

# Prise en charge du cancer du pancréas

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# Conflits d'intérêt

Participation à un board d'experts :

Celgène

Roche

Sanofi

Nucana

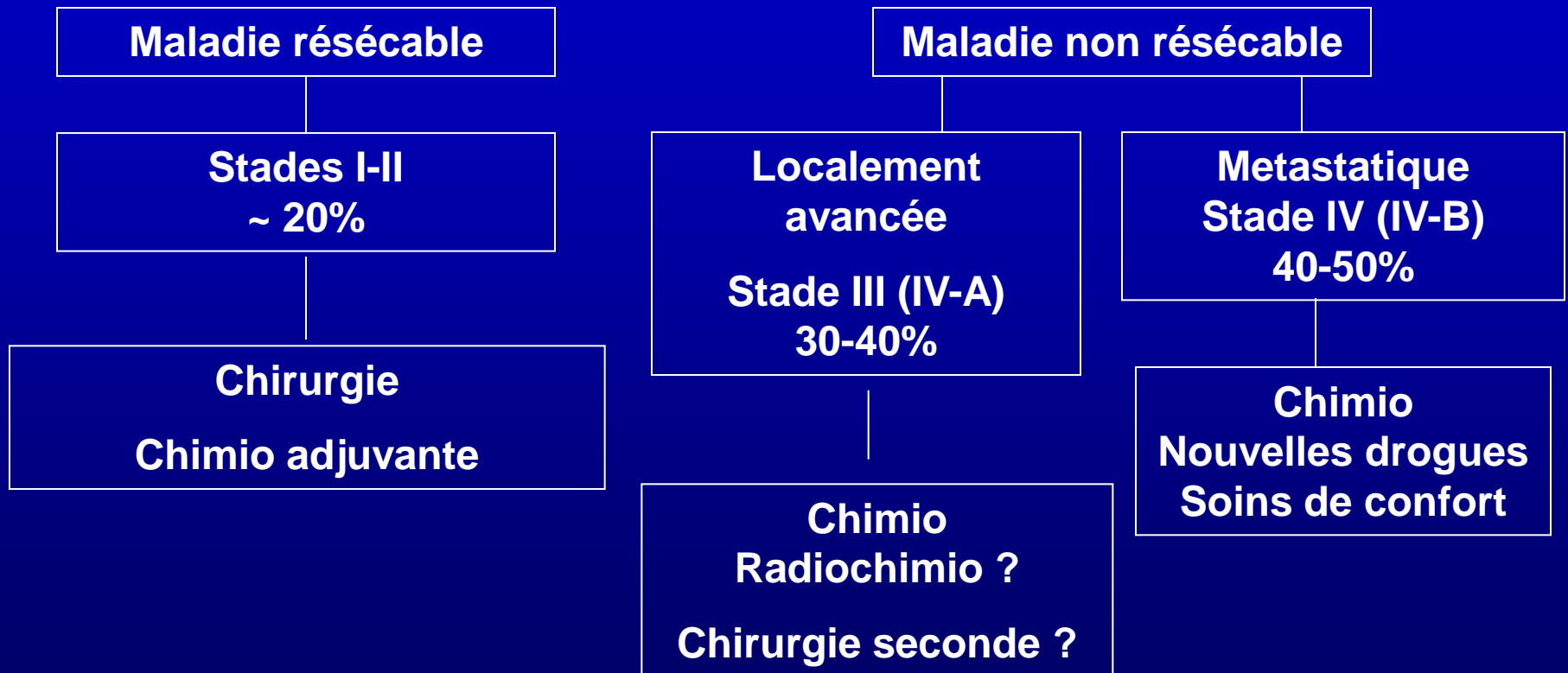
Amgen

Clovis Pharma

# Généralités

- Plus de 210 000 nouveaux cas par an dans le monde (2000).
- 2.1% de tous les cancers
- 10% des cancers digestifs
- + 1.7% / an (homme) ; + 2.1% / an (femme)
  
- 6<sup>ème</sup> cause de décès par cancer
- La mortalité par cancer du pancréas est à peu près égale à l'incidence
- Survie à 5 ans : 4%

# Stratégie globale



# Traitement des formes métastatiques

# ADK pancréatique métastatique: Chimiothérapie ou soins de confort ?

Auteur	Regime	n patients	Med. Surv. (mo)	Qol
Mallinson 1980	5-FU+Mtx+Vcr + cyclo + MMC	21	10.5	
	BSC	19	2.2*	
Frey 1981	5-FU + CCNU	65	3.0	
	BSC	87	3.9	
Andersen 1981	5-FU + BCNU	20	3.2	
	BSC	20	3.4	
Palmer 1994	FAM	23	8.2	
	BSC	20	3.8*	
Glimelius 1996	5-FU + LV + Etoposide	29	6.0	benefice dans le groupe CT
	BSC	24	2.5*	

\* p < 0.05

# L'étude Burris (1997)

	<b>Gemcitabine</b> n=63	<b>5-Fluorouracile</b> n=63
<b>Bénéfice clinique</b>	<b>23.8% *</b>	<b>4.8%</b>
<b>Survie médiane</b>	<b>5.65 mois **</b>	<b>4.41 mois</b>

**\*  $p = 0.0022$**

**\*\*  $p = 0.0025$**

**Burris H A, et al.: JCO 15: 2403, 1997**

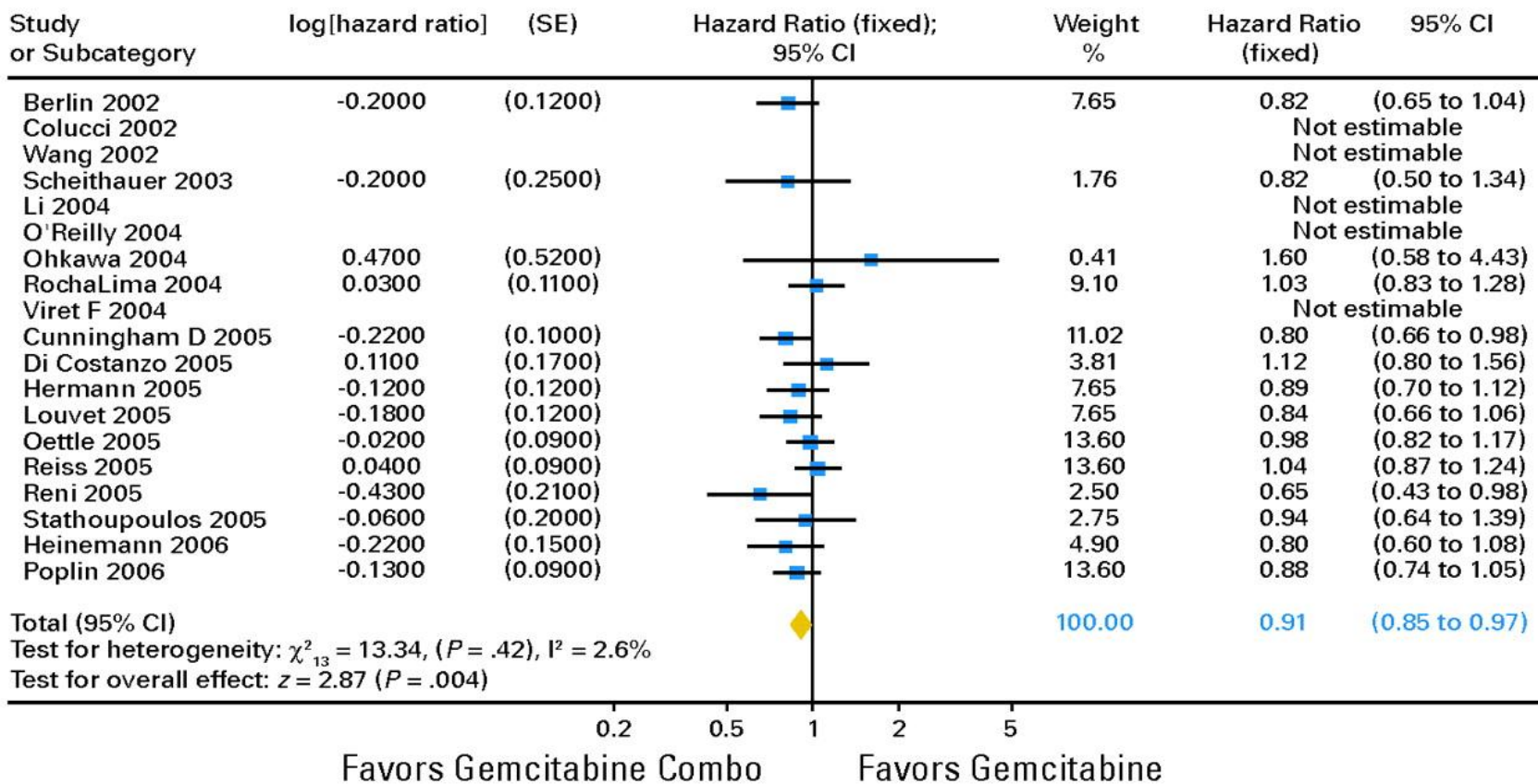
# Etudes de phases III dans les cancers du pancréas (chimiothérapie conventionnelle)

	Gem	Gem + X	p
Gem ± Exatecan (Abou-Alfa, JCO 2006)	6.2	6.7	NS
Gem ± CPT-11 (Rocha-Lima, JCO 2006)	6.6	6.3	NS
Gem ± Pemetrexed (Oettle, Ann Oncol 2006)	6.3	6.2	NS
Gem ± 5FU bolus (Berlin, JCO 2002)	5.4	6.7	NS
Gem ± Capecitabine (Herrmann, JCO 2007)	7.3	8.4	NS
Gem ± 5FU/LV (Riess, JCO 2005)	6.2	5.9	NS
Gem ± Capecitabine (Cunningham, JCO 2009)	6.2	7.1	NS
Gem ± Cisplatin (Heinemann, JCO 2006)	6.0	7.5	NS
Gem ± Oxaliplatine (Louvet, JCO 2005)	7.1	9.0	NS
Gem ± Oxaliplatine (Poplin, JCO 2009)	4.9	5.9	NS
Gem ± Cisplatin (Colucci, ASCO 2009)	8.3	7.2	NS



# Méta-analyse de survie: Gemcitabine versus Gemcitabine + autre drogue

Review: Treatment of advanced pancreatic cancer (Version 07; 27 June 2006)  
 Comparison: 04 Gemcitabine v Gemcitabine combo  
 Outcome: 01 Gemcitabine v Gemcitabine combo



# Résumé de la méta-analyse dans les cancers du pancréas avancés

	N pts	HR	p
Gem vs Gem + drogue X	4465	0.91	0.004
Gem vs Gem + sel de platine	1248	0.85	0.01
Gem vs Gem + fluoropyrimidine	1813	0.90	0.03
Gem vs Gem + autre drogue	1404	0.99	NS
Gem vs Gem + sel de platine / fluoropyrimidine (PS 0-1)	1108	0.76	< 0.0001
Gem vs Gem + sel de platine / fluoropyrimidine (PS 2)	574	1.08	NS

**BMC Cancer**



Research article

**Open Access**

**Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer**

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Address: <sup>1</sup>Department of Internal Medicine III, Klinikum Grosshadern, University of Munich, Germany, <sup>2</sup>WiSP, Langenfeld, Germany, <sup>3</sup>Ospedali Riuniti, Bergamo, Italy and <sup>4</sup>Service d'Oncologie, Médecine Interne, Hôpital St. Antoine, Paris, France

# Etudes de phases III dans les cancers du pancréas (thérapies ciblées)

	Gem	Gem + X	p
Gem ± Marimastat (Bramhall, BJC 2002)	5.5	5.5	NS
Gem ± Tifarbinib (Van Cutsem, JCO 2004)	6.0	6.4	NS
<b>Gem ± Erlotinib (Moore, JCO 2007)</b>	<b>5.9</b>	<b>6.4</b>	<b>.03</b>
Gem ± Bevacizumab (Kindler, ASCO 2007)	6.1	5.8	NS
Gem ± Cetuximab (Philip, ASCO 2007)	5.9	6.4	NS
Gem ± GV1001 (Buanes, ASCO 2009)	7.3	5.9	NS
Gem – Erlotinib ± Beva (Van Cutsem, JCO 2009)	6.0	7.1	NS
Gem ± Axitinib (Kindler, ESMO 2009)	7.4	8.2	NS
Gem ± Aflibercept : arrêt pour futilité en 2009			

# Anti-EGFR

**Preuve du concept avec l'erlotinib** *(Moore, JCO 2007)*

**Pas de confirmation avec le cetuximab** *(Philip, ASCO 2008)*

**Pas de synergie avec le bevacizumab** *(Van Cutsem, JCO 2009)*

**Pas de marqueur moléculaire prédictif (K-ras?)**

**Rash prédictif de survie ?** *(Moore, 2007; Van Cutsem, 2009)*

# Antiangiogéniques

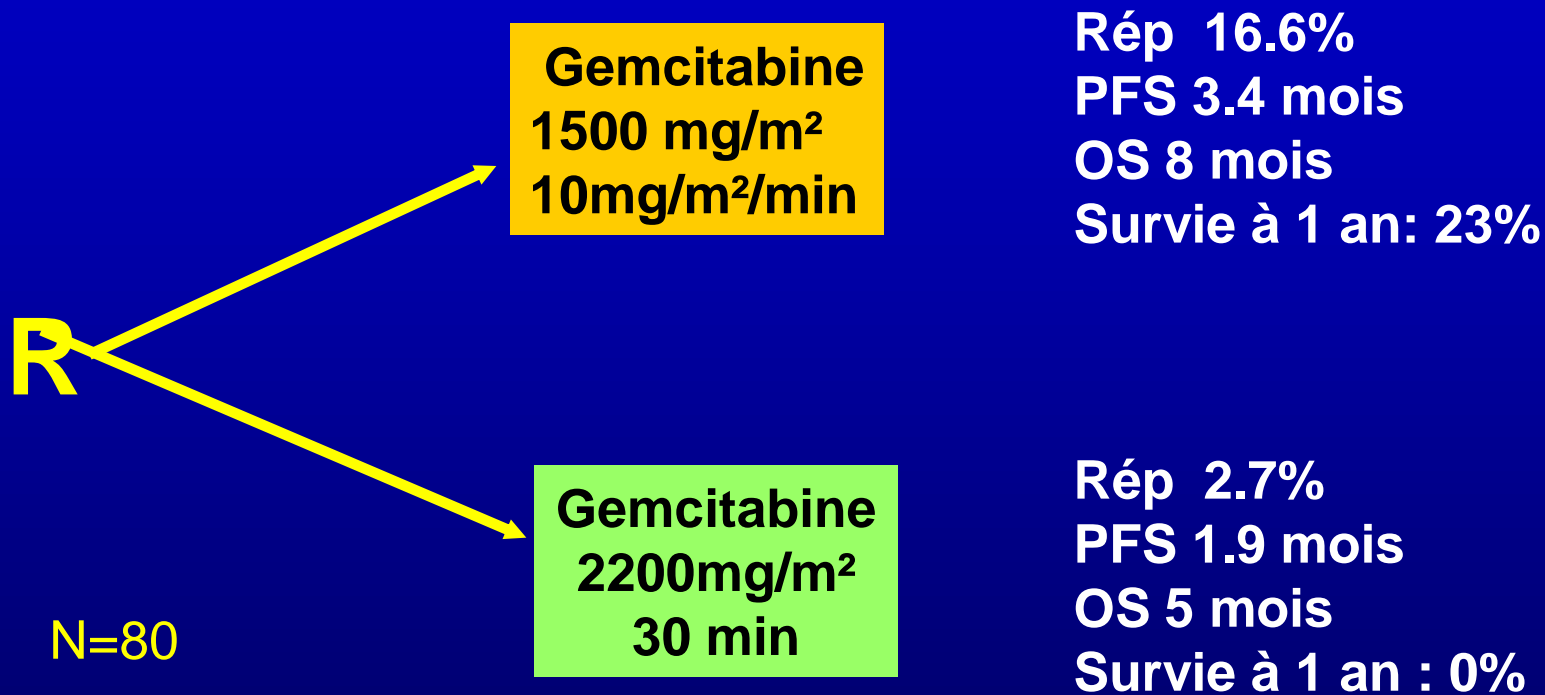
Résultats négatifs en phase III avec mAb, TKI  
et VEGF-trap

- **CALBG (G + Beva)** (*Kindler, JCO 2008*)
- **AVITA (G + B + Erlo)** (*Van Cutsem, JCO 2009*)
- **AGILE (G + Axitinib)** (*Kindler, ESMO/ECCO 2009*)
- **VANILLA (G + Aflibercept)** (*Press release-stop pour futilité*)

Pas de marqueur prédictif (polymorphisme VEGFR-1 ?)

