ESMO Preceptorship on
Non-Small Cell Lung Cancer
Copenhagen July 7-8th 2015

State-of-the-art: standard of care for resectable NSCLC

Adjuvant Chemotherapy

JY DOUILLARD MD PhD
Professor of Medical Oncology
Integrated Centers of Oncology R Gauducheau
University of Nantes
France

UNIVERSITÉ DE NANTES

Institut de Cancérologie de l'Ouest

Adjuvant Chemotherapy in NSCLC

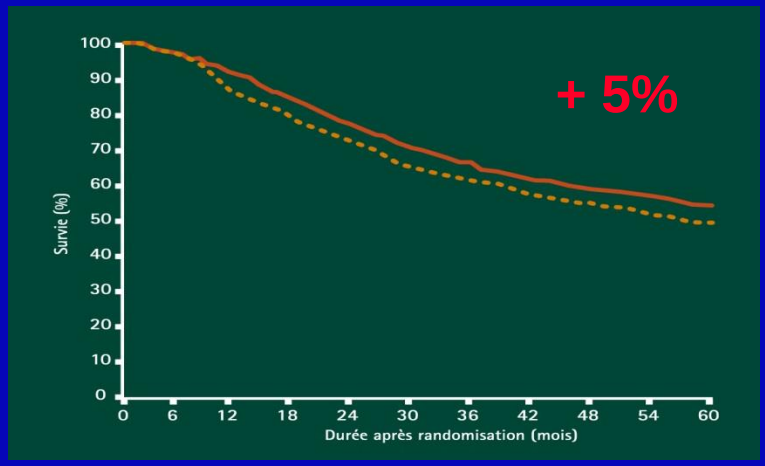
- **Adjuvant chemotherapy is a concept of proven efficacy in several frequent cancers including breast, colon and ovarian.**

- **Its role in NSCLC was still unclear until recent studies provided evidence of benefit.**

But, recent studies results however are still controversial in term of patients to whom adjuvant chemotherapy should be offered.

Adjuvant Chemotherapy in NSCLC:THE BACKGROUND

- **The MRC 1995 meta-analysis: a landmark in adjuvant CT**
  - **14 randomized trials on 4357 patients**
  - **3 groups analyzed according to chemotherapy regimen:**
    - **Alkylating agents-containing regimen:**
      - ***↗ risk of death (+15%), ↘ survival (-4% at 2y, –5% at 5 y.)***
    - **UFT-based CT (Japonese trials):**
      - ***Non conclusive results, ns. ↘ of risk of death***
    - **Cisplatin-based CT (7 trials)**
      - ***↘ risk of death 13%***
      - ***↗ survival (3% at 2y., 5% at 5y.)***
      - ***Non significant (p=0.08) however***



Non-small cell lung cancer collaborative group - BMJ 1995; 311: 899-909

Major Adjuvant Studies in NSCLC

- **7 studies in the past 12 years have been reported with conflicting results*:**

  - **ALPI-EORTC** ***(Scagliotti et al) JNCI october 2003*** **negative**
  - **IALT** ***(Lechevalier et al.) NEJM january 2004*** **positive transient**
  - **Big Lung Trial** ***(Waller D. et al) Eur J Cardi Thoac Surg 2004*** **negative**
  - **KATO et al** ***NEJM april 2004 (UFT stage I)*** **positive in IB only**
  - **BR 10** ***(Winton et al) NEJM june 2005*** **positive in II only**
  - **CALGB 9633** ***(Stauss et al) JCO 2008*** **positive transient**
  - **ANITA 01** ***(Douillard et al.) ASCO 2005*** **positive in II and IIIA only**

*** TNM V and VI classification**

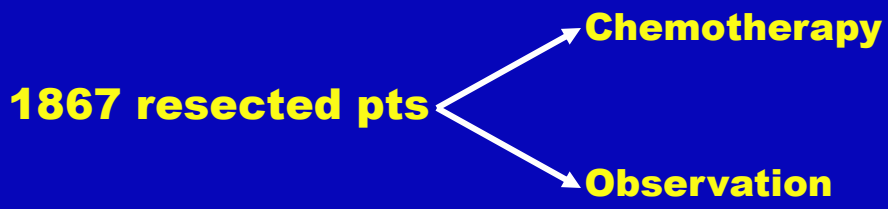
Major Adjuvant Studies in NSCLC

- **Additional meta-analysis have brought new information:**
  - **Hotta meta-analysis 2004[1]**
    - **11 trials (6 UFT based) on 5716 patients since the 1995 meta-analysis**
      - ***Significant reduction of risk of death in both UFT single agent (p=0.015) or cisplatin-based CT (p=0.012)***
  - **Hamada meta-analysis 2005[2]**
    - **UFT single agent-based adjuvant CT in Japan**
    - **6 studies, 2003 pts, mostly early stage (65% pT1, 96% pN0, 84% adenocarcinomas)**
      - ***↘ risk of death 26%,***
      - ***↗ survival (4.3% at 5y., 7% at 7y., p= 0.011 and 0.001)***

(1)Hotta at al. JCO 22; 19, october 2004 (2) Hamada et al JCO 23; 22 august 2005

Major Adjuvant Studies in NSCLC: IALT

- **Randomized phase III, Ist end point: SURVIVAL**



Optional adjuvant RT 50Gy med. dose

Population: -Stage I: 36%, II 24%, IIIA 40%,
-pneumonectomy 35%
-squamous 46%

Radiation: 31% of patients

The International Adjuvant Lung Cancer Trial Collaborative Group NEJM january 22 2004, 351-360

Major Adjuvant Studies in NSCLC: IALT

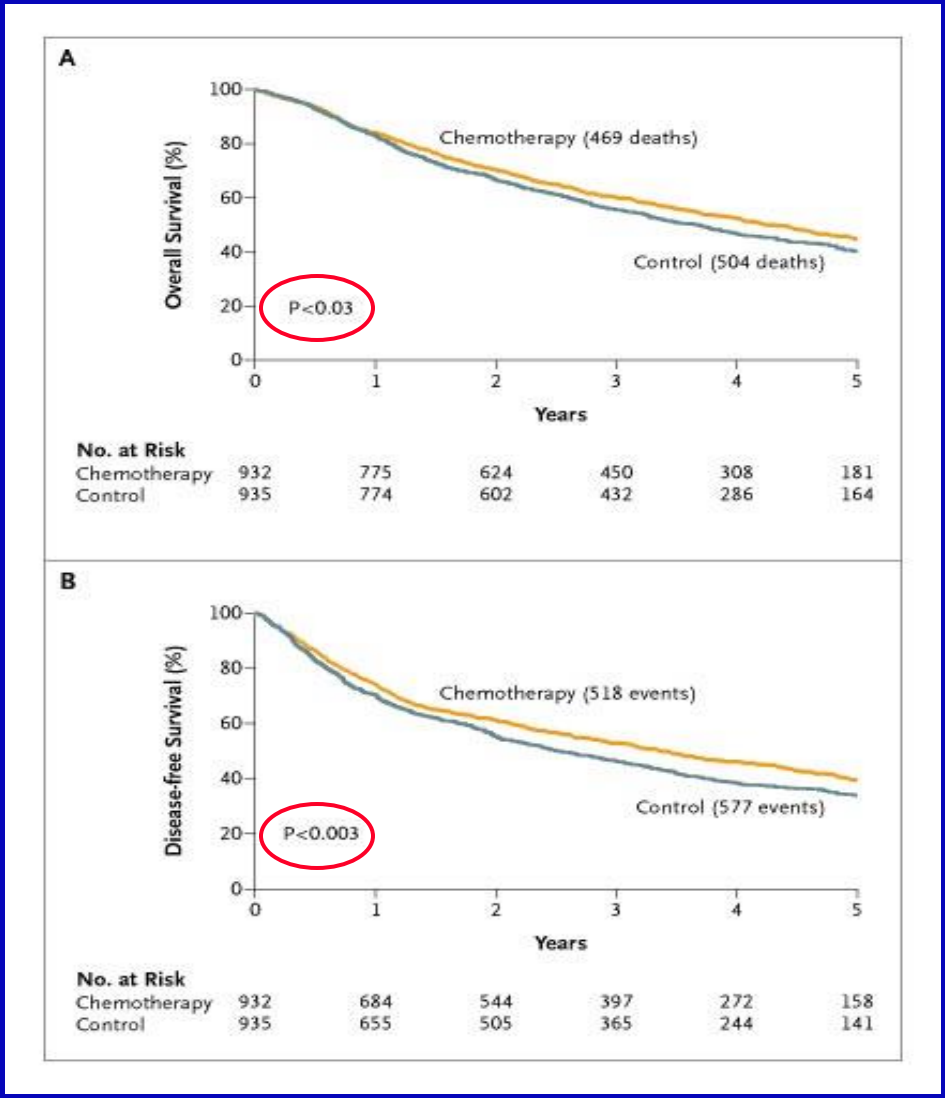
CHEMOTHERAPY REGIMEN ADMINISTERED

Table 3. Distribution of Patients as Stratified According to the Chemotherapy Options Chosen before Randomization.

Dose of Cisplatin	Drug Combined with Cisplatin				
	Vindesine	Vinblastine	Vinorelbine	Etoposide	Total
	number of patients				
80 mg/m² of body-surface area for 4 cycles	4	105	124	94	327
100 mg/m² for 3 cycles	103	43	185	484	815
100 mg/m² for 4 cycles	0	57	48	436	541
120 mg/m² for 3 cycles	1	0	143	40	184
Total	108	205	500	1054	1867

The International Adjuvant Lung Cancer Trial Collaborative Group NEJM january 22 2004, 351-360

Major Adjuvant Studies in NSCLC: IALT



- **Significant benefit of cisplatin-based CT:**

HR 0.86 p=0.03

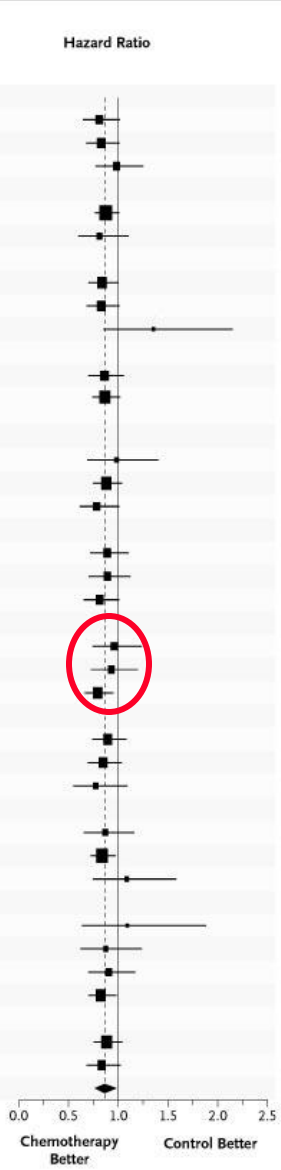
+4.1 % at 5 years,

- 74% received at least 240 mg/m2 of CDDP
- Toxic death:0.8%
- This study is probably underpowered since initial statistics were based on an accrual of 3000pts

The International Adjuvant Lung Cancer Trial Collaborative Group NEJM january 22 2004, 351-360

