TH-302 plus Gemcitabine vs. Gemcitabine in Patients with Untreated Advanced Pancreatic Adenocarcinoma

MJ Borad, Mayo Clinic, Scottsdale, AZ
et al.

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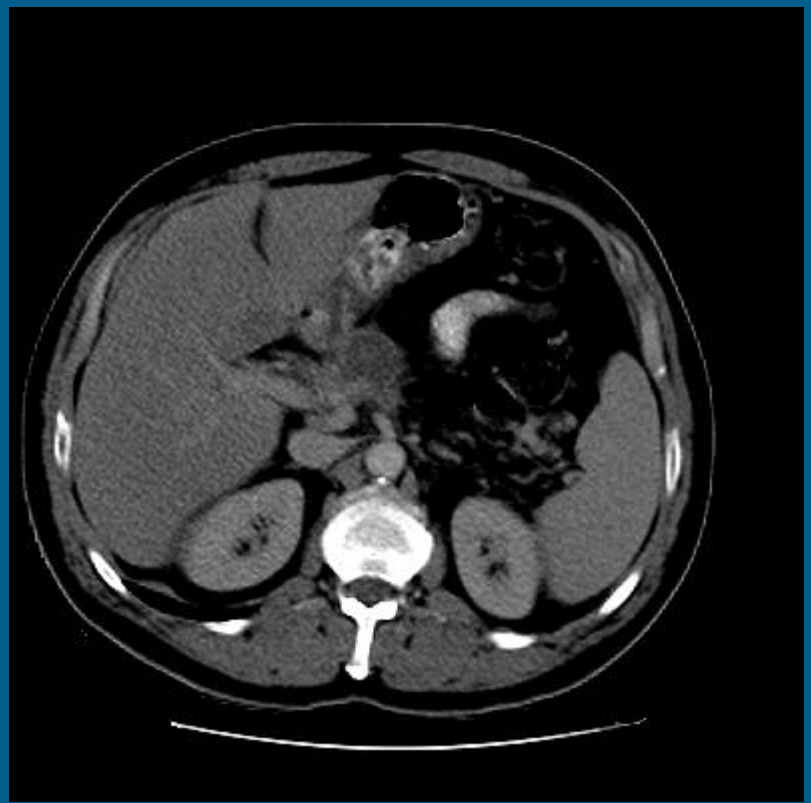
Institut Gustave Roussy, Villejuif France

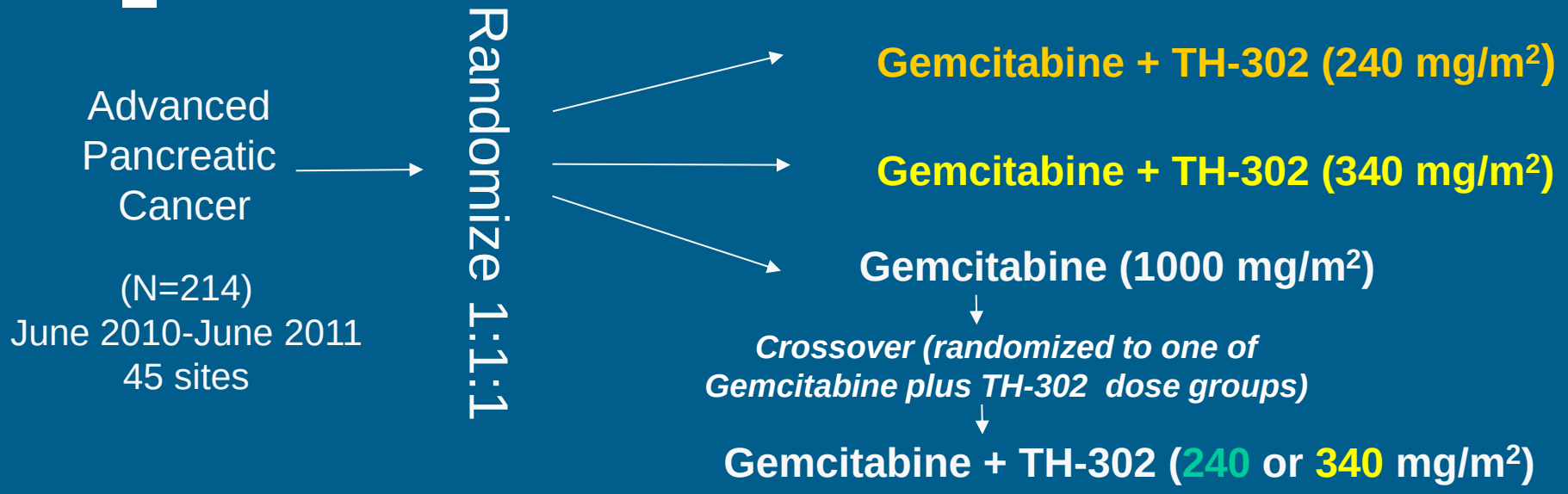
New drug, new concept, microenvironment

- Pancreatic cancers are frequently hypovascularised (at least the primary)



Good rationale for the use of a drug that is cytotoxic under hypoxic conditions

Design of the trial



Stratification: Stage (Unresectable Locally Advanced vs. Distant Metastases)

Large randomised phase II, rapid inclusion

Previous single arm trial: Greater efficacy at higher doses

240 mg/m2: 0% Response, **5.4 mo median PFS**

Reason to continue at low dose is not clear, better DI???