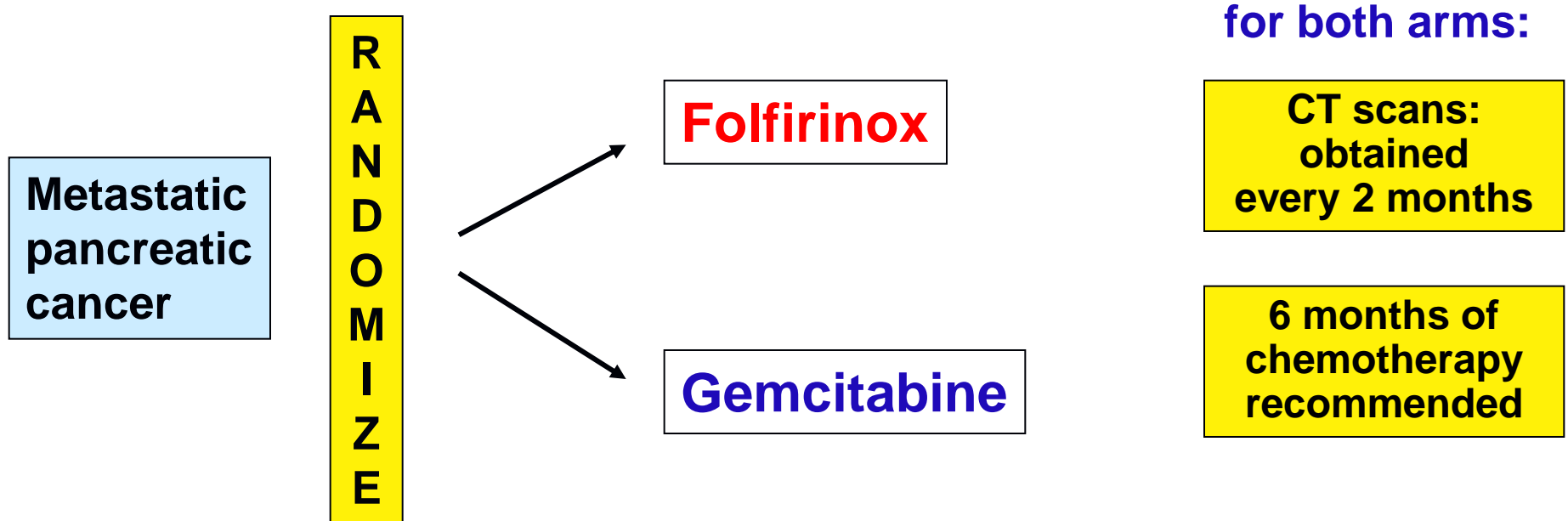
Pas de “surrogate marker” (PA diastolique?) (*Spano, Lancet 2008*)

# Gemcitabine perfusion de 30mn ou de 10 mg/m<sup>2</sup>/mn?



# Prodige 4 - ACCORD 11 trial design

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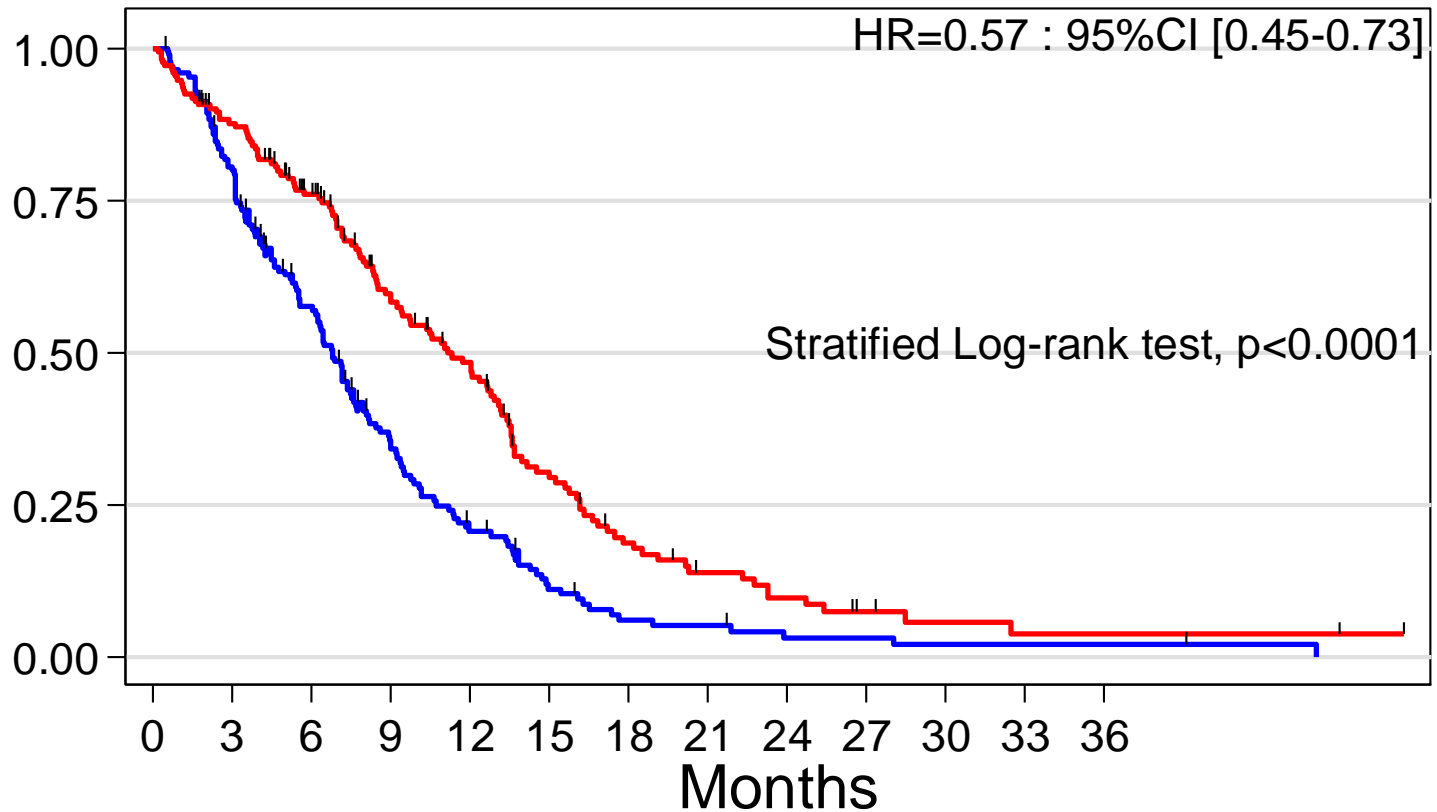
## Stratification :

- center
- performance status: 0 versus 1
- location of the tumor: head versus other location of the primary

	<b>Folfirinox</b> N=171	<b>Gemcitabine</b> N=171	p
<b>Complete response</b>	<b>0.6%</b>	<b>0%</b>	<b>0.0001</b>
<b>Partial response</b>	<b>31%</b>	<b>9.4%</b>	
<b>CR/PR 95% CI</b>	<b>[24.7-39.1]</b>	<b>[5.9-15.4]</b>	
<b>Stable disease</b>	<b>38.6%</b>	<b>41.5%</b>	
<b>Disease control</b> <b>CR+PR+SD</b>	<b>70.2%</b>	<b>50.9%</b>	<b>0.0003</b>
<b>Progression</b>	<b>15.2%</b>	<b>34.5%</b>	
<b>Not assessed</b>	<b>14.6%</b>	<b>14.6%</b>	
<b>Median duration</b> <b>of response</b>	<b>5.9 mo.</b>	<b>4 mo.</b>	<b>ns</b>



# Overall Survival



Number at risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2
Folfirinox	171	146	116	81	62	34	20	13	9	5	3	2	2

— Gemcitabine — Folfirinox

# Inclusion Criteria

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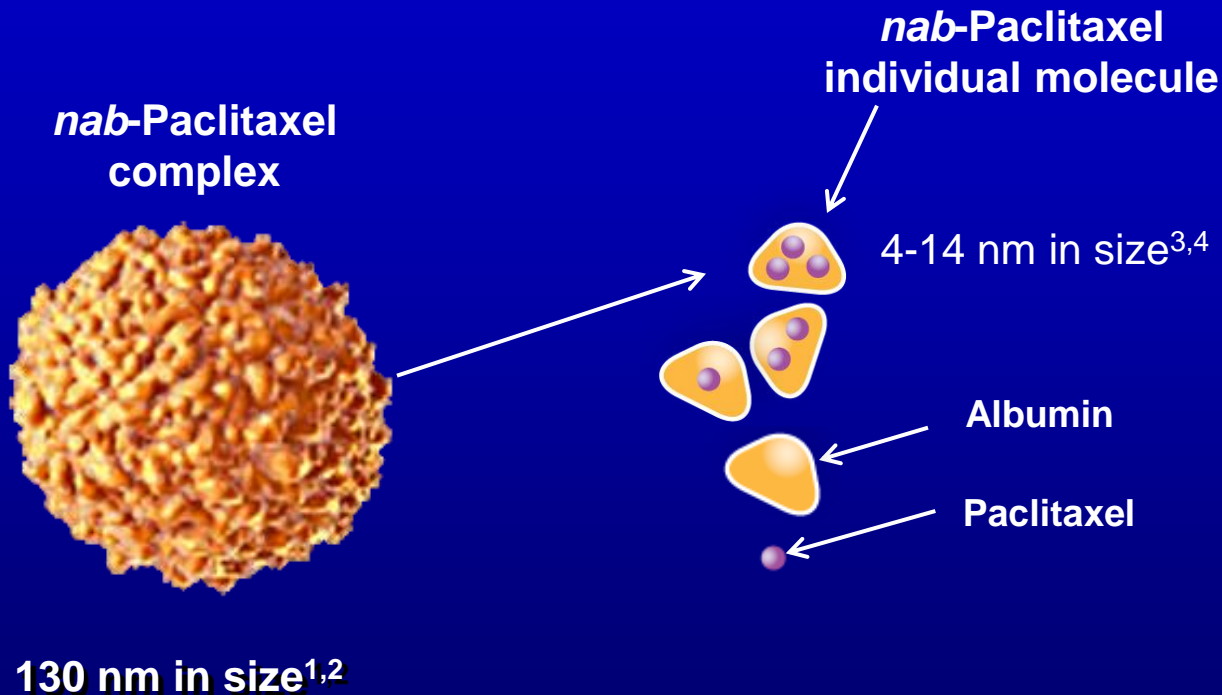
- **Histologically/cytologically confirmed pancreatic adenocarcinoma**
- **ECOG performance status of 0 or 1**
- **Measurable metastases**
- **No prior cytotoxic chemotherapy**
- **No prior abdominal radiotherapy**
- **Age 18-75 years**
- **Adequate hematopoietic, hepatic and renal function**
- **Bilirubin < 1.5 UNL**
- **No unstable angina or myocardial infarction within 12 months before entry**
- **Written informed consent**

AE, % per patient	<b>Folfirinox</b> N=167		<b>Gemcitabine</b> N=169		<b>p</b>
	All	Grade 3/4	All	Grade 3/4	Grade 3/4
Neutropenia	79.9	45.7	54.8	18.7	0.0001
Febrile Neutropenia	7.2	5.4	2.4	0.6	0.009
Anemia	90.4	7.8	94.6	5.4	NS
Thrombocytopenia	75.2	9.1	54.8	2.4	0.008

**42.5 % of the pts received G-CSF in the F arm vs 5.3% in the G arm**  
**One toxic death occurred in each arm**

	<b>Folfirinox N=167</b>		<b>Gemcitabine N=169</b>		
<b>AE, % per patient</b>	<b>All</b>	<b>Grade 3/4</b>	<b>All</b>	<b>Grade 3/4</b>	<b>p</b>
<b>Infection without neutropenia</b>	<b>6</b>	<b>1.2</b>	<b>7.1</b>	<b>1.8</b>	<b>NS</b>
<b>Peripheral neuropathy</b>	<b>70.5</b>	<b>9</b>	<b>0.6</b>	<b>0</b>	<b>0.0001</b>
<b>Vomiting</b>	<b>61.4</b>	<b>14.5</b>	<b>43.2</b>	<b>4.7</b>	<b>0.002</b>
<b>Fatigue</b>	<b>87.3</b>	<b>23.2</b>	<b>78.7</b>	<b>14.2</b>	<b>0.036</b>
<b>Diarrhea</b>	<b>73.3</b>	<b>12.7</b>	<b>30.8</b>	<b>1.2</b>	<b>0.0001</b>
<b>Alopecia (grade 2)</b>	<b>32.5</b>	<b>(11.4)</b>	<b>3.0</b>	<b>(0.6)</b>	<b>0.0001</b>
<b>ALT</b>	<b>64.8</b>	<b>7.3</b>	<b>83.8</b>	<b>18.6</b>	<b>0.0022</b>

# ***nab*<sup>®</sup>-Paclitaxel is the First Tumor-Targeted Nanomedicine to Leverage the Natural Transport Properties of Albumin**

