



**EDUCATIONAL SESSION**

**Challenges in the treatment of early NSCLC:  
What is the standard, what are the challenges  
and what is the future?**

***Systemic treatment***

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## **Lung Cancer: U.S. Males & Females, 2004**

- **Estimated New Cases = 175,000**
- **Estimated Deaths = 157,200**
- **Percent of all New Cancer Cases = 13%**
- **Percent of all Cancer Deaths = 28%**
- **In 2000, deaths from lung cancer account for nearly 2.3 *million* person years of life lost**

*Source: ACS Facts & Figures, 2003*

# Combined Modality Therapies in Early NSCLC - *Rationale*

- Suboptimal survival rates following surgery
- Majority of patients develop disseminated disease
- Clinical Trials : Chemotherapy +/- TRT
  - ✓ Postoperative (Adjuvant)
  - ✓ Preoperative (Neo-adjuvant, Induction)

# NSCLC Meta-analysis

## *Results with DDP-based CT*

Treatments	H.R. (95 C.I.)	P value	Reduction Risk of Death	% Abs Benefit	
				2-yr	5-yr
<b>Surg vs Surg+CT</b>	<b>0.87 (0.74-1.02)</b>	<b>0.08</b>	<b>13%</b>	<b>3</b>	<b>5</b>
<b>Surg+RT vs Surg+RT+CT</b>	<b>0.94 (0.79-1.11)</b>	<b>0.46</b>	<b>6%</b>	<b>2</b>	<b>2</b>
<b>RT vs RT+CT</b>	<b>0.87 (0.79-0.96)</b>	<b>&lt;0.01</b>	<b>13%</b>	<b>4</b>	<b>2</b>
<b>SC vs SC+CT</b>	<b>0.73 (0.63-0.96)</b>	<b>&lt;0.001</b>	<b>27%</b>	<b>10% (1-yr)</b>	<b>MST &gt;1.5 mos</b>

\* Meta-analysis, Brit Med J, October 1995

# NSCLC- adjuvant chemotherapy: summary of recent trials

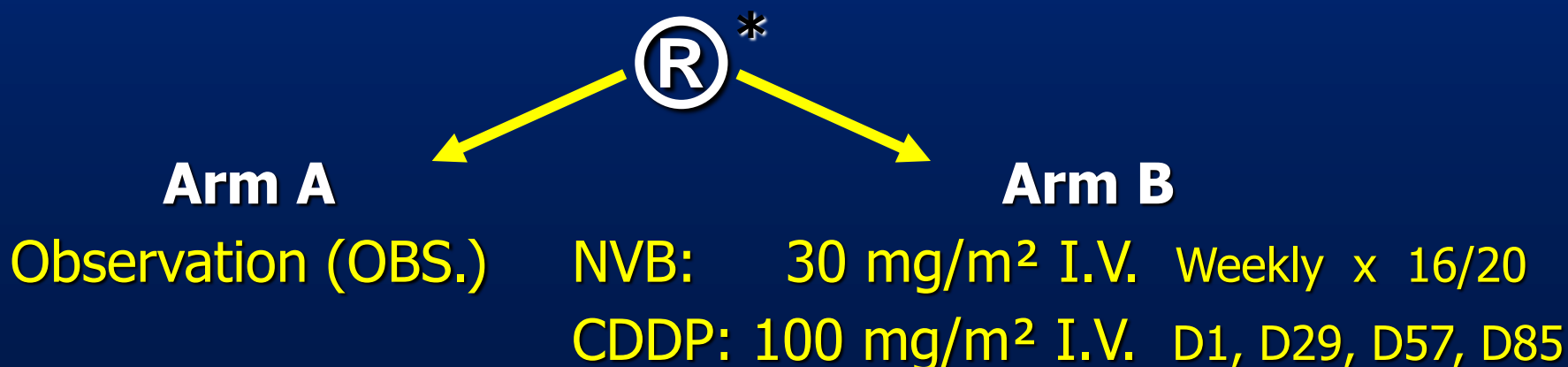
	N	HR (95%CI)	Stage	Year
BMJ meta	1394	0.87 (0.74-1.02)	I-III	1995
IALT	1867	0.86 (0.76-0.98)	I-III	2004
ALPI	1209	0.94 (0.79-1.12)	I-III A	2003
ECOG3590	488	0.93 (0.74-1.18)	II-III A	2000
BLT	381	1.02 (0.77-1.35)	I-III	2004
BR.10	482	0.70 (0.62-0.92)	II	2005
ANITA	840	0.79 (0.66-0.95)	IB-III A	2006
BMJ meta update	8147	0.86 (0.81-0.93)	I-III	2007
French meta	2660	0.89 (0.81-0.97)	I-III A	2007
CALGB9633	344	0.83 (0.64-1.08)	IB	2008
LACE meta	4584	0.89 (0.82-0.96)	IA-IIIB	2008

# Treatment Regimens, Delivery and Toxicity, Selected Adjuvant Phase III Trials

	<b>ALPI</b>	<b>IALT</b>	<b>NCIC-CTG</b>	<b>CALGB</b>	<b>ANITA</b>
<b>Chemotherapy</b>	<b>MVdp</b>	<b>Vc/EP</b>	<b>VbP</b>	<b>PacCb</b>	<b>VBP</b>
<b>Platin dose, mg/m2</b>	<b>100</b>	<b>80-120</b>	<b>50+50</b>	<b>AUC 6</b>	<b>100</b>
<b>Chemotherapy delivery</b>	<b>69</b>	<b>74</b>	<b>59</b>	<b>85</b>	<b>58/88</b>
<b>Grade 3/4 toxicity, %</b>	<b>28</b>	<b>23</b>	<b>73</b>	<b>24</b>	<b>84</b>
<b>Rx death, %</b>	<b>0.005</b>	<b>0.8</b>	<b>0.01</b>	<b>0</b>	<b>1.7</b>
<b>Radiation, %</b>	<b>43</b>	<b>27</b>	<b>0</b>	<b>0</b>	<b>25</b>

# Study Design

- ❑ Open, multicentric, randomized study (1:1).
- ❑ Stratified after surgery by centre, stage and histology.
  - 800 patients to be included . Stage I-III A.
- ❑ Alpha= 5%, Beta= 10%, Power= 90 %
- ❑ One sided test
- ❑ Expected deaths: 466 events



