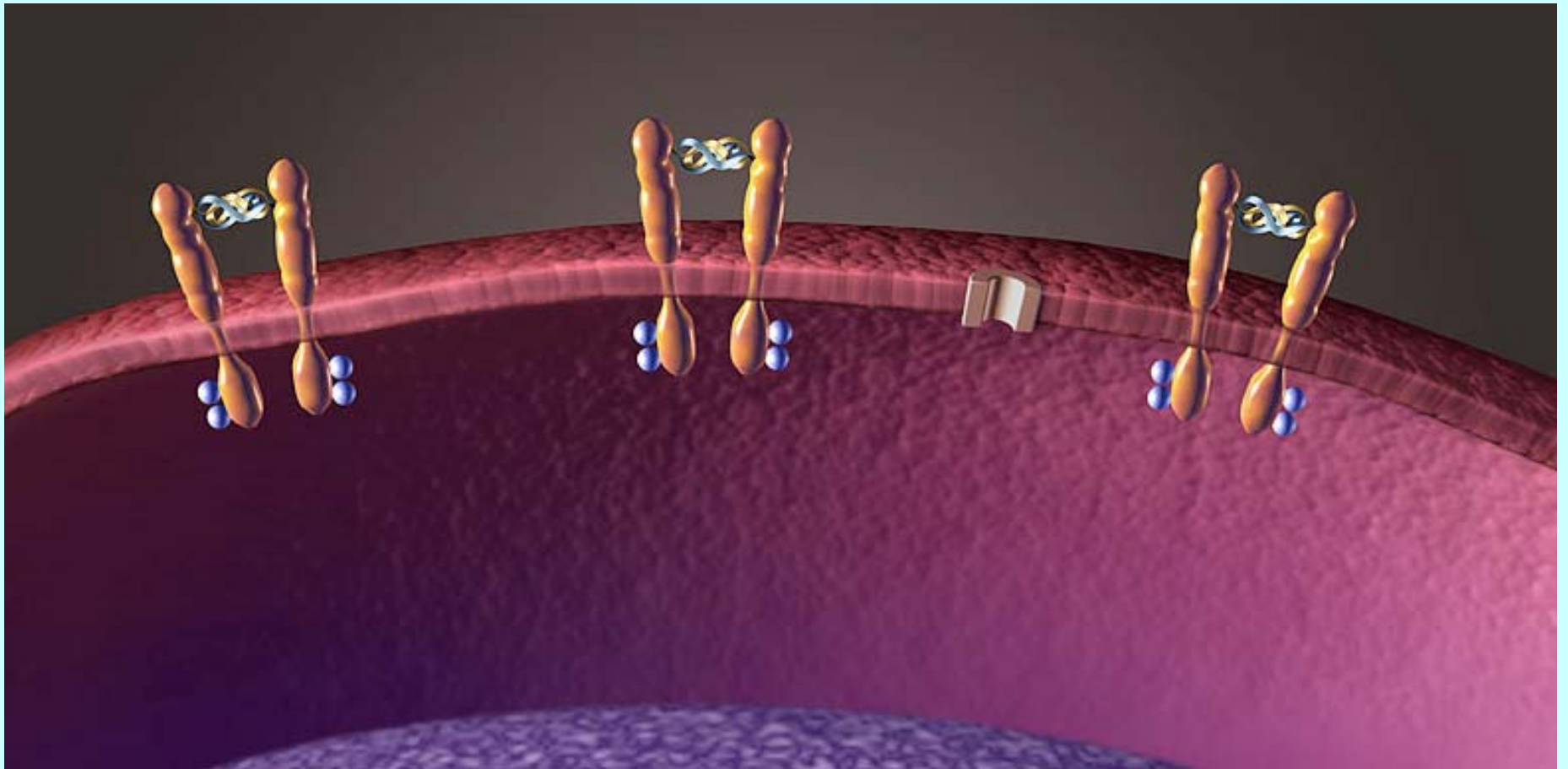


Pancreatic neoplasms and anti-angiogenic agents

Michel Ducreux, MD, PhD
Gustave Roussy Institute
Paul Brousse University Hospital
Villejuif, France

