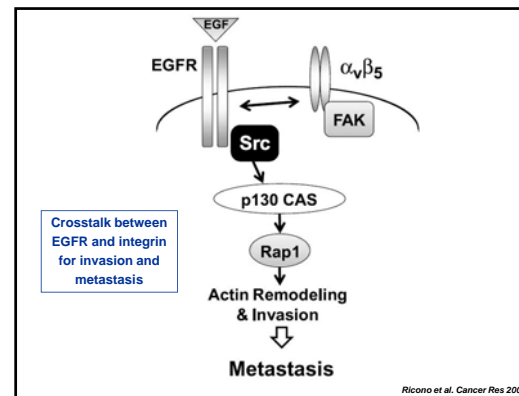
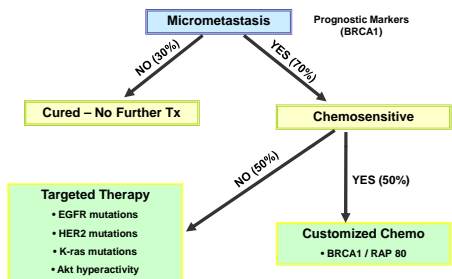


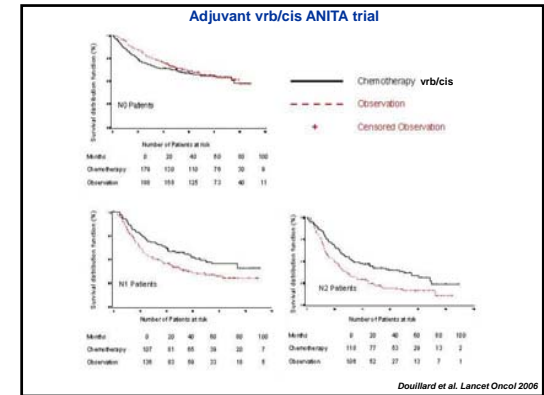
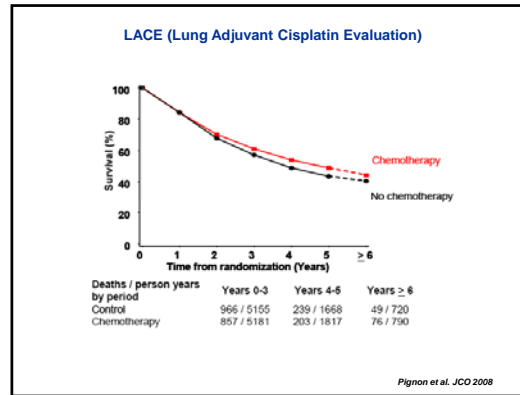
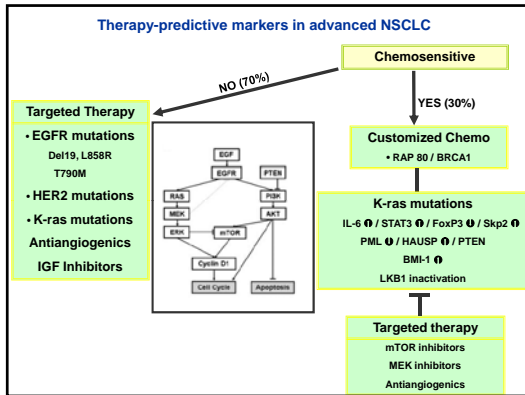
The Evolving Role of Adjuvant Therapies

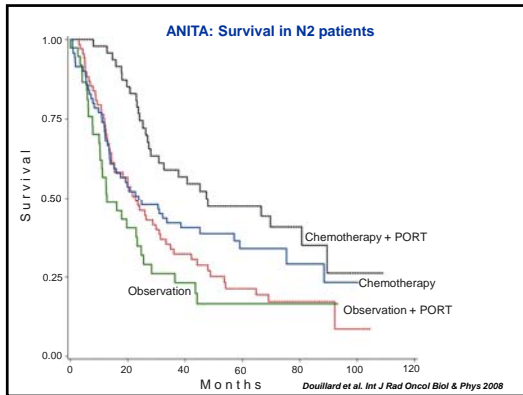
Rafael Rosell

10th European Perspectives in Lung Cancer
Brussels 6-7 March 2009

Therapy-predictive markers for adjuvant chemotherapy







How to predict relapse in stage I NSCLC

- Transcriptional profiling reveals sets of genes ("signatures") for which expression in primary tumors correlates with metastatic relapse and poor survival
- The function of the gene signatures as a whole is poorly understood
- A selection of 29 genes analyzed by TaqMan Low Density Arrays found a 3-gene model (including the CSF-1/EGFR invasive signature) that predicts survival with 70% accuracy (*Skrzypski et al. CCR 2008*)