Toxicity

No major increase in standard toxicity, but….

Laboratory Maximum Grade	**Gemcitabine** (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
Platelets Grade 3/4	5/2 (11%)	11/16 (39%)	23/23 (63%)
ANC Grade 3/4	19/2 (31%)	31/8 (56%)	26/18 (60%)
Hemoglobin Grade 3/4	6/0 (9%)	15/2 (24%)	20/0 (27%)

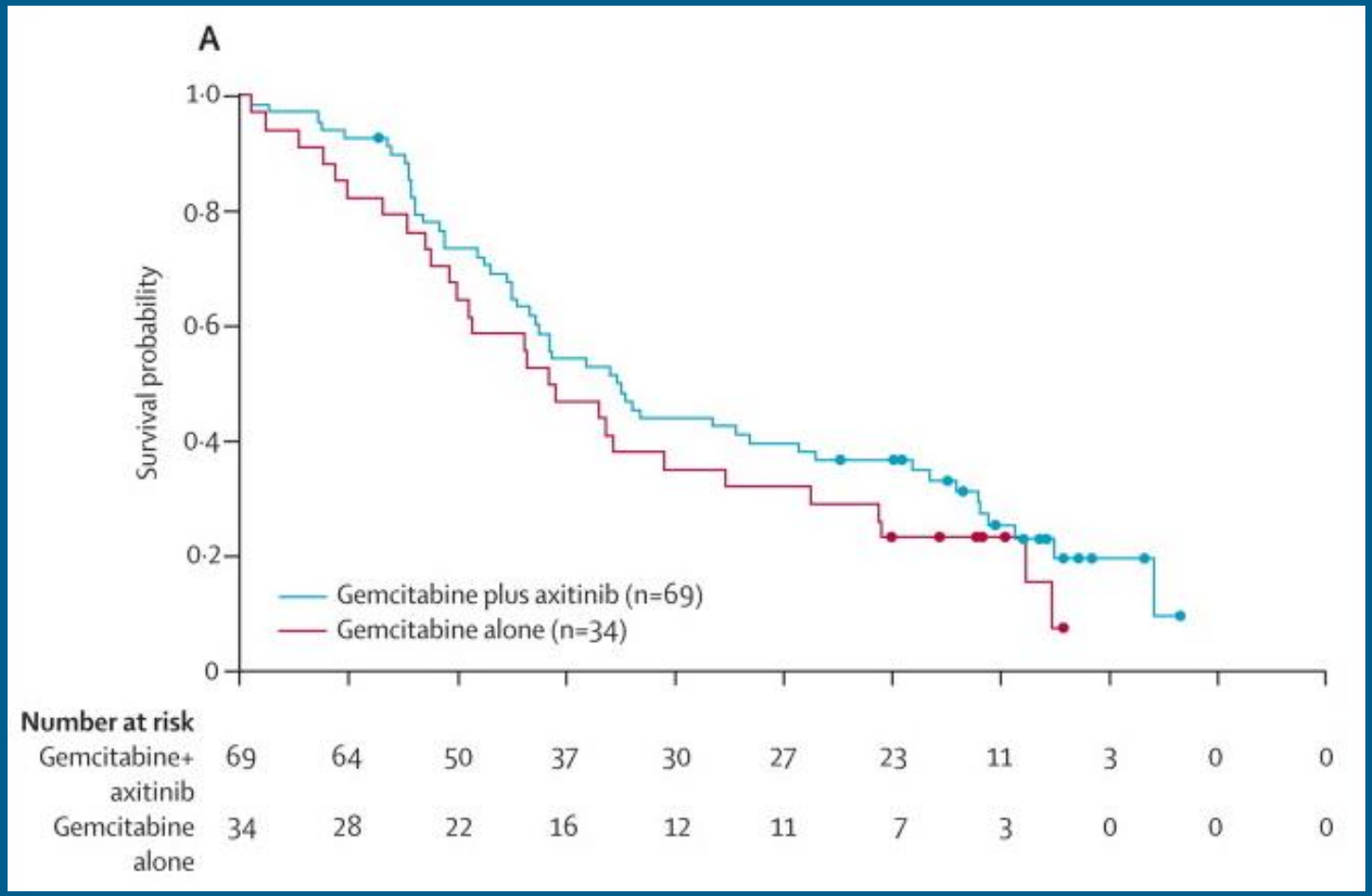
Some concern about hematological toxicity

Population and results

- Well-balanced population

	Gemcitabine (N=69)	**Gemcitabine + TH-302 (240 mg/m²)** (N=71)	**Gemcitabine + TH-302 (340 mg/m²)** (N=74)
ORR (%)	**10**	**17**	**26**
PFS, median (months)	**3.6**	**5.6**	**6.0***
OS, median (months)	**6.9**	**8.7**	**9.2**

