Stefano Cascinu

Medical Oncology

Università Politecnica delle Marche

Ospedali Riuniti di Ancona

Italy

Biology and molecular pathology of pancreatic cancer: Potential clinical application and trials

Prof. Stefano Cascinu:

Conflict of interest disclosure:

- **Consultant or Advisory Board:**
  Roche, Merck; AMGEN; Novartis; Celgene
- **Honoraria:**
  Roche, Merck; AMGEN; Novartis; Pfizer

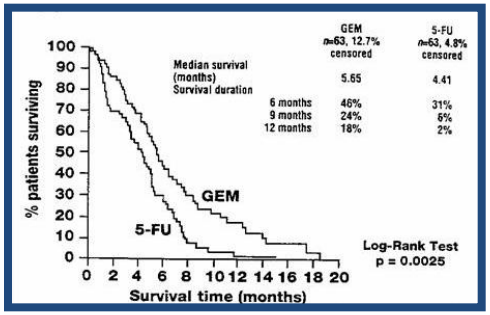
Outline

- Where we are in the medical treatment
- What we achieved till now by using targeted agents
- What is “new” in the biology of pancreatic cancer and how it may influence the clinical practice and trials in the future (near!)

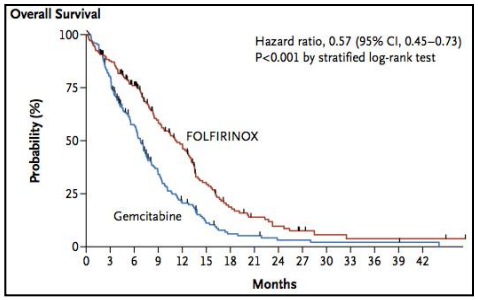
Where are we in the treatment of advanced pancreatic cancer?

We have a standard and half:

Gemcitabine
(1997)



Folfirinox
(2011)

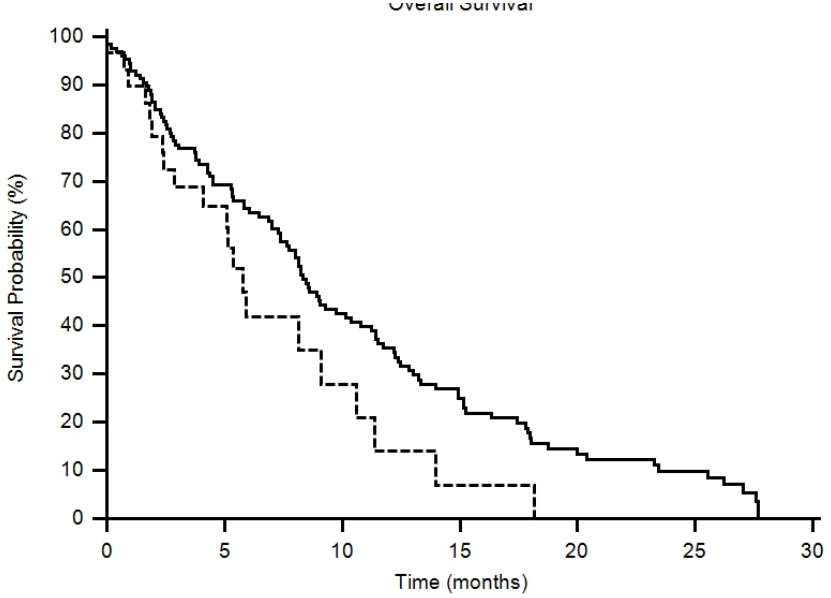


Folfirinox

Biliary stenting may affect the outcome in advanced pancreatic cancer patients receiving an intensive chemotherapy.

Patient selection:

- Good performance status
- No biliary stent
- Metastatic disease



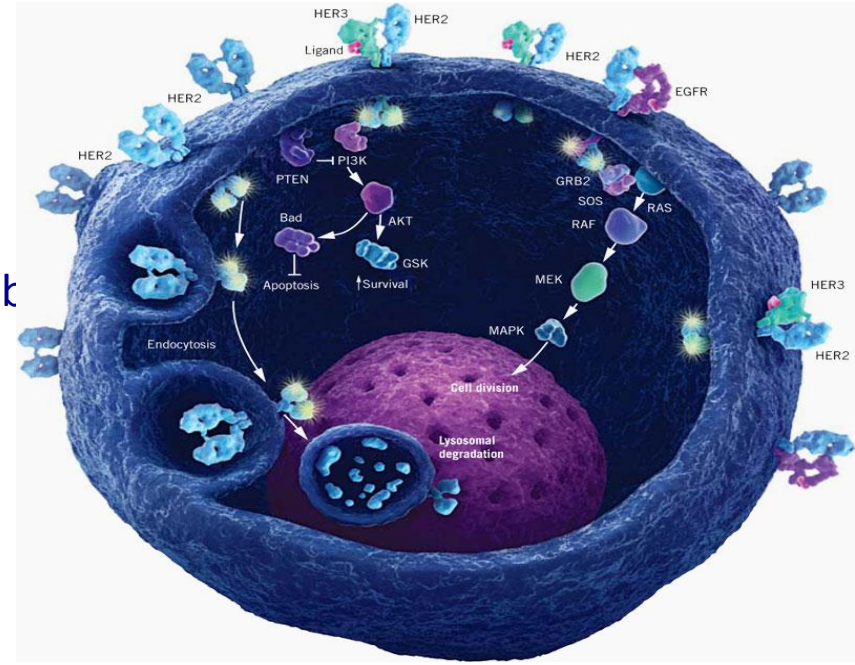
Faloppi L, submitted

Outline

- Where we are in the medical treatment
- **What we achieved by using targeted agents**
- **What is “new” in the biology of pancreatic cancer and how it may influence clinical practice and future trials**

Molecular pathology in pancreatic cancer: Target identification and agent development

- **Tumor cells**
  - K-ras tipifarnib
  - Metalloprotease marimastat
  - EGFR erlotinib/cetuximab
  - HER-2 trastuzumab
- **Microenviroment**
  - VEGF A bevacizumab
  - VEGFR 1,2,3 axitinib
  - VEGFR3; RAF/MEK sorafenib



VOLUME 22 · NUMBER 8 · APRIL 15 2004

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Trial of Gemcitabine Plus Tipifarnib Compared With Gemcitabine Plus Placebo in Advanced Pancreatic Cancer

E. Van Cutsem, H. van de Velde, P. Karasek, H. Oettle, W.L. Vervenne, A. Szawlowski, P. Schoffski, S. Post, C. Verslype, H. Neumann, H. Safran, Y. Humblet, J. Perez Ruixo, Y. Ma, and D. Von Hoff

Table 1. Baseline Characteristics

Patient Characteristic	% of Patients: Tipifarnib + Gemcitabine (n = 341)	% of Patients: Placebo + Gemcitabine (n = 347)
Female	43	42
Age, years		
Median	61	62
Range	29-89	30-88
ECOG		
0	27	28
1	57	59
2	16	13
Metastatic		
Any site	76	77
Liver	63	60
Lung	14	12
Peritoneum	13	14
Histologic degree of differentiation		
Well	7	8
Moderate	27	32
Poor	26	22
Tumor-related symptoms		
Weight loss > 10%	56	56
Tumor pain	76	78
Jaundice in last 6 months	38	37
Time from diagnosis, months		
Median	1	1
Range	0-61	0-78
Previous therapy		
Whipple procedure or pancreatectomy	14	11
Radiotherapy	4	4
FU radiosensitization	3	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; FU, fluorouracil.

Table 2 Efficacy Parameters

Efficacy	Tipifarnib + Gemcitabine (n = 341)	Placebo + Gemcitabine (n = 347)	*P*
Overall survival			
Median, days	193	182	.75
95% CI	176 to 218	155 to 206	
6-month survival, %	53	49	
1-year survival, %	27	24	
Progression-free survival			
Median, days	112	109	.72
95% CI	105 to 119	101 to 118	
Best response reconciled, %			
CR or PR	6	8	
Stable disease	53	52	
Progression	28	30	
Not assessable	13	10	
Time to PS deterioration, days	142	125	.50
95% CI	121 to 176	107 to 144	

Abbreviations: CR, complete response; PR, partial response; PS, performance status.

