Update on Pancreatic Cancer

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Overview

- Current Systemic Treatments
  - Adjuvant Chemotherapy in resected PDAC
  - Neoadjuvant Treatment
  - Metastatic Disease
- New Developments

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Principles of Multidisciplinary Treatment Based on Resectability

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Q: Which Patients Need Chemotherapy????

A: All Patients!!!

- Resectable:
  - *Before (=neoadjuvant) OR after surgery (adjuvant)*
- Borderline resectable / locally advanced
  - *Neoadjuvant, followed by surgery if resectable*
- Metastatic
  - *Combo or single agent based on patient's status*

Important: Discuss Goals of Chemotherapy (potentially curable vs life extending vs palliative) ahead of time

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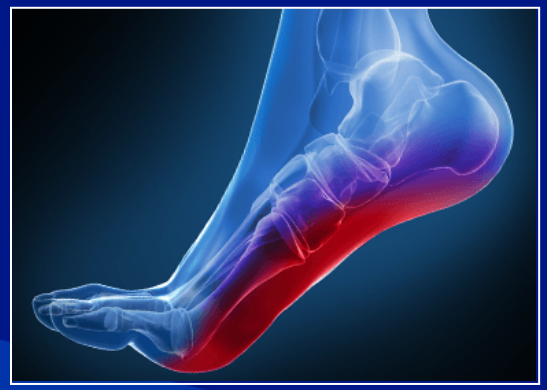
Chemotherapy Side Effects

- **Q:** If the patient is symptomatic from the cancer (abdominal pain, anorexia, nausea/vomiting, weight loss etc), and the chemo shrinks the tumor, what will happen?
- **A:** The patient actually starts feeling better!!! First symptom to improve is usually the pain.
- **Main side effects expected:**

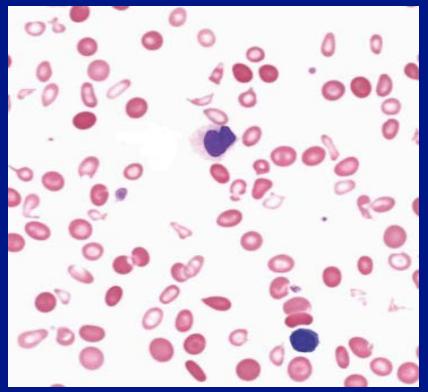
Fatigue

Diarrhea
Constipation

Nausea
Vomiting



Numbness
Tingling



Cytopenia

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Adjuvant Chemotherapy

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

Prof John P Neoptolemos, MD, Prof Daniel H Palmer, PhD, Prof Paula Ghaneh, MD, Eftychia E Psarelli, MSc, Juan W Valle, MD, Christopher M Halloran, MD, Olusola Faluyi, MD, Derek A O'Reilly, MD, Prof David Cunningham, MD, Prof Jonathan Wadsley, MD, Suzanne Darby, MD, Prof Tim Meyer, MD, Roopinder Gillmore, MD, Alan Anthoney, MD, Pehr Lind, MD, Bengt Glimelius, MD, Stephen Falk, MD, Prof Jakob R Izbicki, MD, Gary William Middleton, MD, Sebastian Cummins, MD, Paul J Ross, MD, Harpreet Wasan, MD, Alec McDonald, MD, Tom Crosby, MD, Yuk Ting Ma, MD, Kinnari Patel, MD, David Sherriff, FRCR, Rubin Soomal, MD, David Borg, MD, Sharmila Sothi, MD, Prof Pascal Hammel, MD, Thilo Hackert, MD, Richard Jackson, PhD, Prof Markus W Büchler, MD

The Lancet
Volume 389, Issue 10073, Pages 1011-1024 (March 2017)
DOI: 10.1016/S0140-6736(16)32409-6

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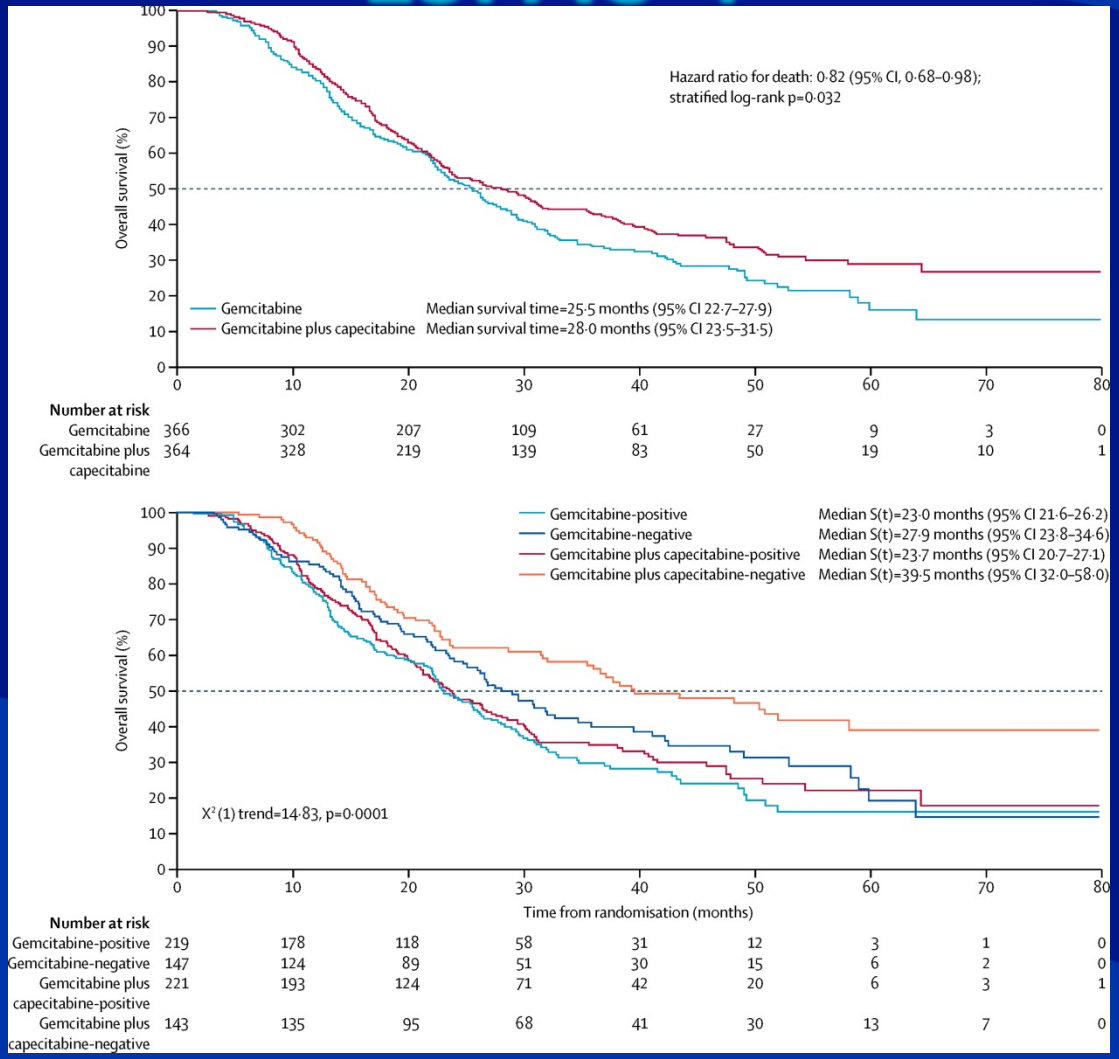
ESPAC-4