Major Adjuvant Studies in NSCLC: IALT

Covariate	Chemotherapy Group	Control Group	P Value for Interaction	P Value for Trend
	No. of deaths/No. of patients			
Age			0.46	0.26
<55 yr	141/314	163/316		
55–64 yr	181/355	214/386		
>64 yr	147/263	127/233		
Sex			0.65	—
Male	390/752	417/750		
Female	79/180	87/185		
WHO performance status			0.14	0.21
0	240/505	259/499		
1	186/355	213/372		
2	43/72	32/64		
Type of surgery			0.98	—
Pneumonectomy	182/324	193/324		
Lobectomy or segmentectomy	287/608	311/611		
Tumor stage			0.57	0.32
1	67/169	59/151		
2	282/570	314/603		
3 or 4	120/193	131/181		
Nodal status			0.80	0.56
0	164/423	174/427		
1	144/271	155/267		
2	161/238	175/241		
Stage			0.41	0.21
I	115/333	122/348		
II	123/230	126/222		
III	231/369	256/365		
Histologic type			0.77	—
Squamous cell	205/428	223/444		
Adenocarcinoma	199/386	208/368		
Other	65/118	73/123		
Dose of cisplatin per cycle			0.45	0.63
80 mg/m²	85/163	93/164		
100 mg/m²	334/679	360/677		
120 mg/m²	50/90	51/94		
Drug combined with cisplatin			0.77	—
Vindesine	26/52	26/56		
Vinblastine	62/103	70/102		
Vinorelbine	113/248	128/252		
Etoposide	268/529	280/525		
Planned radiotherapy			0.66	—
No	287/648	303/647		
Yes	182/284	201/288		
Total	469/932	504/935		



- **According to the author, all test for interaction are negative, not allowing p values among groups**
- **A different analysis on stage published by Strauss *et al* showed a significant p value for stage III only (p=0.035)** *(Hematol Oncol Clin N Am 2005 19, 263-281)*
- **The study was initially calculated on 3000 pts and therefor lacks power for subgroup analysis**

The International Adjuvant Lung Cancer Trial Collaborative Group NEJM january 22 2004, 351-360

Recent Adjuvant Studies in NSCLC: IALT

- **The IALT study was initially published after 5y FU (2004)**
- **An updated analysis was later published at 7.5 y (2010)**

Follow-up in years	5	7.5
HR survival	**0.86**	**0.91**
Pvalue	**0.03**	**0.10**

- **A excess of non-cancer related deaths was noticed in the chemotherapy arm with time**
- **Long FU is needed to really eveluate the benefit of ajuvant CT**

Recent Adjuvant Studies in NSCLC: CALGB 9633

- **Randomized phase III primary end-point: SURVIVAL**

344 resected pts

Closed early (384)

→ **Observation**

→ **4 cycles TAXOL 200mg/m2**
Carboplatin AUC=6 Q 3w

Population: **-Stage IB**
-lobectomy 89%
-squamous 39%

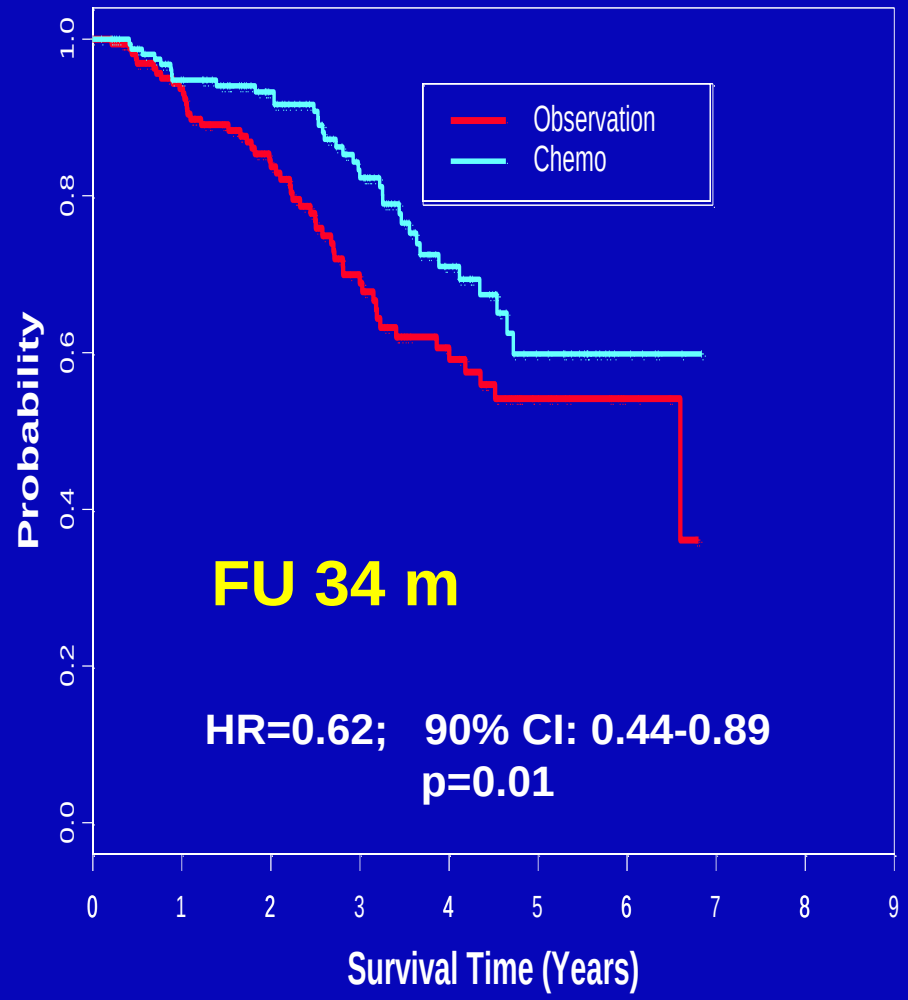
Tolerance (n=149/173): neutropenia grade 3-4 36%, no toxic death

Compliance (n=124/173): 4 cycles 85%, 55% at full dose (68/124)

