Nab-paclitaxel nella neoplasia pancreatica

Carmine Pinto
Segretario Nazionale AIOM
Oncologia Medica, Policlinico S. Orsola-Malpighi, Bologna

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“Improvements in survival and clinical benefit” – Burris et al, J Clin Oncol 1997

GEM more effective than 5FU in alleviating disease-related symptoms and conferred a modest survival advantage over 5FU therapy

Years later….

where are the improvements ?

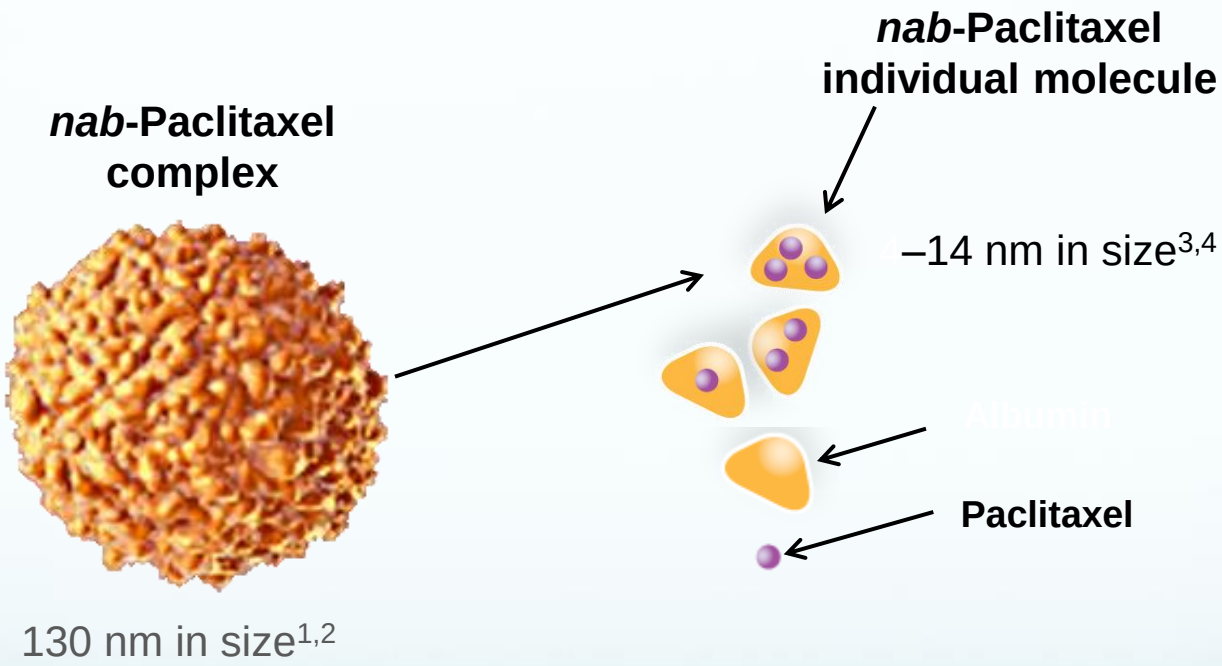
Studi randomizzati con doppiette a base di gemcitabina nel carcinoma del pancreas avanzato

Studio	Regime	Pazienti (No.)	OS (mesi)	p
Berlin, 2002	Gem vs Gem/5FU	322	5,4 vs 6,7	0,09
Cunningham, 2009	Gem vs Gem/Cape	533	6,2 vs 7,1	0,08
Herrmann, 2007	Gem vs Gem/Cape	319	7,2 vs 8,4	0,234
Heinemann, 2006	Gem vs Gem/CDDP	195	6,0 vs 7,5	0,15
Colucci, 2010	Gem vs Gem/CDDP	400	8,3 vs 7,2	0.38
Louvet, 2005	Gem vs GEMOX	313	7,1 vs 9,0	0,13
Poplin, 2009	Gem vs GEMOX	832	4,9 vs 5,7	0,09
Stathopoulos, 2006	Gem vs GEM/IRI	145	6,5 vs 6,4	0,97
O'Reilly, 2004	Gem vs Gem/Exatecan	349	6,2 vs 6,7	0,52
Oettle, 2005	Gem vs Gem/Pemetrexed	565	6,3 vs 6,2	0,85
Ueno, 2013	Gem vs S1 vs Gem/S1	834	8,8 vs 9,7 vs 10,1	0,15

Studi di fase III con gemcitabins vs gemcitabina/ biologici nel carcinoma del pancreas avanzato

Studio	Regime	Pazienti (No.)	OS (mesi)	p
Moore, 2007	Gem vs Gem/Erlotinib	569	5,9 vs 6,2	0,038
Philip, 2010	Gem vs Gem/Cetuximab	745	5,9 vs 6,3	0,23
Kindler, 2010	Gem vs Gem/Bevacizumab	602	5,9 vs 5,8	0,95
Van Cutsem, 2008	Gem/Erlotinib +/- Bevacizumab	607	6,0 vs 7,1	0,208
Kindler, 2011	Gem vs Gem/Axitinib	632	8,3 vs 8,5	0,543
Concalves, 2011	Gem vs Gem/Sorafenib	104	9,2 vs 8,5	0,146

nab-Paclitaxel is The First Tumor-Targeted Nanomedicine to Leverage the Natural Transport Properties of Albumin

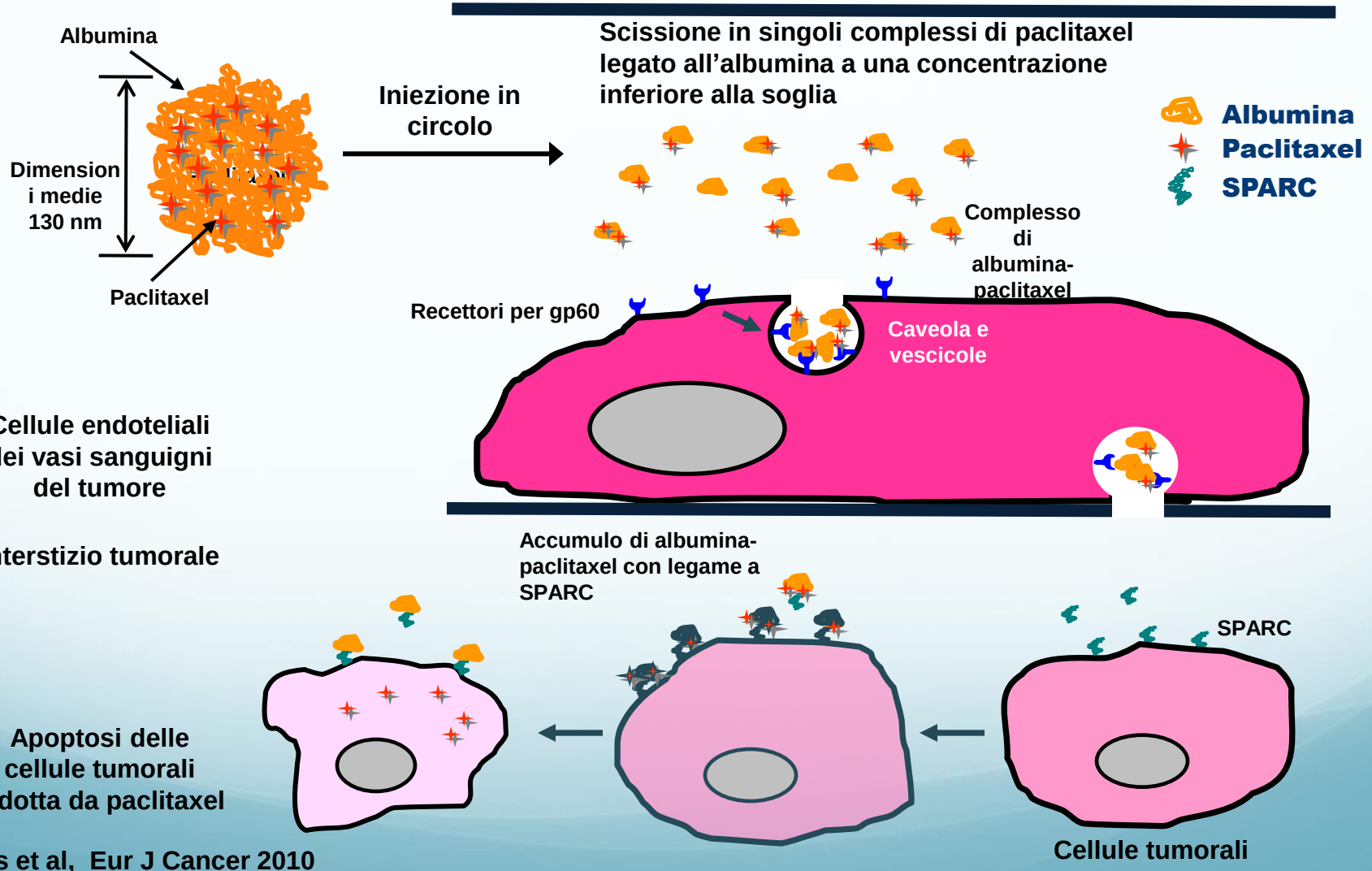


- A single molecule of albumin can bind up to 6 or 7 molecules of paclitaxel[5]

1. Desai et al. SABCS. 2004 [Abstract 1071].
2. Kratz et al. *J Control Release.* 2008;132(3):171-183.
3. Peters, Jr. *Adv Protein Chem*. 1985;37:161-245.
4. Desai. *Drug Delivery Report*. 2008;Winter 2007/2008(16):35-41.
5. Paal et al. *Eur J Biochem*. 2001;268:2187-2191.

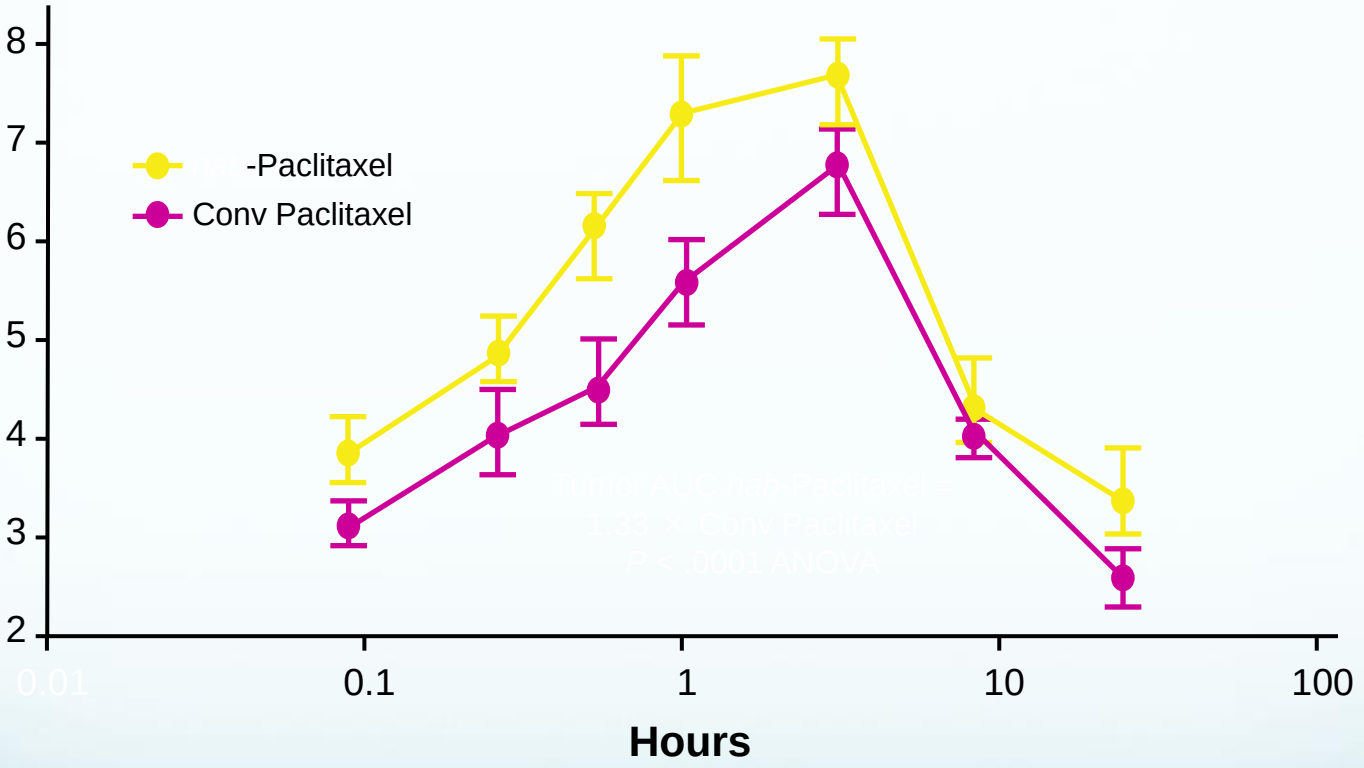
Meccanismi mediati dalle vie dell'albumina endogena