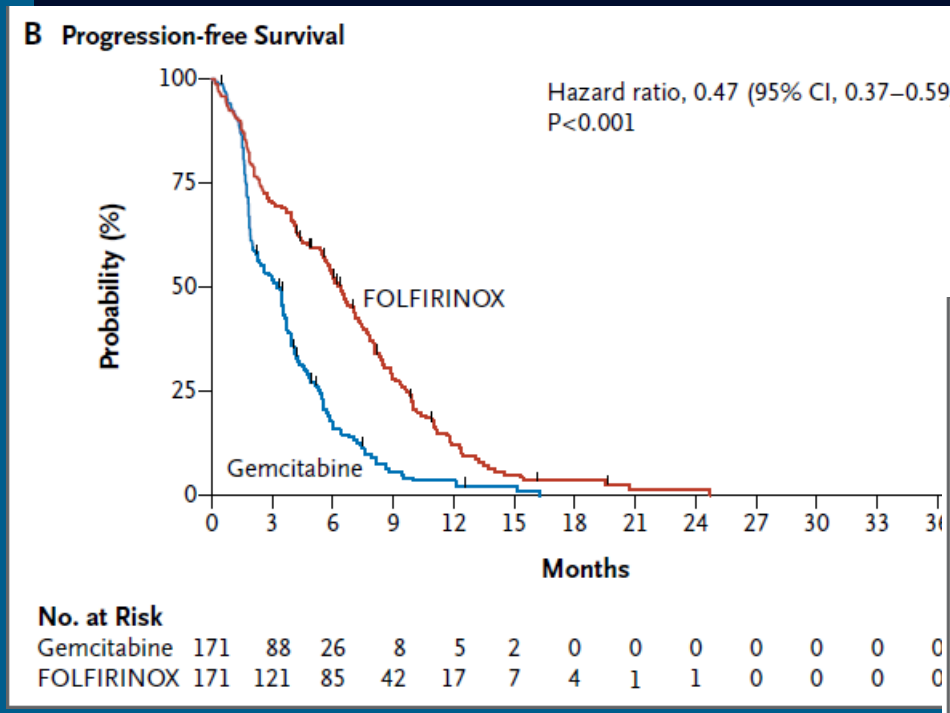
We have to keep in mind the axitinib story…

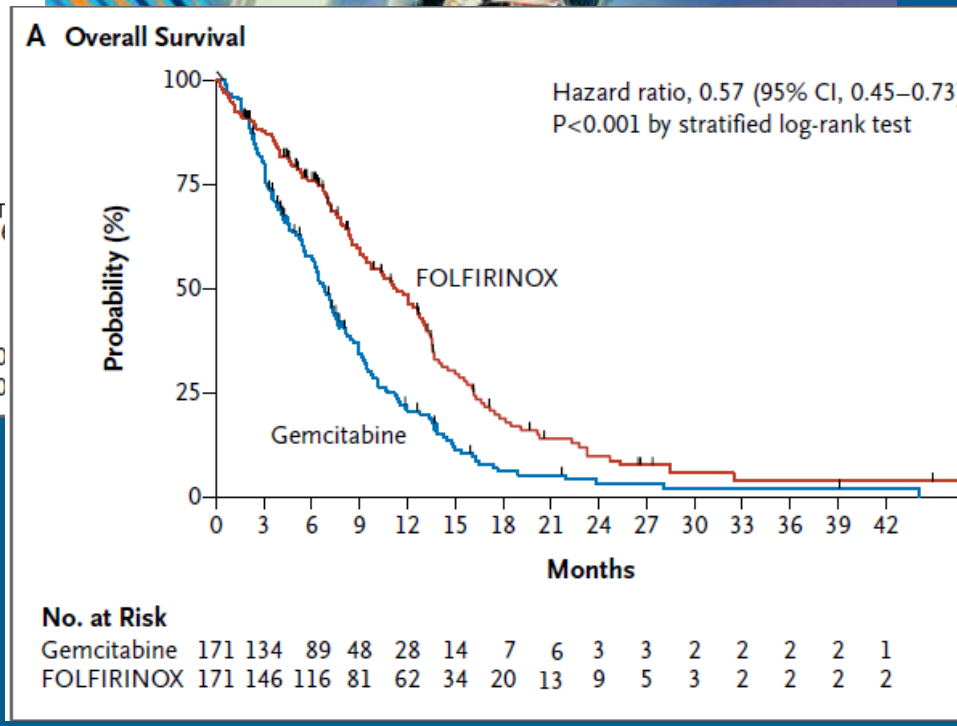


Spano et al, Lancet 2008:371:2101

Followed by a totally negative randomised phase III trial

Folfirinox as active and less toxic???