Metastatic pancreatic carcinoma : a difficult task

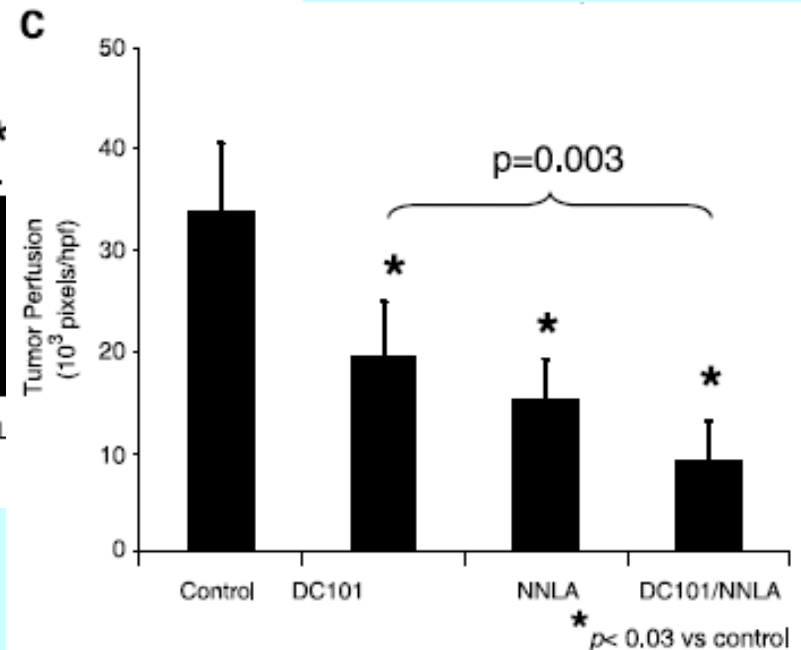
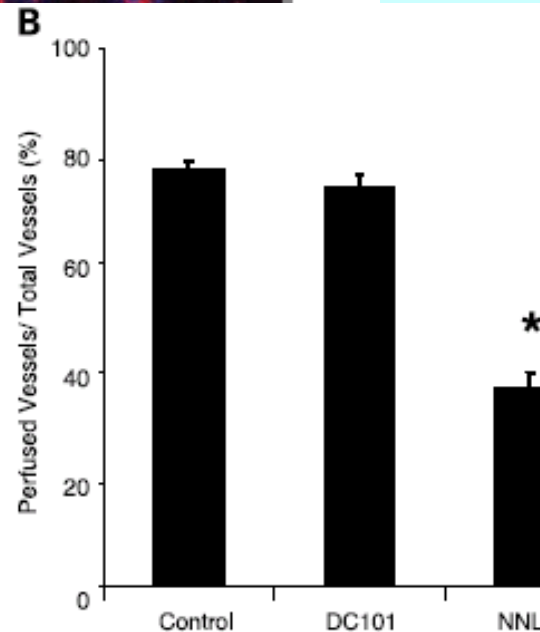
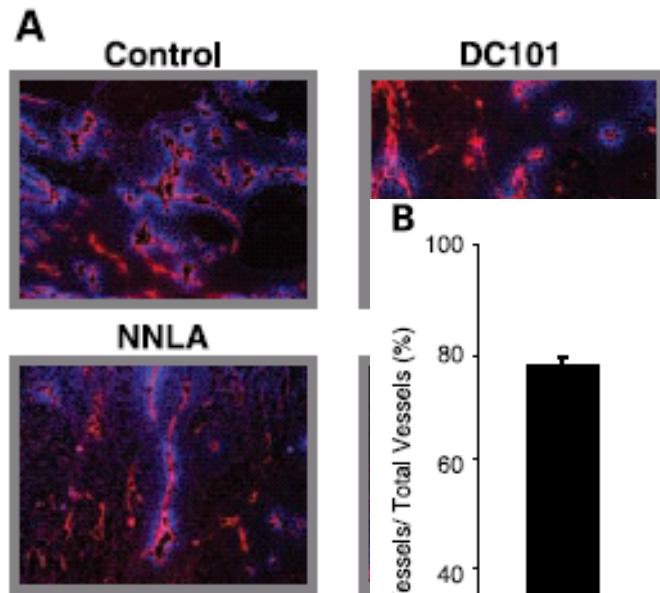