1. Trasporto attivo mediato dai recettori (transcitosi) tramite gp60 e caveola
2. Legame attivo del complesso di albumina-farmaco tramite SPARC nel tumore



Cortes et al, Eur J Cancer 2010

At the Same Dose and Same Duration, Tumor Uptake is 33% Higher for *nab*-Paclitaxel[1]



- Dose of both *nab*-paclitaxel and conventional paclitaxel = 20 mg/kg dose of paclitaxel; experiments in human breast tumor xenografts in nude mice.

ANOVA, analysis of variance; AUC, area under the curve; conv, conventional.

1. Desai et al. *Clin Cancer Res*. 2006;12:1317-1324.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Gemcitabine Plus *nab*-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial

Daniel D. Von Hoff, Ramesh K. Ramanathan, Mitesh J. Borad, Daniel A. Laheru, Lon S. Smith, Tina E. Wood, Ronald L. Korn, Neil Desai, Vuong Trieu, Jose L. Iglesias, Hui Zhang, Patrick Soon-Shiong, Tao Shi, N.V. Rajeshkumar, Anirban Maitra, and Manuel Hidalgo

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

Phase I
Gemcitabine 1000 mg/m^2
Followed by paclitaxel albumin 100, 125 or 150 mg/m^2 QW 3/4
Dose escalation of paclitaxel albumin according to a standard 3+3 design

→

Phase II:
Accrual expanded to ≥42 patients
Treatment at the MTD

Von Hoff, J Clin Oncol 2011

Patient Demographics and Baseline Characteristics

	nab-Paclitaxel mg/m^2		
	100 (n = 20)	125 (n = 44)	150 (n = 3)
Age (years), median (range)	62 (30, 86)	61 (28, 78)	69 (53, 72)
<65 years, n (%)	11 (55)	30 (70)	1 (33)
Female	9 (45)	25 (57)	1 (33)
ECOG, n (%)			
0	9 (45)	22 (50)	2 (67)
1	11 (55)	22 (50)	1 (33)
Site of Metastatic Relapse, n (%)			
Lung	5 (25)	18 (41)	1 (33)
Liver	11 (55)	34 (77)	2 (67)
Abdomen	16 (80)	37 (84)	2 (67)
Other	12 (60)	15 (35)	1 (33)
Previous Treatment			
XRT	3 (15)	6 (14)	0
Adjuvant gemcitabine	1 (5)	8 (18)	0
Adjuvant capecitabine	1 (5)	4 (9)	0
Adjuvant 5-FU	2 (10)	1 (2)	0
Adjuvant docetaxel	0	2 (5)	0
Adjuvant erlotinib	0	0	0

Von Hoff, J Clin Oncol 2011

Safety

Most common ≥ Grade 3 and 4 Adverse Events During Therapy						
	nab-Paclitaxel mg/m^2					
	100 (n = 20)		125 (n = 44)		150* (n = 3)	
Adverse Events, n (%)	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	2 (10)	0	10 (23)	0	1 (33)	0
Neutropenia	7 (35)	2 (10)	14 (36)	9 (23)	1 (33)	0
Thrombocytopenia	4 (20)	1 (5)	5 (11)	4 (9)	0	1 (33)
Sensory Neuropathy	1 (5)	0	4 (9)	0	0	0

* There was one grade 5 neutropenic sepsis death.

- Of 67 treated patients, the combination of *nab*-paclitaxel + gemcitabine was well tolerated
- The MTD was 125 mg/m^2 *nab*-paclitaxel + 1000 mg/m^2 gemcitabine
- Fifteen of 17 patients with dose reduction had a dose reduced due to AEs: 6, 8, and 1, in the 100, 125, and 150 mg/m^2 *nab*-paclitaxel arms, respectively

Von Hoff, J Clin Oncol 2011

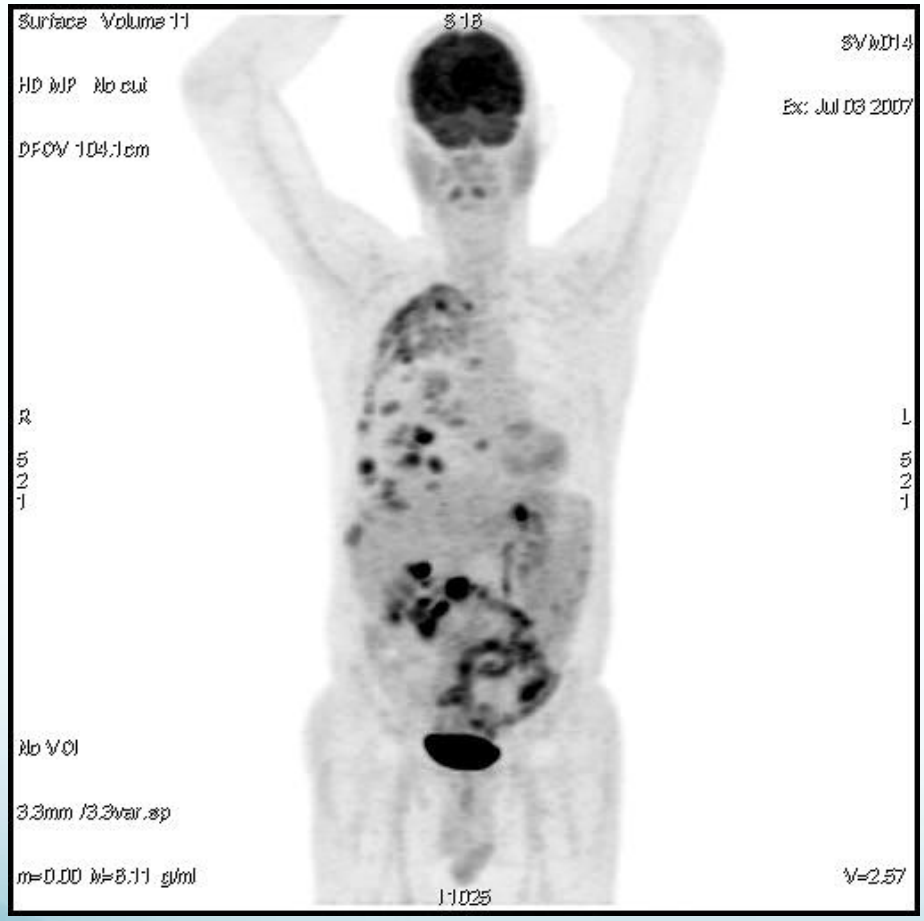
Response Evaluation by PET and CT

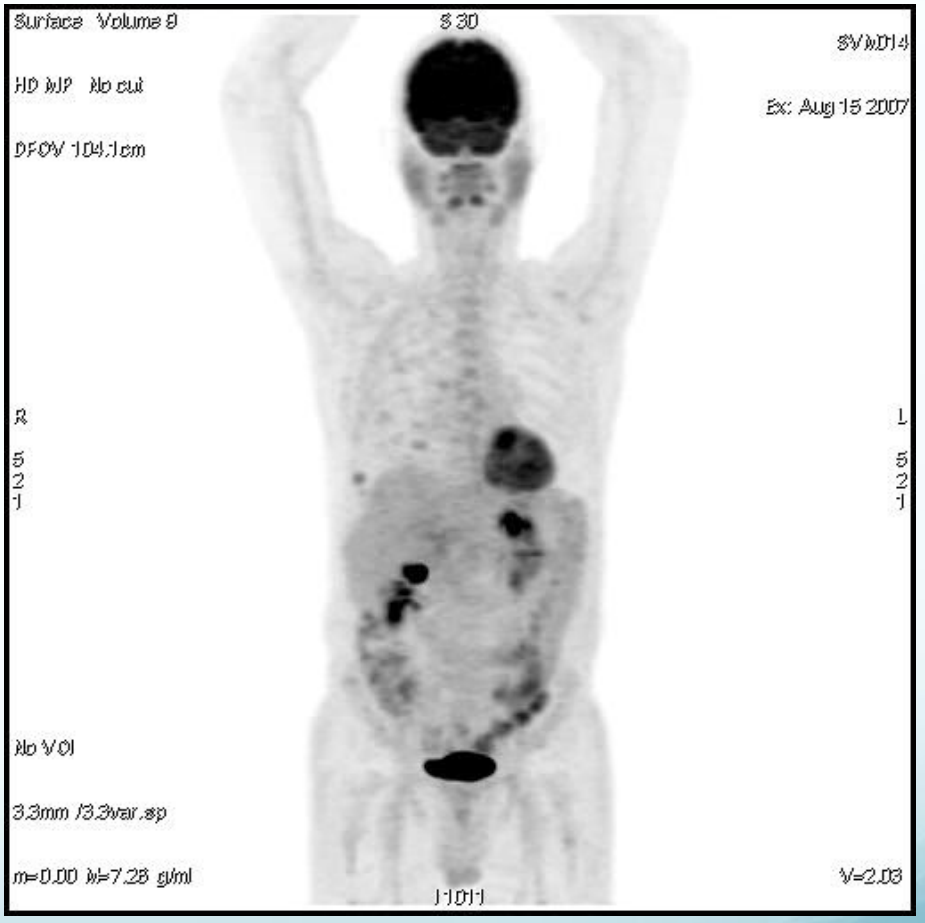
	Confirmed CR	Confirmed PR	SD ≥16 weeks	PD	DCR[a]
Independent Radiologist Assessment, n (%)					
PET, N = 45 CT, N = 58	6 (13)[b] 0	20 (44)[b] 23 (40)[c]	1 (2)[b] 22 (37)[c]	0 4 (7)	27 (60) 45 (78)
Investigator Assessment, n (%)					
CT, N = 61[d,e]	3 (5)	24 (39)	16 (26)	13 (21)	43 (70)

[a] DCR = Disease Control Rate (confirmed CR+PR+SD $\geq$ 16 weeks)
[b] There were 6 more unconfirmed CRs, 10 more unconfirmed PRs and 2 more unconfirmed SD
[c] There were 5 more unconfirmed PRs and 4 more unconfirmed SD
[d] Sixty-one of the 67 treated patients had post baseline CT scans (3 off early, patient discretion; 2 off for adverse events; 1 off for other reason)
[e] Also includes 3 SD < 16 weeks, 1 unconfirmed PR, and 1 unable to evaluate