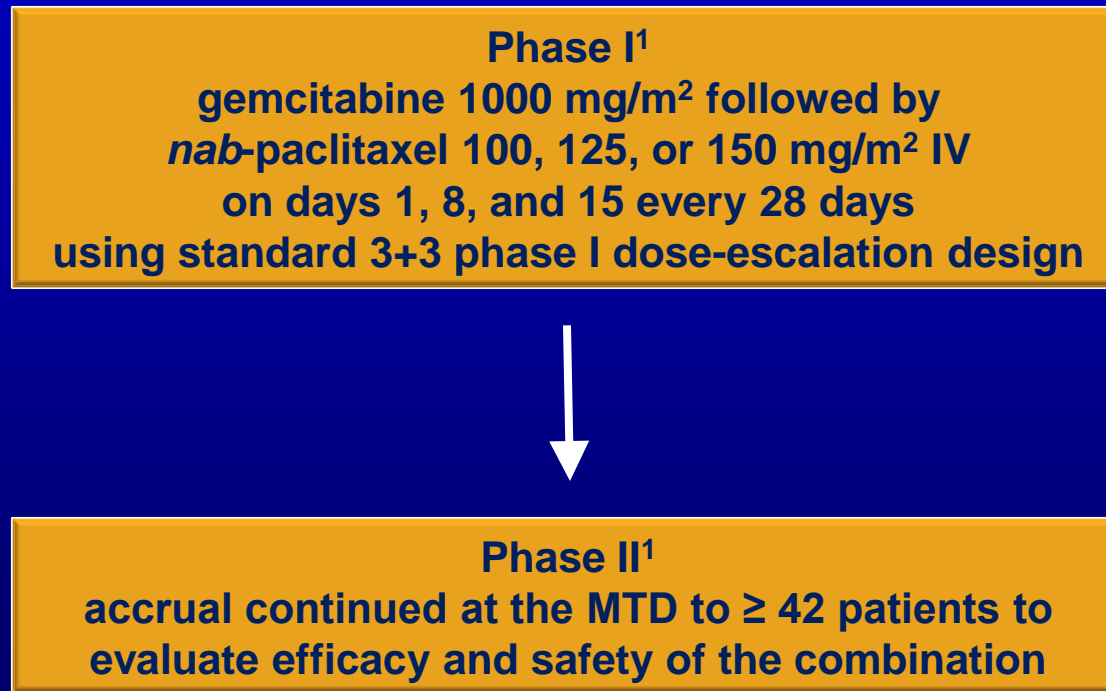


- A single molecule of albumin can bind up to 6 or 7 molecules of paclitaxel<sup>5</sup>

# ***nab*<sup>®</sup>-Paclitaxel + Gemcitabine In Patients With Metastatic Pancreatic Cancer**

## ***Study Design***

Open label phase I/II study in chemotherapy-naive patients with metastatic adenocarcinoma of the pancreas<sup>1</sup>



IV, intravenous; MTD, maximum tolerated dose.

# Randomized Phase III Study of Weekly *nab*-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT)

Daniel D. Von Hoff,<sup>1</sup> Thomas Ervin,<sup>2</sup> Francis P. Arena,<sup>3</sup> E. Gabriela Chiorean,<sup>4</sup> Jeffrey Infante,<sup>5</sup> Malcolm Moore,<sup>6</sup> Thomas Seay,<sup>7</sup> Sergey A. Tjulandin,<sup>8</sup> WenWee Ma,<sup>9</sup> Mansoor N. Saleh,<sup>10</sup> Marion Harris,<sup>11</sup> Michele Reni,<sup>12</sup> Ramesh K. Ramanathan,<sup>1</sup> Josep Taberero,<sup>13</sup> Manuel Hidalgo,<sup>14</sup> Eric Van Cutsem,<sup>15</sup> David Goldstein,<sup>16</sup> Xinyu Wei,<sup>17</sup> Jose Iglesias,<sup>18</sup> Markus F. Renschler<sup>17</sup>

1 TGen, Scottsdale Healthcare, AZ, USA; 2 Cancer Specialists, Fort Myers, FL, USA; 3 Arena Onc Assoc, Lake Success, NY, USA; 4 Indiana Univ, IN, USA; 5 Sarah Cannon Res Inst, Nashville, TN, USA; 6 Princess Margaret Hosp Toronto, Canada; 7 Atlanta Cancer Care, GA, USA; 8 Blokhin Cancer Res Ctr, Moscow, Russia; 9 Roswell Park Cancer Inst, Buffalo, NY, USA; 10 Cancer Specialists, Atlanta, GA, USA; 11 Southern Health, East Bentleigh, VIC, Australia; 12 San Raffaele Sci Inst, Milan, Italy; 13 Vall d'Hebron Univ Hosp, Barcelona, Spain; 14 Centro Integral Oncológico Clara Campal, Madrid, Spain; 15 Leuven Univ, Belgium; 16 Prince of Wales Hosp, Sydney, NSW, Australia; 17 Celgene, Summit, NJ, USA; 18 Bionomics, Thebarton, Australia

# Study Design

**Planned N = 842**

- Stage IV
- No prior treatment for metastatic disease
- KPS  $\geq 70$
- Measurable disease
- Total bilirubin  $\leq$ ULN

***nab*-Paclitaxel**

125 mg/m<sup>2</sup> IV qw 3/4 weeks

+

**Gemcitabine**

1000 mg/m<sup>2</sup> IV qw 3/4 weeks

1:1, stratified by KPS, region, liver metastasis

**Gemcitabine**

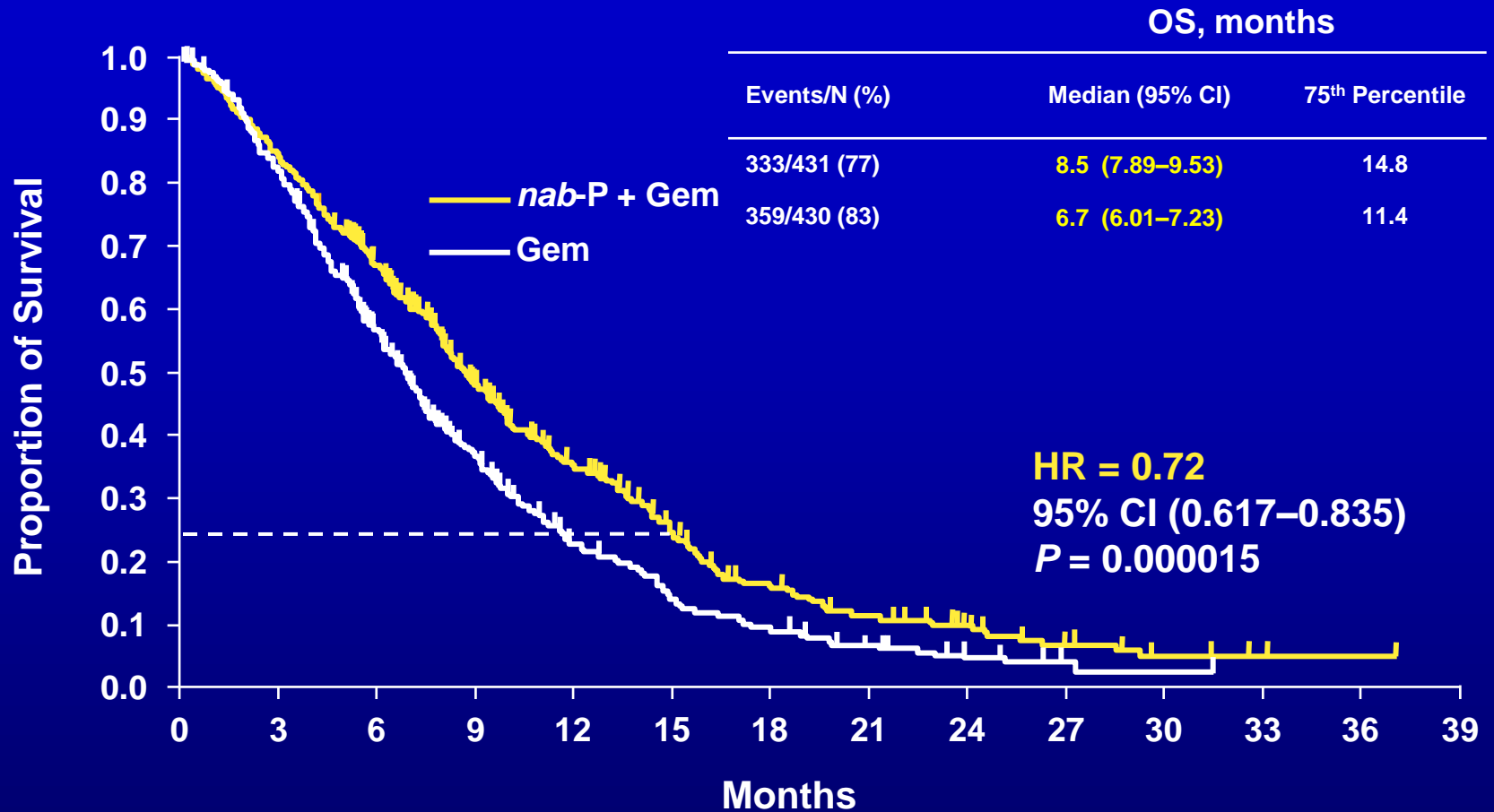
1000 mg/m<sup>2</sup> IV qw for 7/8 weeks  
then qw 3/4 weeks

- Primary Endpoint:
  - OS
- Secondary Endpoints:
  - PFS and ORR by Independent Review (RECIST)
- Safety and Tolerability
  - by NCI CTCAE v3.0

- With 608 events, 90% power to detect OS HR = 0.769 (2-sided  $\alpha = 0.049$ )
- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks