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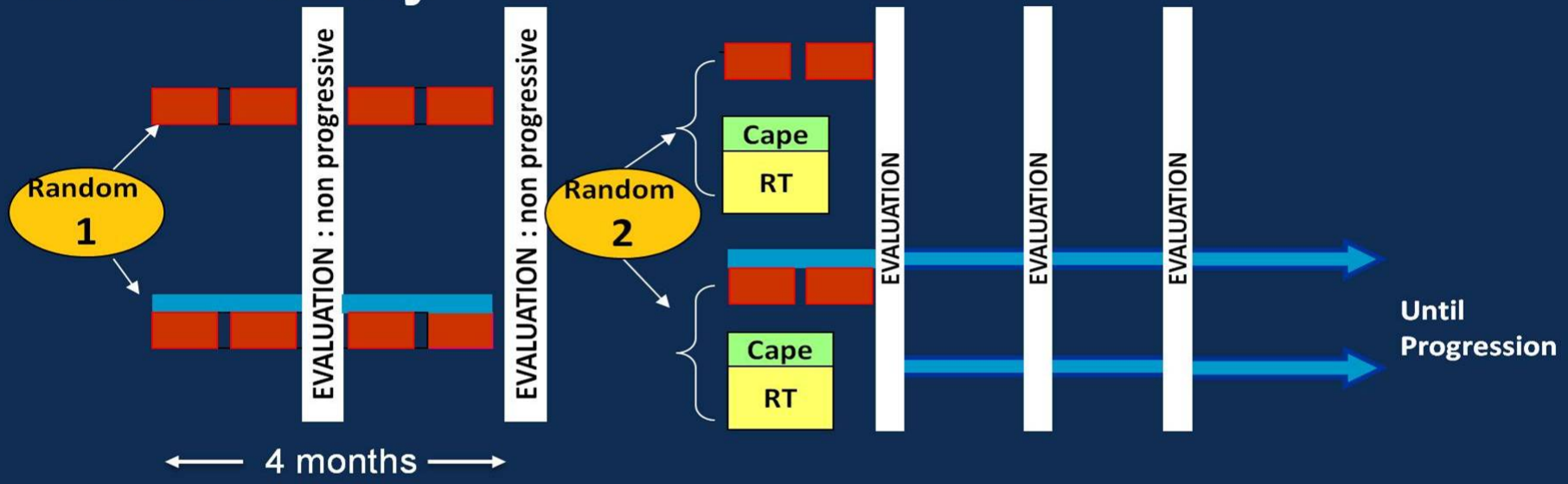
Locally Advanced Pancreatic Cancer: LAP-07 study



1 month = Gemcitabine 1000 mg/m²/wk x 3

Cape / RT — *Capecitabine 1600 mg/m²/d plus radiation therapy 54 Gy (5 x 1.8 Gy/d)*

Erlotinib with gem : 100 mg/d

150 mg/d as single agent (maintenance)

Secondary surgery allowed at any time

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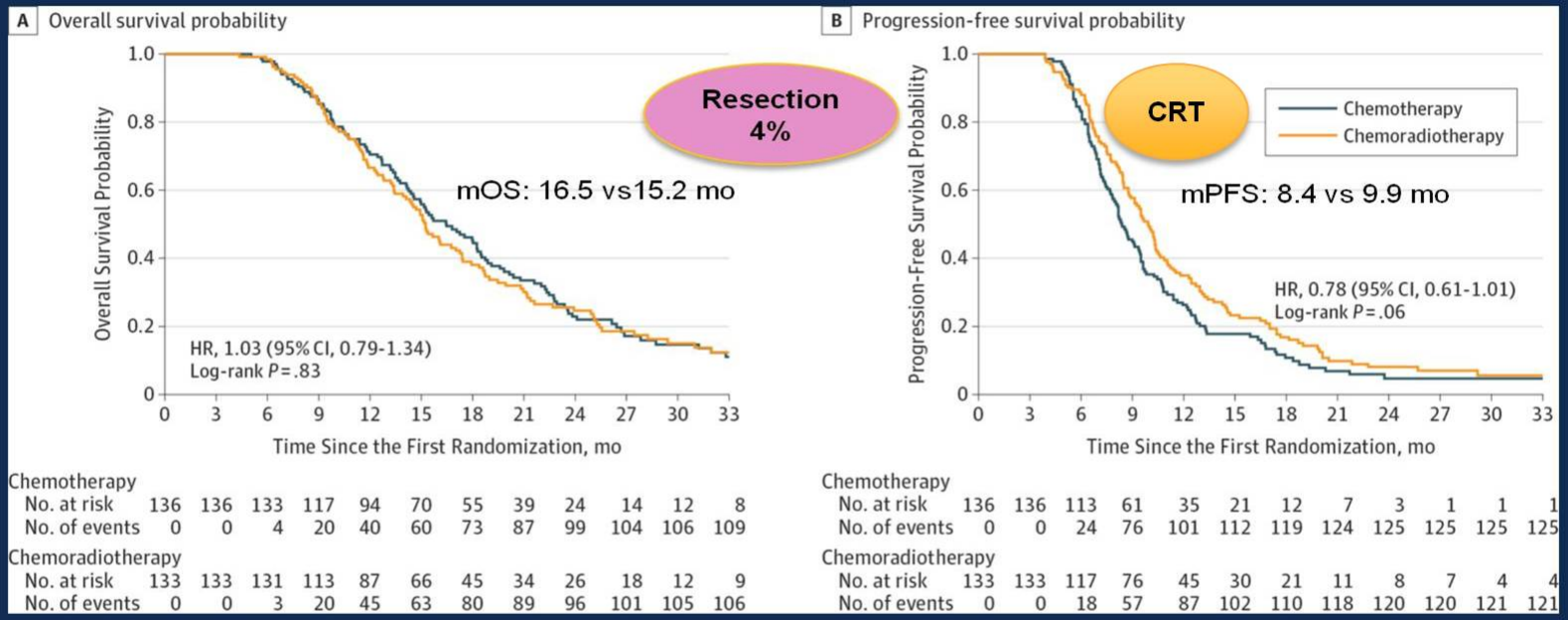
OS and PFS by Second Randomization



