

# **Pharmacogenomic Approaches**

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# Pharmacogenetics & Pharmacogenomics

“Medicine tailored to the individual”

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- Genetic information, including the sequence of the human genome, is allowing for a more systematic understanding of the relationship of genetic variations to drug efficacy.
- The Study of how genetic differences influence variability in patients' responses to drugs.
- Personalized drugs.



# Pharmacogenetics & Pharmacogenomics

“Medicine tailored to the individual”

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- So, we need to know

- target
- PK determinants

**Biomarkers of Genetic variability**

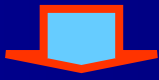
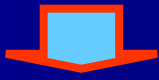
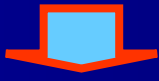
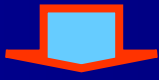


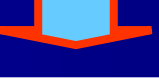


- Where to look

- tumor
- individual (blood !)

- What to analyze

- DNA, RNA, Proteins, biochemical activity
- Single or complex biomarkers

# Predictive Tumor Markers for NSCLC Treatment

Gene	Abnormality	Drug	Response
p53	Mutation	Multiple	
K-ras	Mutation	Platinum	
$\beta$ tubulin	Increased Isotype 3	Taxanes	
RRM1	Increased Expression	Gemcitabine	
ERCC 1	Increased Expression	Platinum	
BRCA1	Increased Expression	Platinum	
TS	Increased Expression	Antifolates	
ALK fusion genes	Present	ALK inh	
EGFR mutation	Present	EGFR TKIs	

# Some Examples

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- Chemotherapy
  - DNA repair genes (ERCC1, RRM1, BRCA1)
  - Folate Path (TS, MTAP,...)
- Targeted therapy
  - EGFR
  - ALK

# Some Examples

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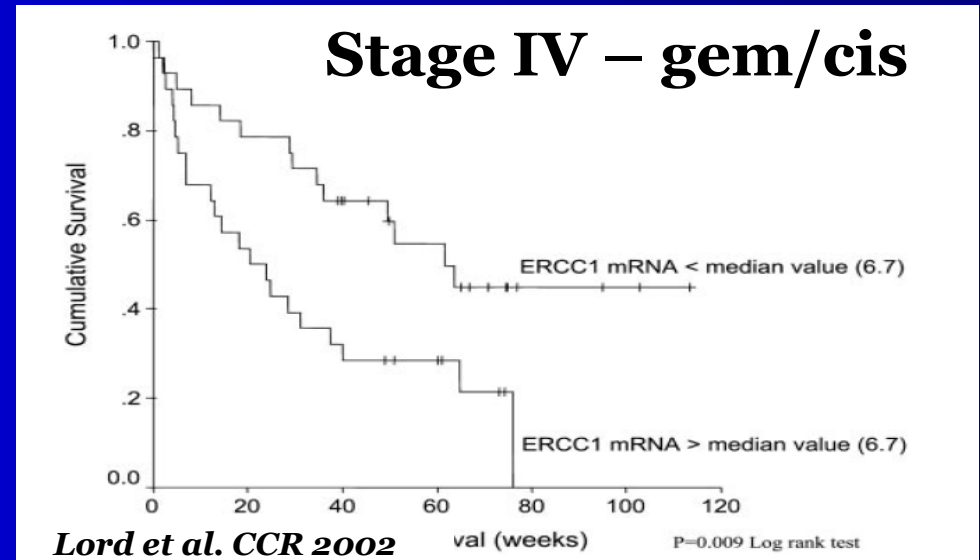
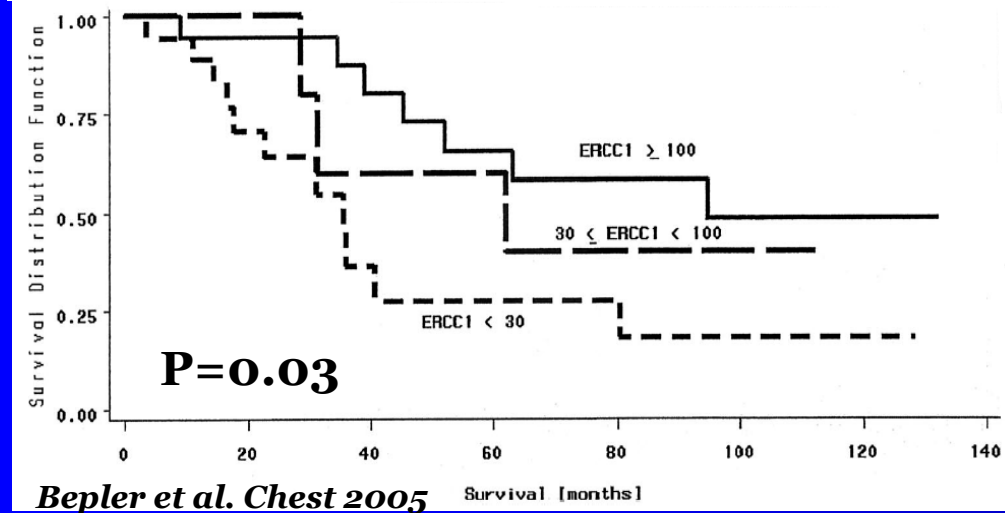
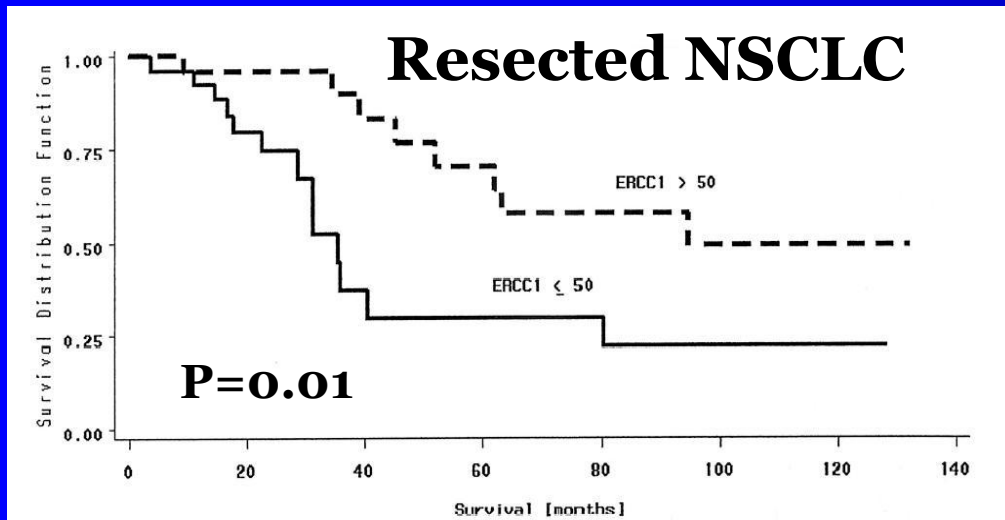
- **Chemotherapy**
  - **DNA repair genes (ERCC1, RRM1, BRCA1)**
  - Folate Path (TS, MTAP,...)
- Targeted therapy
  - EGFR
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## ERCC1 in Platinum-based Treatments