Strauss et al ASCO 2004 and J clin Oncol 2008; 26: 5043-5041

OVERALL SURVIVAL

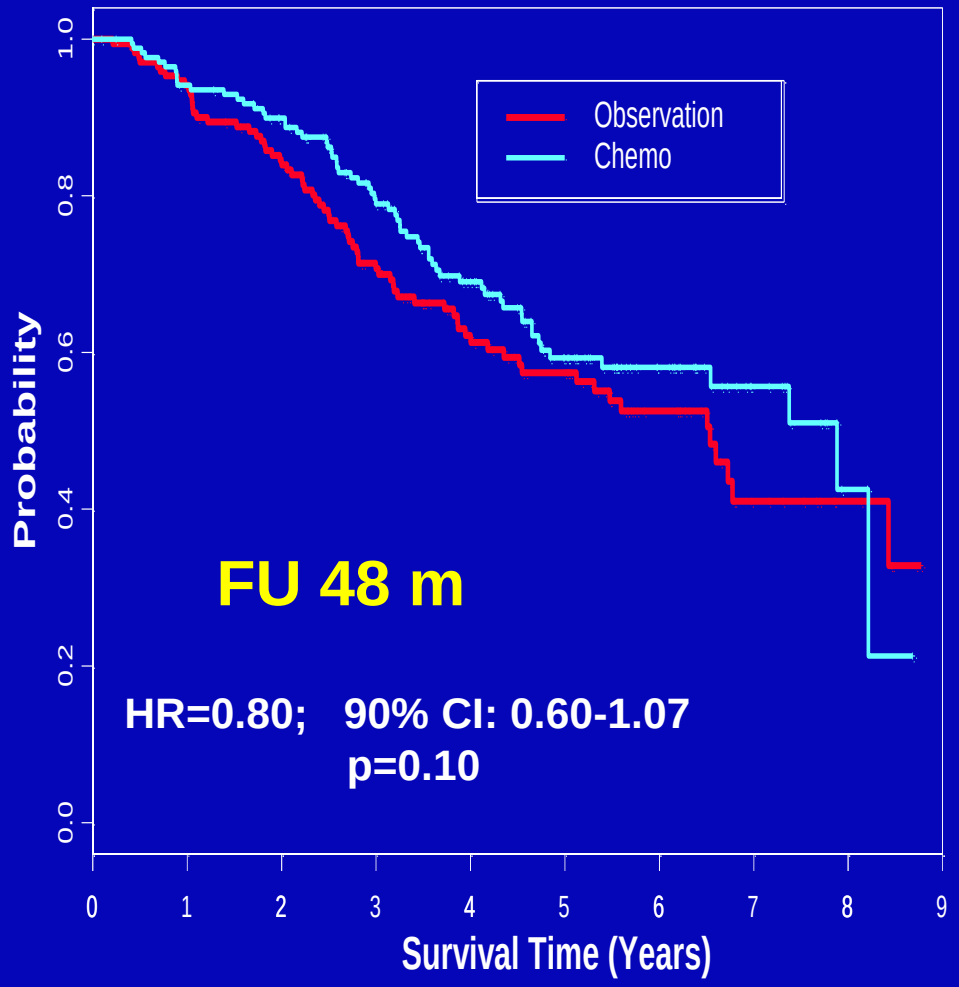
THEN AND NOW



FU 34 m

HR=0.62; 90% CI: 0.44-0.89
p=0.01

ASCO: 2004



FU 48 m

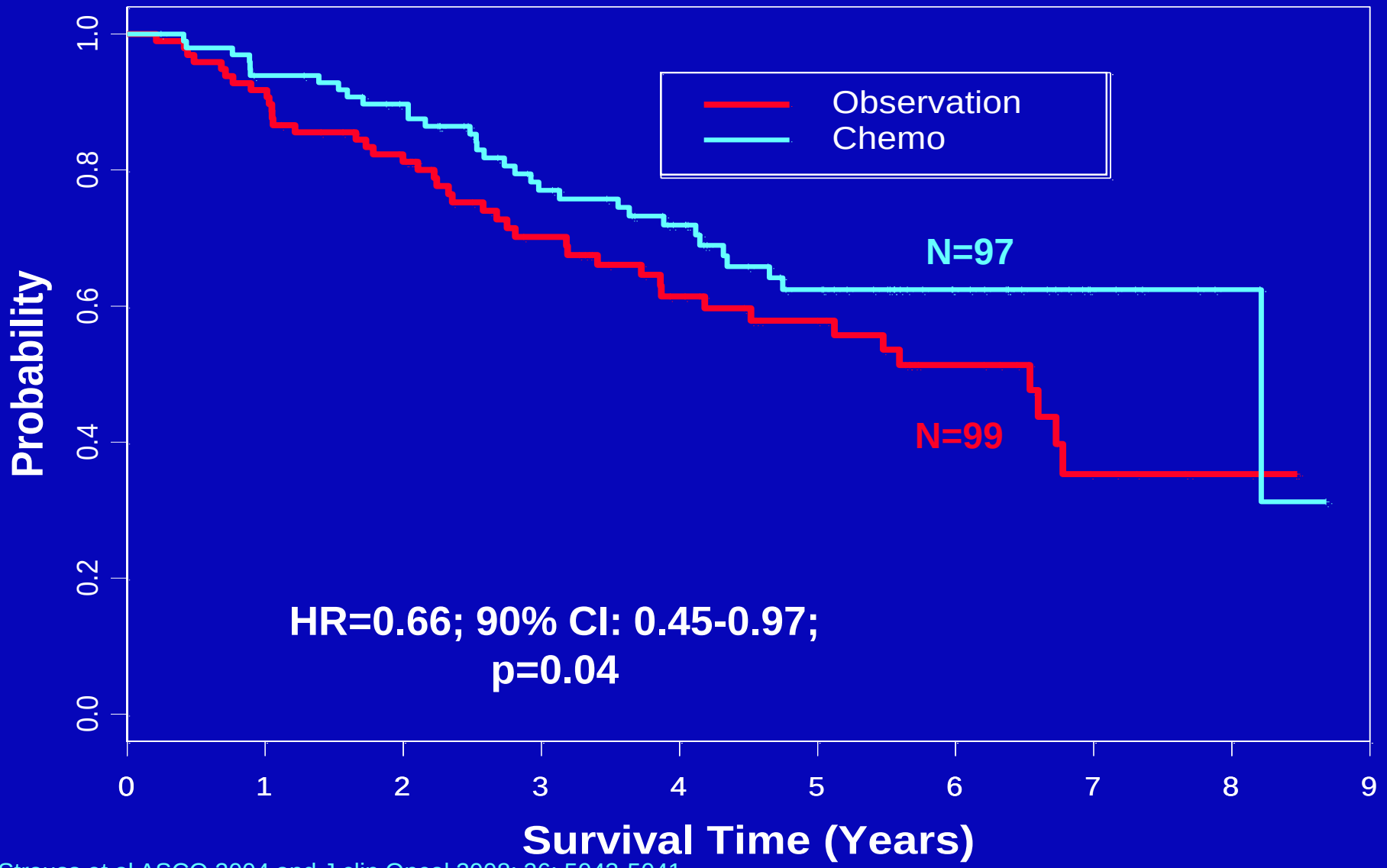
HR=0.80; 90% CI: 0.60-1.07
p=0.10

ASCO: 2006

Strauss et al ASCO 2004 and J clin Oncol 2008; 26: 5043-5041

CALGB 9633

Survival: Patients with Tumor ≥ 4.0 cm



Strauss et al ASCO 2004 and J clin Oncol 2008; 26: 5043-5041

CALGB 9633
FINAL CONCLUSIONS

- **Significant advantages in disease-free survival and 3-year survival → provide some evidence that adjuvant chemotherapy is effective**
  - *raise possibility that adjuvant chemotherapy may delay recurrence, even if it does not enhance curability*
  - *exploratory analysis → suggests that benefit of adjuvant chemotherapy may be limited to patients with large tumors*

- **Results of CALGB 9633 → do not mandate adjuvant chemotherapy as the standard of care in all stage IB patients**

Recent Adjuvant Studies in NSCLC: BR 10

- **Randomized phase III, primary end-point: SURVIVAL**

482 resected pts

→ **Observation**

→ **4 cycles CDDP (50mg/m2 D1 and 8) Q 4 w**
NVB weekly 25mg/m2 x 16w (initially 30mg/m2 in 18 pts)

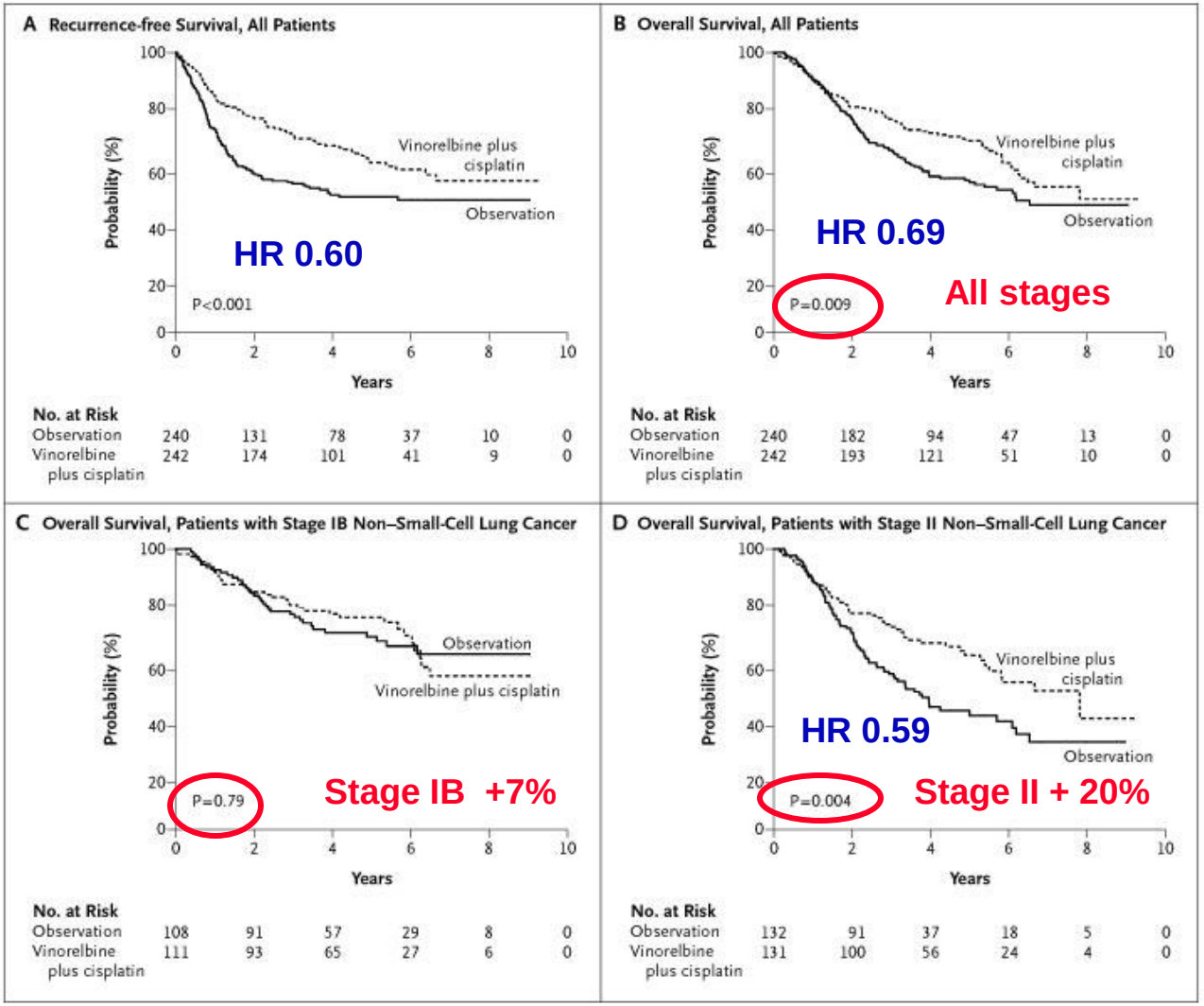
Population: -Stage IB: 45%, IIA 15% IIB 40% ,
-lobectomy 69% bilobectomy 8% pneumonectomy 23%
-adenocarcinoma 53%

Tolerance: neutropenia 88% (73% grade 3-4), 7% Febrile Neutropenia

Compliance: 68% 2 cycles, 58% 3 cycles, 48% 4 cycles

Winton T. et al. NEJM June 2 3 2005, 352; 25: 2589-2597

Recent Adjuvant Studies in NSCLC: BR 10



Overall benefit on:

- **RFS (61 vs. 49% at 5y)**
- **OS (MS 94 vs 73m)**

Demonstrated in stage II only (+20% at 5y)

Not in stage IB (+7% at 5y)

Biomolecular markers:

- **Pts with mutated Ras do not benefit from adjuvant CT as opposed to wild type Ras, the interaction test between Ras status and treatment outcome however is not statistically significant.**

The first study to show a clear benefit of modern chemotherapy overall but mainly in stage II

Winton T. et al. NEJM June 2 3 2005, 352; 25: 2589-2597

Adjuvant Studies in NSCLC: J-BR 10 Updated survival analysis

- **J-BR10: 5 year survival benefit: + 15%**

- **J-BR10 updated analysis at 9.3 years: benefit preserved**

Follow-up in years	5	9.3
HR survival	**0.69**	**0.78**
Pvalue	**0.009**	**0.04**

- **Benefit maintained with time with adjuvant Vinorelbine-Cisplatin**
- **Still restricted to stage II**
- **HR of 0.66 (P 0.13) in stage 1 > 4cm**

Recent Adjuvant Studies in NSCLC: ANITA 1

- **Randomized phase III primary end-point: SURVIVAL**

Radiation left to the investigator choice for N+ patients

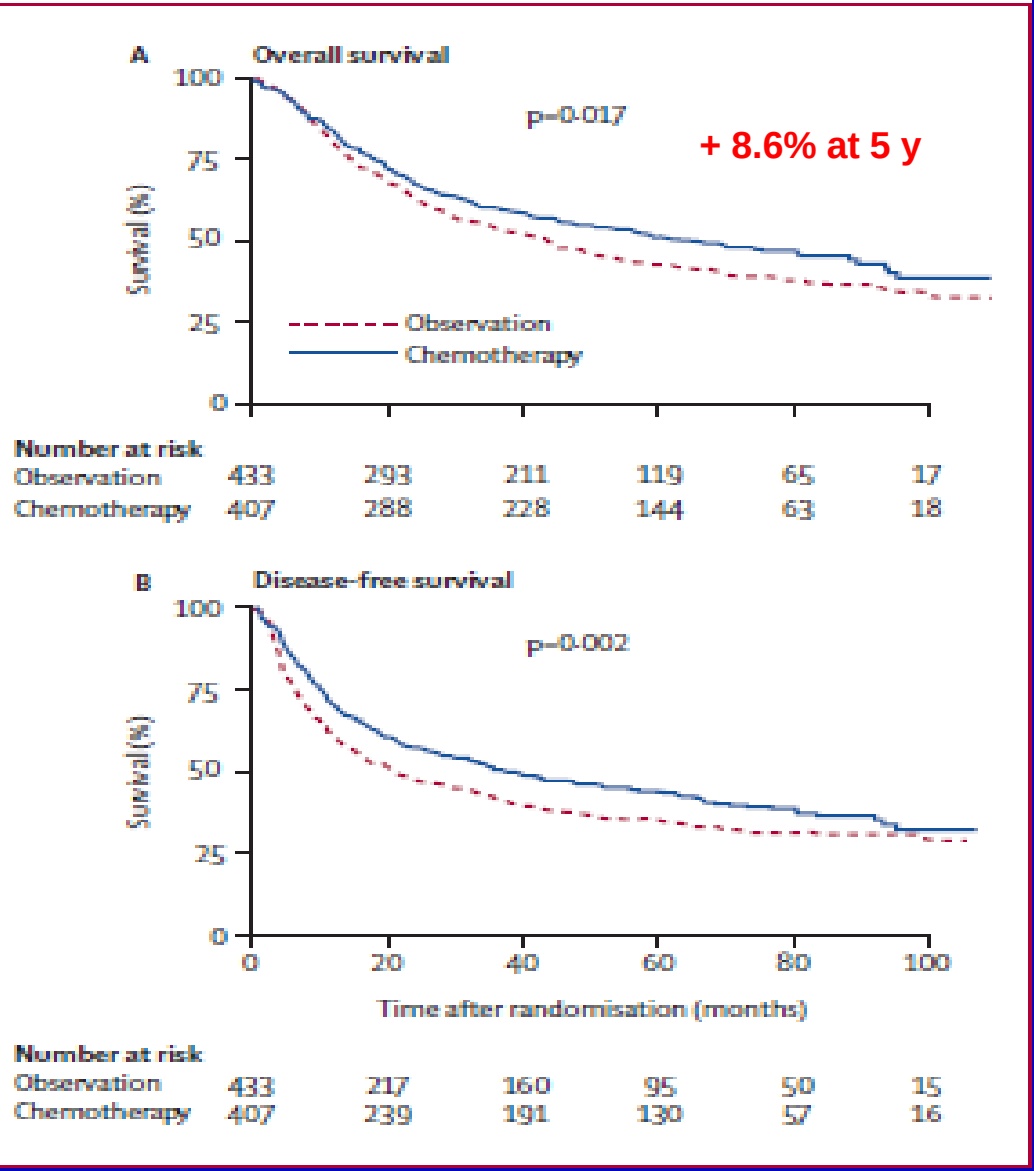
Population: -Stage IB: 35%, II 30% IIIA 35% ,
-Lobectomy 58% pneumonectomy 37%
-Squamous 59%

