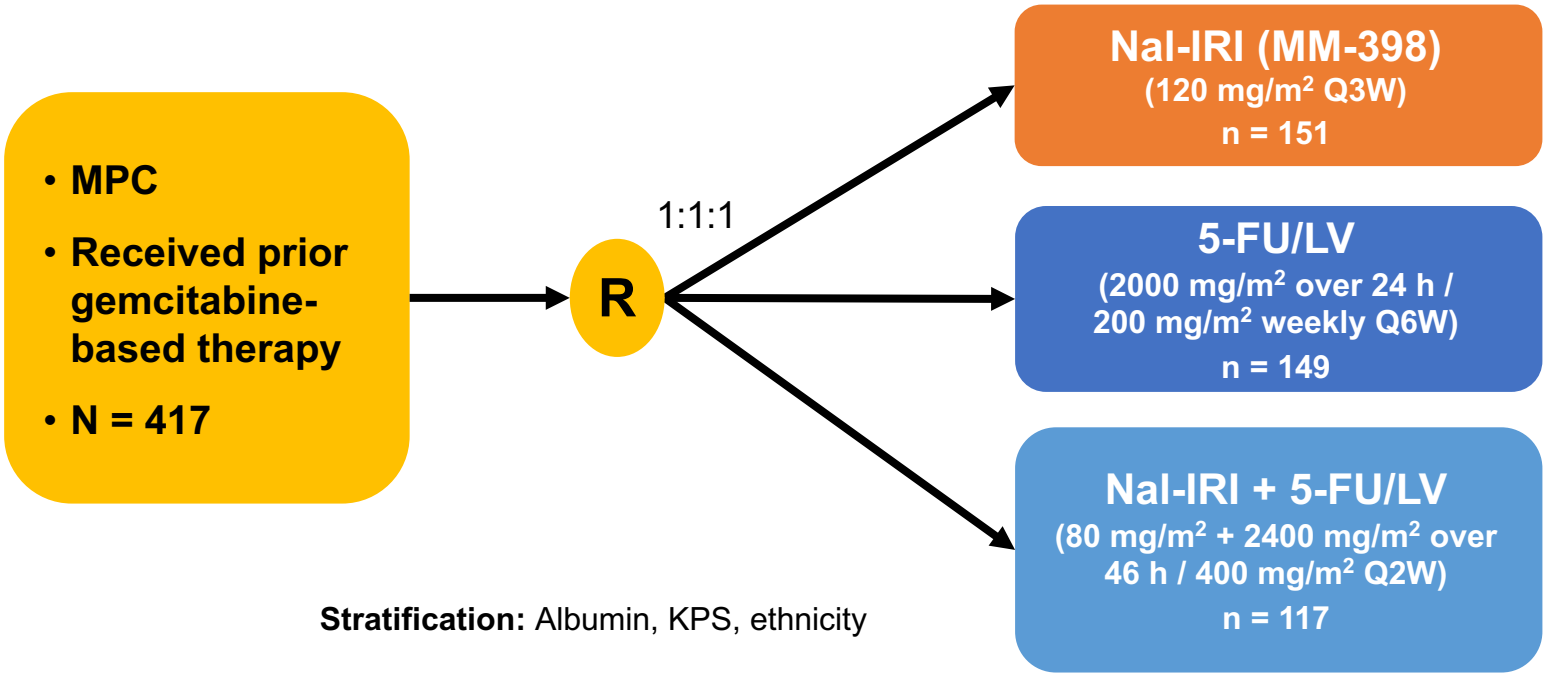

| | Free IRI | nal-IRI |
|---|---|---|
| $AUC_{0\text{-}00}$ | 26,159 | 1,812,221 |
| Plasma Clearanace $mL/h/m^2$ | 12,886 | 191 |
| Half life in hours | 7.7 | 21.2 |




Kalra et al, Cancer Res, 74:7003-7013, 2014; Ko A, Int J Nanomedicine, 11:1225-1235, 2016; Kalra et al, Cancer Res; 74(23); 7003–13. 2014