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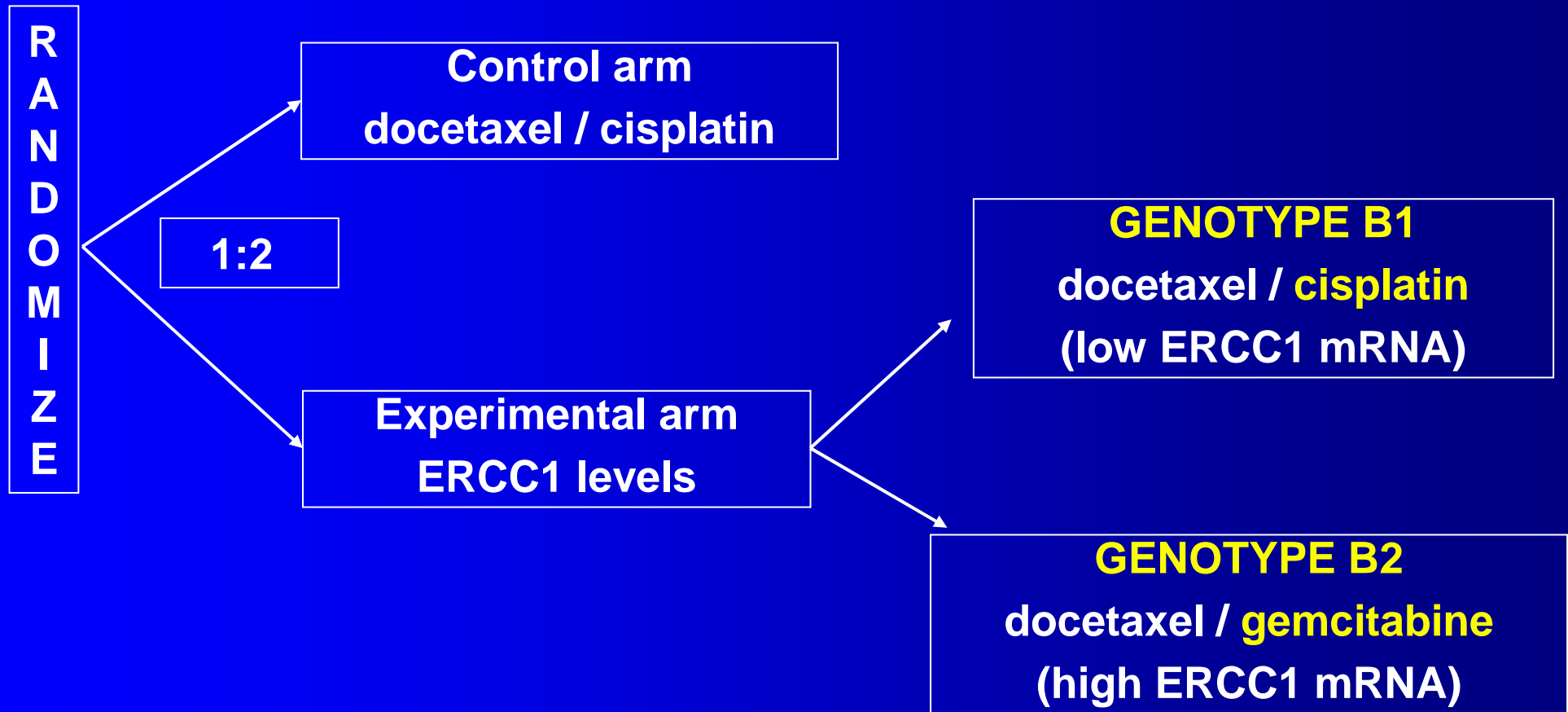
- ERCC1 is part of the DNA repair system NER
- Increased ERCC1 levels: better DNA repair (better prognosis!!)
- Low ERCC1 levels: Poor DNA repair efficiency (platinum treatments more efficacious)