Von Hoff, J Clin Oncol 2011

PET response



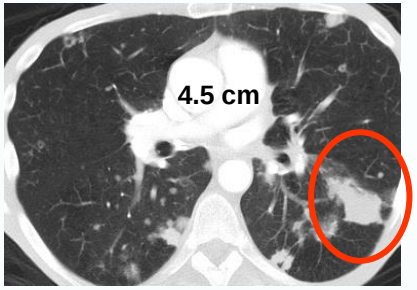


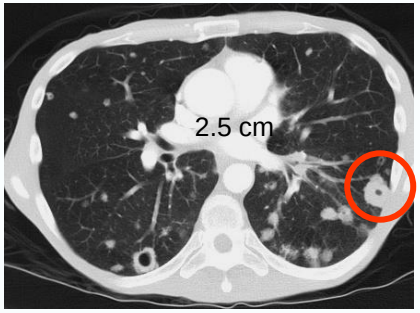
Baseline **6 weeks**

Von Hoff, J Clin Oncol 2011

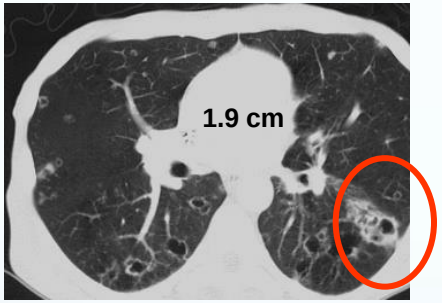
CT response

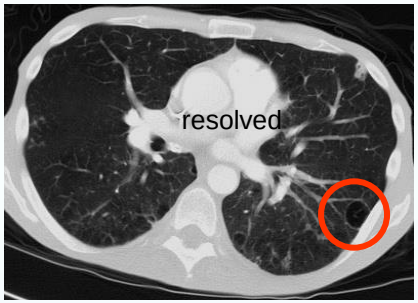
Baseline



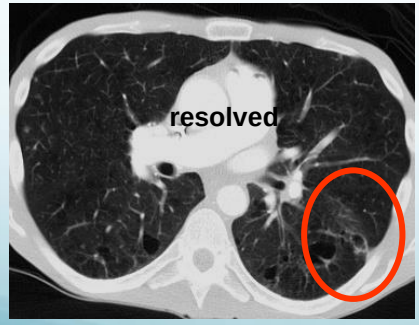


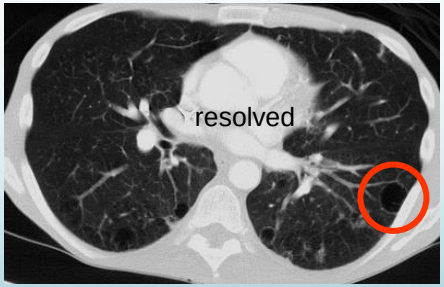
2 mo.

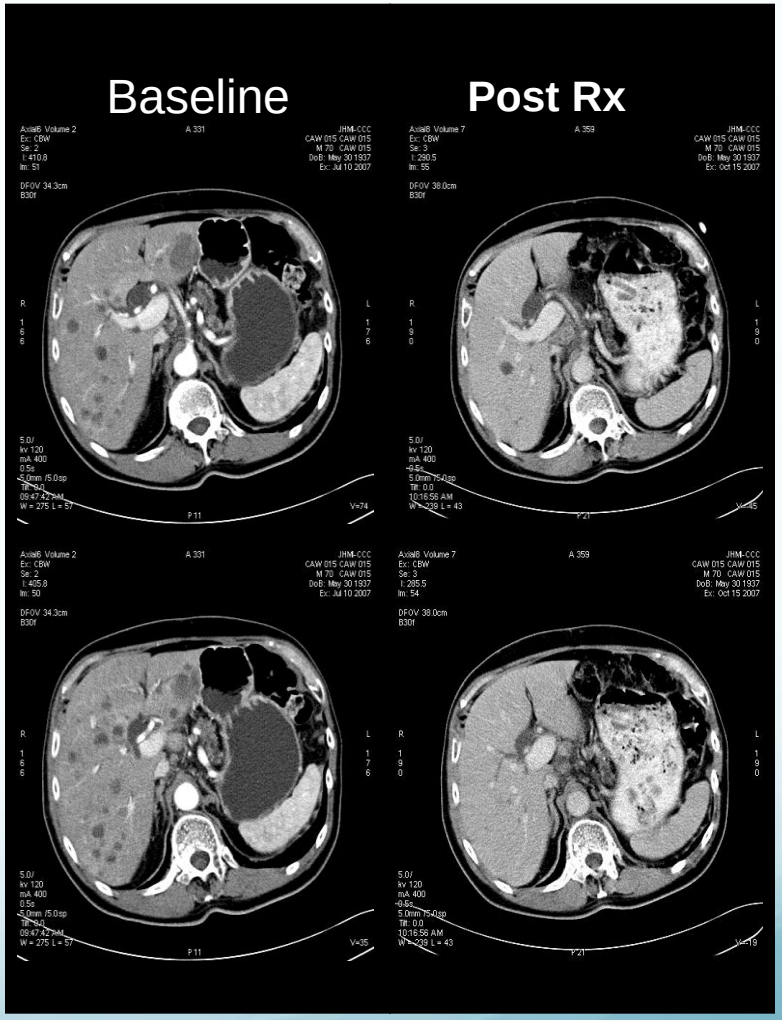




3 mo.



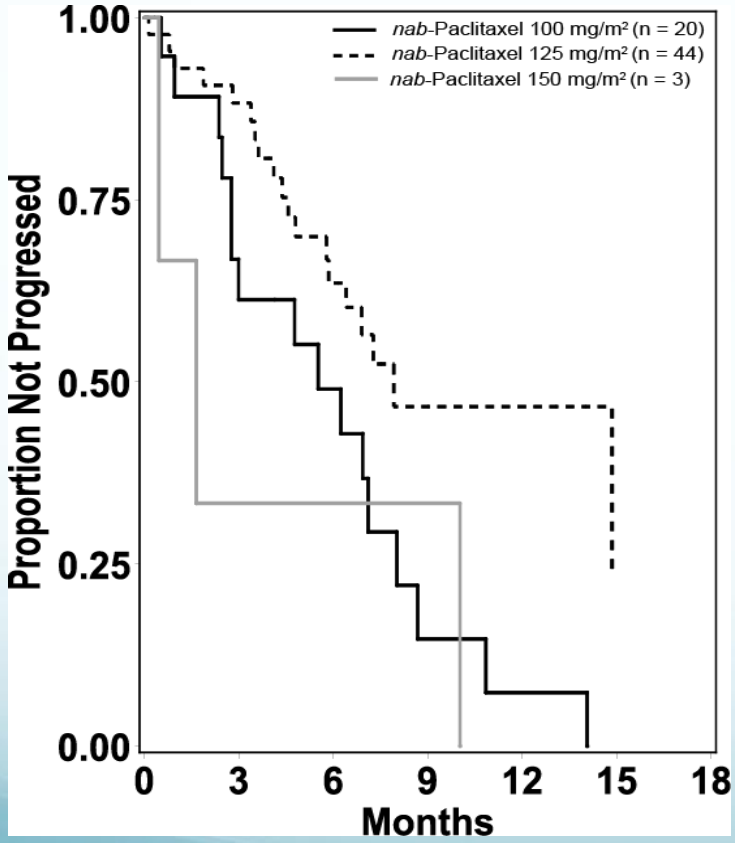


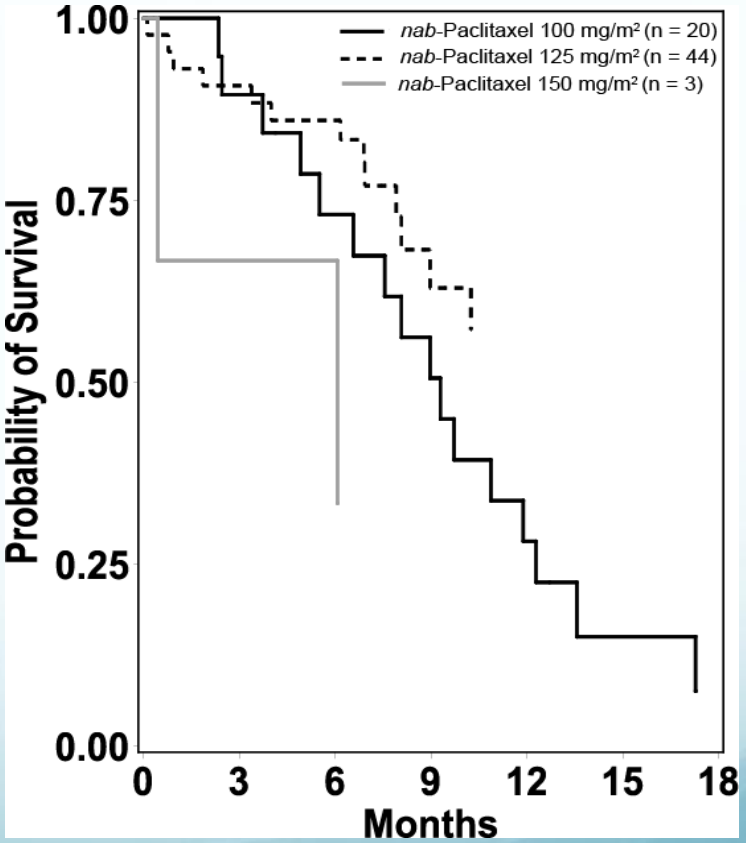


Von Hoff, J Clin Oncol 2011

Progression-free Survival and Overall Survival

- For all patients (N = 67), the median time for PFS was 6.9 months, and median time for OS was 10.3 months to date
- For patients at the recommended dose of 125 mg/m^2 *nab*-paclitaxel, the median PFS was 7.9 months, and the OS time was not yet reached

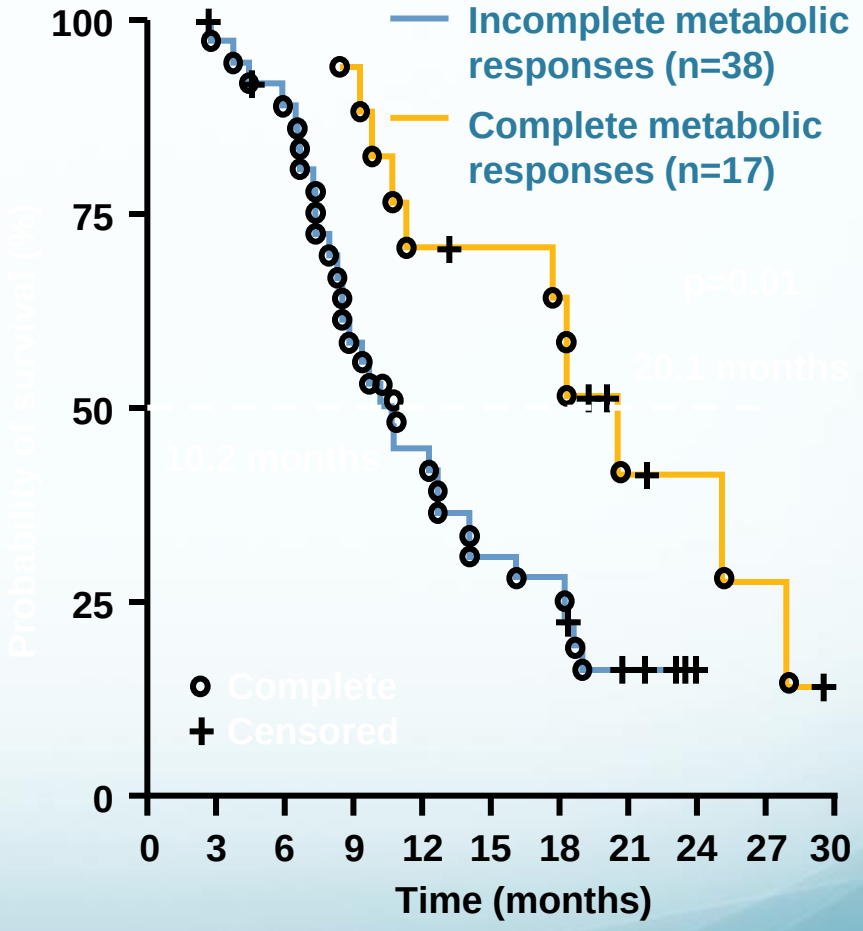




Von Hoff, J Clin Oncol 2011

PET-FDG response

- FDG PET scans were available for 55 patients
- Median decrease in metabolic activity at 12 weeks:
  - 79% (all patients)
- Patients with a metabolic response (defined by EORTC as absence of FDG uptake) had a significantly improved OS:
  - Median OS: 20.1 vs 10.3 mo, p=0.01