Local Progression: 32% CRT vs 46% Chemo

Hammel P, et al, *JAMA 2016*

Time to treatment reintroduction: 6.1 m CRT vs 3.7 m Chemo

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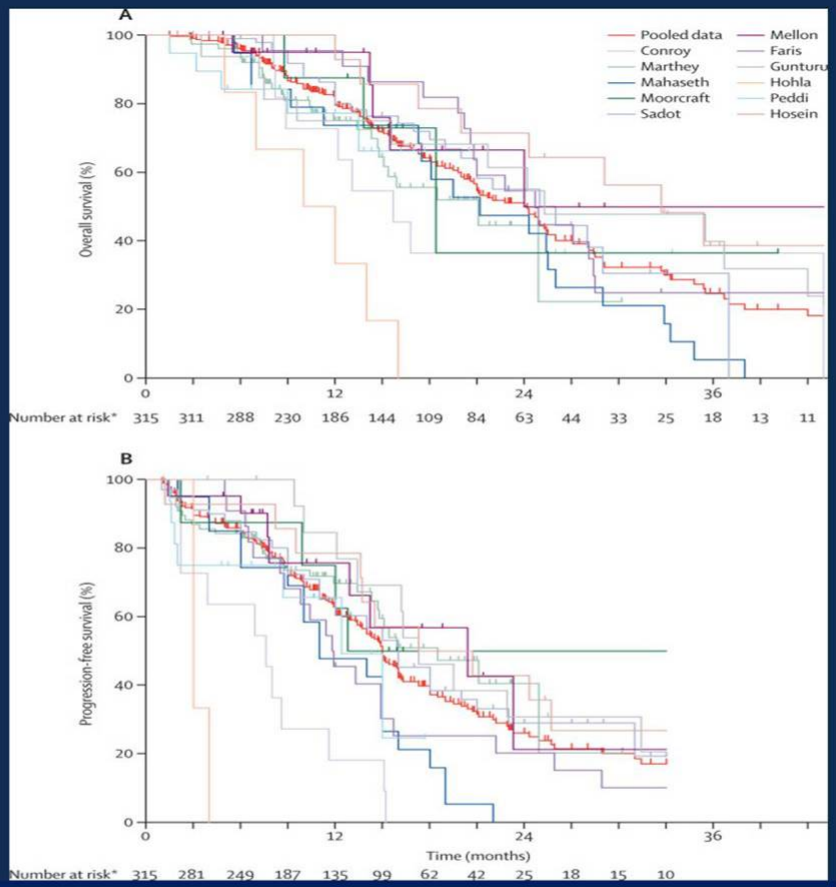
Meta-analysis FOLFIRINOX in LAUPC

11 studies / 315 patients

RT: 30-100%

Resection: 26% / R0 74%

OS: range 10-33 mos
PFS: range 3-20 mos



mOS
24.2 mos

mPFS
15.0 mos

Sucker M, et al, Lancet Oncol 2016

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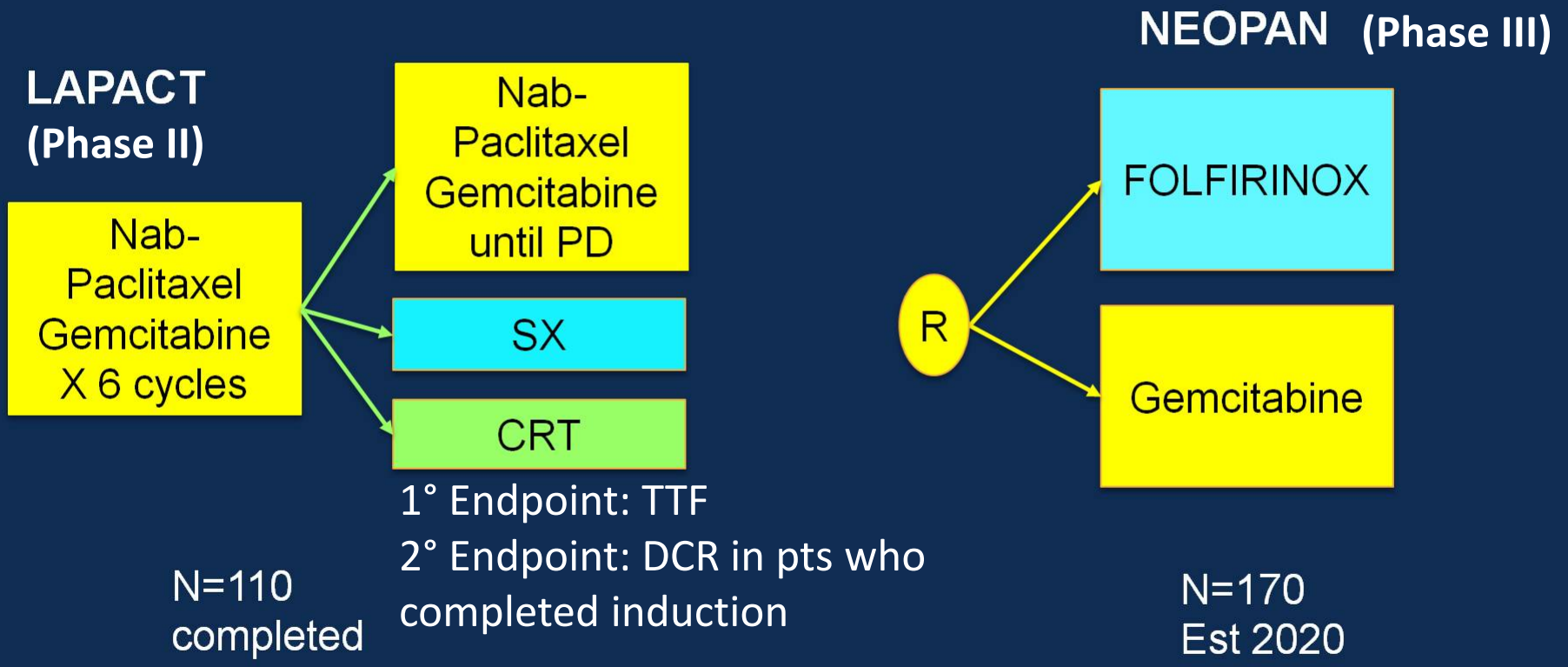
Contemporary LAUPC Trials