# ERCC1 in NSCLC



- Prognosis and predicting survival according to ERCC1 levels (terciles)
  - Low levels → gem/cis
  - Etoposide – a better partner than gemcitabine

# GILT Trial: ERCC1-customized chemotherapy in advanced NSCLC



# GILT Trial: ERCC1-customized chemotherapy in advanced NSCLC

Table 2. Outcome According to Treatment Arm

Outcome	Control (n = 141)			Genotypic Group (n = 225)			Low Genotypic Group (n = 129)			High Genotypic Group (n = 96)		
	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
<b>Response</b>												
Complete response		4.3		3.1			2.3			4.2		
Partial response		33.3		44.4			48.1			39.6		
Stable disease		40.4		28			28.7			27.1		
Progressive disease		17.7		18.2			15.5			21.9		
Could not be determined		4.3		6.3			5.4			7.3		
<b>Overall response rate</b>		<b>39.3*†</b>		<b>51.2*</b>			<b>53.2†</b>			<b>47.2</b>		
Intent to treat		37.6		47.5			50.4			43.8		
<b>Survival</b>												
<b>Median, months</b>	<b>9.82</b>	<b>8.90 to 10.74</b>	<b>9.8</b>	<b>8.7 to 10.9</b>	<b>10.35</b>	<b>7.86 to 12.83</b>	<b>9.49</b>					<b>8.17 to 10.80</b>
1 year	39	31 to 48	40.8	32.4 to 49.2	44	35 to 53	33			13		13 to 43
2 years	19	4 to 26	20	12.6 to 27.4	16	8 to 23	12			4		4 to 19
3 years	9	2 to 16	8.9	2.3 to 15.5	10	3 to 17						
										Last death at 27 months; longest alive at 33 months		
Median PFS, months	5.19	4.42 to 5.96	6.1	4.9 to 7.2	6.74	5.68 to 7.81	4.76					3.42 to 6.10

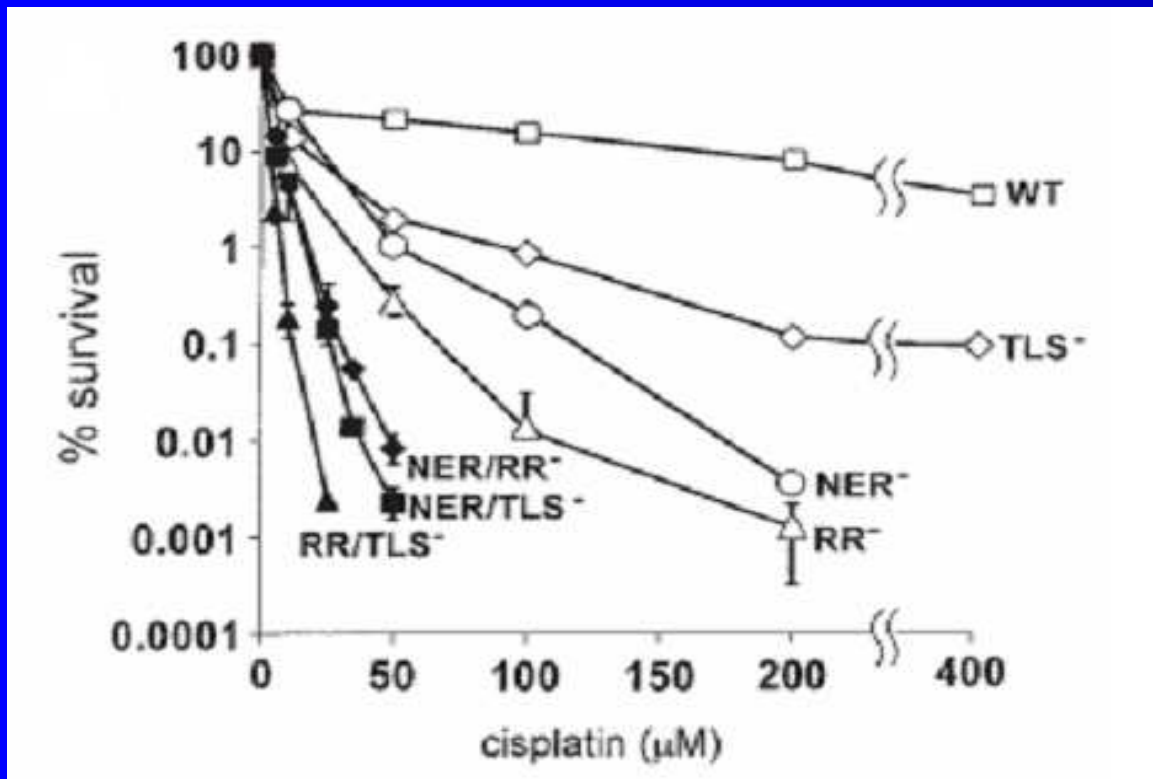
Abbreviation: PFS, progression-free survival.