Conroy T et al, NEJM 2011;364:1817-25

Folfirinox trial, G3-4 toxicity

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

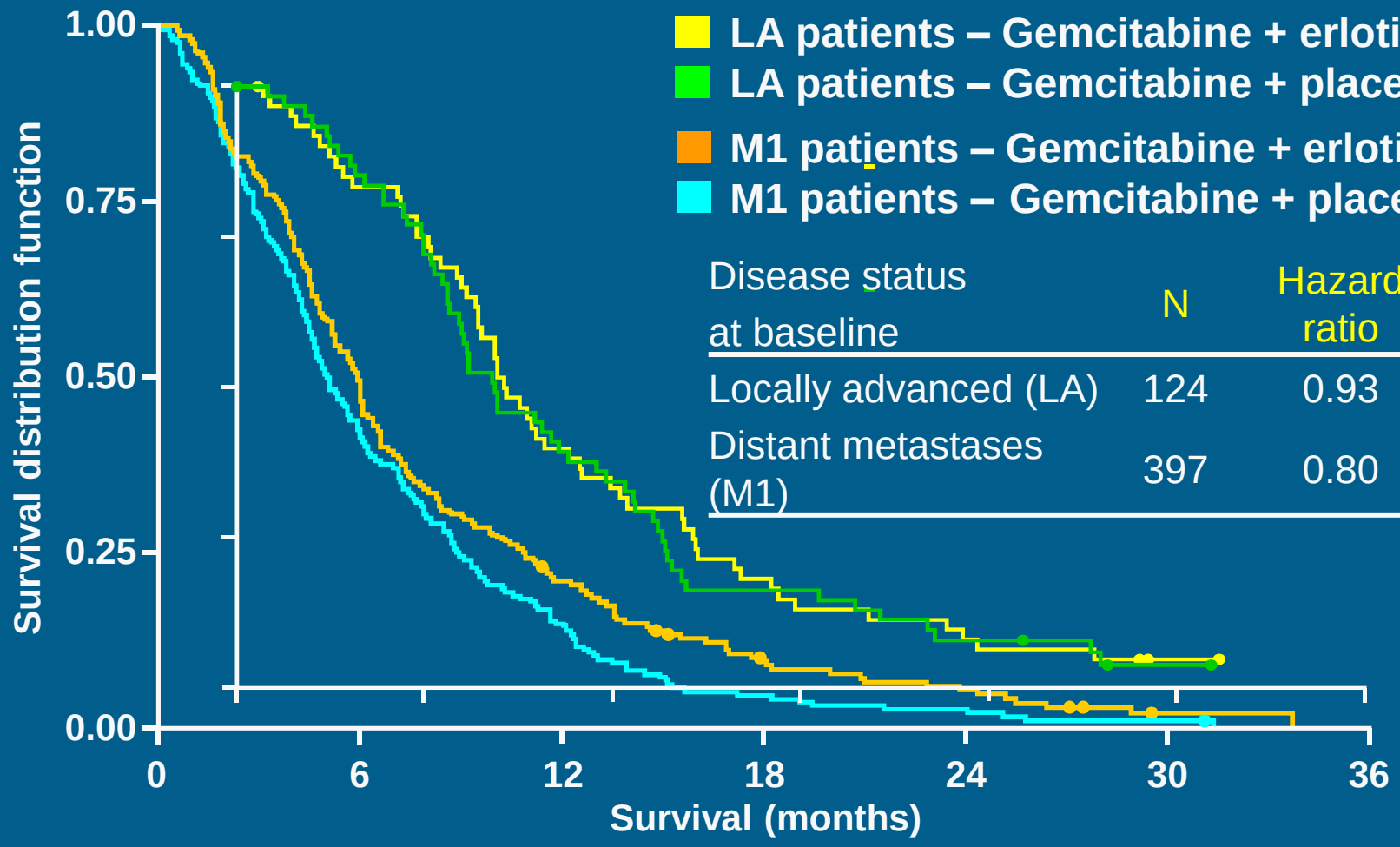
56% - 60%

39% - 63%

Mixed population of locally advanced and metastatic

- Different natural stories
- Different in terms of overall survival:
- A problem in phase III studies
  - Gem + erlotinib versus Gem (Moore et al, JCO 2007;25:1960)
  - Gem +oxaliplatin versus Gemcitabine (Louvet et al JCO 2005;23:3509)

PA 2 trial: M1 patients derive more benefit from erlotinib



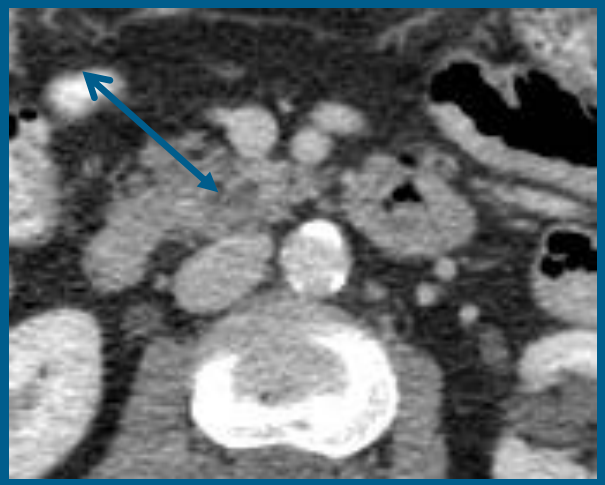
Disease status at baseline	N	Hazard ratio	p-value
Locally advanced (LA)	124	0.93	0.713
Distant metastases (M1)	397	0.80	0.029

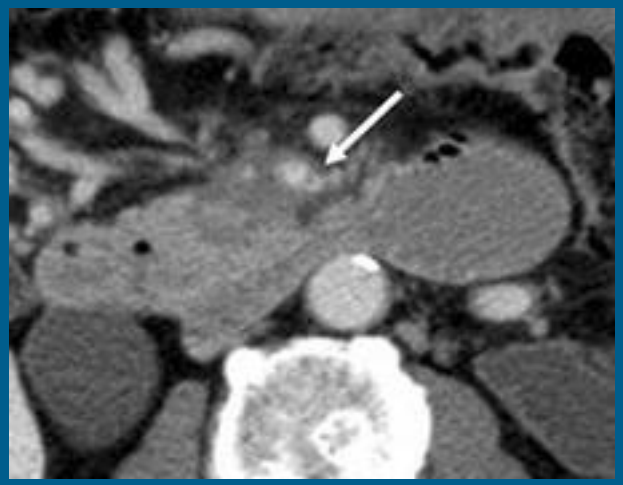
Even different types of locally advanced disease!