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LAPACT Trial

- N= 101 pts included
- N= 60 (59%) completed induction
- N= 93 evaluable; DCR= 82% (n= 33 PR)
- N=14 (13.9%) underwent surgery (R0, n = 4; R1, n = 6; R2, n = 1; 3 missing)

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LAUPC Treatment Guidelines: NCCN / ASCO

- Multi-agent chemotherapy such as FOLFIRINOX or nab-Paclitaxel / Gemcitabine
- Induction chemotherapy – adequate course (NCCN)
  - at least 6 months (ASCO)
- Unknown if CRT benefits after induction FOLFIRINOX or NabP/Gem (not after Gem)
- If local PD (no mets) after induction chemo: ⇒ CRT or SBRT
- If PR or SD after induction chemo but + toxicity: ⇒ CRT or SBRT
- If no benefit from 1st line induction chemo: 2nd line chemo (~ metastatic regimen)

NCCN 2016, Balaban EP et al, JCO 2016

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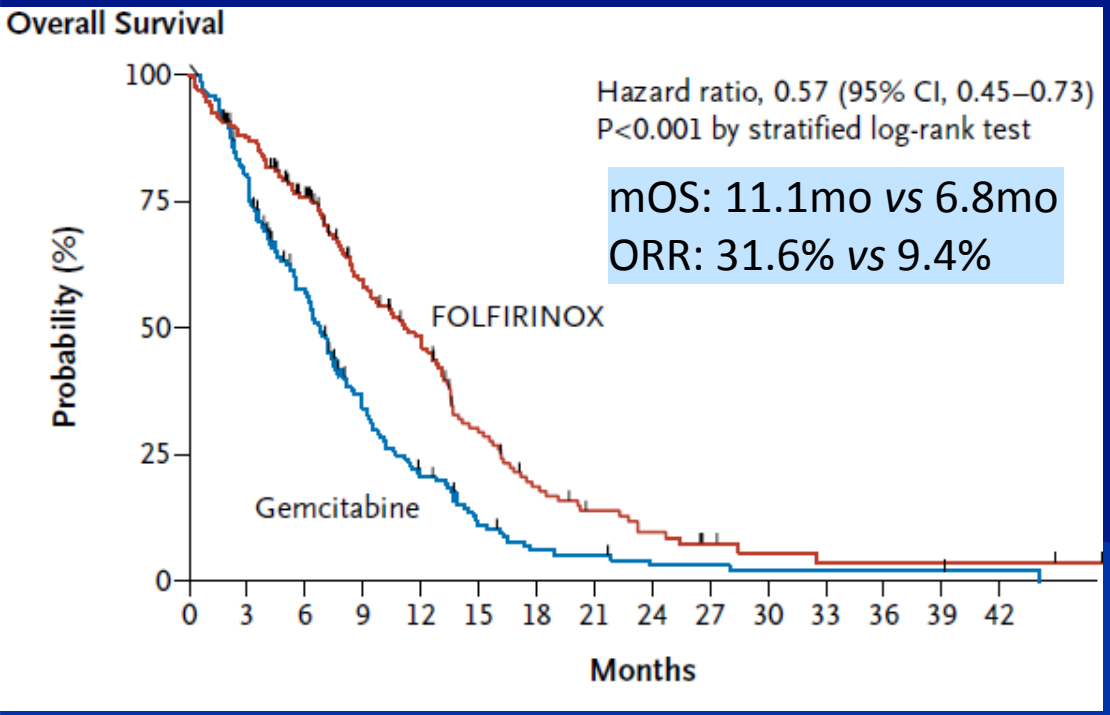
Recurrent/Metastatic

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

The NEW ENGLAND JOURNAL *of* MEDICINE



mOS: 11.1mo *vs* 6.8mo
ORR: 31.6% *vs* 9.4%

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

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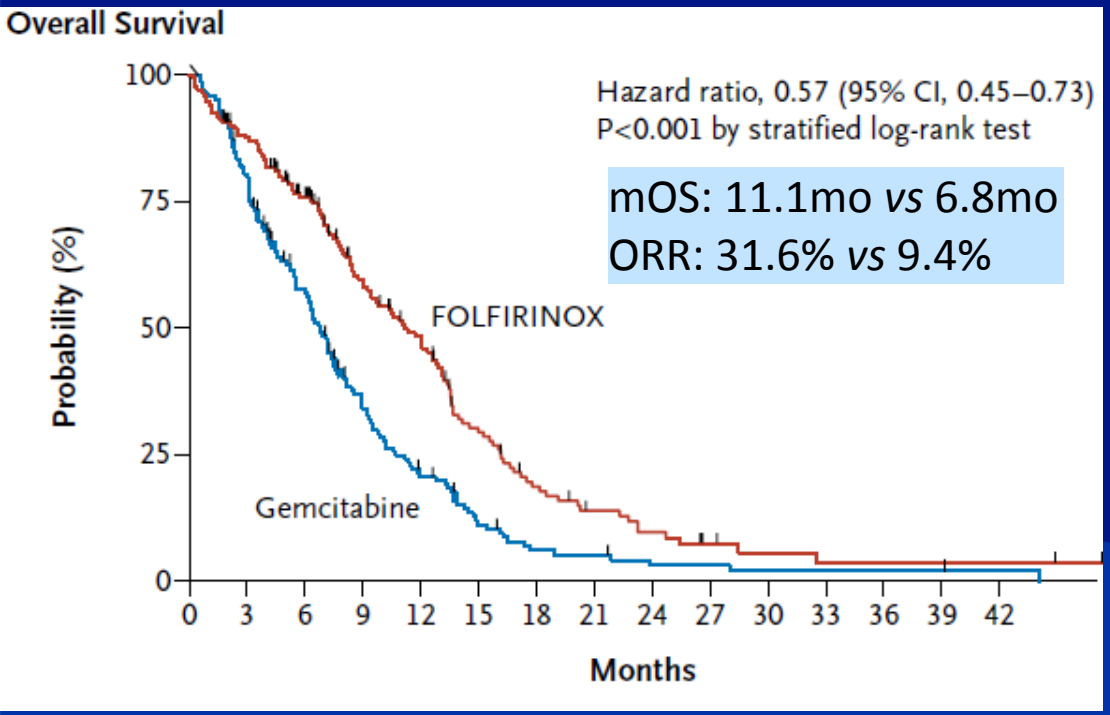
N Engl J Med 2011;364:1817-25.