Experimental data

- ◆ VEGF-D induces lymphogenesis and lymphatic metastases (Von Marshall, 2005)
 - ◆ Overexpression VEGF-R3 and VEGF-D in 19 pancreatic cancers versus 10 normal pancreas tissue
- ◆ VEGF antisense therapy inhibits the tumor growth and improves survival in experimental pancreas cancer models (Hotz 2005)
- ◆ Plasminogen activator inhibitor-1 (PAL-1) gene transfection inhibits the liver metastases of pancreatic cancer by preventing angiogenesis (Inoue 2005)

Fighting angiogenesis in animal models

Camp, Clin Cancer Res, 2006



Evaluation of angiogenesis in pancreatic carcinoma

- ◆ Contrast enhanced ultrasonography (Okamoto 2007)
 - ◆ 62 consecutive patients, 53 with pancreatic adenocarcinoma
 - ◆ Tumour vessels around and/or in the tumor at the vascular image phase : 79%
 - ◆ At the perfusion image phase, hypo-enhancement type : 96%
 - > However : Tiny-spotty or irregular heterogenous enhanced in 84% of these patients
- ◆ CT scan evaluation (Zhongqiu 2004)
 - ◆ The microvessel density in the hot spot of neoplastic parenchyma cells was proportional to the malignancy degree of the tumor

Replacing gemcitabine : a difficult challenge

Moore, 2001

- ◆ Phase III trial : 350 advanced pancreatic carcinomas planned, 277 included
- ◆ Treatment with :
 - ◆ Weekly gemcitabine : 1000 mg/m² IV
 - ◆ BAY12-9566 : oral metalloproteinase inhibitor
- ◆ PFS : 3.5 months GEM vs 1.8 months, $p = 0.012$
- ◆ Overall survival : 6.4 months vs 3.2 months, $p = 0.0001$

Marimastat : another MMI challenger

Is Marimastat able to replace gemcitabine ?

- ◆ Marimastat 5,10 or 25 mg bid or gemcitabine
- ◆ 414 patients
- ◆ Median survival days : 111, 105, 125 days versus 167 for Gem...

Gem Marimastat versus Gem : the first randomised trial evaluating an anti-angiogenic agent

- ◆ Marimastat 10 mg versus placebo :
- ◆ 239 patients
- ◆ Median survival time 165.5 days versus 164 days...

Gem + bevacizumab very promising data

Kindler, JCO 2005

- ◆ 45 patients
- ◆ Gemcitabine + bevacizumab
- ◆ 10 mg/kg/biweekly
- ◆ Response rate : **21%**
- ◆ Tumor growth control : **66%**
- ◆ Median TTP : **5.4 months**
- ◆ Overall median survival : **8.8 months**

CALGB 80303 phase III trial

- ◆ n = 602) Stratification factors

- ◆ PS (0/1 versus 2)
- ◆ stage (locally advanced versus metastatic)
- ◆ Adjuvant radiotherapy (yes/no)

- ◆ Exclusion criteria

- ◆ Local regional invasion
- ◆ High risk of haemorrhage

- ◆ Primary endpoint : overall survival

R

**G : 1 000 mg/m²/week 30 mn inf
3 weeks./4
+ B : 10 mg/kg every 14 days
(n = 302)**

**G : 1 000 mg/m²/week 30 mn inf
3 weeks./4
+ P : every 14 days
(n = 300)**

CALGB 80303 phase III trial

Clinical characteristics

	GB (n = 302)	GP (n = 300)
Median age (years)	63.8	65.0
PS 0/1 (%)	36/53	39/52
LA/M (%)	15/85	16/84
Previous RT (%)	11	11