Erlotinib Plus Gemcitabine Compared to Gemcitabine Alone in Patients With Advanced Pancreatic Cancer

National Cancer Institute of Canada Clinical Trials Group – Study PA.3

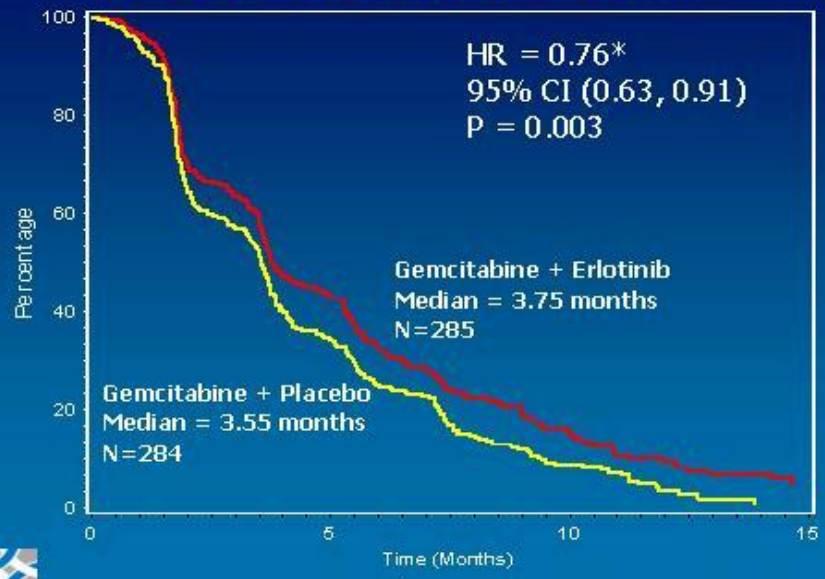
MJ Moore, D Goldstein, J Hamm, A Figer, JR Hecht, S Gallinger, HJ Au, K Ding, M Ptaszynski, WR Parulekar

National Cancer Institute of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe des essais cliniques

PA.3 Patient Characteristics

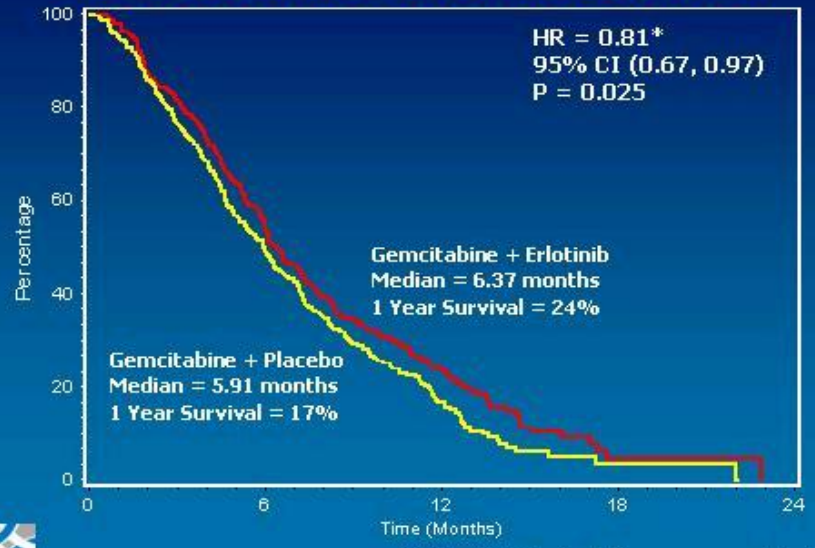
Characteristic	Erlotinib N = 285	Placebo N = 284
Median age (years)	63	64
Female / Male (%)	52/48	43/57
PS 0 / 1 / 2 (%)	30/51/19	30/52/18
Loc. Adv / metastatic (%)	24/76	25/75
Pain ≤ 20 / > 20 / UNK (%)	46/51/3	45/53/2
US/Canada/ROW [%]	38/20/42	36/21/43
Measurable disease (%)	94	92

Progression-Free Survival



* Adjusted for PS, pain and disease extent at randomization

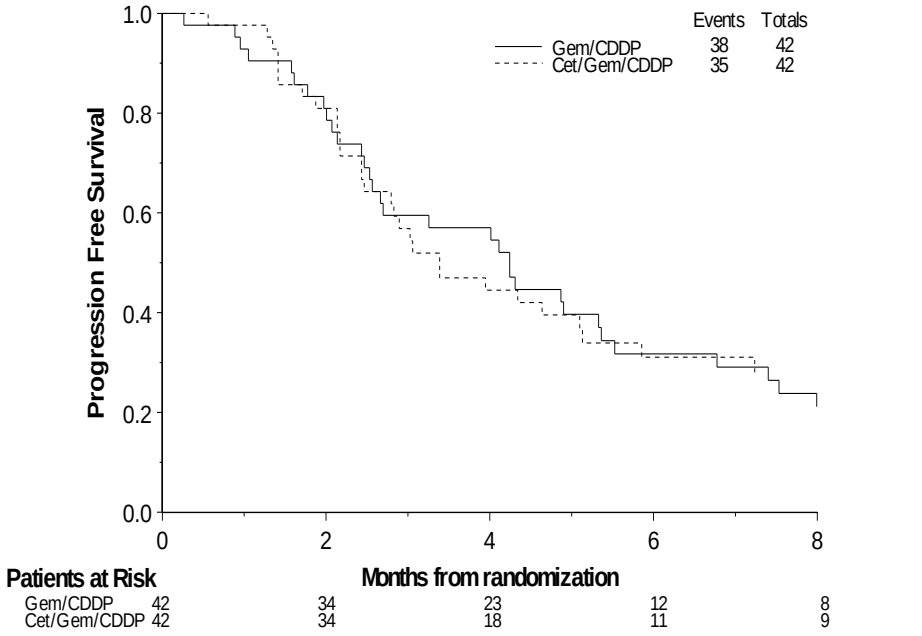
Overall Survival for All Patients

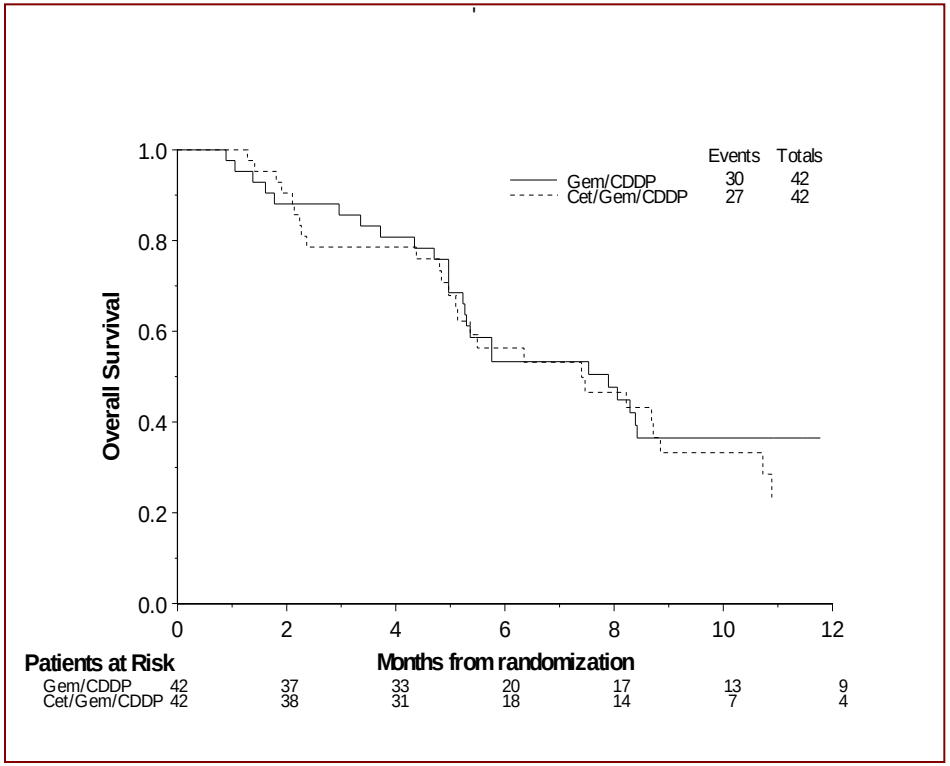


* Adjusted for PS, pain and disease extent at randomization

Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial

Stefano Cascinu, Rossana Berardi, Roberto Labianca, Salvatore Siena, Alfredo Falcone, Enrico Aitini, Sandro Barni, Francesco Di Costanzo, Elisa Dapretto, Giuseppe Tonini, Chiara Pierantoni, Salvatore Artale, Silvia Rota, Irene Floriani, Mario Scartozzi, Alberto Zaniboni, for the Italian Group for the Study of Digestive Tract Cancer (GISCAD)