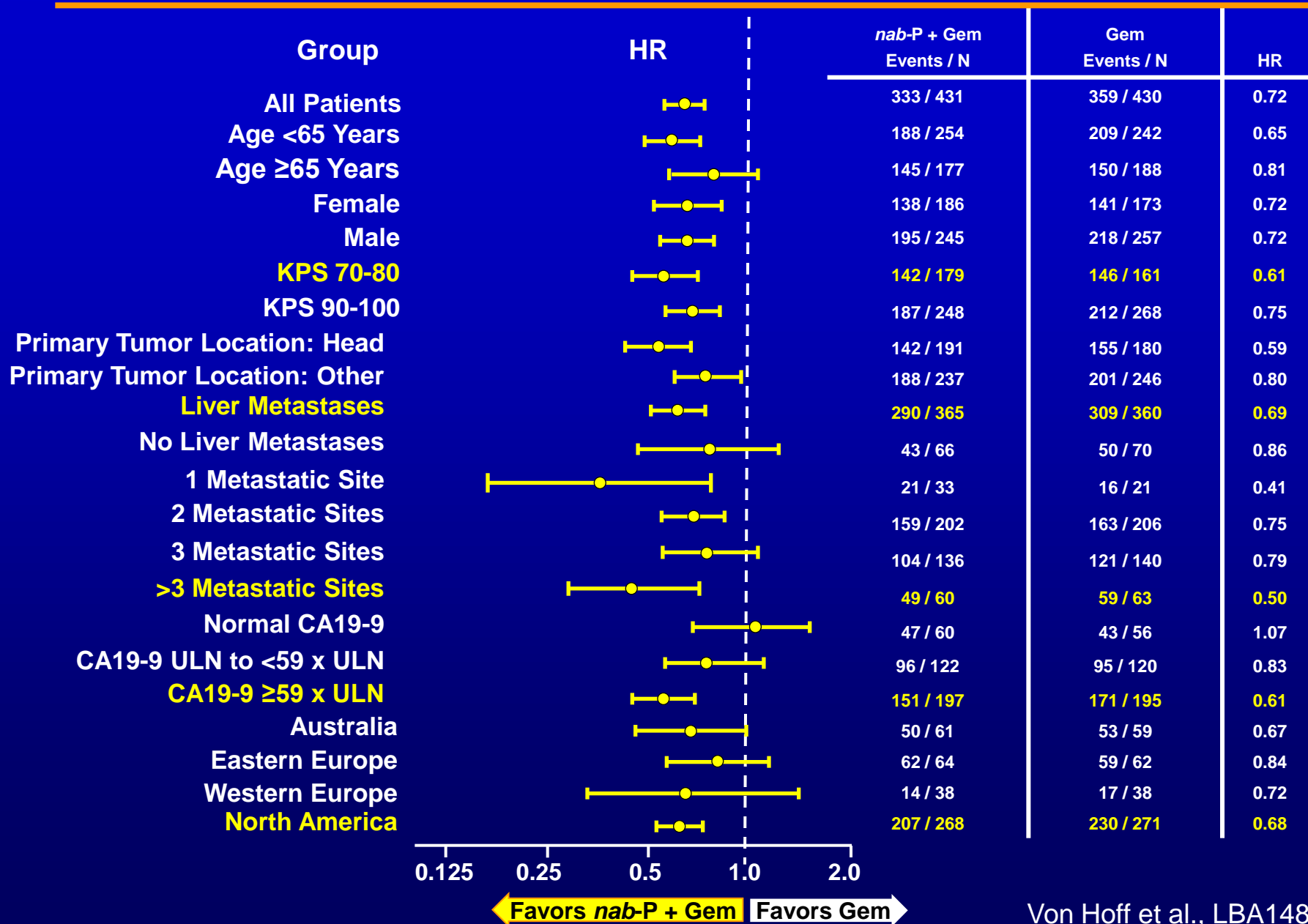
# Overall Survival



## Pts at Risk

<i>nab</i> -P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

# OS - Prespecified Subgroups



# EVOLUTION

Soins de confort

1997

Gemcitabine

2005

Gemcitabine; option « doublet » si IP 0-1

2007

Gemcitabine; option « doublet » si IP 0-1;  
option Gemcitabine + Erlotinib

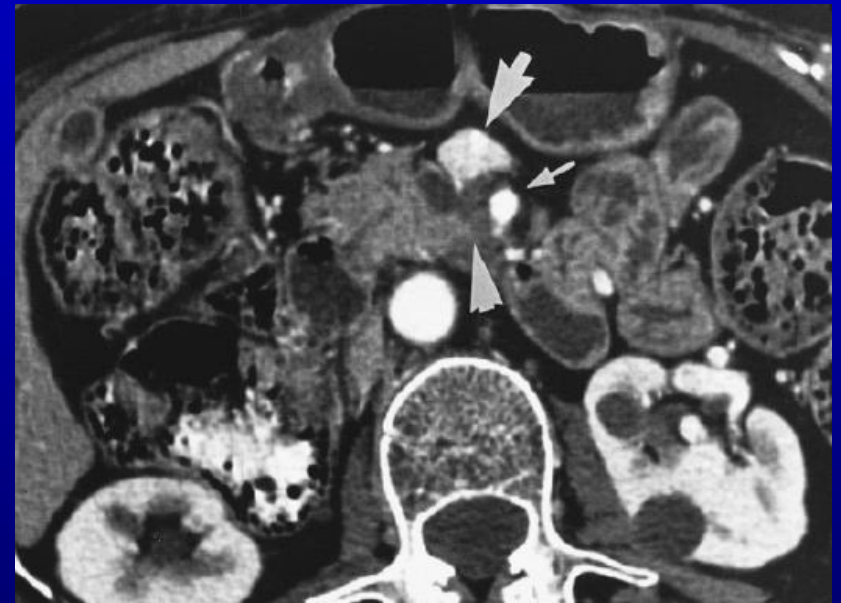
2011

FOLFIRINOX si IP 0-1; Gemcitabine si IP 2

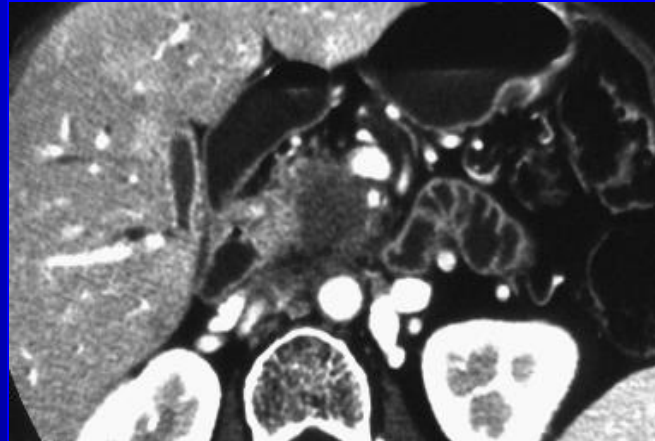
2013

FOLFIRINOX ou Gemcitabine + Abraxane si IP 0-1 ? ;  
Gemcitabine si IP 2

# Maladie localement avancée



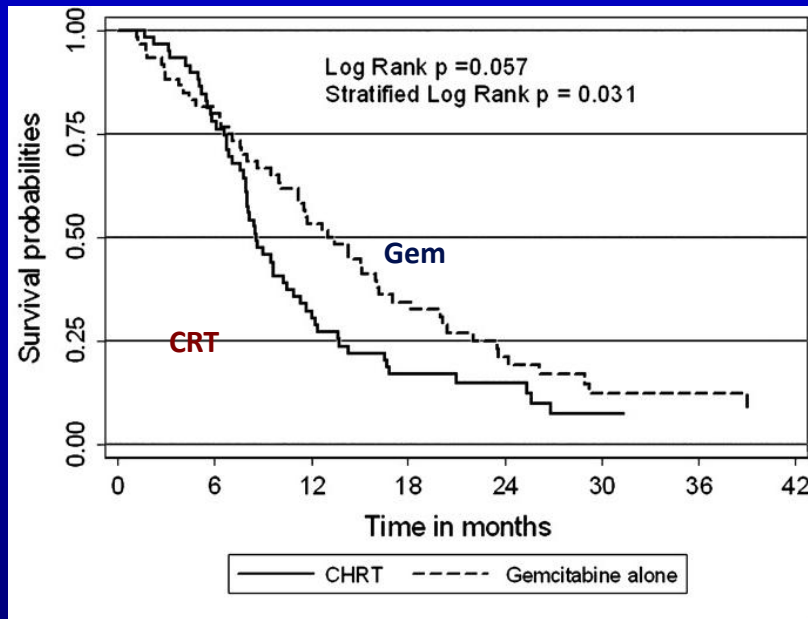
# Background



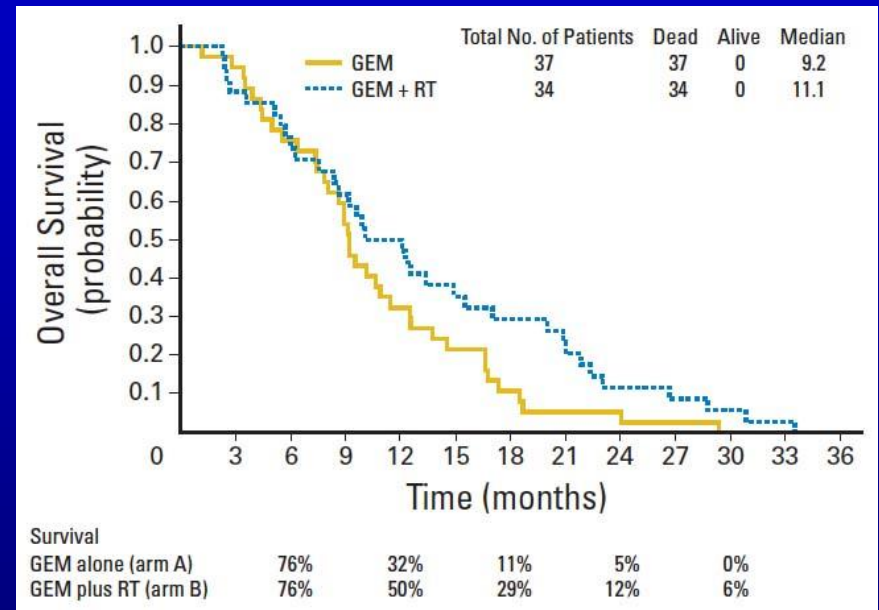
**Role of radiation therapy in locally advanced pancreatic cancer highly debated**

- **Local control** remains an important issue
  - chemoradiation (CRT)
- High rate of **distant metastasis**
  - chemotherapy

# Frontline CRT versus chemotherapy in LAPC



*Chauffert B et al. Ann Oncol 2008*

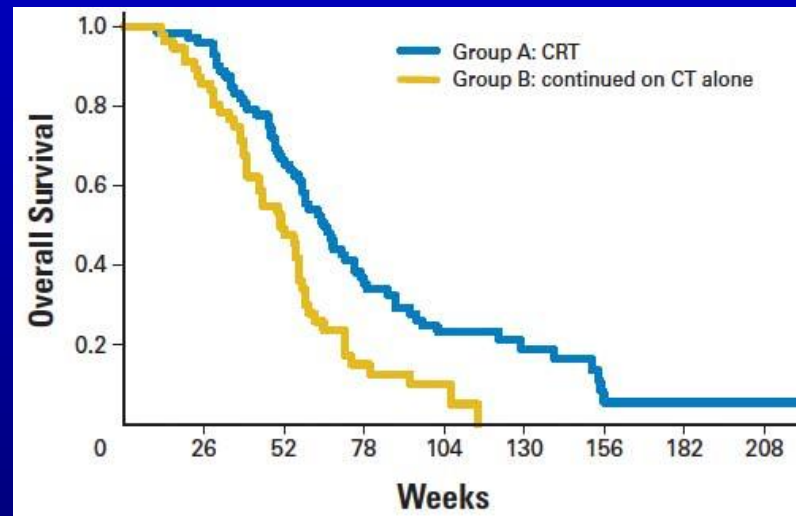


*Loehrer P et al. J Clin Oncol 2011*

→ **Contradictory** results

# Induction CT followed by CRT in LAPC

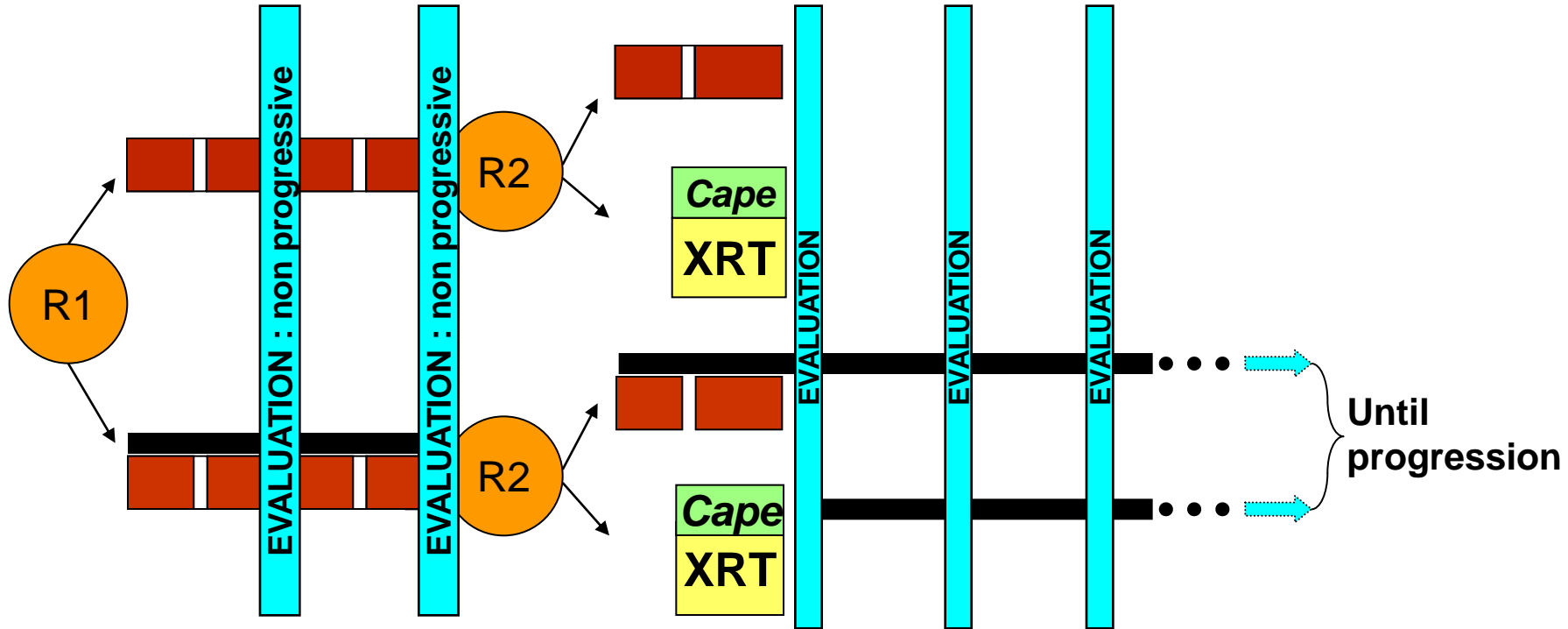
CRT after 3 months of induction chemotherapy




*Huguet F et al, J Clin Oncol 2007*

→ **Promising** strategy

# LAP07 study



 1 month = Gemcitabine ( $1000 \text{ mg/m}^2$ )/wkX3

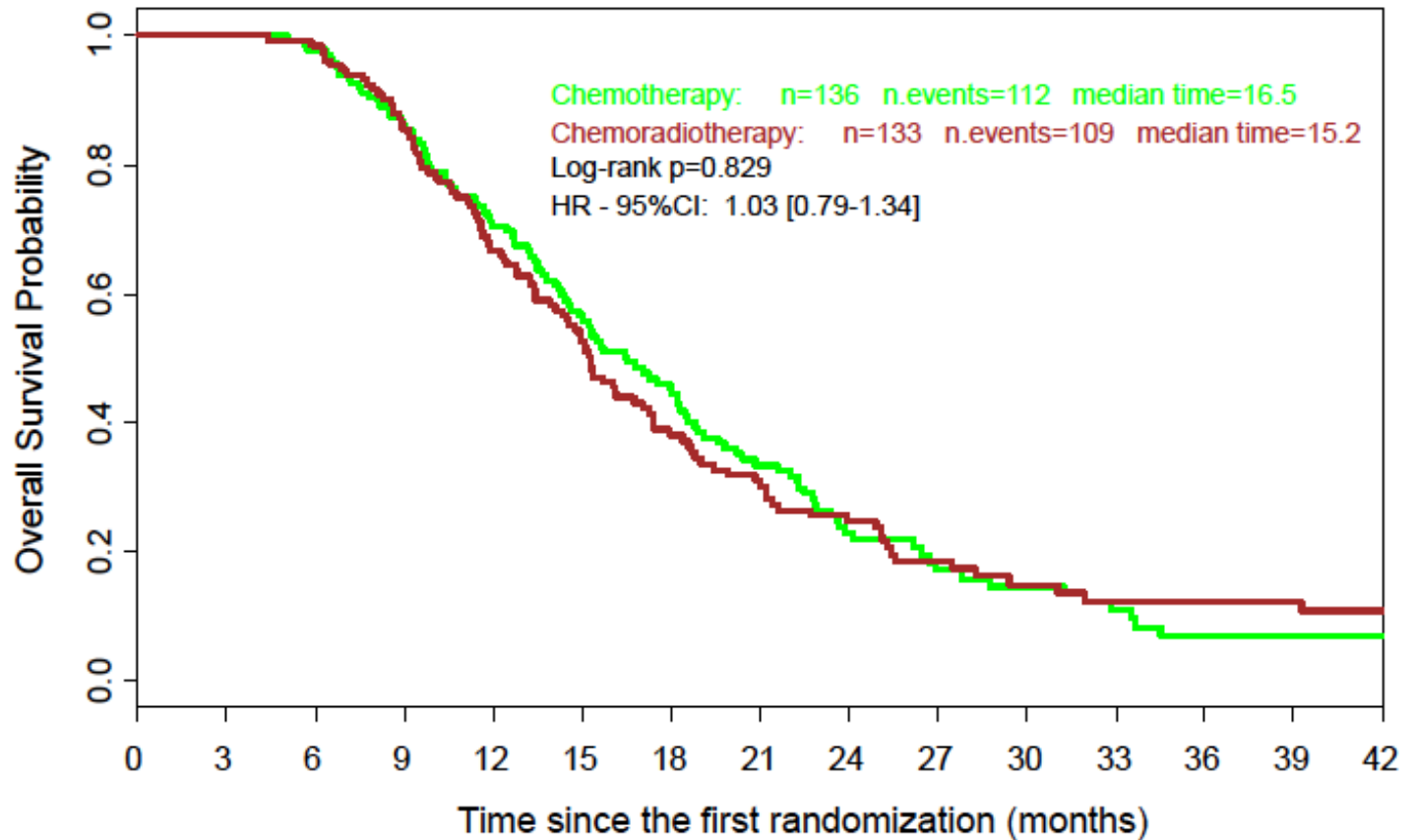
 Erlotinib : 100 mg/d with gem  
150 mg/d as single agent