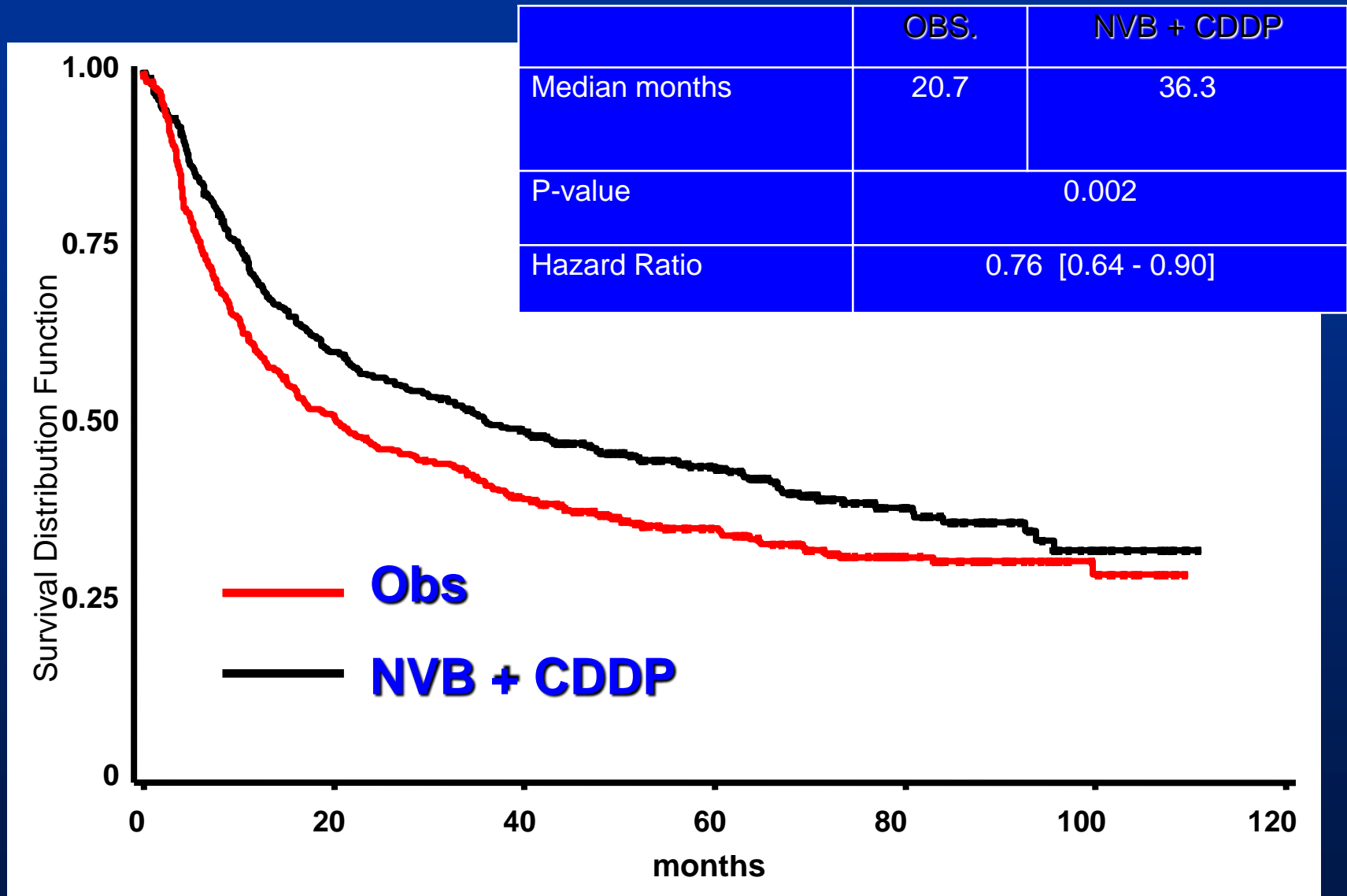
\* Radiation therapy was upon center choice

# Treatment compliance

	<b>NVB</b> <i><b>n = 368</b></i>	<b>CDDP</b> <i><b>n = 367</b></i>
Theoretical dose	30 mg/m <sup>2</sup> /w 16 adm./20w	100 mg/m <sup>2</sup> D1 every 4w
Median No. of Administrations	10 [1-17]	4 [1-4]
<b>Median DI / Theoretical (mg/m<sup>2</sup>/week)</b>	<b>17.6/30</b>	<b>22.2/25</b>
Median Relative Dose Intensity (%)	58.6%	88.9%

