



Educational session - Developments in early NSCLC

When to use chemotherapy

*Benjamin Besse,
MD, PhD*

VIENNA
2012

ESMO congress

Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

→ Disclosures

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
 - Abbott, Amgen, AstraZeneca, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis

→ Systemic chemotherapy

Metastatic

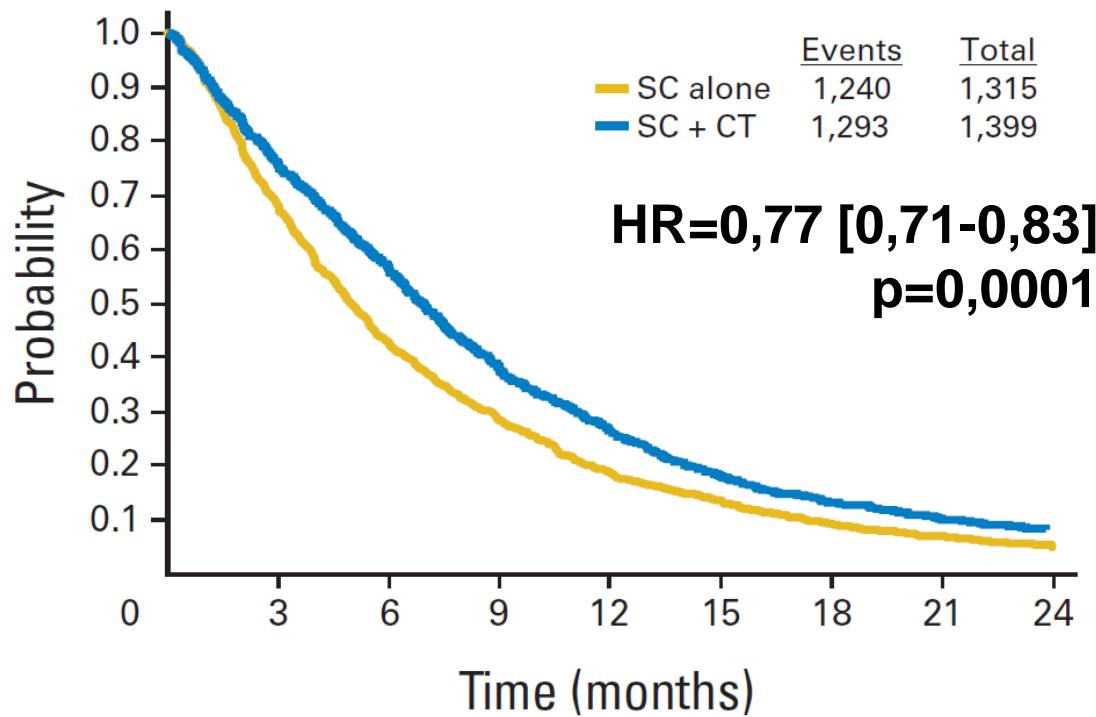
Survive more

Adjuvant

Cure more

→ CT vs BSC: meta-analysis IGR/MRC

- 2714 patients, 16 trials (9 with platin).
1 yr absolute benefit : 9% (20% to 29%).



Patients at risk

SC alone

1,315 884 552 363 231 161 107 77 55

SC + CT

1,399 1,052 779 519 349 233 165 115 91

→ Systemic chemotherapy

Survive more

Chemo

Metastatic 1st line - platin
 HR=0.77
 p=0.0001

Adjuvant

?

Cure more

HR: Hazard ratio for overall survival

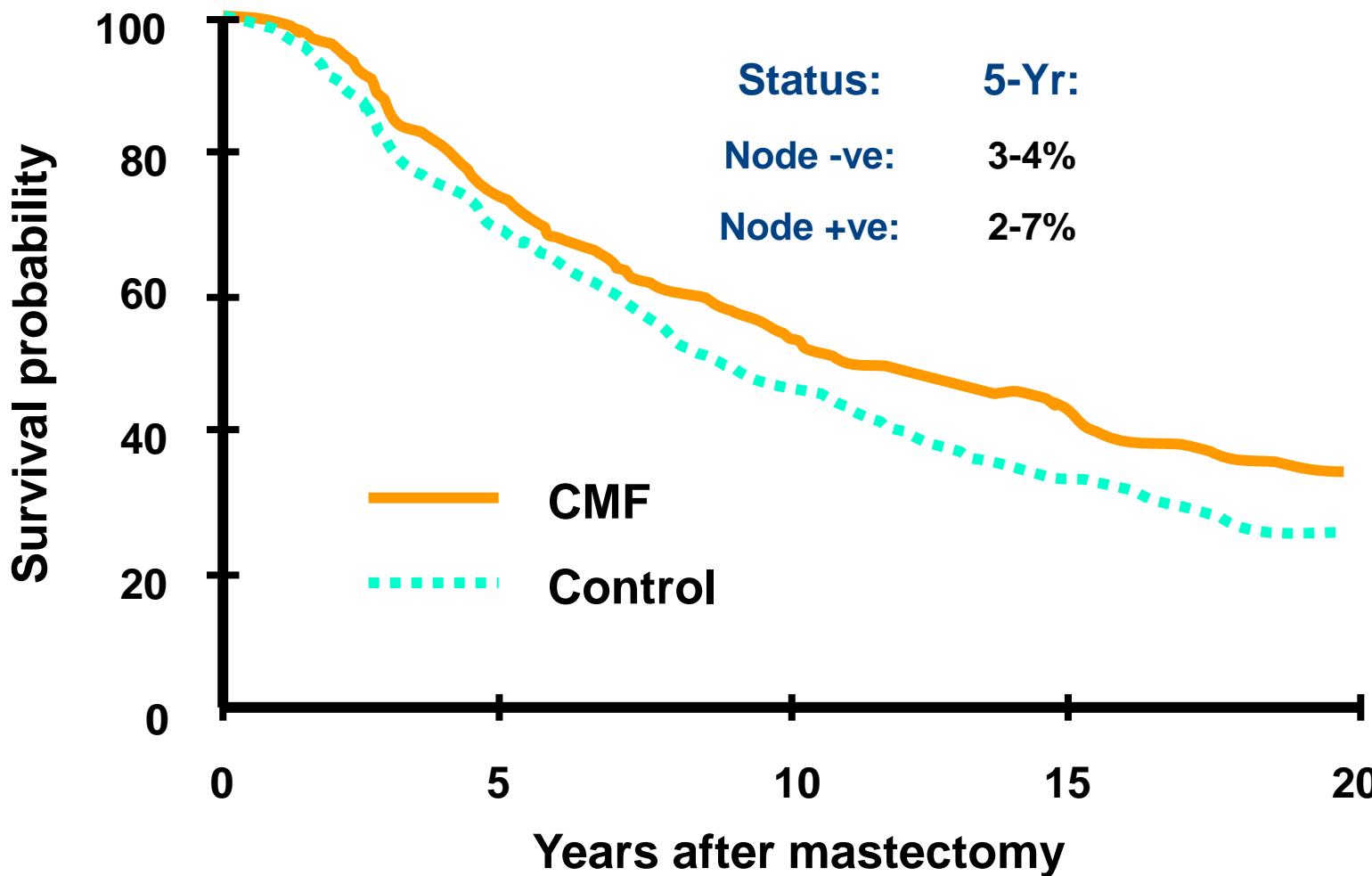
→ META-ANALYSIS ON THE ROLE OF CHEMOTHERAPY IN NSCLC IGR - MRC (BMJ 1995)

Absolute benefit with cisplatin containing regimens

14 trials available
4,357 patients

	$S \pm CT$	$S + RT \pm CT$
2 years	3%	2%
5 years	5%	2%

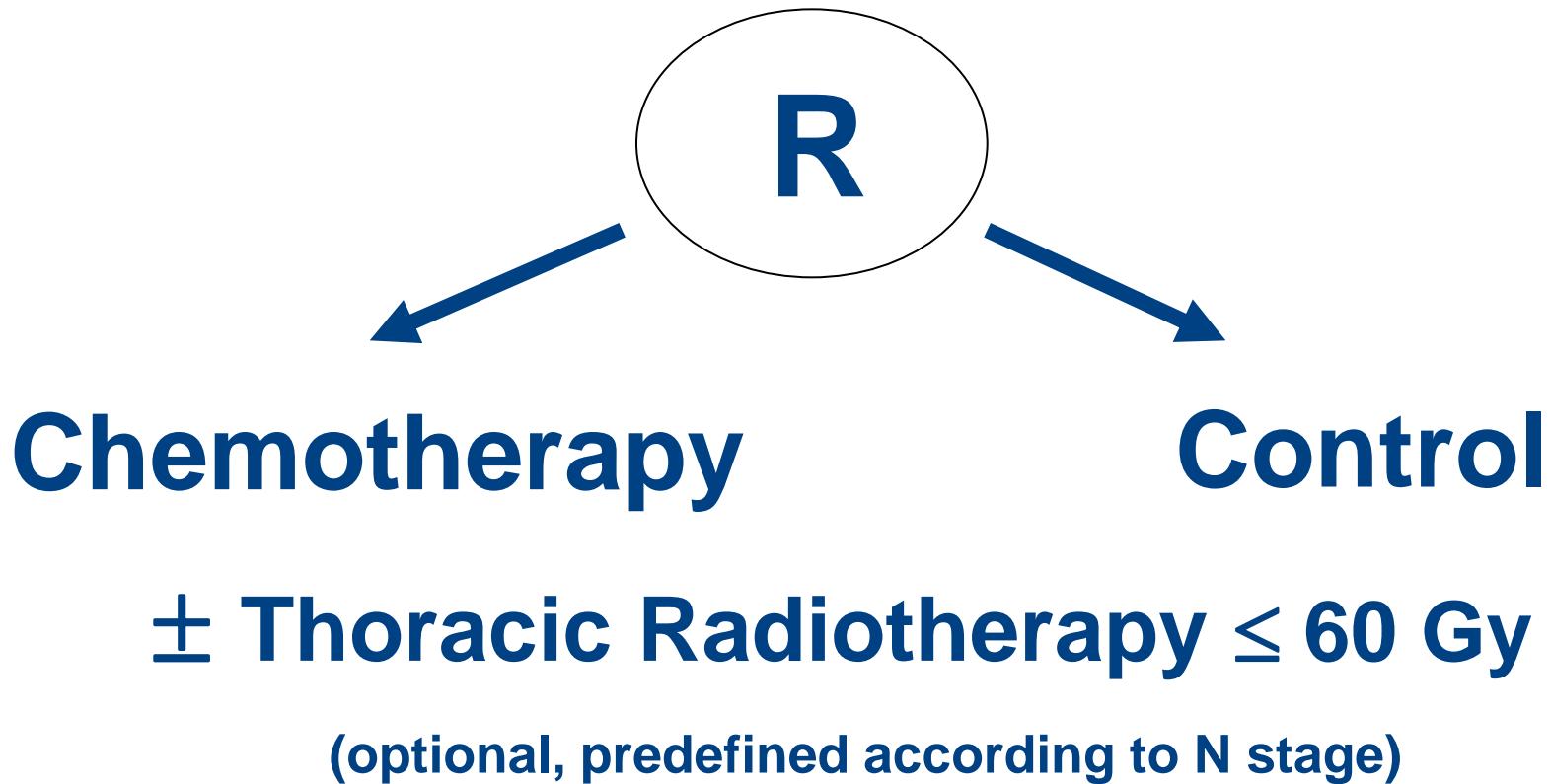
→ CMF ADJUVANT - Breast Cancer



→ IALT Design

RESECTED NSCLC

Stratified by center, stage and type of surgery



→ IALT - Chemotherapy

Cisplatin

	80 mg/m²	q 3 weeks x 4
or	100 mg/m²	q 4 weeks x 3 or 4
or	120 mg/m²	q 4 weeks x 3

+

Etoposide

100 mg/m²	x 3 days
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or **Vinorelbine**

30 mg/m²	weekly
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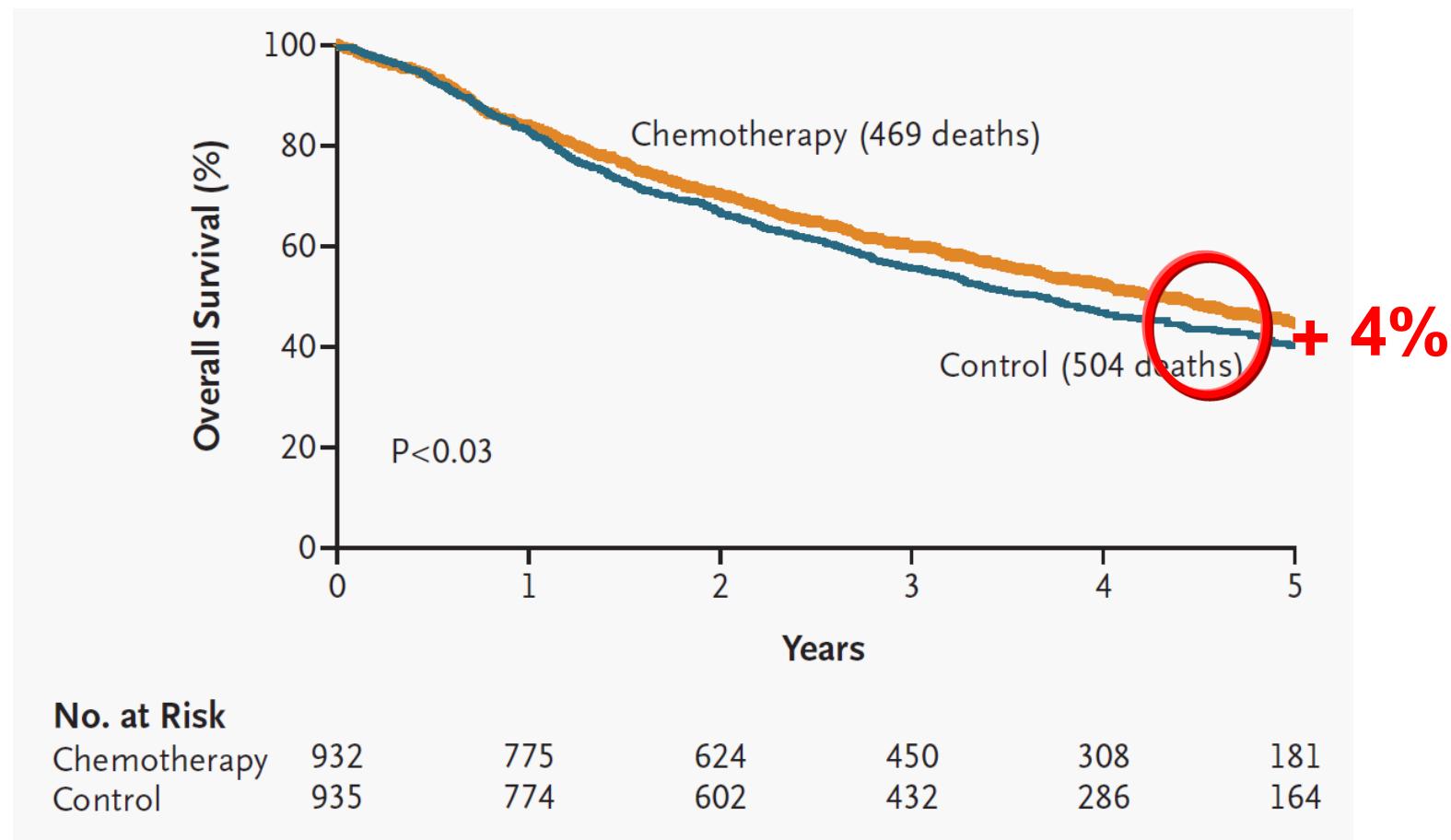
or **Vinblastine**

4 mg/m²	weekly
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or **Vindesine**

3 mg/m²	weekly
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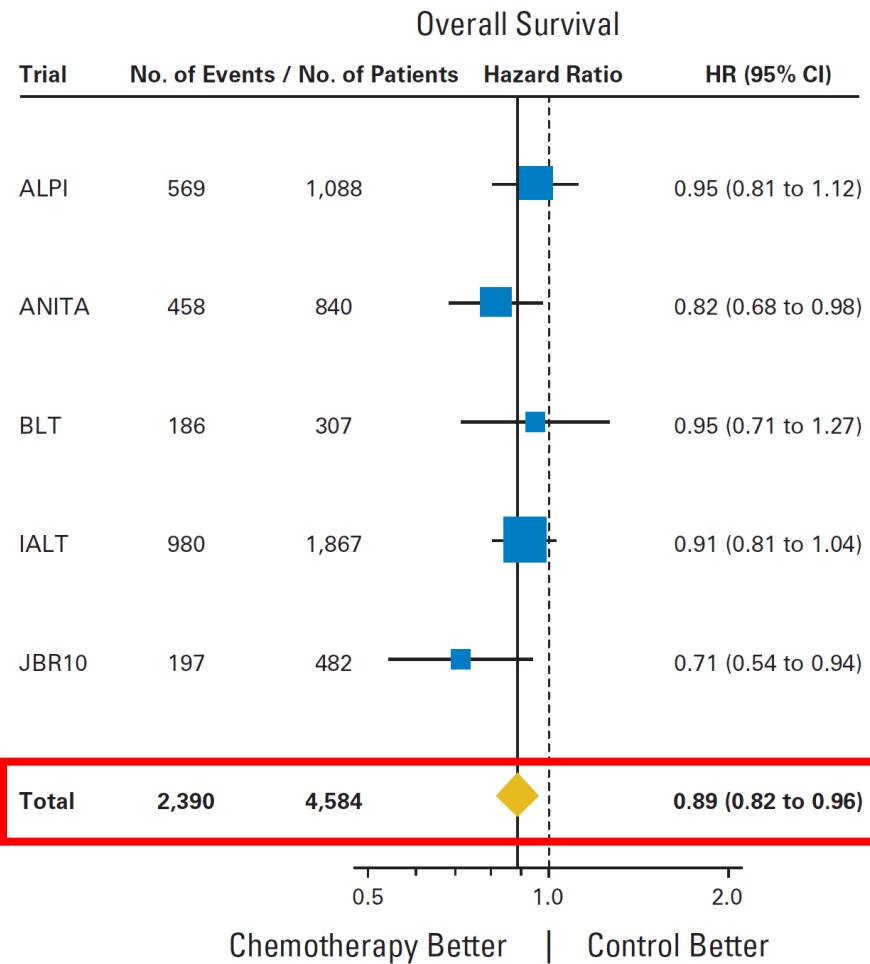
→ IALT - OS



→ Adjuvant trials (platinum-based)