Tolerance: -Neutropenia 85% grade 3-4, 9.3% Febrile Neutropenia
-Nausea, vomiting grade 3-4 27%
-Toxic death 1.7%

Compliance: Median % planned dose: CDDP 76%, NVB 56%

Douillard JY et al. The Lancet Oncol. 2006; 7: 719-727

ANITA: DFS and OS

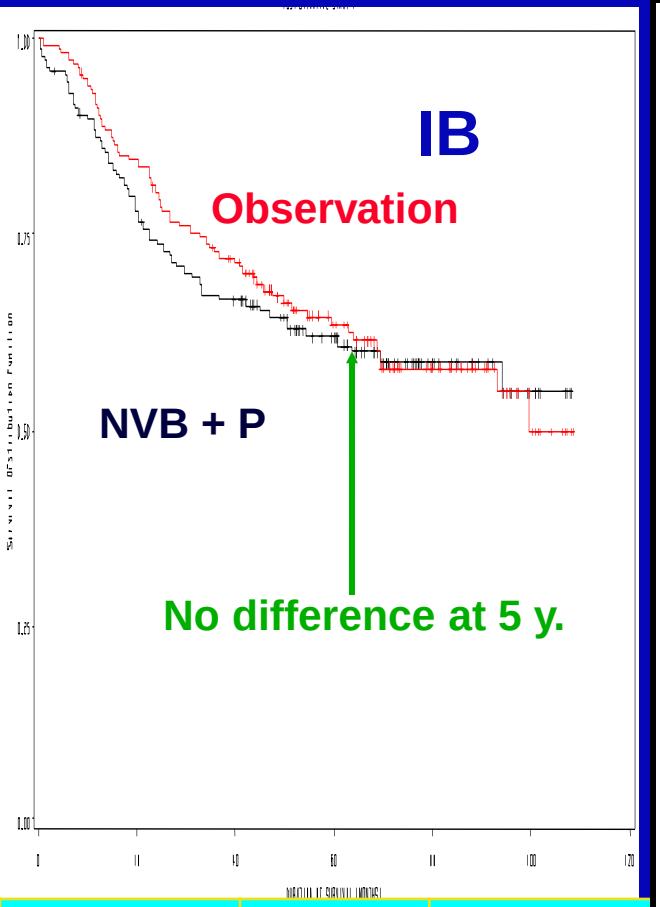


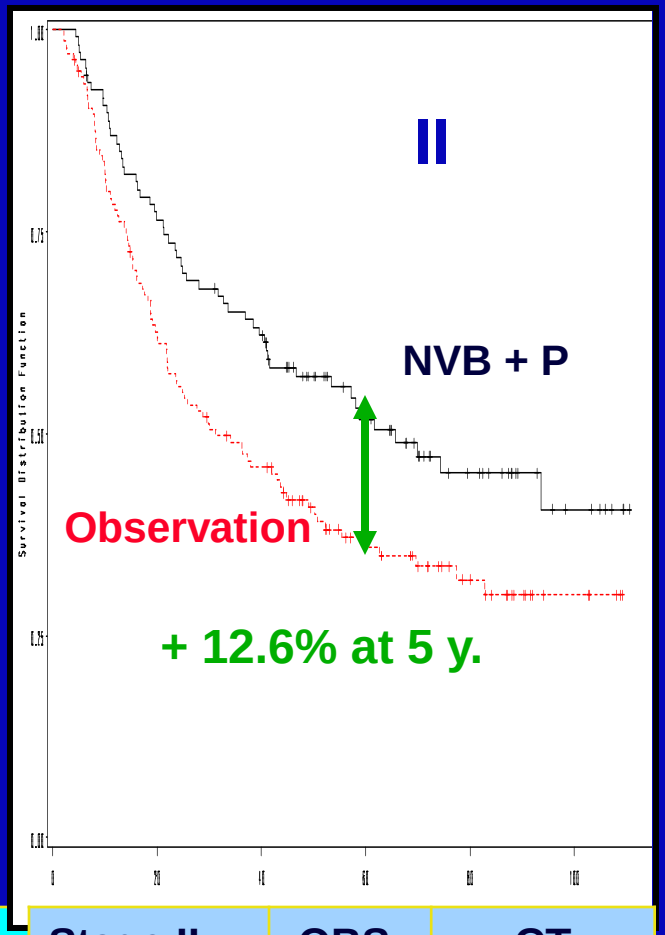
OS	OBS.	NVB + CDDP
Median m	**43.7**	**65.7**
P-value	**0.017**	
HR	**0.80 [0.66 - 0.96]**	

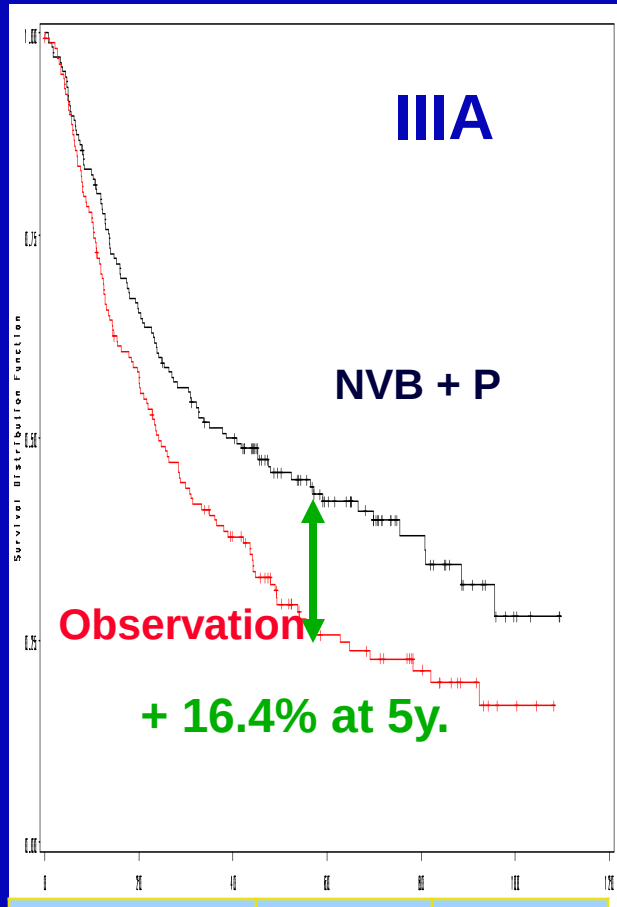
	% benefit in OS
1 years	**+3.1**
2 years	**+5.1**
5 years	**+8.6**
7 years	**+8.4**

Douillard JY et al. The Lancet Oncol. 2006; 7: 719-727

OS according to pTNM stage





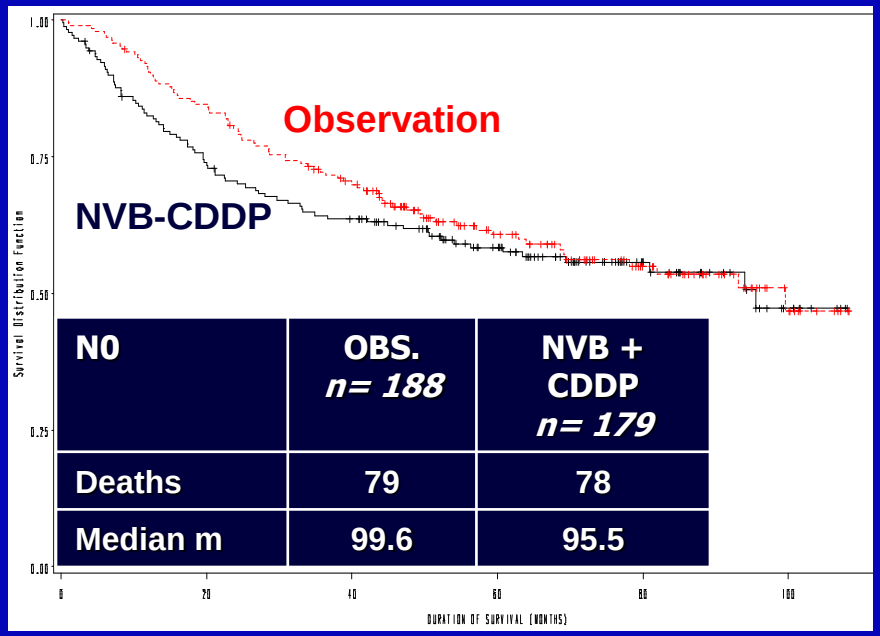


Stage I	OBS. n=155	CT n=146
% 5 y. OS	63.5	61.9
Median months	99,7	Not reached

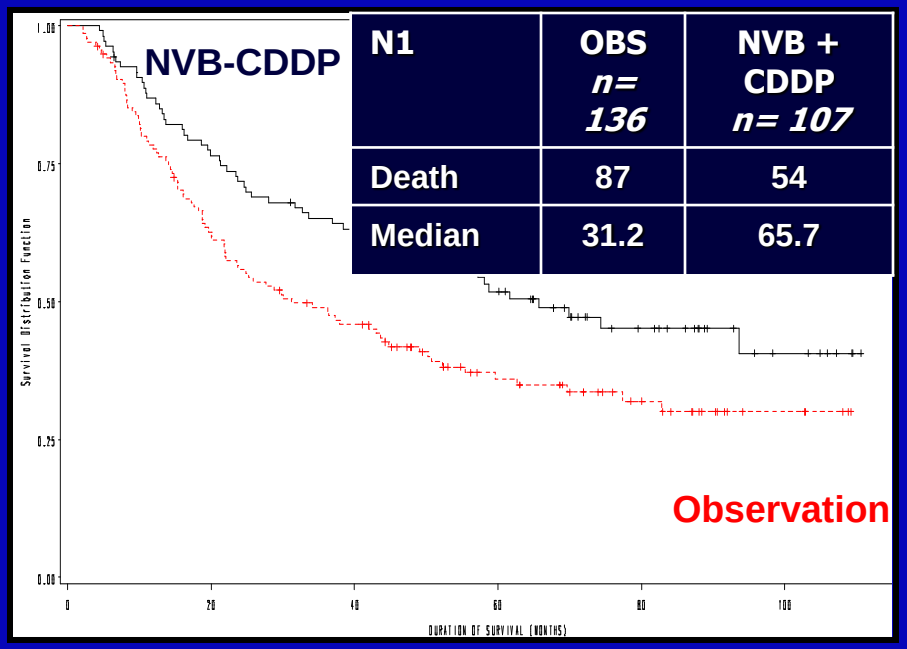
Stage II	OBS. n=114	CT n=89
% 5 y. OS	39.1	51.7
Median m	36,5	65,8