Lancet Oncol 2009

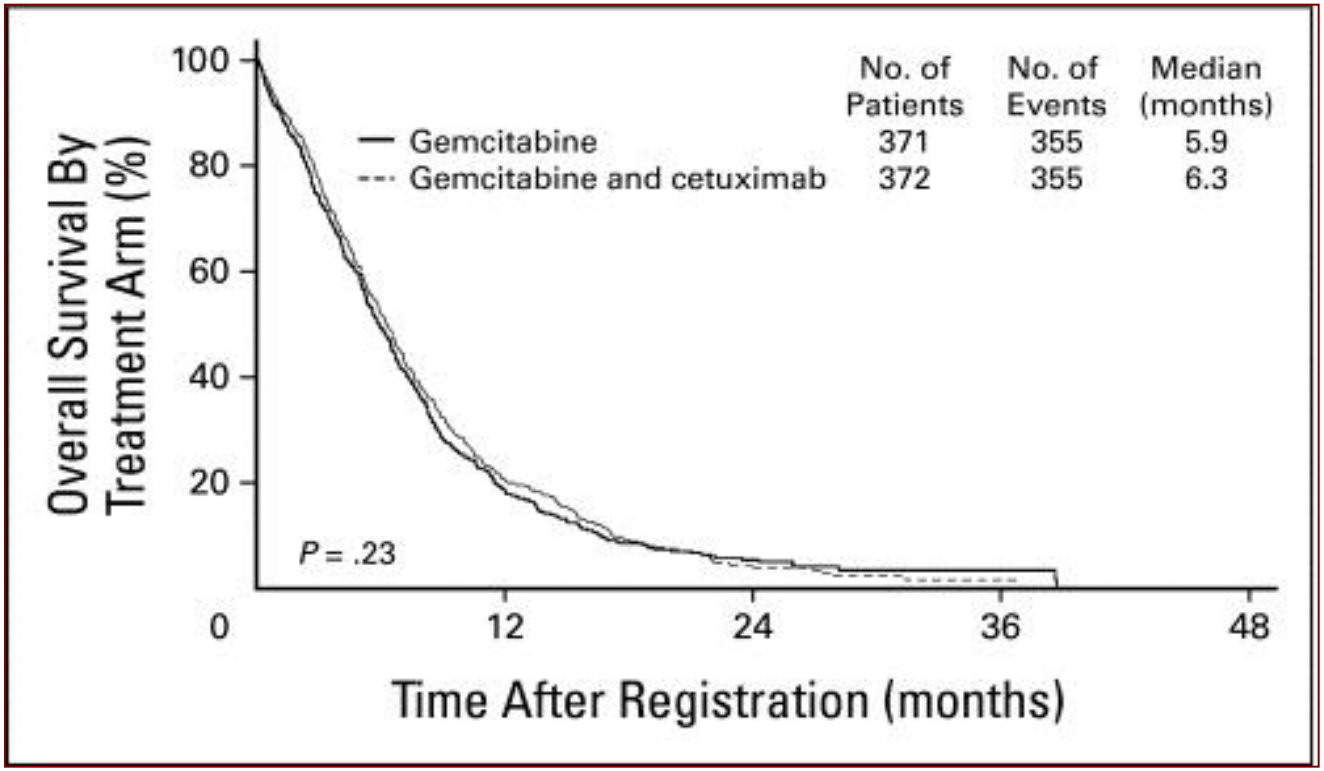
VOLUME 28 · NUMBER 22 · AUGUST 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study Comparing Gemcitabine Plus Cetuximab Versus Gemcitabine in Patients With Advanced Pancreatic Adenocarcinoma: Southwest Oncology Group–Directed Intergroup Trial S0205

Philip A. Philip, Jacqueline Benedetti, Christopher L. Corless, Ralph Wong, Eileen M. O'Reilly, Patrick J. Flynn, Kendrith M. Rowland, James N. Atkins, Barry C. Mirtsching, Saul E. Rivkin, Alok A. Khorana, Bryan Goldman, Cecilia M. Fenoglio-Preiser, James L. Abbruzzese, and Charles D. Blanke



HER Family - Her2

HER-2 positivity 16%

Cancer Invest. 2004;22(5):706-12.

Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu.

Safran H, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, Hesketh P, Rathore R, Wolff R, Trevathan S, Hughes TM, Maia C, Pasquariello T, Goldstein L, King T, Tsai JY, Kennedy T.

The Brown University Oncology Group, Providence, Rhode Island, USA. hsafran@lifespan.org

Abstract

PURPOSE: To determine the response rate and toxicities of Herceptin and gemcitabine for patients with metastatic pancreatic adenocarcinomas that overexpress HER-2/neu.

METHODS AND MATERIALS: Patients with metastatic pancreatic cancer with 2+/3 + HER-2/neu expression by immunohistochemistry were eligible. Patients received gemcitabine, 1 g/m2/week, for four weeks followed by 3 of every 4 weeks, and Herceptin, 4 mg/kg loading dose, followed by 2 mg/kg/week.

RESULTS: Screening logs demonstrated the rate of HER-2/neu overexpression was 16%. Thirty-four patients were enrolled. Thirty patients (88%) had pancreatic cancers with 2+ overexpression and 4 patients (12%) had 3+ overexpression. Toxicity was similar to gemcitabine alone. Confirmed partial responses were observed in 2 of 32 patients (6%). Thirteen of 32 patients (41%) had either a partial response or a >50% reduction in CA 19-9. The median survival for 34 patients was 7 months, and the 1-year survival was 19%.

CONCLUSION: The response rate of Herceptin and gemcitabine is similar to gemcitabine alone. The 7-month median survival in patients with metastatic pancreatic cancer suggests there may be a modest benefit for some patients. Infrequent HER-2/neu overexpression limits the role of targeting the HER-2/neu gene and prevents definitive conclusions on the addition of Herceptin to gemcibine for patients with pancreatic cancer.

HER-2 positivity 11%

Trastuzumab and capecitabine in patients with HER2-expressing metastatic pancreatic cancer: A multicenter phase II study of the AIO pancreatic cancer group (on behalf of the German AIO group [AIO PK-0204]).

Abstract:

Background: In metastatic pancreatic cancer (mPaCa) overexpression of the human epidermal growth factor receptor 2 (HER2) has been reported in up to 82% of cases, suggesting its use as a therapeutic target. Therefore, the study was conducted to determine the efficacy and toxicity of capecitabine (CAP) and TRAS in pts with mPaCa. **Methods:** Eligible pts had histologically confirmed mPaCa. The primary endpoint was PFR at 12 weeks. Pts with mPaCa immunohistochemically overexpressing HER2 grade 3 or grade 2 with gene amplification (FISH) received TRAS 4 mg/kg initially followed by weekly 2 mg/kg combined with CAP 1250 mg/m² bid day 1-14, q21. The study with planned 37 pts was prematurely closed due to unexpected low HER2 expression. **Results:** Between May 1994 and February 1998 a total of 212 pts with a median age 64 years (range 30-86) were centrally screened for HER2 expression. In 207 pts the tumor specimens could be assessed for IHC expression and gene amplification: By IHC 83 (40%) were grade 0, 71 (34%) grade 1, 31 (15%) grade 2, 22 (11%) grade 3, respectively. One IHC grade 2 and all IHC grade 3 specimens showed gene amplification by FISH. From the 23 pts with HER2 gene amplification 17 could be assessed for response to treatment and toxicity in an intention-to treat analysis. Reported grade 3/4 toxicities in 88 cycles of chemotherapy were: leucopenia 6%, diarrhea 6%, nausea 6%, hand-foot syndrome 6%. There was no TRAS-attributable cardiac toxicity. 83.8% of treated patients were progression free at 12 weeks, the median overall survival was 211 days. **Conclusions:** In concrast to previous findings, this multicenter study demonstrated HER2 overexpression and gene amplification in only 11% of pts with mPaCa. This discrepancy can be explained by the use of centrally reviewed standardized HER2 test methods and the examination of a large unselected cohort in the present study. Although the therapy was well tolerated, PFS and OS did not perform favourably compared to standard gemcitabine chemotherapy. Due to the low HER-2 overexpression found in this study we do not recommend further evaluation of anti-HER2 treatment in pts with mPaCa.

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

HER-2 expression does not represent a relevant molecular alteration in advanced pancreatic cancer patients: preliminary results from a multifactorial biological analysis.

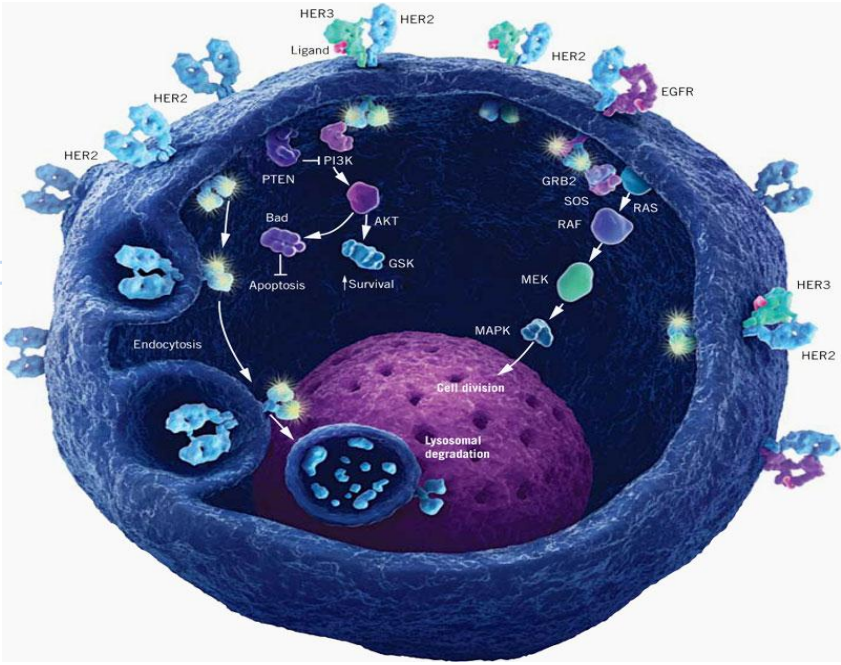
HER-2 positivity 8%
Her-3 positivity 25%

Results: 62 specimens were analyzed in our centre. 30 samples were K-ras wild-type, 70% of these were EGFR positive. While 32 samples have a mutant form of K-ras, 87.1% were EGFR positive. HER-2 resulted negative in all specimens. In the K-ras wild-type group, 17% have high expression of HER-3, 20% a low one; in mutant K-ras group 16% are high expressing while 34% have a low HER-3.