	<i>N</i>	<i>HR (IC 95%)</i>	
• BMJ meta	1394	0,87 (0,74-1,02)	
• IALT	1867	0,91 (0,81-1,02)	←
• ALPI	1209	0,94 (0,79-1,12)	←
• E3590	488	0,93 (0,74-1,18)	
• BLT	381	1,02 (0,77-1,35)	←
• NCIC JBR.10	482	0,70 (0,52-0,92)	←
• CALGB 9633	330	0,83 (0,64-1,08)	
• ANITA 1	840	0,79 (0,66-0,95)	←

→ LACE : 5 adjuvant cisplatin-based regimens



**Absolute OS benefit
at 5 years
5.3% ±1.6%**

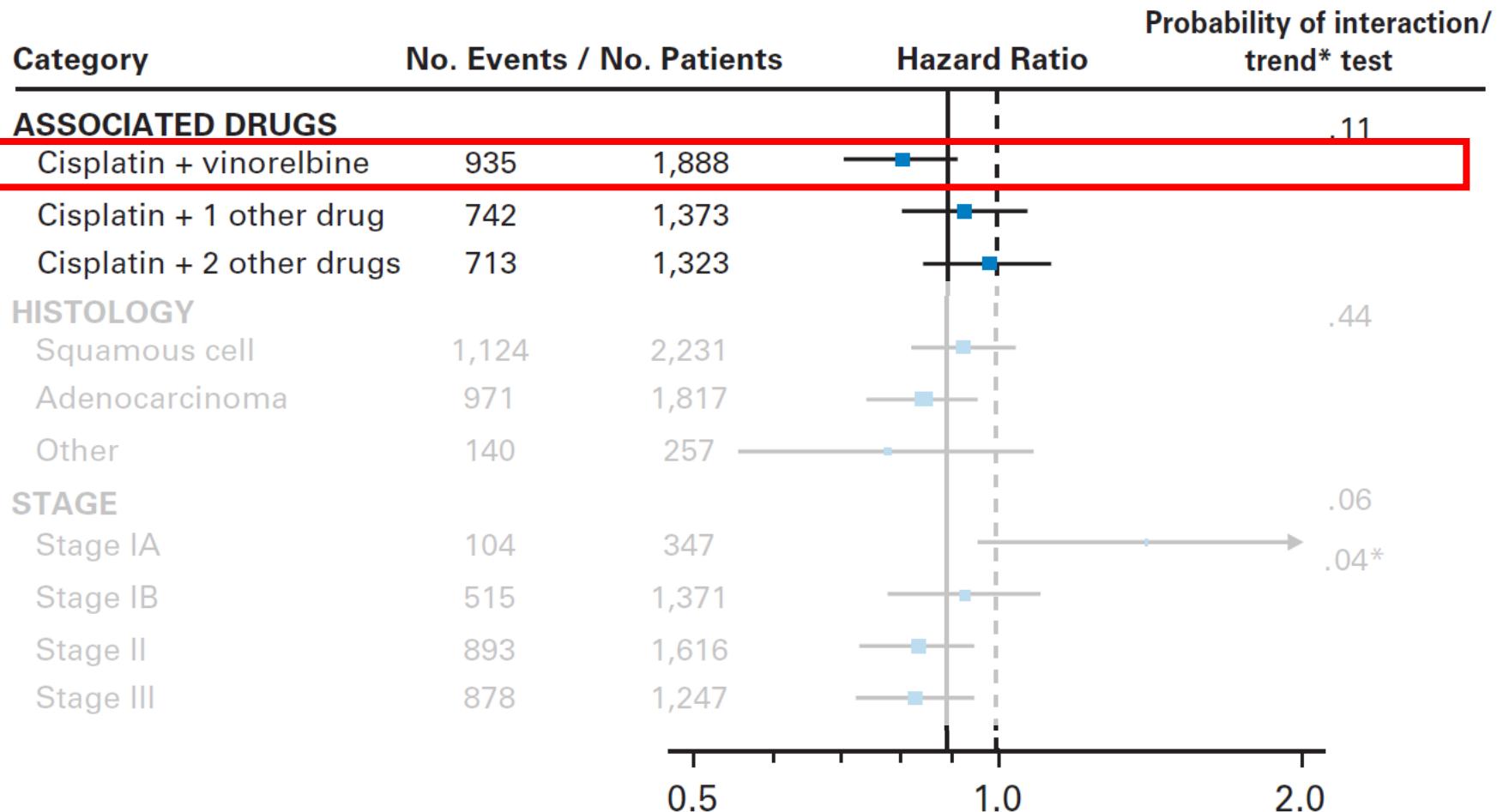
**Toxic death
0.8 to 2 %**

Chemotherapy effect: Logrank statistic = 8.5, P = .005

Test for heterogeneity: $\chi^2_4 = 4.25$, P = .37, $I^2 = 6\%$

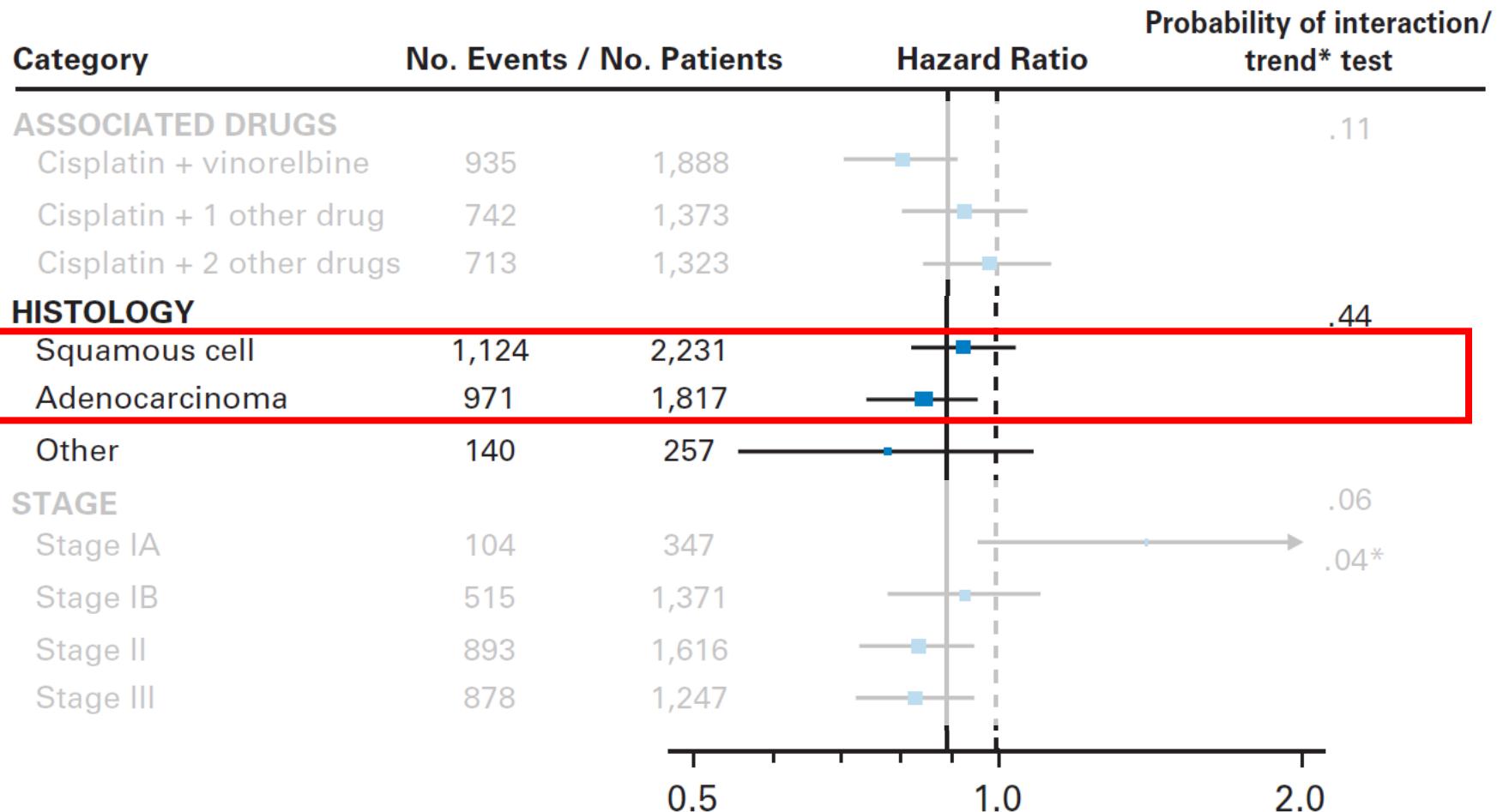
→ LACE

Overall Survival



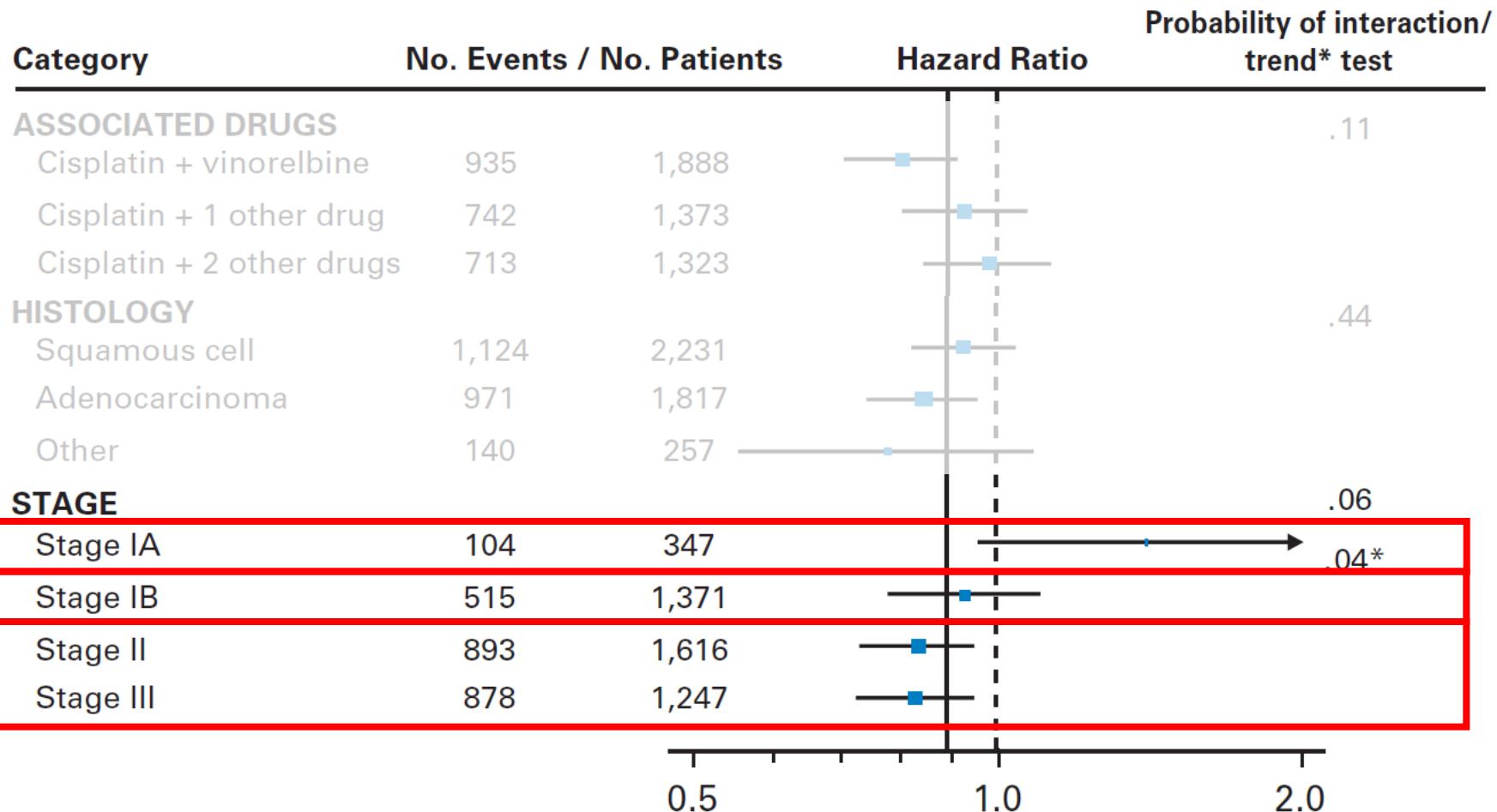
→ LACE

Overall Survival



→ LACE

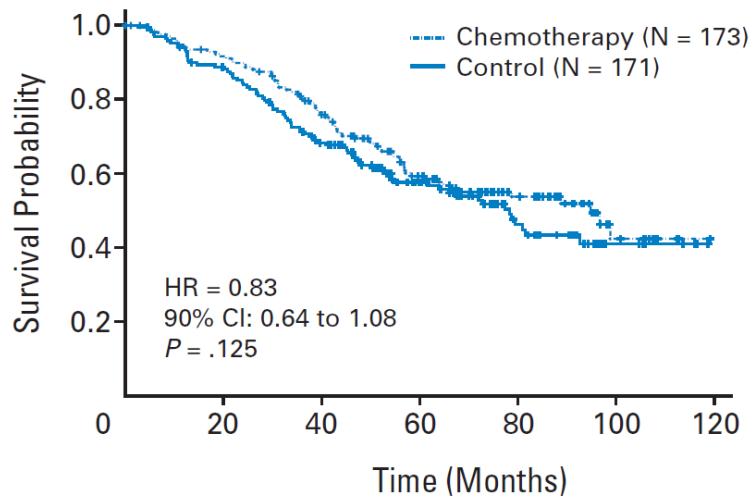
Overall Survival



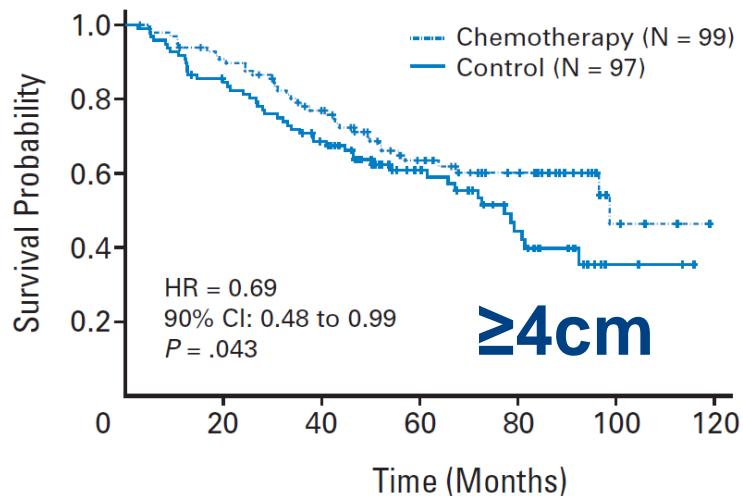
→ Adjuvant trials

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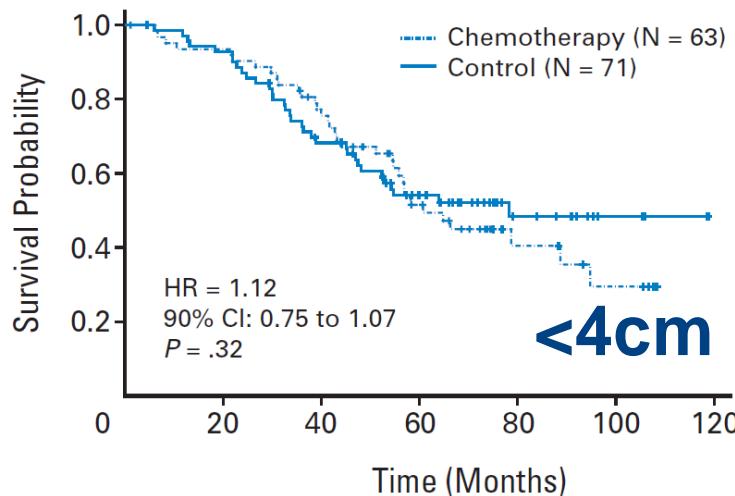
→ Stage IB?