TaqMan low-density array outcomes in early SCC of the lung

Survival univariate analysis

Analysis by quartiles

M-CSF	p=0.003
Fibronectin	p=0.009
CA IX	p=0.04
PH4	p=0.01
CXCR4	p=0.03
ANLN	p=0.04
PGK1	p=0.02
VEGFC	p=0.03
NTRK1	p=0.06
Ezrin	p=0.003

Analysis by median

M-CSF	p=0.002
Fibronectin	p=0.002
CA IX	p=0.009
PH4	p=0.01
KIAA0974	p=0.02
ANLN	p=0.02
Insulin R	p=0.03
VEGFC	p=0.03
NTRK1	p=0.04
EGFR	p=0.05

Predicting survival in SCC by low-density arrays
(29 genes examined)

	Hazard Ratio	95% CI	p
Tumor size			
≤4	1 (ref.)		
>4	2.7	1.1-6.6	0.02
CSF1			
≤0.90	1 (ref.)		
>0.90	3.5	1.5-8.5	0.005
EGFR			
≤0.76	1 (ref.)		
>0.76	2.7	1.2-6.4	0.02
CA IX			
≤0.56	1 (ref.)		
>0.56	0.2	0.07-0.43	<0.0001

Skrzypski et al. CCR 2008

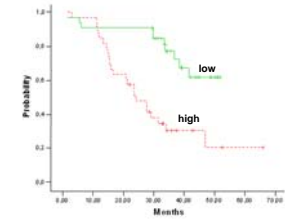
3-gene model by TaqMan low density arrays

	β	HR	95% C.I.	p
CSF-1 (>0.9)	0.93	2.5	1.2-5.3	0.01
CA IX (≤0.56)	1.4	4.1	1.8-9.1	0.001
EGFR (>0.76)	1.1	3.1	1.4-6.9	0.006

$$\text{Risk score} = (0.93 \times \text{CSF-1}) + (1.4 \times \text{CA IX}) + (1.1 \times \text{EGFR})$$

Skrzypski et al. CCR 2008

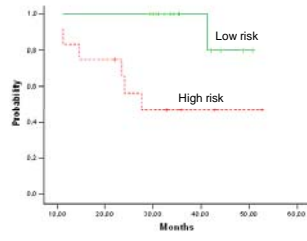
Survival according to 3-gene model in resected SCC of the lung



	N	Median	95% C.I.	p
Low	33	NR		<0.00001
High	33	24	17.1-30.9	

Skrzypski et al. CCR 2008

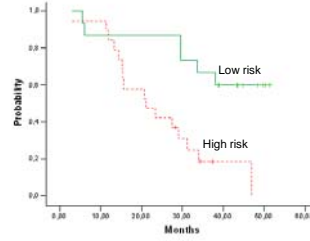
Survival according to 3-gene model in resected SCC of the lung, tumor size < 4 cm.



	N	Median	95% C.I.	p
Low	15	NR	-	0.006
High	12	27.5	-	

Skrzypski et al. CCR 2008

Survival according to 3-gene model in resected SCC of the lung, tumor size > 4 cm.