Conclusions: Our analysis show a low rate of k-ras mutations (52%) and seems to suggest that anti-EGFR strategies may represent an interesting treatment option in pancreatic cancer as long as a preliminary molecular selection is applied. Numerous international trials are evaluating the role of new drugs targeting HER2 in association with chemotherapy in metastatic pancreatic cancer. On the contrary, our data suggest that HER-2 directed therapies are not likely to represent a relevant choice in this setting.

Molecular pathology in pancreatic cancer: Target identification and agent development

- Tumor cells
  - K-ras tipifarnib
  - Metalloprotease marimastat
  - EGFR erlotinib/cetuximab
  - HER-2 trastuzumab
- **Microenviroment**
  - VEGF A bevacizumab
  - PDGF axitinib
  - PDGF sorafenib



VOLUME 28 · NUMBER 22 · AUGUST 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gemcitabine Plus Bevacizumab Compared With Gemcitabine Plus Placebo in Patients With Advanced Pancreatic Cancer: Phase III Trial of the Cancer and Leukemia Group B (CALGB 80303)

Hedy Lee Kindler, Donna Niedzwiecki, Donna Hollis, Susan Sutherland, Deborah Schrag, Herbert Hurwitz, Federico Innocenti, Mary Frances Mulcahy, Eileen O'Reilly, Timothy F. Wozniak, Joel Picus, Pankaj Bhargava, Robert J. Mayer, Richard L. Schilsky, and Richard M. Goldberg

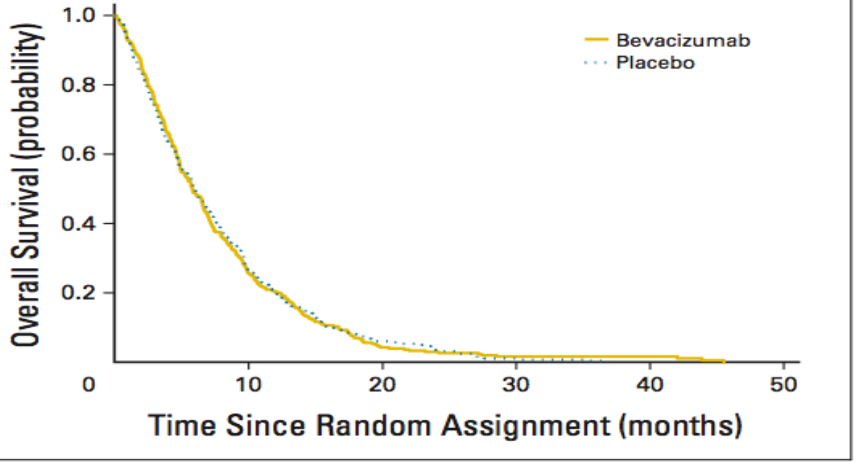


Fig 2. Overall survival by treatment arm.

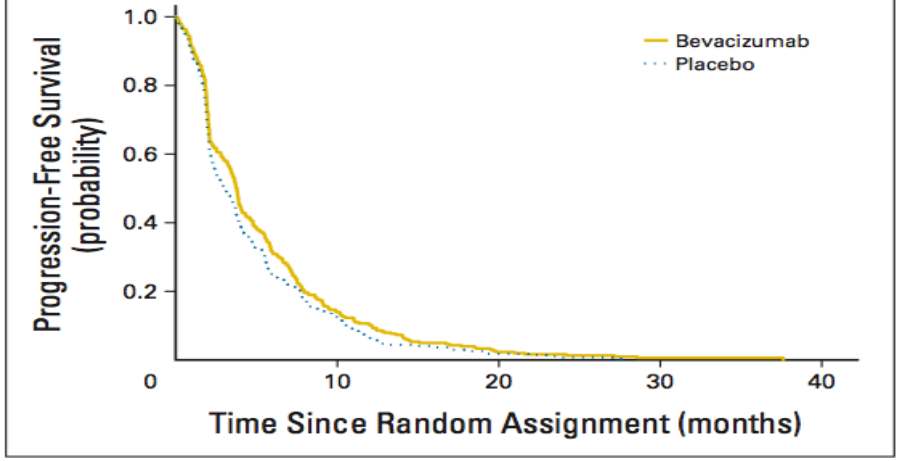


Fig 5. Progression-free survival by treatment arm.

Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study

Hedy L Kindler, Tatsuya Ioka, Dirk J Richel, Jaafar Bennouna, Richard Létourneau, Takuji Okusaka, Akihiro Funakoshi, Junji Furuse, Young Suk Park, Shinichi Ohkawa, Gregory M Springett, Harpreet S Wasan, Peter C Trask, Paul Bycott, Alejandro D Ricart, Sinil Kim, Eric Van Cutsem

	Axitinib plus gemcitabine	Placebo plus gemcitabine	Hazard ratio (95% CI)	One-sided p value
Best response*				
Overall objective response rate	12 (5%, 2·5–8·3)	4 (2%, 0·4–4·0)	-	0·0180
Complete response	1 (<1%)	0	-	..
Partial response	11 (4%)	4 (2%)	-	..
Stable disease	74 (30%)	83 (33%)	-	..
Median survival (months)†				
Overall survival	8·5 (6·9–9·5)	8·3 (6·9–10·3)	1·014 (0·786–1·309)	0·5436
Locally advanced	9·5 (7·4–NR)	10·6 (9·9–NR)	-	..
Metastatic	7·0 (5·8–9·3)	6·9 (6·2–8·0)	-	..
Progression-free survival	4·4 (4·0–5·6)	4·4 (3·7–5·2)	1·006 (0·779–1·298)	0·5203
Locally advanced	5·9 (4·2–7·3)	9·1 (5·8–10·6)	-	..
Metastatic	4·2 (3·7–5·4)	3·8 (3·6–4·5)	-	..

Data for best response are n (%, 95% CI); data for survival are median (95% CI). NR=not reached. *Only patients with measurable disease at baseline were included in the analysis; n=247 for axitinib plus gemcitabine, n=255 for placebo plus gemcitabine. †Analysis included all patients randomly assigned to treatment groups; n=314 for axitinib plus gemcitabine (data missing from database at time of analysis for two patients), n=316 for placebo plus gemcitabine.