Stage III A	OBS. n=159	CT n=166
% 5 y OS	25.7	42.1
Median m	24,14	38,6

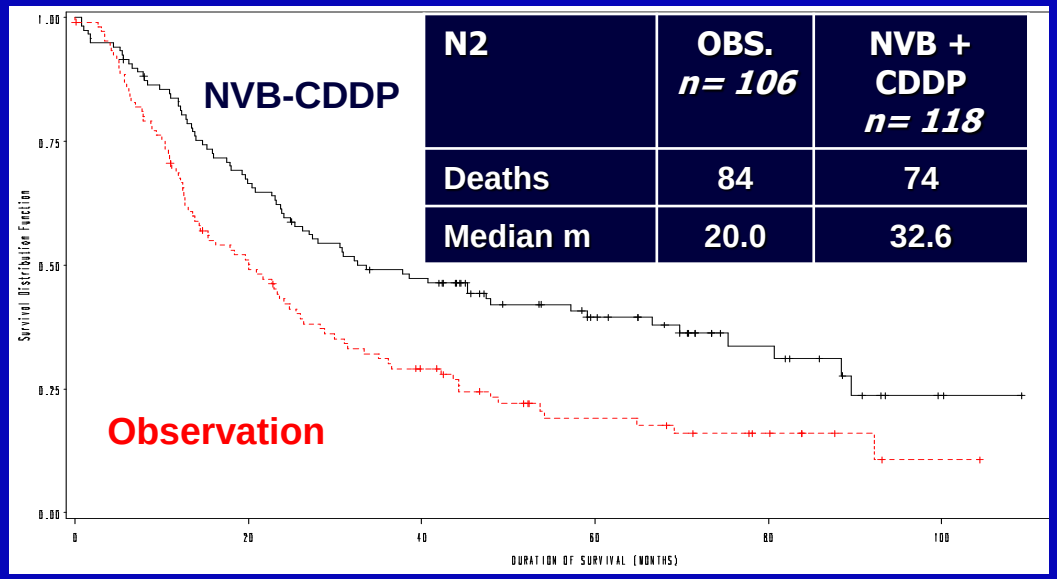
ANITA: outcome according to N stage



N0	OBS. *n= 188*	NVB + CDDP *n= 179*
Deaths	79	78
Median m	99.6	95.5



N1	OBS *n= 136*	NVB + CDDP *n= 107*
Death	87	54
Median	31.2	65.7



N2	OBS. *n= 106*	NVB + CDDP *n= 118*
Deaths	84	74
Median m	20.0	32.6

Survival: Univariate analysis

Covariates		Univariate	
		P value	Hazard ratio [95% CI]
Age:	≥ 55 years	*0.04*	1
	< 55 years		0.81 [0.67 - 0.99]
WHO Performance Status:			
	0	*0.012*	1
	1-2		1.27 [1.05 - 1.52]
Type of surgery:			
Pneumonectomy		*0.001*	1
Other type			0.73 [0.60 - 0.88]
PORT: No	*0.003*		1
	Yes		1.34 [1.10 - 1.63]
Stage:	IIIA	*< 0.001*	1
	IB-II		0.54 [0.45 - 0.65]
Lymph Nodes N:	N+	*< 0.001*	1
	N0		0.53 [0.44 - 0.65]
Histological type:			
Adenocarcinoma		*0.733*	1
Other type			0.97 [0.80 - 1.17]

Recent Adjuvant Studies in NSCLC: ANITA 1

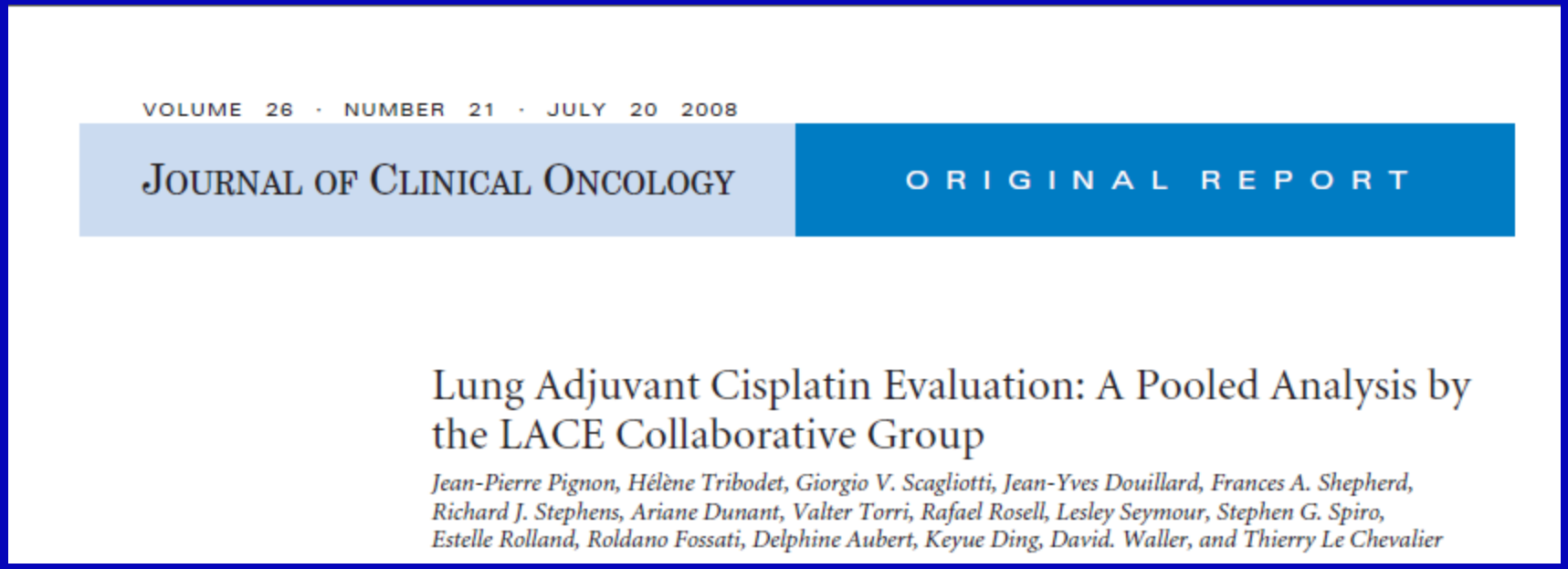
Conclusions

- Significant improvement in survival with adjuvant navelbine/cisplatin
- The effect of navelbine/cisplatin is demonstrated in stage II and IIIA but not in IB
- The effect of post-operative radiotherapy should be investigated in randomized studies for N2 patients in combination with chemotherapy

Douillard JY et al ASCO 2005 Abst. 7013

Lung Adjuvant Cisplatin Evaluation (LACE)

A Pooled Analysis of 5 Randomized Trials Including 4,584 Patients



VOLUME 26 · NUMBER 21 · JULY 20 2008

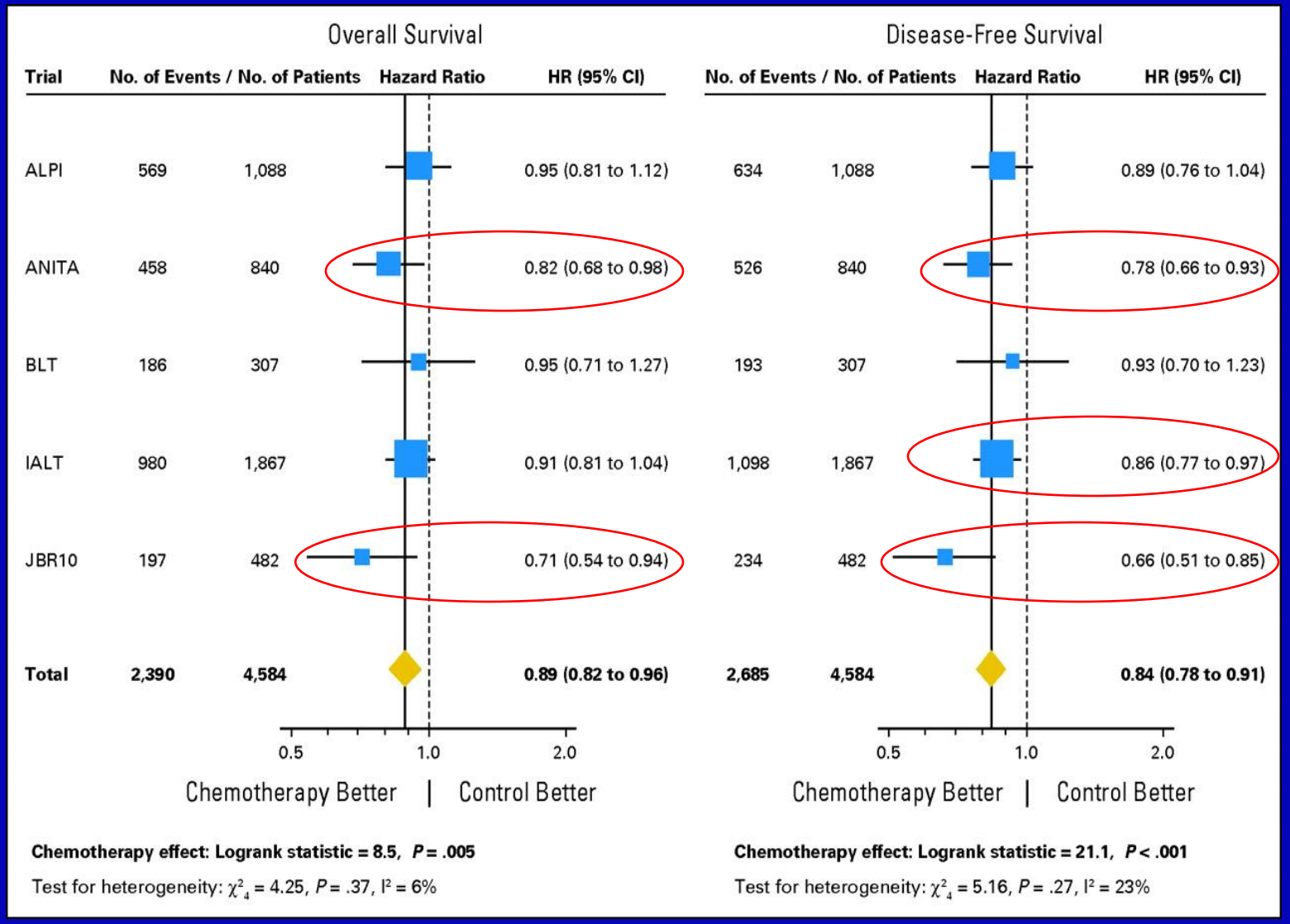
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