\*Control v genotypic ( $P = .02$ ).

†Control v low genotypic ( $P = .03$ ).

# BRCA1: a determinant of cisplatin response

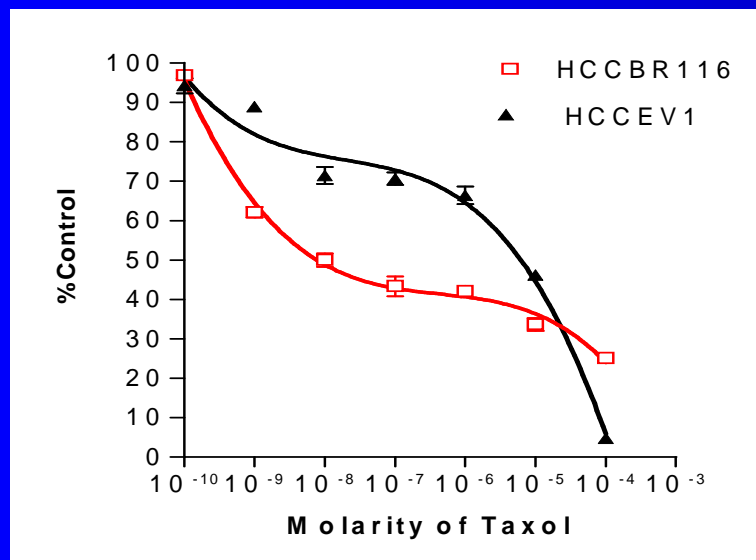
- Increased BRCA1 in MCF-7 & SKOV-3 cisplatin-resistant cell lines  
(Husain et al. Cancer Res 1998)



- Predictive power of ERCC1 ~ XPD < RRM1 < BRCA1 in gem/cis (Rosell et al. Oncogene 2003, CCR 2004, CCR 2004; Taron et al. Hum Molec Gen 2004)

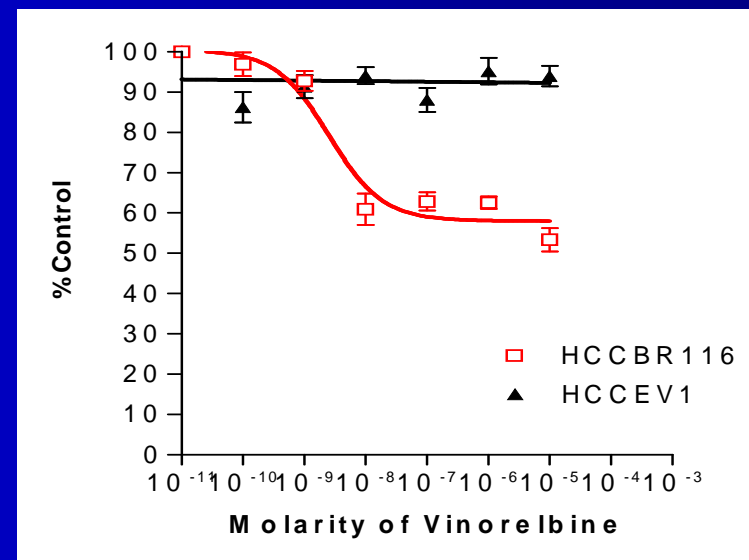
# Restoring BRCA1 confers paclitaxel & vinorelbine sensitivity in BRCA1 mutant HCC1937 cell line