Table 2: Efficacy results

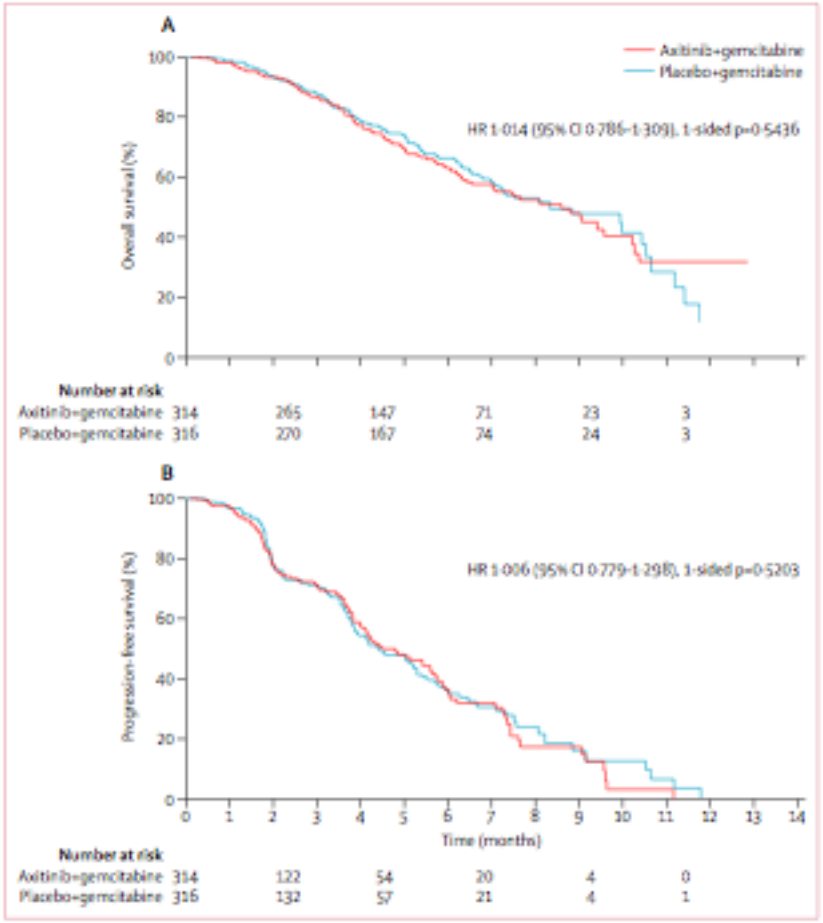


Figure 2: Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival

Maps Study

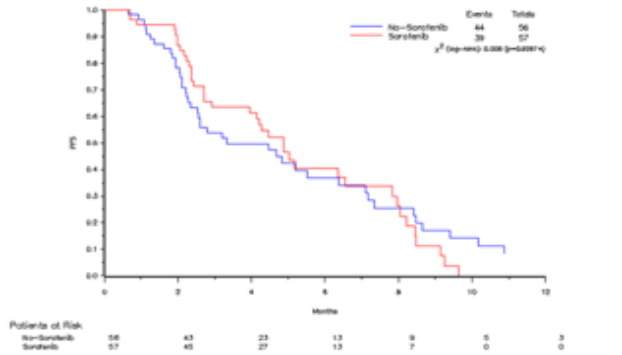
GISCAD

ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

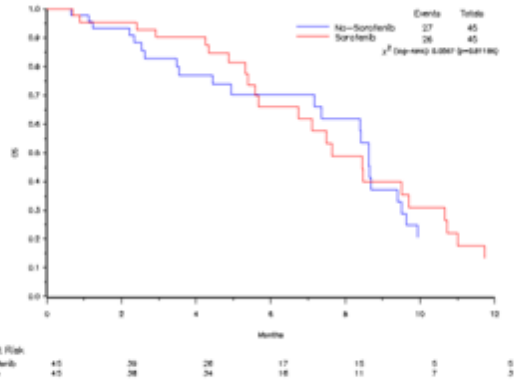
Locally advanced or metastatic pancreatic cancer patients, PS=0/1

Gemcitabine 1000 mg/sqm day 1 and 8
Cisplatin 25 mg/sqm day 1 and 8
every 21 days

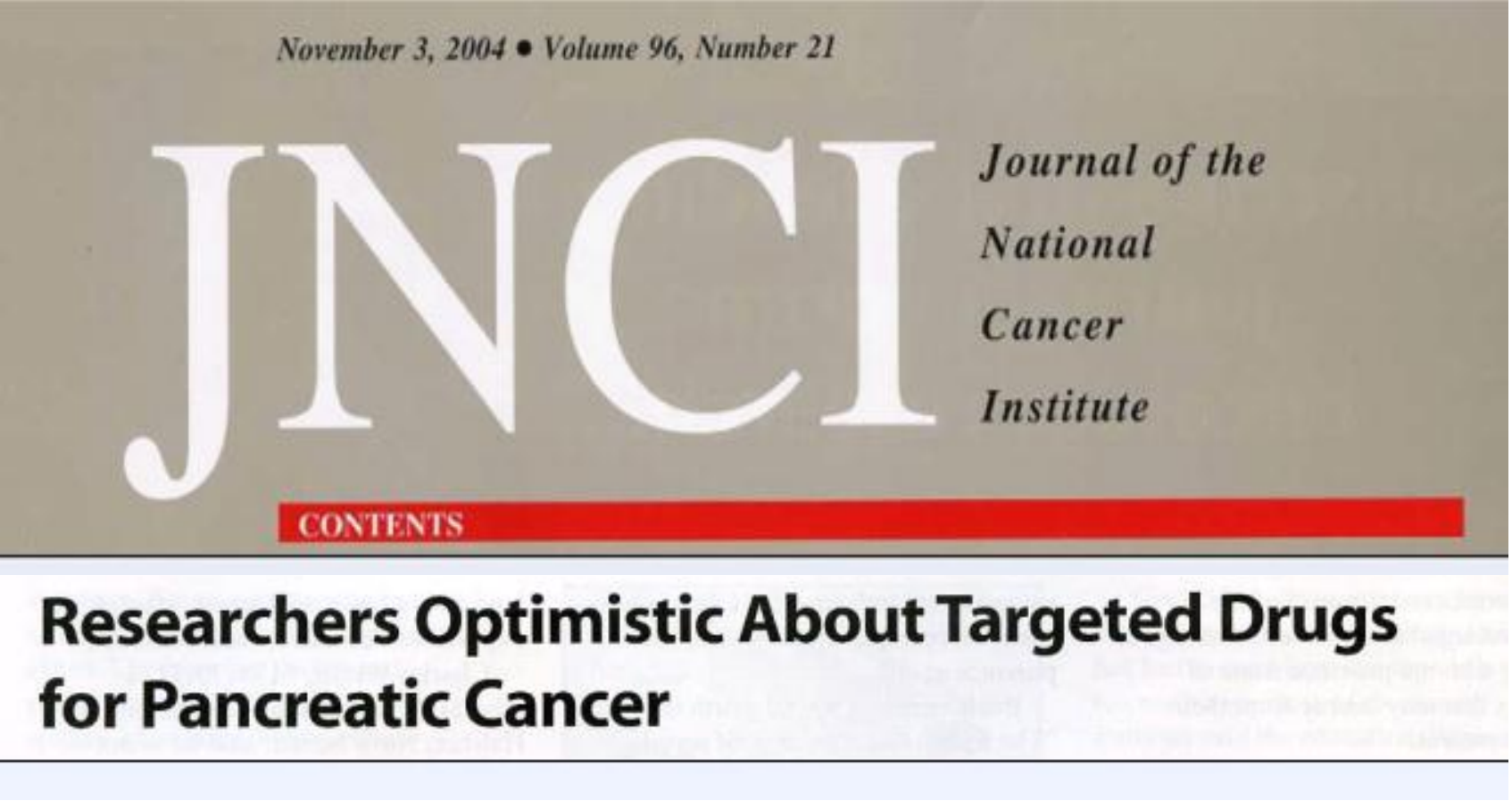
Gemcitabine 1000 mg/sqm day 1 and 8
Cisplatin 25 mg/sqm day 1 and 8
every 21 days
Sorafenib 400 mg bid



Nei primi 6 mesi si osserva un (modesto) aumento della sopravvivenza libera da progressione, che poi però si perde totalmente nel periodo successivo. Complessivamente, per il PFS si ha alla fine un peggioramento dell'HR che si traduce in un decremento della mediana – stimato dal HR- di 1.52 giorni, cioè 2 giorni in meno

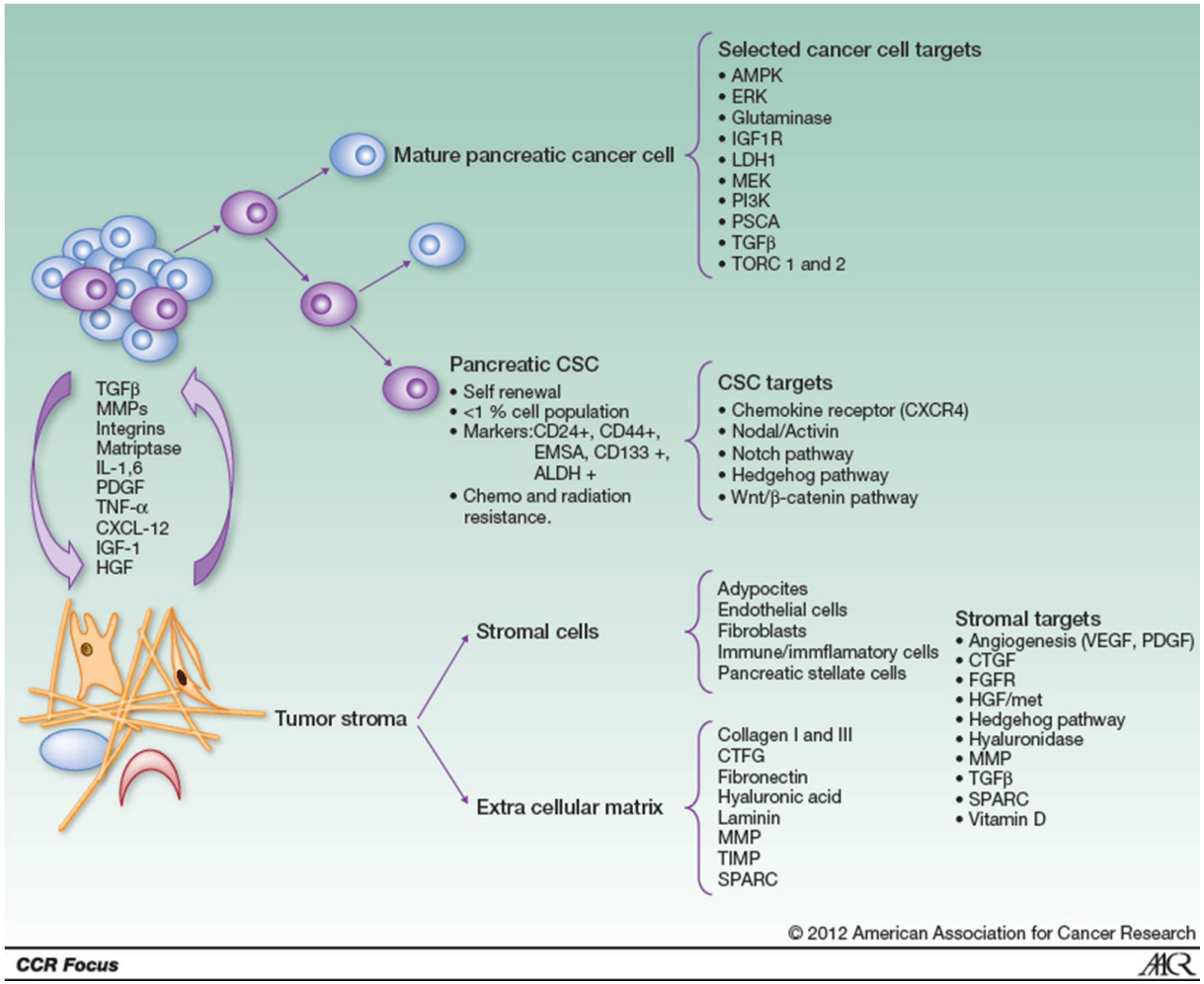


Nei primi 6 mesi si osserva un (modesto) aumento della sopravvivenza, che poi però si perde totalmente nel periodo successivo. Complessivamente, per l'OS si ha alla fine un peggioramento dell'HR che si traduce in un decremento della mediana – stimato dal HR- di 13.8 giorni, cioè 14 giorni in meno



Should we be optimistic about the role of target agents, yet?