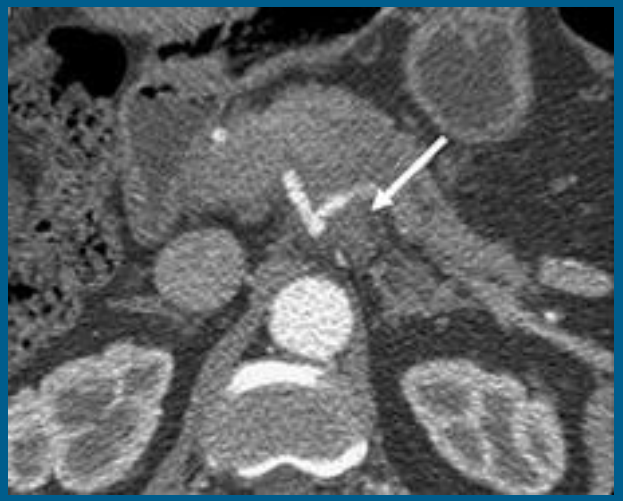
RESECTABLE Lesions

Locally Advanced BORDERLINE Lesions

UNRESECTABLE Lesions







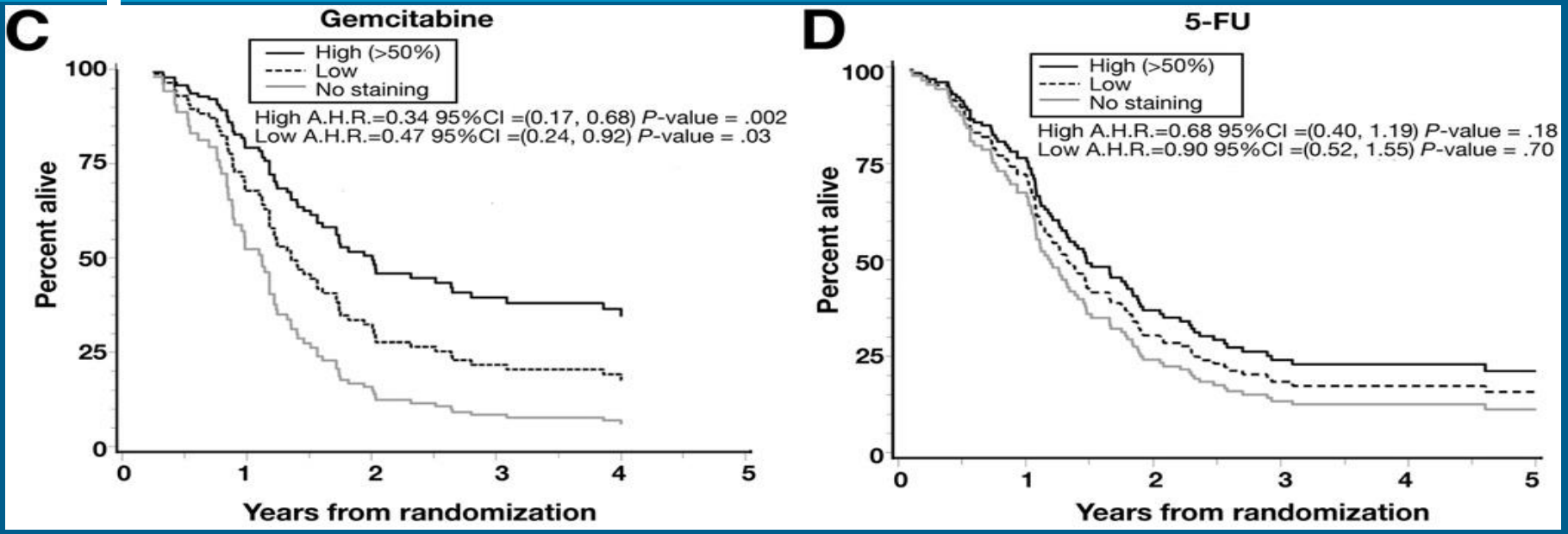
Callery et al. Expert consensus statement Ann Surg Oncol 2009 National Comprehensive Cancer Network 2012 www.nccn.org

On-going trials

- Locally advanced pancreatic carcinoma
  - 251 studies
- Metastatic pancreatic carcinomas
  - 604 studies
- Both
  - 173 studies