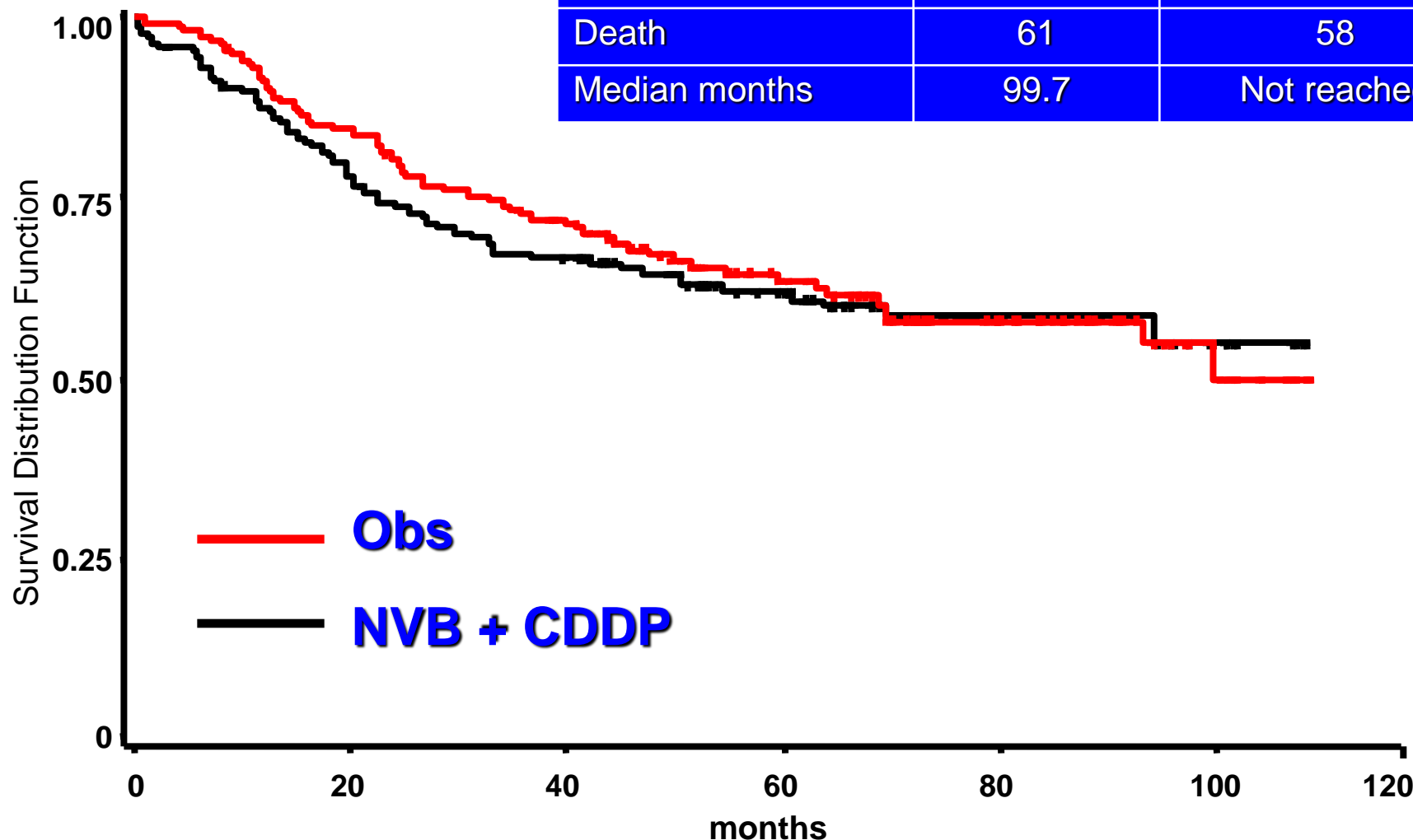


# Relapse-Free Survival - ITT population

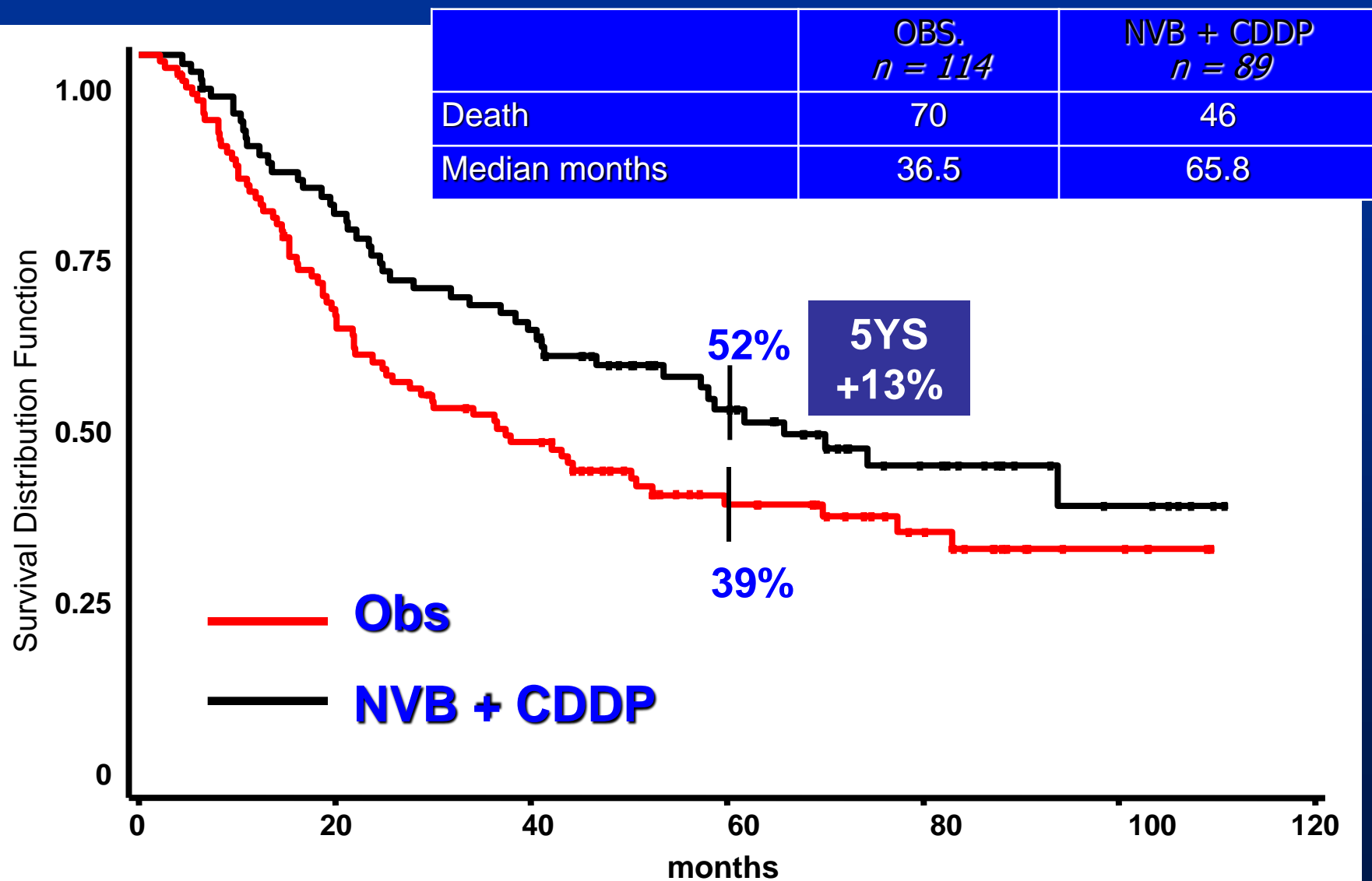


# Overall Survival - Stage I (pT2N0)

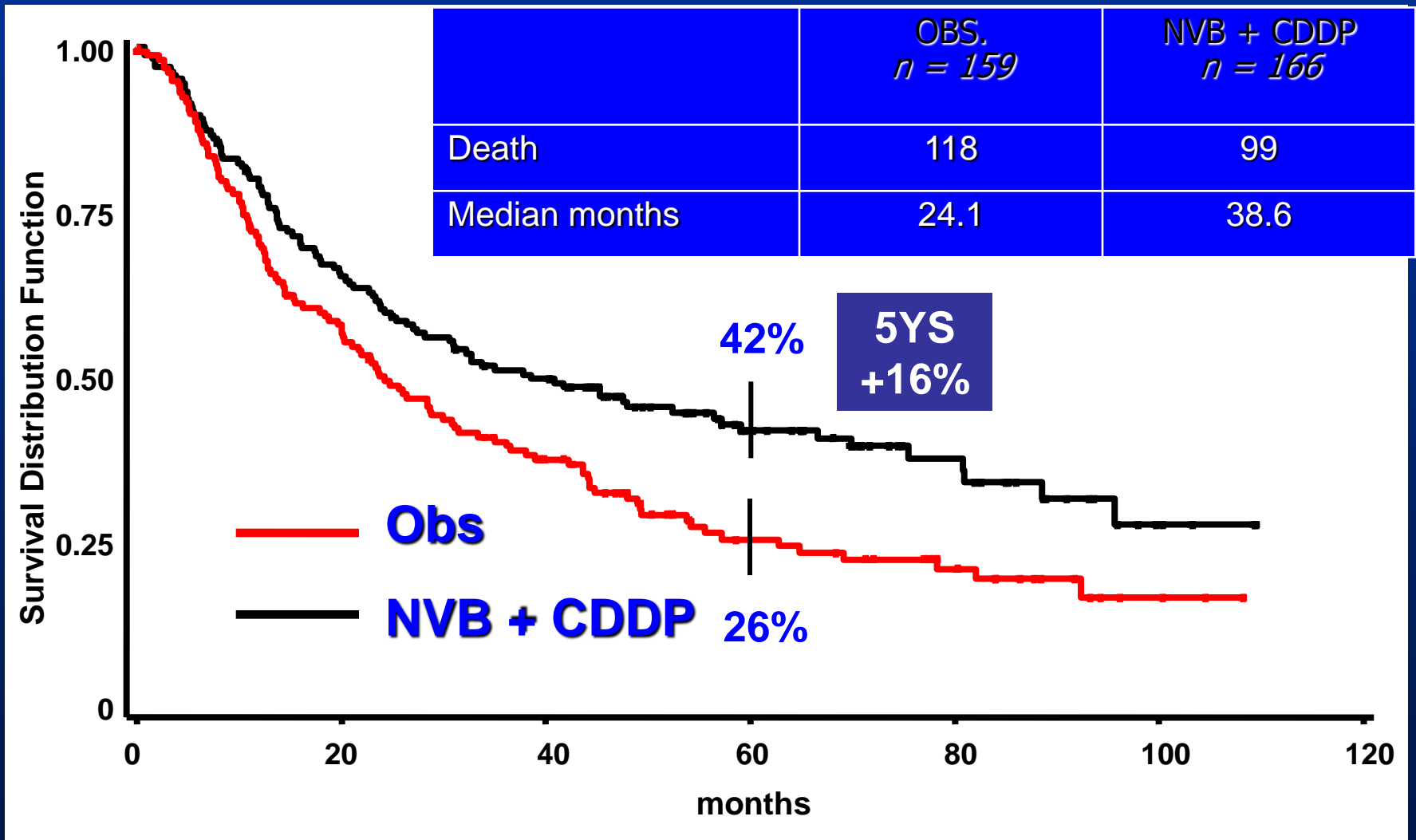
