

XXV CONGRESSO NAZIONALE

**AIRO 2015**

PALACONGRESSI - Rimini, 7-10 novembre



# **CHEMIOTERAPIA ADIUVANTE NEL NSCLC**

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## **DICHIARAZIONE**

**Relatore: RITA CHIARI**

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(BOHERIGER INGHELEIM, ASTRAZENECA, PFIZER)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

# Presentation' Outline



- **What do we expect today from adjuvant chemotherapy**
- **Which data do we have with targeted agents in the adjuvant setting**
- **What we (foresee) or we would love to expect with targeted agents**
  - ....according to molecular predictors

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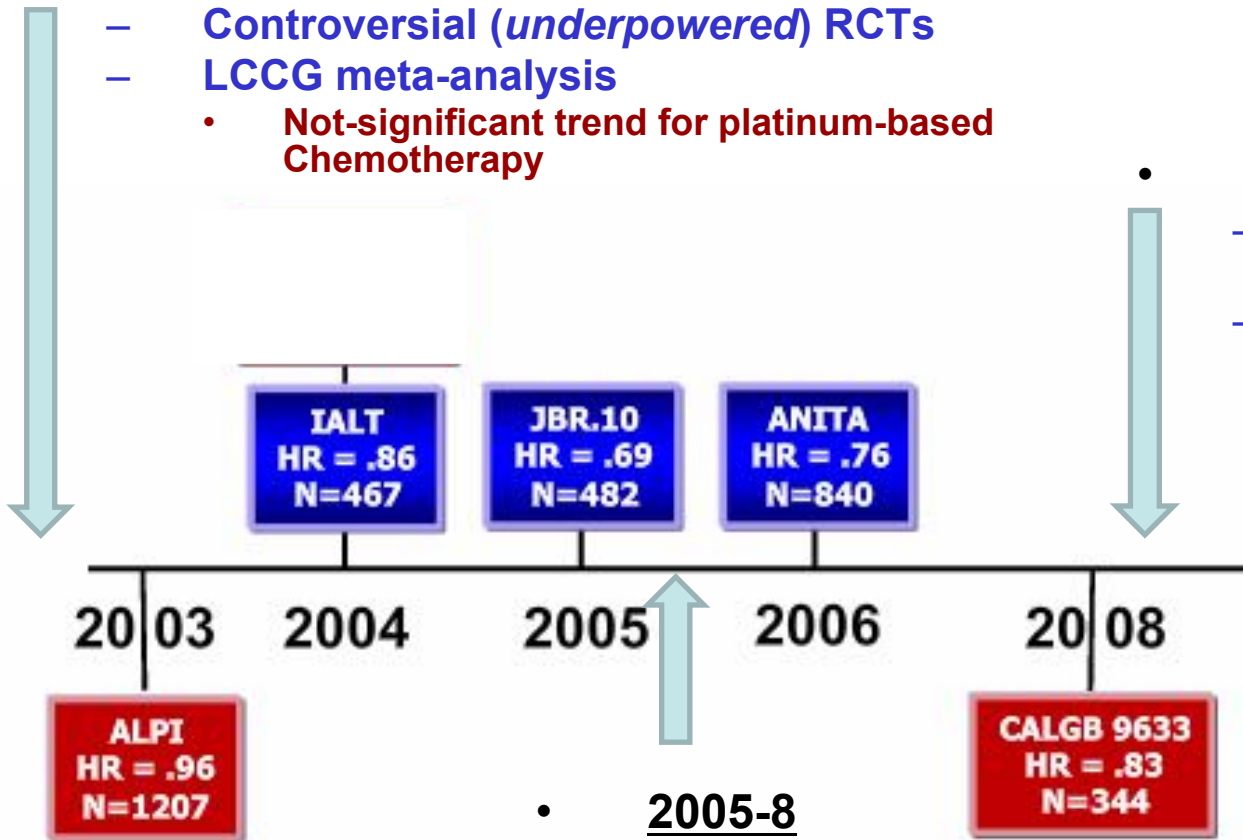
# Adjuvant Therapy Timeline

- **1995:**

- Controversial (*underpowered*) RCTs
- LCCG meta-analysis
  - Not-significant trend for platinum-based Chemotherapy

- **2008-10:**

- Long-term concerns for chemo.....?
- LCCG final release



- **2005-8**

- Powered RCTs
- Several meta-analyses
- LCCG update plus LACE
  - Significant benefit for Chemo

*Modified by Kelly K, WCLC 2013*

Magnitude of benefit of adjuvant chemotherapy for non-small cell lung cancer:  
 Meta-analysis of randomized clinical trials

Emilio Brià<sup>a,\*</sup>, Richard J. Gralla<sup>b</sup>, Harry Raftopoulos<sup>b</sup>, Federica Cuppone<sup>a</sup>,  
 Michele Milella<sup>a</sup>, Isabella Sperduti<sup>c</sup>, Paolo Carlini<sup>a</sup>, Edmondo Terzoli<sup>a</sup>,  
 Francesco Cognetti<sup>a</sup>, Diana Giannarelli<sup>c</sup>

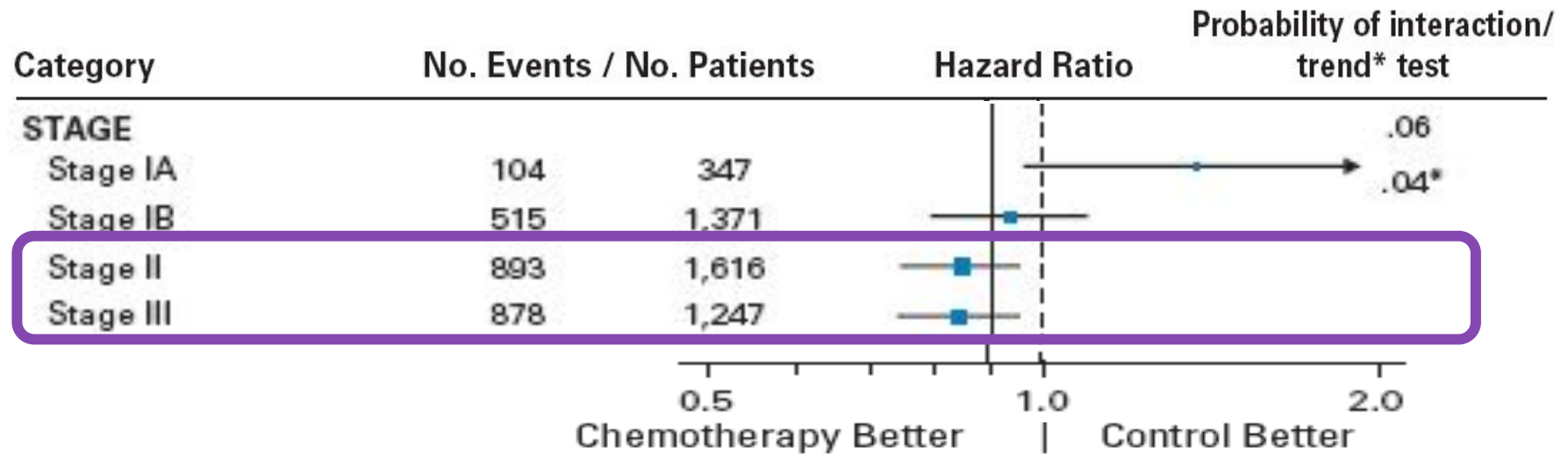
**Overall Relative Benefit of Adjuvant Chemo is  
 Consistent across all Meta-Analyses Results  
REGARDLESS of the Method (IPD/AD)**

Author	Meta-analysis (method)	Number of patients	HR/RR (95% CI)
NSCLC-CG-MA [6]	IPD	1,394	0.87 (0.74, 1.02)
Pignon et al. [36]	IPD	4,584	0.89 (0.82, 0.96)
Hotta et al. [42]	AD	3,786	0.89 (0.81, 0.97)
Sedrakyan et al. [43]	AD	3,518	0.89 (0.82, 0.96)
Berghmans et al. [41]	AD	4,602	0.83 (0.80, 0.92)
Present meta-analysis	AD	7,334	0.93 (0.88, 0.97)

**Platinum-based Adjuvant Chemo for NSCLC**

Lung Cancer 63 (2009) 50–57

# 'The Stage Effect' according to RCTs & LACE



RCTs	Stage IA	Stage IB	Stage II	Stage IIIA
ALPI	Negative	Negative	Negative	Negative
IALT	Negative	Negative	Negative	Positive
JBR.10	<del></del>	Negative	Positive	<del></del>
CALGB	<del></del>	Negative	<del></del>	<del></del>
ANITA	<del></del>	Negative	Positive	Positive

LACE Group, JCO 2008

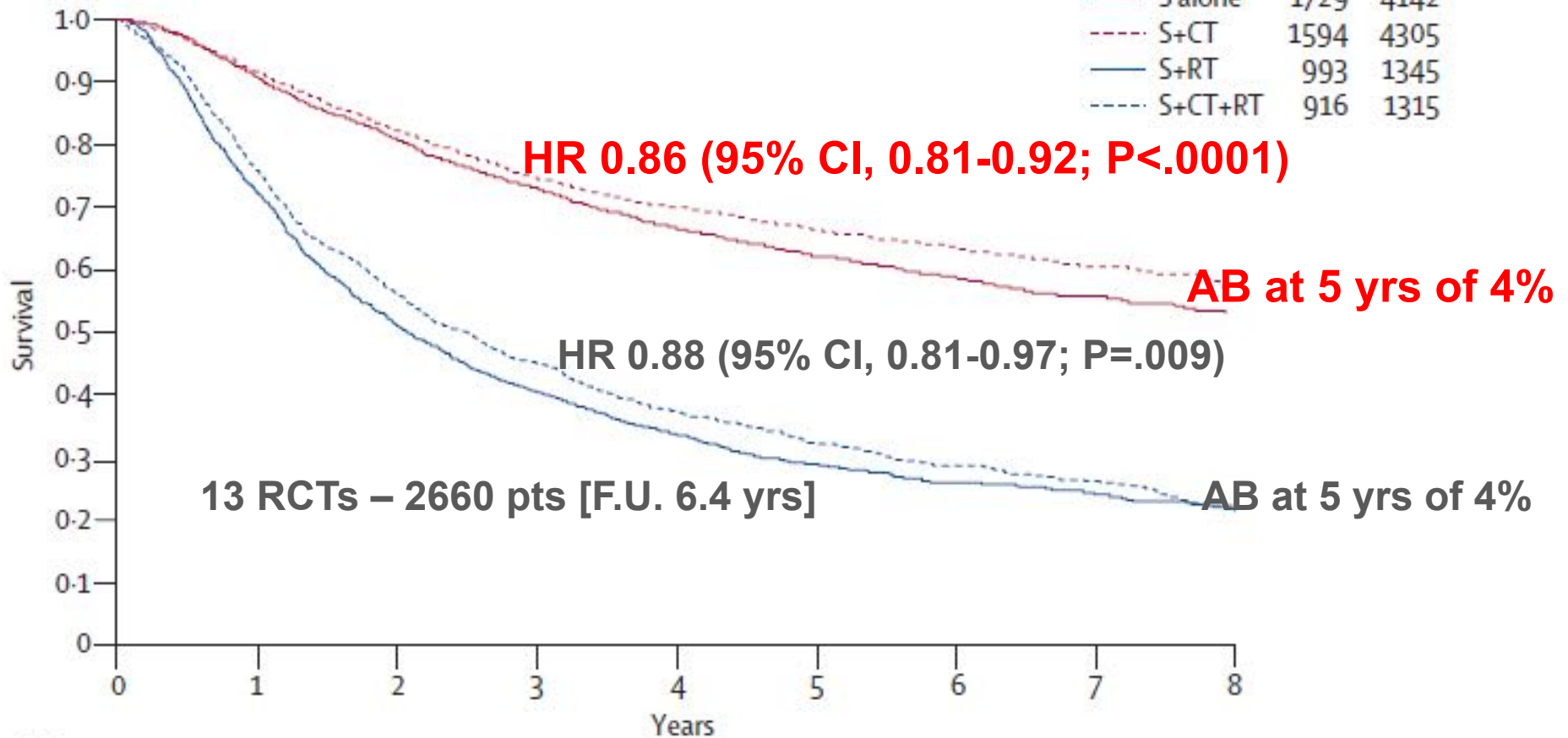
# Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