Recurrent/Metastatic- 1st Line

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

The NEW ENGLAND JOURNAL of MEDICINE



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N Engl J Med 2011;364:1817-25.

Recurrent/Metastatic- 1st Line

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

The NEW ENGLAND JOURNAL of MEDICINE

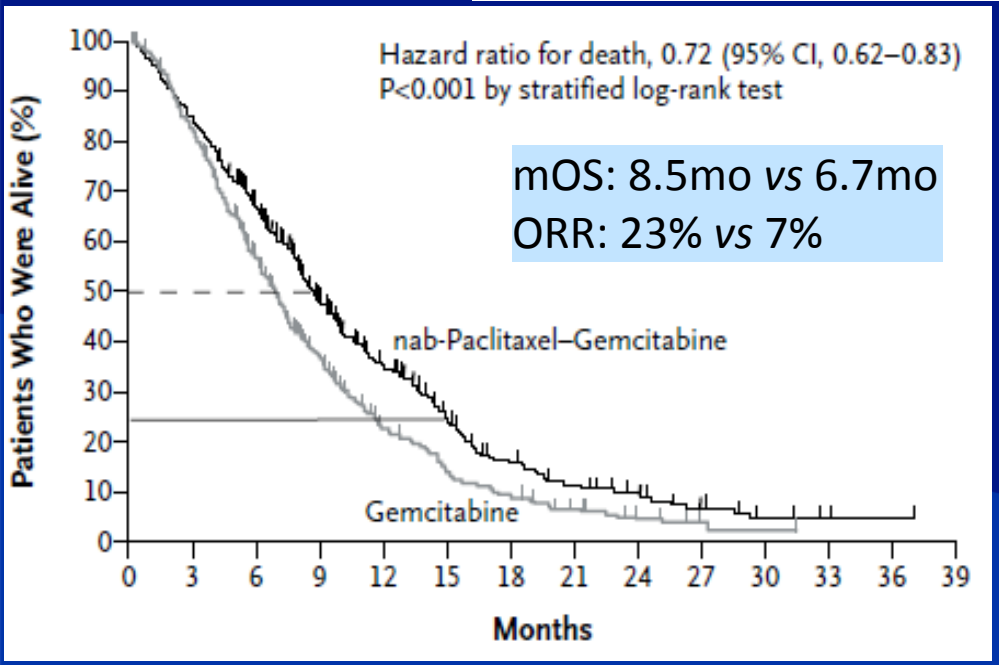

Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

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)

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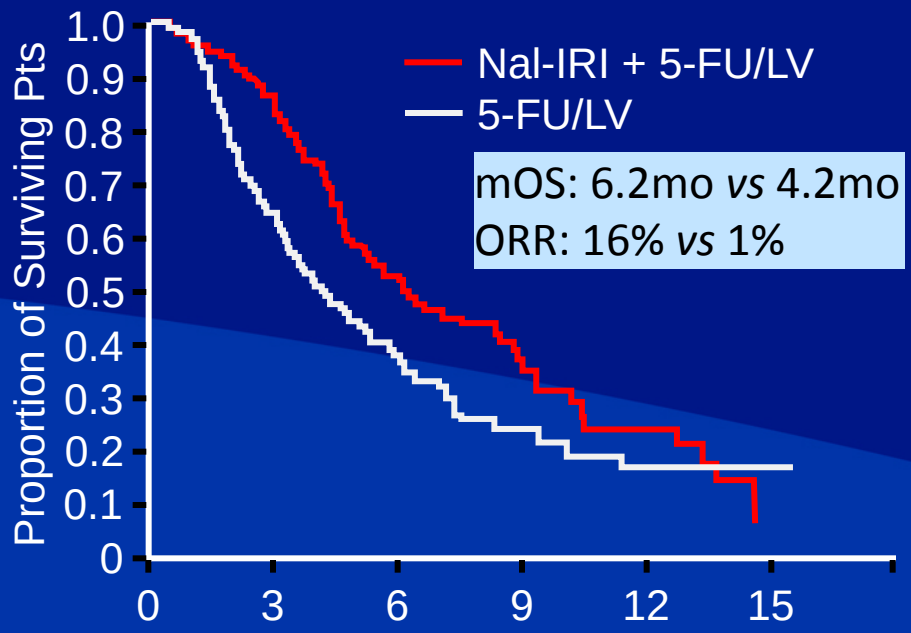
N Engl J Med 2013;369:1691-703.

Recurrent/Metastatic- 2nd Line

NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV—OS



AEs, %	Safety Population*	
	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 134)
Grade ≥ 3 nonhematologic AEs†		
▪ Fatigue	14	4
▪ Diarrhea	13	5
▪ Vomiting	11	3
▪ Nausea	8	3
▪ Asthenia	8	7
▪ Abdominal pain	7	6
Grade ≥ 3 hematologic AEs‡		
▪ ANC decrease	20	2
▪ Anemia	6	5

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Wang-Gillam A, et al. Lancet. 2016;387:545-557.

Slide credit: clinicaloptions.com

New Directions in the Treatment of Pancreatic Cancer

Investigational Agents for Advanced Pancreatic Cancer

Class	Examples
Novel cytotoxics	▪ TH-302 (evofosfamide, hypoxia-activated mustard) did not improve OS in pancreatic trial (2015)—negative trial results
Stromal-depleting agents	▪ PEGPH20 (recombinant hyaluronidase) ▪ Vitamin D analogues ▪ Necuparanib
Signal transduction inhibitors	▪ JAK inhibitors (ruxolitinib)—negative trial results ▪ MM-141 (bispecific anti-IGFR/HER3 antibody) ▪ BTK inhibitors (ibrutinib) ▪ Notch inhibitors (eg, demcizumab, tarextumab)—negative trial results ▪ PARP inhibitors (eg, olaparib)