	OBS. <i>n</i> = 155	NVB + CDDP <i>n</i> = 146
Death	61	58
Median months	99.7	Not reached



# Overall Survival - Stage II (pT 1-2, N1)



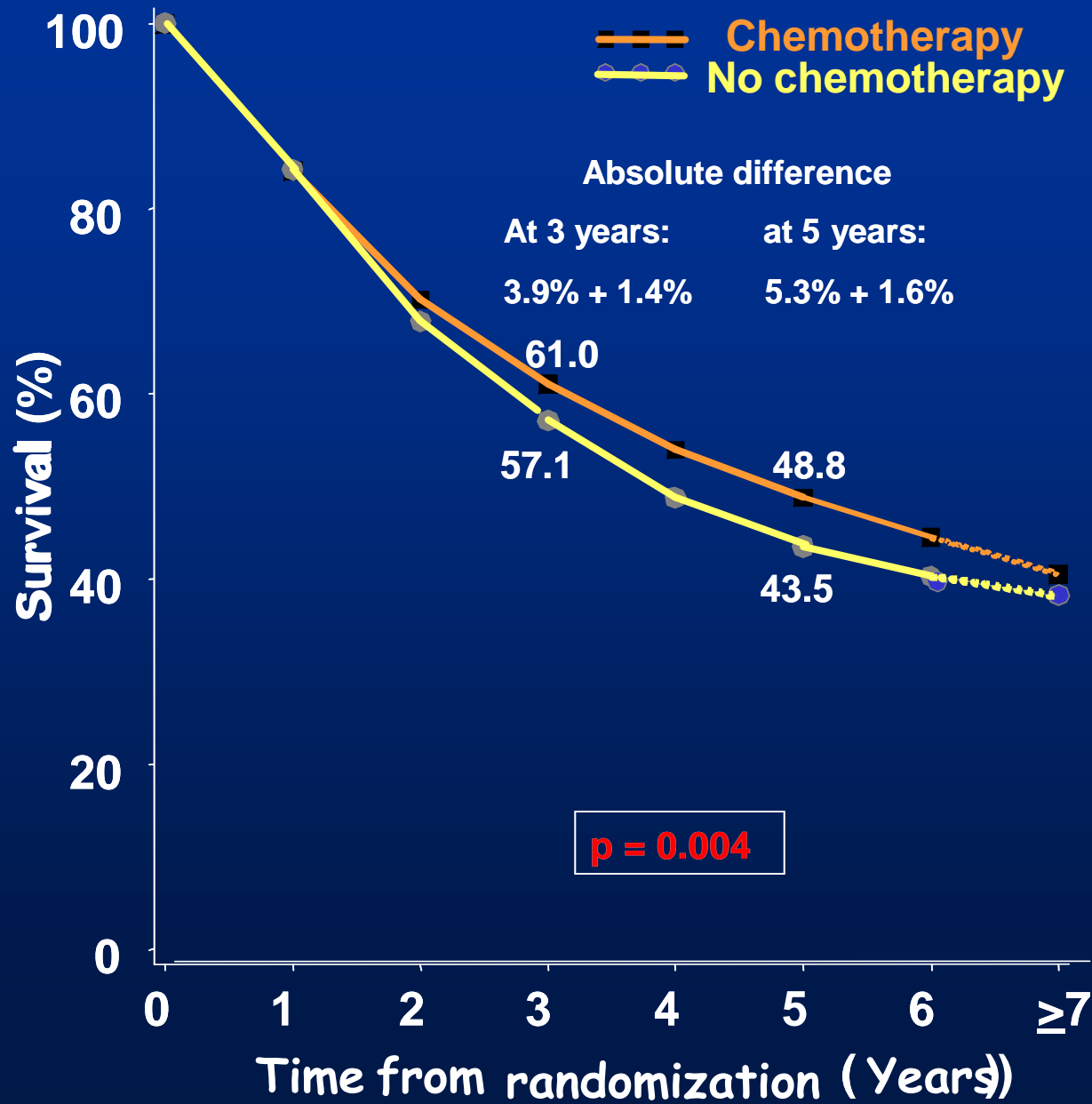
# Overall Survival - Stage III A (pT1-2 N2, pT3 N 0-1-2)