## paclitaxel



**HCCBR116:**  $IC_{50} = 7.73 \times 10^{-9}M$   
**HCCEV1:**  $IC_{50} = 6.21 \times 10^{-6}M$

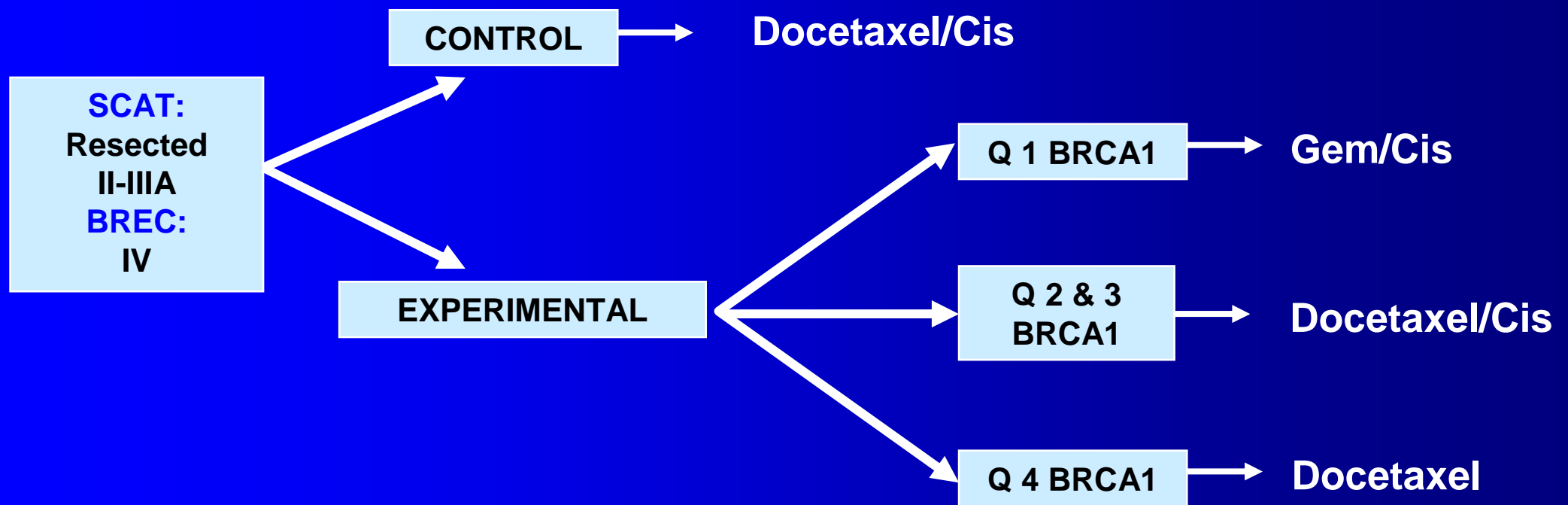
## vinorelbine



**HCCBR116:**  $IC_{70} = 1.9 \times 10^{-9}M$   
**HCCEV1:**  $IC_{70} = 1.7 \times 10^{-5}M$

# Spanish Customized Adjuvant Therapy (SCAT) and BRC A1 Expression Customization (BREC)

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## Customized Treatment in NSCLC Based on EGFR Mutation and BRCA1 mRNA Expression

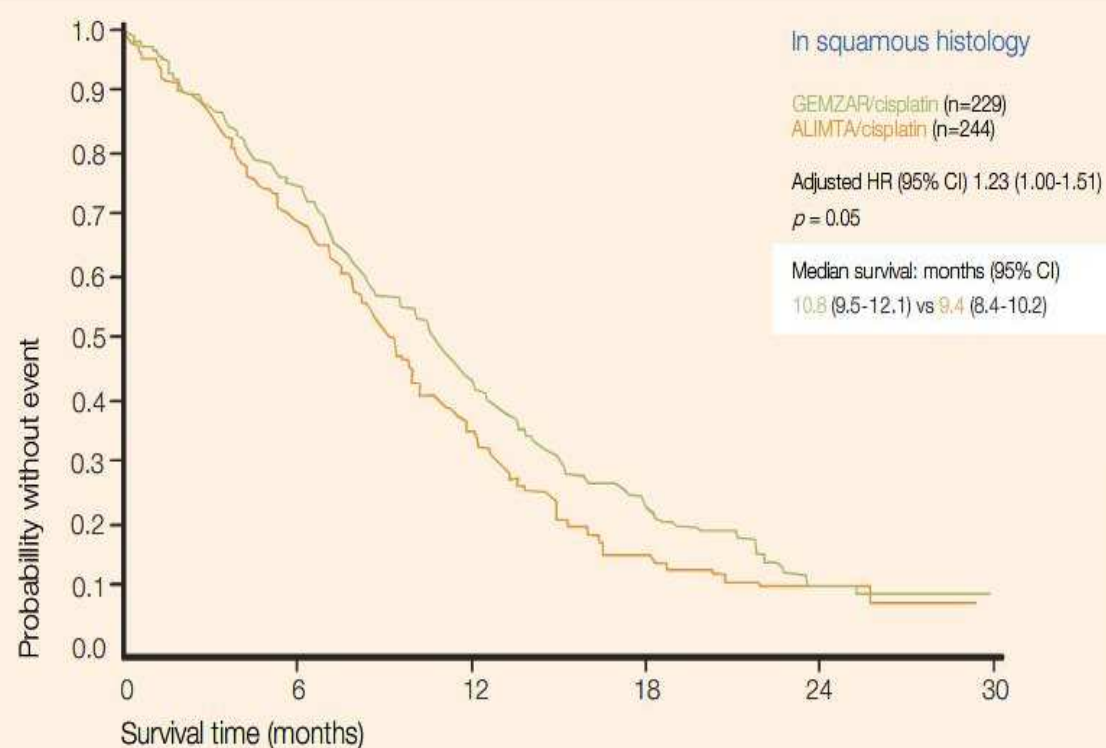
	All Patients (n=123)	EGFR Group (n=12)	Low BRCA1 Group (n=38)	Intermediate BRCA1 Group (n=40)	High BRCA1 Group (n=33)
<b>Outcome</b>	%	%	%	%	%
Complete response	3.3	16.7	0	2.5	3
Partial response	34.1	58.3	21.1	37.5	36.4
Stable disease	30.1	8.3	47.4	17.5	33.3
Progressive disease	20.3	0	15.8	30	21.2
Not be determined	12.2	16.7	15.8	12.5	6.1
<b>Overall response rate</b>	43.6	90	25	45.7	41.9
<b>Intent to treat</b>	37.4	75	21.1	40	39.4
<b>Survival</b>					
Median, mo	12 mo	NR (>28 mo)	11 mo	9 mo	11 mo
1-year	49.2	91.7	47.8	41.1	42.4
2-year	31.5	73.3	41.2	15.6	0
28 months	24.5	73.3	35.3	0	0