NSCLC Meta-analyses Collaborative Group\*

**34 RCTs – 8447 pts [F.U. 5.5 yrs]**

Events Totals

—	Salone	1729	4142
- - -	S+CT	1594	4305
—	S+RT	993	1345
- - -	S+CT+RT	916	1315

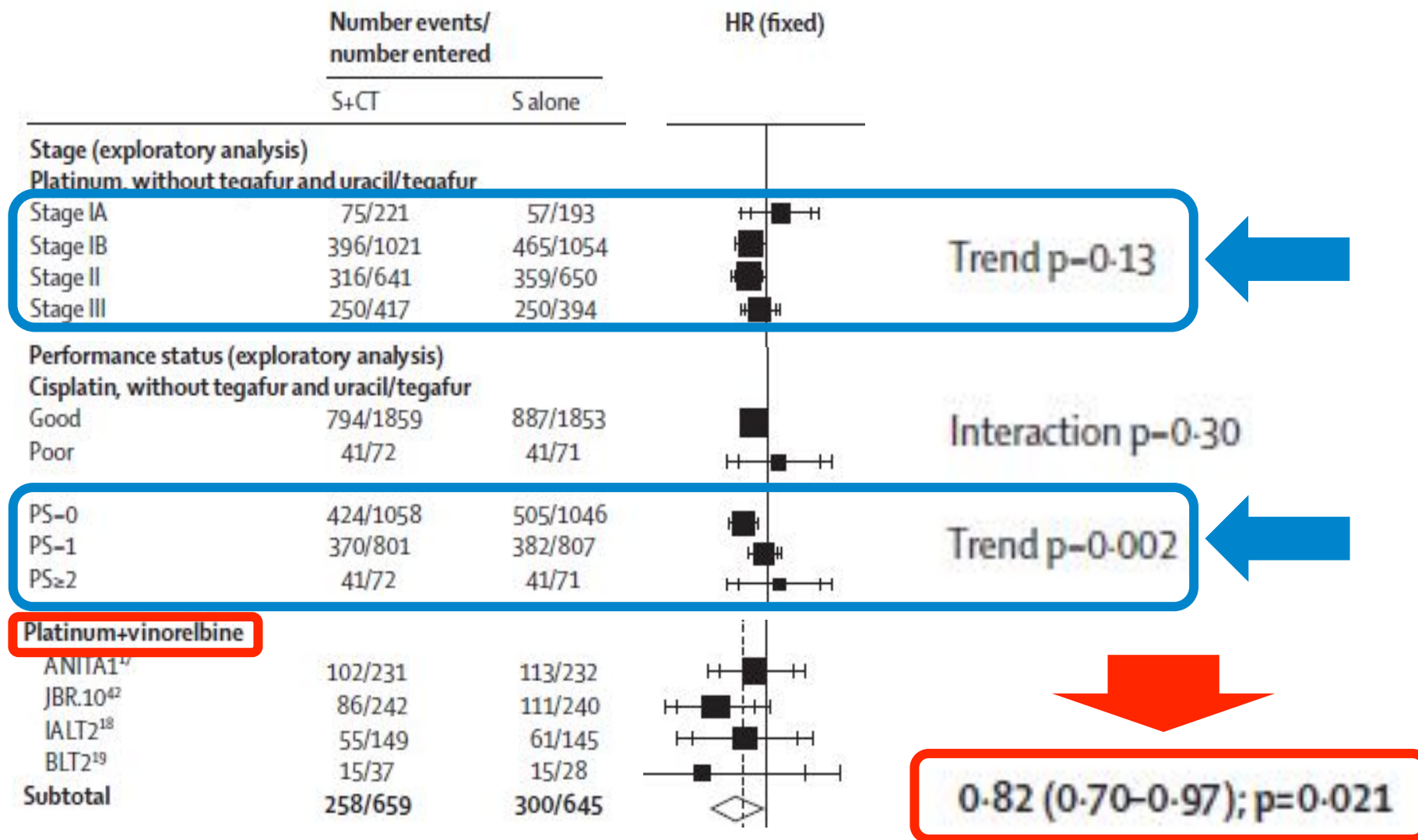


**NSCLC MACG, Lancet 2010**



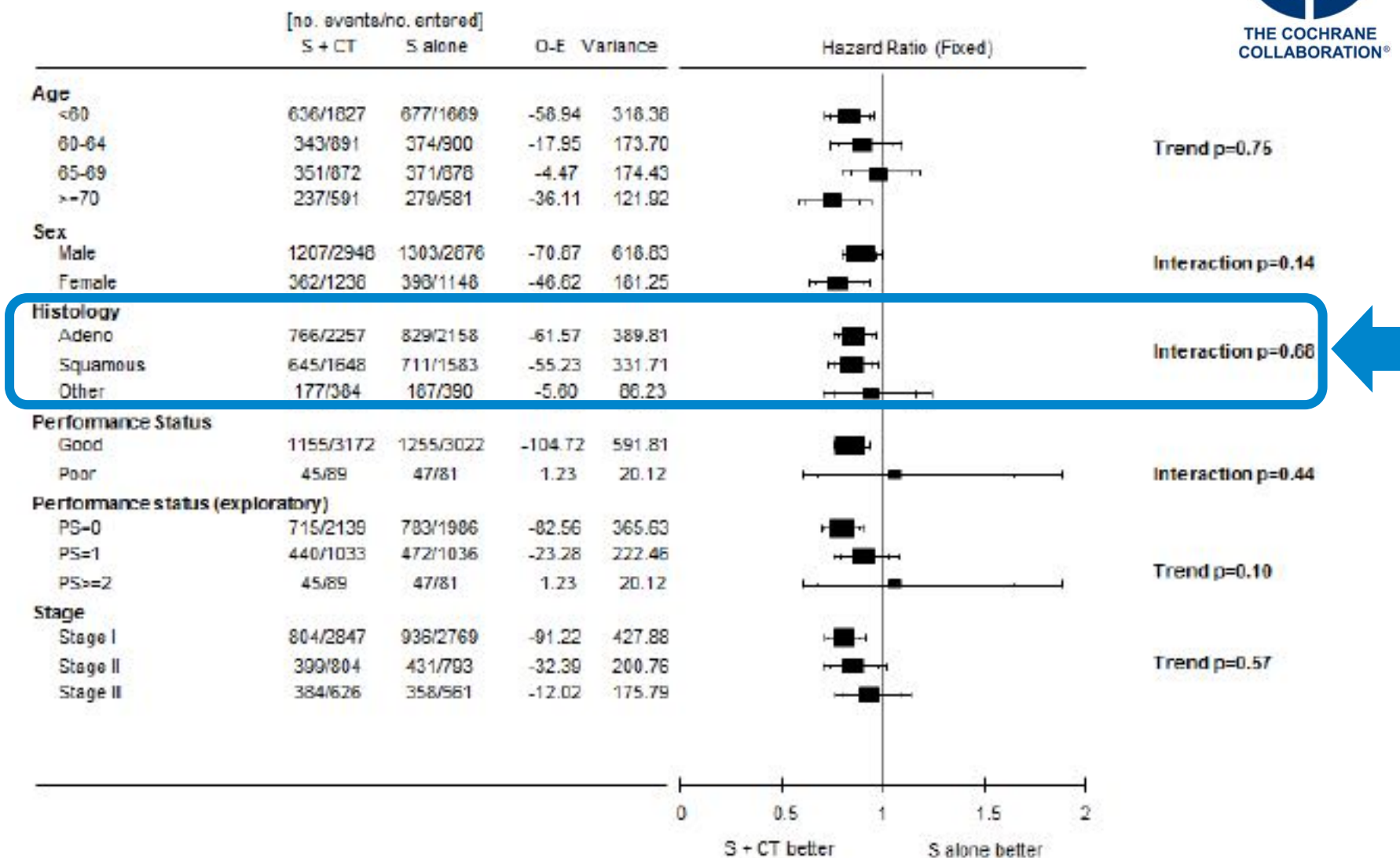
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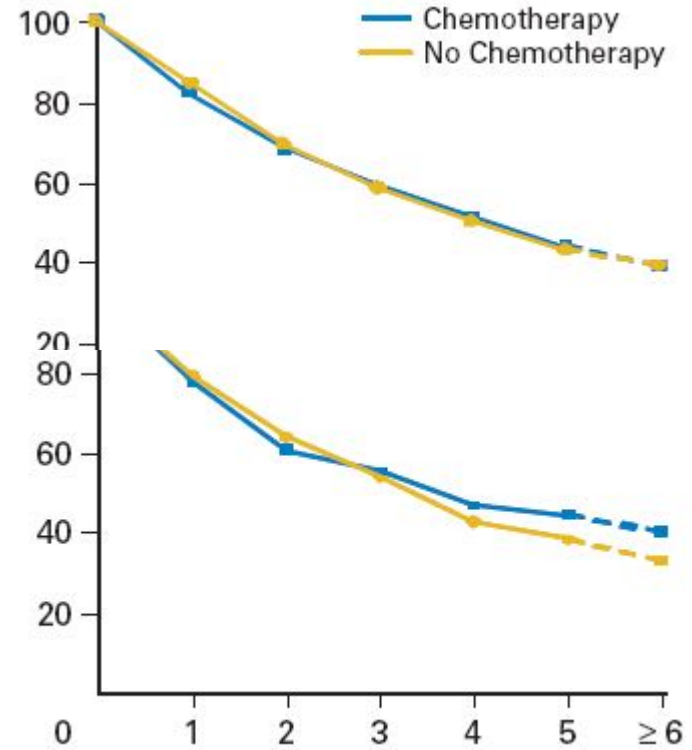
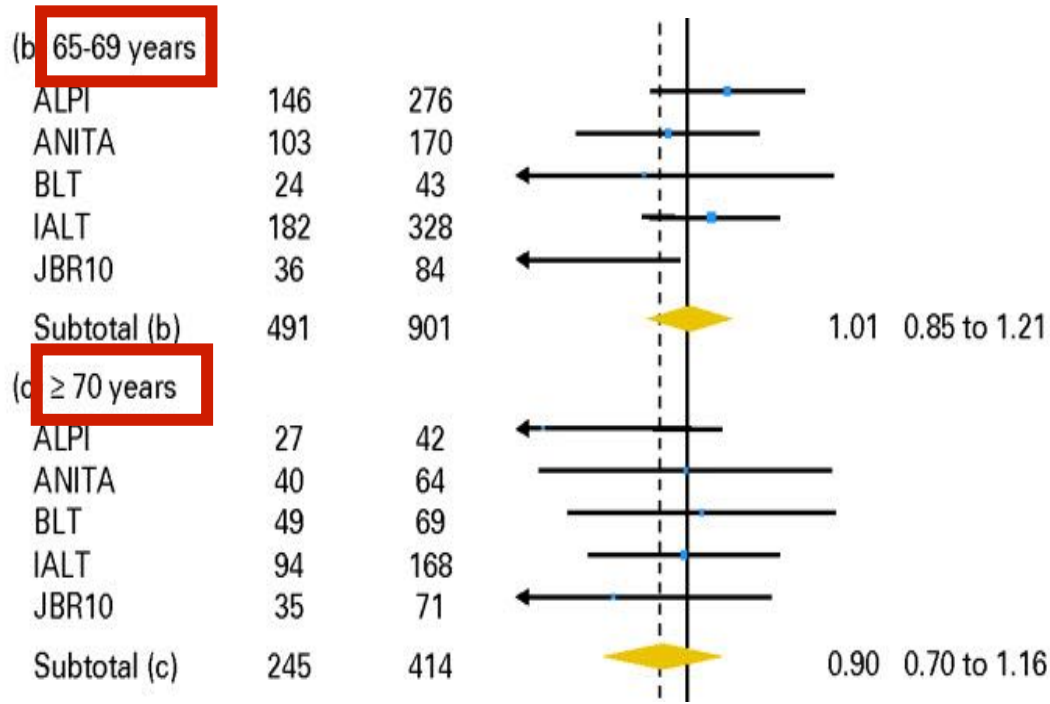
**NSCLC MACG, Lancet 2010**

# Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)



*Burdett, Cochrane Dat. 2015*

# 'The Age Effect' according to LACE



No differences in severe toxicity rates were observed.

No statistically significant interaction ( $P=.26$ ) or test for trend ( $P=.29$ )

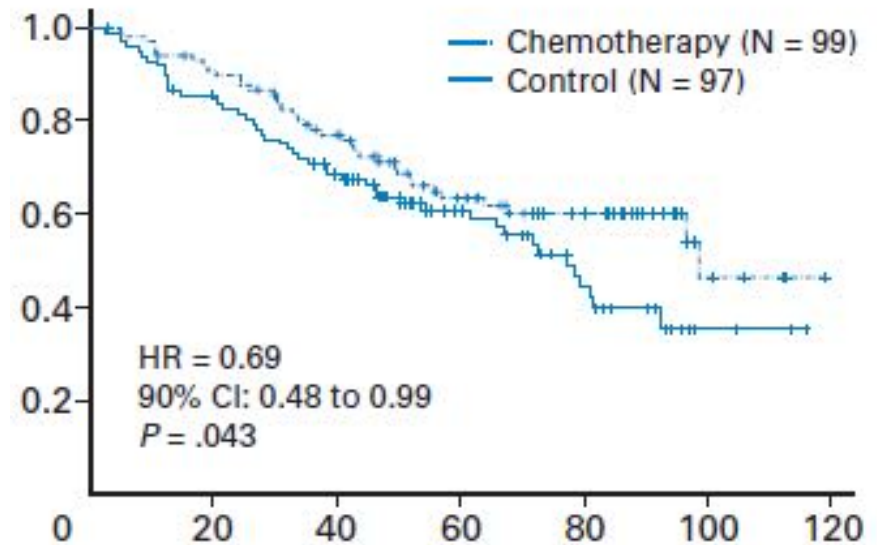
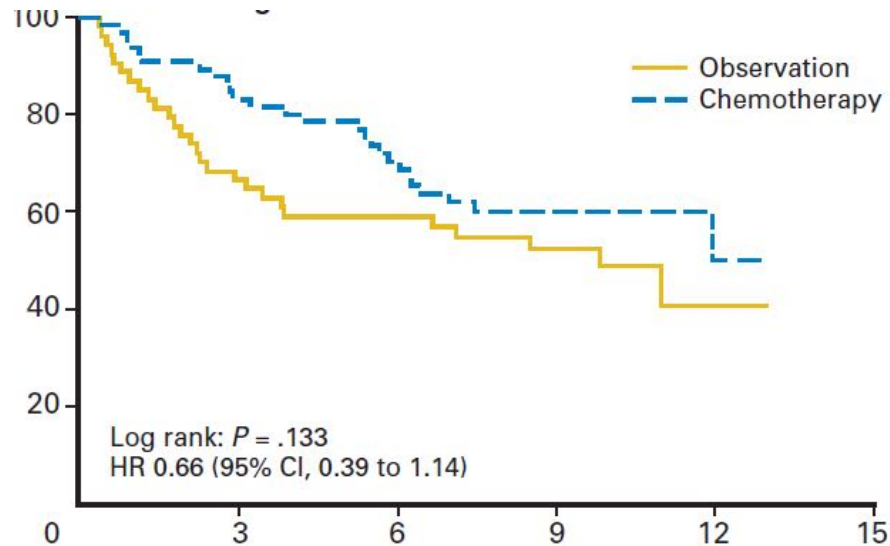
LACE Group, JCO 2008