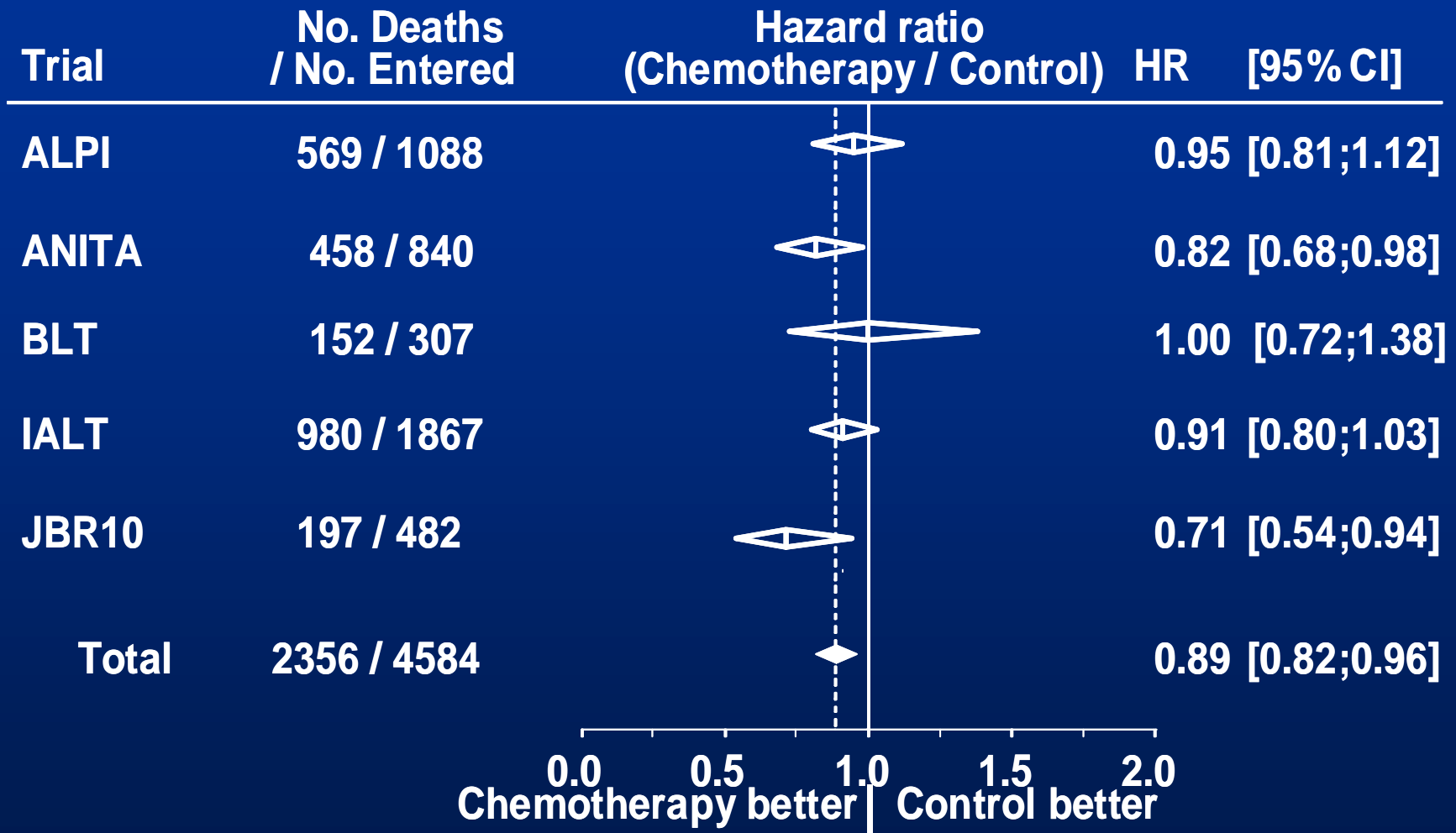
# Toxicity (WHO grade 3-4)

	OBS		NVB + CDDP	
	% cycles	% patients	% cycles	% patients
Neutropenia	0.1	0.3	69.7	84.6
Febrile Neutropenia	0	0	4.7	12.5
Infection	0.4	1.6	3.6	11.2
Anemia	0	0	5.4	13.7
Nausea/Vomiting	0.1	0.3	11.6	27.2
Anorexia	0.5	1.6	5.9	14.9
Asthenia	0.8	2.6	11.4	27.8
Neuropathy	0	0	1.0	3.2
Phlebitis	0	0	1.0	2.9
Alopecia	-	0	-	5.2
Toxic death	-	0	-	1.7