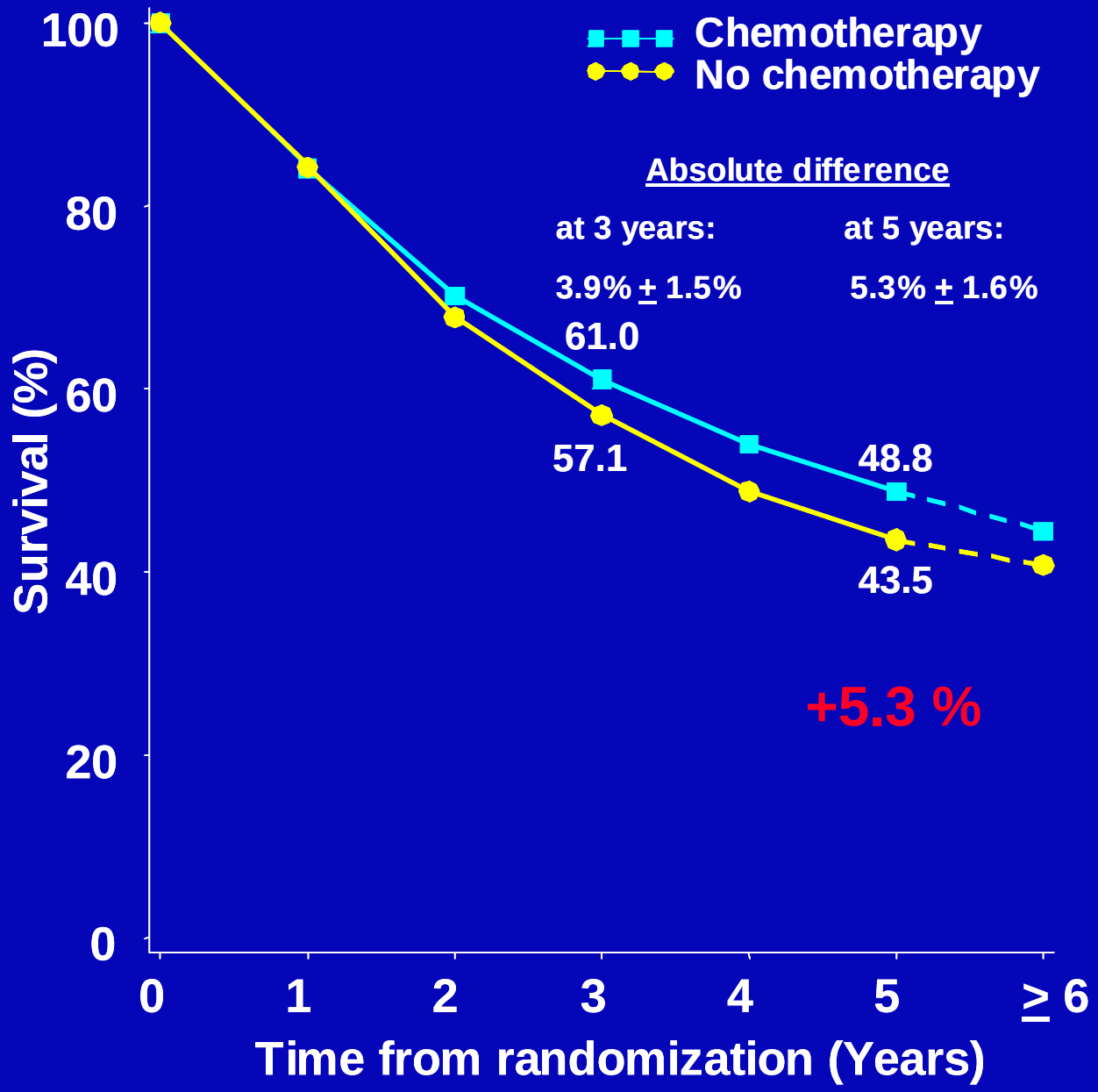
Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

(A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy).

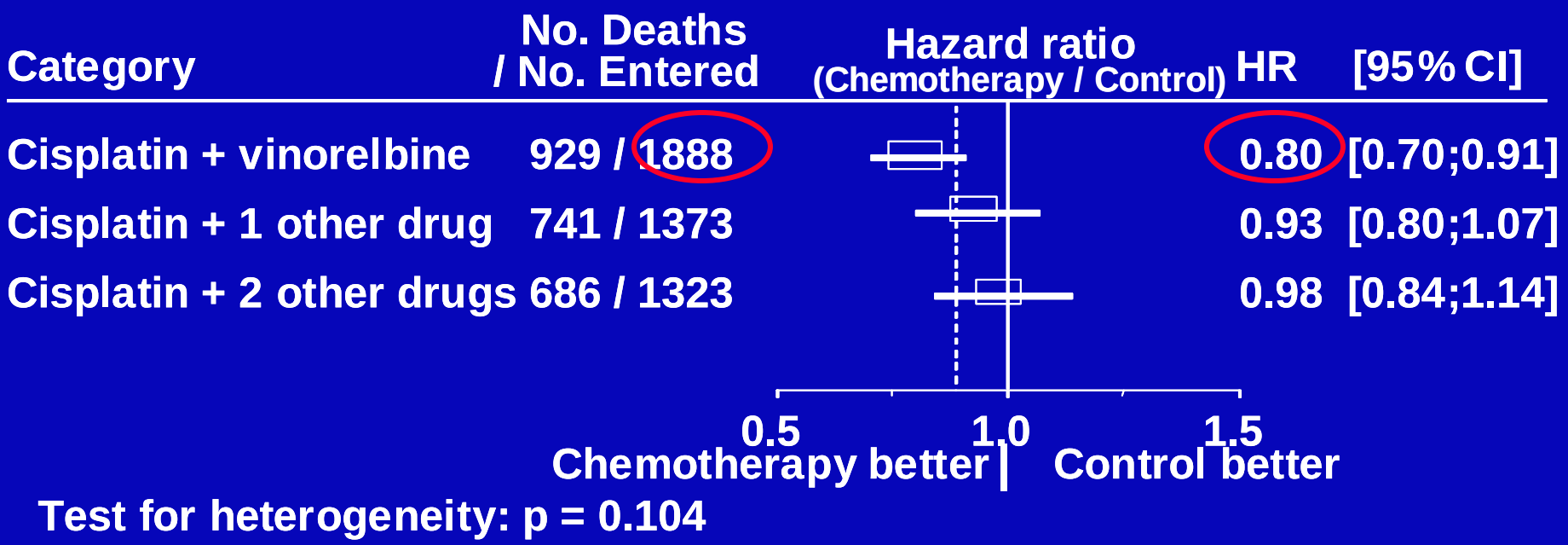


Pignon J et al. JCO 2008;26:3552-3559

Survival curves



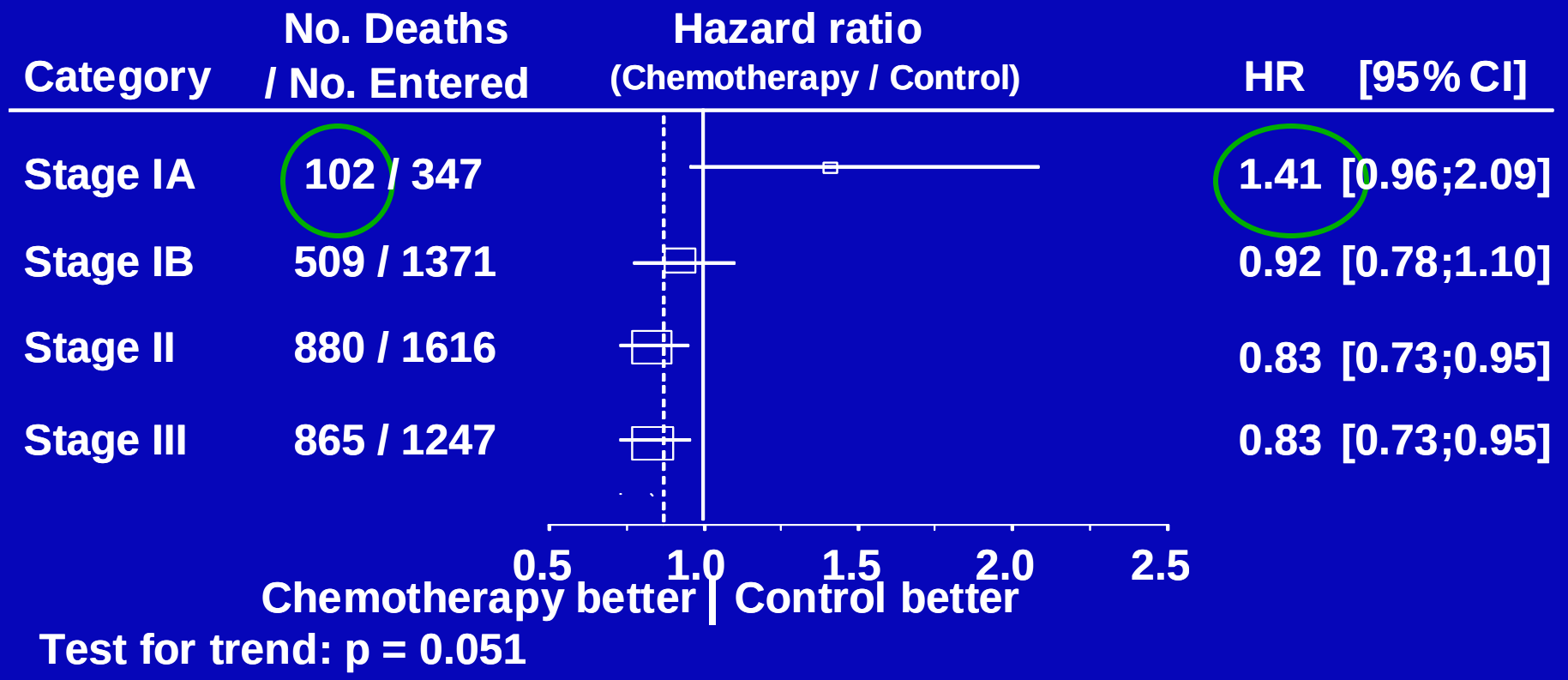
CT effect & associated drugs



Test for heterogeneity: p = 0.104

The effect of cisplatin+vinorelbine was marginally better than the effect of other drug combinations, this is significant when the other combinations are pooled (p=0.04, post-hoc analysis)

LACE: CT effect & stage



Test for trend: p = 0.051

CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin+vinorelbine (13% of stage IA patients versus ~43% for other stages)

Conclusions

- Cisplatin-based adjuvant CT improves overall and disease-free survivals of patients with NSCLC
- Vinorelbine associated with 320 to 400 mg/m² of cisplatin appears as the most promising drug combination
- Despite the large number of patients, multivariate analyses were not able to study the respective role of the associated drug and cisplatin dose

LACE Vinorelbine meta-analysis

ORIGINAL ARTICLE

Adjuvant Cisplatin and Vinorelbine for Completely Resected Non-small Cell Lung Cancer

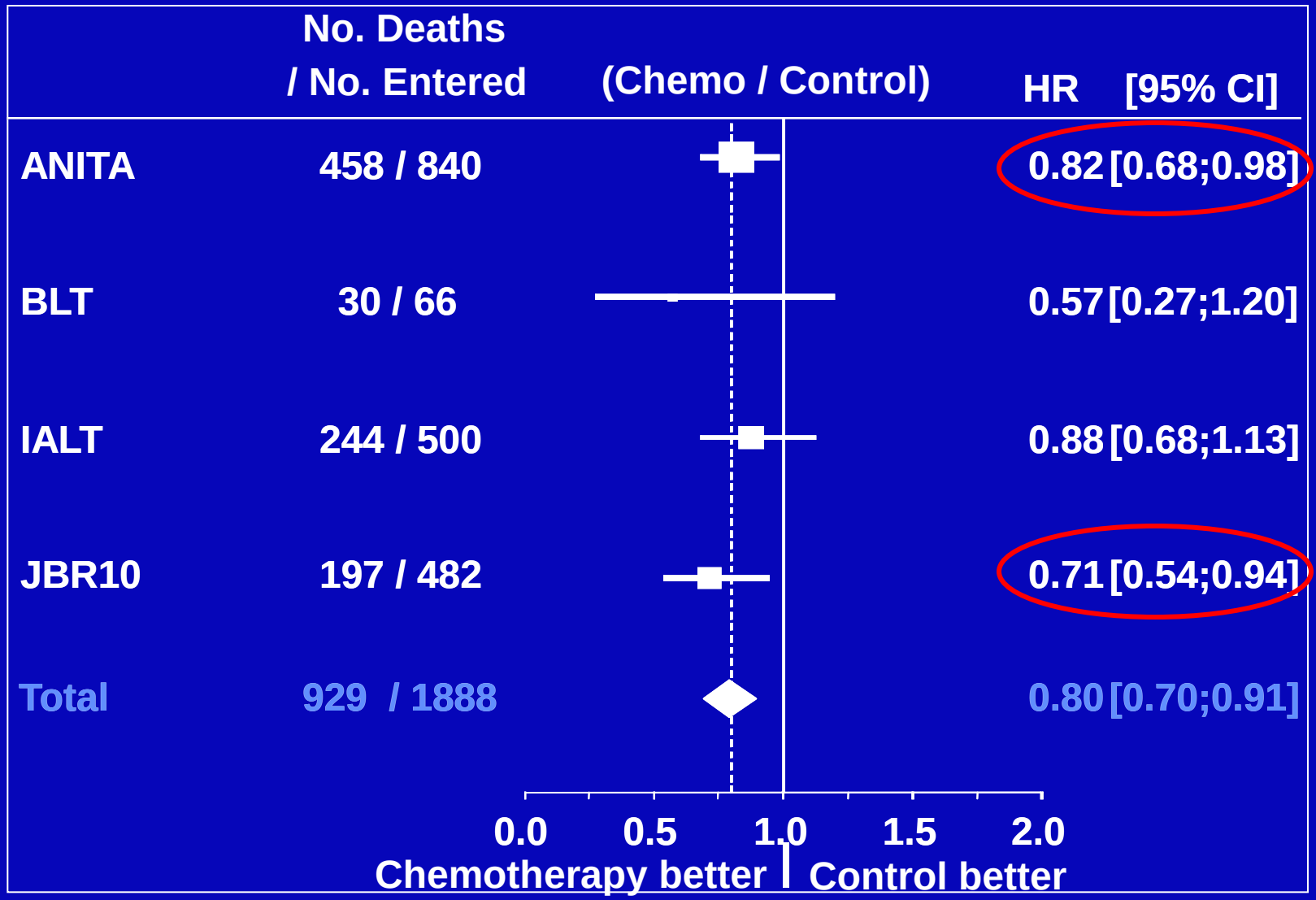
Subgroup Analysis of the Lung Adjuvant Cisplatin Evaluation