# Cis/Pem vs Cis/Gem in First-line NSCLC

## Overall survival: non-squamous histology

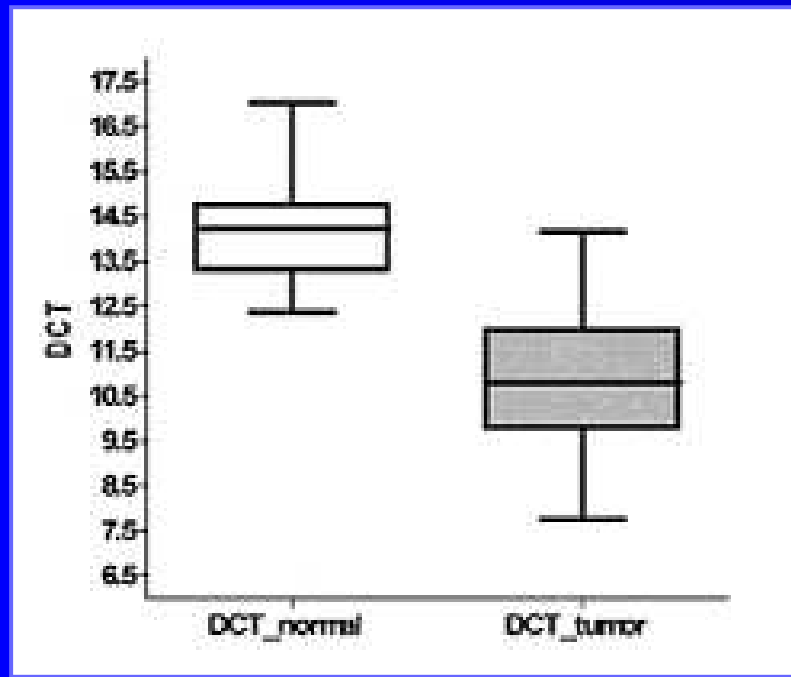


## Overall survival: squamous histology



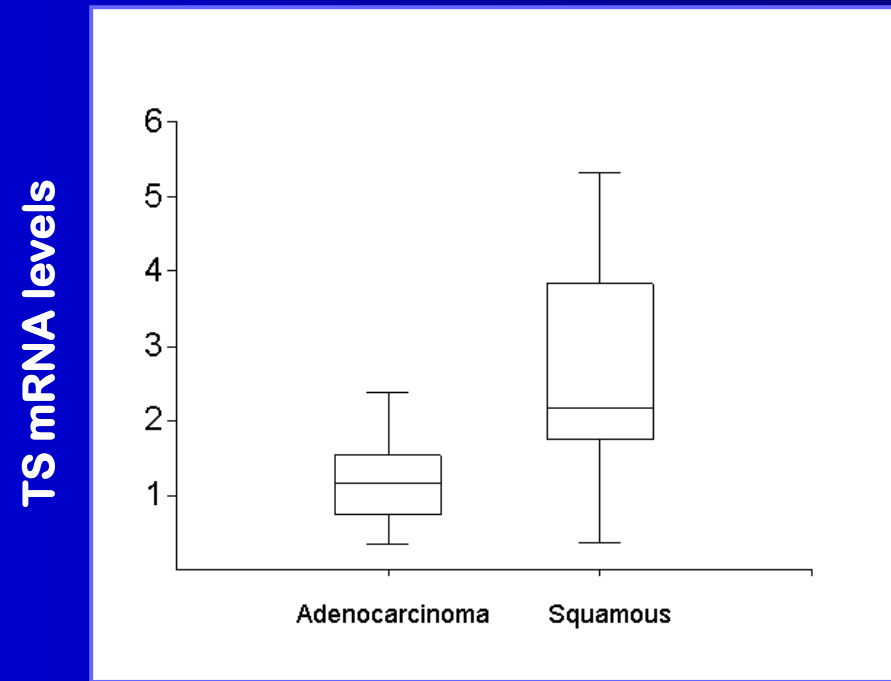
# Thymidilate Synthase Expression in Normal Lung Tissue & Lung Cancer (N=56)