# 'Big/High-Risk' Stage I

## [INCON]?

**JBR.10**

**CALGB 9633**

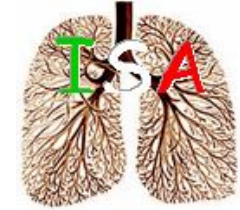


Butts, JCO 2010

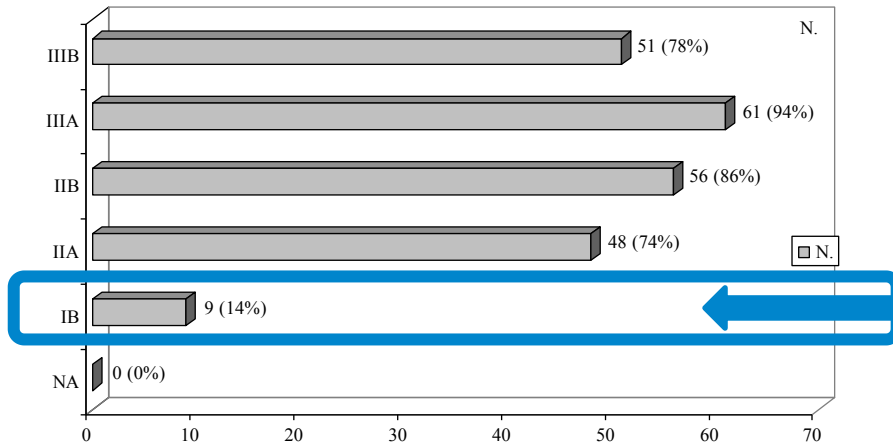
Strauss G, JCO 2008

**T-size  $\geq$  4 cm**

# Italian Survey on Adjuvant Treatment of Non-Small Cell Lung Cancer (ISA)

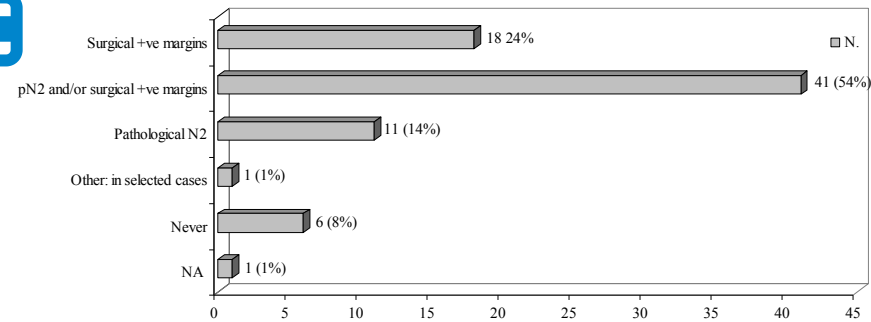


## Indication for adjuvant chemotherapy by stage

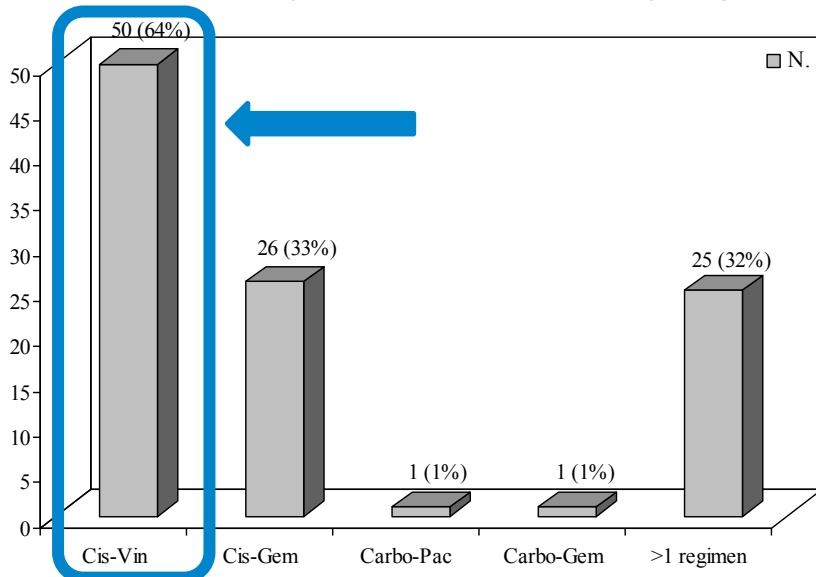


- 46-item questionnaire
- 78 physicians - 68 out of 98 Italian Centers (53% North – 4 % South-Centre-Islands)
- Disclosed adherence to GL 97%
- 3 confirmation questions by 65 phys.

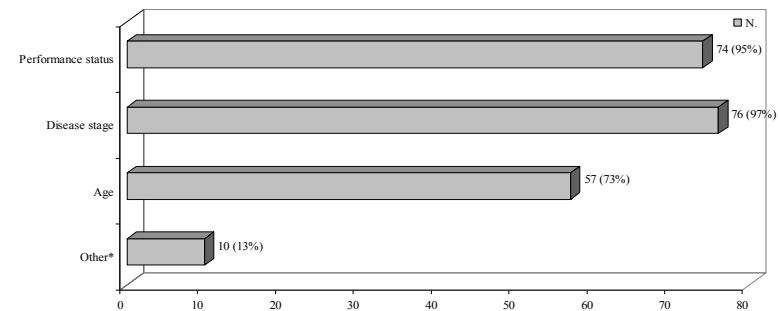
## Indication for post-operative radiotherapy



## Preferred adjuvant chemotherapy regimen



## Prognostic factor used for indication for AT



Banna G, ISA Investigators, Lung Cancer 2011

# Adjuvant Chemotherapy – Optimal Regimen



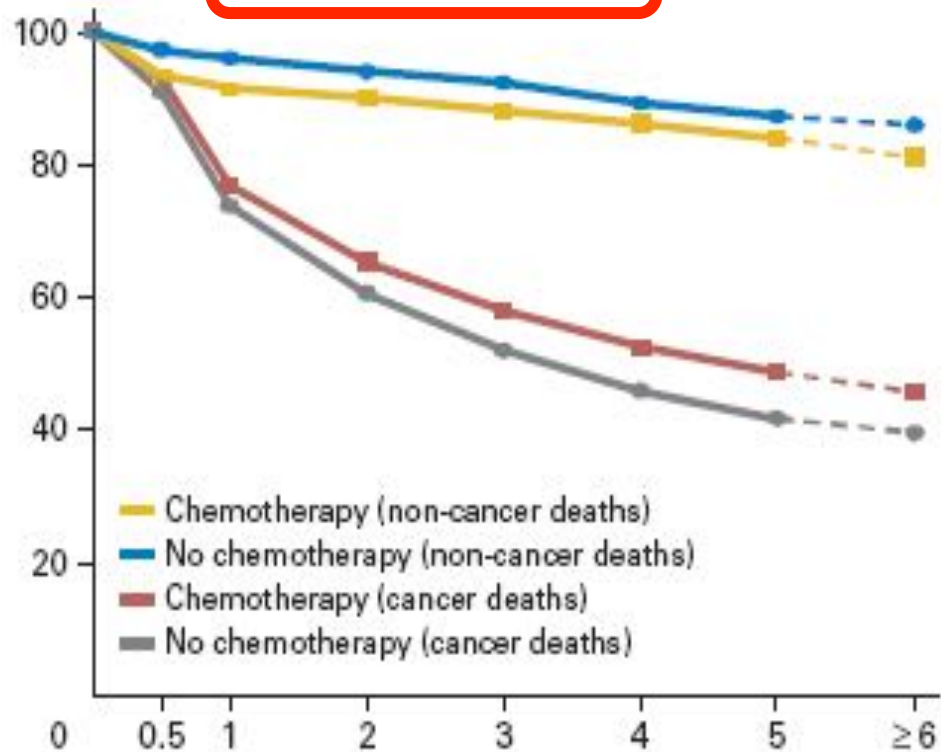
**Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study**

*Kueter M et al. Ann Oncol 24: 986-992;2012*

	Cis/Vb N-67	Cis/Pem N-65
Feasibility	74%	96%
Completion of Therapy	63%	22%
Grade 3-4 hematological toxicity <span style="border: 1px solid red; padding: 2px;">p = .001</span>	78%	11%
Grade 3-4 non-hematological toxicity	33%	31%
Dose Delivery (% Planned)	Cis 66%	Cis 90%
	Vb 64%	Pem 90%

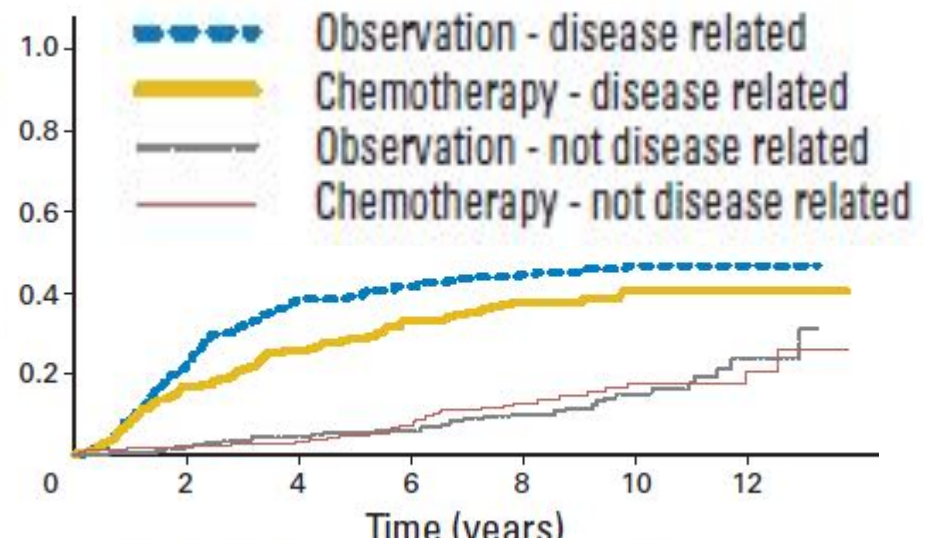
# 'Late events' at longer F.U.

**LACE**



Pignon, JCO 2008

**JBR.10**



Test for Non-Disease-Related Deaths

Log-rank  $P = .660$

Fine-Gray test  $P = .622$

Test for Disease-Related Deaths

Log-rank  $P = .027$

Fine-Gray test  $P = .023$

Butts, JCO 2010

# What do we expect today from Adjuvant chemotherapy

- CDDP-based (not carboplatin) adjuvant CHT is indicated for stage II and IIIA PS 0-1 pts (controversy upon Stage IB)
  - *Subset analyses suggest a benefit for pts with a tumor size > 4 cm*
- Elderly patients should not be excluded
- Clear benefit...but somewhat small
  - .....*may be smaller at longer follow-up?*
- Non-cancer related mortality may be higher in pts receiving adjuvant CHT



**Can we do better with curves?**



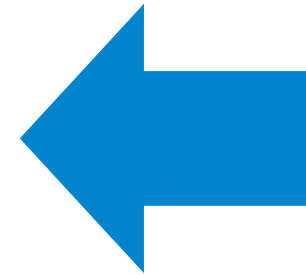
# Presentation' Outline



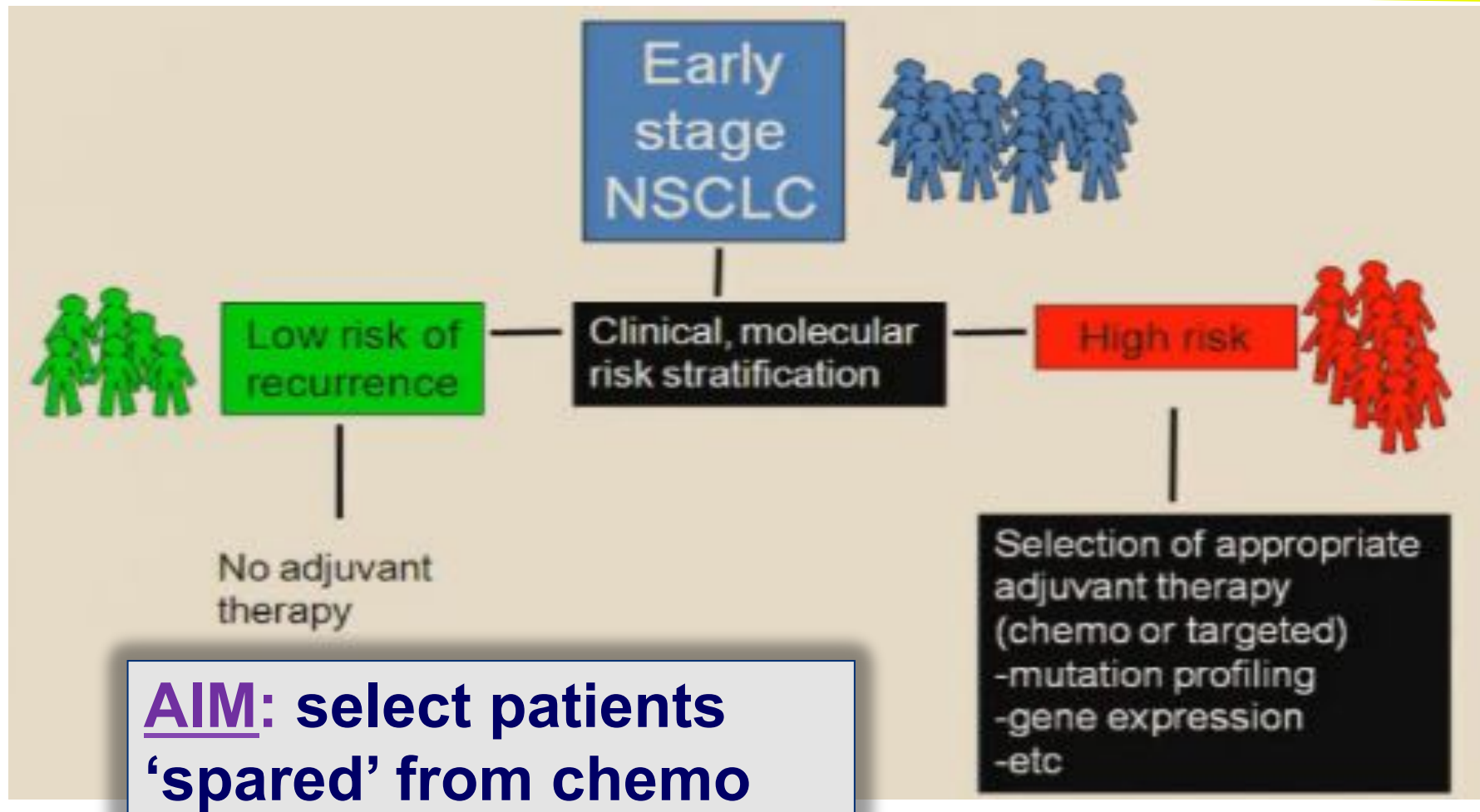
- What do we expect today from adjuvant chemotherapy
- **Which data do we have with targeted agents in the adjuvant setting**
- What we (foresee) or we would love to expect with targeted agents
  - ....according to molecular predictors

# 'Maximization' Of Benefit

- **Increasing the 'clinical therapeutic index' of drugs, so 'tailoring' the treatment, on the basis of:**
  - **New predictive factors, through, for example genomics:**
    - Increase the rate of 'sensitive' patients
    - Decrease the rate of 'resistant' patients
- **Improving the clinical trial design**
  - Clinical and Molecular Surrogates of survival
    - Smaller sample size
    - Earlier indication of benefit