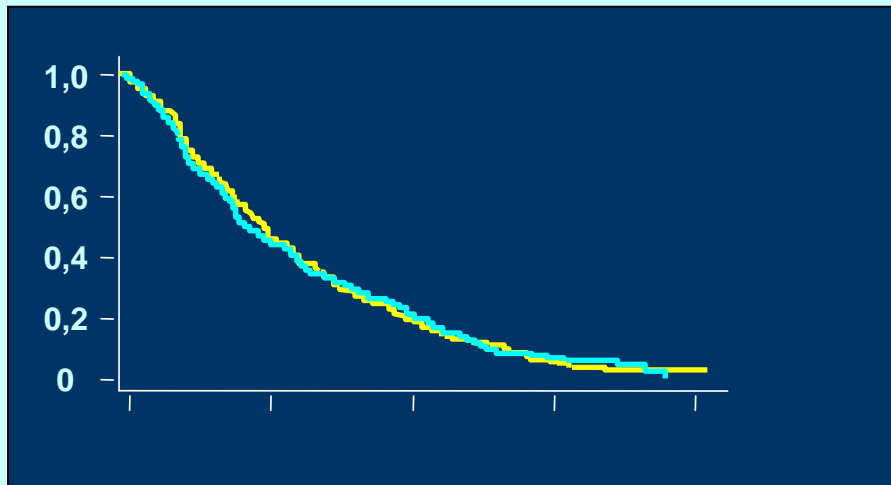
CALGB 80303 phase III trial

%	Grade 3/4 Toxicity	
	GB (n = 268)	GP (n = 257)
Neutropenia	33	30
Anemia	5	8
Thrombopenia	12	12
Stroke	2	2
GI Haemorrhage	3	2
<i>Hypertension</i>	<i>8</i>	<i>2</i>
<i>GI Perforation</i>	<i>0.4</i>	<i>0</i>
<i>Proteinuria</i>	<i>4</i>	<i>1</i>
Deep venous thr.	9	9

%	Response	
	GB (n = 302)	GP (n = 300)
CR	1.9	3.0
PR	11.2	8.3
Stabilisation	40.7	35.7
<i>Tumor growth control</i>	<i>53.8</i>	<i>47.0</i>

ASCO GI 2007 – Kindler et al., Chicago, USA, abstr. 108 actualised

CALGB 80303 phase III trial



Median PFS (months)

GP 4.3 (3.8-5.6)

GB 4.8 (4.3-5.7)

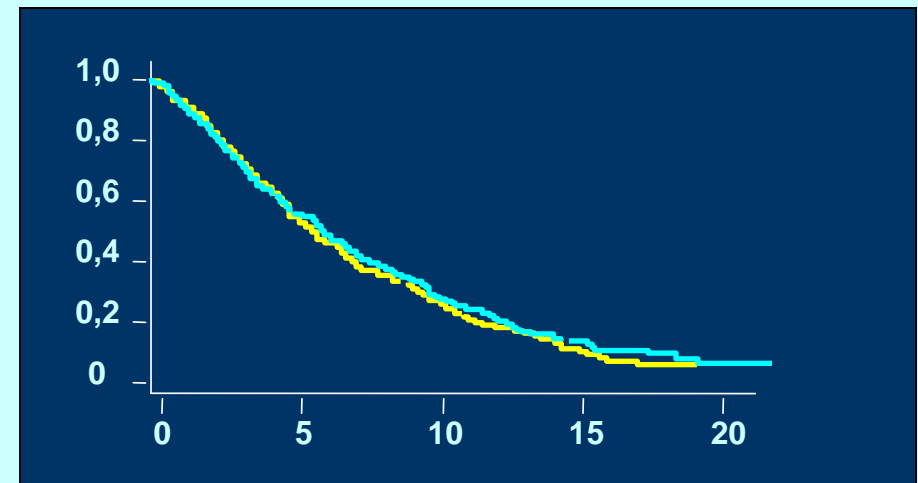
p = 0.99 (HR : 1,0)

Median overall survival

GP 6.0 (5.0-6.9)

GB 5.7 (4.9-6.5)

p = 0.40 (HR : 1.09)



Gemox + bevacizumab : phase II

	Jafari et al.	Kim et al.
N (planned)	38 (50)	82 (ND)
Centres	2	Multicentric
Main endpoint	1-year OS	6 months OS
LA/M+ (n)	7/31	0/82
Median age	ND (40-77)	62.5 (32-86)
PS 0-1/2	35/3	78/4
Evaluables (n)	23	80
◆ CR/PR (%)	0/9 (39)	2/7 (11)
◆ Stabilisation (%)	11 (48)	47 (59)
◆ Progression (%)	3 (13)	24 (30)
Median PFS (months)	ND	5.7 (43.7 % at 6 months)
Median OS (months)	ND (72 % at 6 months)	8.1 (65 % at 6 months)