 **Capecitabine plus radiation**

Secondary surgery allowed at any time



# Overall Survival



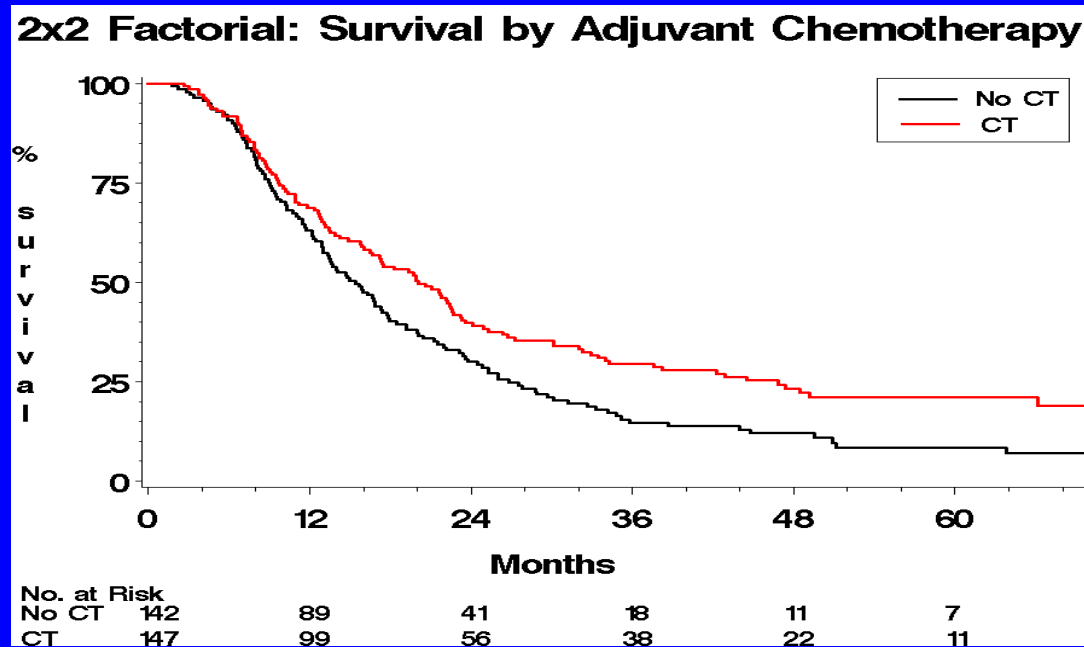
N at risk

Chemotherapy	136	136	133	117	94	70	55	39	24	14	12	8	4	4	4
Chemoradiotherapy	133	133	131	113	87	66	45	34	26	18	12	9	9	8	6

Traitement adjuvant

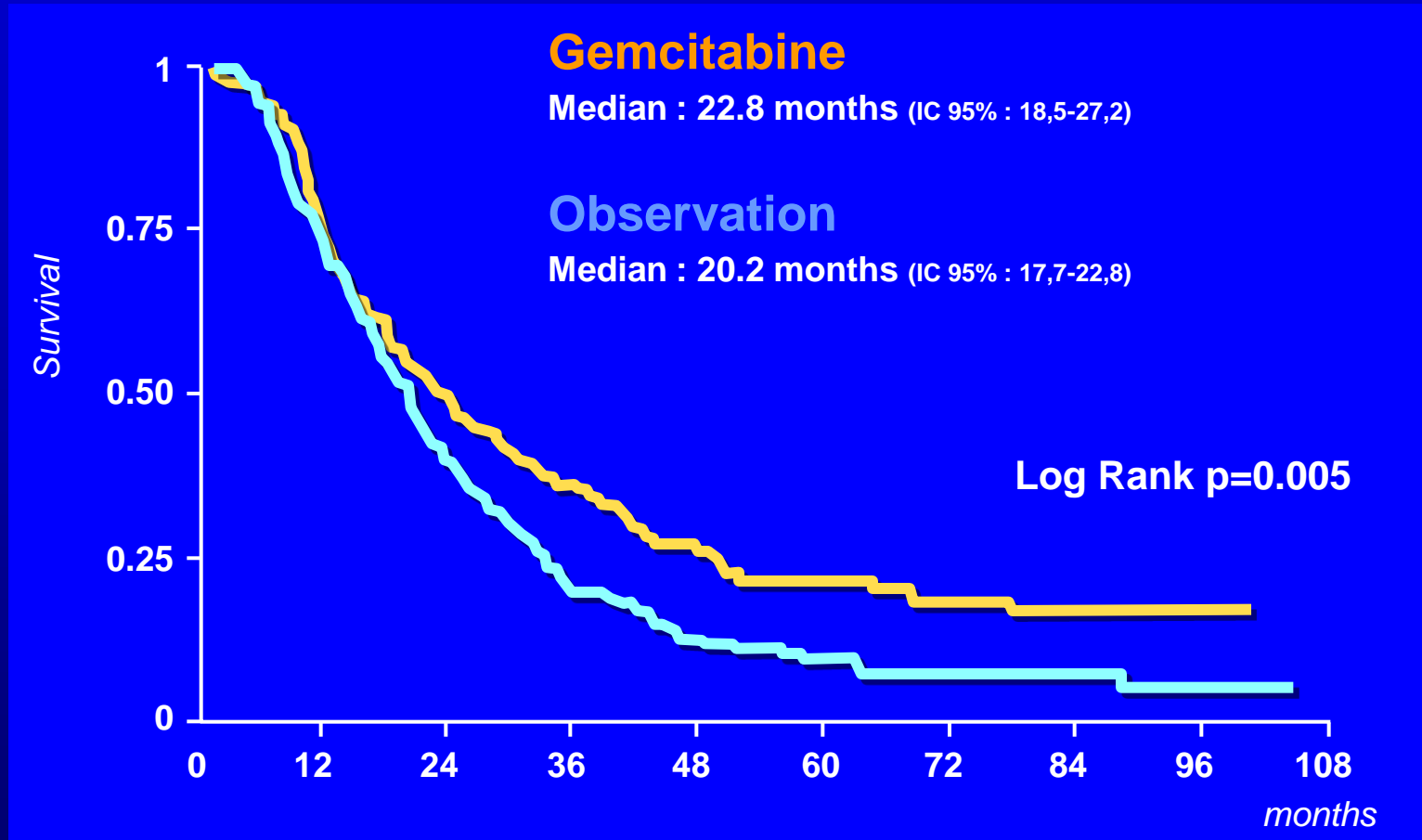
# ESPAC-1 :

Démonstration du bénéfice d'une chimiothérapie adjuvante (5FU / AF)

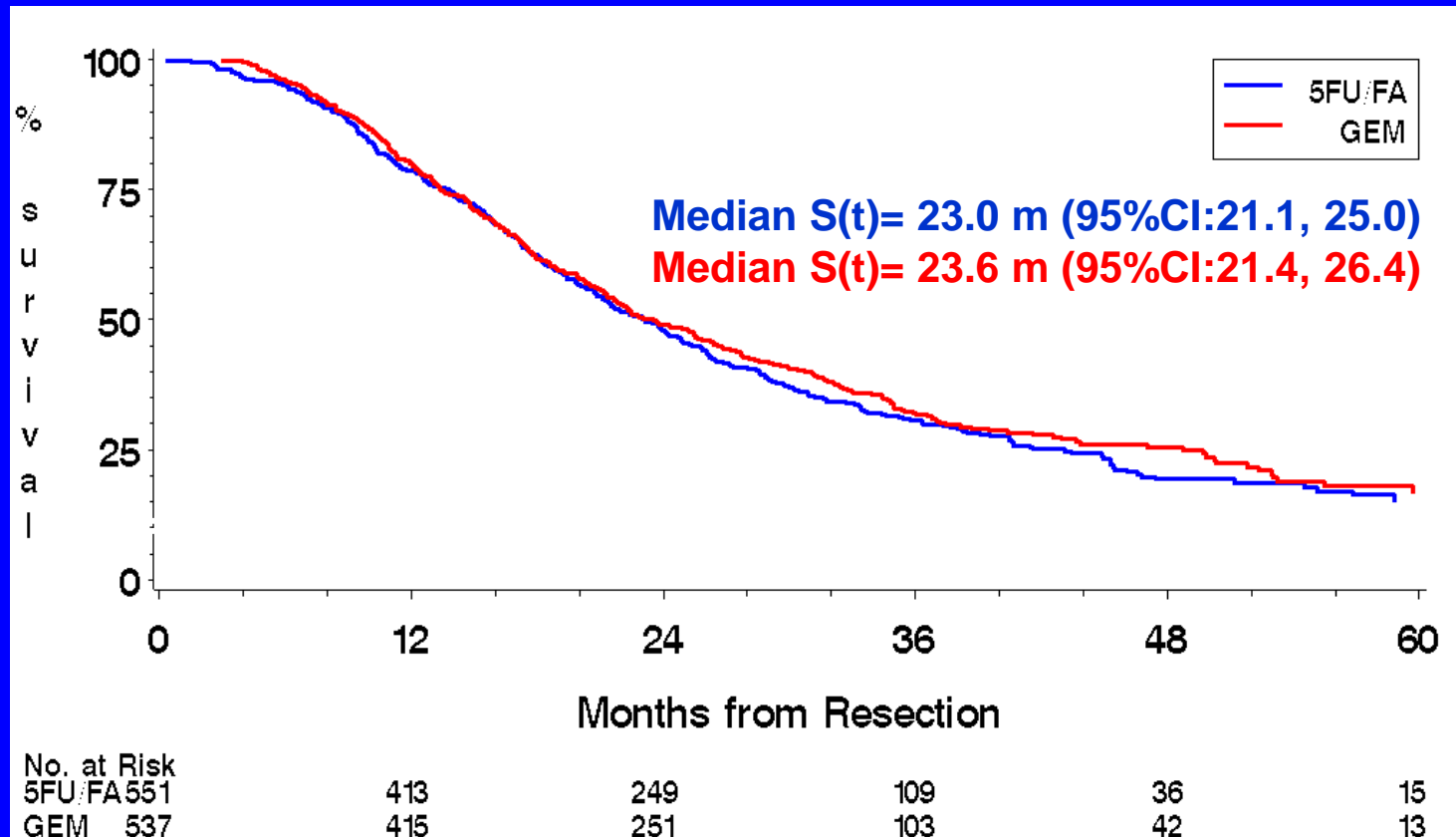


Neoptolemos et al, NEJM 2004; 350:1200-10

# CONKO 01: gemcitabine vs observation



# ESPAC-3 : 5FU / AF vs Gemcitabine



# Synthèse

La chimiothérapie adjuvante double le % de survie à 5 ans

	Chirurgie		Chirurgie + CT	
	médiane survie	survie à 5 ans	médiane survie	survie à 5 ans
ESPAC-1 (5FU/AF)	14 mois	8.4%	19.7 mois	21.1%
CONKO 01 (gem)	20.2 mois	11.5%	22.1 mois	22.5%
ESPAC-3 (5FU/AF)			23.0 mois	20% *
ESPAC-3 (gem)			23.6 mois	22% *

\* : estimation

Confirmation des facteurs pronostiques (quel que soit l'étude ou le traitement)

Grade, Stade, N0 vs N+, R0 vs R1

La gemcitabine n'est pas supérieure au 5FU/AF (efficacité) : HR 0.94,  $p = 0.39$

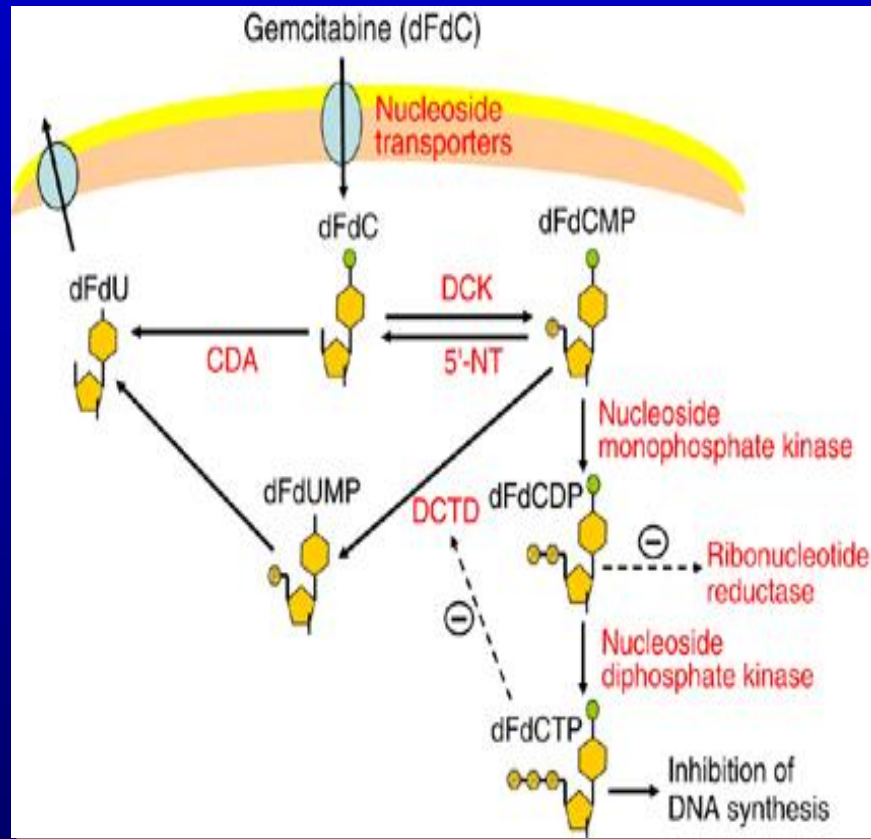
tendance pour les N+ , tendance pour les résections R1

La gemcitabine est supérieure au 5FU/AF pour les paramètres suivants :

tolérance, incidence des SAE, compliance / dose-intensité

Biomarker	Prognostic	Predictive	Current clinical impact
CA 19.9	Yes	No	No
CTC / cDNA	Yes	No	No
miRNAs	Yes	No	? (Anti-sens)
Proteomic / LAMC	Yes	No	No
Genomic profiles	Yes	No	No
hENT1	No	Yes (Gem)	Likely (Gem)
dCK	No	Yes (Gem)	Likely (Gem)
CDA	No	Yes (Gem toxicity)	Likely (Gem)
SPARC	Yes	?	? (Abraxane)
Histone modifications	Yes	?	? (5FU)
Hedgehog	Yes	?	? (HH inhibitors)
CXCR4	Yes	?	? (CXCR4 inhibitors)
HGF / c-Met	Yes	?	? (c-Met inhibitors)
SMAD4	?	?	?
HER2	?	?	? (HER2 inhibitors)
EGFR	? (No)	No	No
VEGFR	? (No)	No	No
IGFR	? (No)	No	No