# LACE - Survival Curves



# LACE Meta-analysis - OS by trial



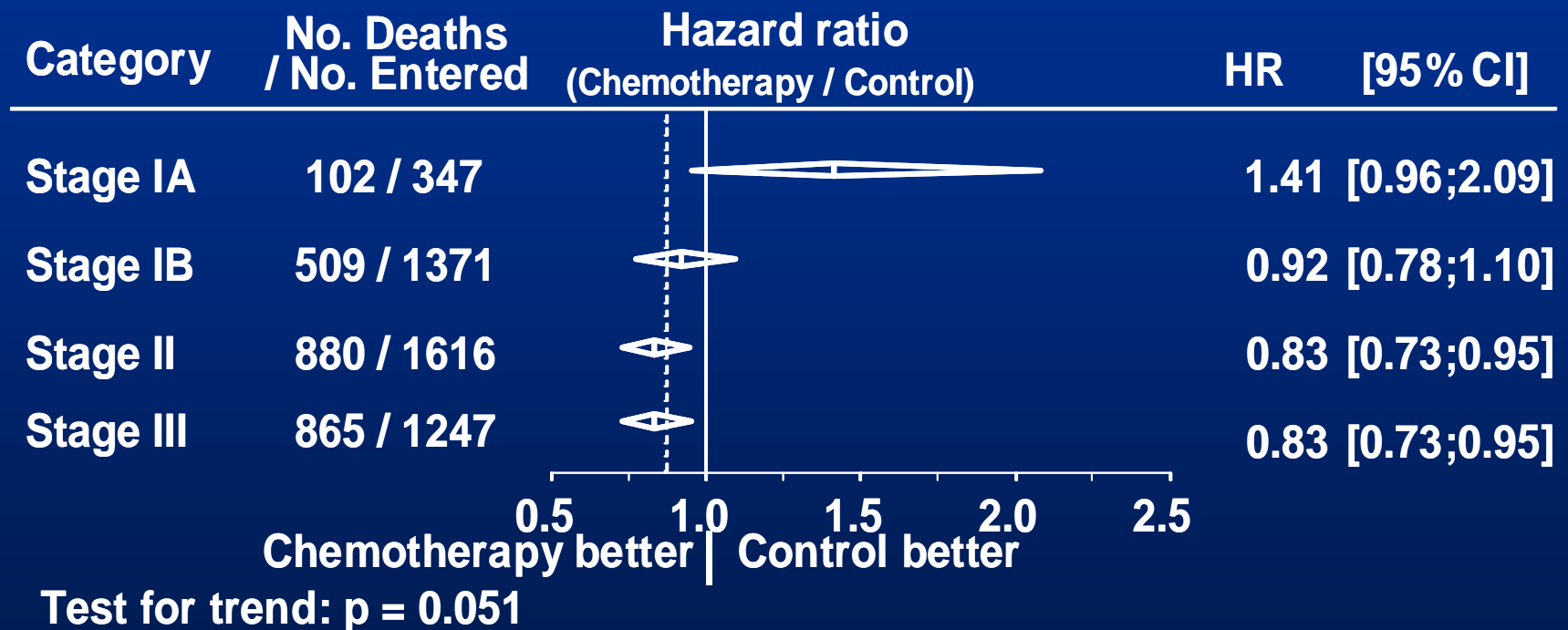
Test for heterogeneity:  $p = 0.34$

Chemotherapy effect:  $p = 0.004$

*Pignon JP et al. Proc ASCO 2006*

# LACE Meta-analysis

## CT effect & stage





# DISEASE-FREE SURVIVAL

## LACE METAANALYSIS

### Overall effect

HR=0.84 (0.78-0.90)  $p < 0.001$

5 years absolute benefit 5.8-5.5%

## BMJ METAANALYSIS

### Overall effect

HR=0.87 (0.74-1.02)  $p = 0.008$

5 years absolute benefit 5%

### CT effect & associated drug

Test for heterogeneity:  $p = 0.069$

### CT effect & stage

Test for trend:  $p = 0.055$

# Best Candidates to Adjuvant CT

- Lobectomy
- Complete recovery from surgery
- No co-morbid conditions
- Age < 70 years
- PS 0 -1
- ???? Non- and former smokers
- ???? Absence of vascular invasion

# Which Chemotherapy ?

In the adjuvant setting two trials (NCIC & ANITA) showed Cisplatin - Vinorelbine as a very active combination BUT.....

- therapeutic schedule is not widely used.
- too toxic (G3-4 neutropenia > 80% of cases, Febrile neutropenia > 8-10%)
- Delivery: 56% (NCI) and 76% (ANITA)
- Question : Is vinorelbine d. 1 & 8 q3 weeks is equally active?

# NSCLC - adjuvant chemotherapy

## Phase II Cis/Pemetrexed vs. Cis/Vinorelbine (TREAT)

- Cis/Pemetrexed is similar effective
- Cis/Pemetrexed less toxic
- Cis/Pemetrexed with superior dose delivery
- Cis/Pemetrexed with higher dose density

*Kreuter et al. Annals of Oncology 24: 986–992, 2013*

# Systemic therapy in early stage NSCLC

Adjuvant chemotherapy is recommended in stage II - III radically resected NSCLC

- Cisplatin-based chemotherapy improves OS and DFS
- Benefit is greatest in stage II and III, and in PS 0-1
- There is no significant interaction between CT and type of surgery, histology, age, gender, or planned RT
- Current trials investigate the role of pharmacogenomics

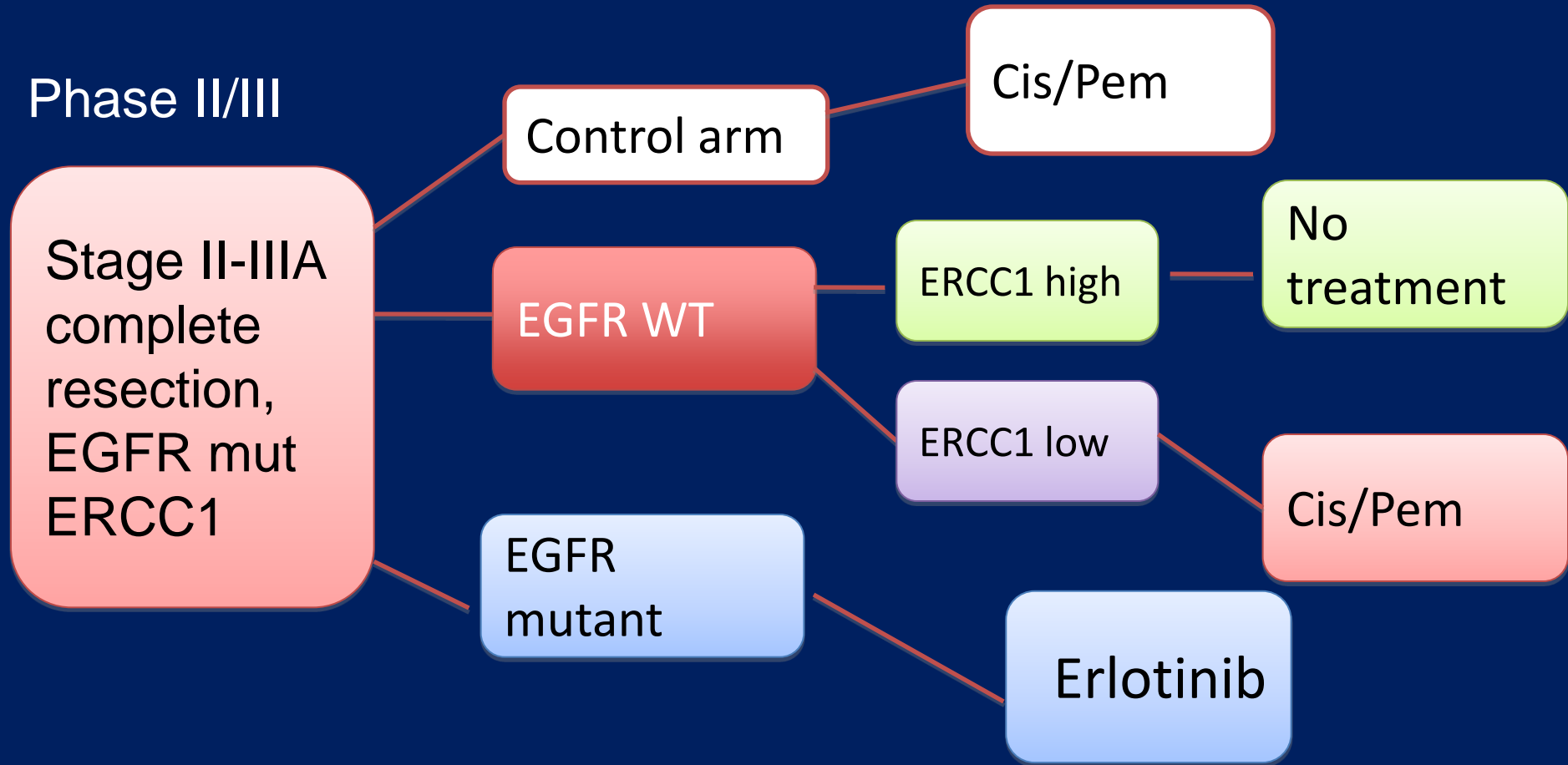
Neo-adjuvant cisplatin-based chemotherapy is recommended in stage IIIA/N2- radically resected NSCLC