CALGB Stage IB trial



Paclitaxel – carboplatin X4



→ Adjuvant trials

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→ Adjuvant trials

	<i>N</i>	<i>HR (IC 95%)</i>	
• BMJ meta	1394	0,87 (0,74-1,02)	
• IALT	1867	0,91 (0,81-1,02) 0,86 (0,76-0,98)	▼
• ALPI	1209	0,94 (0,79-1,12)	
• E3590	488	0,93 (0,74-1,18)	
• BLT	381	1,02 (0,77-1,35)	
• NCIC JBR.10	482	0,70 (0,52-0,92) 0,78 (0,61-0,99)	▼
• CALGB 9633	330	0,83 (0,64-1,08) 0,80 (0,60-1,07) 0,62 (0,41-0,95)	▼
• ANITA 1	840	0,79 (0,66-0,95)	

→ META-ANALYSIS ON THE ROLE OF CHEMOTHERAPY IN NSCLC IGR - MRC (BMJ 1995)

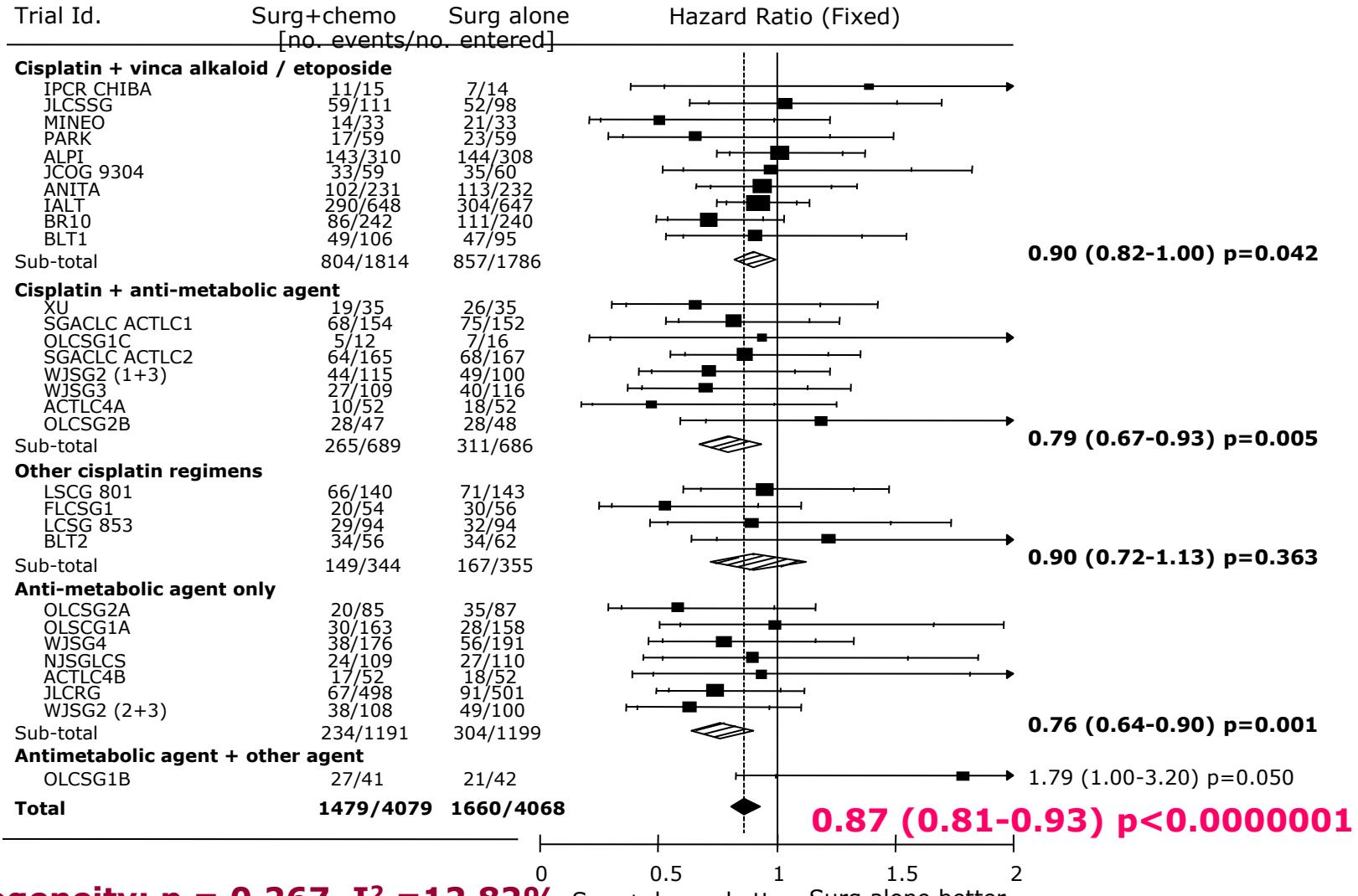
Absolute benefit with cisplatin containing regimens

14 trials available
4,357 patients

Updated in 2008
30 trials available
8,147 patients

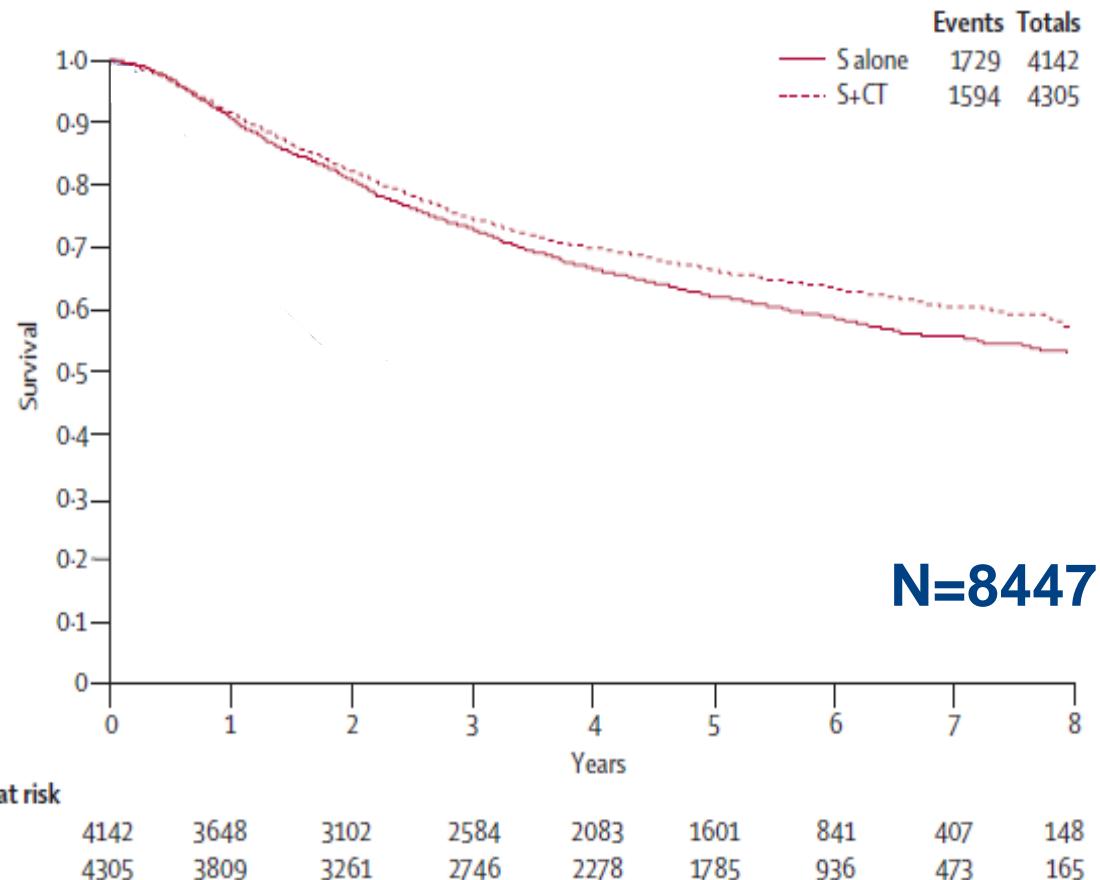
	$S \pm CT$	$S + RT \pm CT$
2 years	3%	2%
5 years	5%	2%

→ Overall survival



Heterogeneity: p = 0.267, I² =12.82%

→ Meta-analysis IGR-MRC



HR = 0.87 (0.81-0.93) p<0.000001

Absolute benefit of 4% at 5 years

→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin

HR=0.77

p=0.0001



Adjuvant

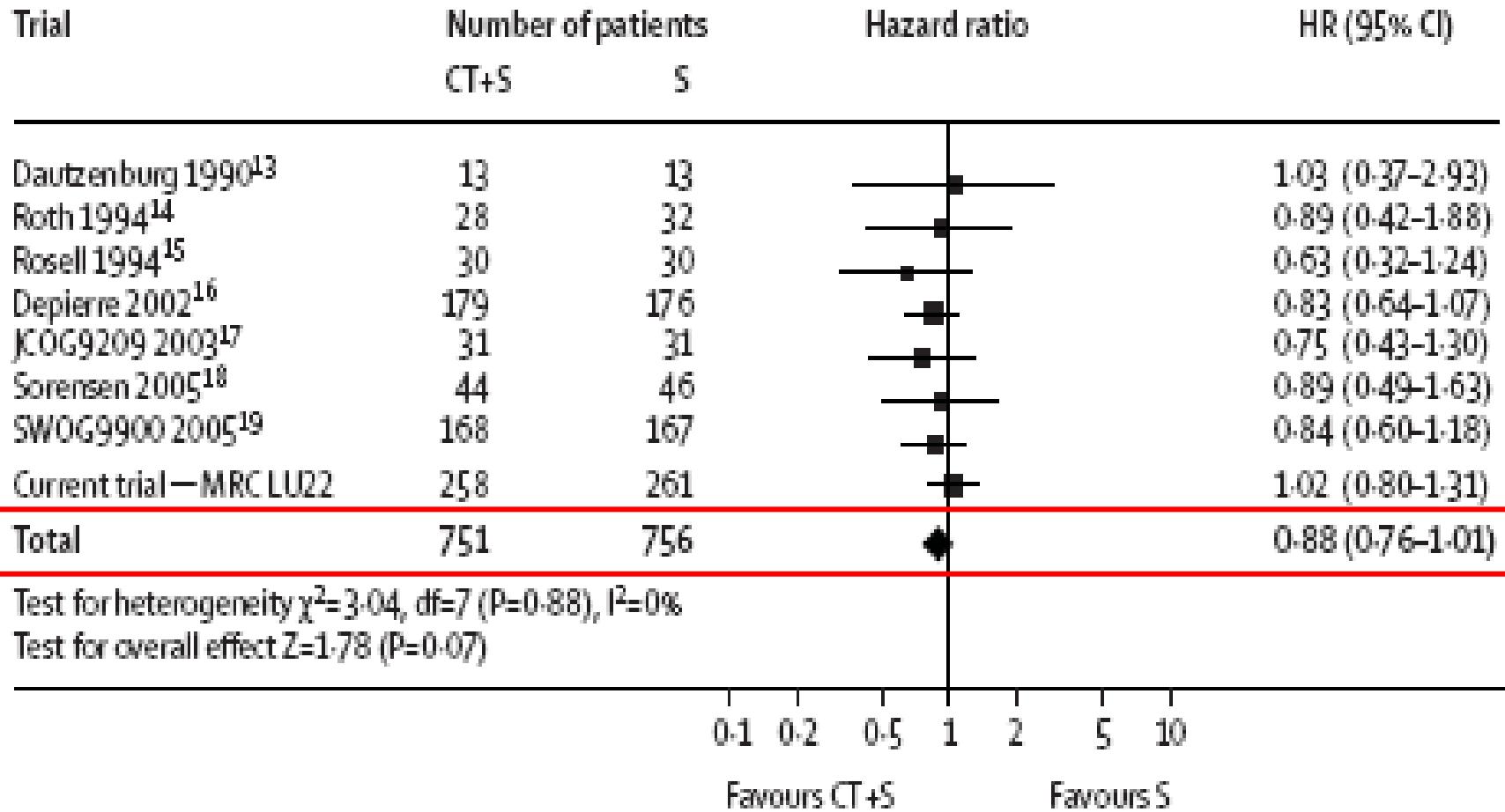
HR=0.89

p=0.005

Cure more

HR: Hasard ratio for overall survival

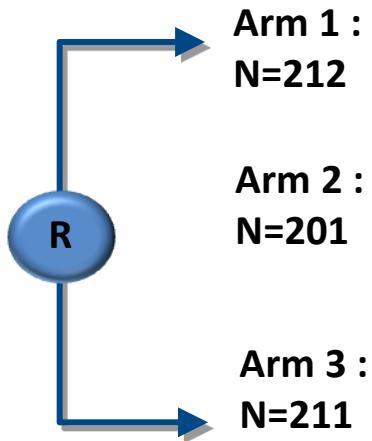
→ Neo-adjuvant



→ NATCH

Phase III

624 patients
IA (>2 cm),
IB, II, T3N1



Surgery

**Pacli/Carbo
3 cycles**

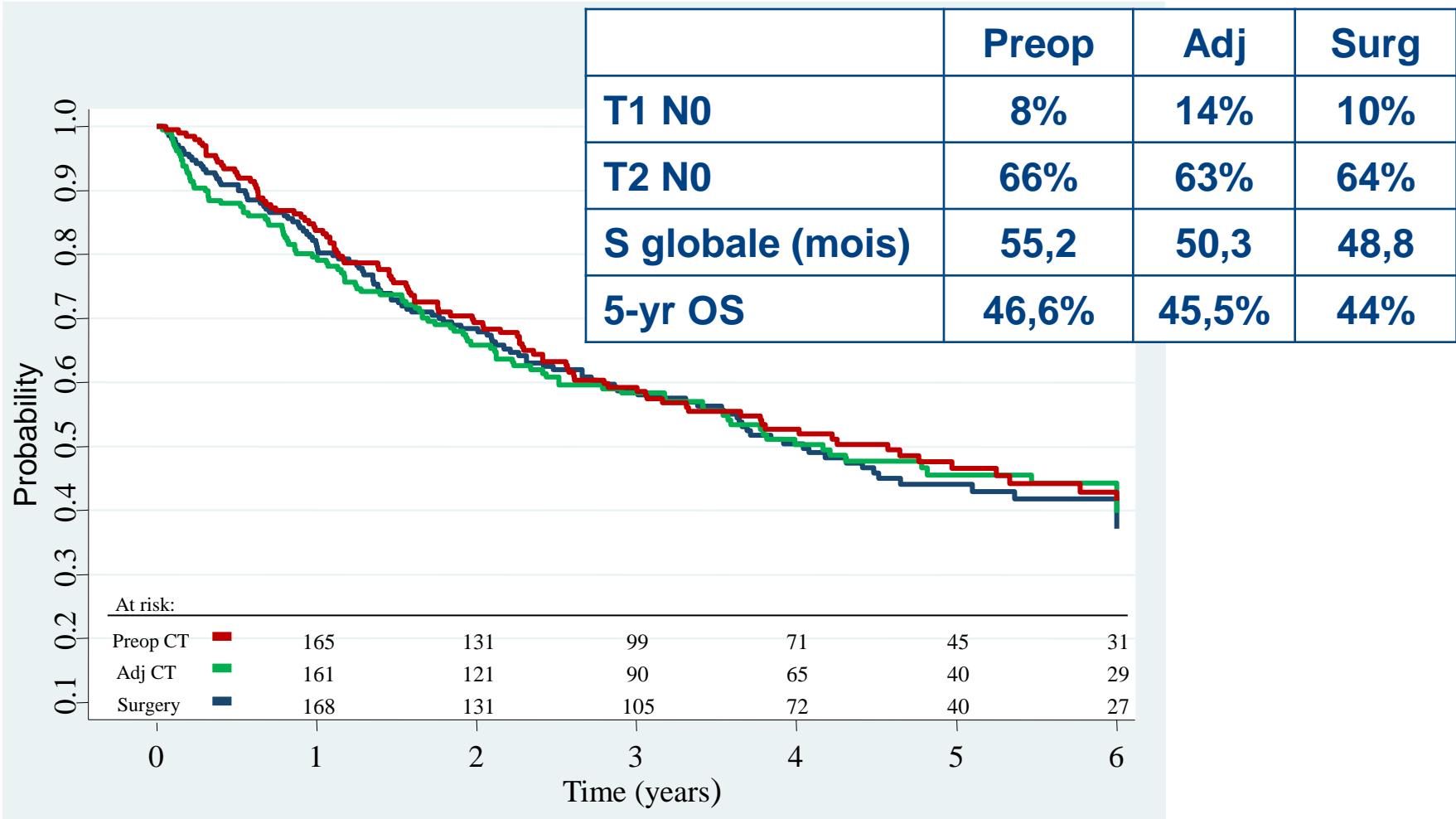
Surgery

Surgery

**Pacli/Carbo
3 cycles**

Paclitaxel 200 mg/m² + carboplatin AUC 6 /3w

→ NATCH : OS



Surg vs Adj: HR=0.99 (0.75-1.3); $p=0.93$ - Surg vs Preop: HR=0.96 (0.84-1.1); $p=0.56$