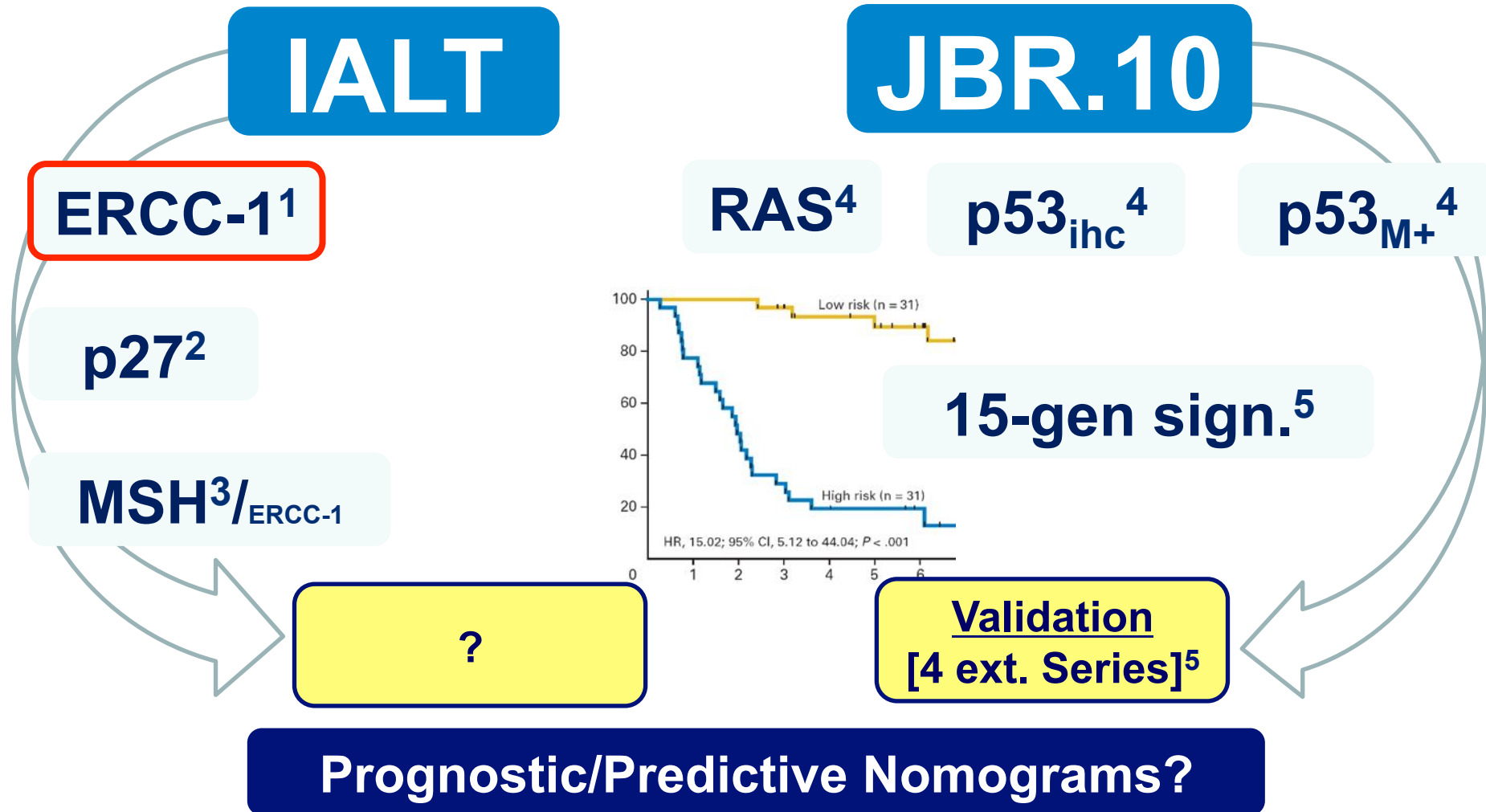


# What should we expect?



*Modified - Heymach, ASCO 2010*

- Retrospective Analyses -  
**‘Seeking for a biomarker’**

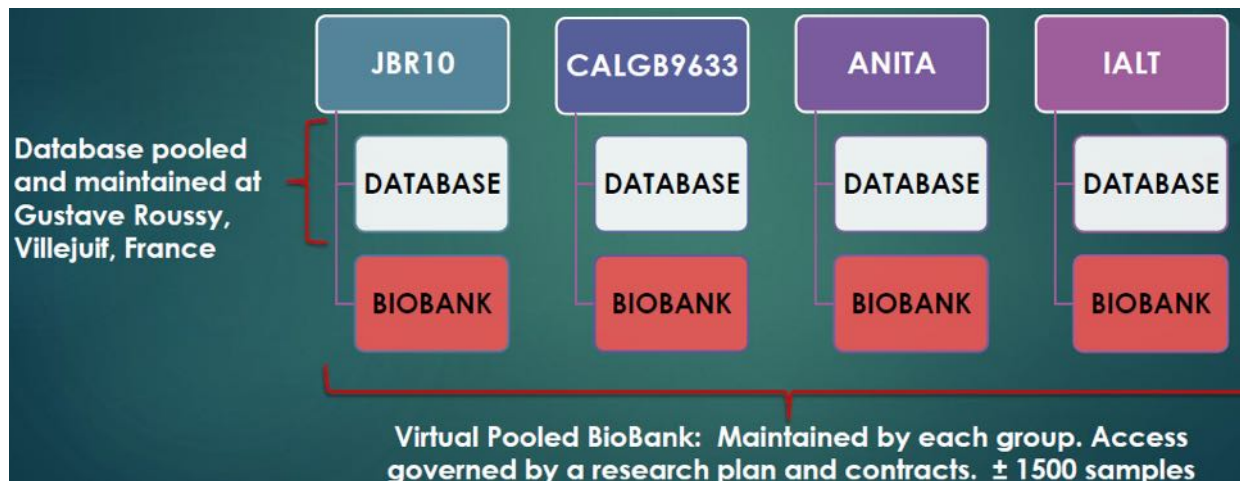


<sup>1</sup>Olaussen NEJM 2006; <sup>2</sup>Filipits JCO 2007; <sup>3</sup>Kamal CCR 2010; <sup>4</sup>Tsao JCO 2007; <sup>5</sup>Zhu JCO 2010

# LACE-Bio

► The validation of biomarkers, based on immunohistochemical (IHC) tests\* which are prognostic for relapse/death or predictive of benefit from ACT.

	Stage	Chemotherapy	RT	N	Year	Biobank
NCIC CTG JBR10	I, II	Cisplat, vinorelbine	No	482	1994-2001	Y
ALPI	I, II, IIIA	Cisplat, MMC/ vindesine	Opt.	1088	1994-1999	N
ANITA 01	I, II, IIIA	Cisplat, vinorelbine	Opt.	840	1994-2000	Y
IALT	I, II, III	Cisplat, vinca or etoposide	Opt.	1867	1995-2001	Y
BLT	I, II, III	Cisplat, vinca/MMC/ifos	Opt.	307	1995-2001	N
CALGB 9633	IB	Carboplat, paclitaxel	No	344	1996-2003	Y



► For lymphocyte infiltration  
 ► slides were reviewed by both pathologists  
 ► any discrepancies were reconciled



# Prognostic and predictive biomarkers for ACT (adjuvant chemotherapy) in resected non-small cell lung cancer (R-NSCLC): [LACE-Bio](#)

While a number of biomarkers were identified in single studies that could have predictive or prognostic value, cross-validation with the other studies did not confirm the utility of the majority of markers (see table on next slide)

Marker	Trial 1 <sup>st</sup> tested in	Predictive?	Prognostic?	Validated?
ERCC1	IALT	Yes	Yes	No
<b>Lymphocyte infiltrate</b>	<b>IALT</b>	<b>No</b>	<b>Yes</b>	<b>Prognostic (OS/DFS)</b>
Mucin	CALGB	No	Yes	No
<b>β-tubulin</b>	<b>JBR10</b>	<b>Trend</b>	<b>Yes</b>	<b>Prognostic (OS/DFS)</b>
P27	IALT	Yes	No	No
<b>FASL</b>	<b>IALT</b>	<b>Trend</b>	<b>No</b>	<b>Predictive (OS)</b>
FAS/FASL	IALT	Yes	Yes	No
BAX	IALT	Trend	No	No
Cyclin E/P16*	IALT, JBR10	No	No	No
P53*	IALT, JBR10, CALGB	Yes**	Yes**	No

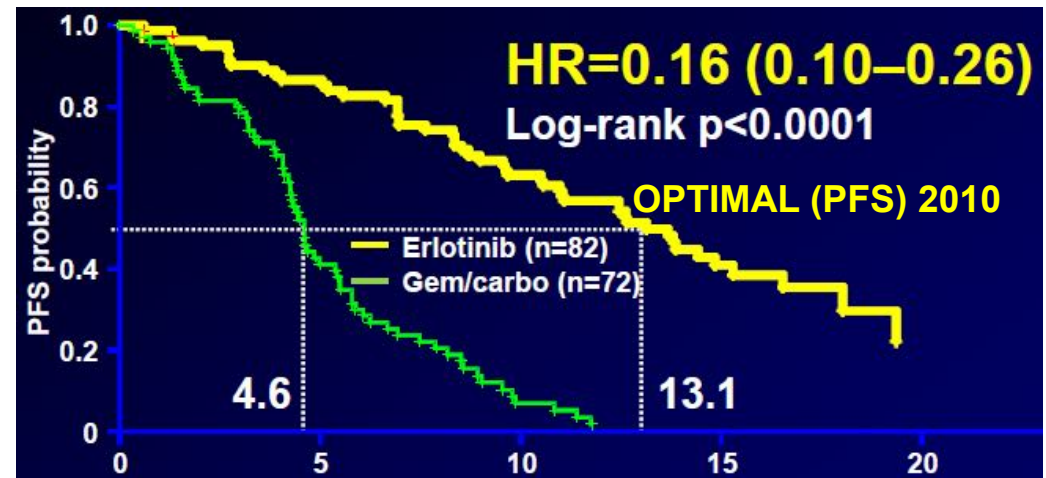
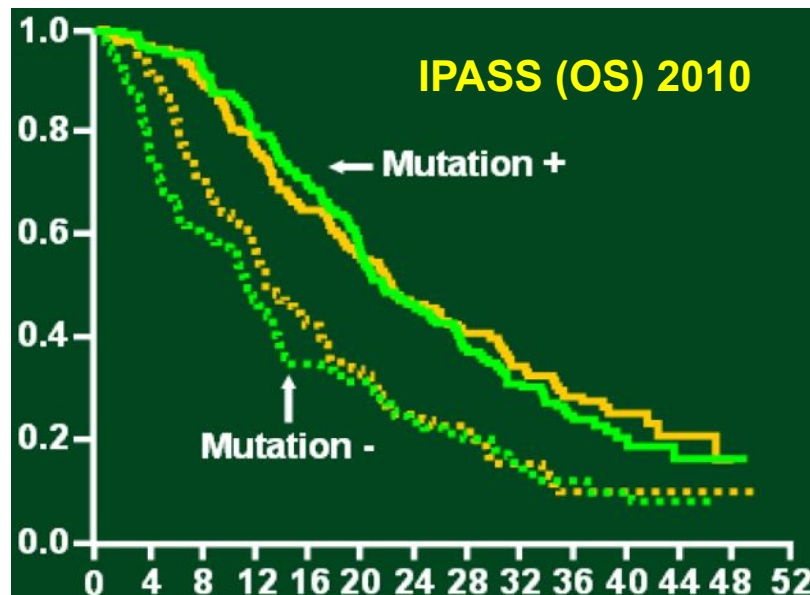
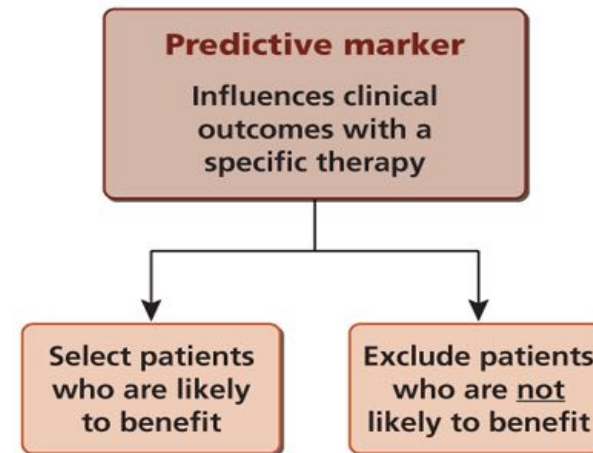
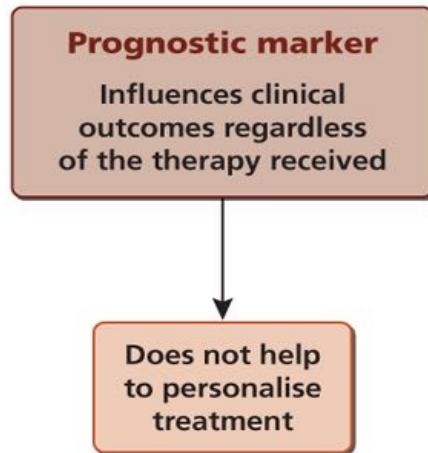
- **Conclusion**

- IHC assays from single trials may be misleading and should be validated before being implemented

*Seymour et al, ESMO 2014*

# A Single Biomarker Can Have Both Prognostic and Predictive Values

## The Case of EGFR-M+



Courtesy of Zhou & Soria, ESMO 2010; Wolf J, PeerView Press 2010

# Adjuvant Gefitinib: JBR 19

- Path stage IB - III NSCLC
- Complete surgical resection
- PS 0-2
- Adjuvant chemo and /or XRT allowed