*Jafari et al., Oklahoma, abstr. 141,
et Kim et al., Rochester, abstr. 169,*

Gemcitabine + cisplatin + bevacizumab

◆ Phase II, first line, 42 metastatic patients

GEM	+	CDPP	+	BEV
300 mg/m ² 10 mg/m ² /mn		20 mg/m ²		10 mg/Kg

Neutropenia	4.8%
Hypertension	9.5%
GI haemorrhage	9.5%
Thrombo-embolic event	9.5%
GI perforation	4.8%
Toxic death	7.1%

Confirmed OR	21%
CR	2.6%
SD	50%
PFS	5.8 months

Gemcitabine + capecitabin + bevacizumab

- ◆ Locally advanced or metastatic patients
- ◆ 26 include patients (34 planned)
- ◆ Gem 1 g/m² D1+D8 + Cap 1.3 g/m² D1-14 + Bev 15 mg/kg D1, D1=D22

- ◆ Efficacy results (n = 22)
 - ◆ **PFS (main endpoint) : 8.2 months**
 - ◆ OR : 31.8% (0 CR) - SD : 54.5% - PD : 13.6%
 - ◆ OS : 9.1 months

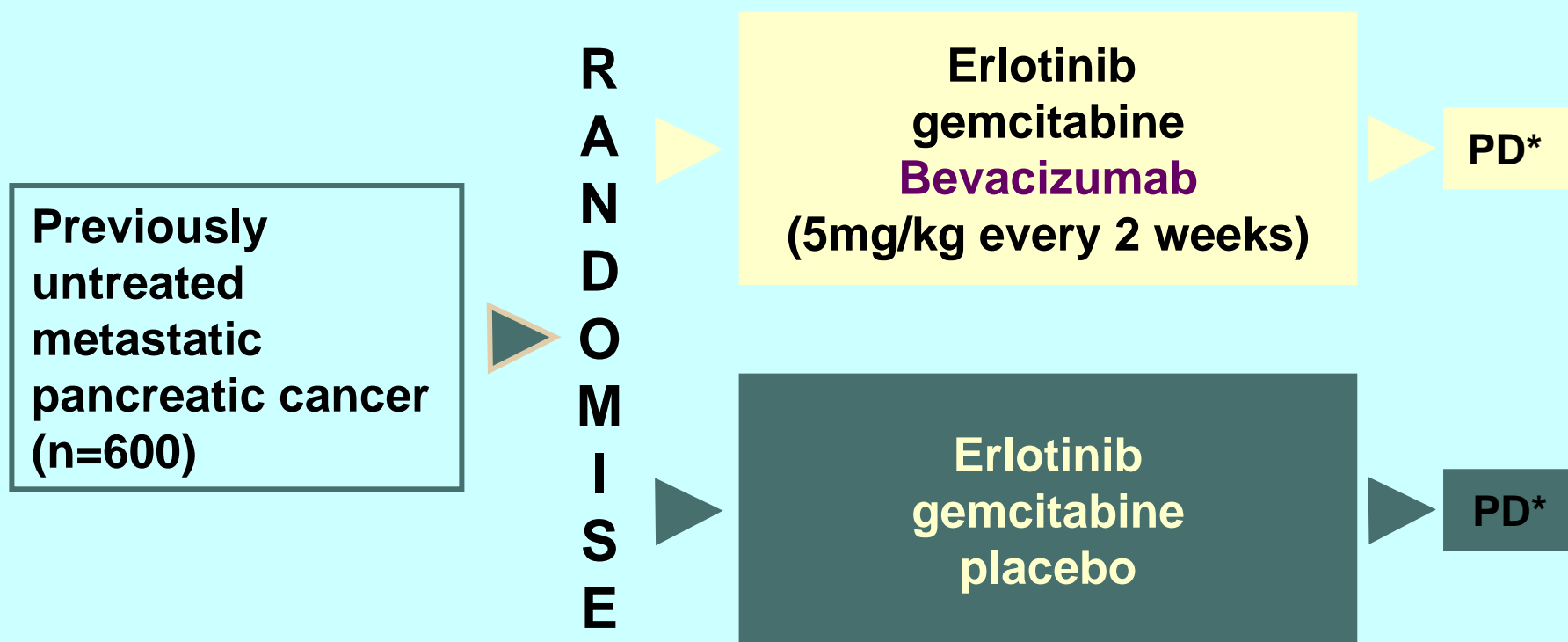
- ◆ Quality of life improvement : 47% of the patients
- ◆ Grade 3-4 toxicity potentially related to bevacizumab
 - ◆ **One toxic death (GI haemorrhage)**
 - ◆ **One stroke**
 - ◆ **Two pulmonary embolisms**