→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin

HR=0.77

p=0.0001



Adjuvant

HR=0.89

p=0.005

Preoperative

HR=0.88

p=0.07

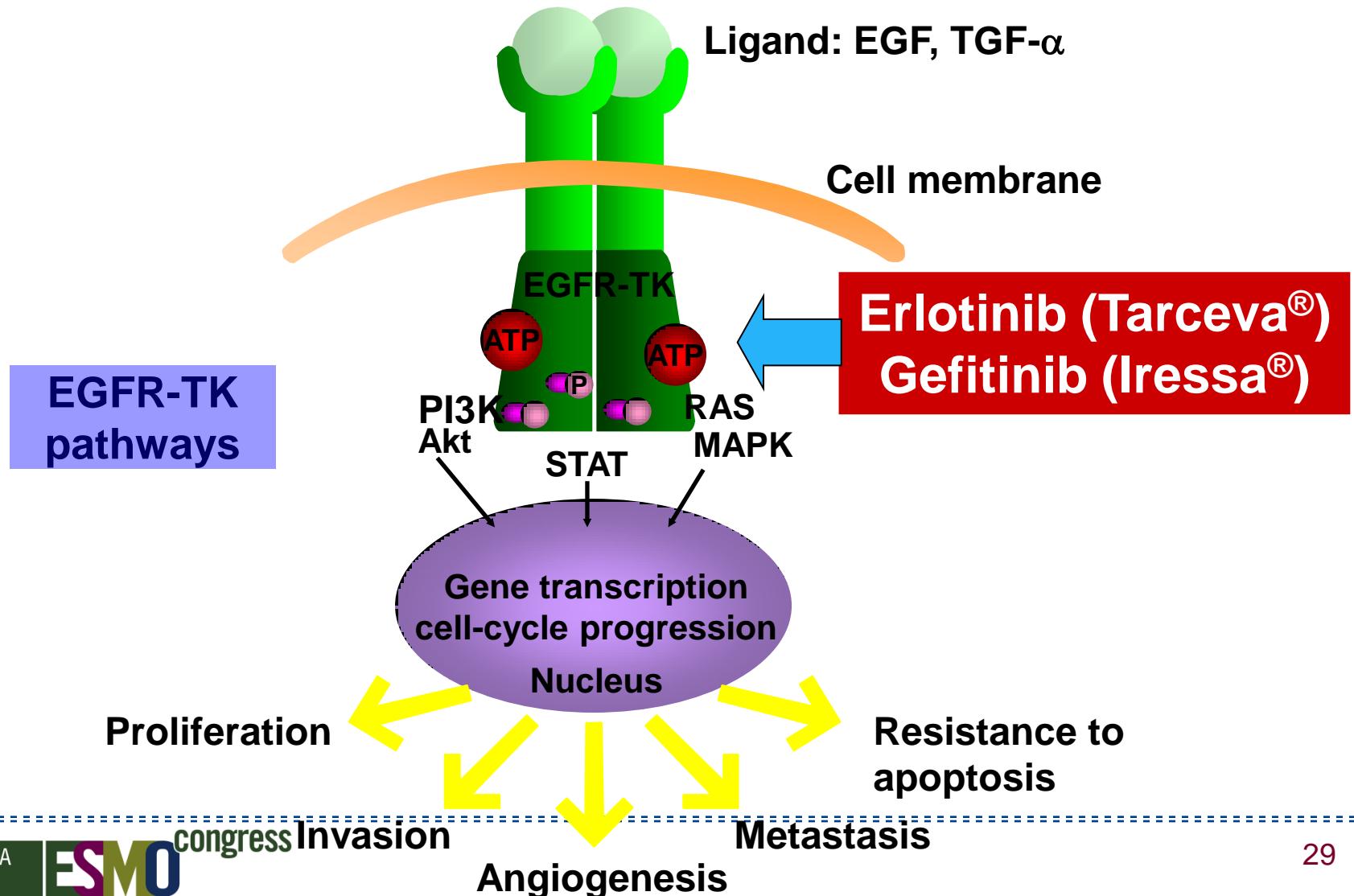
Cure more

HR: Hazard ratio for overall survival

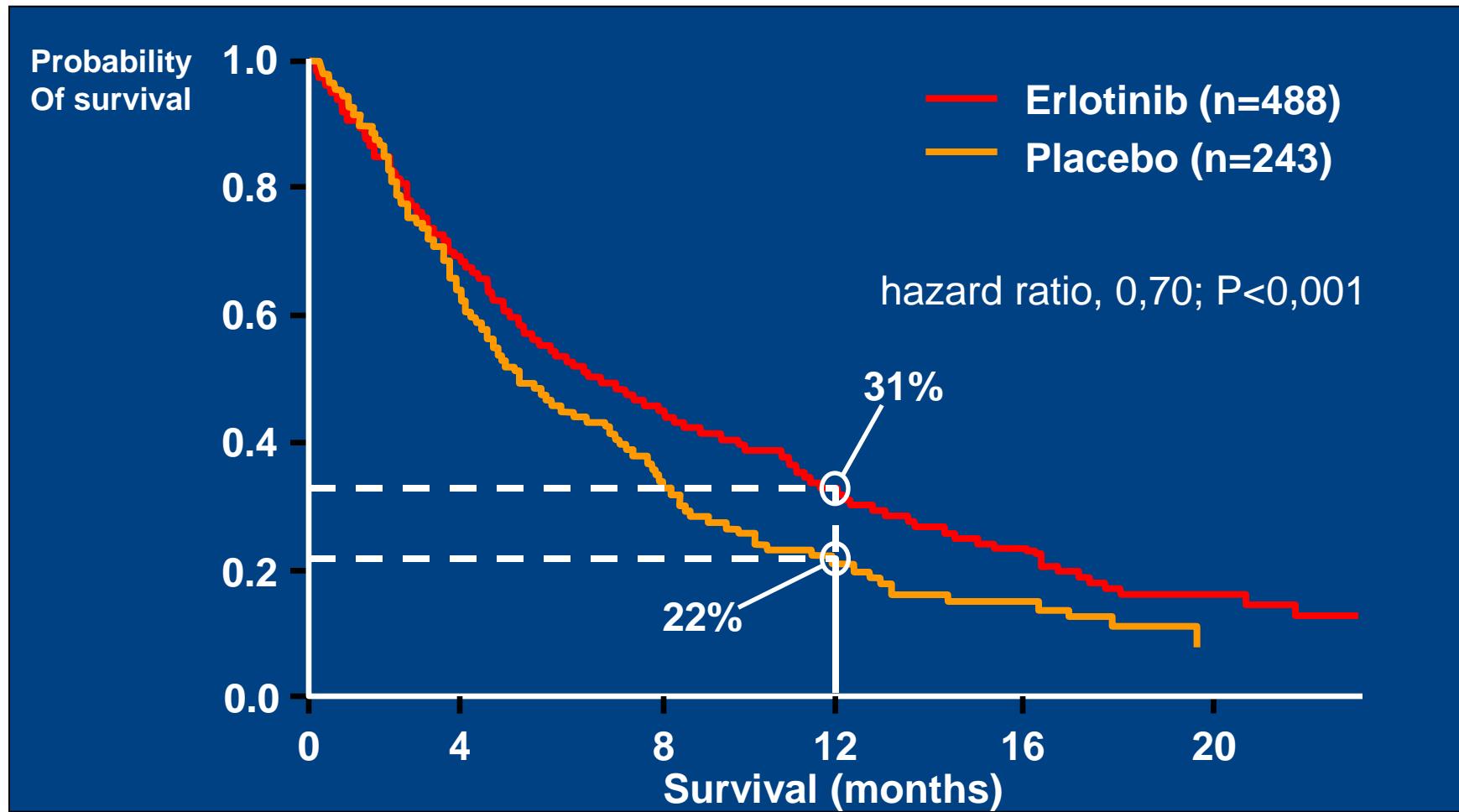
→ Adjuvant Chemotherapy in 2012

- Standard : Cisplatin based chemotherapy
- Standard : Stage II-IIIA
- Option : IB (>4 cm recommended)
- Option : carboplatin
- Criteria
 - <75 yrs
 - <2 months after surgery
 - PS 0-1
 - No post-operative complications
- Never use targeted therapy (erlotinib, gefitinib, bevacizumab) ?

→ EGFR pathway



→ Erlotinib 2nd-3rd line - approved in 2005



→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin

HR=0.77
p=0.0001

EGFRi

2-3rd line
HR = 0.70
p<0.001
erlotinib

Adjuvant

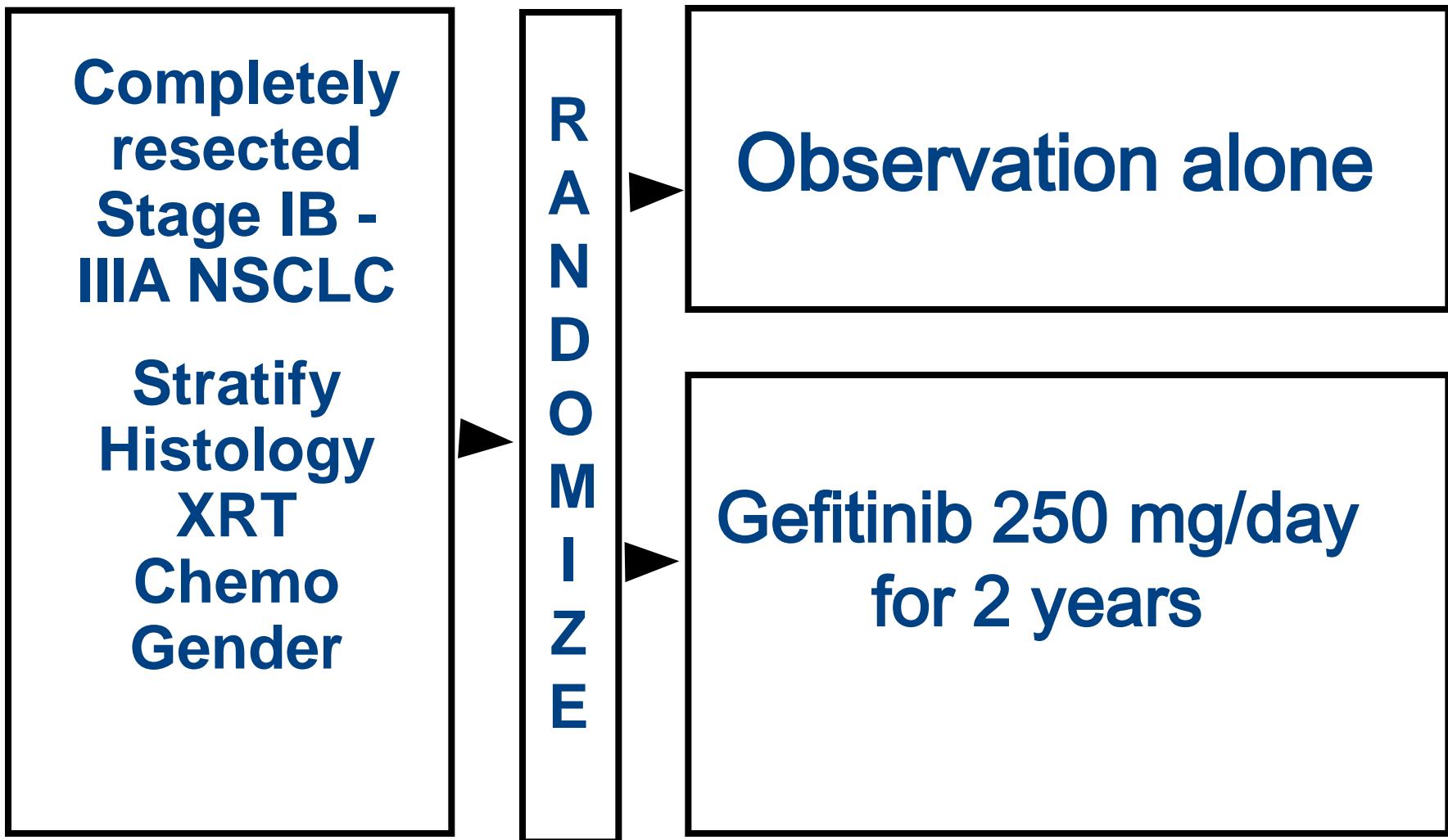
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Preoperative
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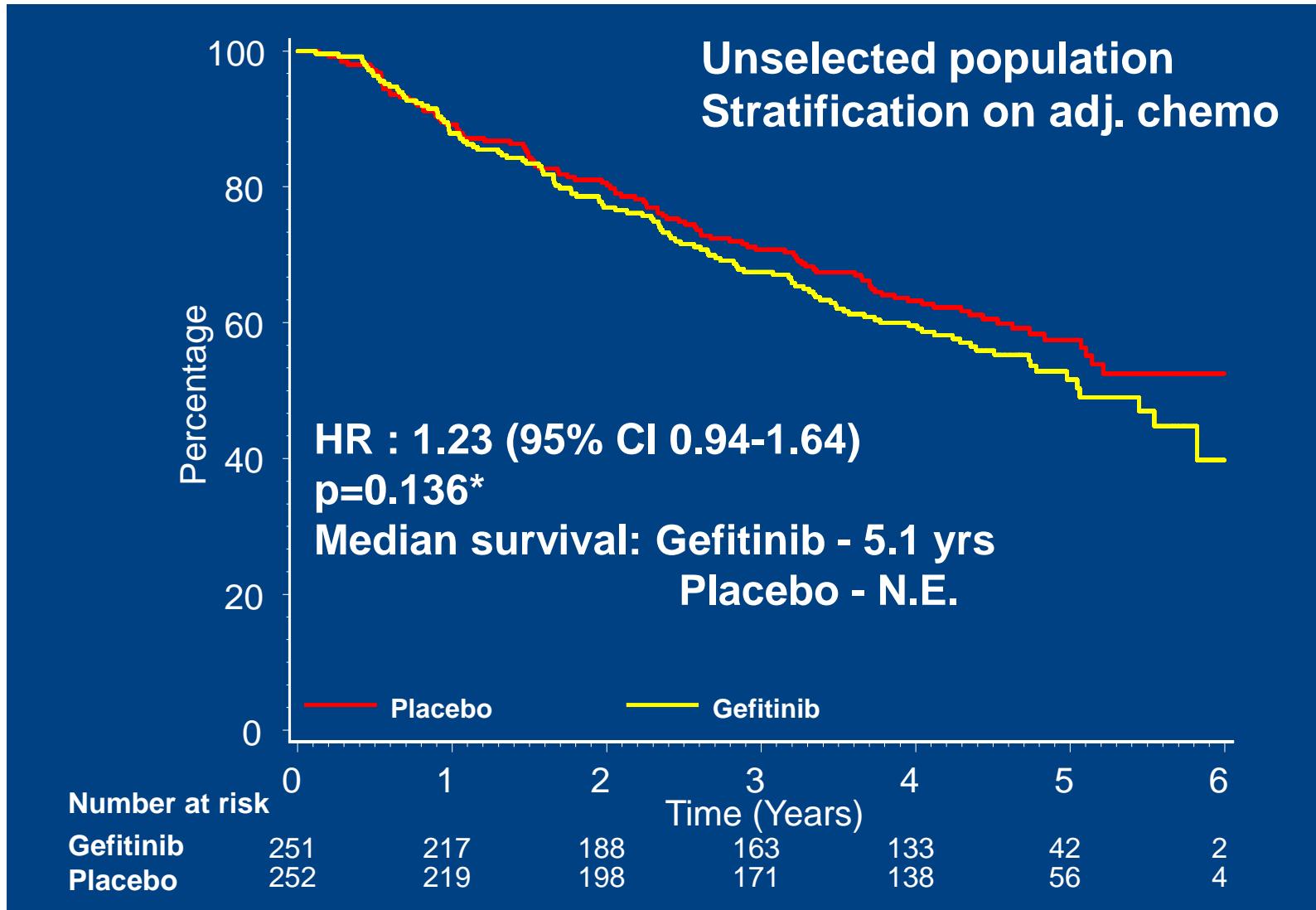
Cure more