Jean-Yves Douillard, MD, PhD, Hélène Tribodet, MSc,† Delphine Aubert, MSc,‡*
Frances A. Shepherd, MD,§ Rafael Rosell, MD, PhD,‖ Keyue Ding, PhD,¶ Anne-Sophie Veillard, MSc,†
*Lesley Seymour, PhD,¶ Thierry Le Chevalier, MD,# Stephen Spiro, MD,** Richard Stephens,††*
Jean Pierre Pignon, MD, PhD,† and on behalf of the LACE Collaborative Group

JY DouillardJ Thorac Oncology 2010 5 220-228

ESMO 2006 Annals of Oncology 17 (Supplement 9): 213, 2006. Abstract 710 O

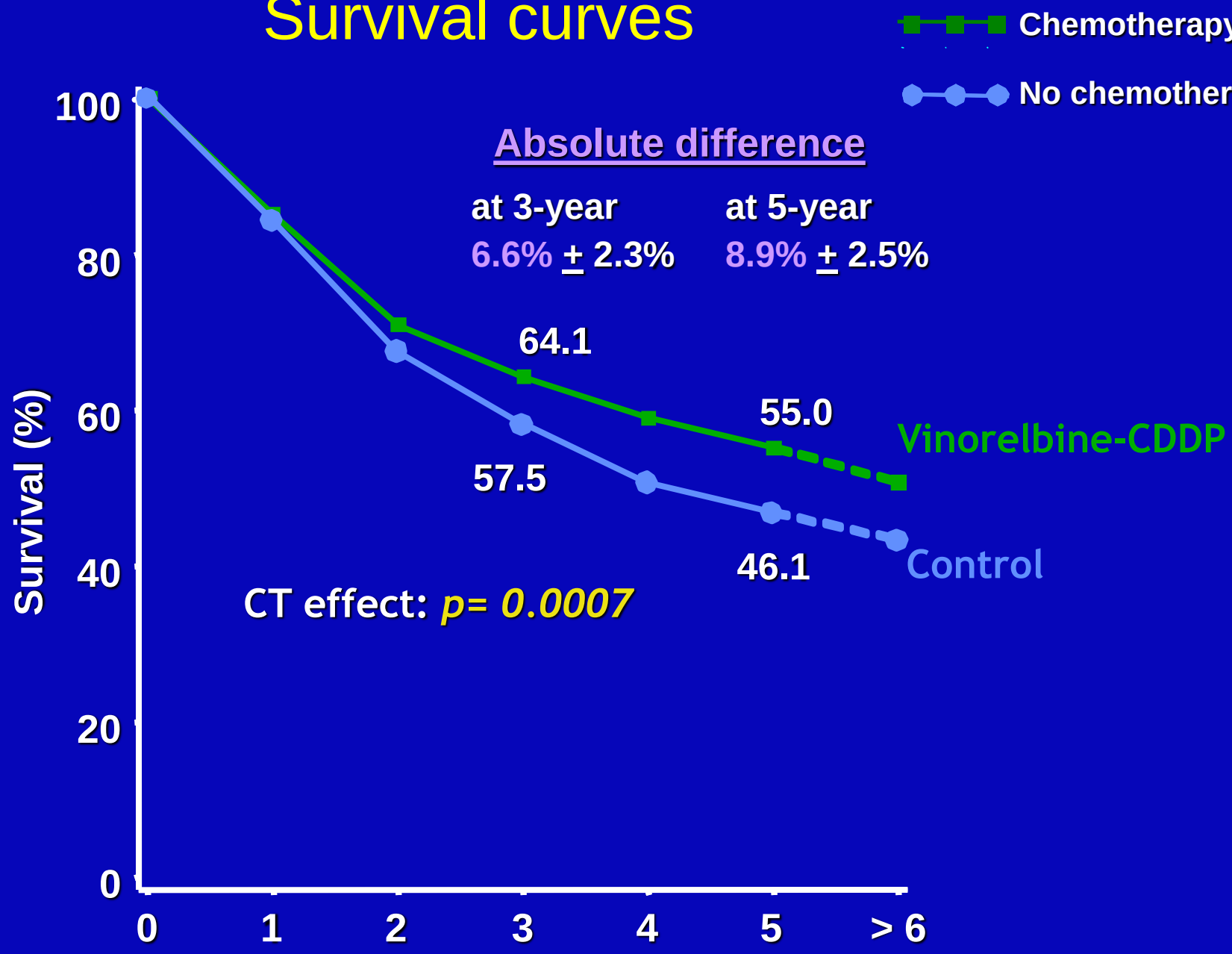
OS by trial



Heterogeneity test: p= 0.57

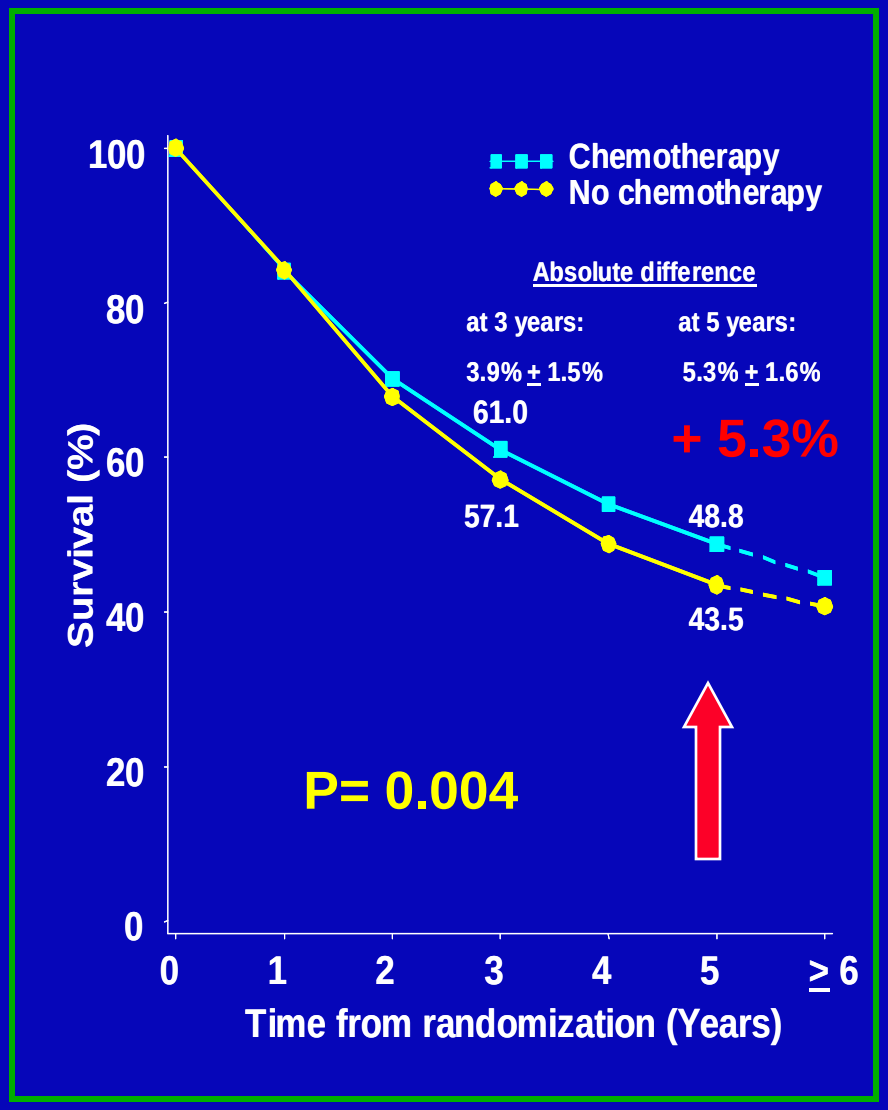
CT effect: *p= 0.0007*

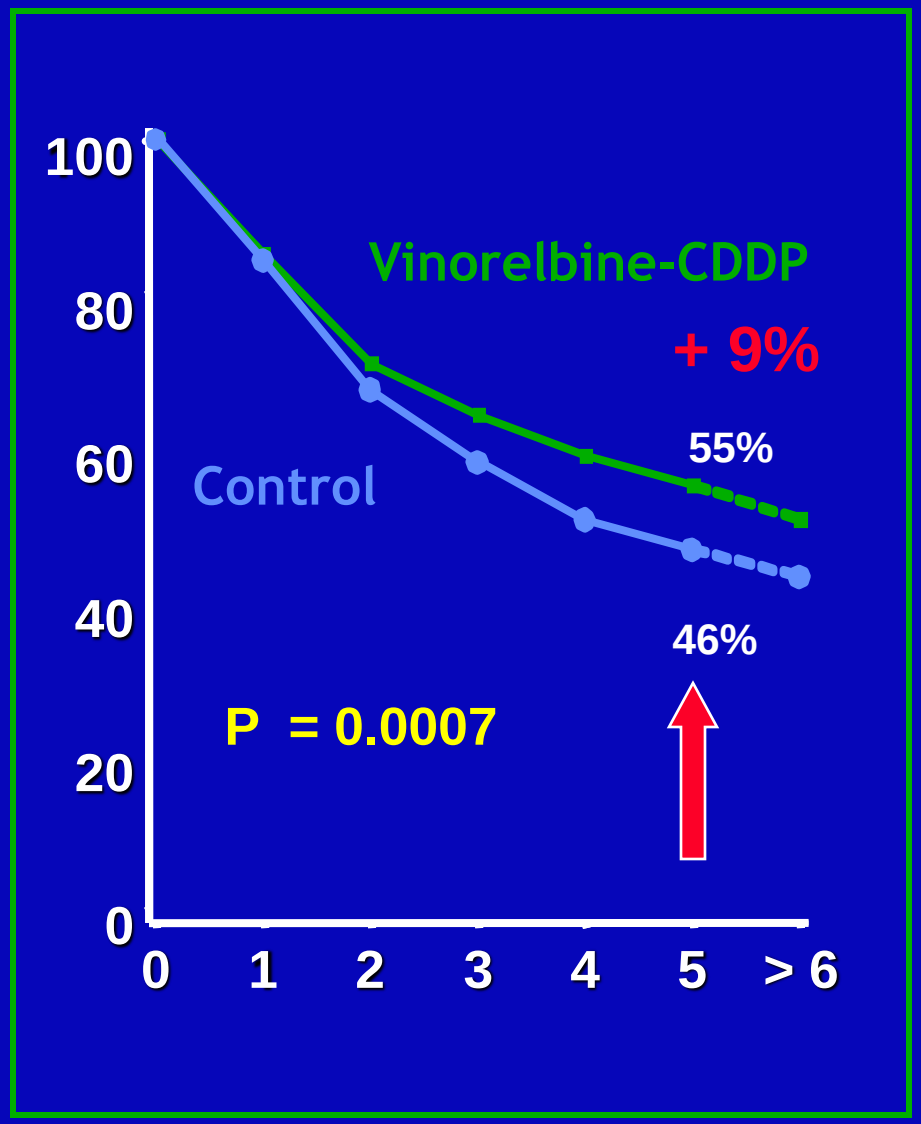
Survival curves



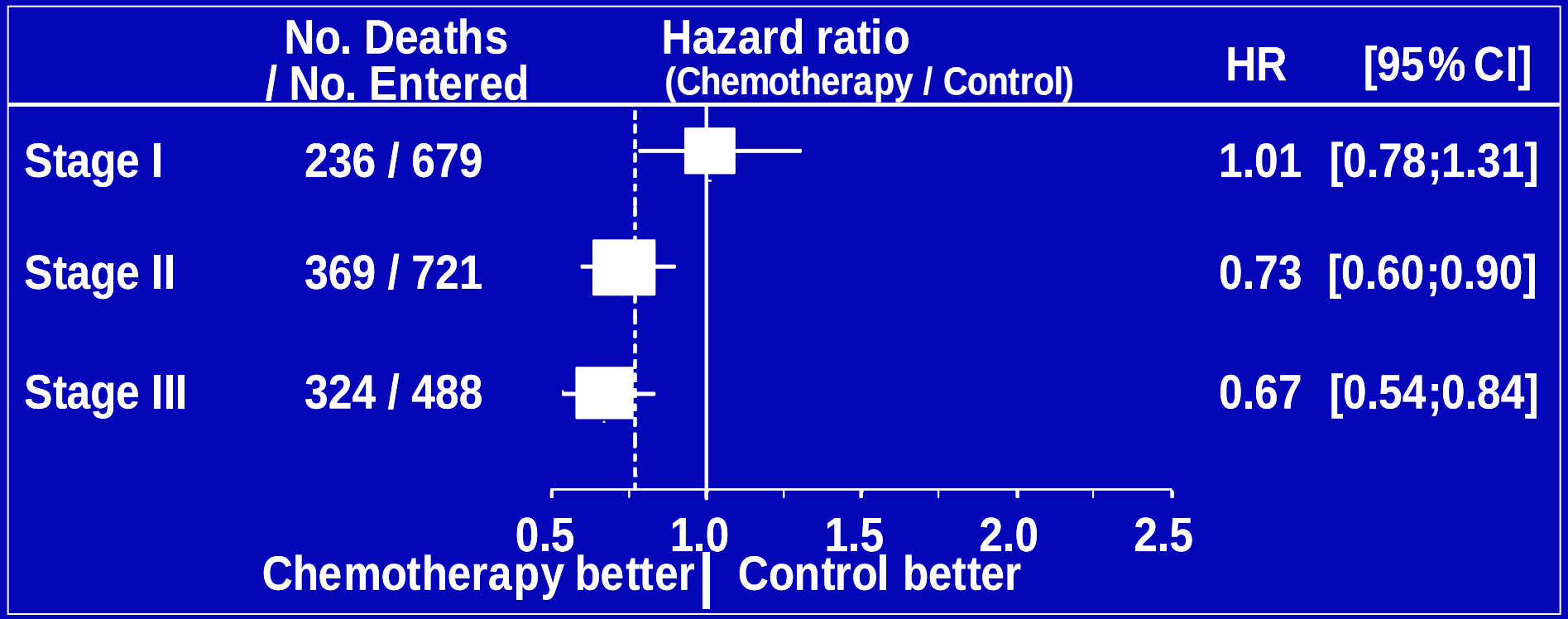
ESMO 2006 Annals of Oncology 17 (Supplement 9): 213, 2006. Abstract 710 O

Contribution of vinorelbine in adjuvant treatment of resected lung cancer





CT effect on survival and Stage



Test for trends: *p= 0.02*

ESMO 2006 Annals of Oncology 17 (Supplement 9): 213, 2006. Abstract 710 O

Adjuvant chemotherapy for Non-small Cell Lung Cancer

Special populations:

- **Elderly**

Adjuvant chemotherapy for Non-small Cell Lung Cancer in the Elderly

	Median age yr (range)	% ≥ 65 yrs	% ≥ 70 yrs	% ≥ 75 yrs	Subset analyses according age
IALT	59 (27-77)	27%	1%;	p older than 75 yrs excluded	No significant interaction between treatment effect and age (<55, 55-64, > 64 yr)
JBR.10	61	32%	15%	5%	p > 65 yrs CT prolonged OS (HR 0.61)
ANITA	59 (32-75)	28%	8%;	p older than 75 yrs excluded	No
LACE	60	29%	9%	_	p ≥ 70 yrs OS benefit from *ADJ* CT; HR 0.90

Courtesy of Enriqueta Felip

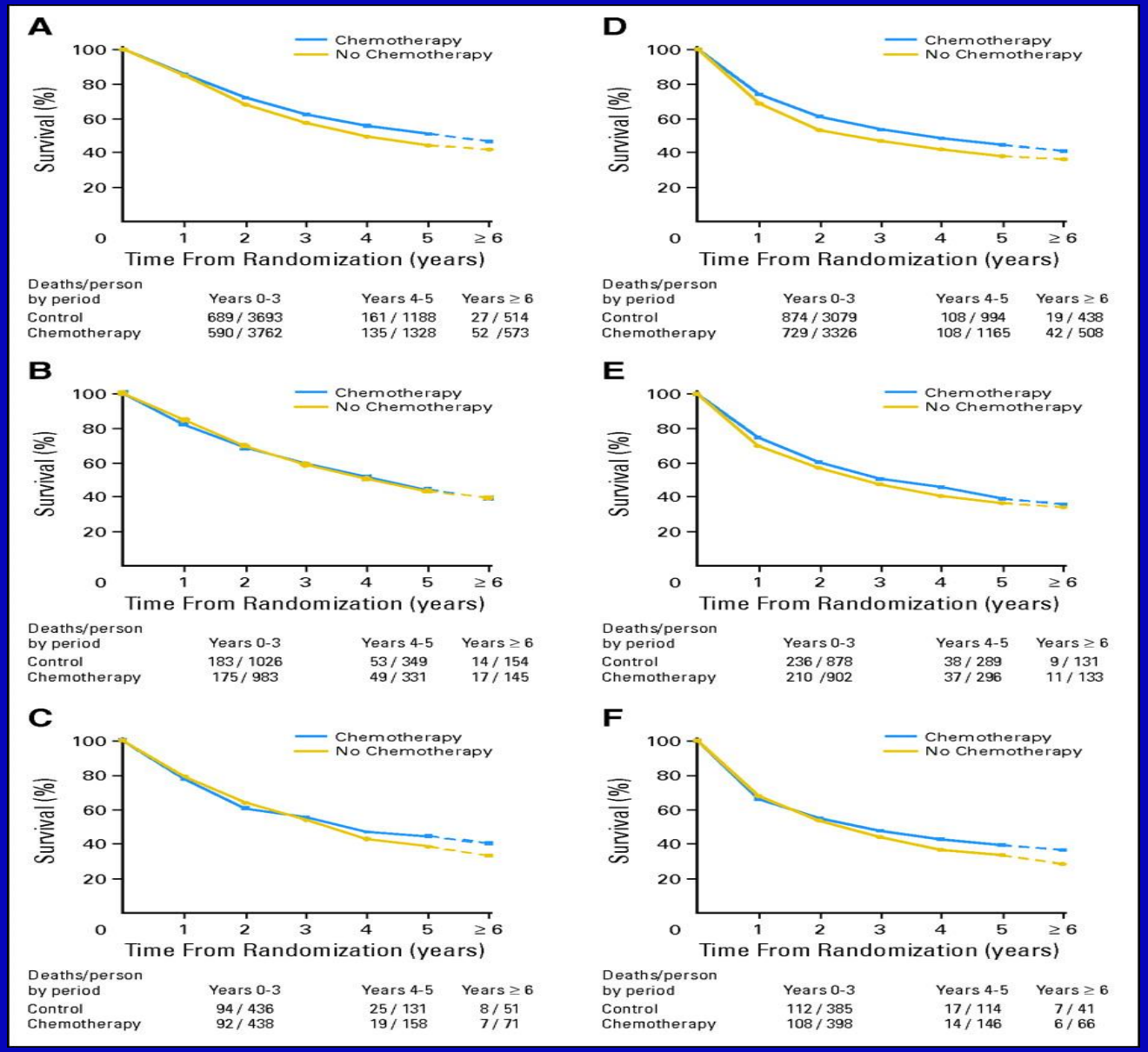
LACE ELDERLY

(A,B,C) Overall survival and (D,E,F) event-free survival by treatment arm and by age group.

< 65 y

65-69 y

≥ 70 y



Früh M et al. JCO 2008;26:3573-3581

JOURNAL OF CLINICAL ONCOLOGY ASCO

Adjuvant Chemotherapy for NSCLC

- Based on present data, chemotherapy should be recommended in stages II and IIIA