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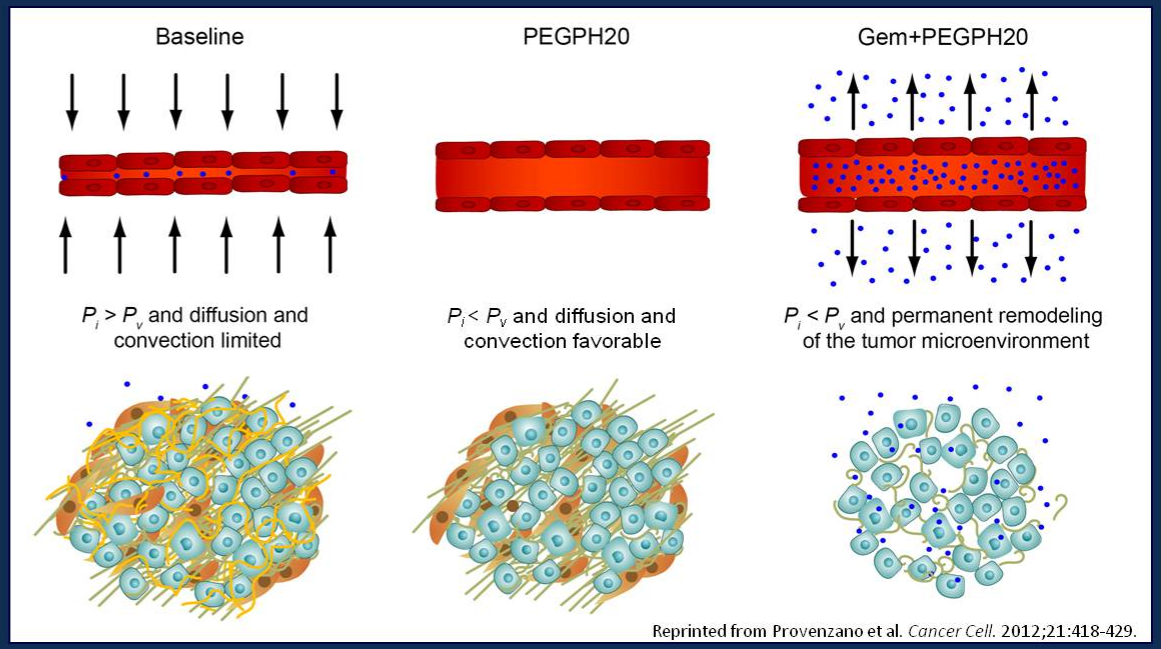
ClinicalTrials.gov.

Slide credit: clinicaloptions.com

PEGPH20 Degrades Hyaluronan in the Tumor Microenvironment

Hyaluronan (HA)

- Naturally occurring, linear, megadalton polysaccharide and major component of the tumor stroma[1]
- HA accumulation increases tumor interstitial gel-fluid pressure, which in turn compresses blood vessels and compromises blood flow[2,3]
- HA accumulation is associated with accelerated tumor growth and is an independent negative predictor of survival in PDA[4]



Reprinted from Provenzano et al. *Cancer Cell*. 2012;21:418-429.

PEGPH20 (pegvorhyaluronidase alfa)

- A PEGylated form of recombinant human hyaluronidase PH20, which degrades HA and remodels the tumor stroma

1. Minchinton AI, et al. *Nat Rev Cancer*. 2006;6:582-592; 2. Thompson CB, et al. *Mol Cancer Ther*. 2010;9:3052-3064; 3. Provenzano PP, et al. *Cancer Cell*. 2012;21:418-429; 4. Whatcott CJ, et al. *Clin Cancer Res*. 2015;21:151.

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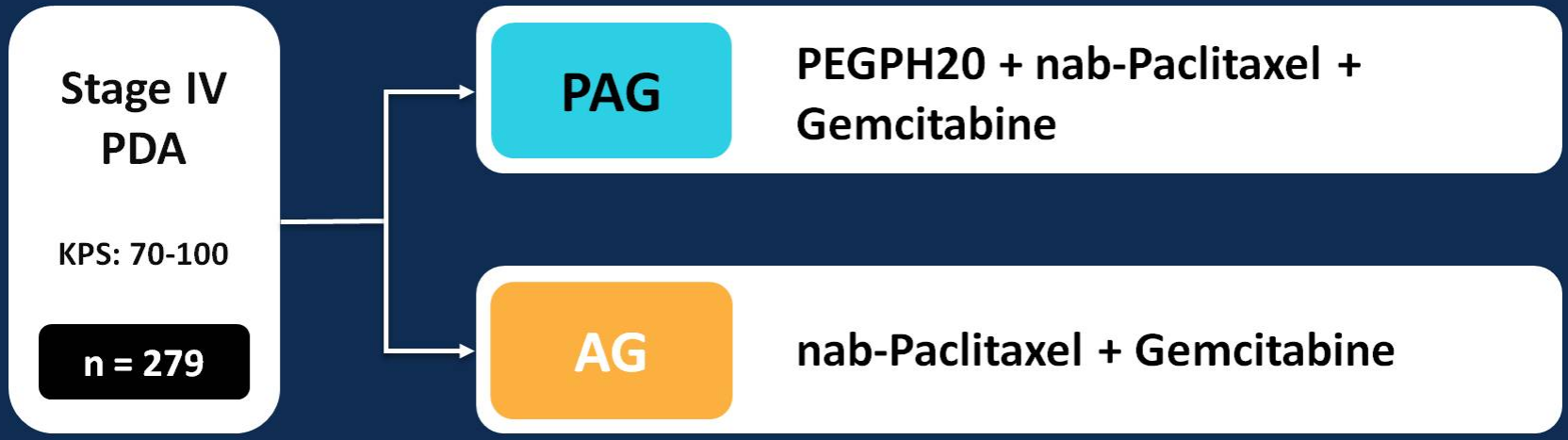
HALO-202: Phase 2 Randomized Multicenter Study



Primary Endpoints:

- PFS
- Thromboembolic Event Rate

Secondary Endpoints:

- PFS by HA Level
- ORR
- OS

Exploratory Endpoints:

- OS by HA Level
- DoR
- DCR (CR+PR+SD)