HR: Hazard ratio for overall survival

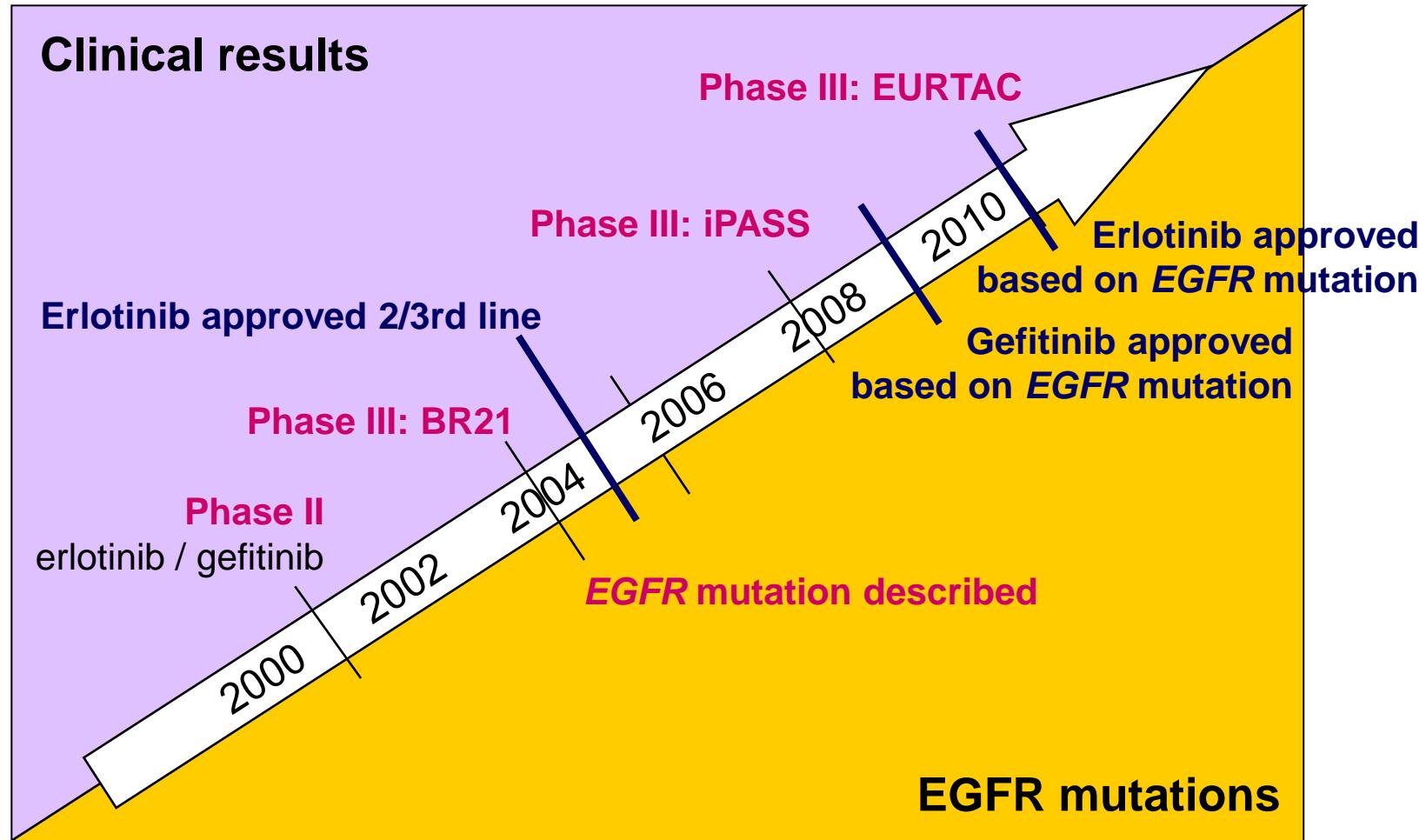
→ **STUDY DESIGN NCIC CTG BR.19**



→ BR 19: gefitinib vs placebo



→ A perspective on EGFR

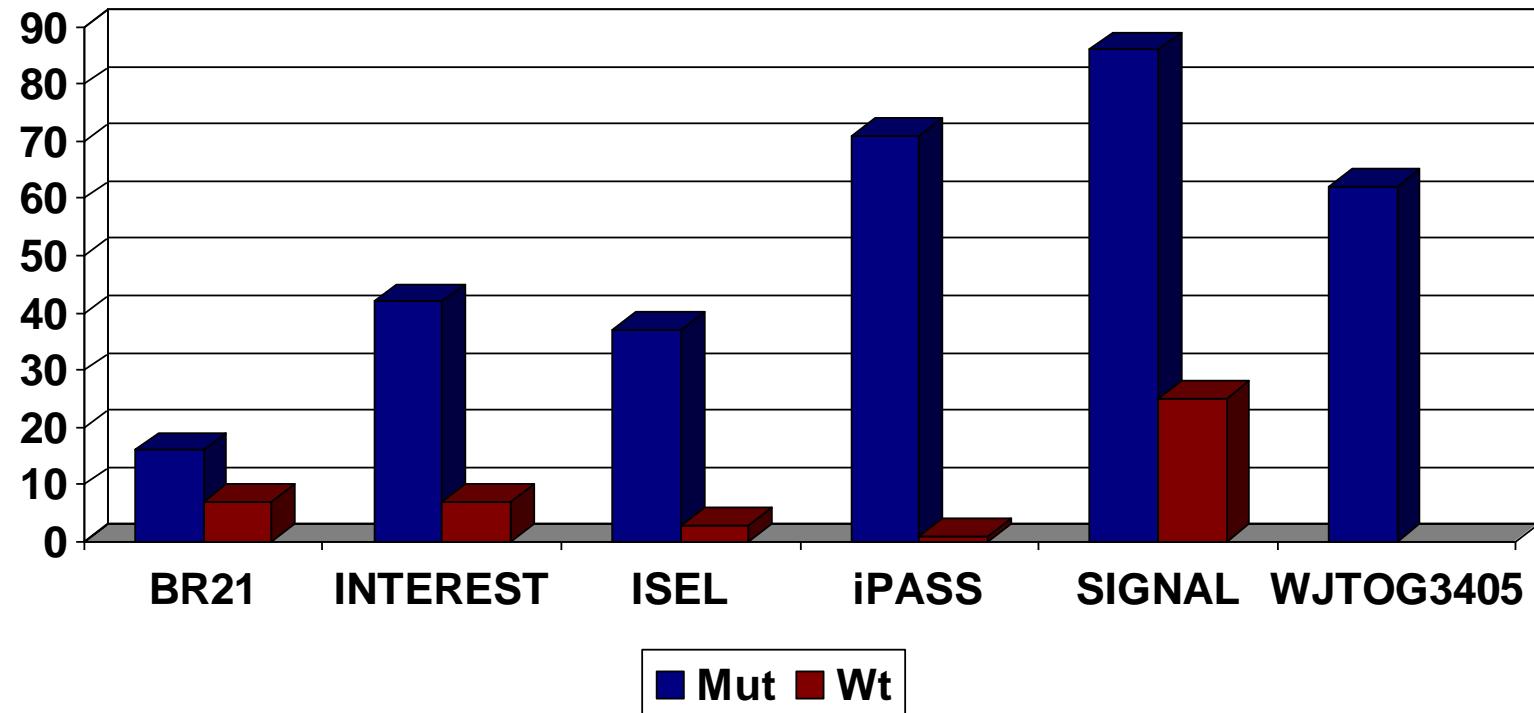


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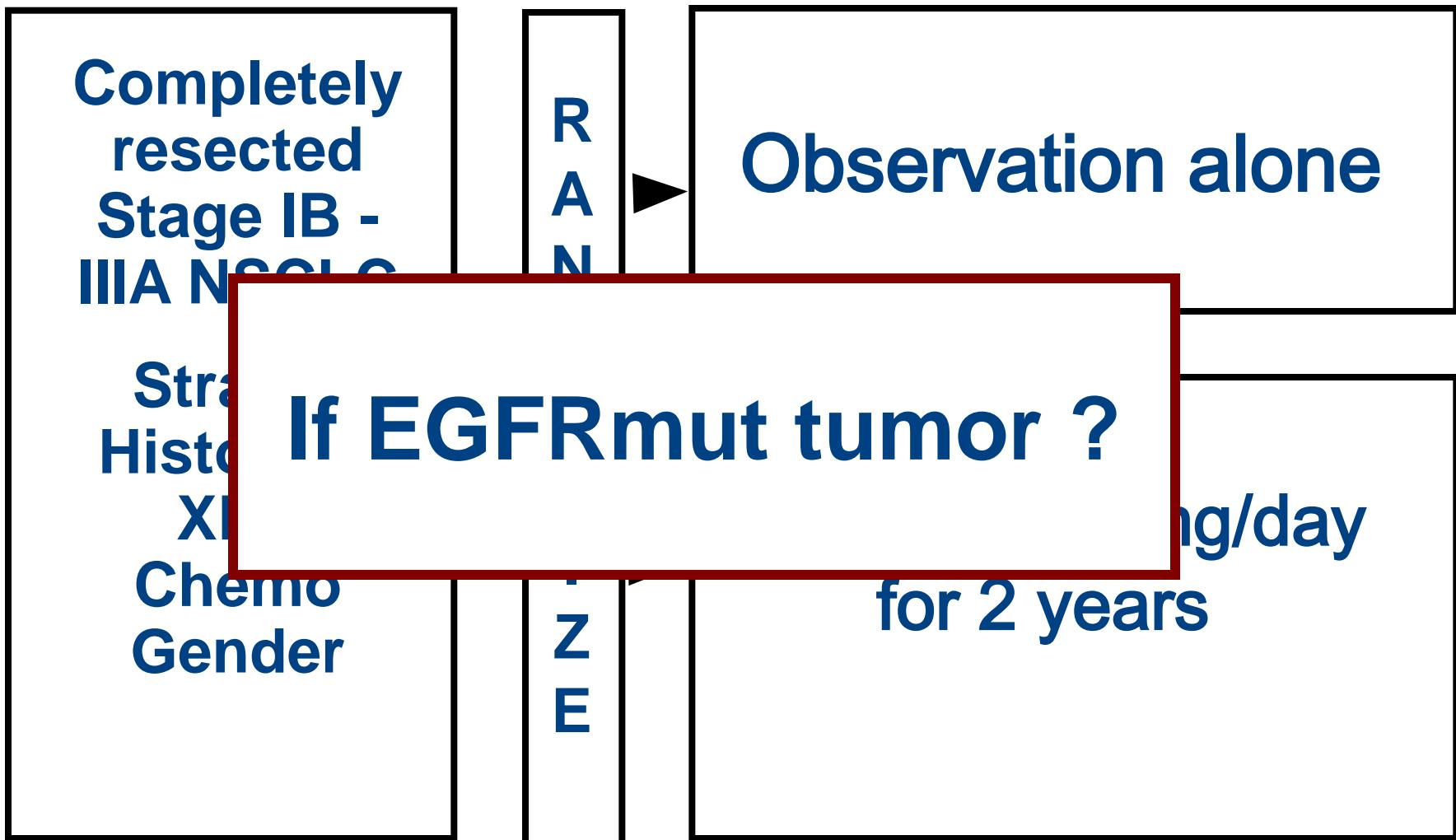
EGFR mutation: a marker of sensitivity

→ EGFR mutations and response to EGFR TKIs

ORR %

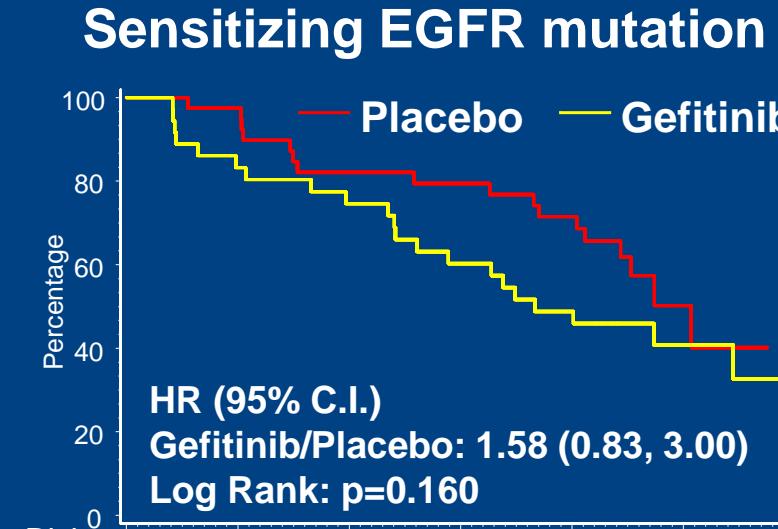
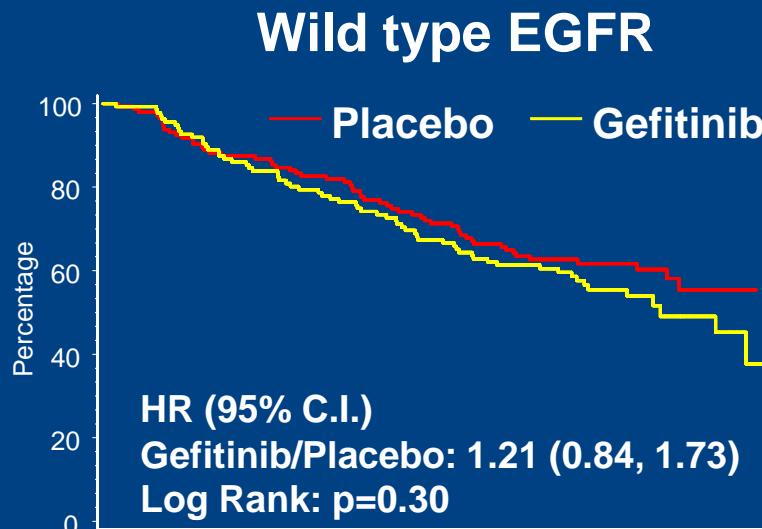


→ **STUDY DESIGN NCIC CTG BR.19**



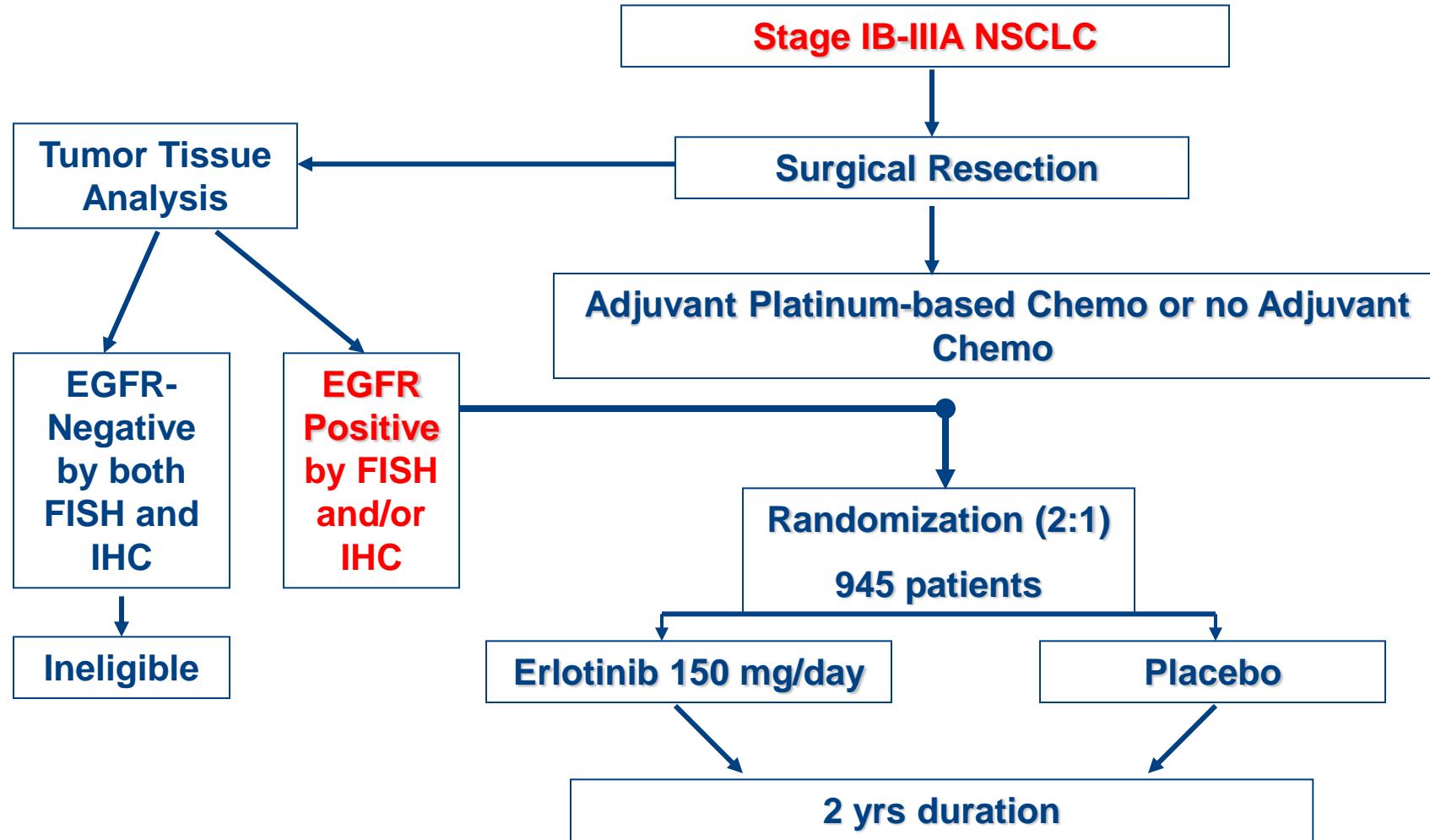


→ BR 19: gefitinib vs placebo (OS)



- Difference in recurrence rate ?
- Effect on normal tissue ?
- Effect on preneoplastic tissue ?