- Benefit similar to adjuvant therapy

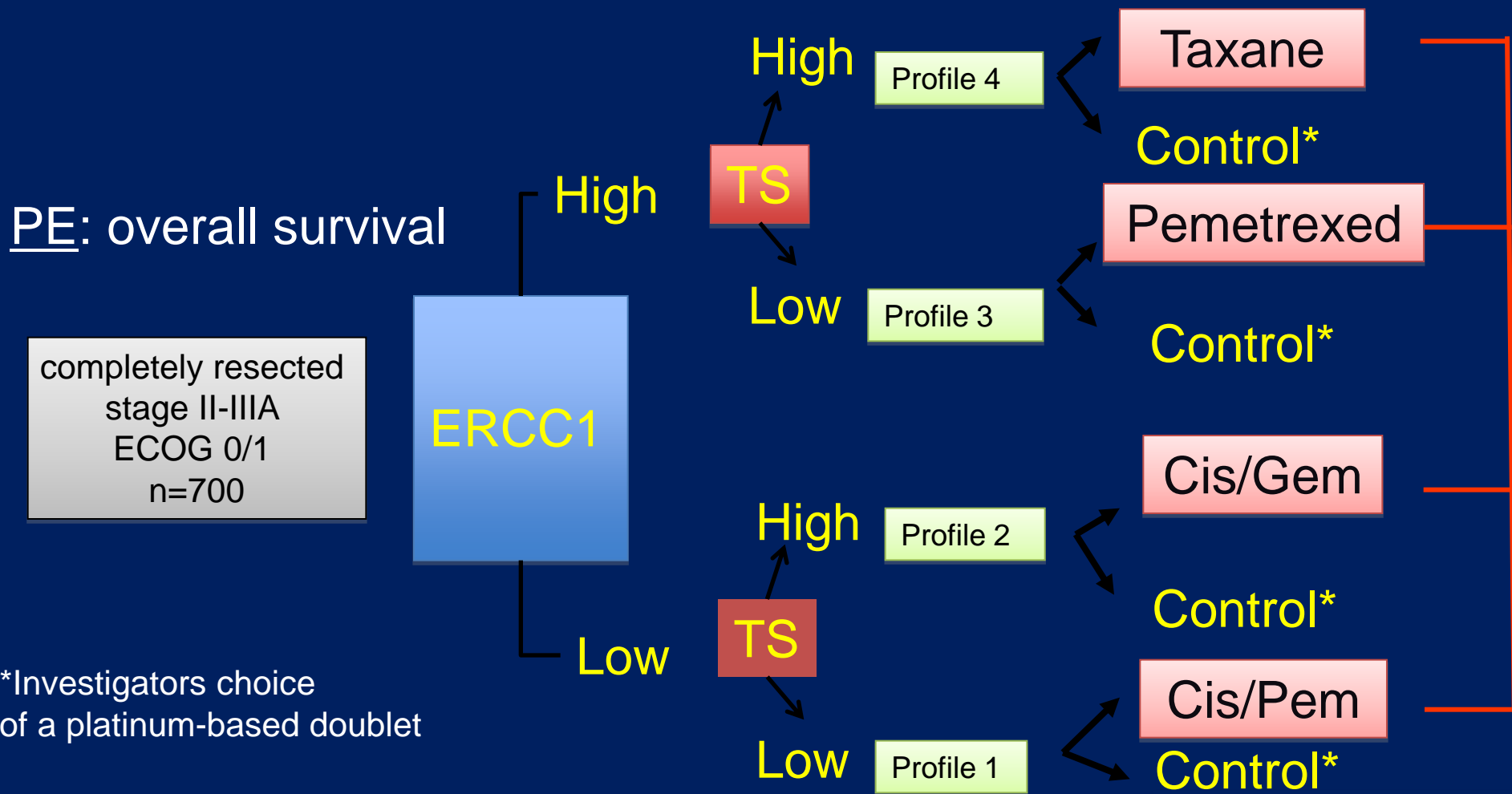
# NSCLC (TASTE trial): tailored (ERCC1, EGFR mut.) adjuvant Therapy