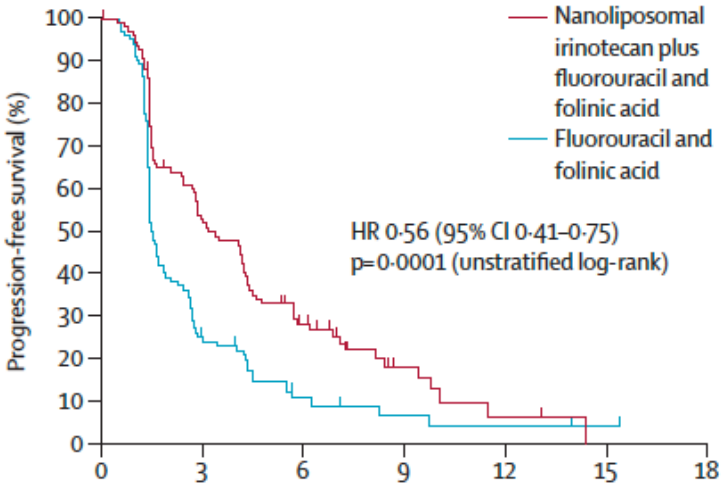
# Phase 3 trial of nano-liposomal irinotecan + 5-FU/LV as 2nd-line therapy for metastatic pancreatic cancer (NAPOLI-1)

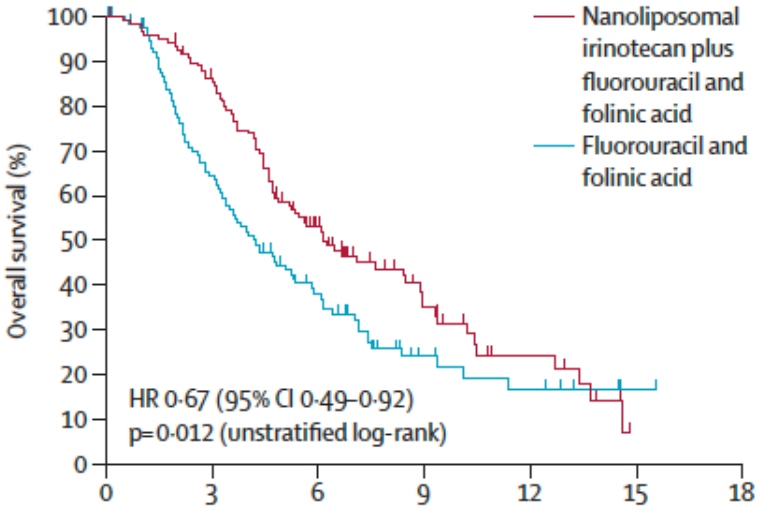
Primary endpoint: OS
Secondary endpoints: PFS, ORR, CA19-9 response, safety




Wang-Gillam et al. Lancet 2016;387:536

# NAPOLI-1: Study outcome




| Grade 3 or 4 Toxicity | Nal-IRI/5-FU/LV | 5-FU/LV |
|---|---|---|
| Diarrhea | 13 | 4 |
| Vomiting | 11 | 3 |
| Appetite | 4 | 2 |
| Fatigue | 14 | 4 |
| Neutropenia | 27 | 1 |

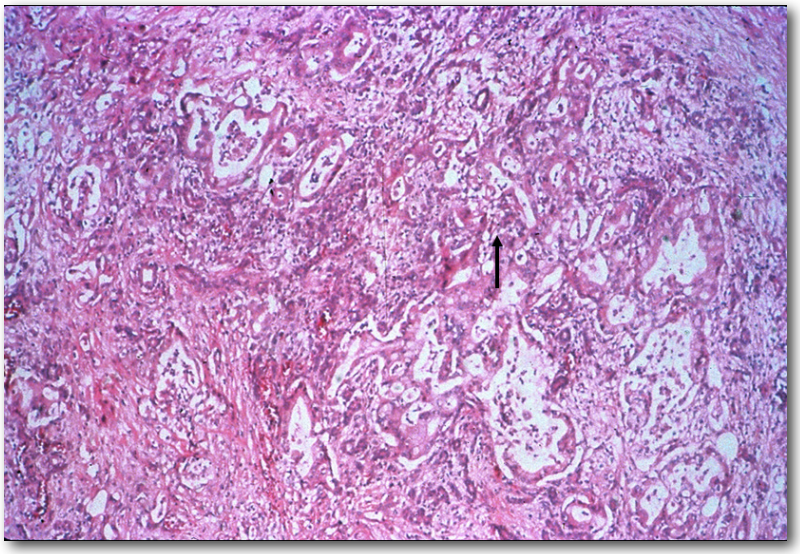
Wang-Gillam A, et al. the Lancet Oncology, 2015; Update Wang-Gillam, et al, JCO, 2016, 34:abstract 2016