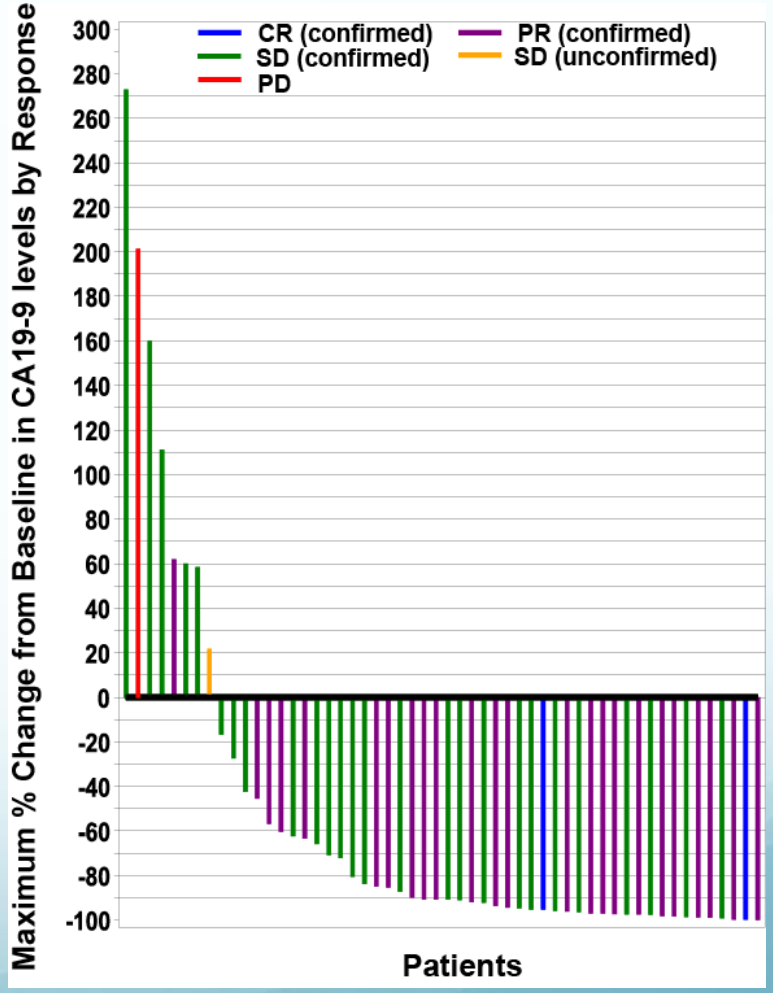
Von Hoff et al. J Clin Oncol 2011

CA19.9 Correlation

- CA19-9 decreases occurred rapidly after treatment initiation
- CA19-9 decrease of ≥50% was observed in 42 (78%) of the 54 patients with available CA19-9 levels (CA19-9 decrease of <50% was 12 [22%])
- Median max % change in 54 patients was 91%

CA19-9 levels correlated strongly with RR, PFS, and OS.

CA19-9 Classification	RR, n (%)	Median PFS, mo	Median OS, mo
≥50% Decrease (n = 42)	24 (57)	8.7	12.3
<50% Decrease (n = 12)	2 (17)	3.6	6.2
P-values	0.021	0.004	<0.001



Von Hoff, J Clin Oncol 2011

Stroma evaluation

Collagen Type I Immuno-staining

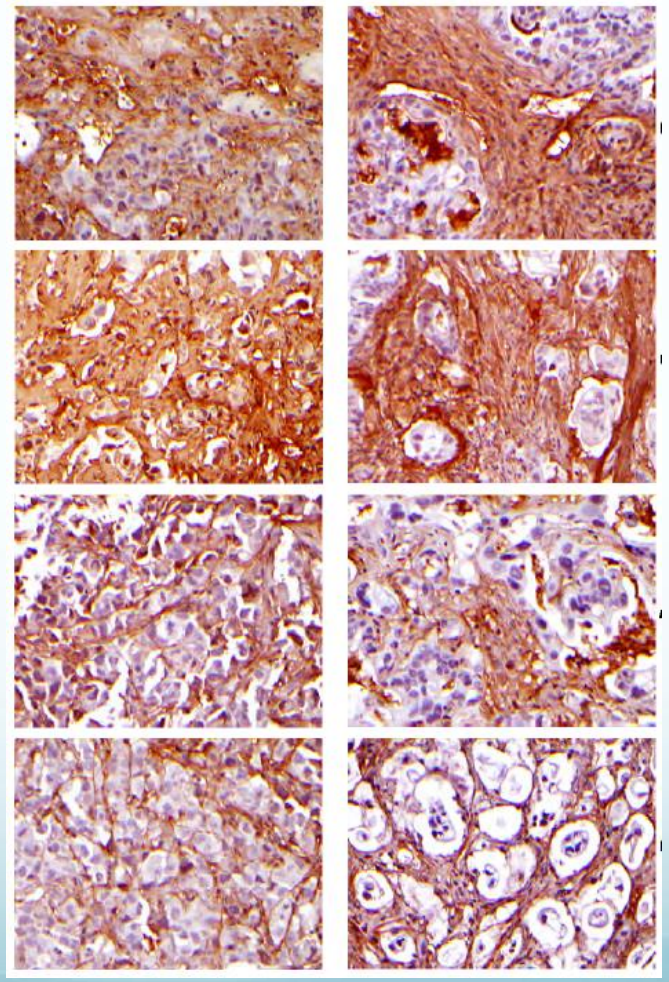
Treatment group

Control

Gemcitabine

NAB-paclitaxel

GEM + NAB-*p*



Profuse Desmoplastic Stroma

Persisting Stroma

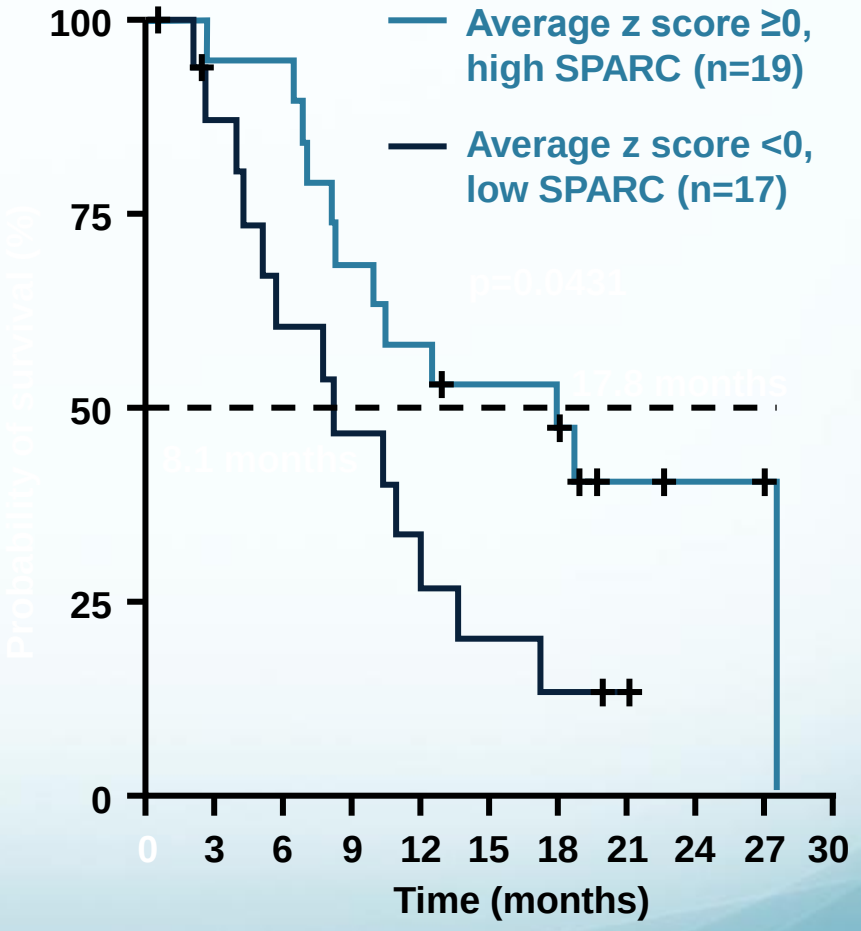
Desmoplastic Stroma Depletion

Dilated blood vessels x3 increase in mNestin

Von Hoff, J Clin Oncol 2011

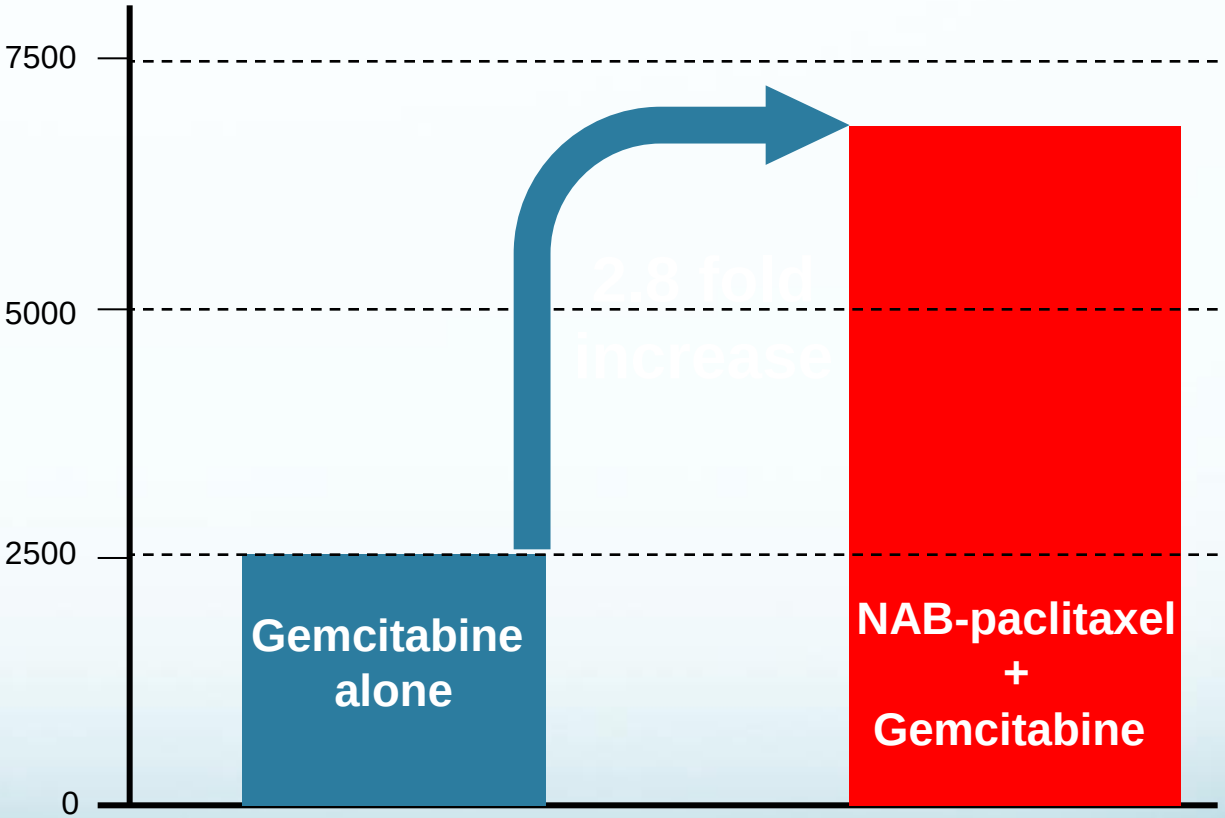
SPARC and NAB-paclitaxel/gemcitabina response