Snap Frozen Tissues



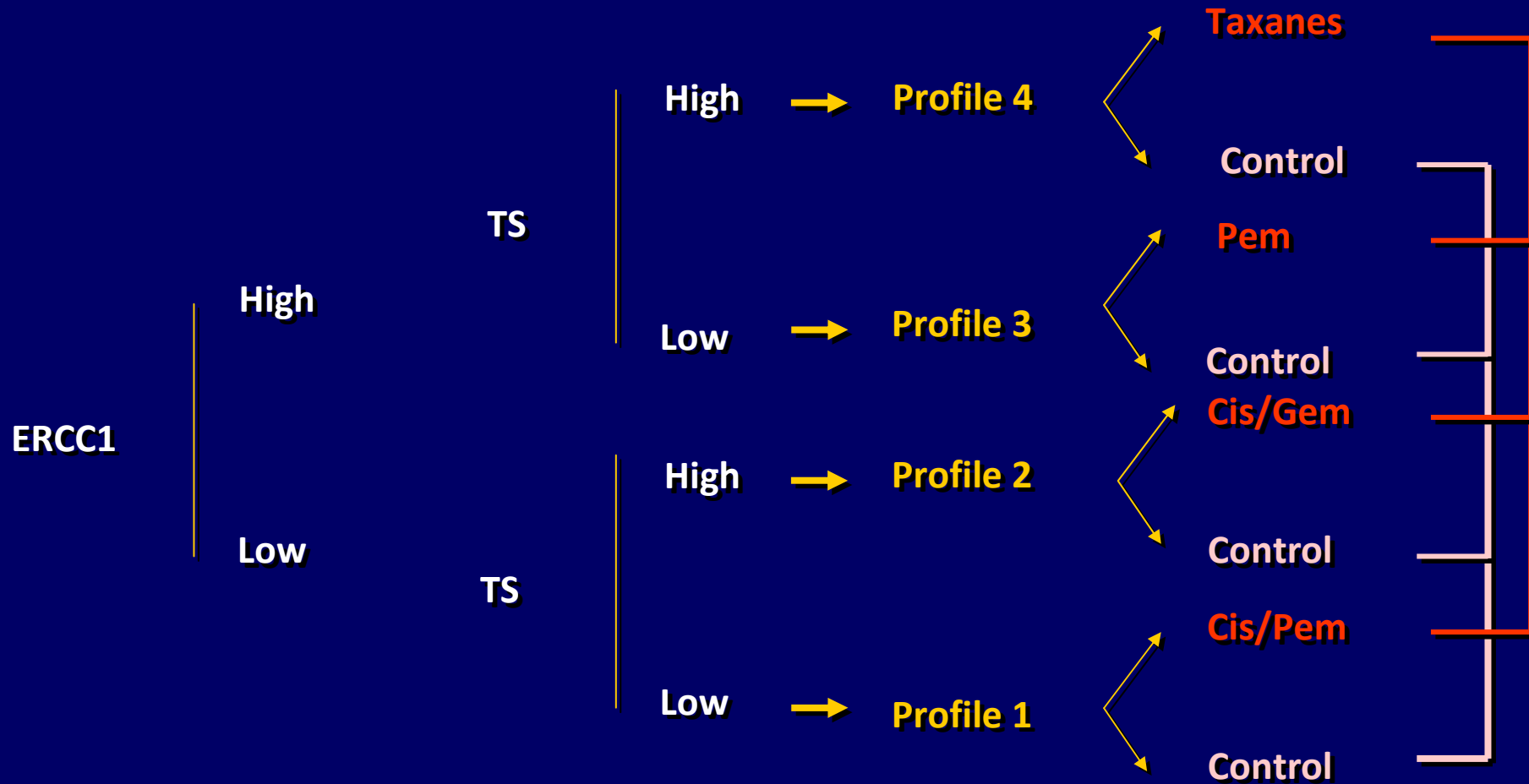
Significantly Higher in Lung Cancer than in normal lung tissue

FFPE Tissues



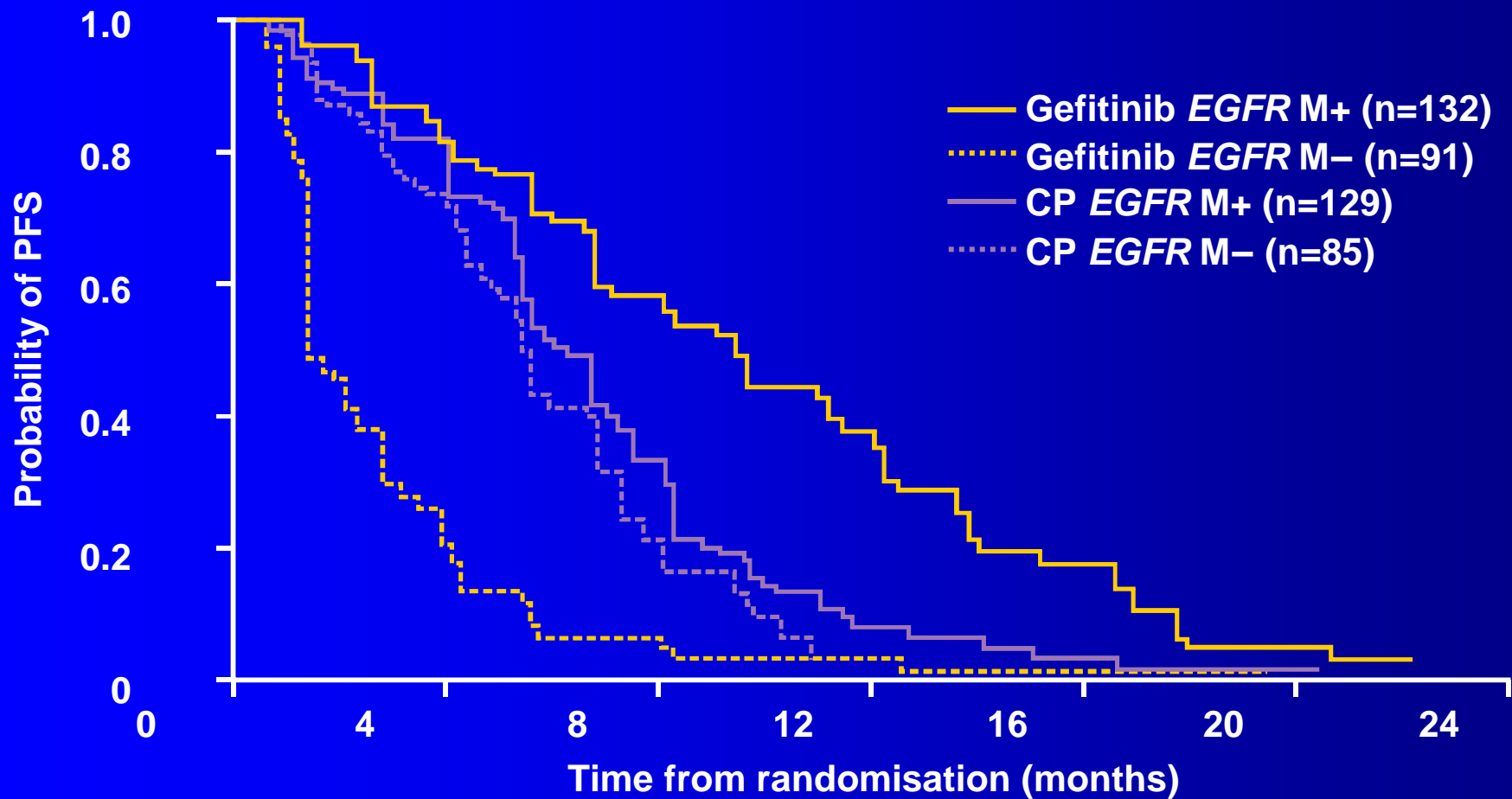
Significantly Higher in Squamous Cell Carcinoma of the Lung