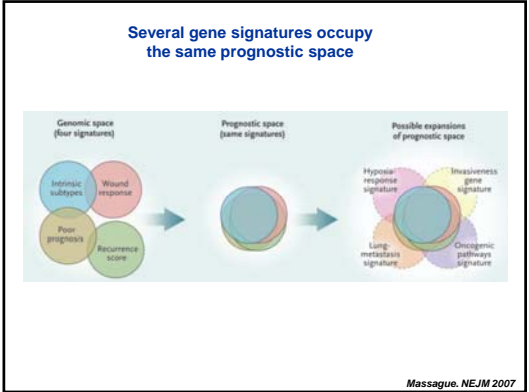
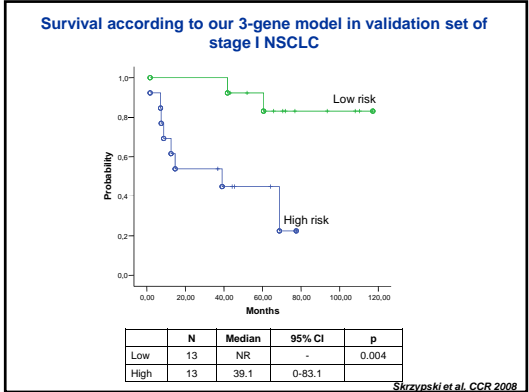


	N	Median	95% C.I.	p
Low	15	NR	-	0.002
High	19	21.1	10-32.1	

Skrzypski et al. CCR 2008

Characteristics	Gdansk, Poland Training Cohort (N=66)	San Francisco, USA Validation Cohort (N=26)
Age - yr		
Median (range)	63 (37-76)	67 (45-65)
Mean	62	66
Sex - N (%)		
Male	52 (78.8)	17 (65.4)
Female	14 (21.2)	9 (34.6)
Race - N (%)		
Caucasian	66 (100)	21 (80.8)
African-American	-	3 (11.5)
Other	-	2 (7.8)
Stage - N (%)		
IA	10 (15.2)	10 (38.5)
IB	32 (48.5)	12 (46.2)
IIA	-	1 (3.8)
IIB	22 (33.3)	3 (11.5)
IIIA	2 (3)	-
Tumor diameter - cm	5.9 (1-9.5)	2.5 (1.5-8)
Predictive accuracy of 3-gene signature	70 %	70 %

Skrzypski et al. CCR 2008



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BRCA1: A Novel Prognostic Factor in Resected Non-Small-Cell Lung Cancer

Rafael Rosell^{1,2}, Marcin Skrzypski^{1,3}, Eva Isasena⁴, Miguel Tamez⁵, Roberta Santoro¹, Jose Javier Sanchez⁶, Pedro Mendez⁷, Inmaculada Chab¹, Iñaki Perez-Roca¹, Amelia Szymonowicz¹, Witold Rzyman¹, Francesco Puma¹, Grazyna Kobierska-Gulida¹, Raffaele Farabi¹, Jacak Jassim⁸

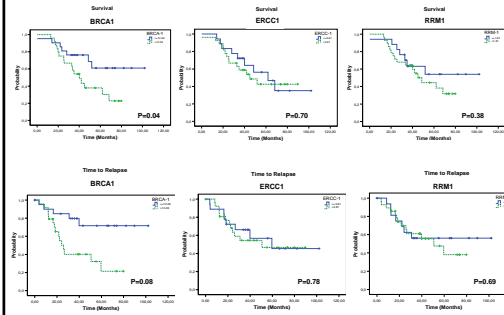
¹Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain, ²Medical University of Gdansk, Gdansk, Poland, ³Azpeta Opedakera Santa Maria, Terni, Italy, ⁴Autonomous University of Madrid, Madrid, Spain

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Multivariate Cox model for survival

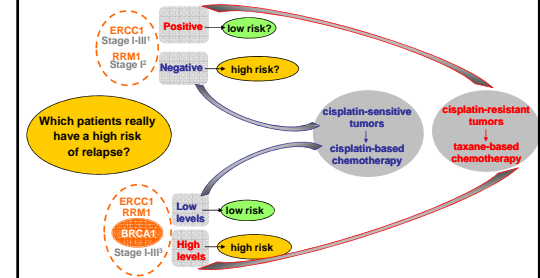
		HR	95% CI	p
Original 126 patients	BRCA1			
	≤5	1		
	>5	1.98	1.11-6	0.02
	Stage			
	IA	1		
	IB	2.41	0.71-8.20	0.16
	IIB	2.21	0.62-7.88	0.22
	IIIA	7.91	2.27-27.54	0.001
Validation cohort of 53 patients	BRCA1			
	<12.01	1		
	>12.01	2.4	1.01-5.92	0.04

Outcome according to BRCA1, ERCC1 & RRM1
(validation cohort)