# Gemcitabine: mechanisms of action



## ■ Intracellular uptake

✓ **hENT1**

✓ **hCNT 3**

## ■ Activation

✓ **dCK**

– **Nucleoside Phosphate Kinase**

## ■ Inactivation

– **CDA**

– **DCTD**

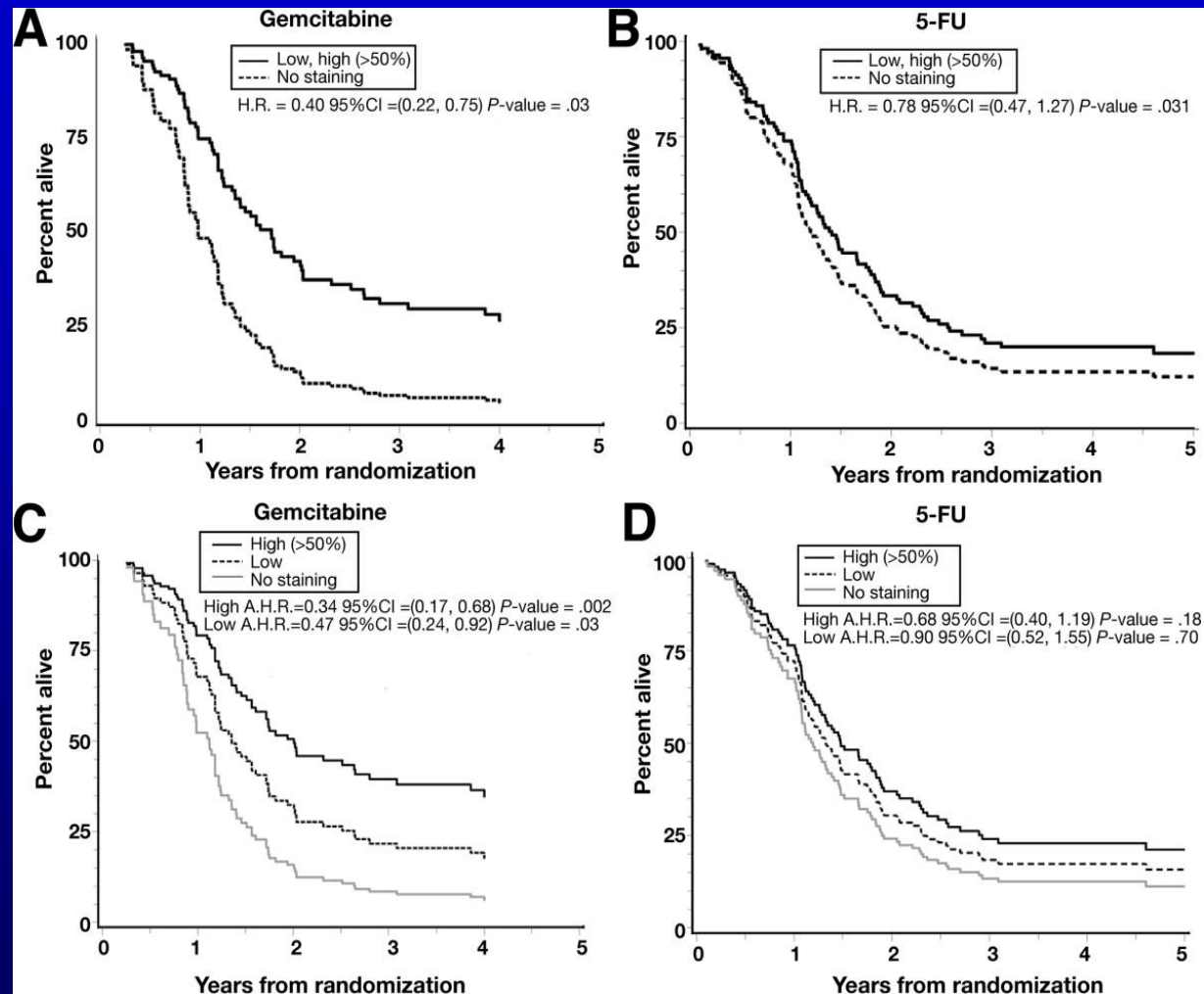
– **5'-NT**

## ■ Action

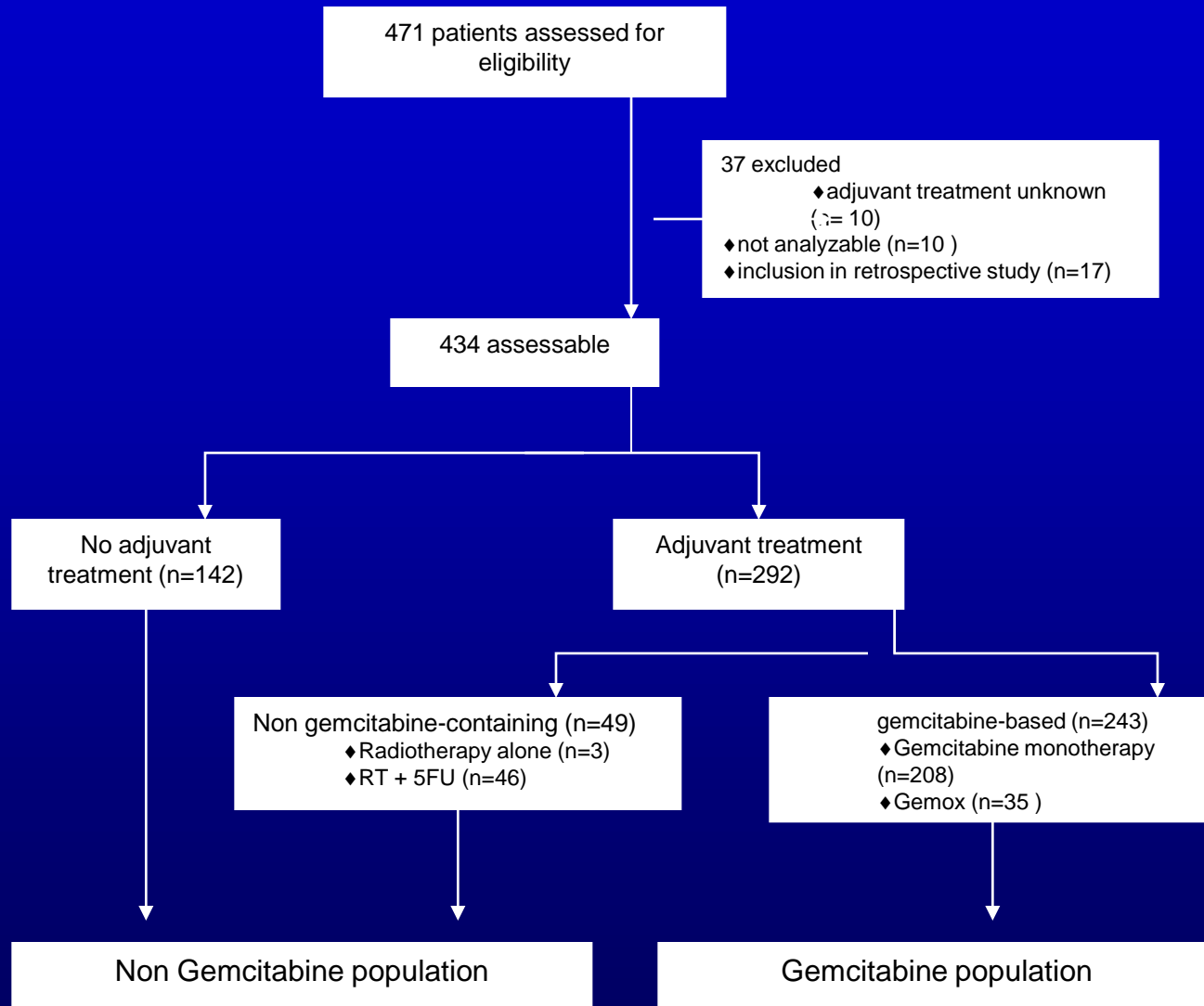
– **Inhibition DNA synthesis**



# Survie selon l'expression de hENT1: Etude RTOG 9074

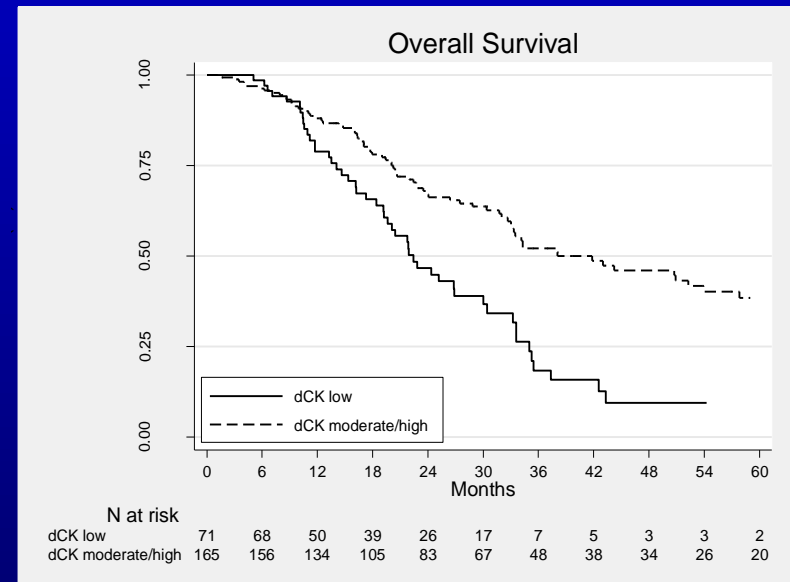
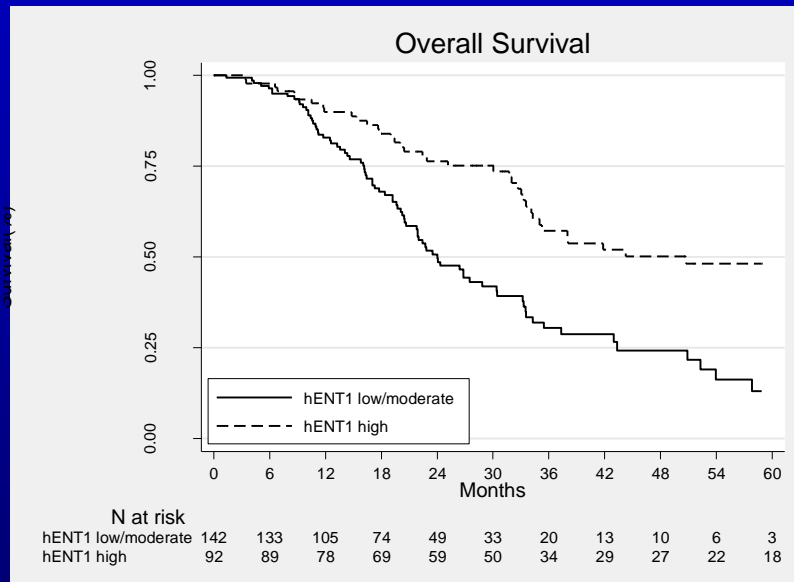


# Expérience Franco-Belge



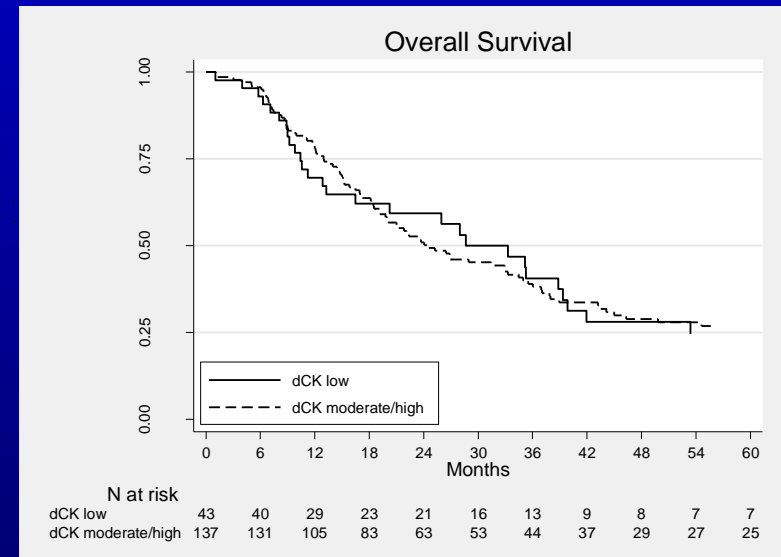
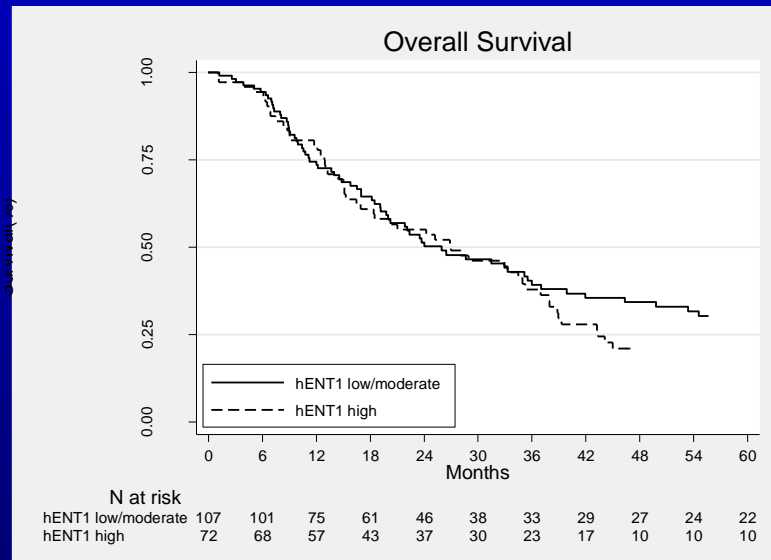
# Expérience Franco-Belge

## Population « gemcitabine »



# Expérience Franco-Belge

## Population « non gemcitabine »



# hENT1 as a predictive marker for patients with resected pancreatic ductal adenocarcinoma with or without adjuvant gemcitabine or 5FU from patients randomized in the ESPAC1/3 trials

JP Neoptolemos, TF Cox, W Greenhalf, L Garner, F Campbell, D Palmer, J Mackey, C Dervenis, A Scarpa, C Bassi, MW Buchler for the European Study Group for Pancreatic Cancer