# ITACA Adjuvant Trial



Control = Investigators' choice; Primary end-point = overall survival; Sample size = 700 patients

# Prognostic and predictive value confirmed in IPASS

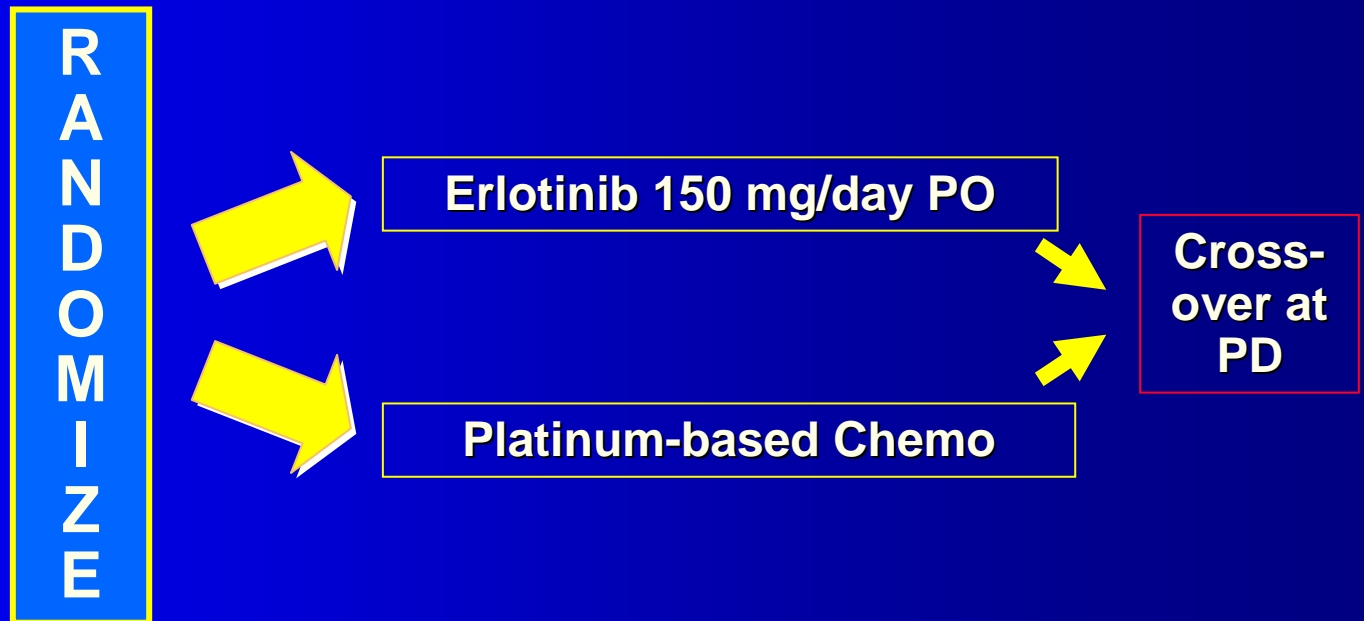


# SLCG Phase III Trial in EGFR-mutated NSCLC EURTAC/GECP 06/01

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## Eligibility:

- No prior Rx
- Stage IIIB or IV
- Mutated EGFR
- ECOG PS 0-2



**PIs: L Paz-Ares & R Rosell**