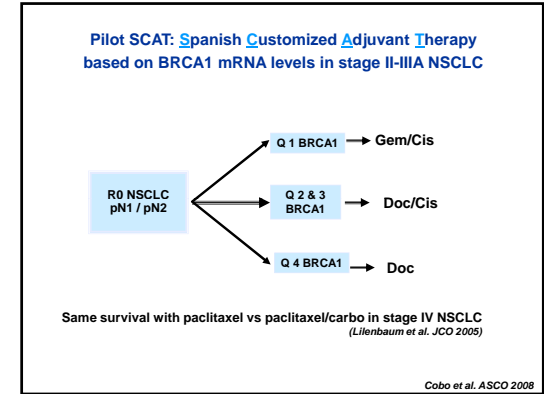
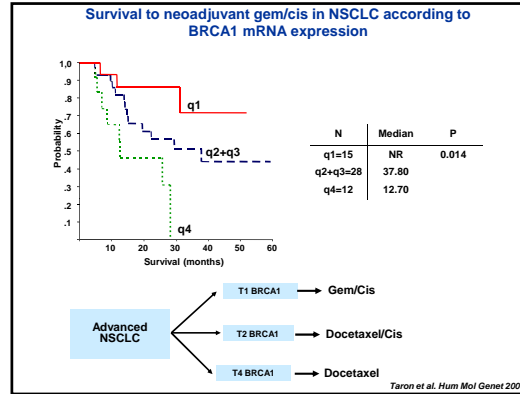
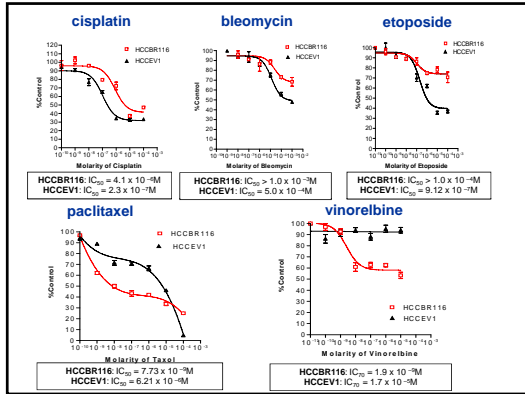