→ RADIANT: Adjuvant Erlotinib Study



→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin

HR=0.77
p=0.0001

EGFRi

2-3rd line
HR = 0.70
p<0.001

erlotinib

HR=0.89
p=0.005

Gefitinib

Radiant
ongoing
Erlotinib

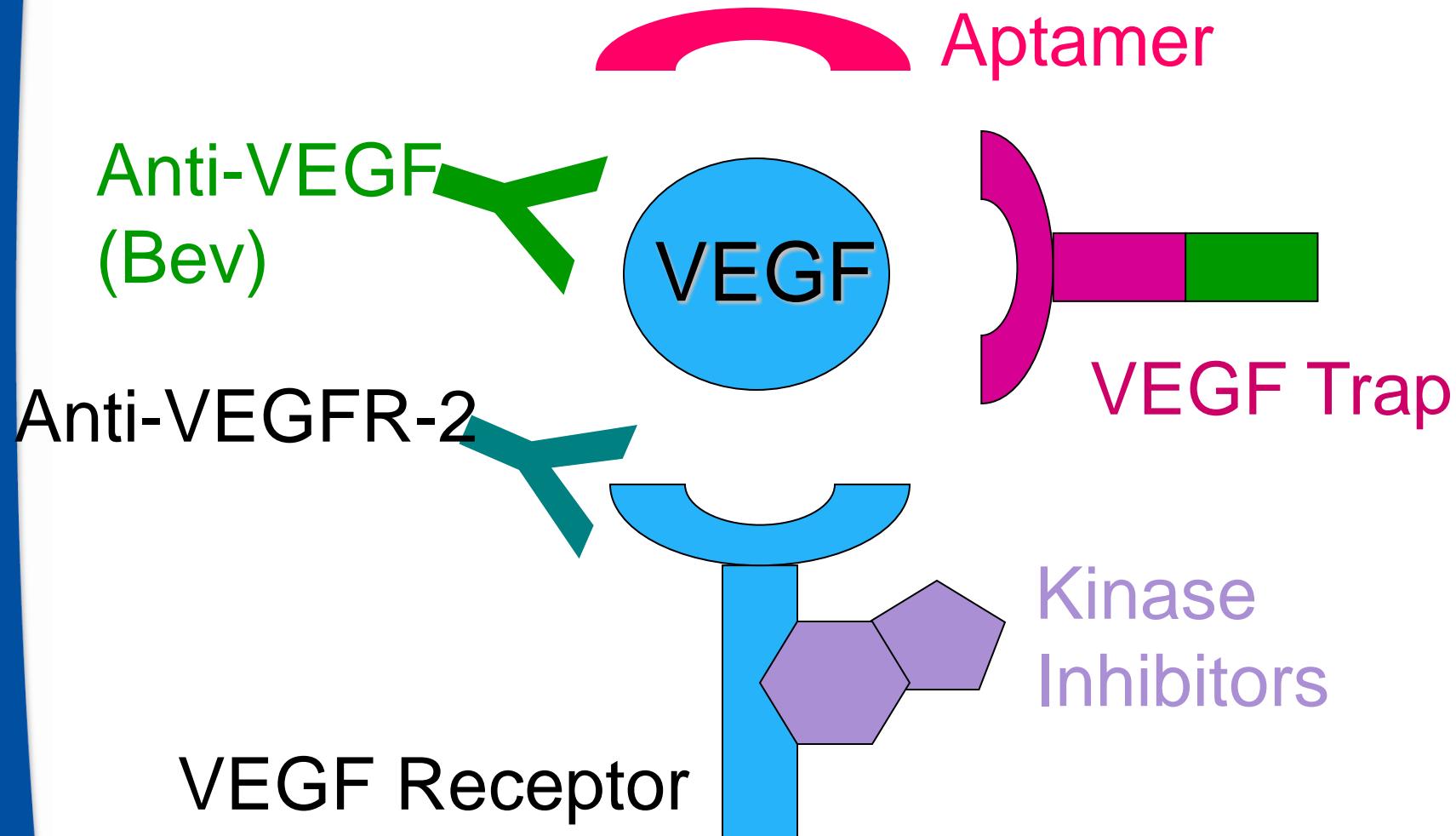
Adjuvant

Preoperative
HR=0.88
p=0.07

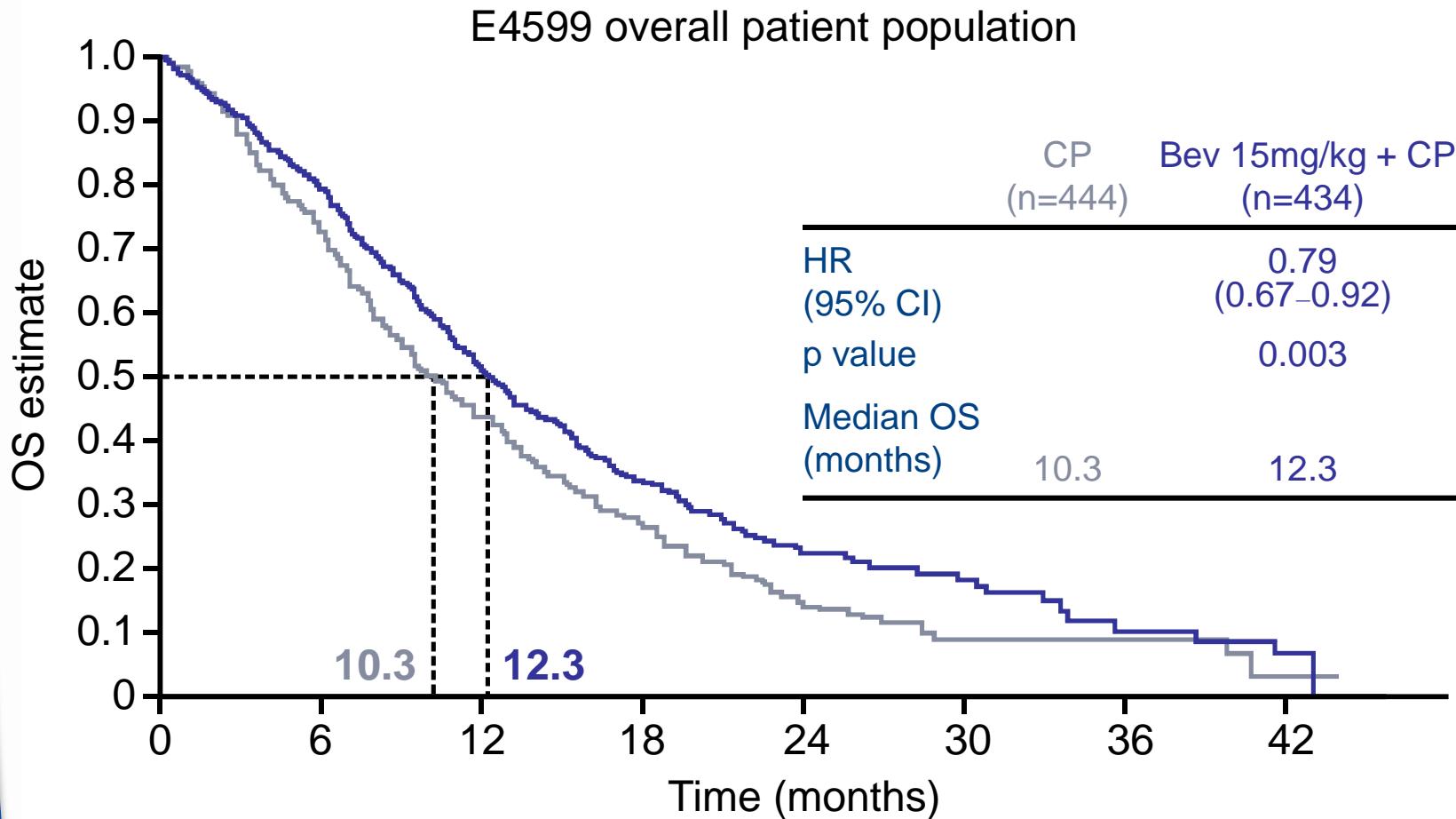
Cure more

HR: Hazard ratio for overall survival

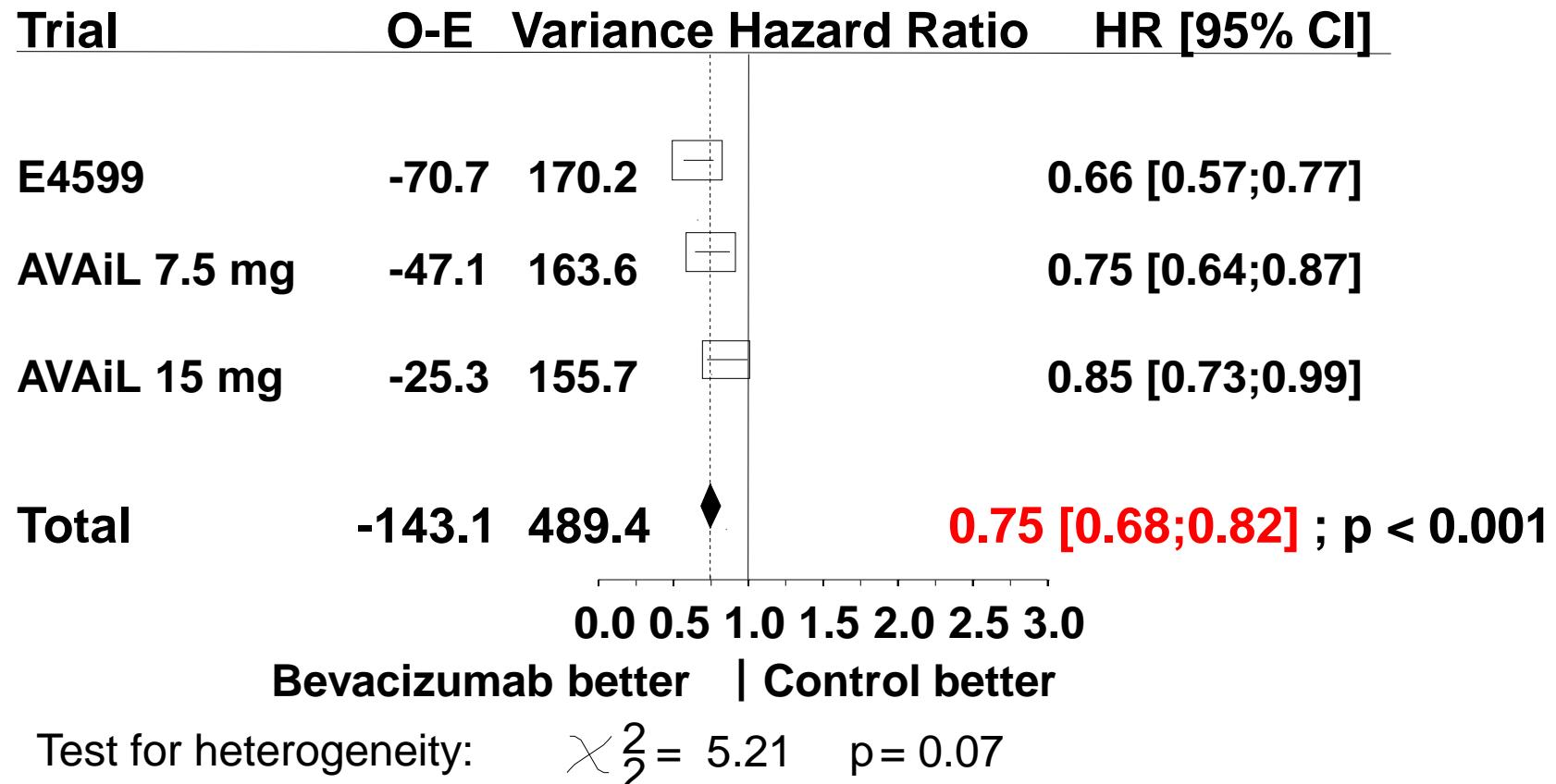
→ Targeting the VEGF Pathway



→ E4599: survival beyond 12 months



→ Bevacizumab : pooled analysis - SSP



→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin
HR=0.77
p=0.0001



EGFRi

2-3rd line
HR = 0.70
p<0.001
erlotinib

Anti-Angio.

1st line
HR=0.89
p = 0.03
bevacizumab



Adjuvant

HR=0.89
p=0.005

Preoperative
HR=0.88
p=0.07

HR=1.23
p=0.136

Gefitinib
Radiant ongoing
Erlotinib

Cure more

HR: Hazard ratio for overall survival

→ E1505: Phase III Adjuvant
Chemotherapy +/- Bevacizumab

Resected IB \geq 4cm–IIIA
No planned XRT
N = 1500



Chemotherapy* x 4 cycles

**Chemotherapy* x 4 cycles +
bevacizumab x 1 year**

- *Specified regimens
- Cisplatin and docetaxel
 - Cisplatin and vinorelbine
 - Cisplatin and gemcitabine

Primary endpoint: overall survival

→ BEACON : bevacizumab perioperative

Phase II Single institution, 47 patients, stages IB-IIIA

Non SCC : Bevacizumab (Bev)+Cisplatin-Docetaxel (DC) x 4 +
Surgery + Bev (1 year)

SCC : DC : (11 pts) : Cisplatin-Docetaxel x 4 + Surgery + Bev (1 year)

	BEV+DC (n=36)	DC (n=11)
ORR	58%	40%
Downstaging	44%	27%
Tox post op Grade 3,4	16%	9%

→ Systemic chemotherapy

Survive more

Metastatic

Chemo

1st line - platin
HR=0.77
p=0.0001



EGFRi

2-3rd line
HR = 0.70
p<0.001

erlotinib

Anti-Angio.

1st line
HR=0.89
p = 0.03

bevacizumab

Adjuvant

HR=0.89
p=0.005

Preoperative
HR=0.88
p=0.07

HR=1.23
p=0.136

Gefitinib
Radiant
ongoing
Erlotinib

ECOG
1505
Ongoing

Avoid preop

Cure more

HR: Hazard ratio for overall survival

→ Challenges in 2012

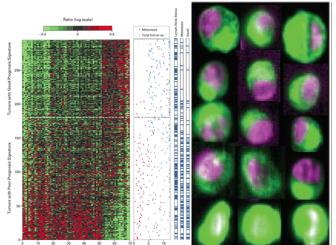
- Customized therapy

Resected Lung Cancer Patient

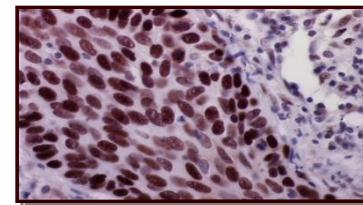


MOLECULAR PORTRAIT

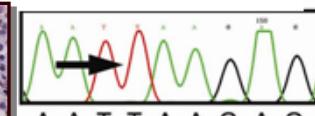
Prognosis



Chemotherapy sensitivity



Targeted therapy sensitivity



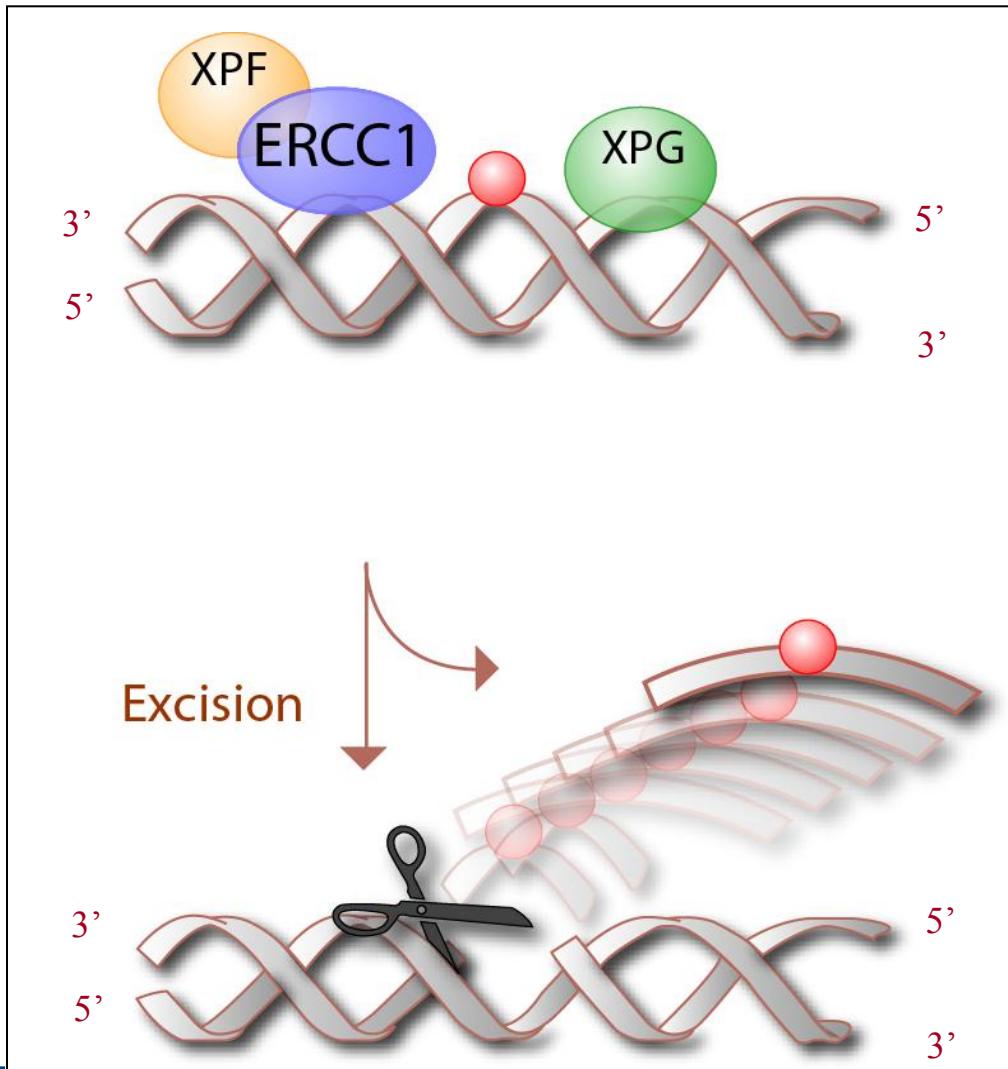
WHO TO TREAT ?

HOW TO TREAT ?

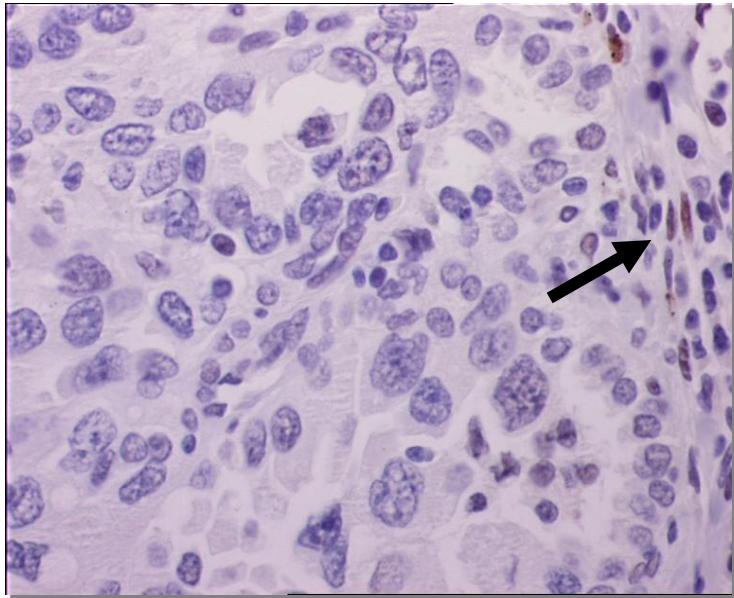
→ Relevant Predictive Biomarkers and NSCLC

Class	Agent	Biomarkers	Robustness
Cytotoxic drugs	Cisplatin	ERCC1 RRM1 BRCA1	+ +
	Gemcitabine	RRM1	+
	Pemetrexed	FPGS TS	- +
	Paclitaxel	MAPtau Beta-tubulin III	+
Targeted therapies	Erlotinib	EGFR mutation FISH EGFR K-Ras wt RASSF1A / 9pLOH	+++ + + +
	Bevacizumab	circulating VEGF	-
	PF-02341066	EML4-ALK	+++

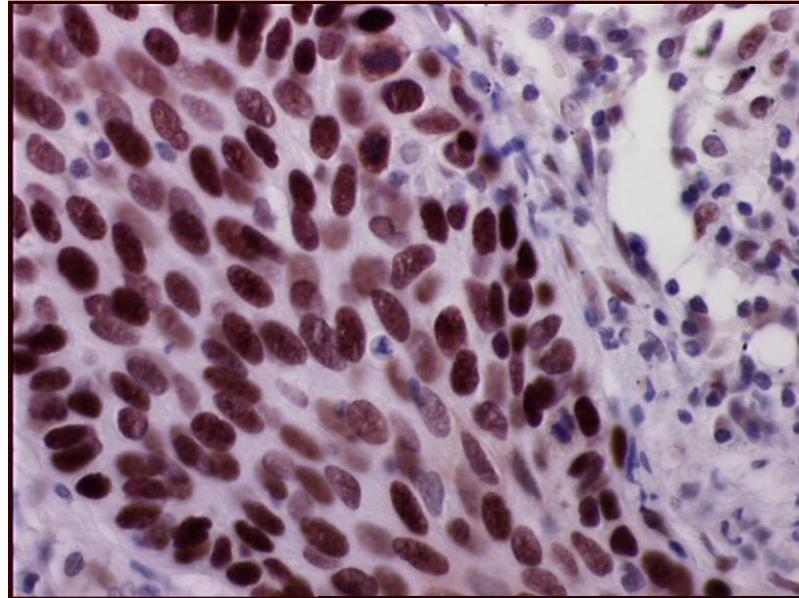
→ ERCC1 enzyme plays a rate-limiting role in the NER pathway