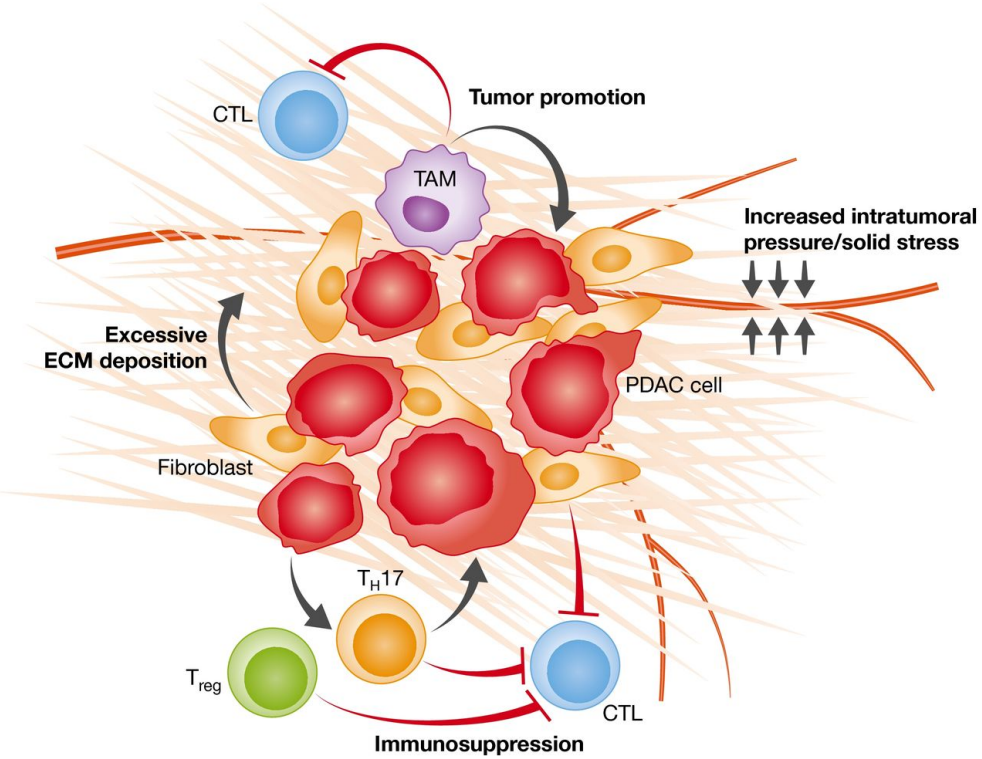
# Comparing second-line phase III trials of 5-FU-based combinations after gemcitabine failure

| | NAPOLI-1 | | CONKO-003 | | PANCREOX | |
|---|---|---|---|---|---|---|
| | Nal-IRI/5-FU/LV | 5-FU/LV | Oxali-FU | 5-FU/LV | mFOLFOX | 5-FU/LV |
| # of centers | 14 | | 1 | | 1 | |
| Patient numbers | 117 | 134 | 76 | 84 | 54 | 54 |
| PFS in months | 3.1 | 1.5 | 2.9 | 2.0 | 3.1 | 2.9 |
| OS in months | 6.2 | 4.2 | 5.9 | 3.3 | 6.1 | 9.9 |
| Withdrawals due to toxicity, % | 11.1 | 7.5 | | | 20 | 1.9 |
| Objective responses, % | 16 | 1 | | | 13.2 | 8.5 |

Wang-Gillam, et al, JCO, 2016, 34:abstract 2016; Oettle et al, JCO, 32:2423-2429, 2014; Gill S et al, JCO 2016

# Targeting the pancreatic cancer microenvironment and the very dense stroma

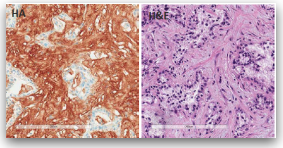





Carr RM and Fernandez-Zapico ME, EMBO Molecular Medicine, 2016

# Targeting hyaluronic acid (HA) in the stroma by pegylated recombinant human hyaluronidase (PEGPH20) in stage 4 pancreatic cancer

| PEGPH20 + | Phase | Status | N |
|---|---|---|---|
| mFOLFIRINOX | Ib/RP2 | Ongoing | 170 |
| Gem/nab-paclitaxel | RP2 | Completed | 279 |
| Gem/nab-paclitaxel | III | Launched 2016 (in high HA only) | 420 |




Expected HA positivity by IHC = 35-40%

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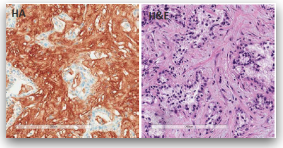
Press release 1/5/2017

| Study 202 | PEG + AG | AG |
|---|---|---|
| mPFS in months | | |
| High HA | 8.6 | 4.5 |
| All evaluable patients | "Statistically significant improvement" | |
| Thrombo-embolic events | "Significant improvement with LWMH in PEG treated pts" | |

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# *Thank You*

philipp@karmanos.org