ClinicalTrials.gov

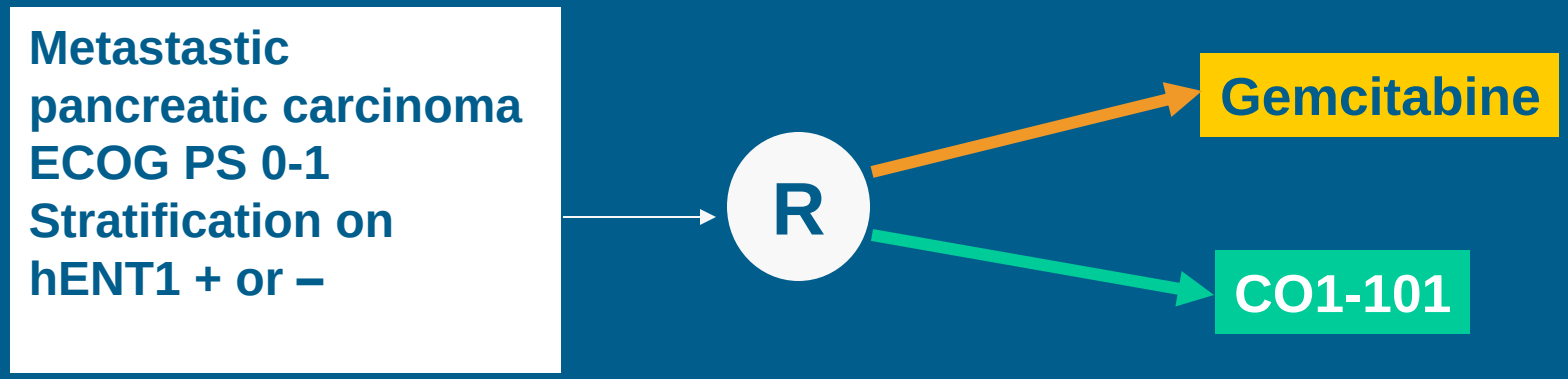
Gemcitabine, the adequate drug to combine with TH-302?



- CO1-101, new drug, gemcitabine + fatty acid tail
- No need for specific hENT1 transporter

Other on-going trials that could change the standard of care

- LEAP study
  - 250 patients enrolled



Microenvironment is a new target for the treatment of APC

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

Phase I:
Gemcitabine 1000 mg/m^2
Foll… *nab*-paclitaxel
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Phase II:
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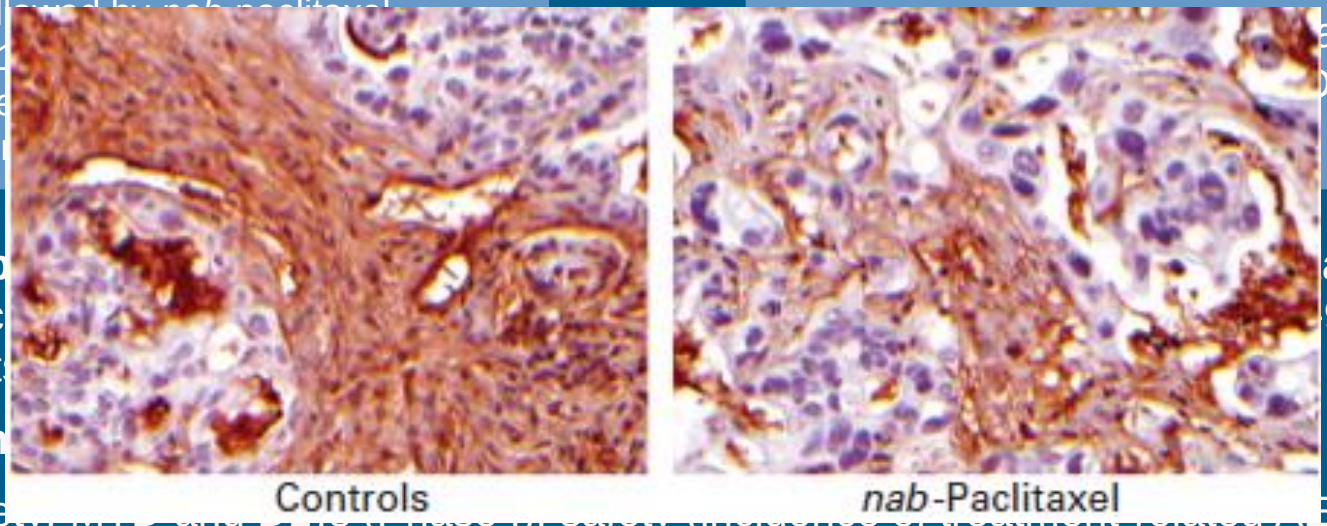
…