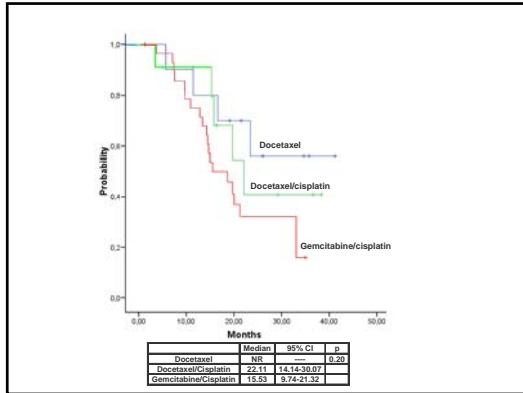
Rosell et al. PLoS ONE 2007

Customizing chemotherapy
Cisplatin-based chemotherapy could be a mistake

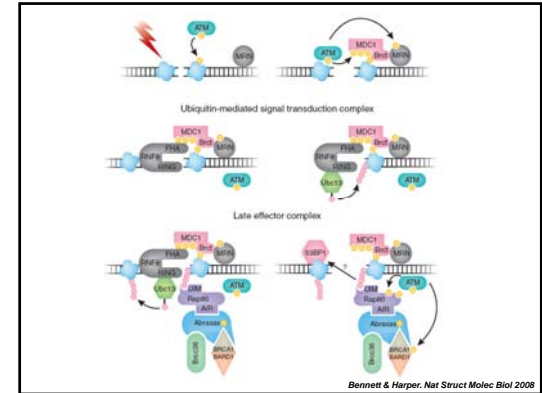


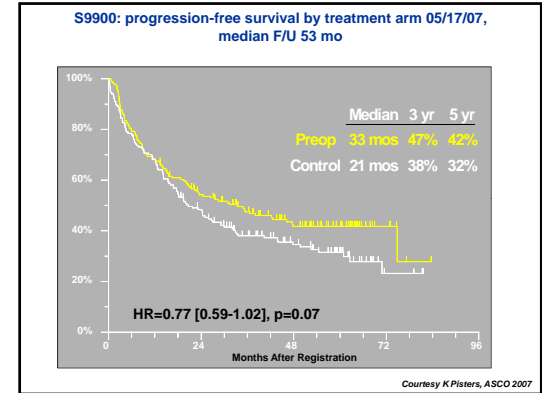
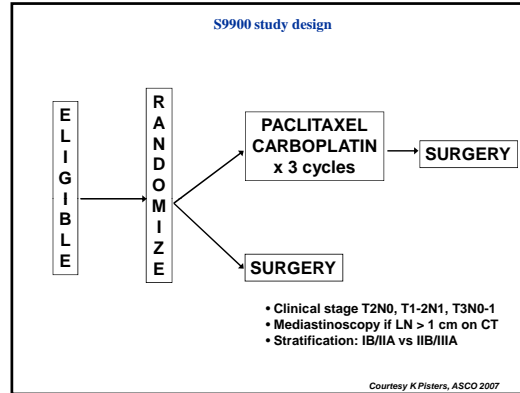
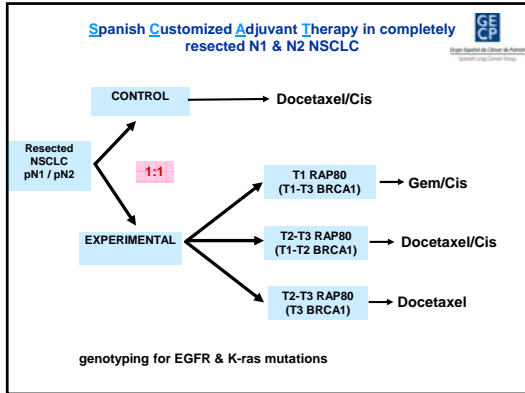
¹Olaussen et al; ²Zheng et al; ³Rosell et al. PLoS ONE 2007

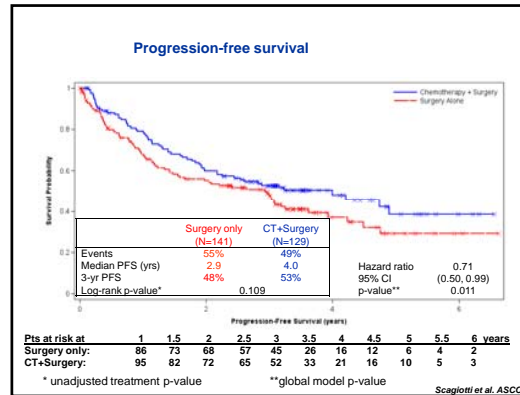
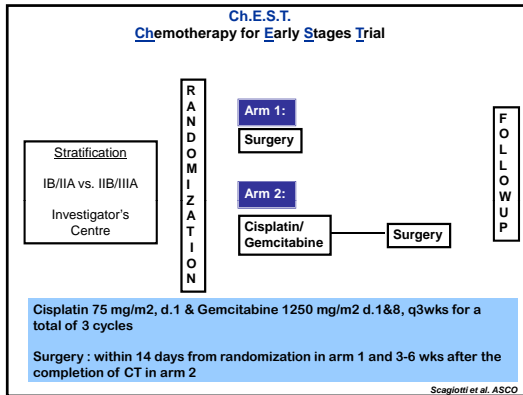




mRNA expression levels	RAP80 T1	RAP80 T2	RAP80 T3	P
Median (min-max)	0.56 (0.11-0.91)	1.26 (0.92-1.51)	2.27 (1.62-5.37)	
BRCA1 T1	8 (40)	7 (35)	5 (25)	0.73
BRCA1 T2	4 (44.4)	3 (33.3)	2 (22.2)	
BRCA1 T3	1 (16.7)	2 (33.3)	3 (50)	







- Conclusions**
- Customized chemotherapy based on RAP 80 / BRCA1 can improve PFS and overall survival both in the adjuvant and neoadjuvant settings
 - Genotyping for EGFR mutations in early resected NSCLC could be useful to customize erlotinib or other EGFR TKIs
 - Genotyping for K-ras mutations is recommended
 - Further research required to identify high-risk stage I patients for appropriate neoadjuvant or adjuvant chemotherapy