Primary & Secondary PFS Endpoints: 80% power at 2-sided alpha level of 0.1

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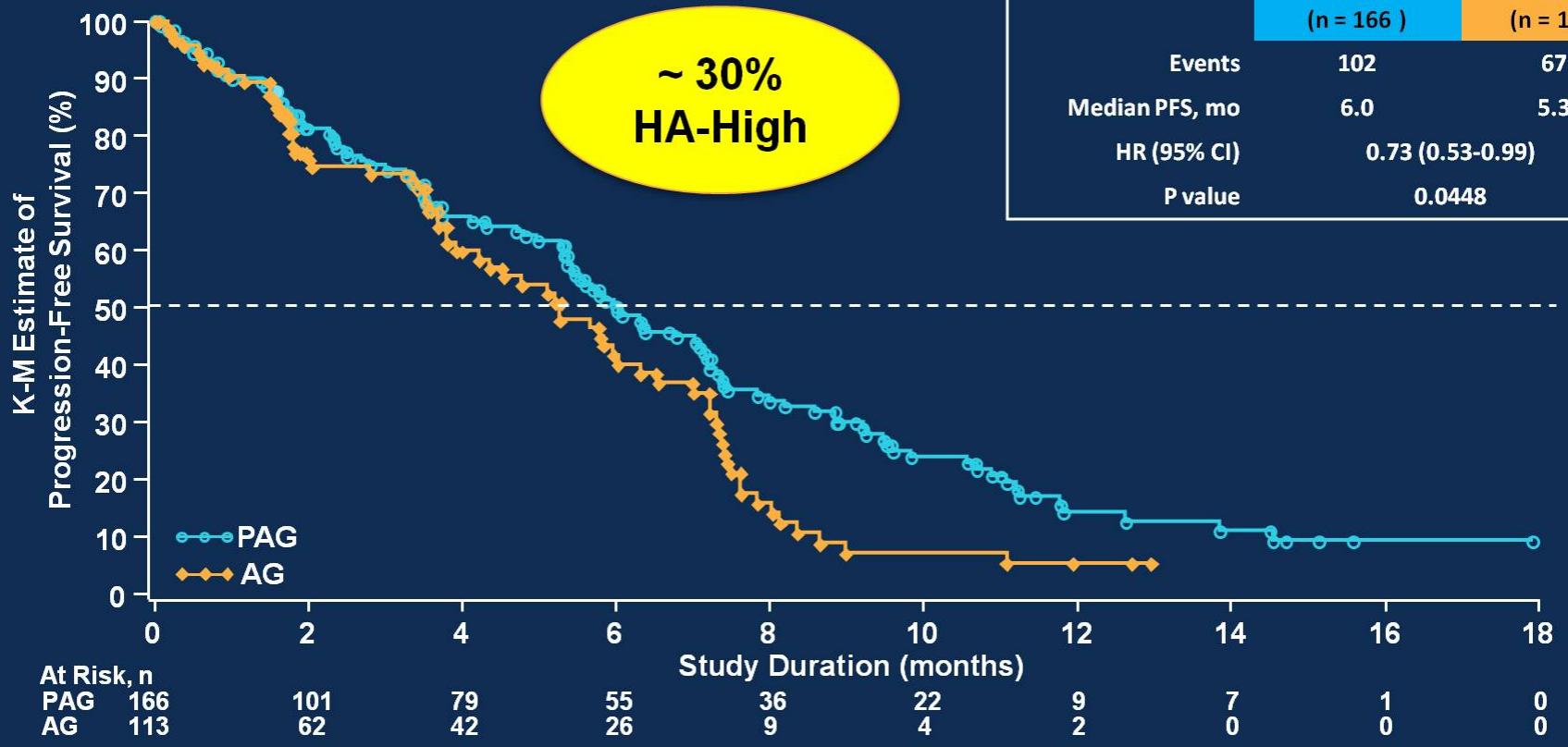
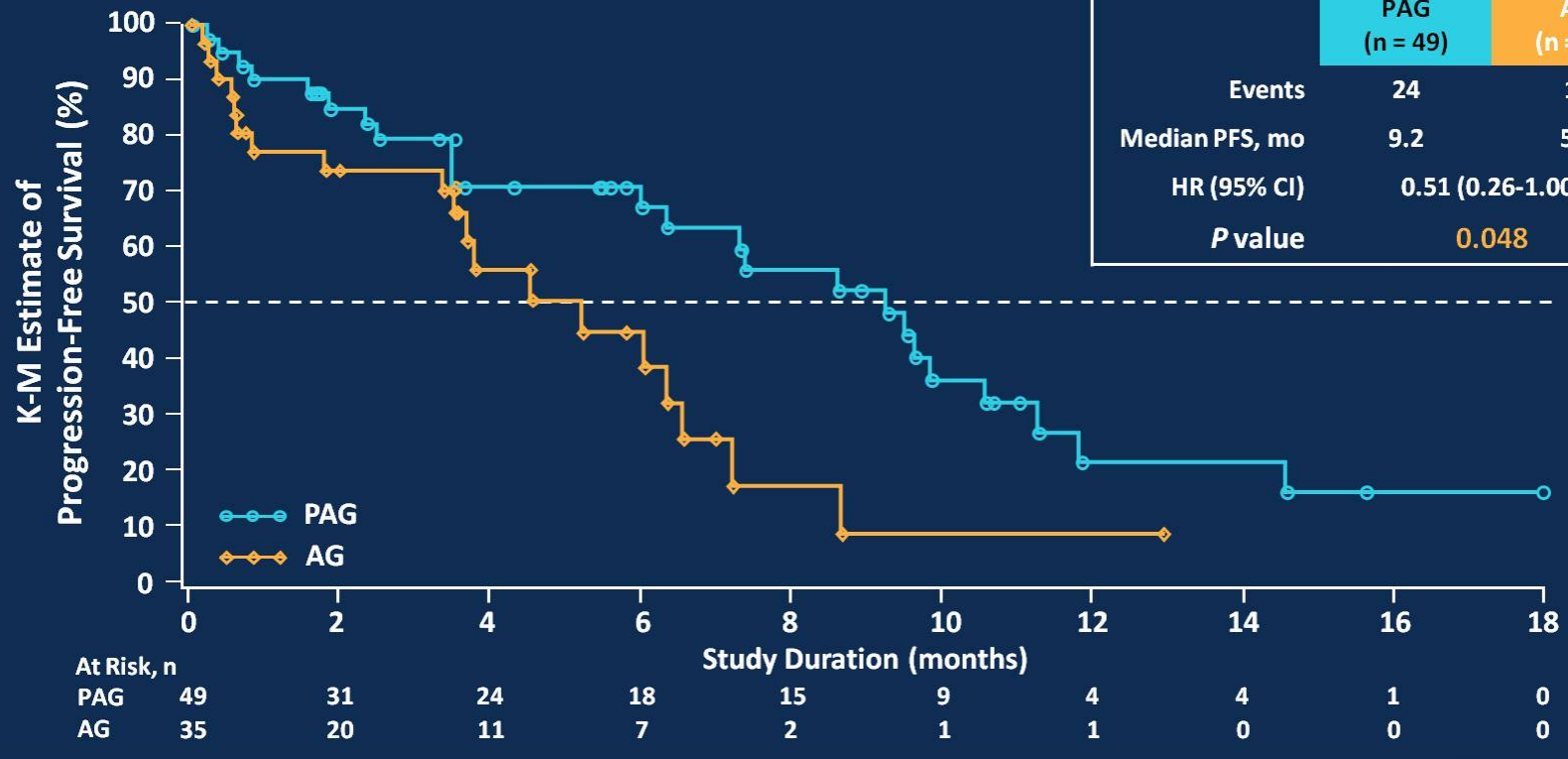
Primary Efficacy Endpoint: PFS (Stages 1 & 2)