N = 503

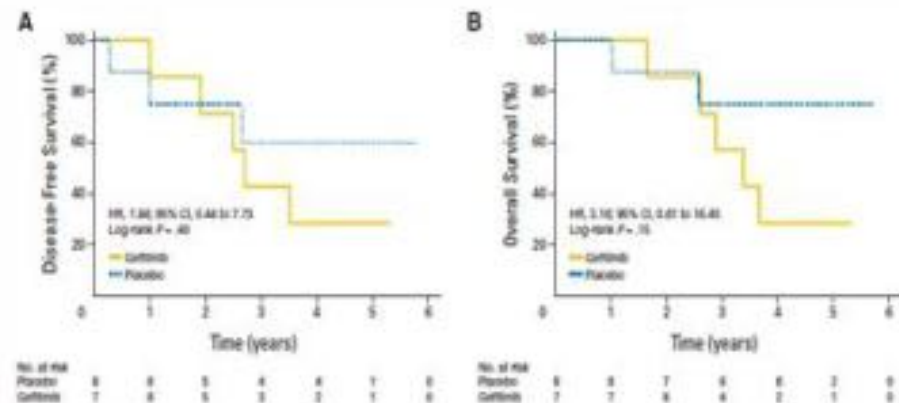
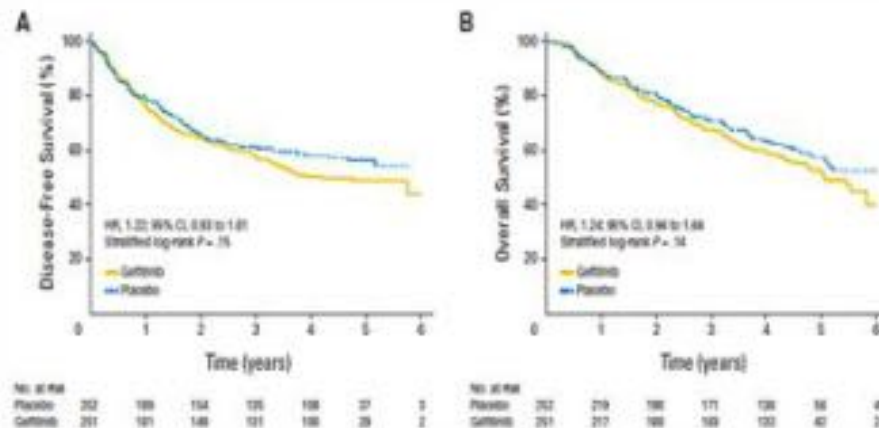


Gefitinib  
250 mg po q day  
x 2 years

Placebo  
PO q day  
x 2 years

All patients

EGFR Mutated

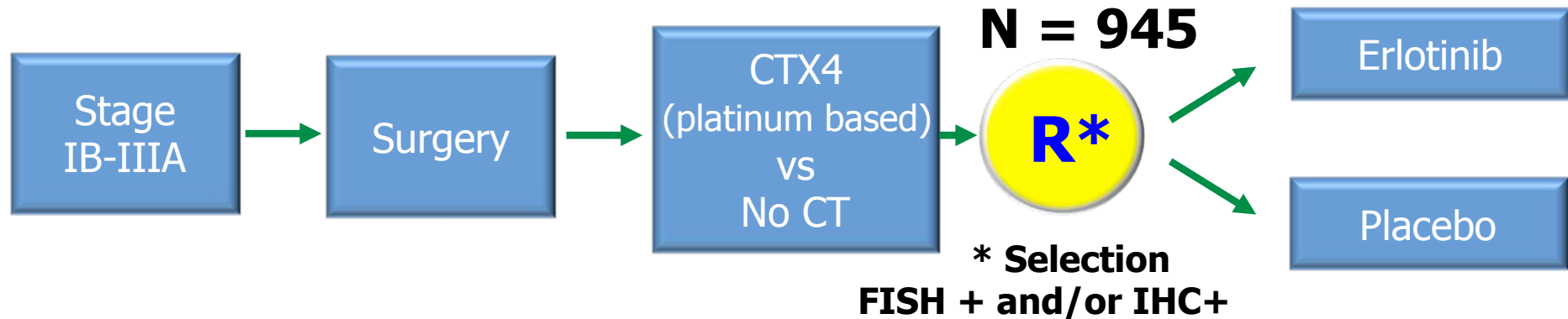




# Adjuvant Therapy: Erlotinib

Unselected for EGFR mut+

## RADIANT



Primary endpoint: Disease Free Survival

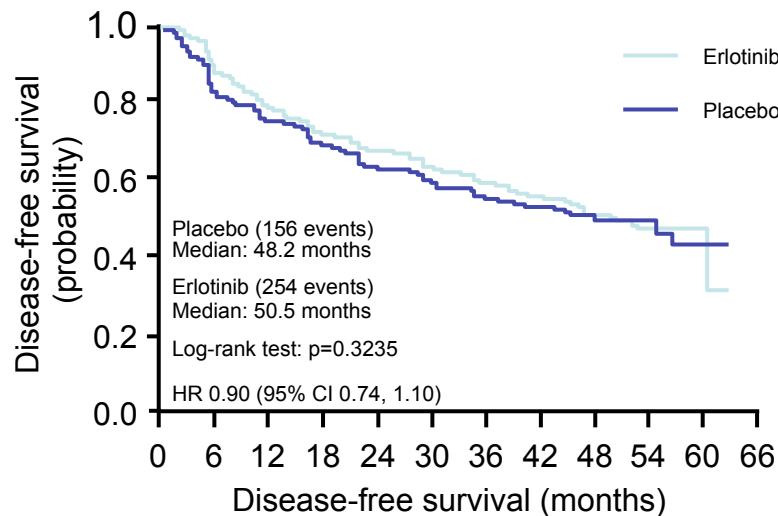
### HISTORICAL CONTEST

Original Protocol	2006 May	(from BR21 data	FISH+ and IHC+)
Amendment	2010	(from Saturn data	FISH+ IHC+ and EGFR mut+)
First Report	2014 May		

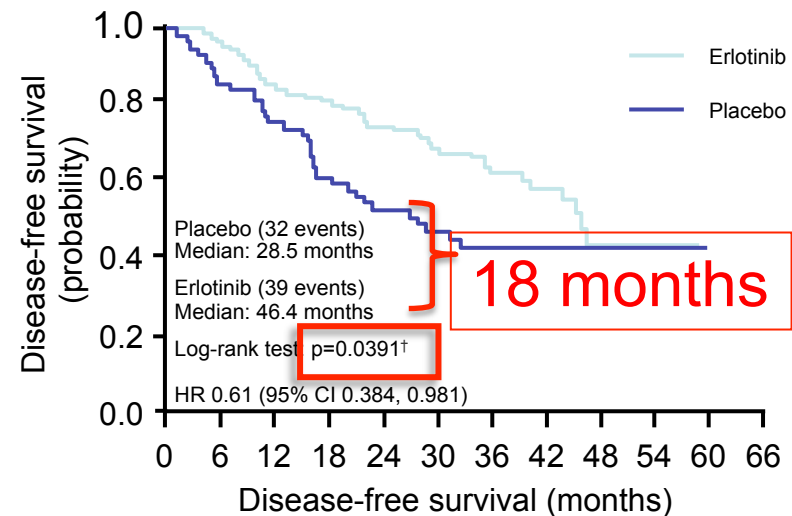
8 years

# RADIANT: Adjuvant erlotinib did not prolong disease-free survival

## DFS (overall population)

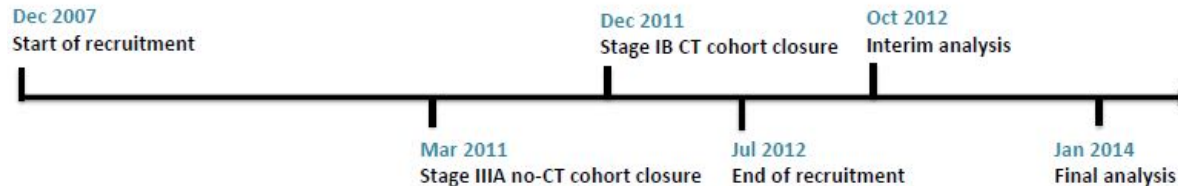
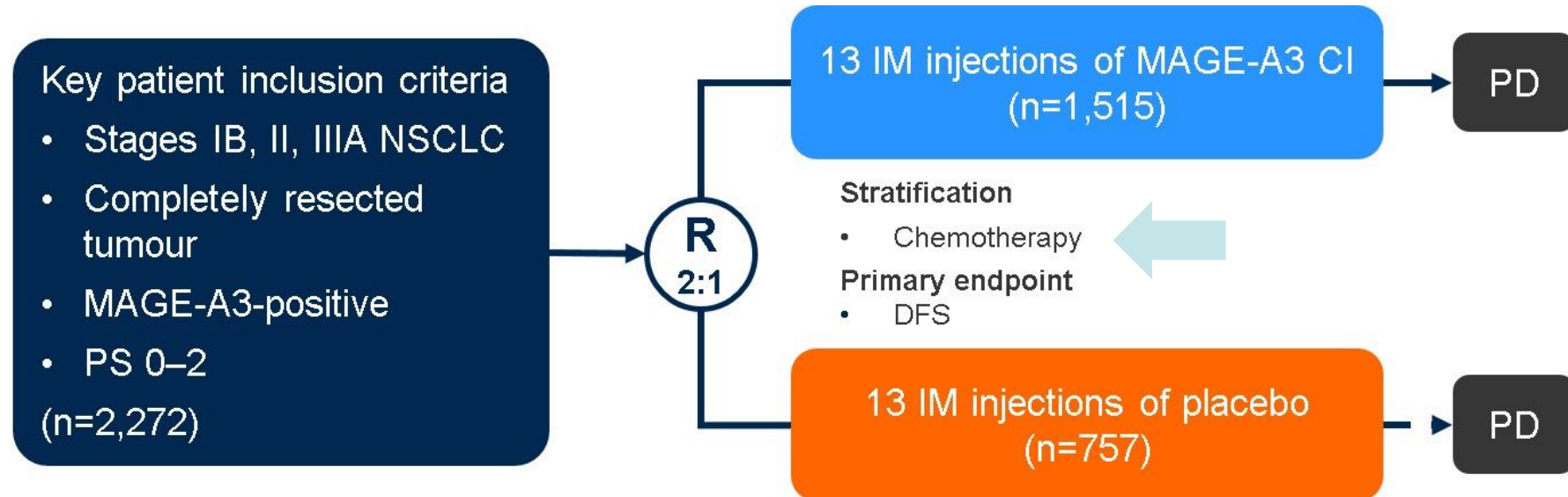


## DFS (del19 and L858R)



†Not significant due to hierarchical testing

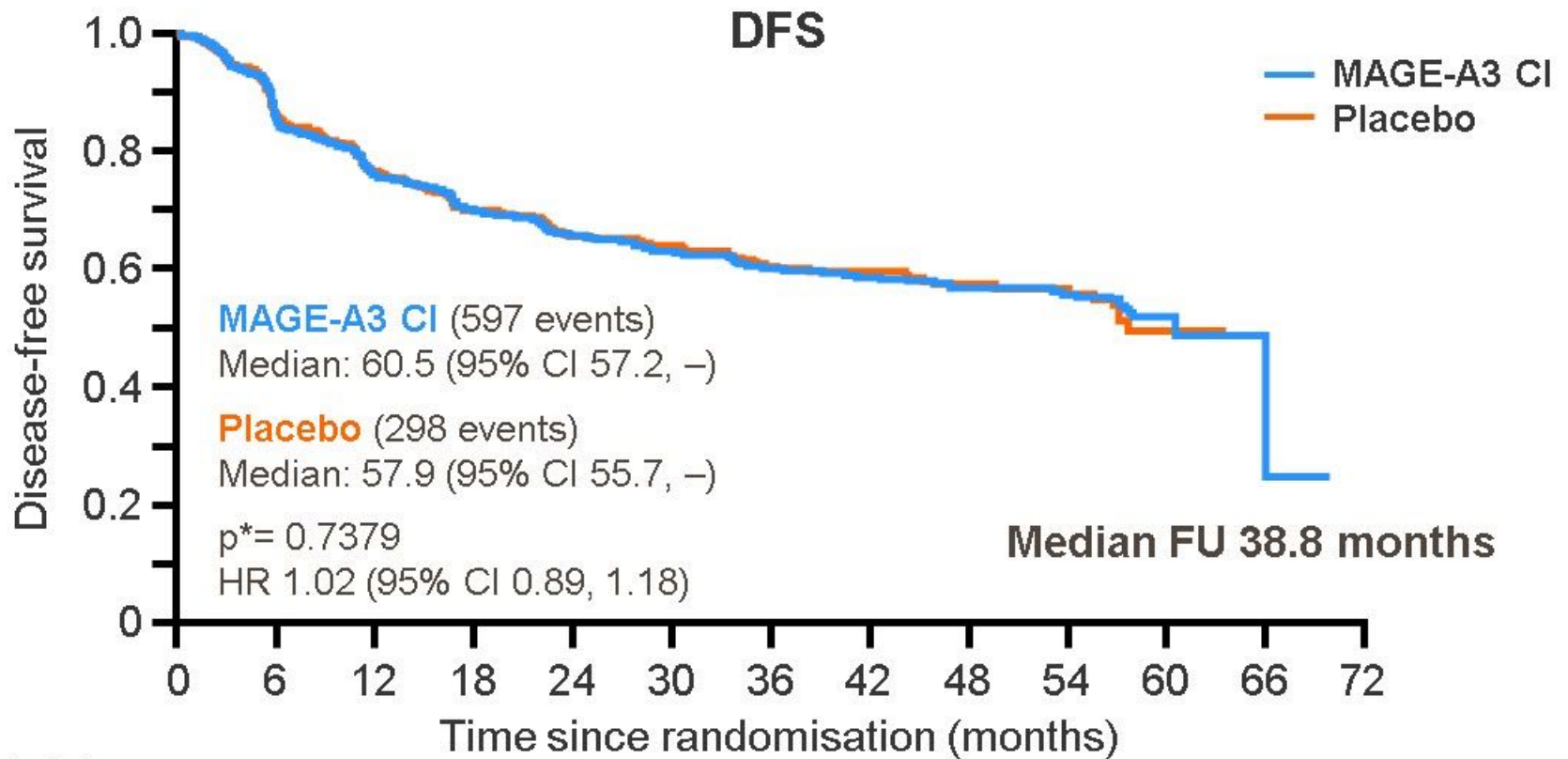
# MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy



Screened	MAGE-A3 Valid test	MAGE-A3 (+) n (%)	Randomized	Treated
13,849	12,820	4,210 (33%)	2,312	2,272

Main protocol amendment: addition of DFS in Gene Signature positive (GS+) patients as co-primary endpoint