- 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, J Clin Oncol 2011

Tumour gemcitabine concentration +/- nab-paclitaxel combination



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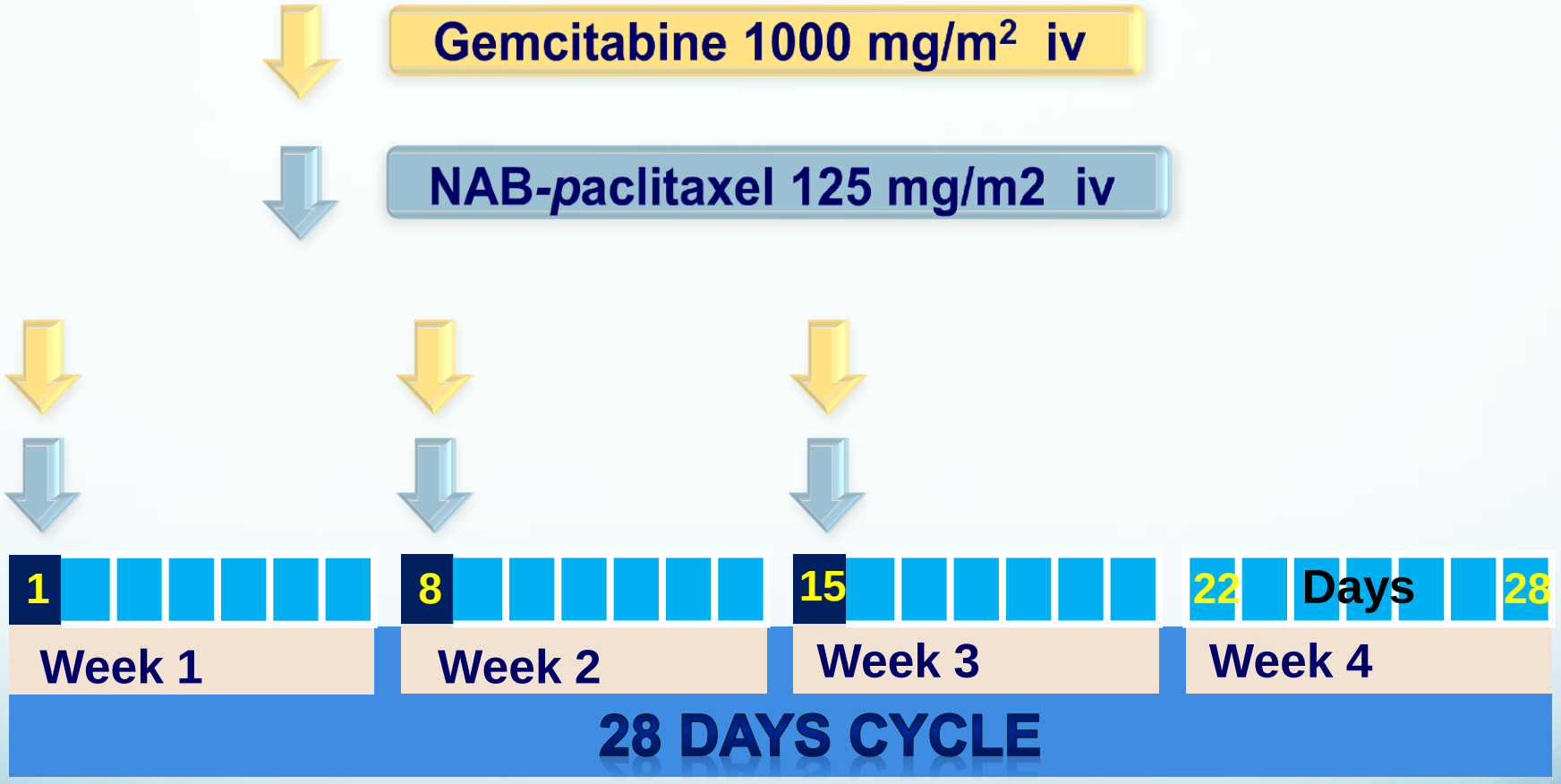
Dose massima tollerata (MTD) identificata per lo studio di Fase II



Von Hoff, J Clin Oncol 2011

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

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

Von Hoff et al., ASCO GI 2013 LBA148

Study Design

Planned N = 842

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥70
- Measurable disease
- Total bilirubin ≤ULN

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

nab-Paclitaxel
125 mg/m^2 IV qw 3/4 weeks
+
Gemcitabine
1000 mg/m^2 IV qw 3/4 weeks

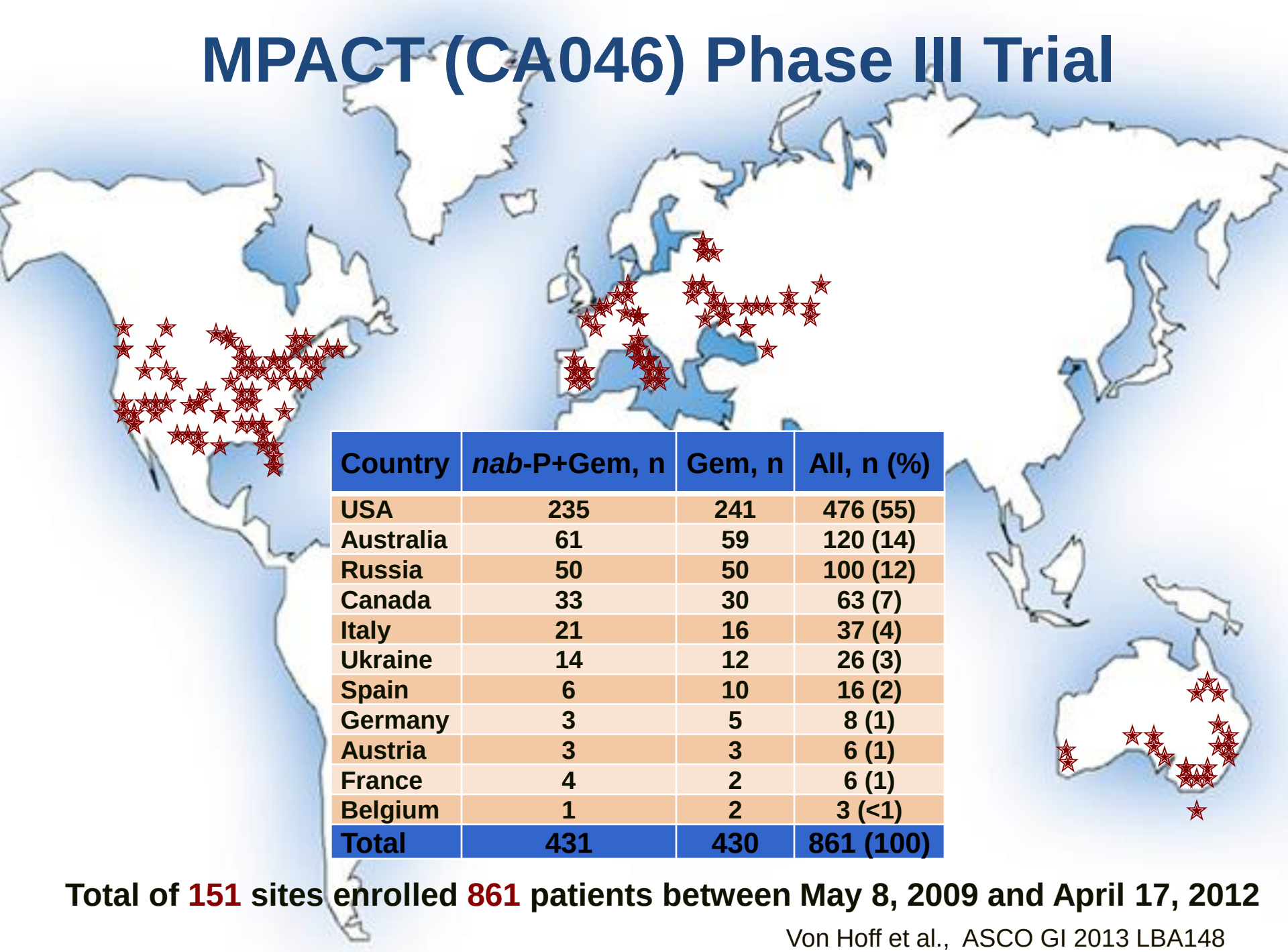
Gemcitabine
1000 mg/m^2 IV qw for 7/8 weeks
then qw 3/4 weeks

- **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 α = 0.049)
- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

Von Hoff et al., ASCO GI 2013 LBA148

MPACT (CA046) Phase III Trial



Country	*nab*-P+Gem, n	Gem, n	All, n (%)
USA	235	241	476 (55)
Australia	61	59	120 (14)
Russia	50	50	100 (12)
Canada	33	30	63 (7)
Italy	21	16	37 (4)
Ukraine	14	12	26 (3)
Spain	6	10	16 (2)
Germany	3	5	8 (1)
Austria	3	3	6 (1)
France	4	2	6 (1)
Belgium	1	2	3 (<1)
Total	431	430	861 (100)