- Its role in stage IB is still unclear, most of the western studies are negative
- Navelbine-Cisplatin is the only « modern » chemotherapy of proven efficacy in stage II and IIIA.
- Elderly patients should not be excluded on the only basis of age

Could other cisplatin doublets be used? From metastatic to adjuvant setting

Colon cancer

- Metastatic setting 1st line
  - FOLFIRI=FOLFOX
- Adjuvant setting:
  - FOLFOX and FLOX
    - Gercor and NSABP
      - 2 positive trials
  - FOLFIRI and IFL
    - Petacc3/Accord2/CALGB
      - 3 negative trials

Breast cancer

- Metastatic setting 1st line
  - Adria-Cytoxan=Adria-Docetaxel
  - AC=AT
- Adjuvant setting:
  - Randomized trial AC vs AT
    - AC < AT

Equi-efficacy in metastatic setting does not translate into equi-efficacy in adjuvant

special articles

Annals of Oncology 25: 1462–1474, 2014
doi:10.1093/annonc/mdu089
Published online 20 February 2014

2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up

J. Vansteenkiste[1], L. Crinò[2], C. Dooms[1], J. Y. Douillard[3], C. Faivre-Finn[4], E. Lim[5], G. Rocco[6], S. Senan[7], P. Van Schil[8], G. Veronesi[9], R. Stahel[10], S. Peters[11], E. Felip[12] & Panel Members*†

- ***« Adjuvant chemotherapy should be offered to patients with resected stage II and III [I,A] and can be considered in patients with resected stage IB disease and a primary tumor > 4cm [II,B].***
- ***Pre-existing comorbidities, time from surgery and post-operative recovery need to be taken into account in this decision in a multidisciplinary tumor board [V,A].***
- ***For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable [I,A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300mg/m², delivered in 3 to 4 cycles.***
- ***The most frequently studied regimen is cisplatin-vinorelbine.***
- ***In the current stage of knowledge, the choice of adjuvant chemotherapy should be guided by molecular analysis such as, e.g. ERCC-1 or mutation testing [IV,B] »***