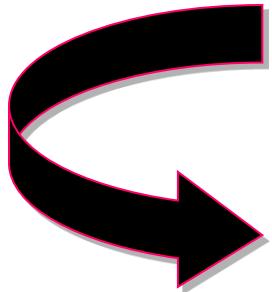
→ ERCC1 and adjuvant chemotherapy



ERCC1 negative

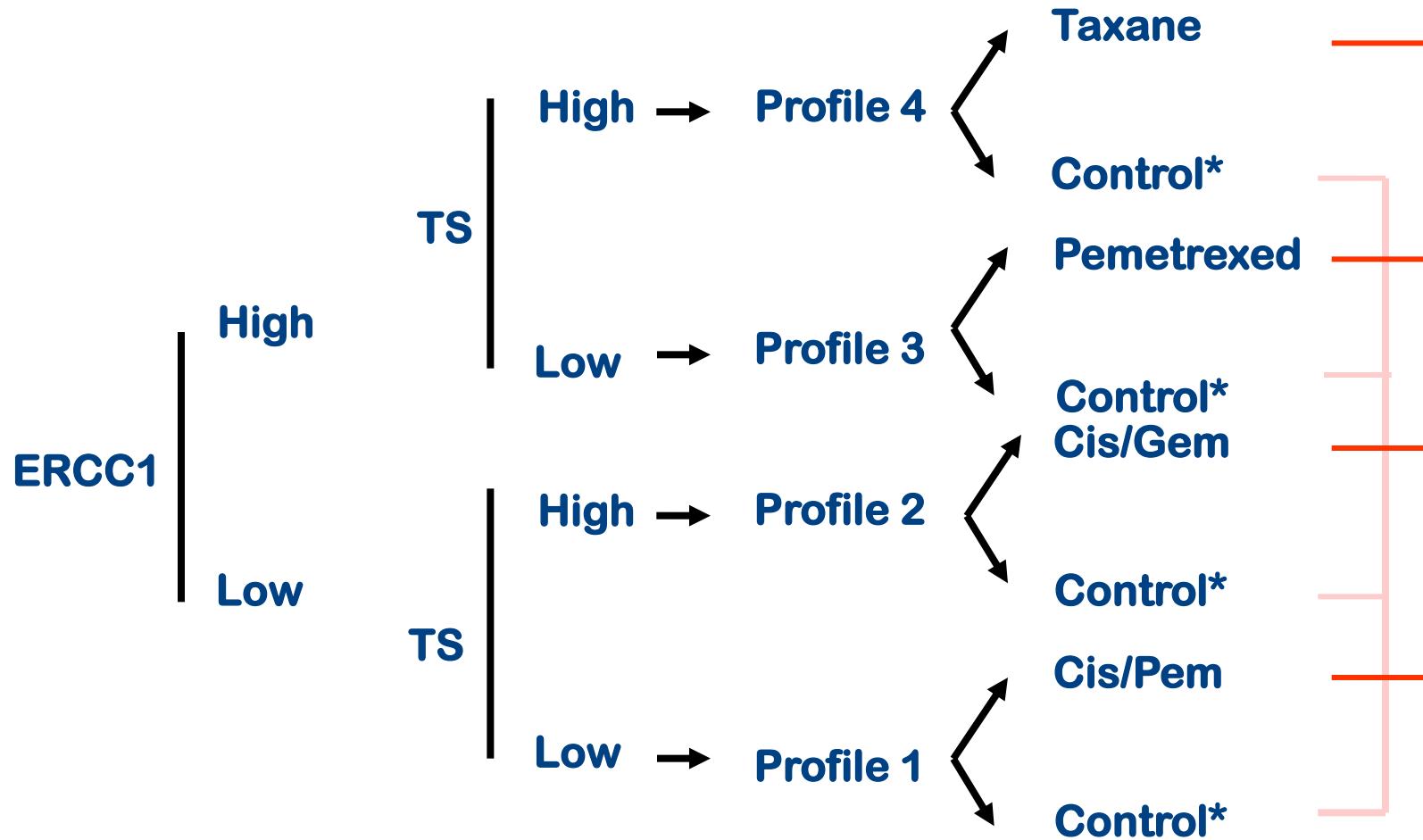


ERCC1 positive



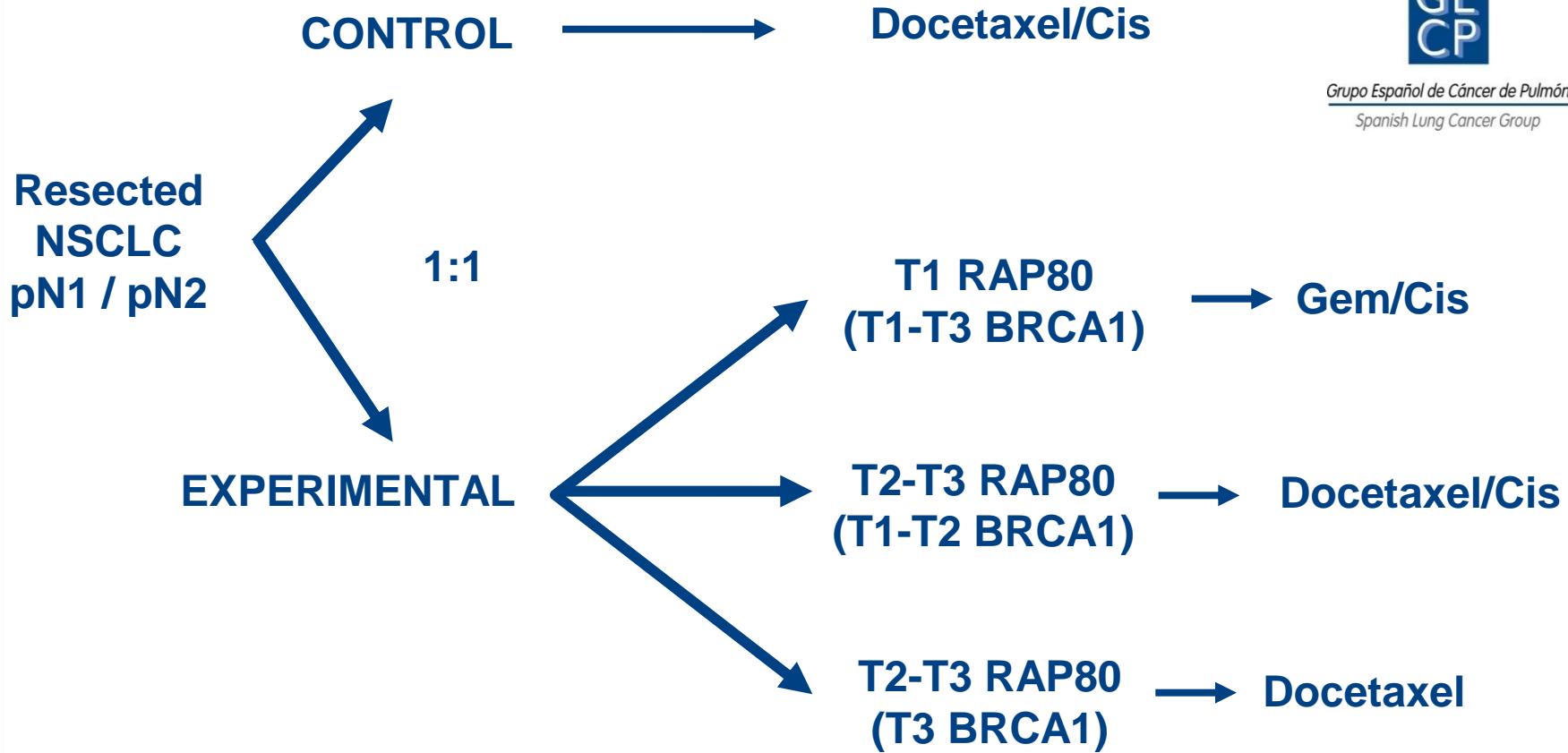
**Benefit of Cisplatin-based CT in
ERCC1 NEGATIVE patients**

→ ITACA: Adjuvant vs.ERCC1 & TS



High/Low ERCC1 & TS selected according to median level of mRNA expression in historical series ; * Control arm – Investigator choice of a DDP-based doublet

→ SCAT vs BRCA1 & RAP80

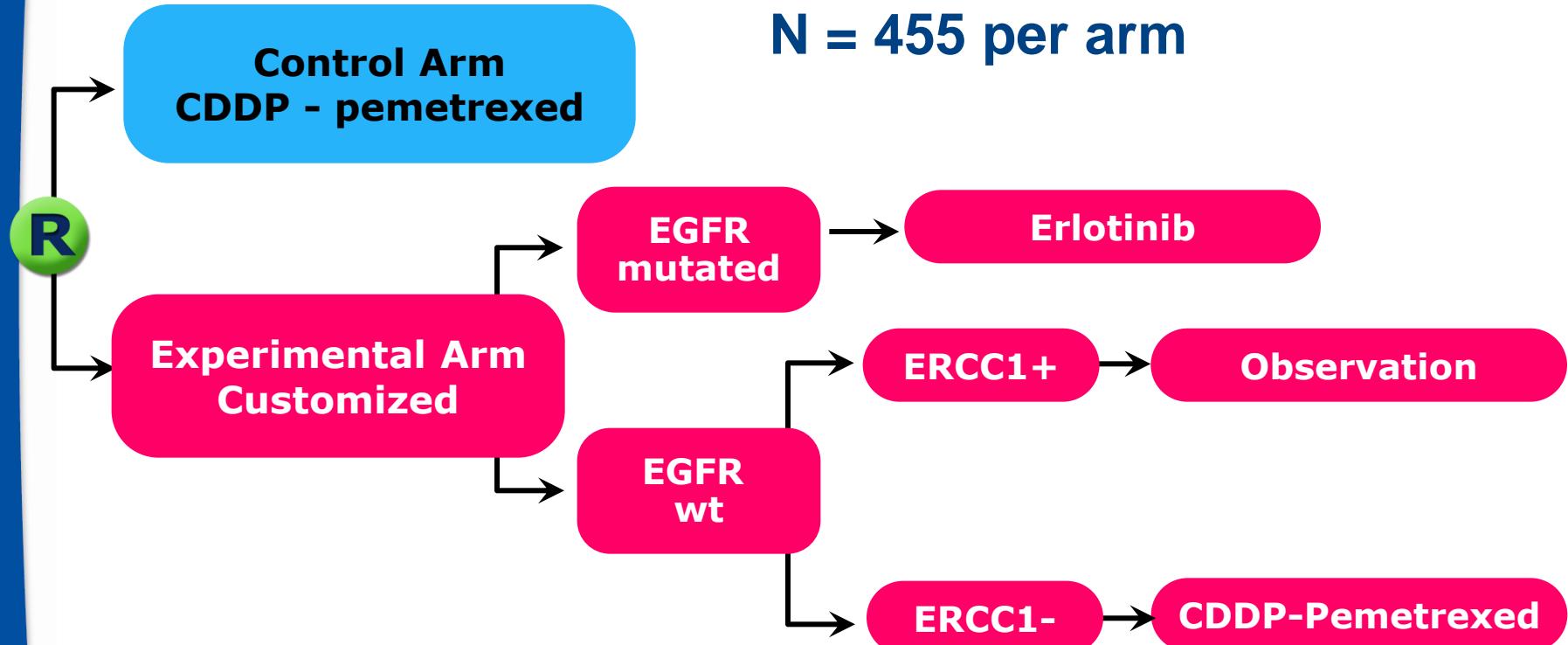



GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Genotyping for EGFR & K-ras mutations

Completely resected N1 & N2 NSCLC

→ TASTE vs. ERCC1 & EGFRmut



**Increase 3 years DFS by 8 %
N = 455 per arm**

Non-SCC NSCLC stage II and IIIA (non-N2)

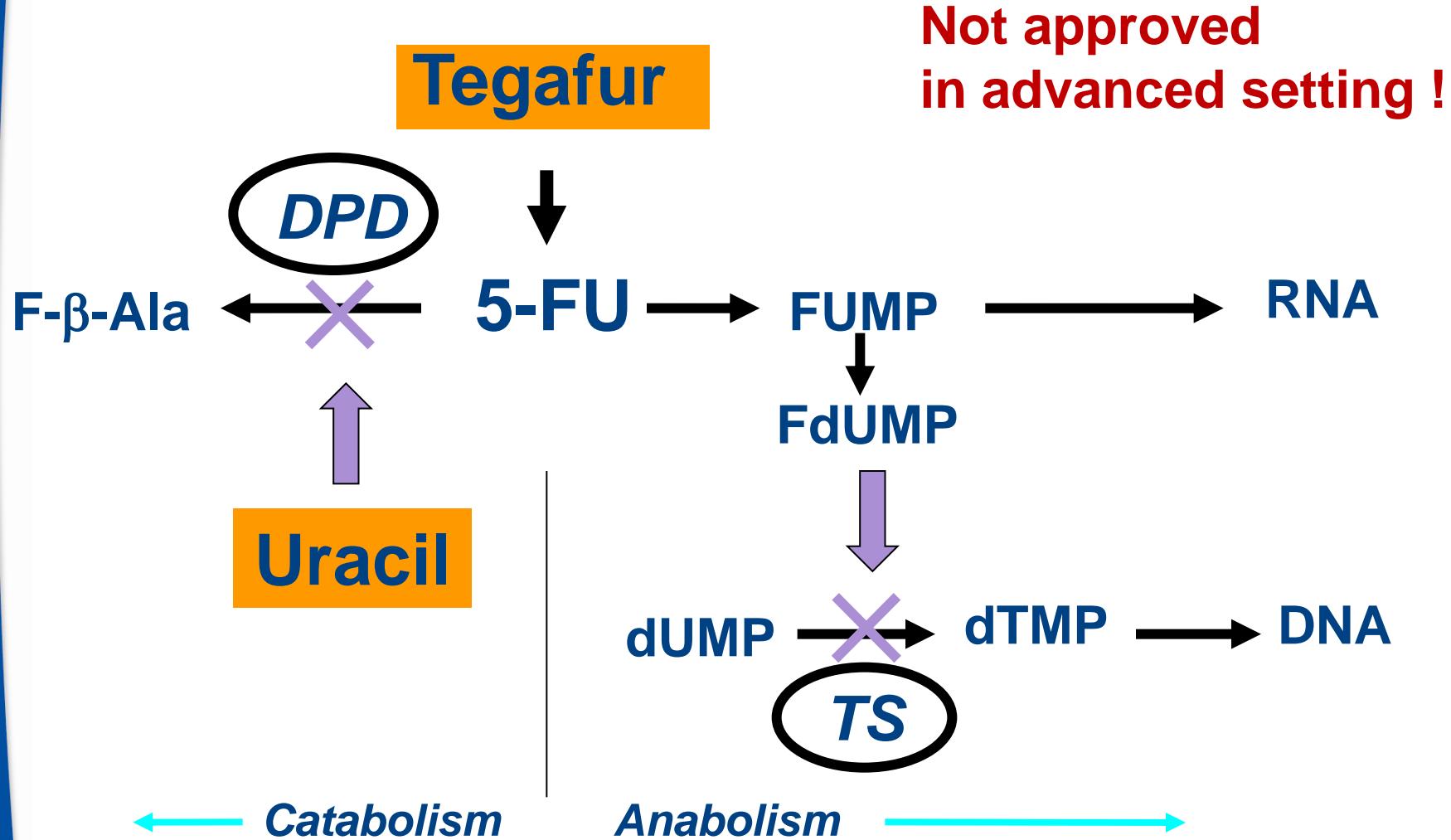
→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?

→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?
- **Unvalidated agent in the metastatic setting**

→ Action Mechanism of UFT



→ UFT JAPANESE STUDY

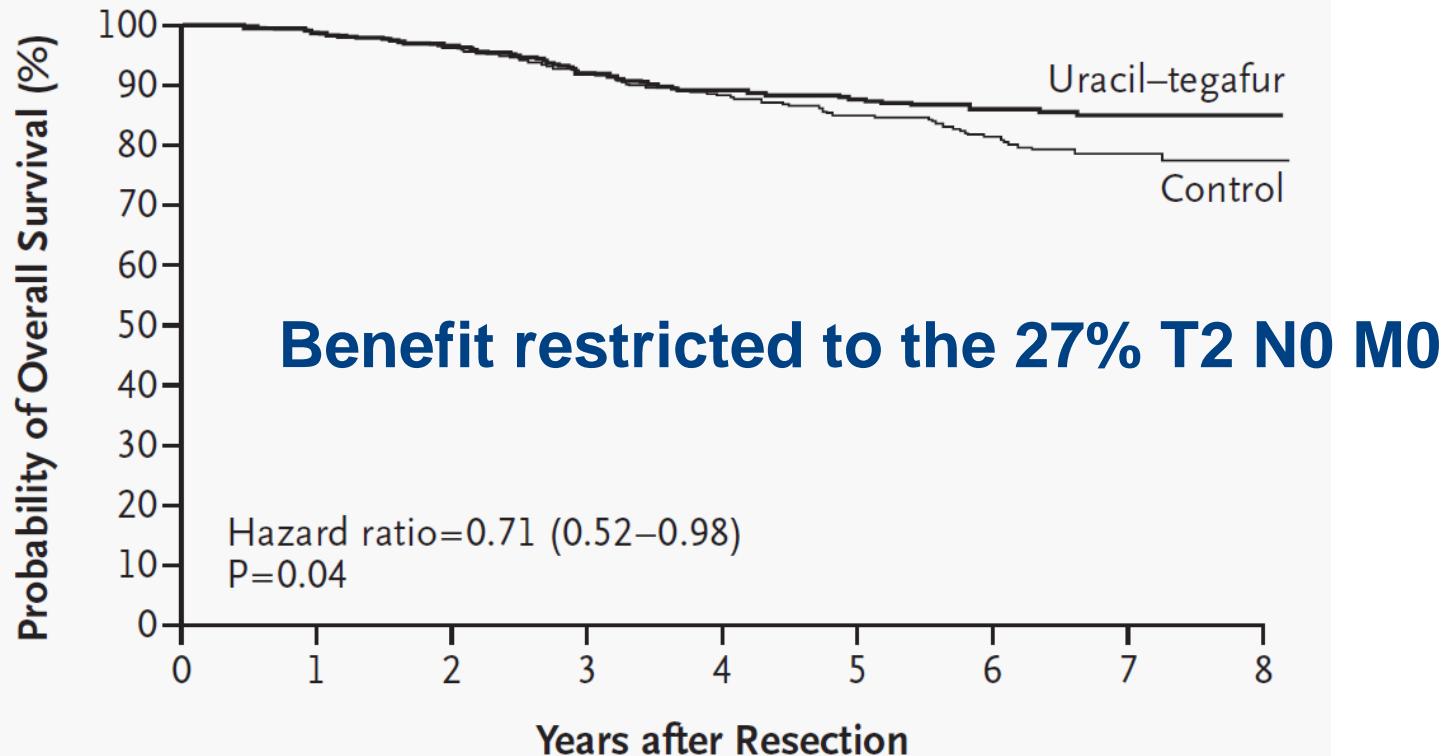
Surgery ± UFT in T1/T2 N0 M0 adenocarcinoma



- **UFT : 250 mg/m² daily x 2 years.**

→ UFT JAPANESE STUDY

A All Patients

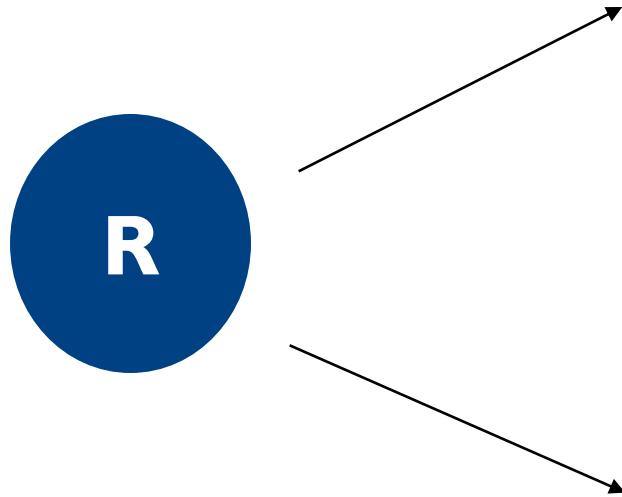


No. at Risk

	0	1	2	3	4	5	6	7	8
Control	488	481	469	445	423	378	219	96	7
Uracil-tegafur	491	482	471	442	416	368	221	105	2

→ IFCT 0703 vs. pazopanib

Surgery
Stage I
All histology



Pazopanib

- 800 mg/d
- 6 months

Phase II-III
Increase 3 years DFS by 10 %
N = 355 per arm

Placebo

- 6 months

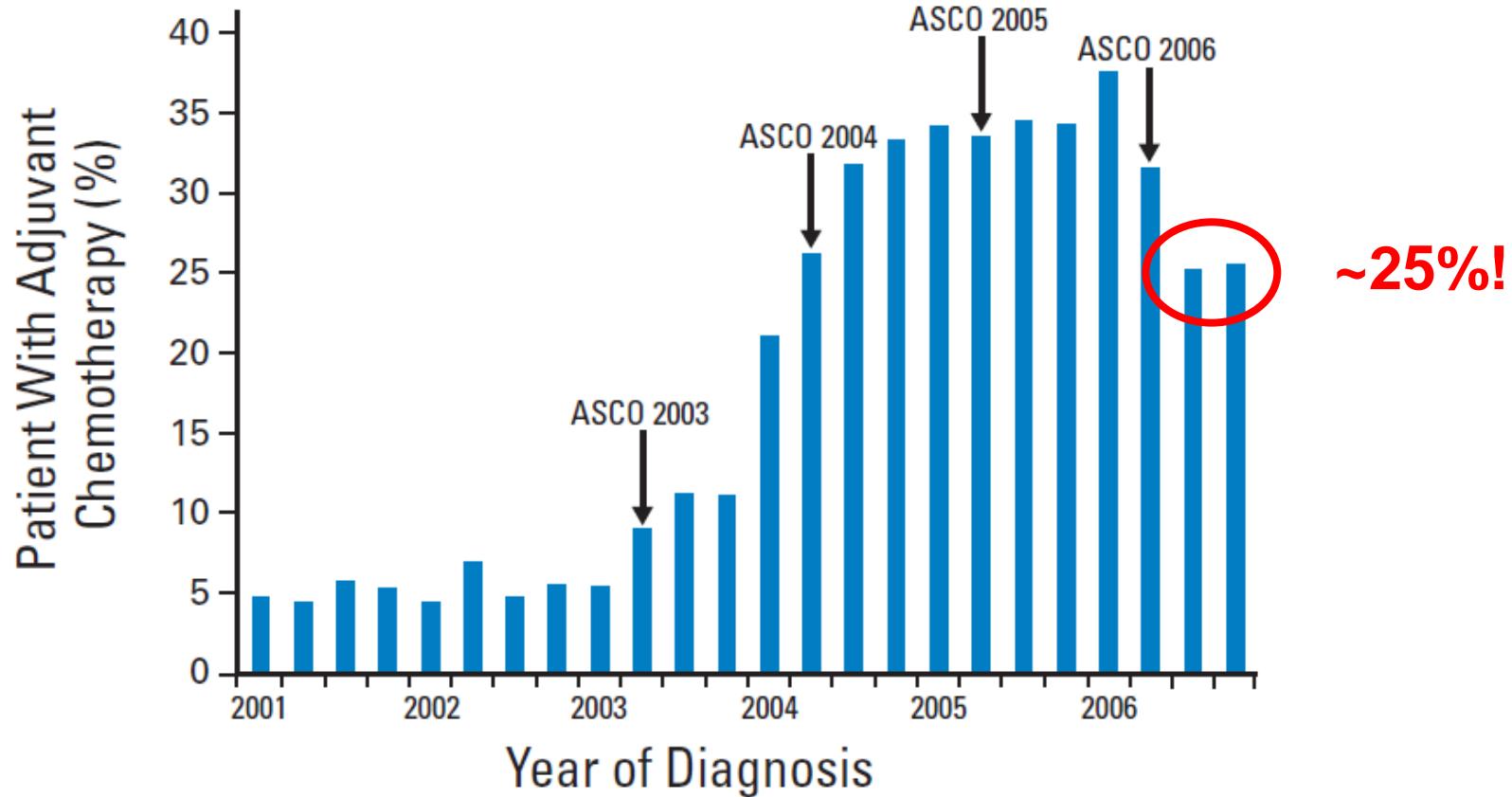
→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?
- **Unvalidated agent in the metastatic setting**
 - Reluctance from community

→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?
- **Unvalidated agent in the metastatic setting**
 - Reluctance from community
- **Alternative approach**

→ Adjuvant chemotherapy uptake



American Society of Clinical Oncology (ASCO) in 2003 IALT, 2004 JBR.10 – CALGB, 2005 ANITA, 2006 updated CALGB.