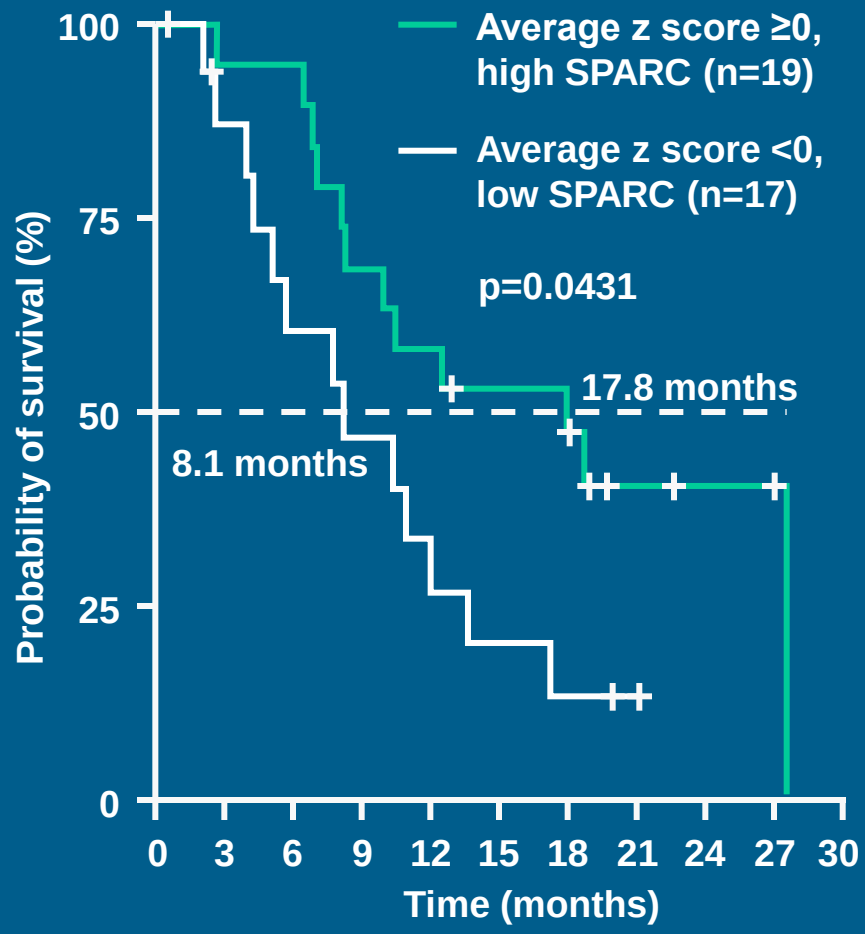


- **Study ob**…abine and the c…9 levels in patient…
- **Study en**…
  - Safe…Es and SAEs)
  - Efficacy: RR, PFS, OS, PET scan response, CA 19-9 and SPARC levels in relation to efficacy

Von Hoff D, et al. *J Clin Oncol.* 2009;27(18S): Abstract 4525.; Von Hoff D, et al. *J Clin Oncol.* 2011;29(34):4548-4554.

An advantage: a predictive biological test

- SPARC status was evaluated in 36 patients
- A significantly longer OS was reported in the high SPARC vs low SPARC group
  - **Median OS: 17.8 vs 8.1 mo, p=0.0431**
- SPARC level remained a significant predictor for OS after adjusting for clinical covariates (eg, age, sex, race, baseline CA 19-9) (p=0.041)



Von Hoff D, et al. *J Clin Oncol.* 2011;29(34):4548-4554.

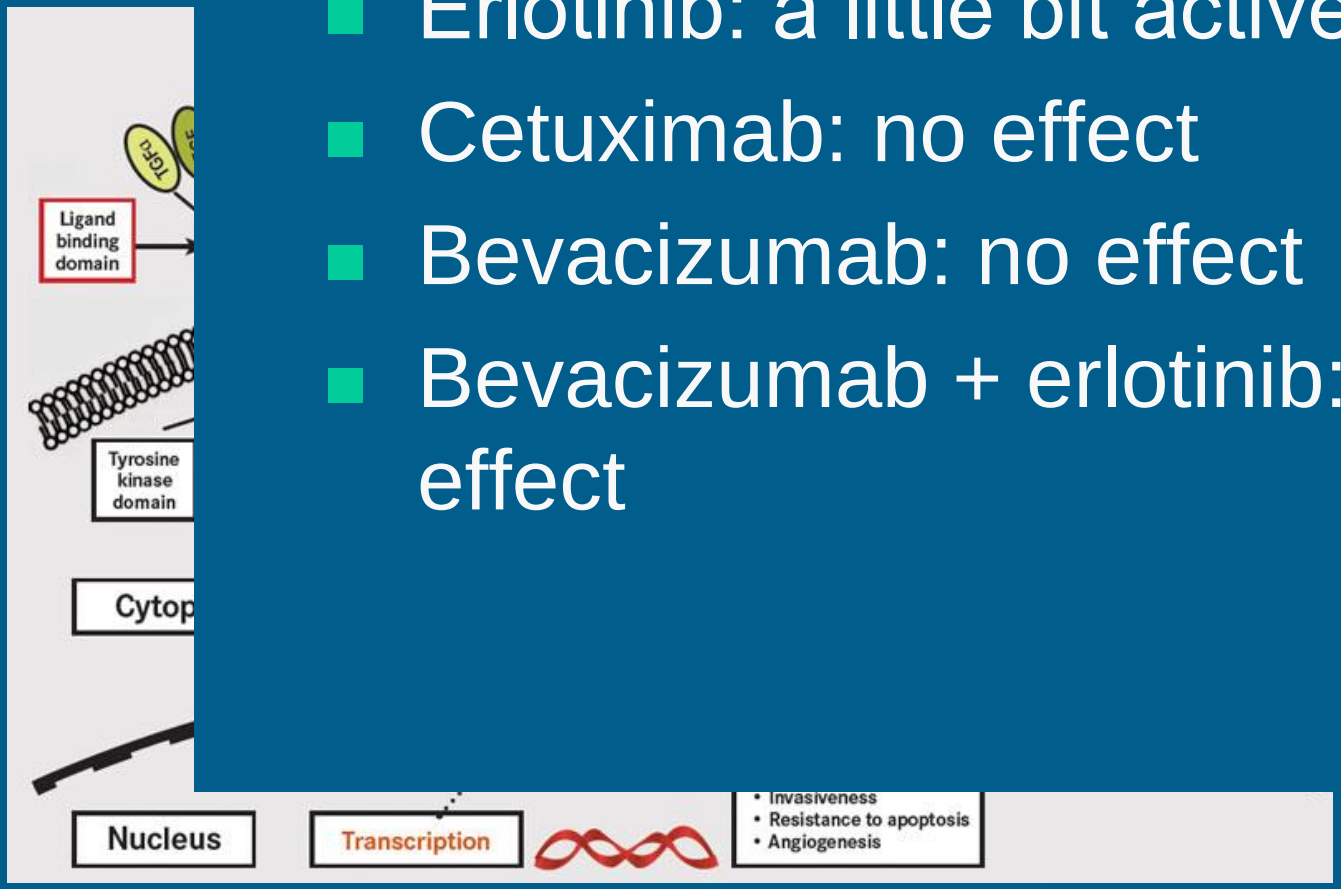
The right way to improve the survival of APC?