Gemcitabine + bevacizumab + anti-EGFR

- ◆ Randomised phase II (Kindler 2006)
 - ◆ GBC with cetuximab
 - ◆ GBE with erlotinib
 - ◆ 49 patients

	ORR	SD	PFS
GBC	19%	59%	3.6 months
GBE	21%	67%	3.6 months

AVITA: Gem + erlotinib ± bevacizumab cancer



◆ Primary end-point: overall survival

◆ Recruitment finished

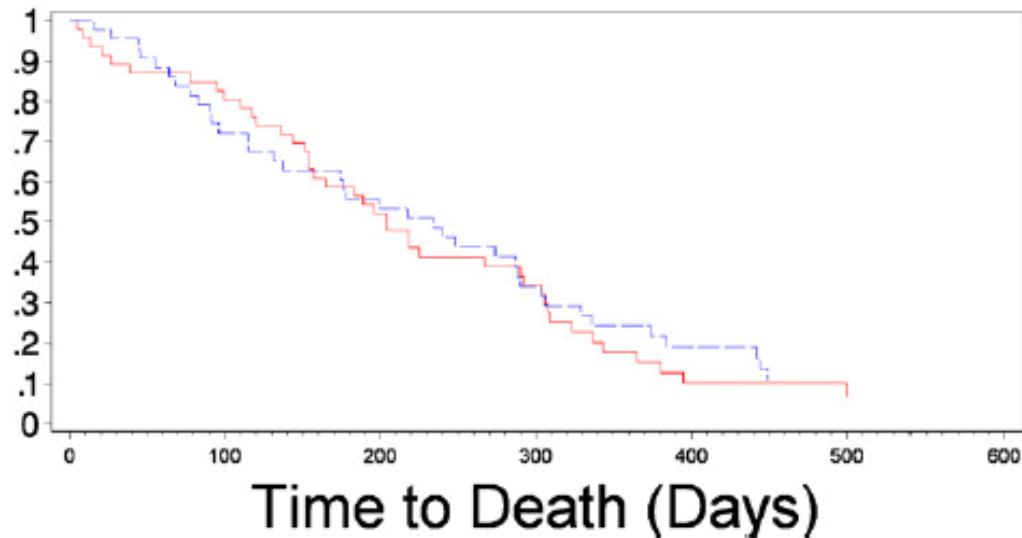
*No cross-over will be permitted

Randomised phase II gem + cilengitide

- ◆ Cilengitide : cyclic peptid inhibitors of integrins
 - ◆ Integrins form the vascular matrix and subendothelial basemant membrane of blood vessels
- ◆ Randomised phase II multicentric trial (Friess 2006)
 - ◆ Cilengitide 600 mg/m² twice weekly
 - ◆ Gem standard doses
- ◆ 89 patients randomised
 - ◆ Locally advanced or metastatic disease

Randomised phase II gem + cilengitide

	ORR %	PFS	OS
Cilengitide	17	3.6	6.7
Placebo	14	3.8	7.7



Other agents

- ◆ Celecoxib : activity against a variety of human cancers. Not truly anti-angiogenic. Cardiac toxicity
- ◆ Thalidomide : phase II Gem + Thal + celecoxib 5 OR among 12 patients...
- ◆ Mammalian Target of Rapamycin (mTOR) inhibitors.
 - ◆ Oral components such as RAD 001
 - ◆ On-going phase II trials

Conclusion and take home message

- ◆ Angiogenesis in pancreatic carcinoma : a strong rationale
- ◆ First results of anti-angiogenic agents : promising
- ◆ Bevacizumab has been the most tested agent in this setting
- ◆ First results of randomised phase III trials : disappointing