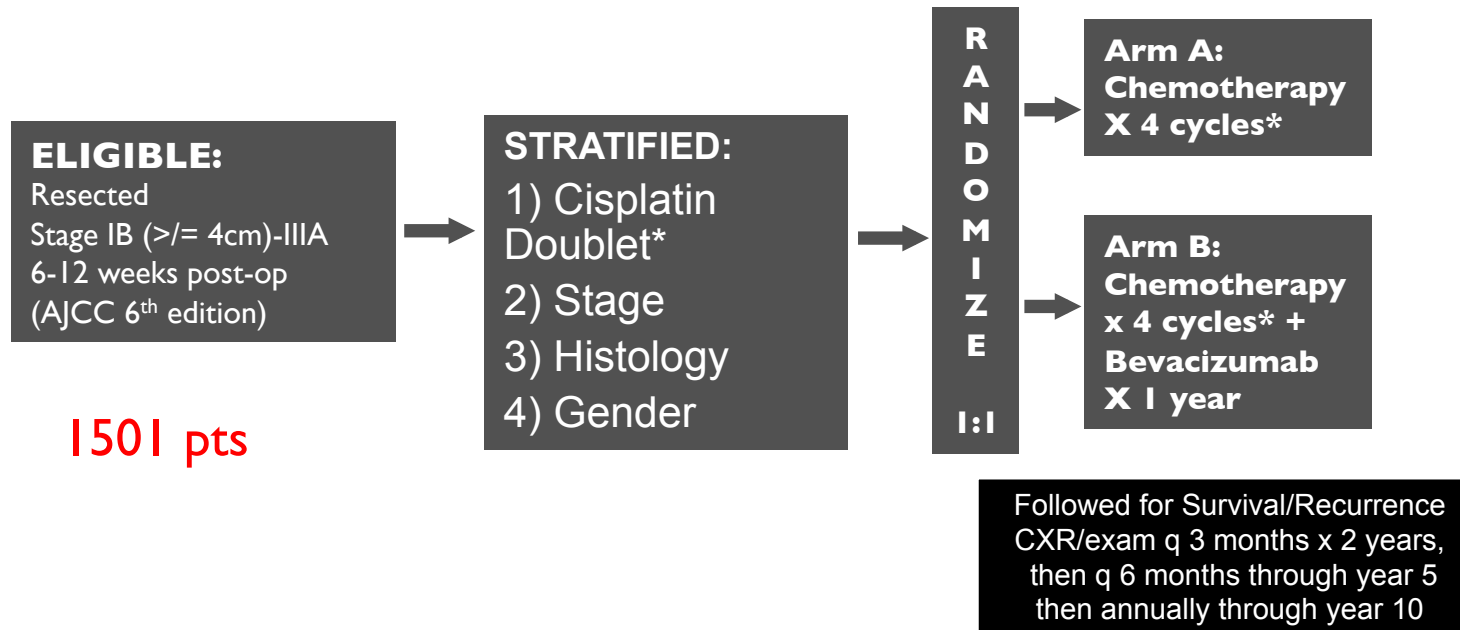
# MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy



Number at risk

<b>MAGE-A3 CI</b>	1,515	1,257	1,115	1,013	887	656	476	339	220	127	19	2
<b>Placebo</b>	757	639	562	514	448	328	253	180	114	62	6	0

# Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected NSCLC: Results of E1505



**\*Investigator Choice of 4 chemotherapy regimens**  
21 day cycles all with Cisplatin given at 75 mg/m<sup>2</sup> on day 1  
Cisplatin /**Vinorelbine**: 30 mg/m<sup>2</sup> day 1, 8  
Cisplatin /**Docetaxel** 75 mg/m<sup>2</sup> day 1  
Cisplatin /**Gemcitabine** 1200 mg/m<sup>2</sup> day 1,8  
Cisplatin /**Pemetrexed** 500 mg/m<sup>2</sup> day 1 (2009 amendment)

**Bevacizumab** 15 mg/kg IV q 3 weeks for up to 1 year

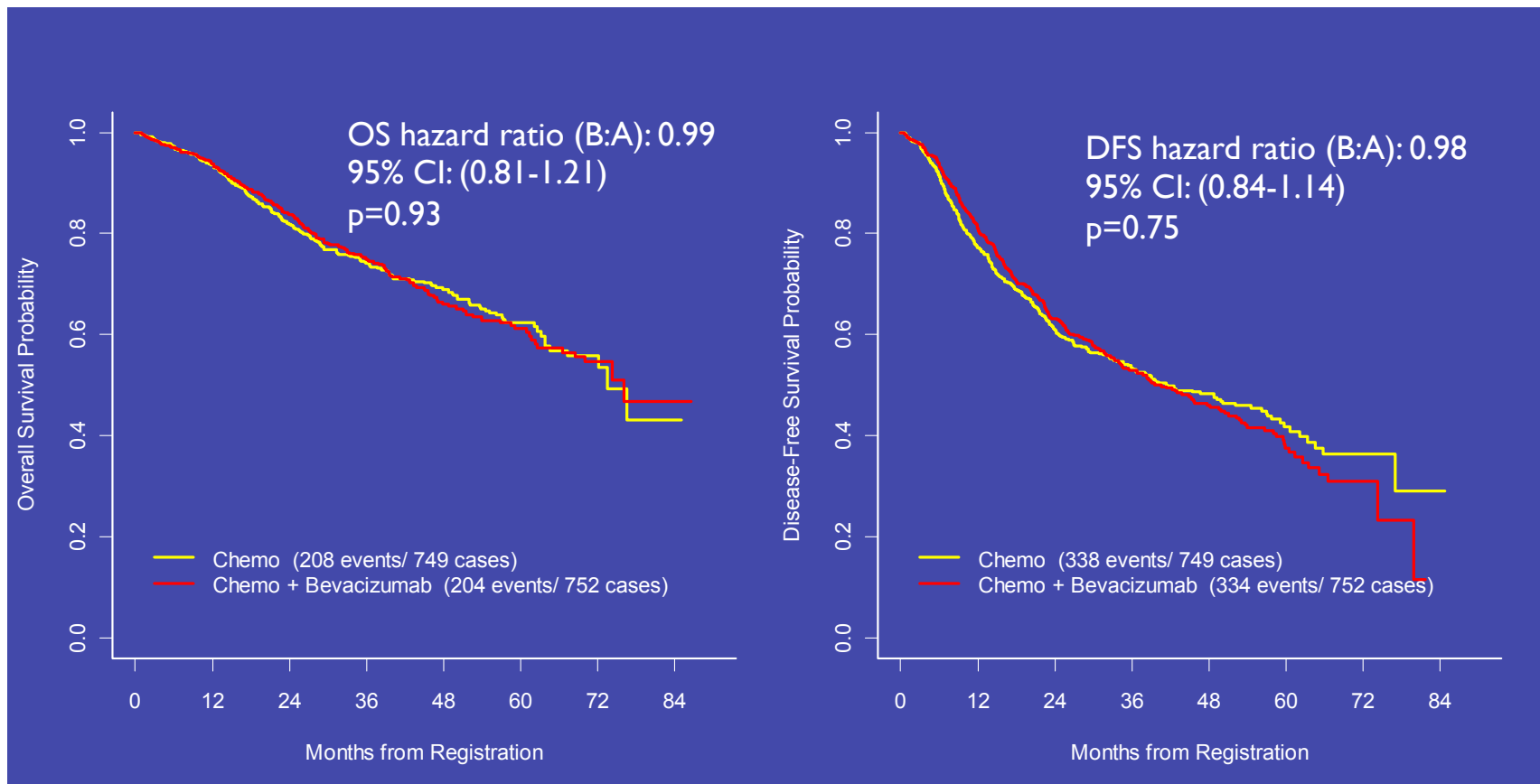
**Primary endpoint: overall survival**  
Median follow-up time 41 months

Wakelee H.A., WCLC 2015

# The addition of bevacizumab to adjuvant chemotherapy **DOES NOT** improve survival for patients with surgically resected early stage NSCLC

Overall Survival

Disease Free Survival



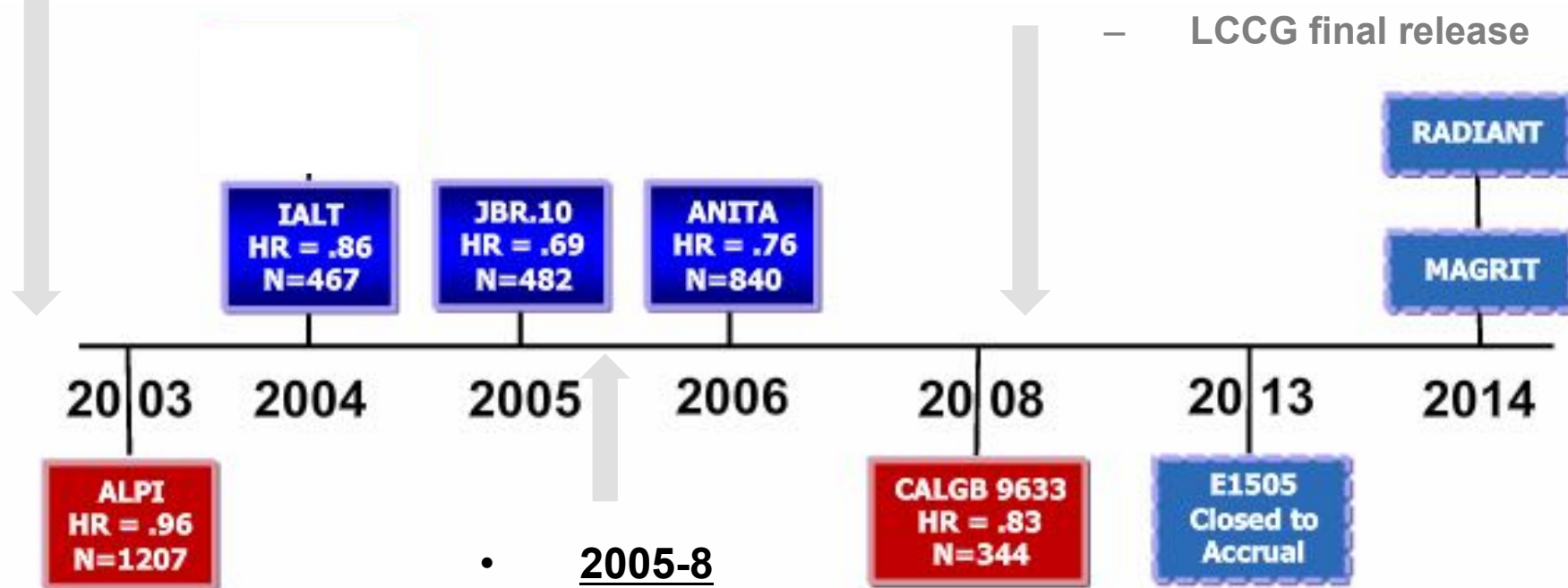
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- **2008-10:**

- Long-term concerns for chemo.....?
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- **2005-8**

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- LCCG update plus LACE
  - Significant benefit for Chemo