## EPC, Prague 21<sup>st</sup> June 2012



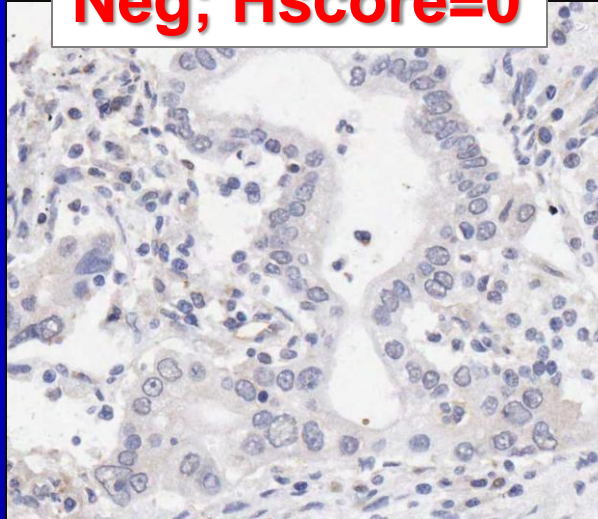
Freedom of the  
City of  
Liverpool



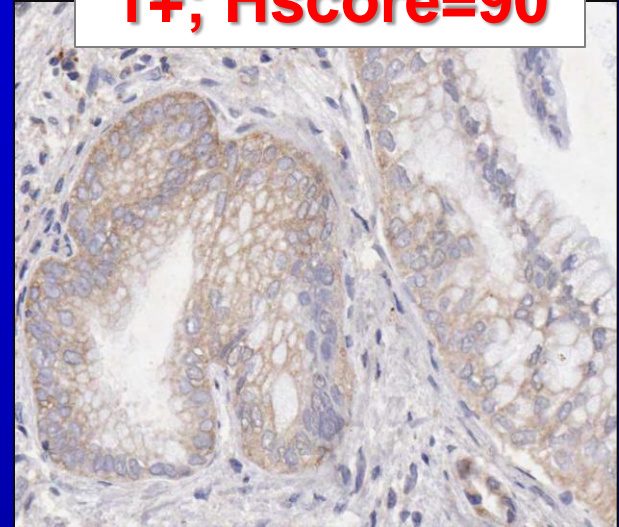
NIHR Liverpool Pancreas  
Biomedical Research Unit

hENT1  
IHC  
TMA  
core  
scoring

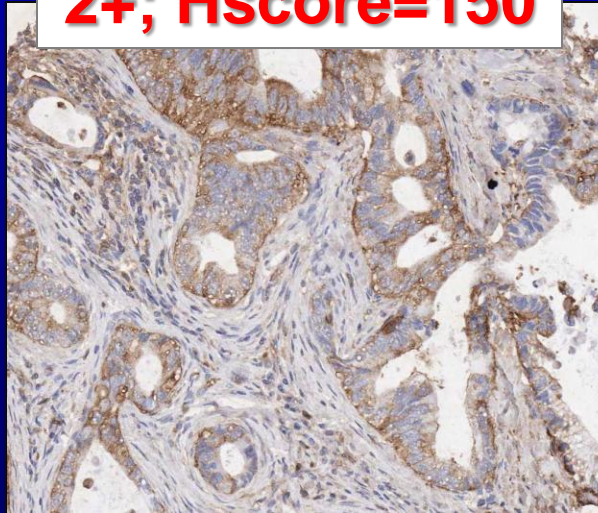
**Neg; Hscore=0**



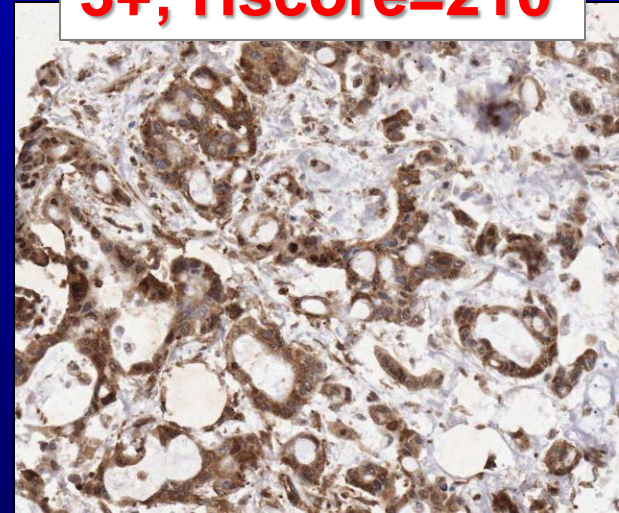
**1+; Hscore=90**



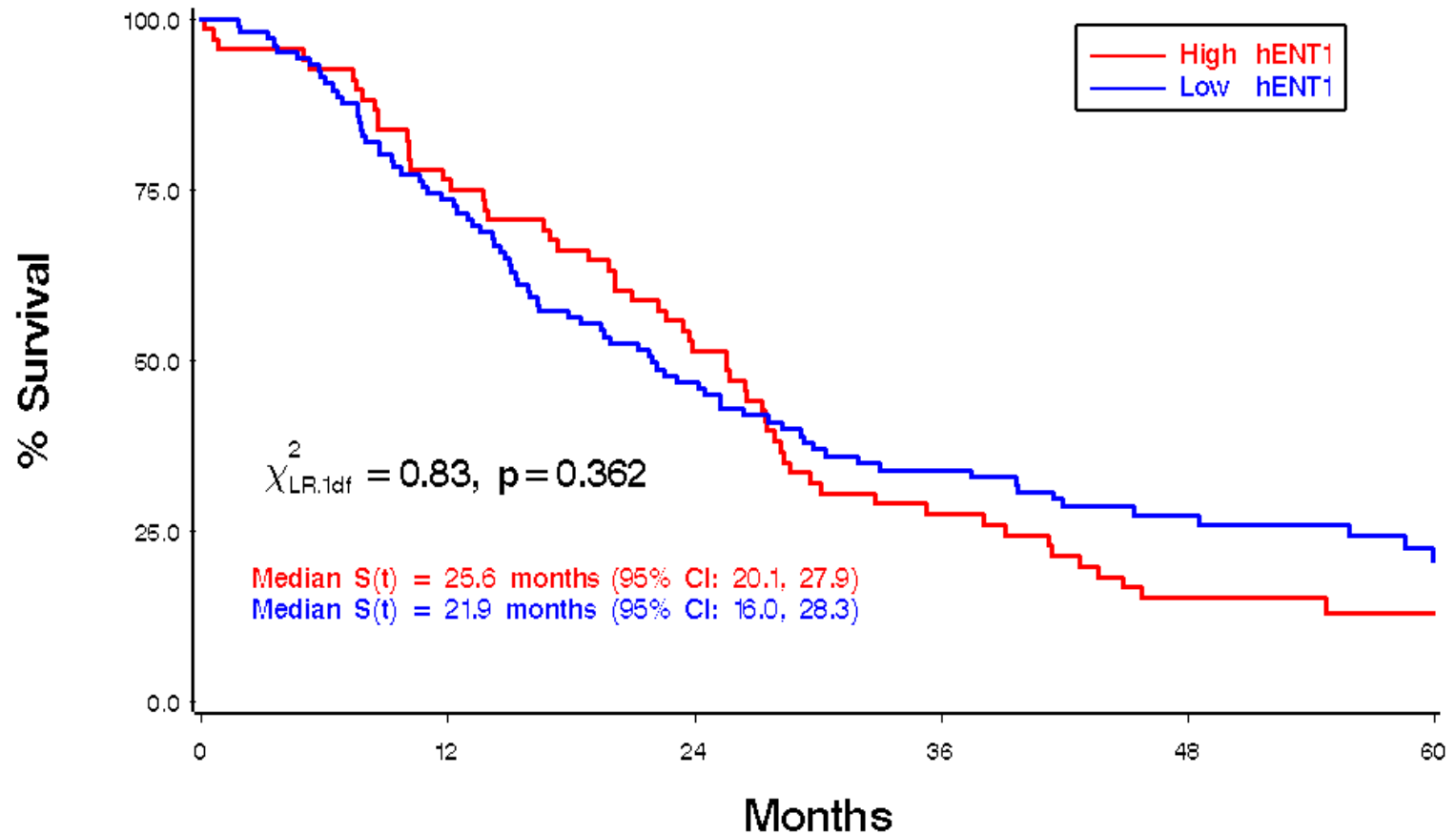
**2+; Hscore=150**



**3+; Hscore=210**

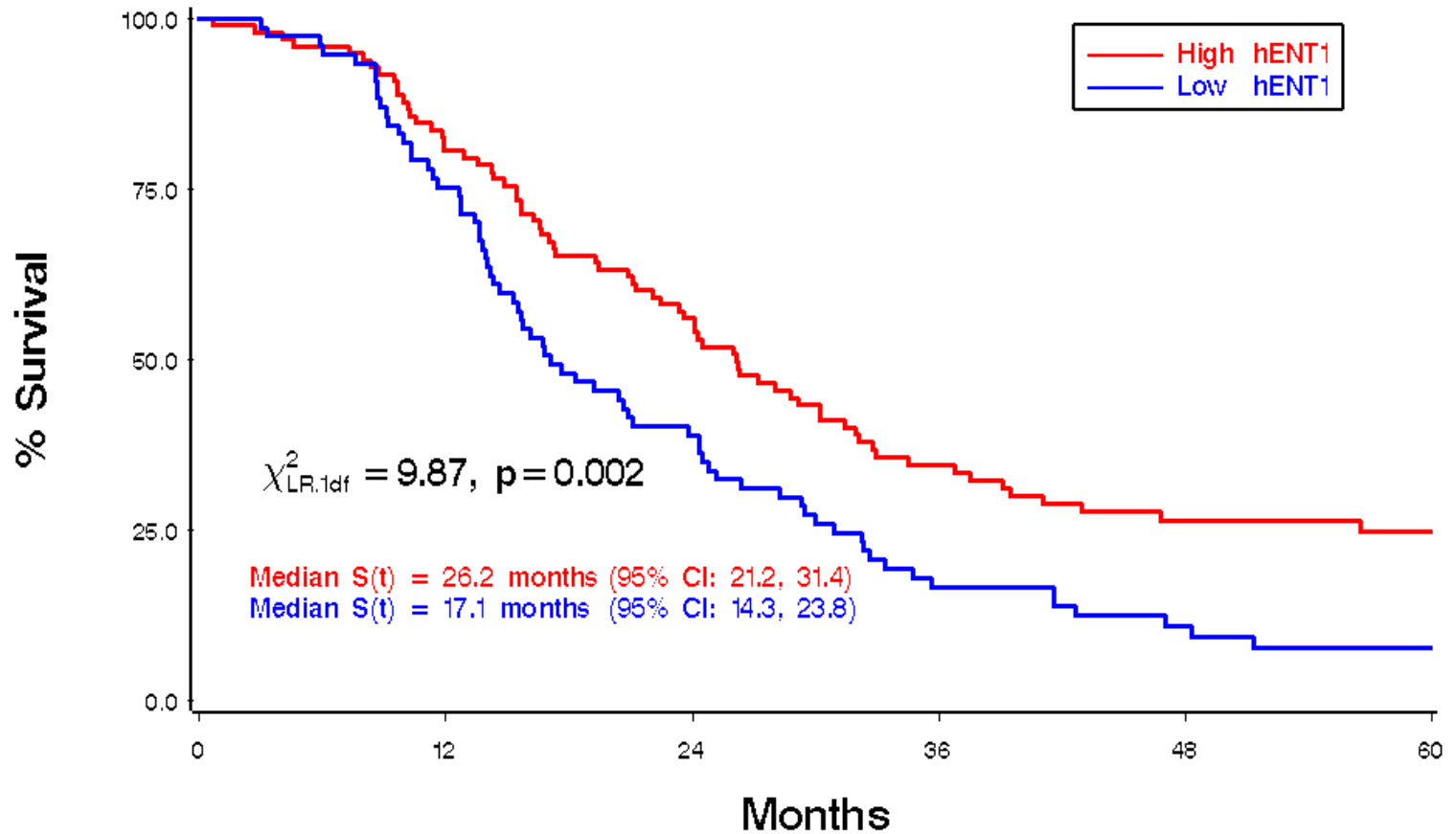


# Survival for 5FU by High/Low hENT1



No. at Risk						
High hENT1	69	52	35	18	10	5
Low hENT1	107	77	41	34	21	11

# Survival for GEM by High/Low hENT1



No. at Risk		12	24	36	48	60
High hENT1	99	79	54	31	20	11
Low hENT1	77	58	30	12	7	4



# Impact de hENT1 sur les études adjuvantes

US « LAP07-like » :

Déséquilibre entre les patients hENT1 low/moderate et les patients hENT1 high pour atteindre la RTCT après 6 mois de traitement....

ESPAC4 :

Gem + Cap probablement > Gem chez les patients hENT1 low/moderate

FOLFIRINOX :

Folfirinox probablement > Gem chez les patients hENT1 low/moderate

—————> **Nécessité (au moins) d'une stratification...**

# **Gemcitabine “optimisée”**

**CO-1.01 :**

**prodrogue de la gemcitabine**

**liposoluble**

**pénétration intracellulaire indépendante des  
transporteurs**

**Etude de phase III (2012, multicentrique, 367  
patients):**

**gemcitabine vs CO-1.01**

**négative, y compris chez les hENT1 –**

**Ac anti-lapin SP120**

# hENT1

## « Positive » trials

RTOG  
(adjuvant, retrospective)



French-Belgium series  
(adjuvant, retrospective)



ESPAC 1&3  
(adjuvant, retrospective)



## Negative trials

Clovis C01-101  
(metastatic, prospective)

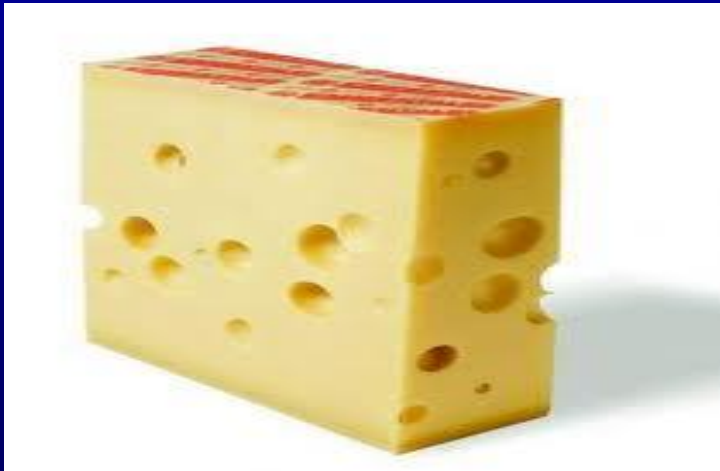


ECOG  
(metastatic, retrospective)



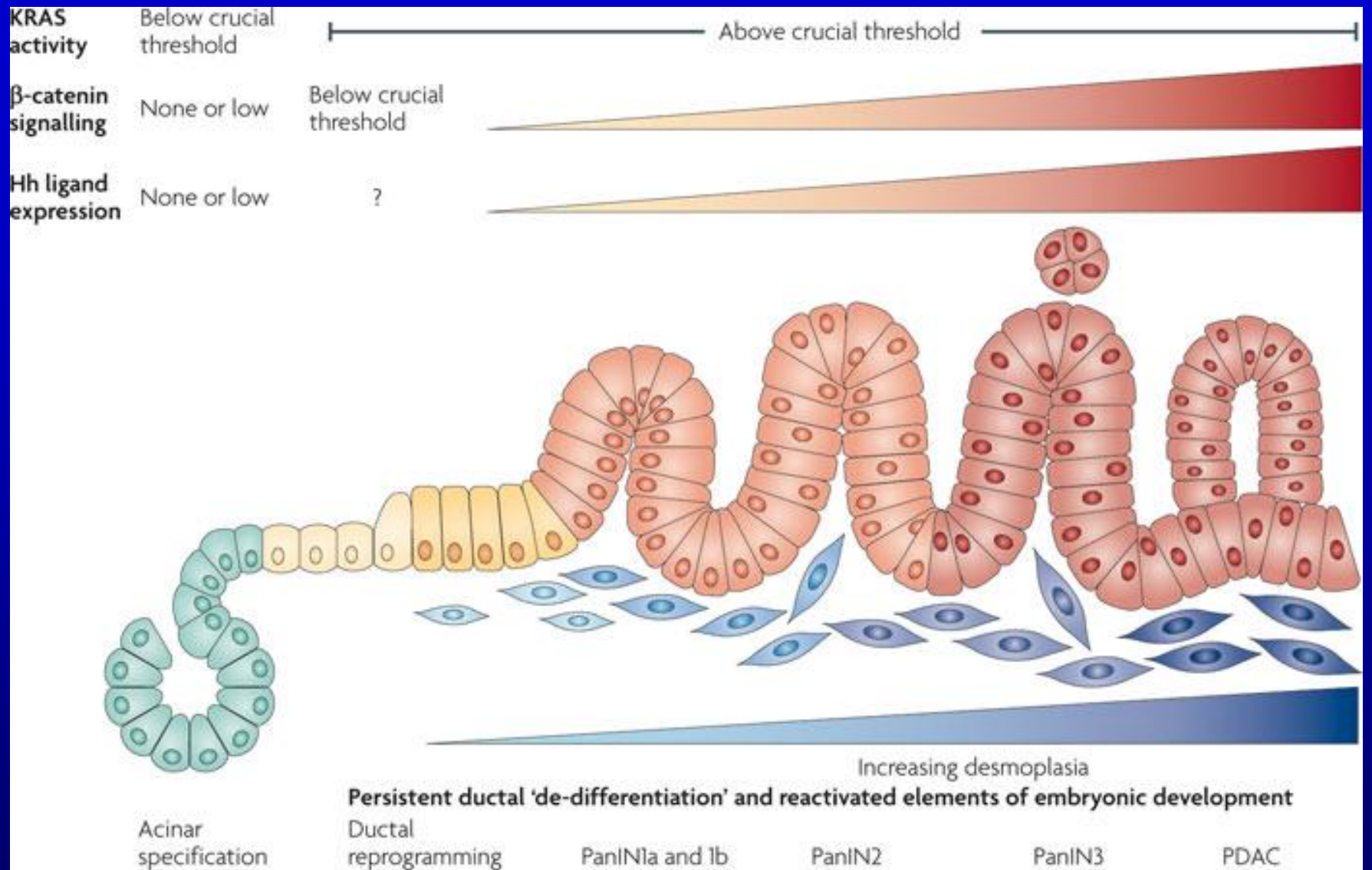
CONKO-01  
(adjuvant, retrospective)





||

?