Total of 151 sites enrolled 861 patients between May 8, 2009 and April 17, 2012

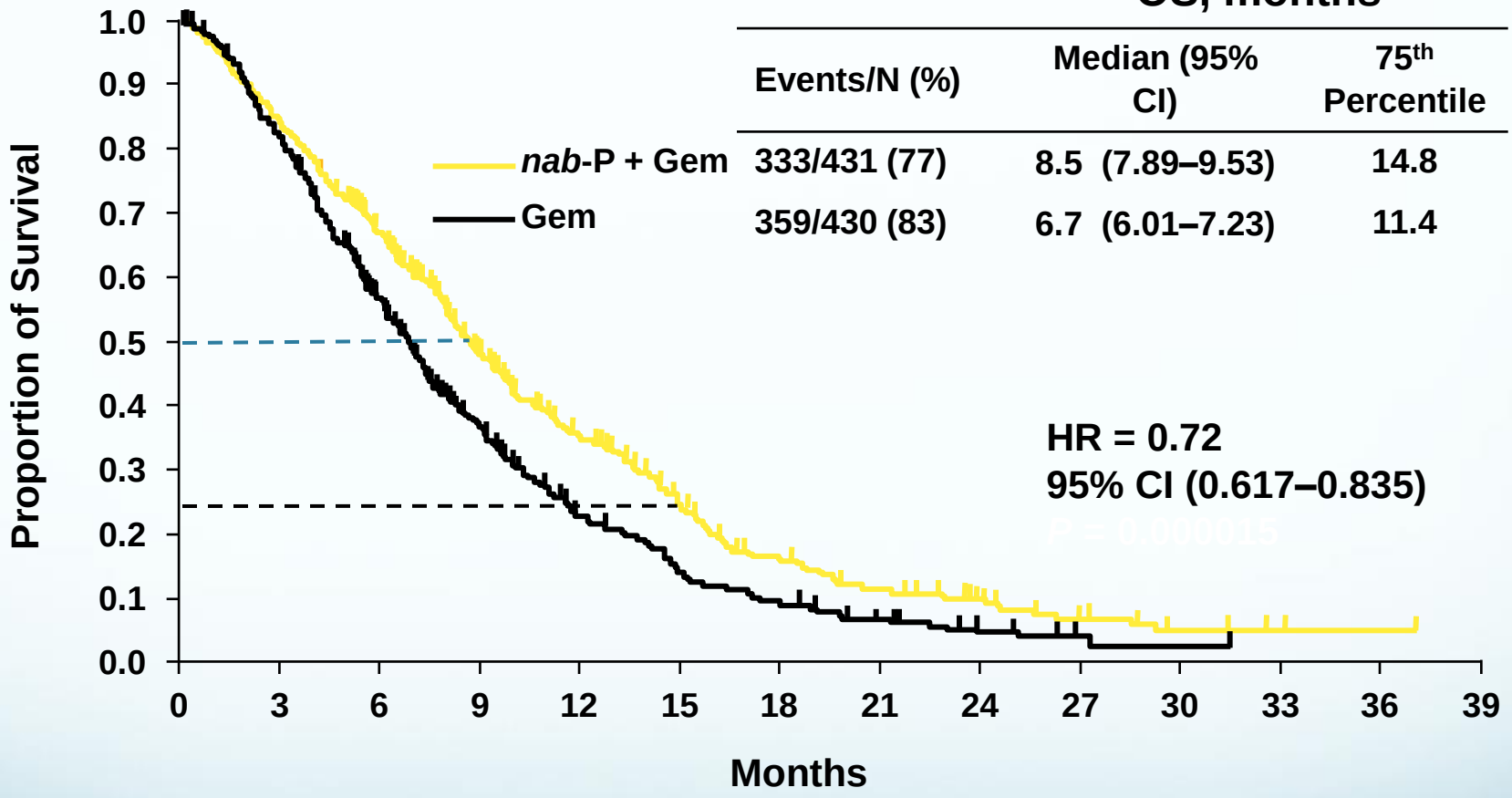
Von Hoff et al., ASCO GI 2013 LBA148

Baseline Characteristics

Variable		nab-P + Gem (n = 431)	Gem (n = 430)	All Patients (N = 861)
Age	Median years (min, max)	62 (27, 86)	63 (32, 88)	63 (27, 88)
	≥65 years old, %	41	44	42
Sex	Male, %	57	60	58
KPS	90 – 100, %	58	62	60
	70 – 80, %	42	38	40
Pancreatic Primary Location	Head, %	44	42	43
	Body, %	31	32	31
	Tail, %	24	26	25
Current Site(s) of Metastasis	Lung, %	35	43	39
	Liver, %	85	84	84
# of Metastatic Sites	1, %	8	5	6
	2, %	47	48	47
	≥3, %	45	47	46
Previous Whipple	Yes, %	7	7	7
Biliary Stent	Yes, %	19	16	17

Von Hoff et al., ASCO GI 2013 LBA148

Overall Survival



OS, months		
Events/N (%)	Median (95% CI)	75th Percentile
333/431 (77)	8.5 (7.89–9.53)	14.8
359/430 (83)	6.7 (6.01–7.23)	11.4

Pts at Risk

nab-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

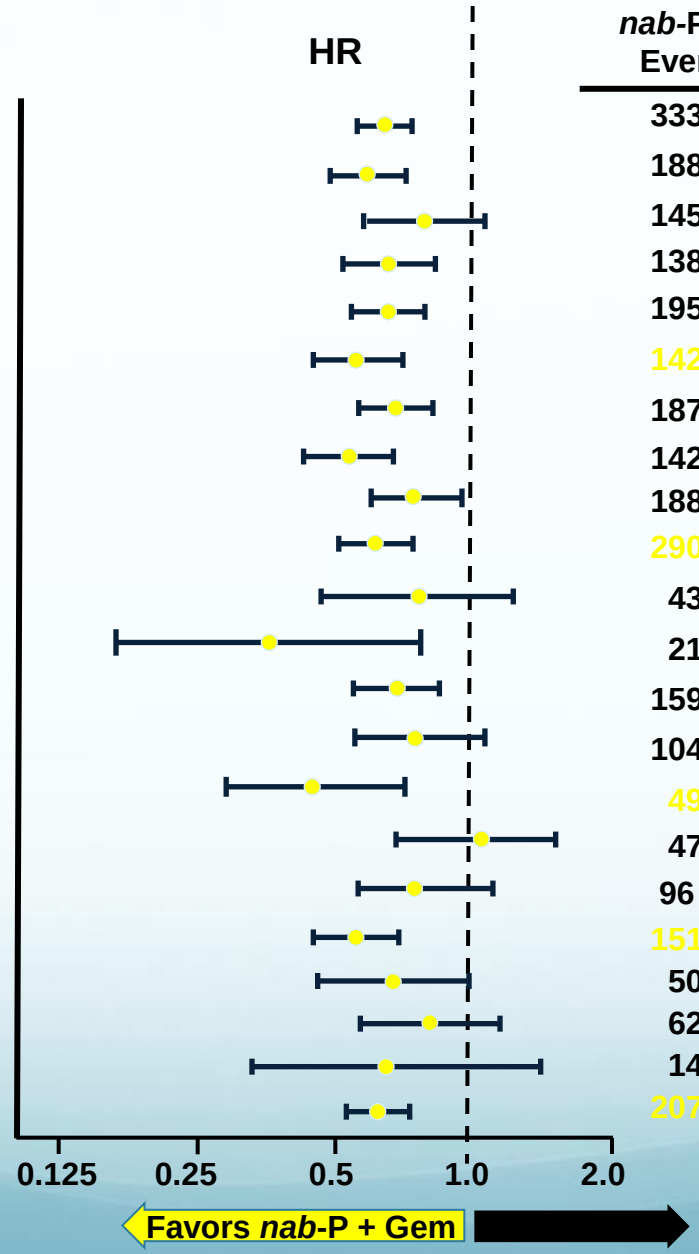
Von Hoff et al., ASCO GI 2013 LBA148

Survival Rate

	nab-P + Gem	Gem		
Time Points, month	Survival, %	Survival, %	Increase, %	P-value
6	67	55	22	0.00074
9	48	36	33	0.00067
12	35	22	59	0.00020
18	16	9	78	0.00803
24	9	4	125	0.02123

Von Hoff et al., ASCO GI 2013 LBA148

OS - Prespecified Subgroups



Group	*nab*-P + Gem Events / N	Gem Events / N	HR
All Patients	333 / 431	359 / 430	0.72
Age <65 Years	188 / 254	209 / 242	0.65
Age ≥65 Years	145 / 177	150 / 188	0.81
Female	138 / 186	141 / 173	0.72
Male	195 / 245	218 / 257	0.72
KPS 70-80	142 / 179	146 / 161	0.61
KPS 90-100	187 / 248	212 / 268	0.75
Primary Tumor Location: Head	142 / 191	155 / 180	0.59
Primary Tumor Location: Other	188 / 237	201 / 246	0.80
Liver Metastases	290 / 365	309 / 360	0.69
No Liver Metastases	43 / 66	50 / 70	0.86
1 Metastatic Site	21 / 33	16 / 21	0.41
2 Metastatic Sites	159 / 202	163 / 206	0.75
3 Metastatic Sites	104 / 136	121 / 140	0.79
>3 Metastatic Sites	49 / 60	59 / 63	0.50
Normal CA19-9	47 / 60	43 / 56	1.07
CA19-9 ULN to <59 x ULN	96 / 122	95 / 120	0.83
CA19-9 ≥59 x ULN	151 / 197	171 / 195	0.61
Australia	50 / 61	53 / 59	0.67
Eastern Europe	62 / 64	59 / 62	0.84
Western Europe	14 / 38	17 / 38	0.72
North America	207 / 268	230 / 271	0.68

Von Hoff et al., LBA148

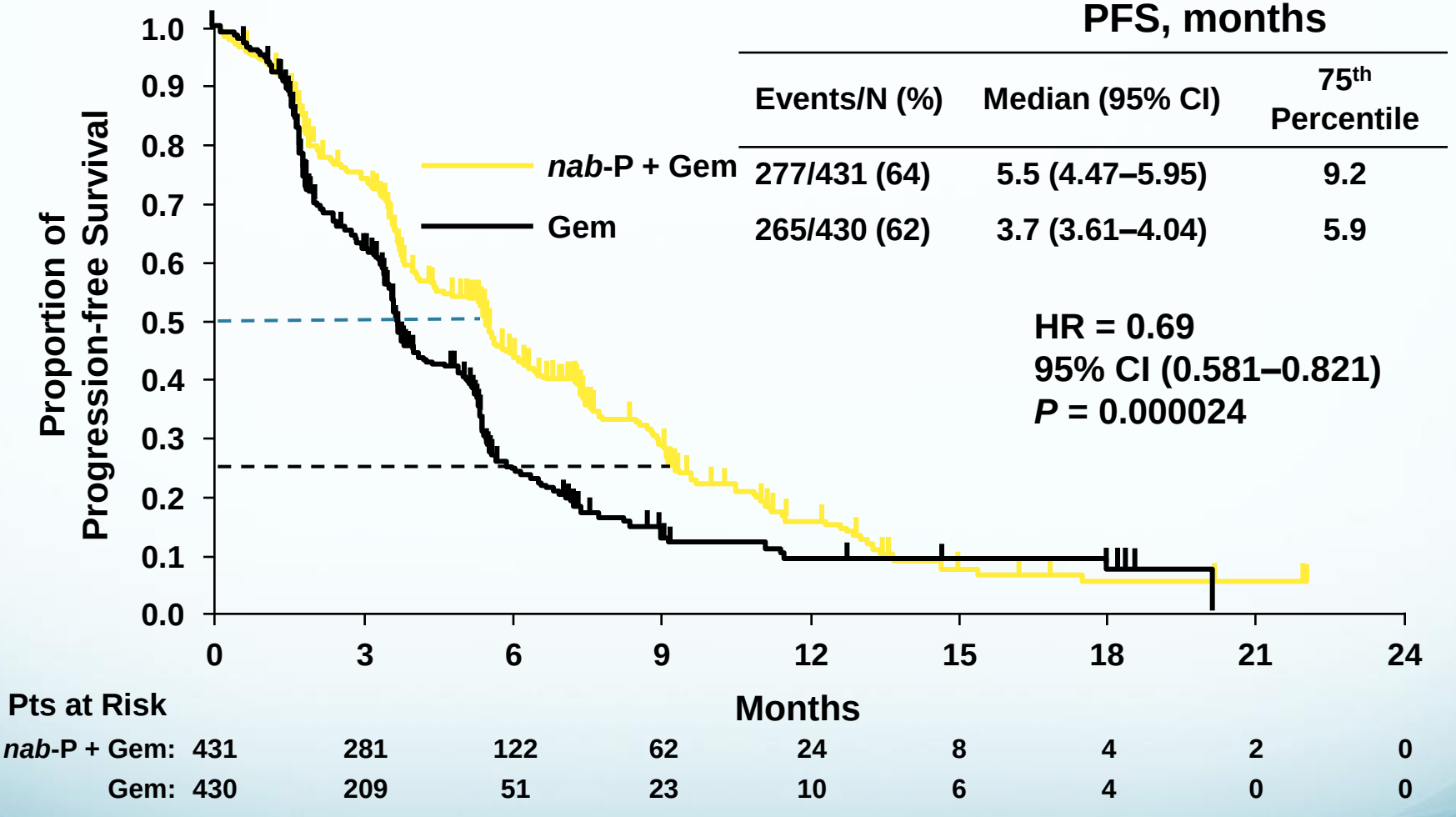
Impact of Subsequent Therapy on OS

Regimen	nab-P + Gem (n = 431)	Gem (n = 430)
Patients with Subsequent Therapy, %	38	42
5-FU/Capecitabine based, % nab-P+ Capecitabine	26 0	30 <1
Folfirinox (Modified/Unmodified), %	4	6
Erlotinib-based, %	3	3
Other, % nab-P-based	10 0	12 6