*Modified by Kelly K, WCLC 2013*

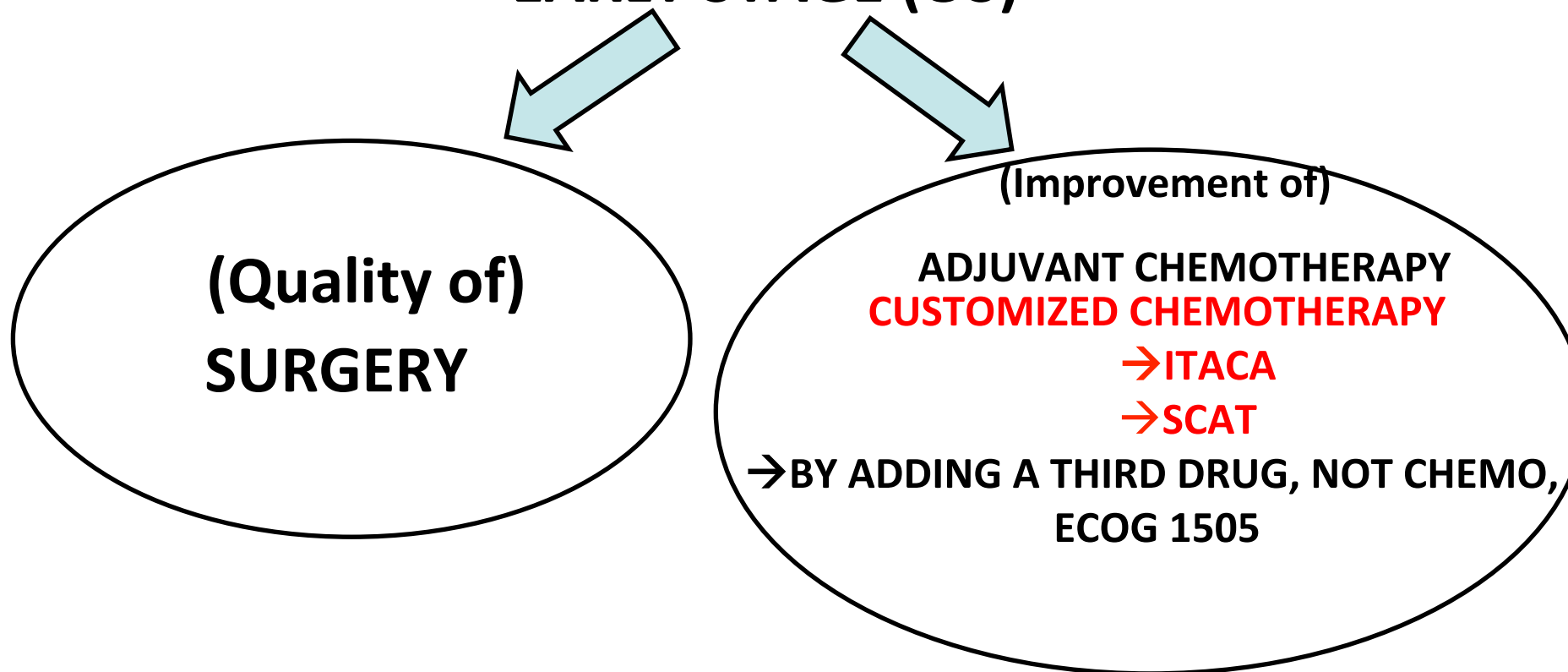
# Presentation' Outline



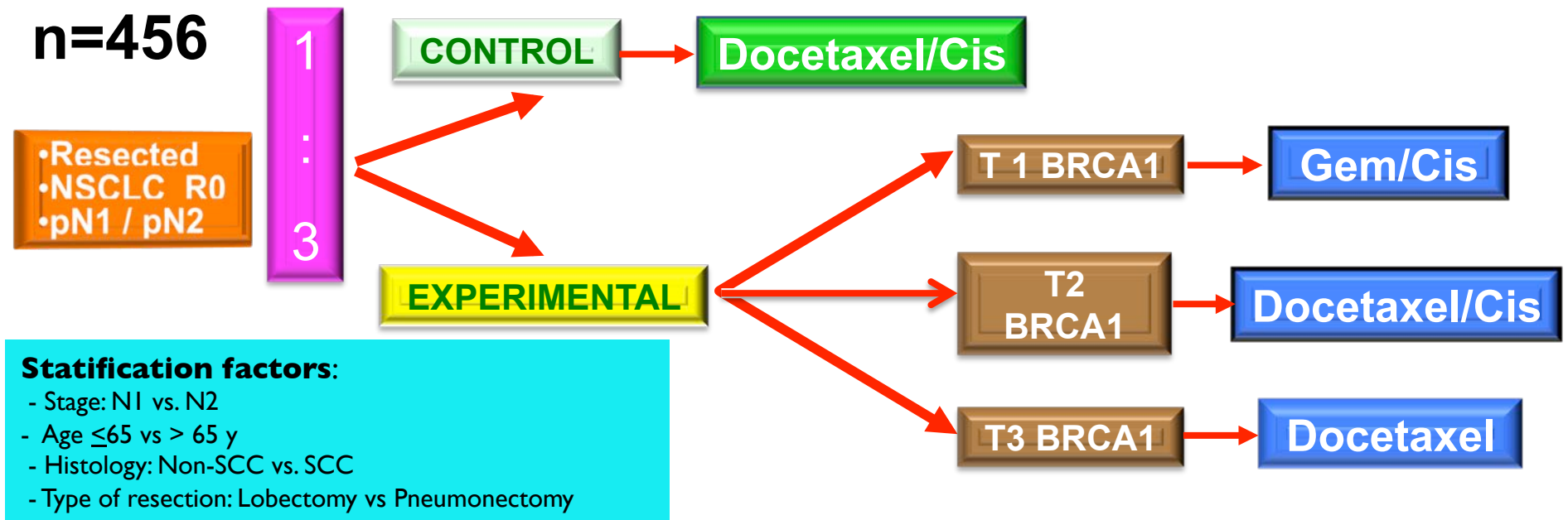
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- 



## EARLY STAGE (OS)



# Results Ph III trial customized adjuvant CT after resection of NSCLC with lymph node metastases SCAT :A Spanish Lung Cancer Group trial



Planned number of patients: 432 (amended)

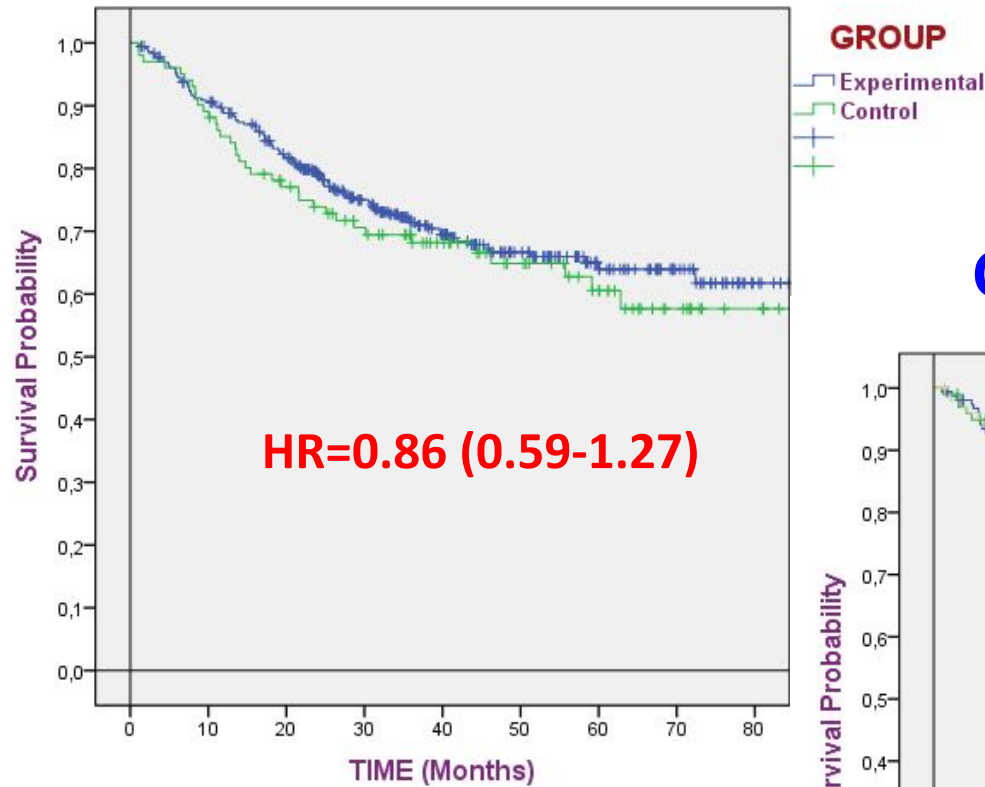
CT should be started before 8 weeks after surgery

PORT in N2 patients

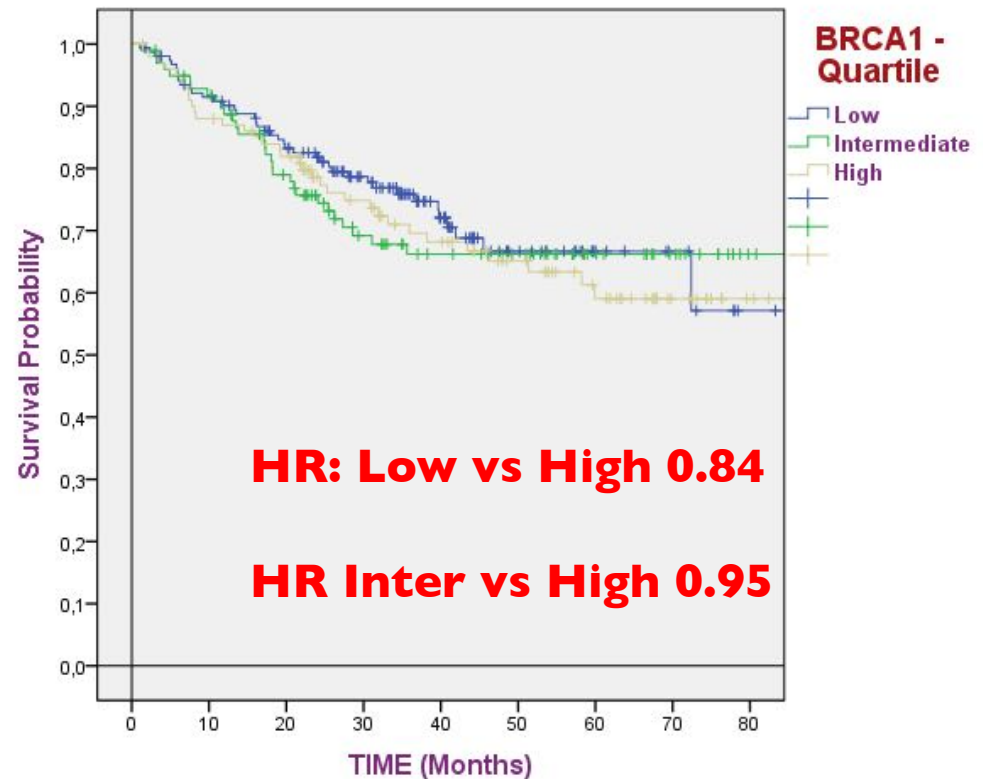
Primary end-point: OS



# Overall survival (cut-off March 15<sup>th</sup> 2015)

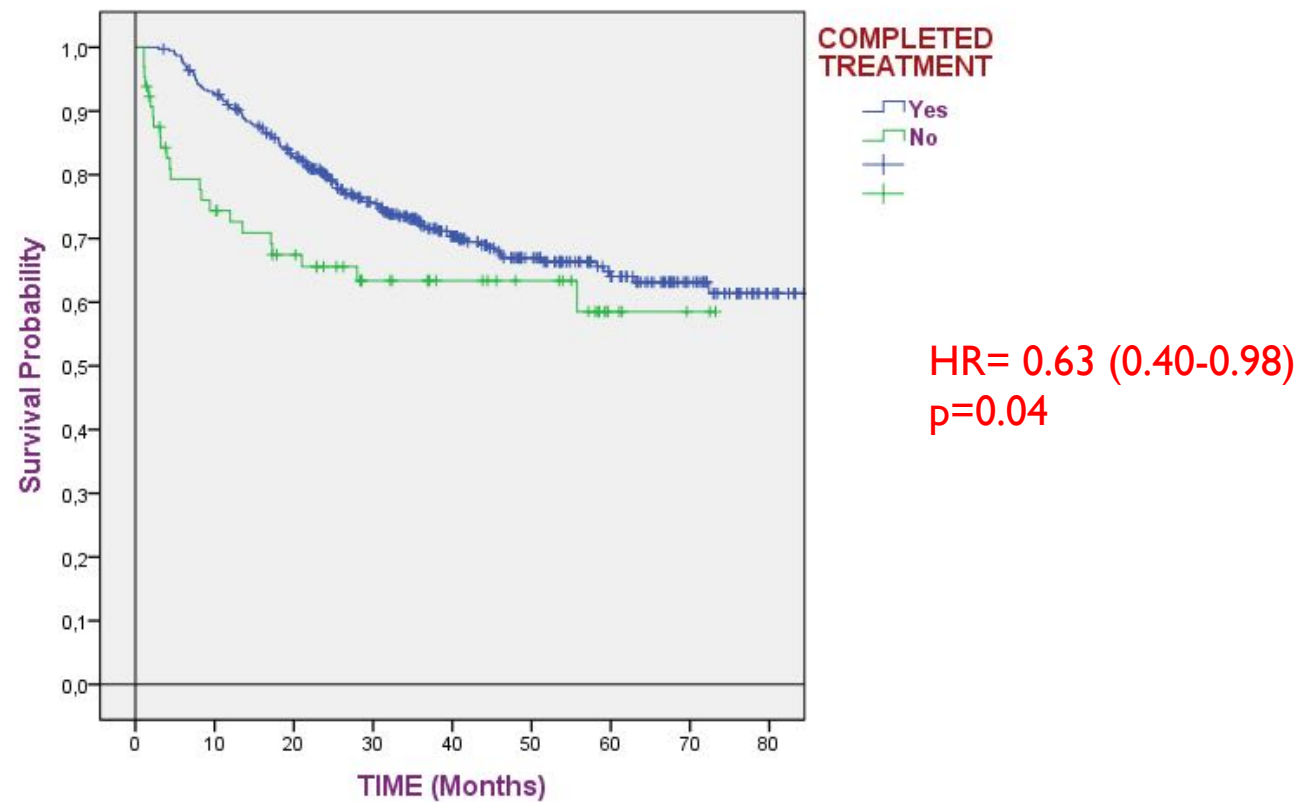


## OS experimental arm

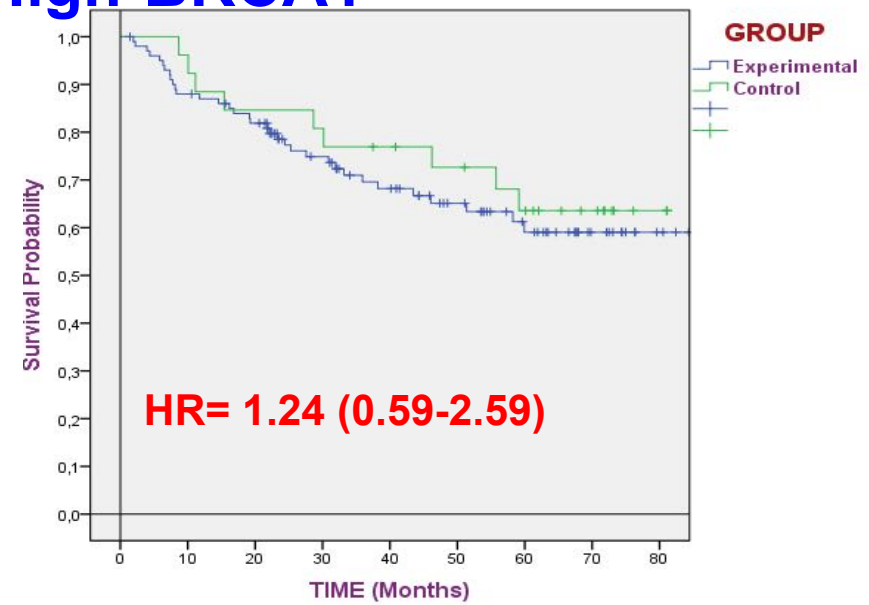
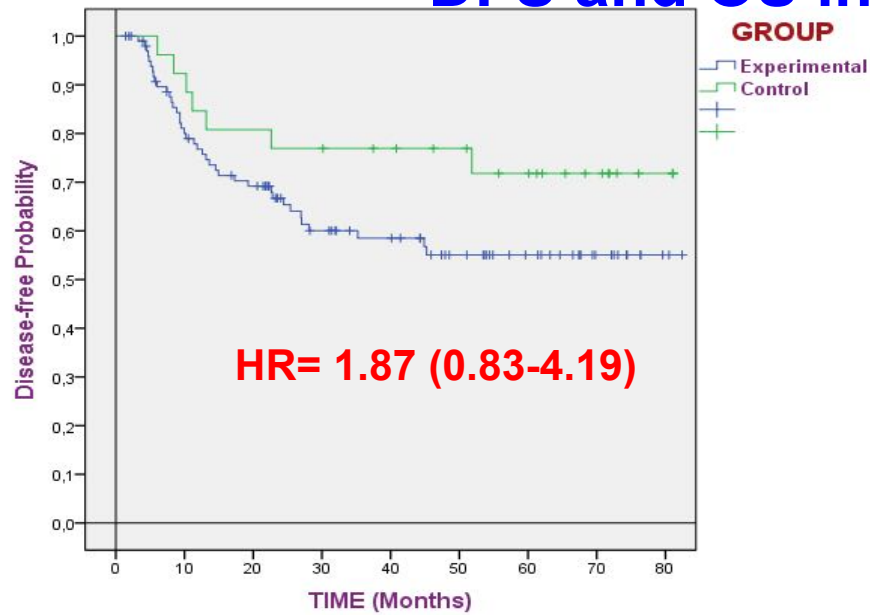