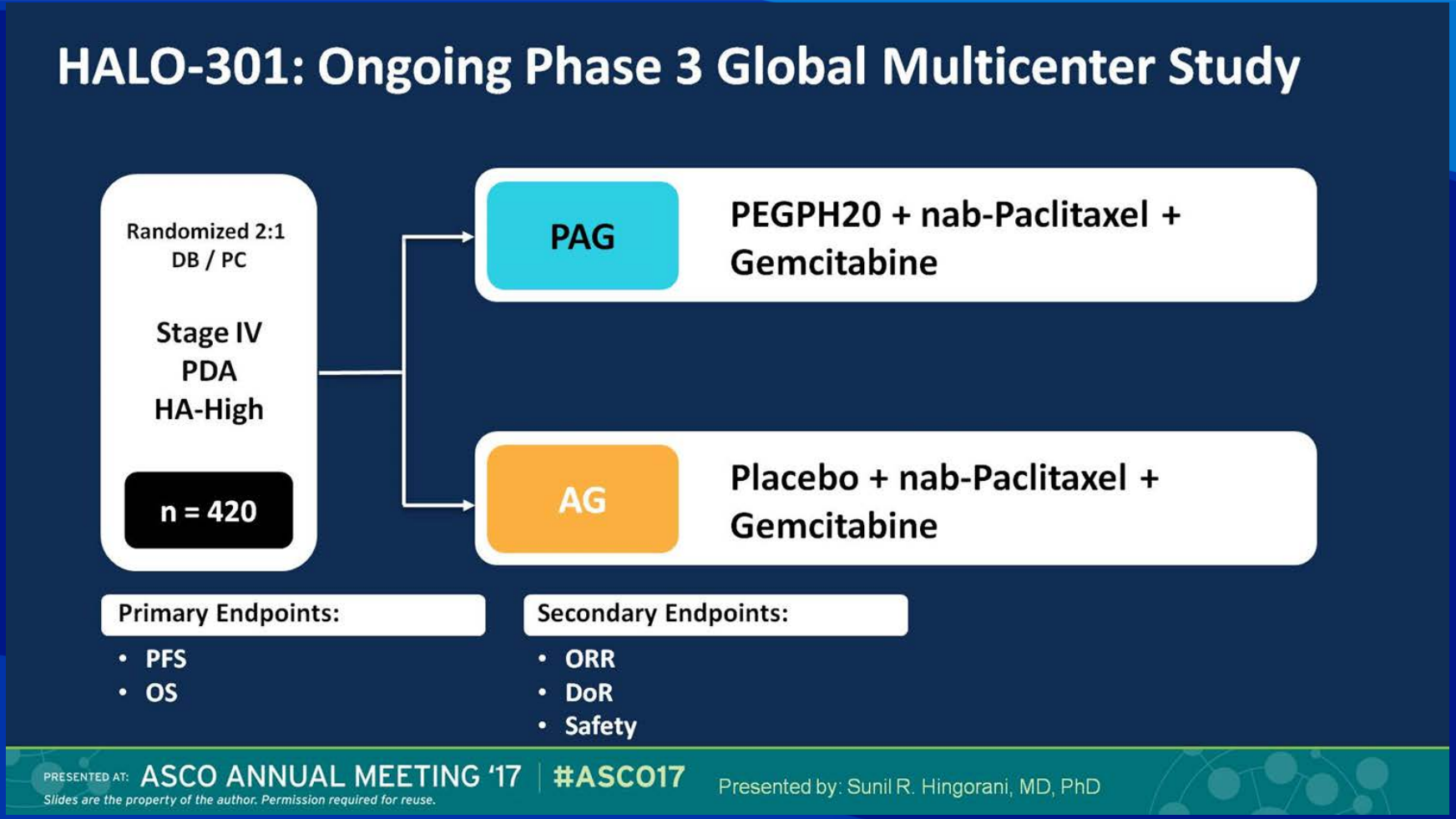
	PAG (n = 166)	AG (n = 113)
Events	102	67
Median PFS, mo	6.0	5.3
HR (95% CI)	0.73 (0.53-0.99)	
P value	0.0448	



Secondary Endpoint: Progression-Free Survival HA-High (Combined Stages 1 & 2)



	PAG (n = 49)	AG (n = 35)
Events	24	19
Median PFS, mo	9.2	5.2
HR (95% CI)	0.51 (0.26-1.00)	
P value	0.048	



→ This Trial is currently available at UC Irvine (UCI 15-94)

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New Trials for Pancreatic Cancer at UCI

- UCI-17-103: **Irinotecan liposomal injection** (lip-IRI)-containing Regimens in Patients with Previously Untreated, Metastatic Pancreatic Adenocarcinoma

- UCI-17-109: **Durvalumab +/- Treme** in combination with Gemcitabine and Abraxane in First Line Pancreatic Ductal Adenocarcinoma

- UCI-15-94: **PEGPH20** in combination with Gemcitabine and Abraxane in First Line Pancreatic Ductal Adenocarcinoma with Hyaluronan-High

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ClinicalTrials.gov.

Slide credit: clinicaloptions.com

Summary

Improving options for all treatment settings

- "Chemo for everybody"
- Adjuvant: Gem-Cap x 6 months
- LAPC: no randomized phase 3 trial (yet); gemcitabine/nab-paclitaxel (LAPACT phase II) and FOLFIRINOX have shown activity
- Metastatic: 2 first-line regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, have demonstrated survival benefit (vs gemcitabine alone) in phase III studies
- Second-line/salvage treatment benefit with nanoliposomal irinotecan and 5-FU after gemcitabine-based therapy

Novel therapeutics

- Active area of research
- Multiple ongoing randomized phase II/III trials at UCI

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Thank You

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