Why not?

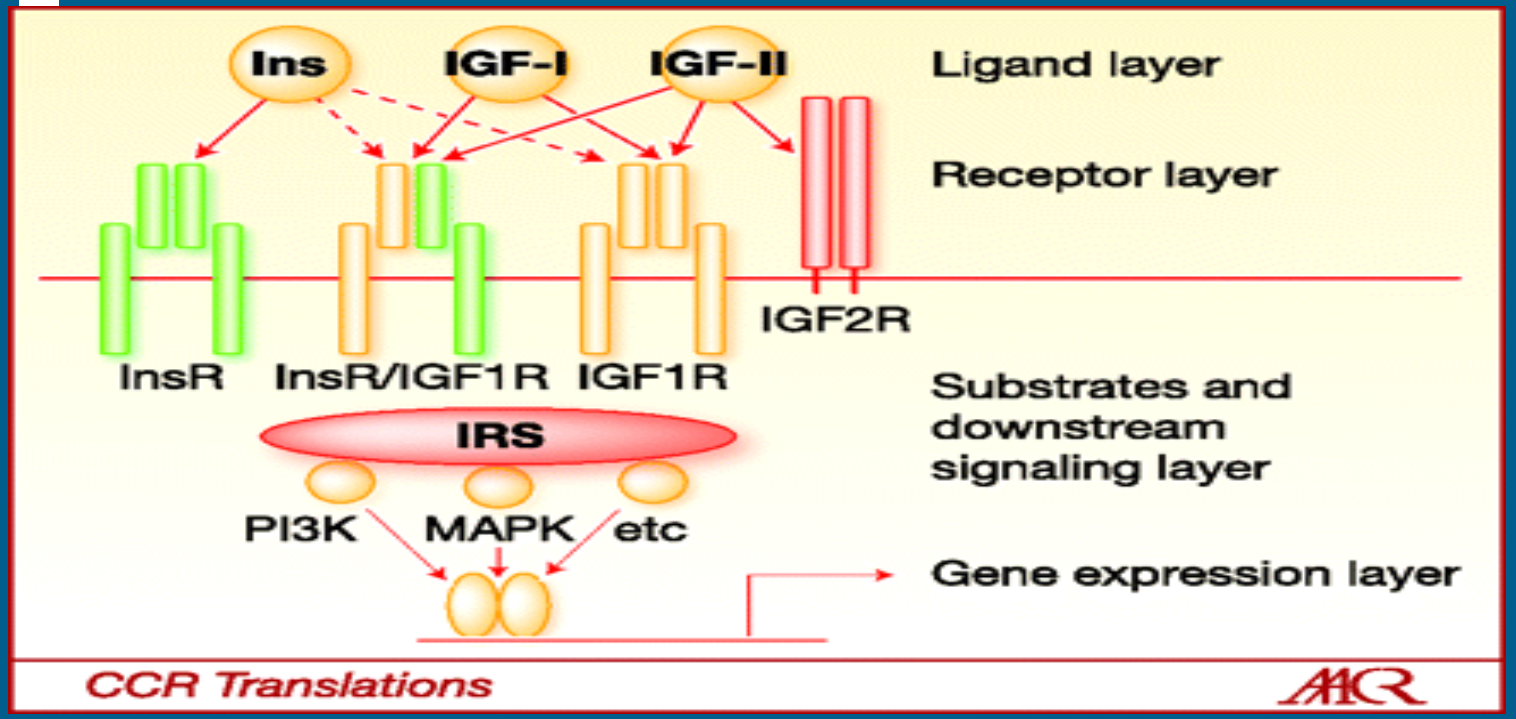
- Improvement obtained with combination chemotherapy
- Targeted therapies have failed to change the dismal prognosis of these tumours
- Even with double blockade

A role for targeted therapy?

- Erlotinib: a little bit active….
- Cetuximab: no effect
- Bevacizumab: no effect
- Bevacizumab + erlotinib: no clear effect



A role for targeted therapy?



- Promising agents: anti IGF
  - Ganitumab: phase III trial of ganitumab (GAN, AMG 479) with gemcitabine[1] (G): negative?

Fuchs CS et al. J Clin Oncol 30, 2012 abstr 4042)

Conclusion

Strenghts

- Cytotoxic drug
- New way of action
- Positive results
- Consistent results
- Favourable toxicity profile

Weaknesses

- Mixed population of LAPC and metastatic
- Another Gem vs Gem + XX without biological selection
- Hematological toxicity