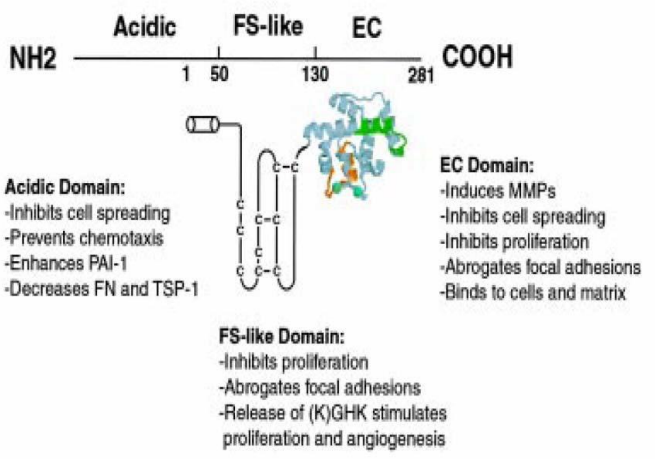
The knowledge of tumor biology:
From the wrong targets to the "good" targets

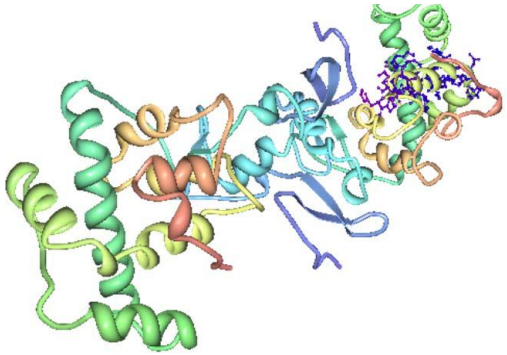


- **SPARC**
- **Notch**
- **Hedgehog**
- **TLR 2/4**

Hidalgo M, et al. *Clin Cancer Res.* 2012;18(16):4249-4256.

SPARC plays a key role in tumor growth and metastasis





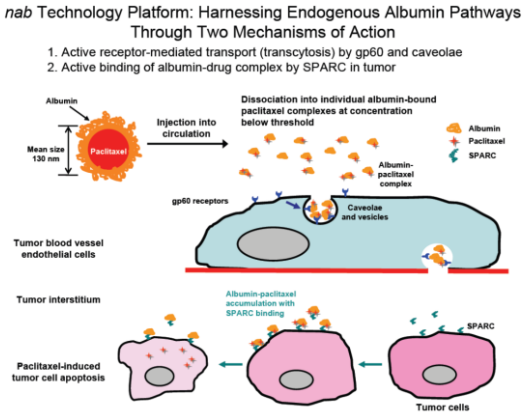
- SPARC is a secreted Ca^{2+} binding & albumin binding glycoprotein of 43 kDa
- SPARC is overexpressed in many tumors and throughout development
- Highest expression during tissue remodeling and repair
- Positive feedback loop with VEGF & TGF-b1
- Mediates epithelial-mesenchymal transition
- Involved in metastatic cell aggressiveness

Paclitaxel albumin in pancreatic cancer: SPARC

Cremophor-free colloidal suspension of nanoparticle paclitaxel stabilized with human serum albumin (130 nm particles)

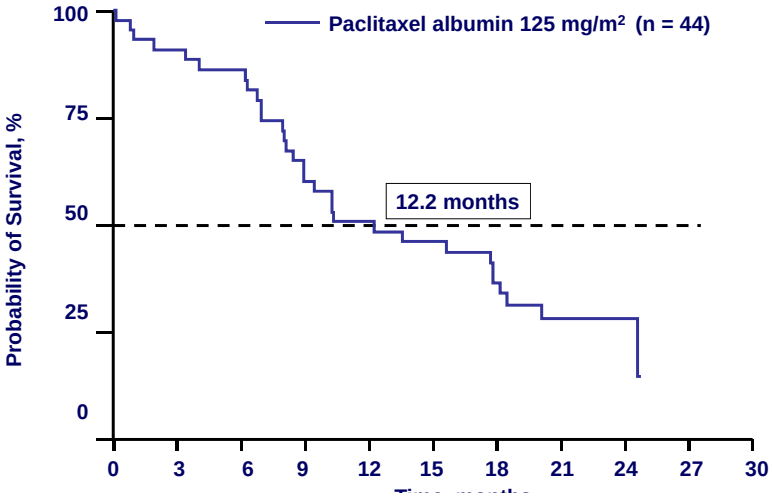
Rapid distribution to tumor[1]

Intratumoral accumulation of *nab*-paclitaxel[2]



1. Sparreboom A, et al. *Clin Cancer Res.* 2005;11(11):4136-4143. 2.

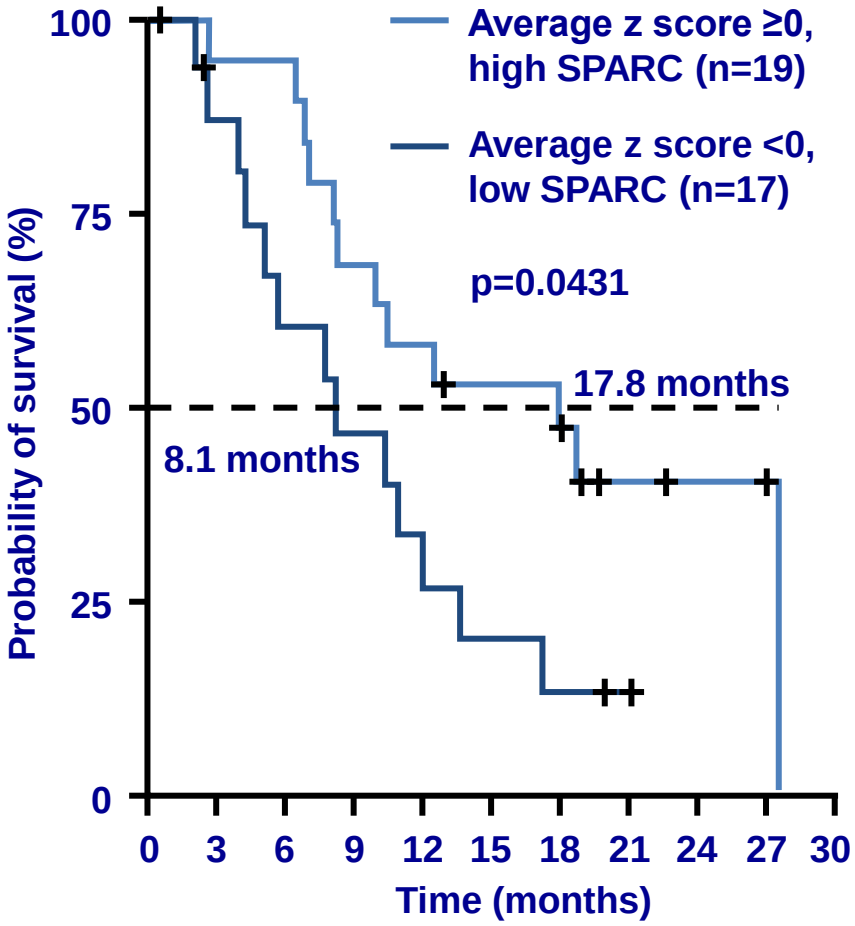
	Paclitaxel Albumin (mg/m^2)	
	125 (n = 44)	All Dose Levels (n = 67)
n, %		
ORR	21 (48)	31 (46)
CR	0	3 (4)
PR	21 (48)	28 (42)
SD	9 (20)	12 (18)
PD	7 (16)	15 (22)
DCR	30 (68)	43 (64)
PFS	7.9 (5.8–11.0)	7.1 (5.7–8.0)
OS	12.2 (8.9–17.9)	10.3 (8.4–13.6)
1-year OS, %	48	



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

Paclitaxel albumin + gemcitabine in patients with metastatic pancreatic cancer: SPARC

- 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)
- Stromal SPARC correlated with OS (p=0.013) but SPARC in tumour cells did not (p=0.15)



Von Hoff et al. J Clin Oncol 2011.