Sensitivity Analysis: Censor at Time of 2nd-line Therapy	nab-P + Gem	Gem	Hazard Ratio (nab-P+G/G)	P-value
Median OS, months	9.4	6.8	0.68	0.000072

Von Hoff et al., ASCO GI 2013 LBA148

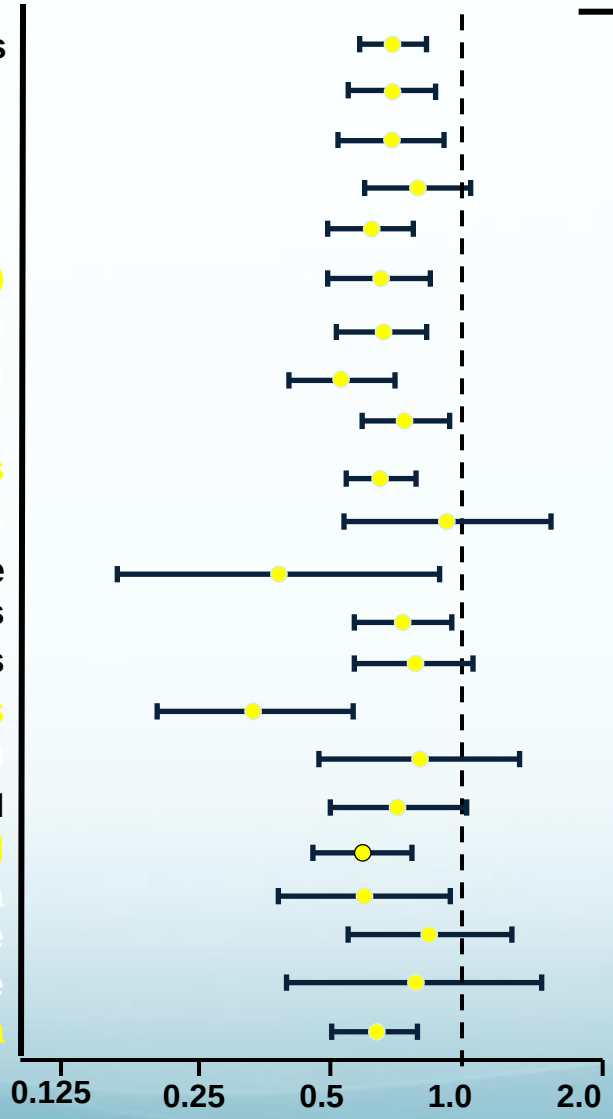
PFS by Independent Review



PFS Rate at	nab-P + Gem	Gem	% Increase
6 months	44%	25%	76%
12 months	16%	9%	78%

Von Hoff et al., LBA148

PFS by Independent Review, Subgroups



Group	*nab*-P + Gem Events / N	Gem Events / N	HR
All Patients	277 / 431	265 / 430	0.69
Age <65 Years	172 / 254	149/ 242	0.69
Age ≥65 Years	105 / 177	116 / 188	0.69
Female	114 / 186	100/ 173	0.79
Male	163 / 245	165 / 257	0.62
KPS 70-80	125 / 179	118 / 161	0.65
KPS 90-100	150 / 248	146 / 268	0.68
Primary Tumor Location: Head	118 / 191	110 / 180	0.53
Primary Tumor Location: Other	158 / 237	155/ 246	0.74
Liver Metastases	242 / 365	238 / 360	0.65
No Liver Metastases	35 / 66	27/ 70	0.92
1 Metastatic Site	17 / 33	17 / 21	0.38
2 Metastatic Sites	130 / 202	118 / 206	0.73
3 Metastatic Sites	89 / 136	88 / 140	0.78
>3 Metastatic Sites	41 / 60	42 / 63	0.35
Normal CA19-9	37 / 60	37 / 56	0.80
CA19-9 ULN to <59 x ULN	84/ 122	68 / 120	0.71
CA19-9 ≥59 x ULN	126 / 197	133 / 195	0.59
Australia	42 / 61	45 / 59	0.60
Eastern Europe	47 / 64	49 / 62	0.84
Western Europe	21 / 38	19/ 38	0.78
North America	167 / 268	152 / 271	0.64

Von Hoff et al., LBA148

Response Rates

Variable	nab-P + Gem (n = 431)	Gem (n = 430)	P-value
Overall Response Rate			
Independent Review, %	23	7	$1.1x10^{-10}$
(95% CI)	(19.1–27.2)	(5.0–10.1)	
Investigator Assessment, %	29	8	$3.3x10^{-16}$
(95% CI)	(25.0–33.8)	(5.3–10.6)	
Disease Control Rate by Independent Review, [a] %	48	33	$7.2x10^{-6}$
(95% CI)	(43.0–52.6)	(28.4–37.5)	

[a] Includes CR + PR + SD ≥16 weeks

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Treatment Exposure

Variable	nab-P + Gem (n = 421)	Gem (n = 402)
Treatment Duration, median months (min, max)	3.9 (0.1, 21.9)	2.7 (0.1, 21.5)
≥6 months, %	32	15
% Protocol Dose, median (min, max)		
nab-P	80.6 (16.7, 100.0)	--
Gem	75.2 (14.3, 97.7)	84.6 (14.1, 100.0)
Cumulative Dose, median mg/m²		
nab-P	1,425.0	--
Gem	11,400.0	9,000.0
nab-P Doses at 125 mg/m², n (%)	4,116.0 (71)	--
Gem Doses at 1000 mg/m², n (%)	3,731.0 (63)	3,762.0 (79)

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Safety

Preferred Term	nab-P + Gem (n = 421)	Gem (n = 402)
Pt with at least 1 AE Leading to Death, %	4	4
Grade ≥3 Hematologic AE, [a] %		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anemia	13	12
Pts Who Received Growth Factors, %	26	15
Febrile Neutropenia, [b] %	3	1
Grade ≥3 Nonhematologic AE [b] in >5% Pts, %		
Fatigue	17	7
Peripheral Neuropathy [c]	17	<1
Diarrhea	6	1
Grade ≥3 Neuropathy		
Time to Onset, median days	140	113
Time to Improvement by 1 Grade, median days	21	29
Time to Improvement to Grade ≤1, median days	29	--
Pts Who Resumed nab-P, %	44	--

[a] Based on lab values; [b] Based on investigator assessment of treatment-related events; [c] grouped term

Von Hoff et al., ASCO GI 2013 LBA148

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*

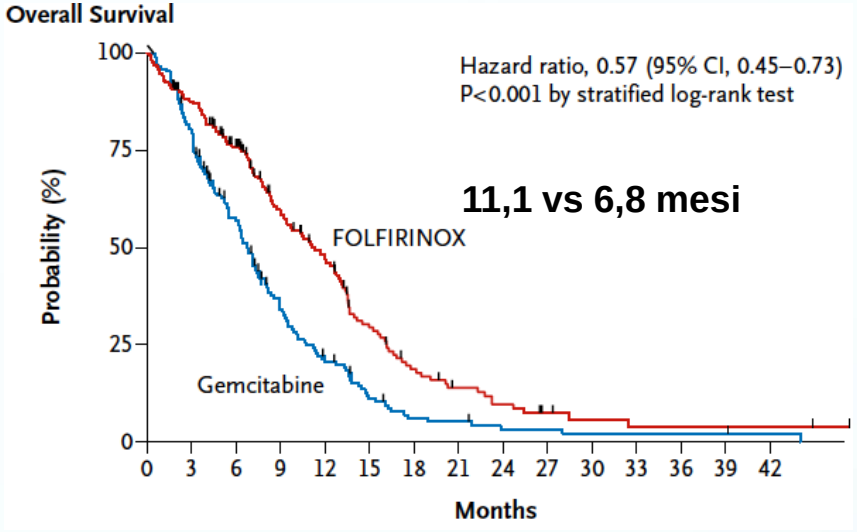
Table 1. Demographic and Baseline Characteristics of Patients in the Intention-to-Treat Population.*

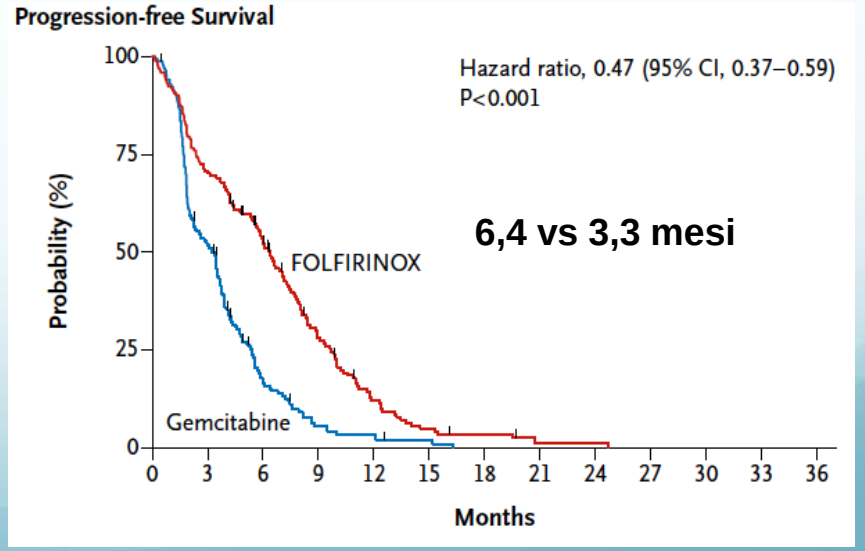
Characteristic	FOLFIRINOX (N=171)	Gemcitabine (N=171)
Age — yr		
Median	61	61
Range	25–76	34–75
Sex — no. (%)		
Male	106 (62.0)	105 (61.4)
Female	65 (38.0)	66 (38.6)
ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
Pancreatic tumor location — no. (%)		
Head	67 (39.2)	63 (36.8)
Body	53 (31.0)	58 (33.9)
Tail	45 (26.3)	45 (26.3)
Multicentric	6 (3.5)	5 (2.9)
Biliary stent — no. (%)		
Yes	27 (15.8)	22 (12.9)
No	144 (84.2)	149 (87.1)
No. of metastatic sites involved		
Median	2	2
Range	1–6	1–6
Level of carbohydrate antigen 19-9 — no./total no. (%)		
Normal	24/164 (14.6)	23/165 (13.9)
Elevated, <59×ULN	72/164 (43.9)	65/165 (39.4)
Elevated, ≥59×ULN	68/164 (41.5)	77/165 (46.7)
Unknown	7/171 (4.1)	6/171 (3.5)
No. of measurable metastatic sites — no. of patients/total no. (%)		
Liver	149/170 (87.6)	150/171 (87.7)
Pancreas	90/170 (52.9)	91/171 (53.2)
Lymph node	49/170 (28.8)	39/171 (22.8)
Lung	33/170 (19.4)	49/171 (28.7)
Peritoneal	33/170 (19.4)	32/171 (18.7)
Other	18/170 (10.6)	29/171 (17.0)

FOLFIRINOX vs gemcitabina nel carcinoma del pancreas avanzato

Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	





Conroy et al, NEJM 2011

FOLFIRINOX vs gemcitabina nal carcinoma del pancreas avanzato

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
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