## Hedgehog Pathway

- In 1980, hedgehog was first described in flies to look like little hedgehog with continuous spiky outer skin due to its mutations.
- Crucial for normal organ development, differentiation and morphogenesis in *Drosophila*
- Conserved from flies to humans





# Story of cyclopamine





# Story of cyclopamine



*Veratrum californicum*  
Inhibits Hh pathway



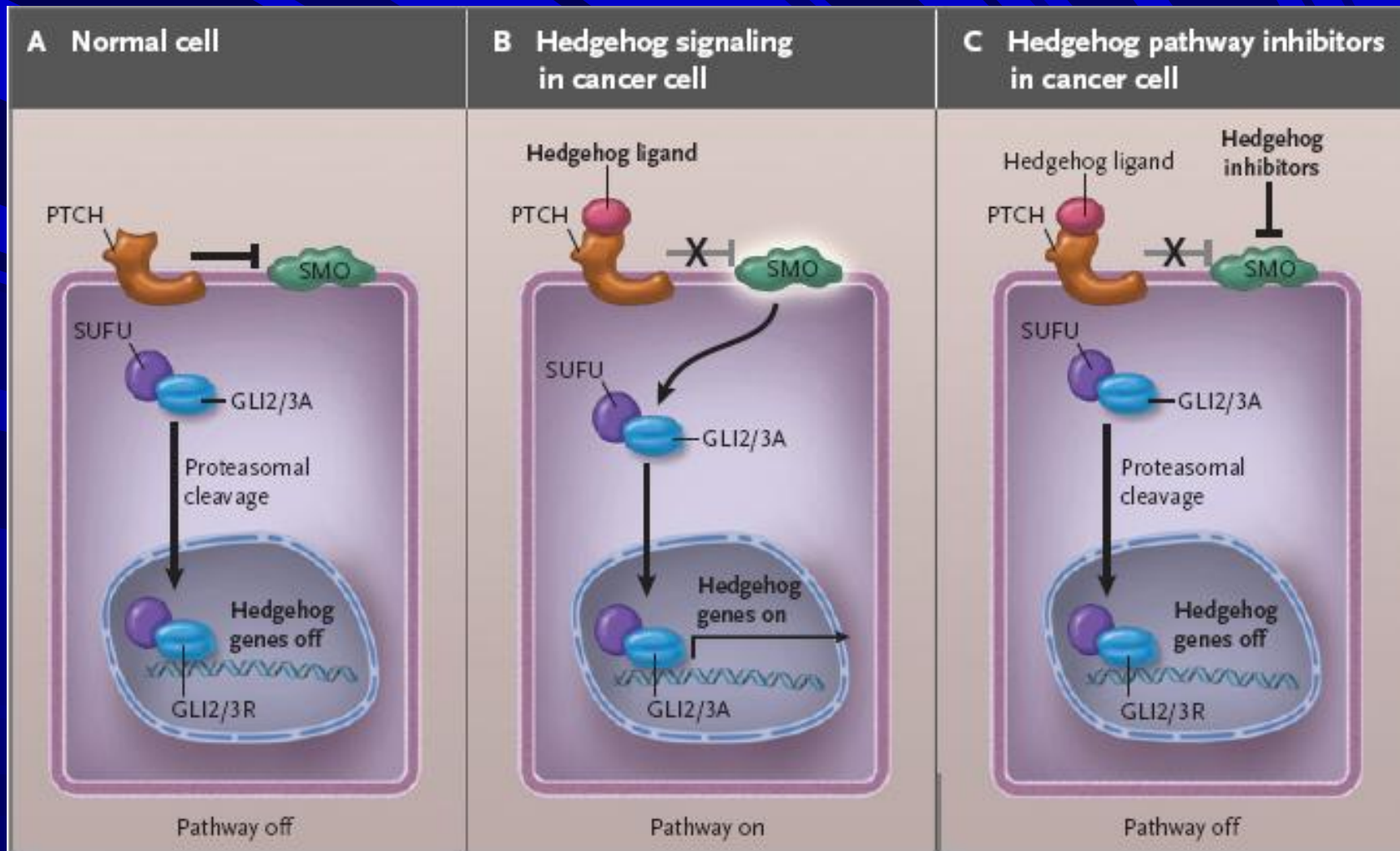


# Hedgehog Pathway

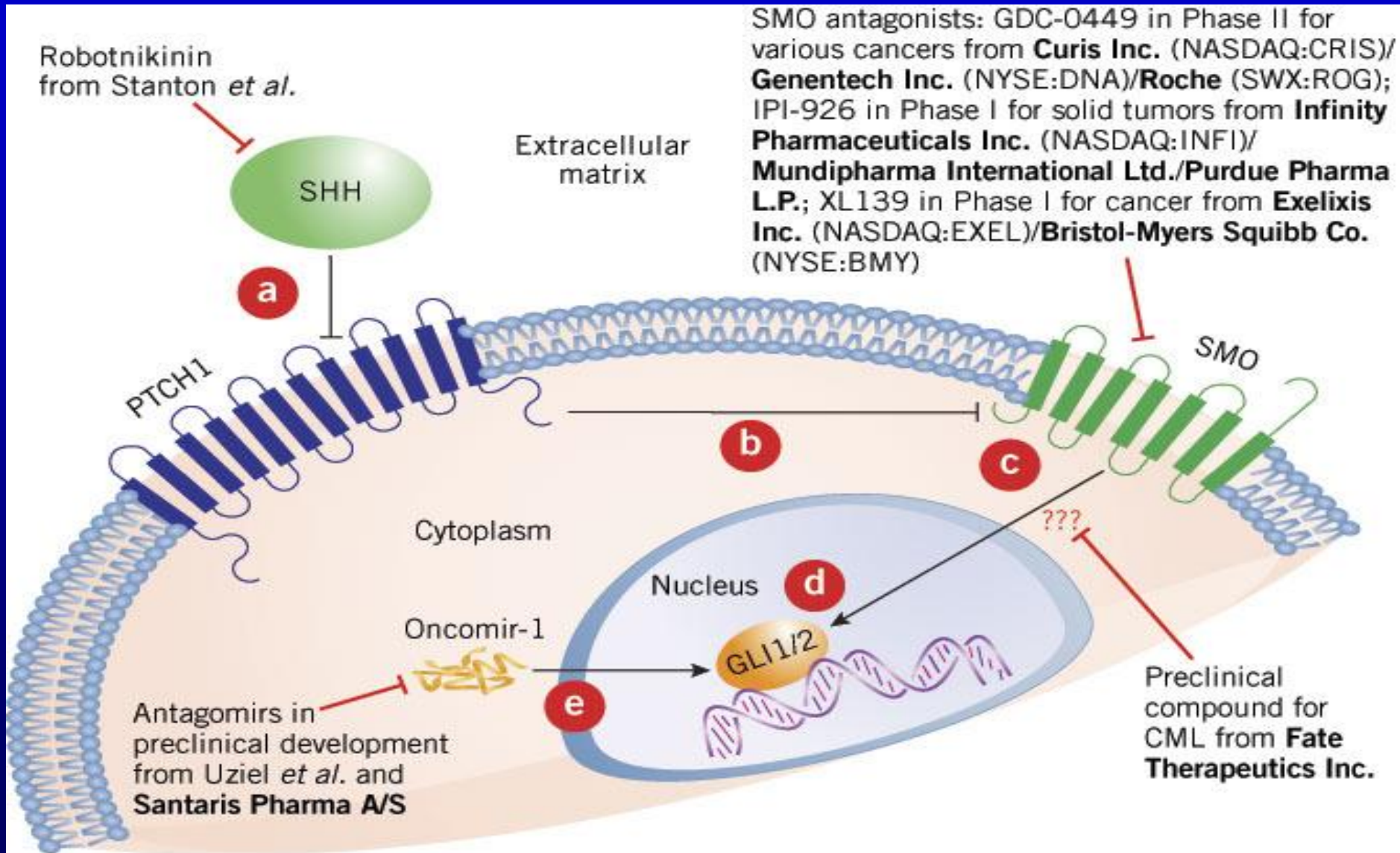
- Three hh genes in mammals
  - *Sonic hh*-broadest expression pattern
  - *Desert hh*-restricted to the developing bone and cartilage, gut and pancreas
  - *Indidan hh*-gonads and testes, peripheral nerves and pancreas



# Hedgehog (hh) pathway



# Hedgehog (hg) pathway



# Cancers du pancréas

- Maladie métastatique
- Maladie localement avancée
- Maladie opérable



Standard :	Folfirinox (IP 0-1), Gemcitabine (IP2)
Options :	Gemcitabine + Abraxane GEMOX, gem FDR
Questions posées :	nouvelles drogues, traitement sans gemcitabine traitements individualisés selon profil génomique

# Cancers du pancréas

- Maladie métastatique
- Maladie localement avancée
- Maladie opérable



Standard :

chimiothérapie

Options :

chimiothérapie suivie de radiochimiothérapie

Questions posées :

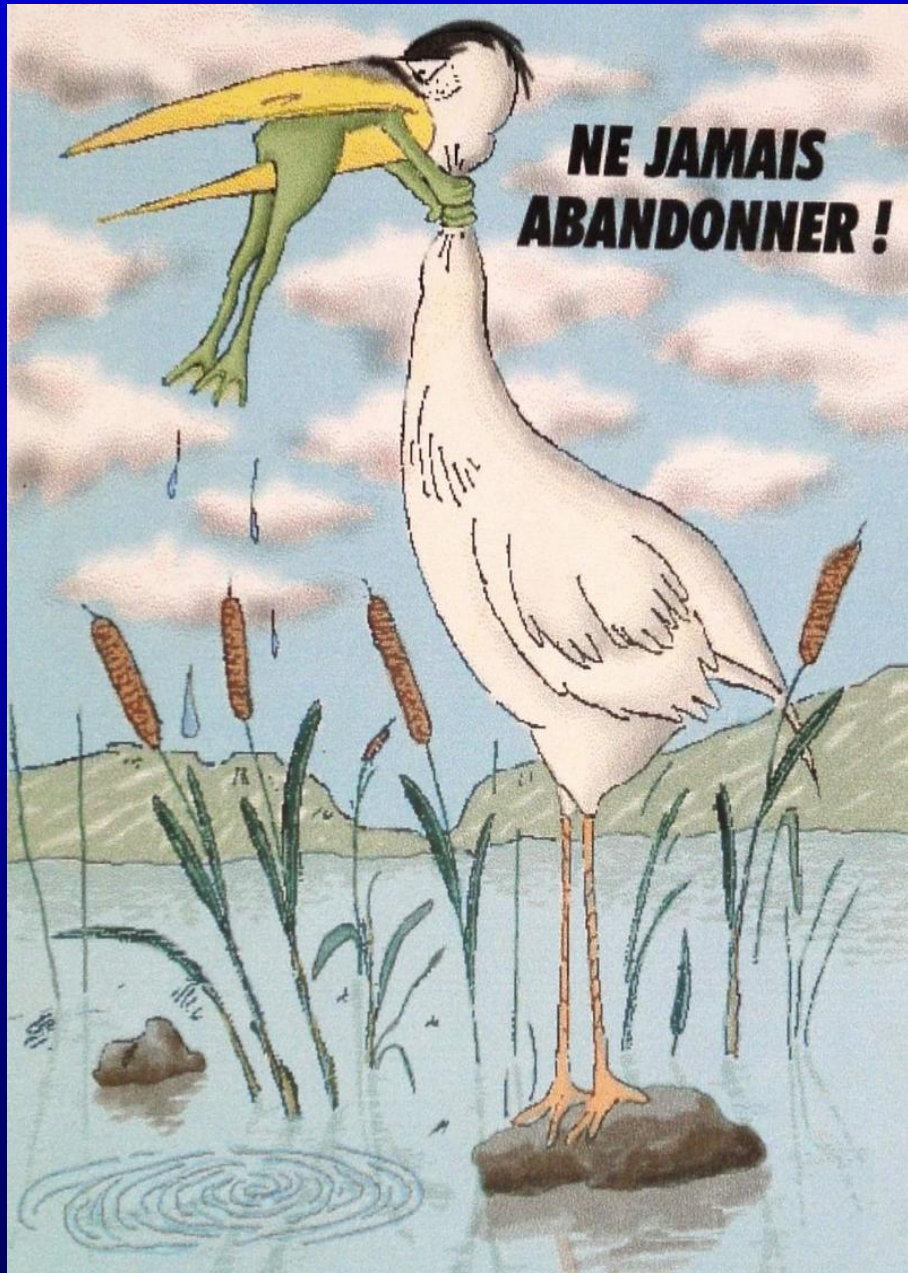
place de la radiochimiothérapie optimisée  
place des résections secondes  
traitements individualisés selon profil génomique

# Cancers du pancréas

- Maladie métastatique
- Maladie localement avancée
- Maladie opérable



Standard :	chirurgie puis gemcitabine x 6 mois en adjuvant
Options :	chirurgie puis chimio suivie de radiochimio
Questions posées :	qualité de la résection R0 Amélioration de la chimiothérapie (Folfirinox ?) place de la radiochimiothérapie adjuvante place du traitement néo-adjuvant traitements individualisés selon profil génomique



**NE JAMAIS  
ABANDONNER !**