Warning:
targeting SPARC could be not always useful and effective

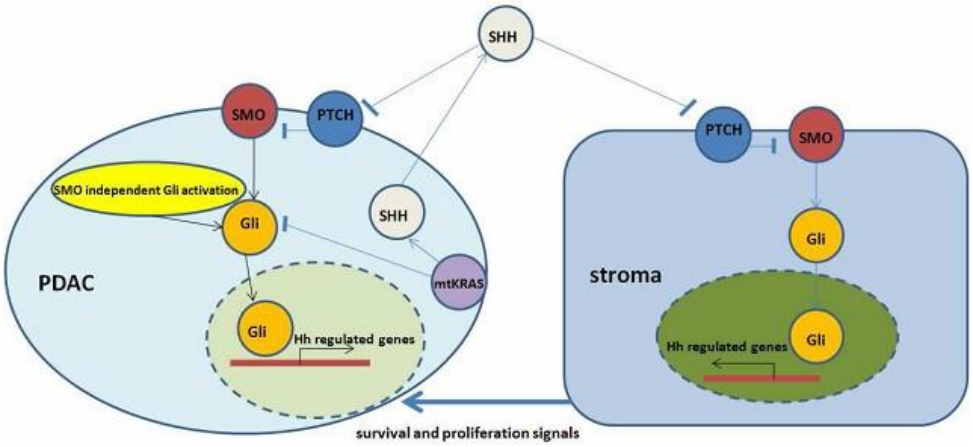
Source	Regulation	Effect in PDA	Relevance
PDA cells	Autocrine regulator Epigenetic silencing (aberrant methylation)	Inhibits PDA growth	Possible tumor suppressor
Fibroblastic cells in tumor stroma	Paracrine regulator	Pro-metastatic	Associated with poor prognosis
	Contributes to formation of dense desmoplastic stroma	Pro-fibrotic	Dense stroma may hamper penetration of chemotherapeutic agents
		Interacts with albumin	Promote accumulation of albumin-paclitaxel nanoparticles

From the wrong targets to the “good” targets?

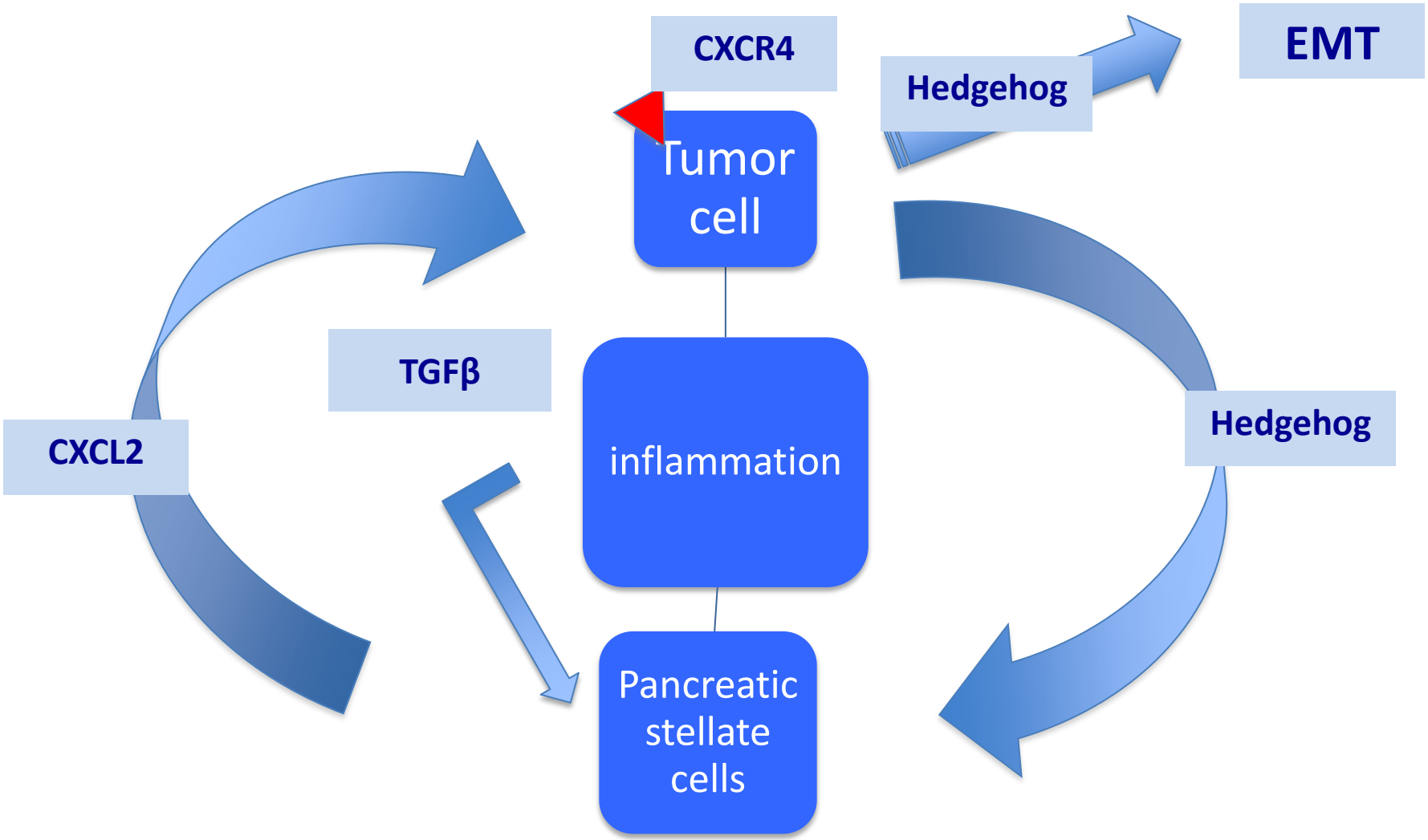
- SPARC
- **Hedgehog**
- **Notch1**
- **TLR 2/4 and inflammation**

Hedgehog and pancreatic cancer

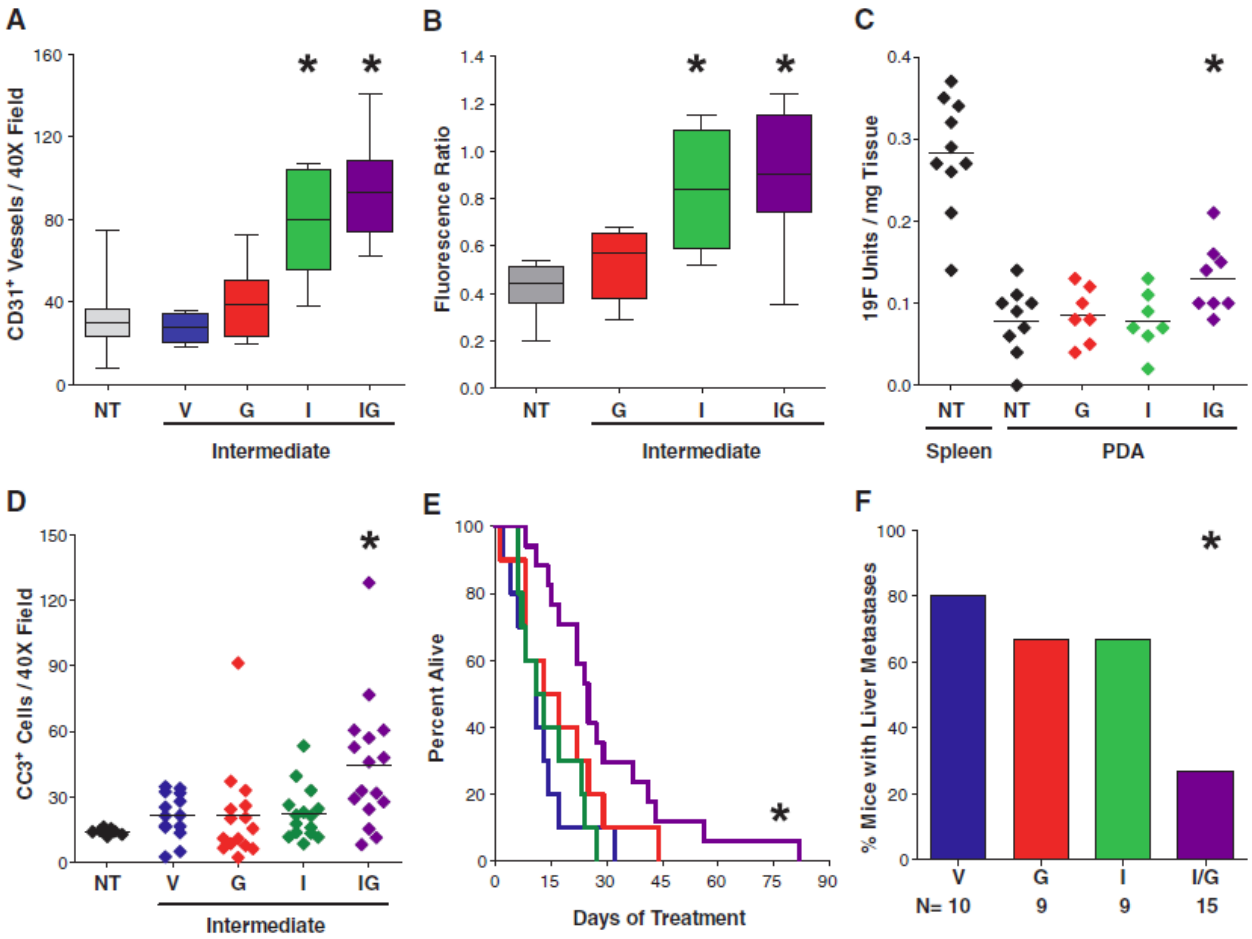
- Hedgehog signaling pathway is a crucial regulator of proliferation and differentiation during embryonic development.
- Hedgehog overexpression in 70% of pancreatic cancer
- Hedgehog signaling is activated as a consequence of K-RAS deregulation
- Hedgehog is responsible for tumor desmoplasia and EMT