Ontario database (n=6,304) from 2001 to 2006.

→ Phase II of MAGE-A-3 in NSCLC Study Design

- Stage **IB or II**
- **MAGE-A3 (+) tumours**
- After surgery
- Recovered (PS 0-1)

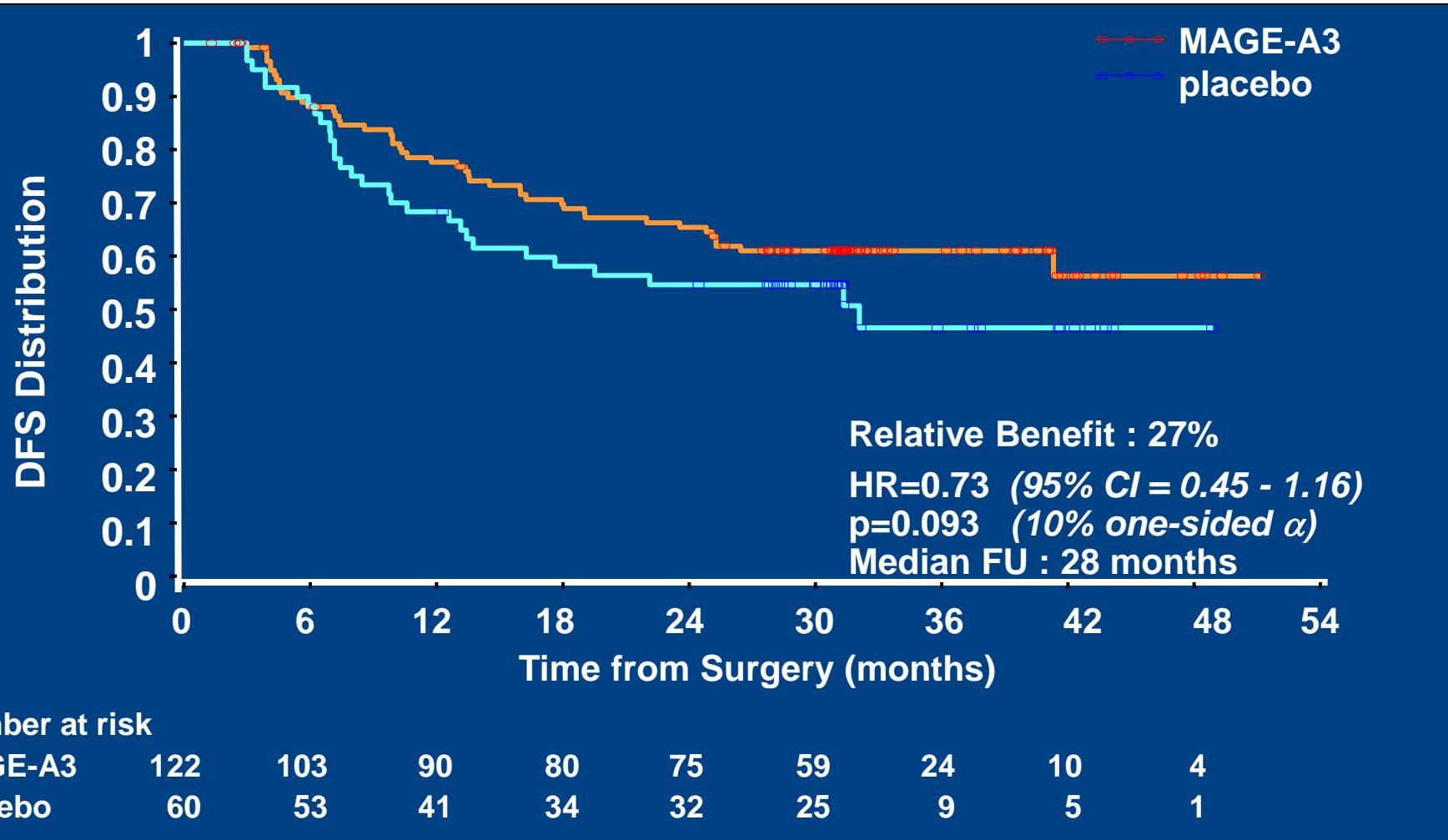


MAGE-A3 ASCI i.m.

- Induction: q3w x 5
- Maintenance: q3m x 8
- Total duration: 27 months

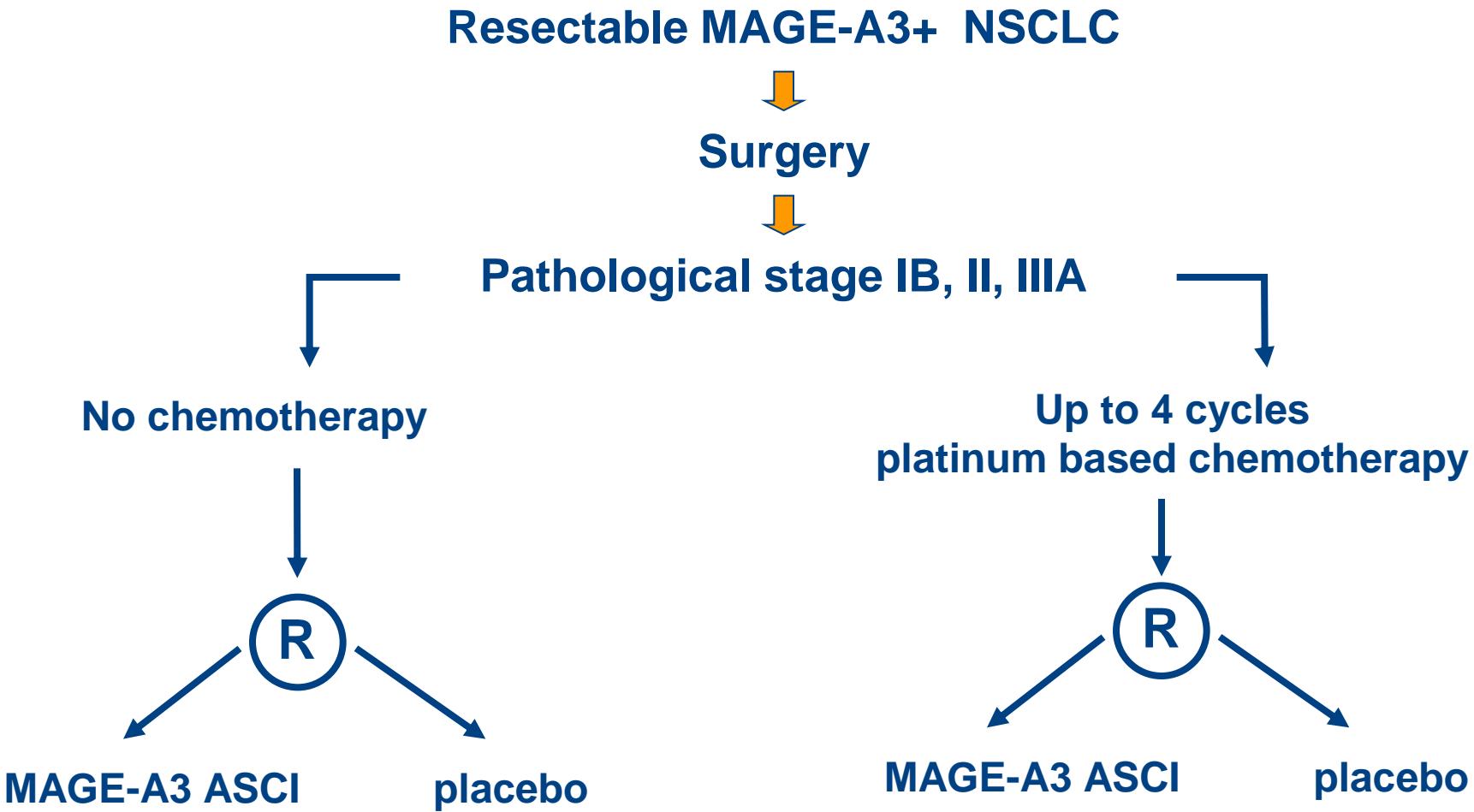
placebo
same schedule

→ Phase II - Efficacy Results: Disease-Free Survival



*DFS: Interval from the date of surgical resection to the date of recurrence OR death,
irrespective of cause of death*

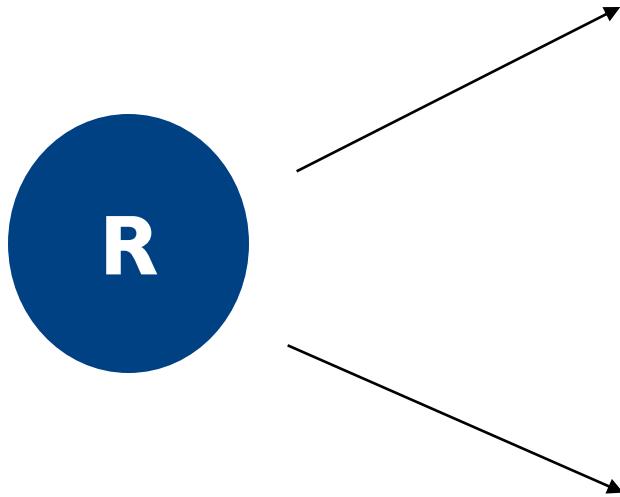
→ Phase III Study Design - MAGRIT



2,270 patients, double blind, 2:1 randomisation

→ TILT : tinzaparin vs observation

Surgery
Any stage
not N2
All histology



Tinzaparin
• 100 UI/kg/d
• 12 weeks

Observation

Decrease 3 years OS by 10 %
N = 400 per arm

→ Challenges in 2012

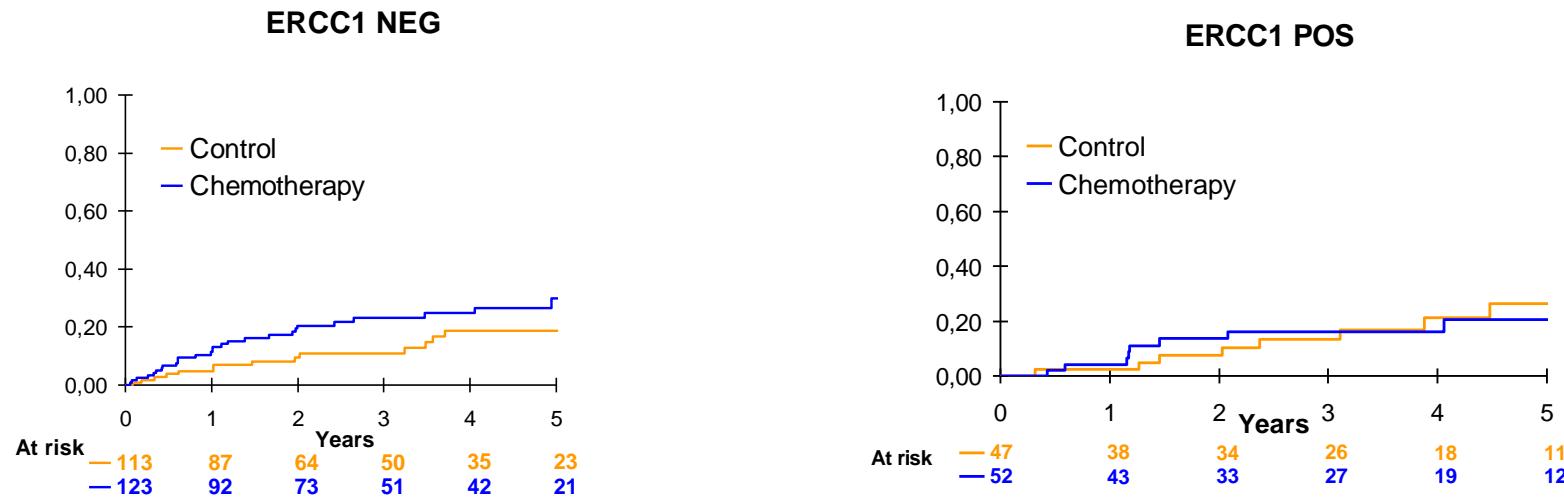
- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?
- **Unvalidated agent in the metastatic setting**
 - Reluctance from community
- **Alternative approach**
 - Effect on tumor ? Host ?

→ Challenges in 2012

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 - Effect on tumor ? Host ?
- **Pattern of relapse**

→ IALT & ERCC1

Subgroups of patients with non squamous histology (N=335)



Brain metastasis occurrence according to treatment

Brain metastasis are increased in ERCC1 NEG patients treated by CT

→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
 - Role of –omics ?
- **Unvalidated agent in the metastatic setting**
 - Reluctance from community
- **Alternative approach**
 - Effect on tumor ? Host ?
- **Pattern of relapse**
 - Customize the follow-up ?

→ Challenges in 2012

- **Customized therapy**
 - Micrometastatic disease different from stage IV?
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- **Unvalidated agent in the metastatic setting**
 - Reluctance from community
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 - Effect on tumor ? Host ?
- **Pattern of relapse**
 - Customize the follow-up ?
- **Chemotherapy is not everything**
 - Need for surgical and radiotherapy trials
 - **LUNGART**

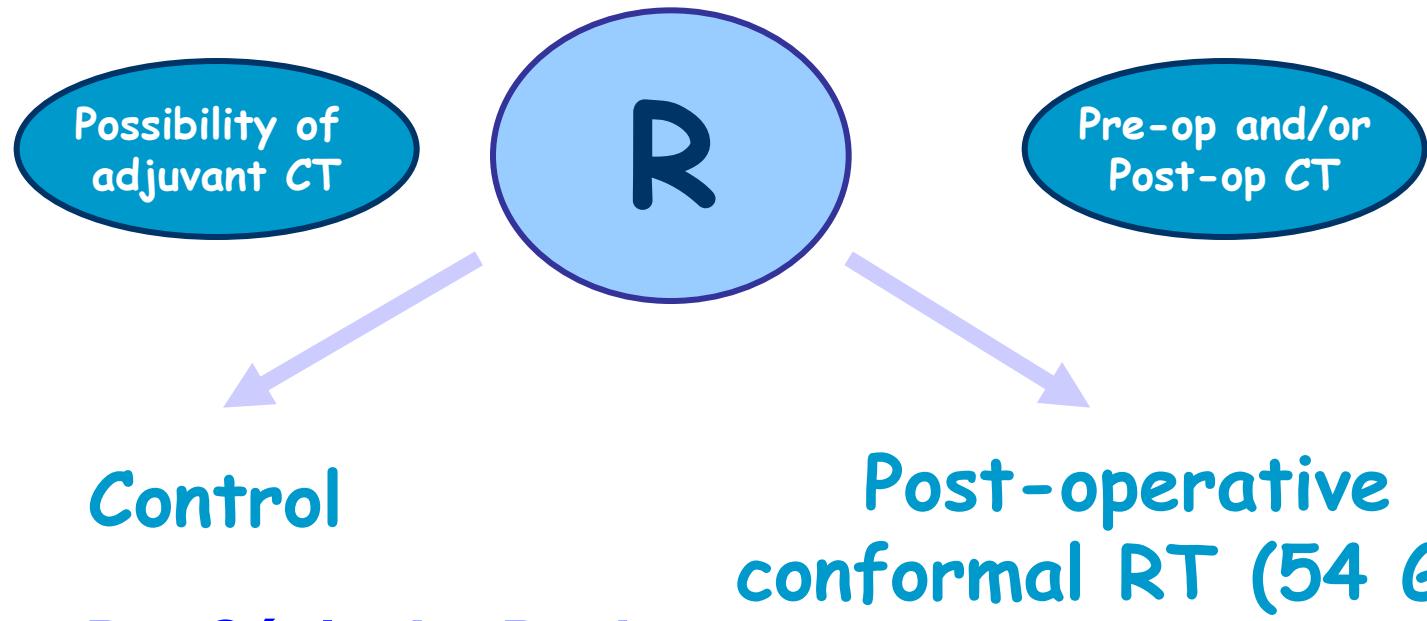
Lung ART

Lung Adjuvant Radiotherapy Trial

Trial registry: NCT00410683



Completely resected NSCLC with mediastinal
histo or cytologically proven nodal involvement



N=700 – PI : Cécile Le Pechoux