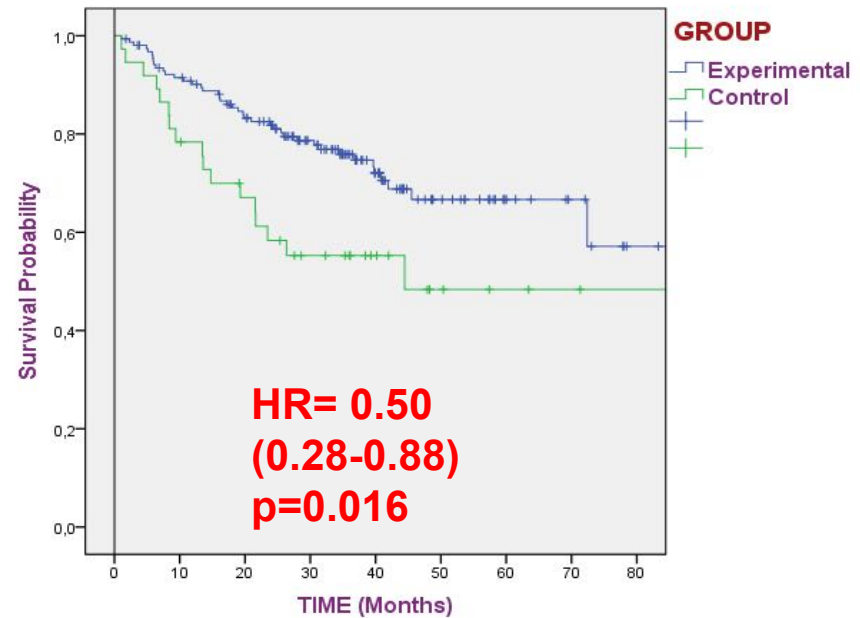
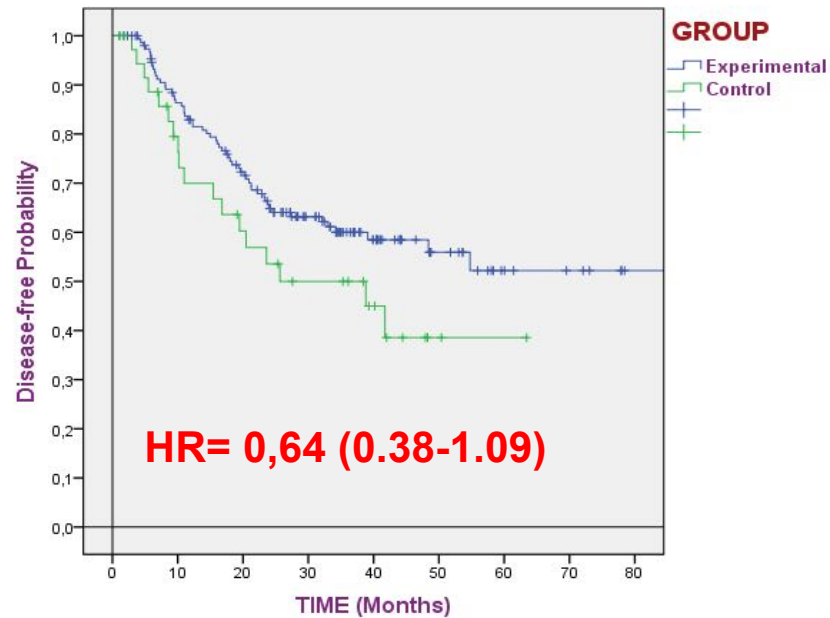
## Overall survival and compliance



## DFS and OS in High-BRCA1

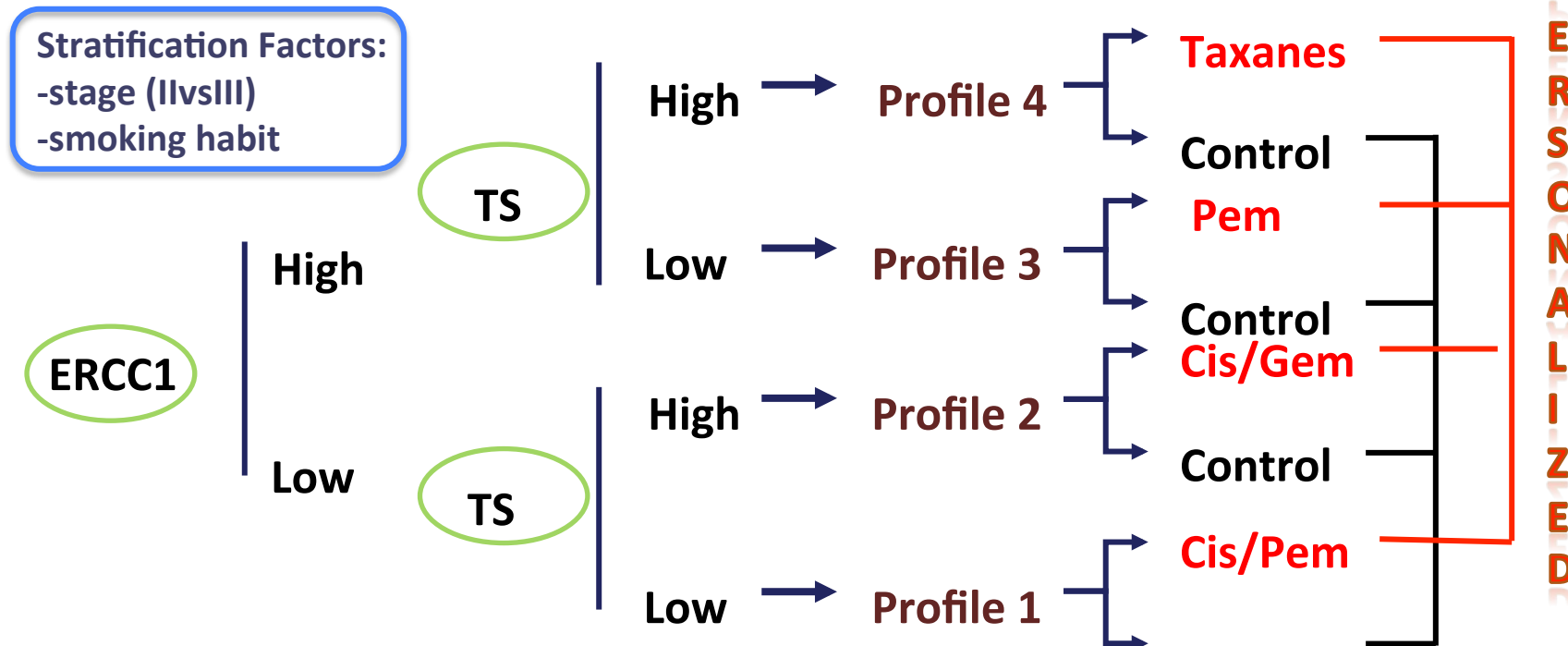


## DFS and OS Low-BRCA1 levels



# Preliminary Results of the International Tailored Chemotherapy Adjuvant Trial: the ITACA Trial

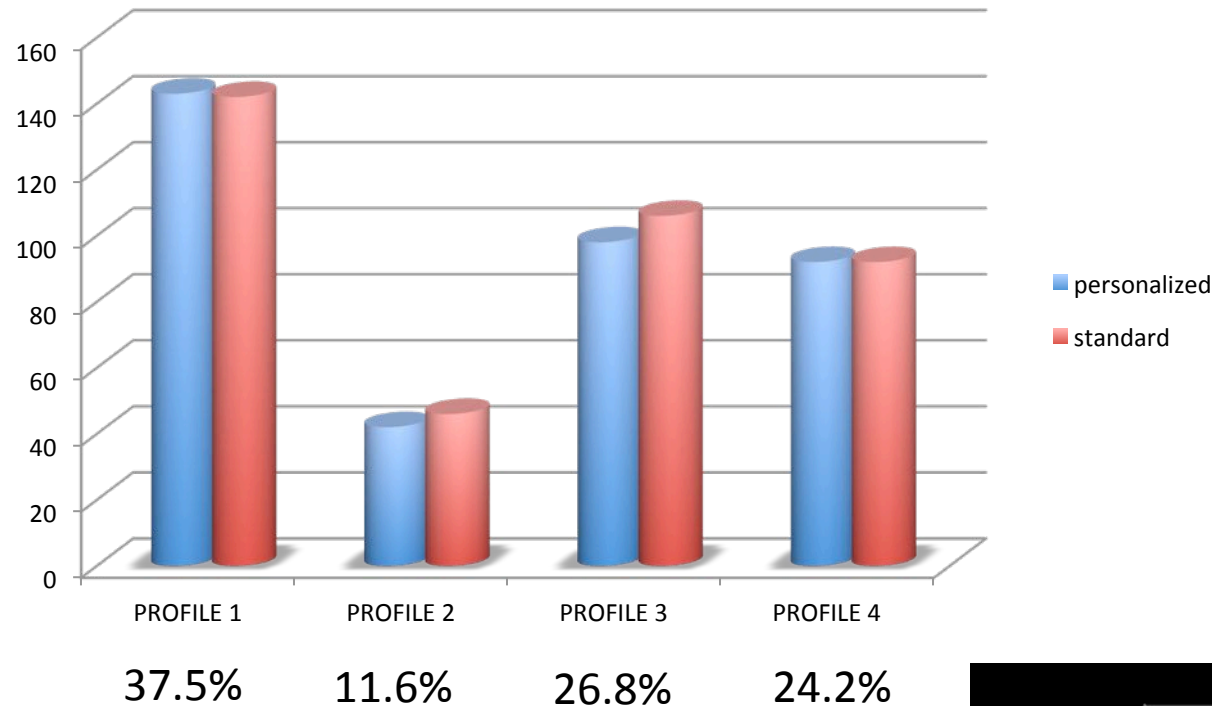
## Trial Design (stage II-III A) n°=761



**Primary End Point: OS**



## Treatment allocation by profile (N=761)



### PROFILE1:

ERCC1 low, TS low

### PROFILE2:

ERCC1 low, TS high

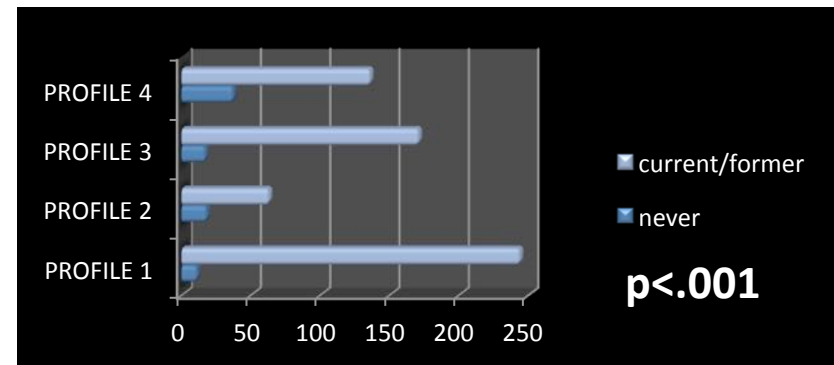
### PROFILE3:

ERCC1 high, TS low

### PROFILE4:

ERCC1 high, TS high

## Profile Distribution according to Smoking Habit



# Conclusions

- **Current Treatment Strategy (mainly based upon Stage):**
  - To treat 20-25 pts for 1 to benefit (4-5% at 5 yrs)
- **Negative results for ‘*targeted*’ agents in unselected populations?**
  - RADIANT, ECOG 1505 and..... MAGRIT!!!!
- **Biomarkers for pts selection are required**
  - To increase PROGNOSTIC accuracy
  - To increase PREDICTIVE accuracy

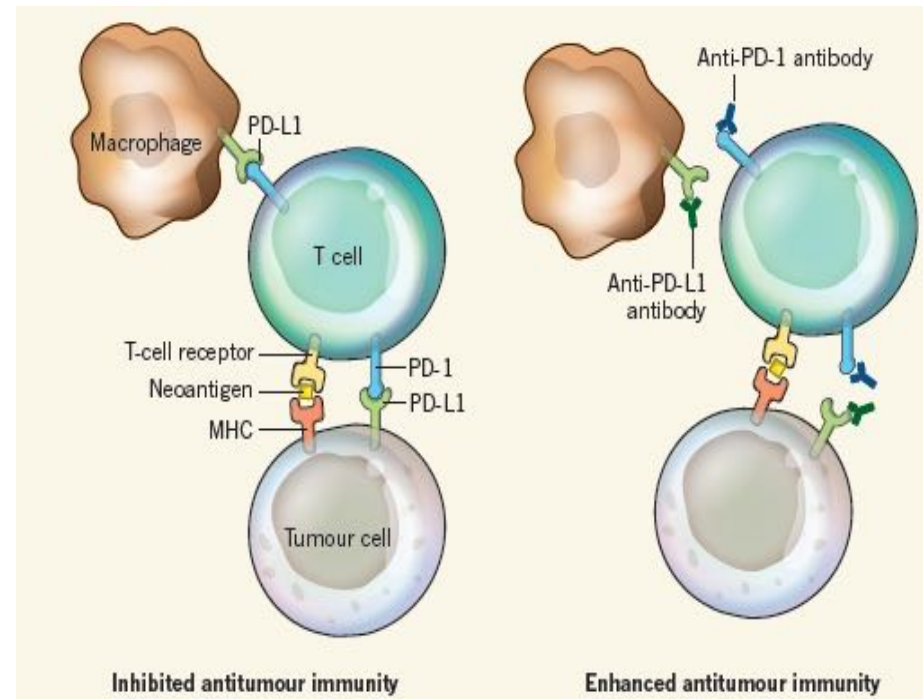


# Perspectives

- What application for the newest insights from immunotherapy in advanced disease?

- Different history for anti PD1/PD-L1 MoAbs

- Advanced SQCC  
[CheckMate 017]: NIVO improves OS **regardless** of PD-L1
- Advanced nonSQCC  
[CheckMate 057]: NIVO improves OS **according** to PD-L1





**Thank you for  
your attention!!**

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