Conroy et al, NEJM 2011

nab-Paclitaxel/gemcitabina e FOLFIRINOX nel carcinoma del pancreas avanzato

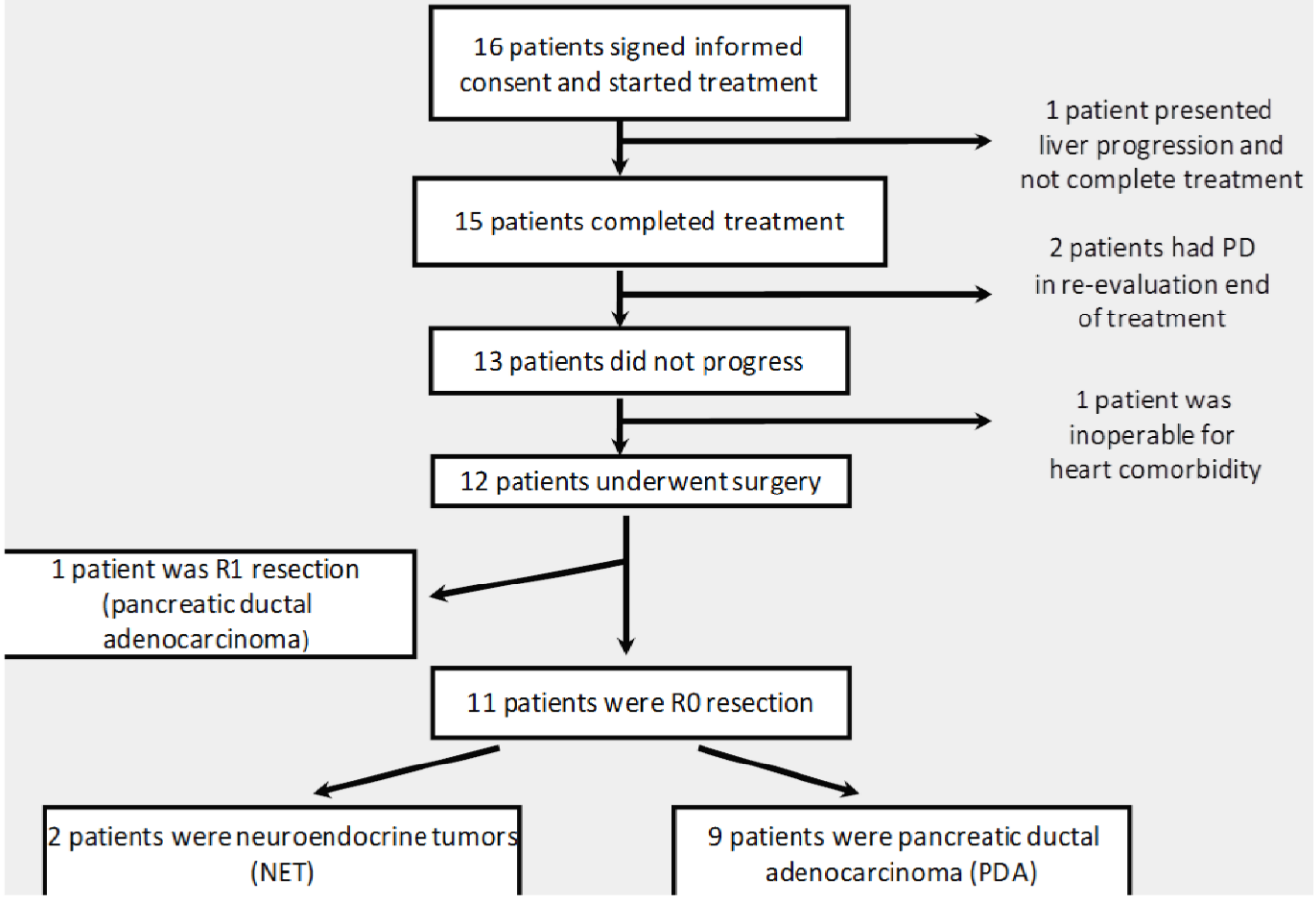
	FOLFIRINOX	nab-Paclitaxel/GEM
N. Pazienti	171	431
Età mediana (anni)	61 (25-76)	62 (27-86)
Sesso M/F (%)	62/38	57/43
PS (%)	ECOG 0/1 37/62	KPS 100-90/80, 70 58/42
Sede testa (%)	39	44
Stent biliare (%)	14,3	19
N. sedi metastatiche	Mediana 2	≥3 nel 45%
RR (%)	31,6	23
OS (mesi)	11,1(HR 0,57),48% a 1 anno	8,5(HR 0,72), 35% a 1 anno
PFS (mesi)	6,4(HR 0,47), 12% a 1 anno	5,5(HR 0,69), 16% a 1 anno
Neutropenia G3/4 (%)	45,7	38
Neutropenia febbrile (%)	5,4	3
Pastrinopenia G3/4 (%)	9,1	13
Diarrea G3/4 (%)	12,7	6
Neuropatia G3/4 (%)	9	17

Conroy et al, NEJM 2011; Von Hoff et al, ASCO GI 2013

nab-Paclitaxel and gemcitabine in resectable pancreatic cancer

Table 1: Baseline patients characteristics (n 16)		
Age (years)	Median	57.8
	Range	41-80
Sex	Men	10
	Women	6
ECOG	0	6
	1	10
Tumor localization	Head	14
	Body	1
	Tail	1
Vein affectation[1]	VMS	6
	Splenic vein	2
	Portal	1
Artery affectation[1]	AMS	3
	Hepatic	1
	Gastric	1
	Splenic	1

1-Affectation by ecoendoscopy or CT



Alvarez-Gallego et al, Abstract 4040, ASCO 2012

nab-Paclitaxel and gemcitabine in resectable pancreatic cancer

Results

	Table 2: Pre and post-treatment evaluation		
n= 16	PET SUV max (Median; range)	CA 19.9 (Mean; range)	Elastography (Ratio)
pre-treatment	7.2 (2.98-13.4)	2588 (1-36376)	36
post treatment	4.5 (1.9-9)	1056 (0.5- 15199)	18
p	0.005	0.001	0.002
	Partial metabolic response: 8 patients (50%)	50% patients have >70% decrease in tumor marker	Correlated with improvement in SUV max (p=0.494) and CA 19.9 (p=0.019)

Alvarez-Gallego et al, Abstract 4040, ASCO 2012

nab-Paclitaxel and gemcitabine in resectable pancreatic cancer

Results

Table 3: Clinical response of patients (n=16)	
Progressive disease	3
No surgery because heart comorbidity	1
Surgery	12
Neuroendocrine tumor	2
Adenocarcinoma	10
GRT0	1
GRT1	6
GRT2	1
GRT3	2

GRT-0: Complete Response. GRT-1: Important partial response (only single cells or cell groups); GRT-2: Partial response but large residual tumor; GRT-3: Low/ no response. Extensive residual cancer.

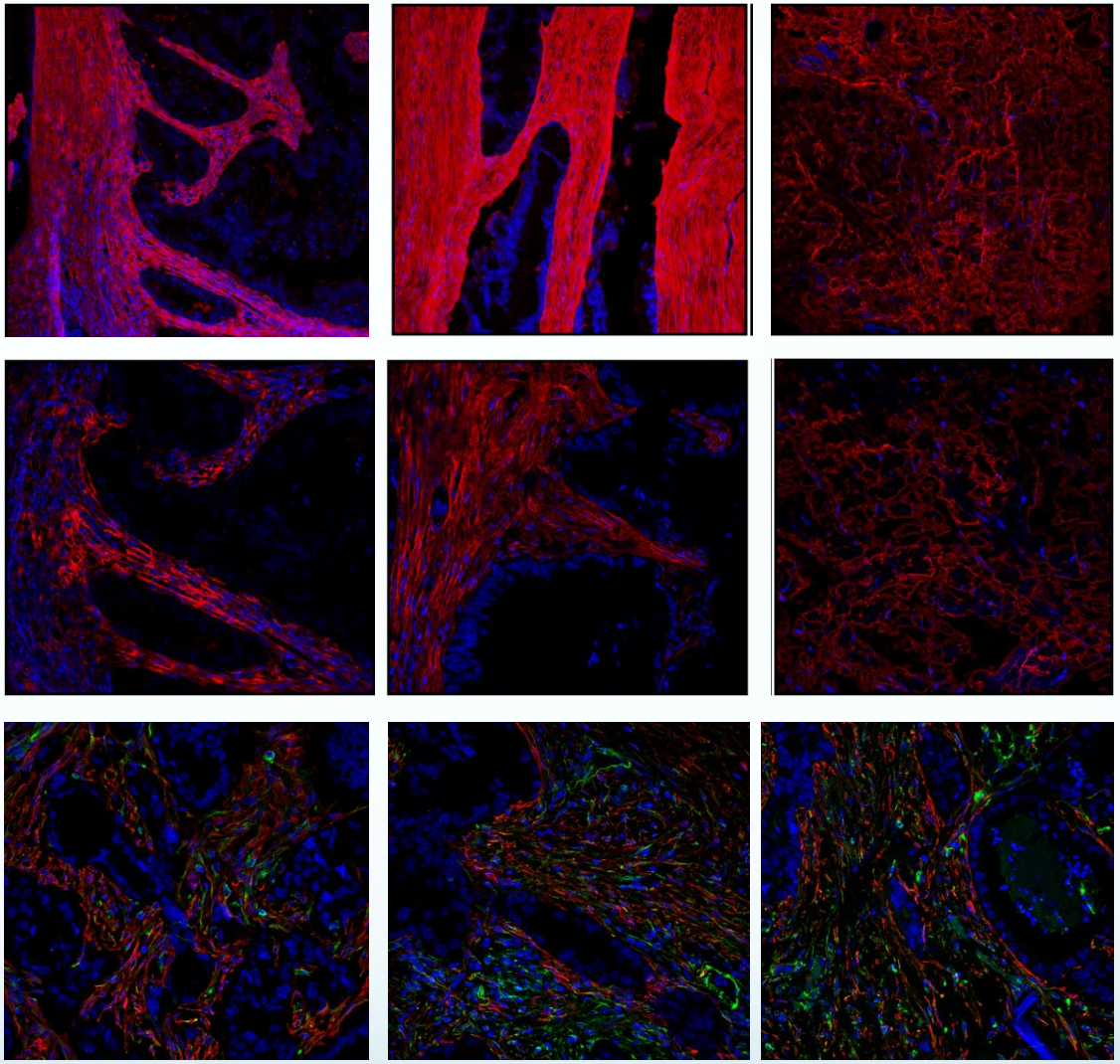
Alvarez-Gallego et al, Abstract 4040, ASCO 2012

Results

- So far 9 patients have been operated and in 8(89%) a complete resection (R0) was achieved.
- 1 patient had a complete pathological response and 4 patients had near complete responses with only a few(< 5%) residual tumor.
- In-depth analysis of stromal composition after treatment showed, compared to a series of 10 cases untreated and treated with conventional chemoradiation, decreased myofibroblast content, increase vessel density and distorted collagen fibers.

Alvarez-Gallego et al, Abstract 4040, ASCO 2012

nab-Paclitaxel and gemcitabine in resectable pancreatic cancer



Long and organized collagen fibers around tumor glands

Amorphous matrix in desmoplastic and tumor regression areas

SMA (red)/ Vimentin (green) / Double staining (yellow)

Untreated | Chemo + Radiotherapy | Nab-paclitaxel

Alvarez-Gallego et al, Abstract 4040, ASCO 2012

Le prospettive di trattamento nel carcinoma del pancreas avanzato