Hedgehog and pancreatic cancer



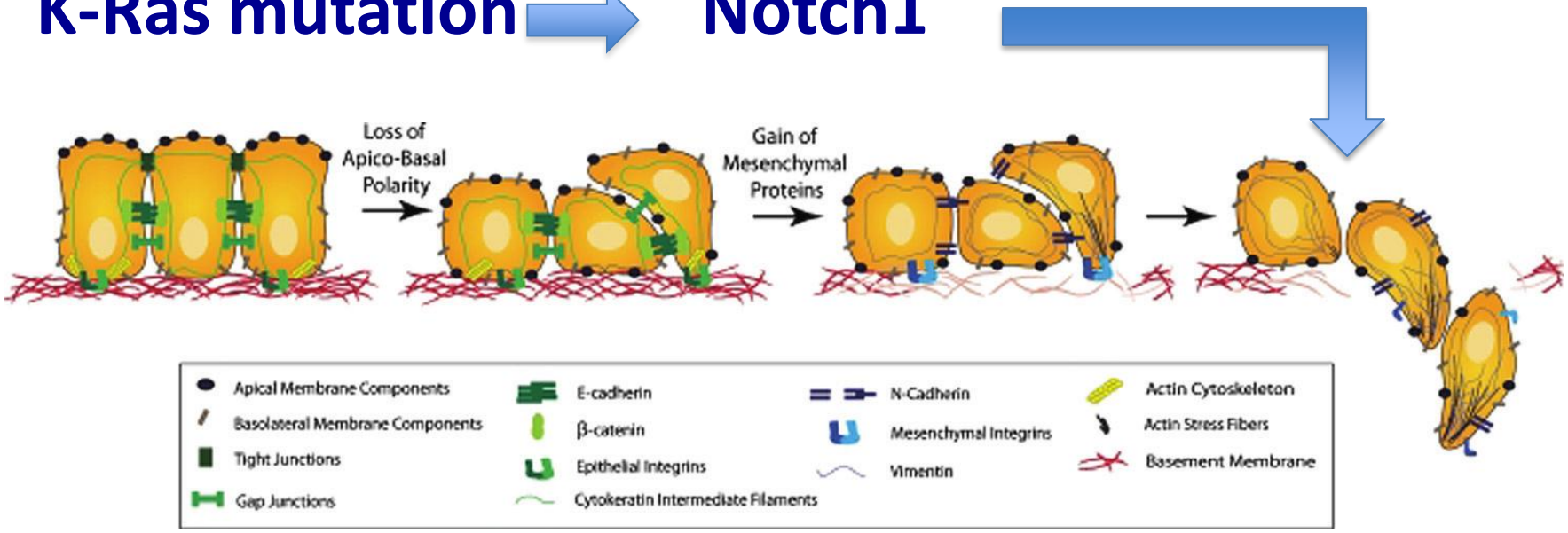
Hh inhibition increases vascularity and antitumor effects



Olive KP, et al. *Science.* 2009;324(5933):1457-1461.

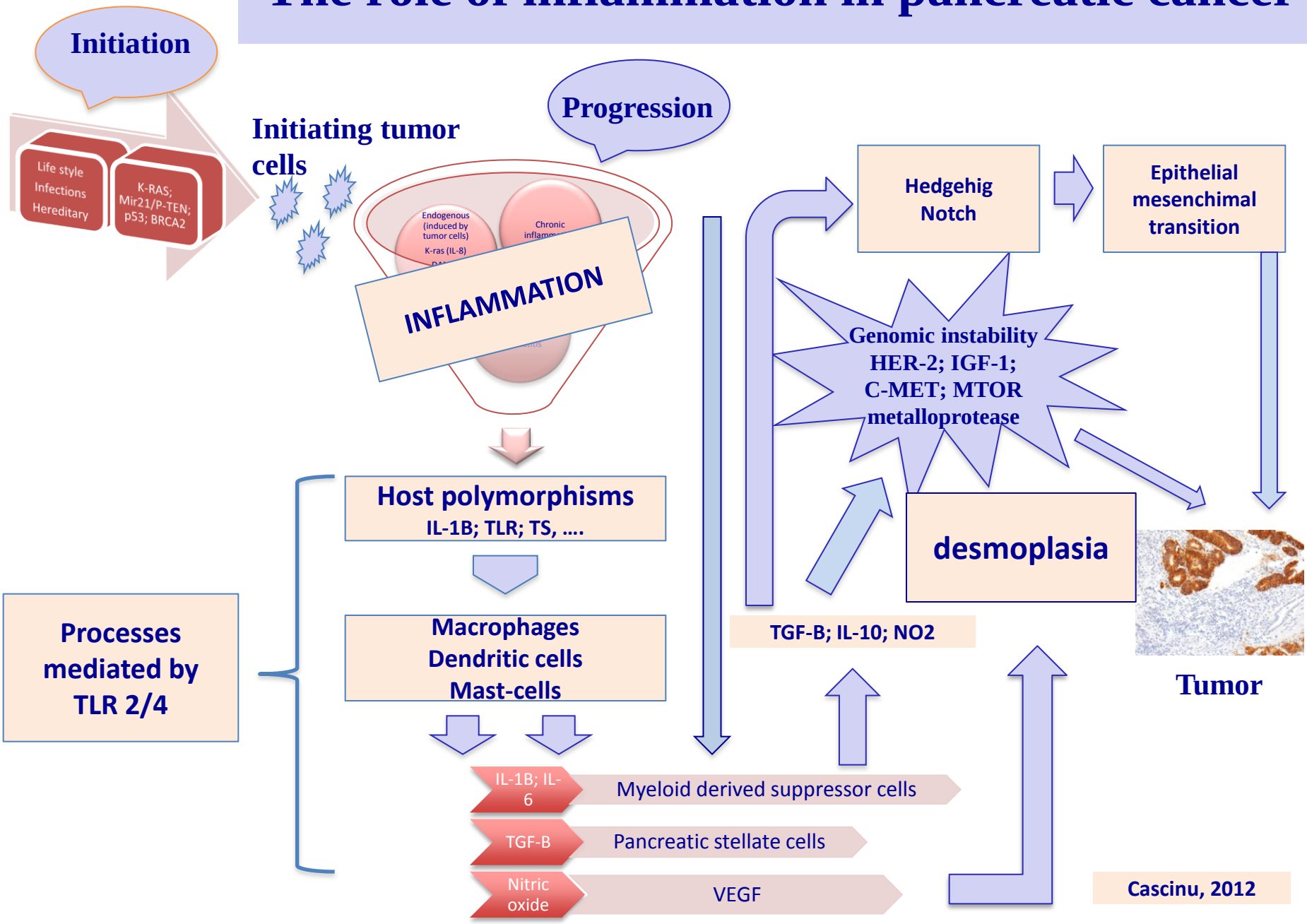
Notch and pancreatic cancer

K-Ras mutation → **Notch1**



- **NOTCH signaling pathway is an evolutionarily conserved pathway that plays a major role in cell fate decisions in various tissues during the development of multicellular organisms**
- **Down regulation of NOTCH determines a reduction of cell growth and cell survival; K-RAS mutation activates NOTCH signaling**

The role of inflammation in pancreatic cancer



110 pancreatic cancer patients. Preliminary results on 60 patients

		SPARC stroma	SMAD inact.	Notch	Hedgehog	EMT	metastatic	Locally advanced
	Mut 42	72%	75%	90%	80%	75%	36	6
K-RAS								
	Wt 18	28%	14%	15%	5%	20%	3	15

Potential implications of these data

- **Inflammation:** a key role in tumor progression and in tumor heterogeneity. It may be a relevant target for prevention and therapy
- **Hedgehog and Notch:** not only promising therapeutic targets but can allow the identification of tumors at risk of developing early metastases and resistant to treatment (desmoplasia and EMT)
- **Locally advanced and metastatic disease:** probably not different stages but tumors with different activated pathways (role of radiotherapy!).
- **KRAS wt tumors:** around 30-40%, representing a different entity from KRAS mut


Don't worry, I had the same thing, and they cured me!