## Tailored Post-Surgical Therapy in Early Stage NSCLC

Phase II/III



# NSCLC (ITACA – phase III): International Tailored (ERCC1/TS) adjuvant chemotherapy

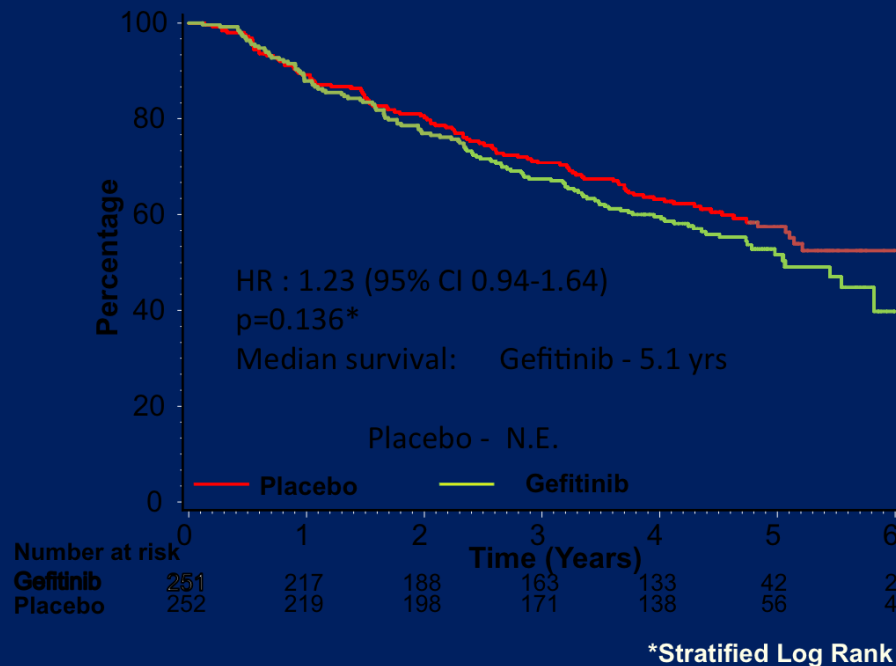


ERCC1: Excision repair cross complementing group 1 gene

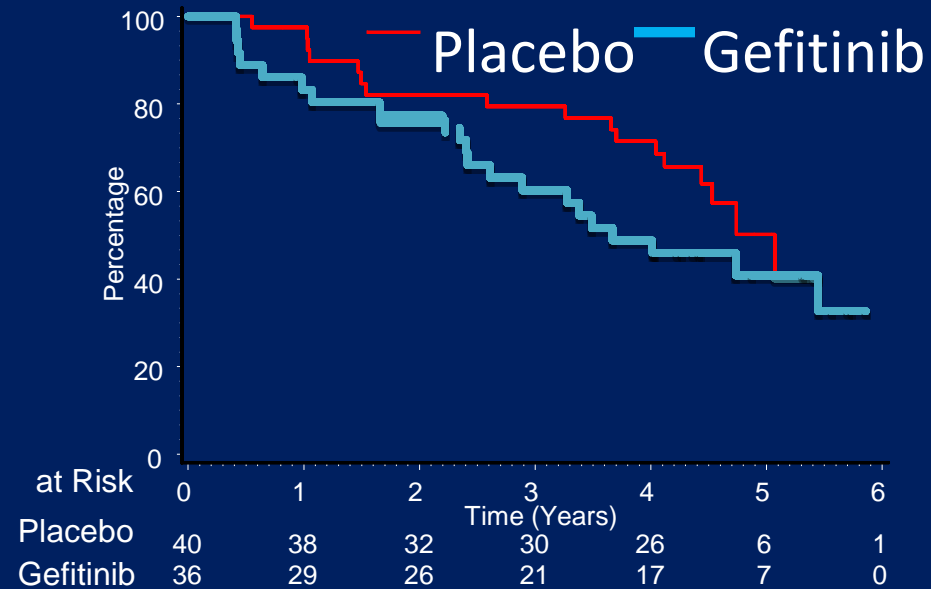
TS: Thymidilate Synthase

# NSCLC (BR19): adjuvant therapy by Gefitinib - overall survival

Overall population

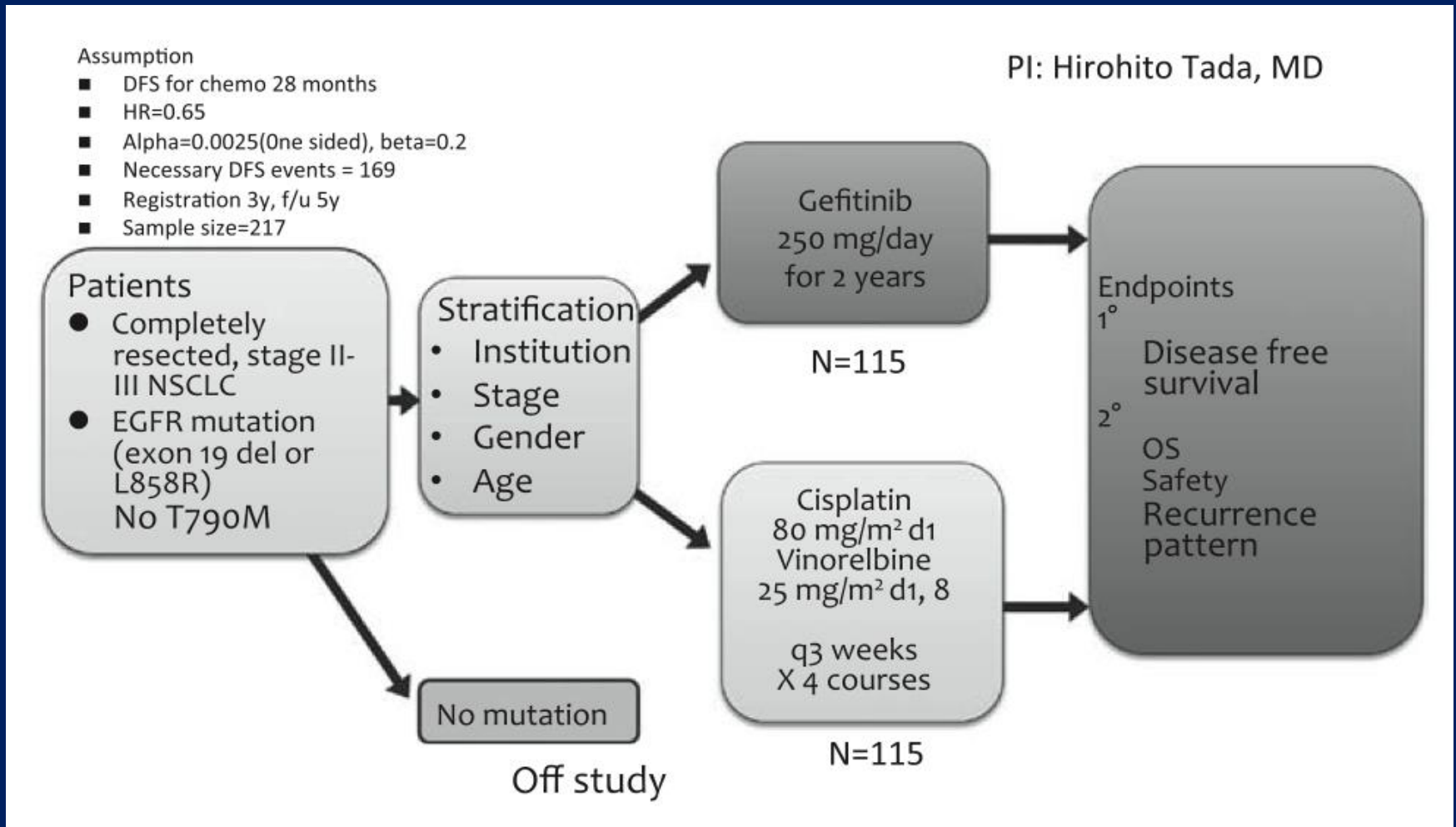


Sensitizing mutation



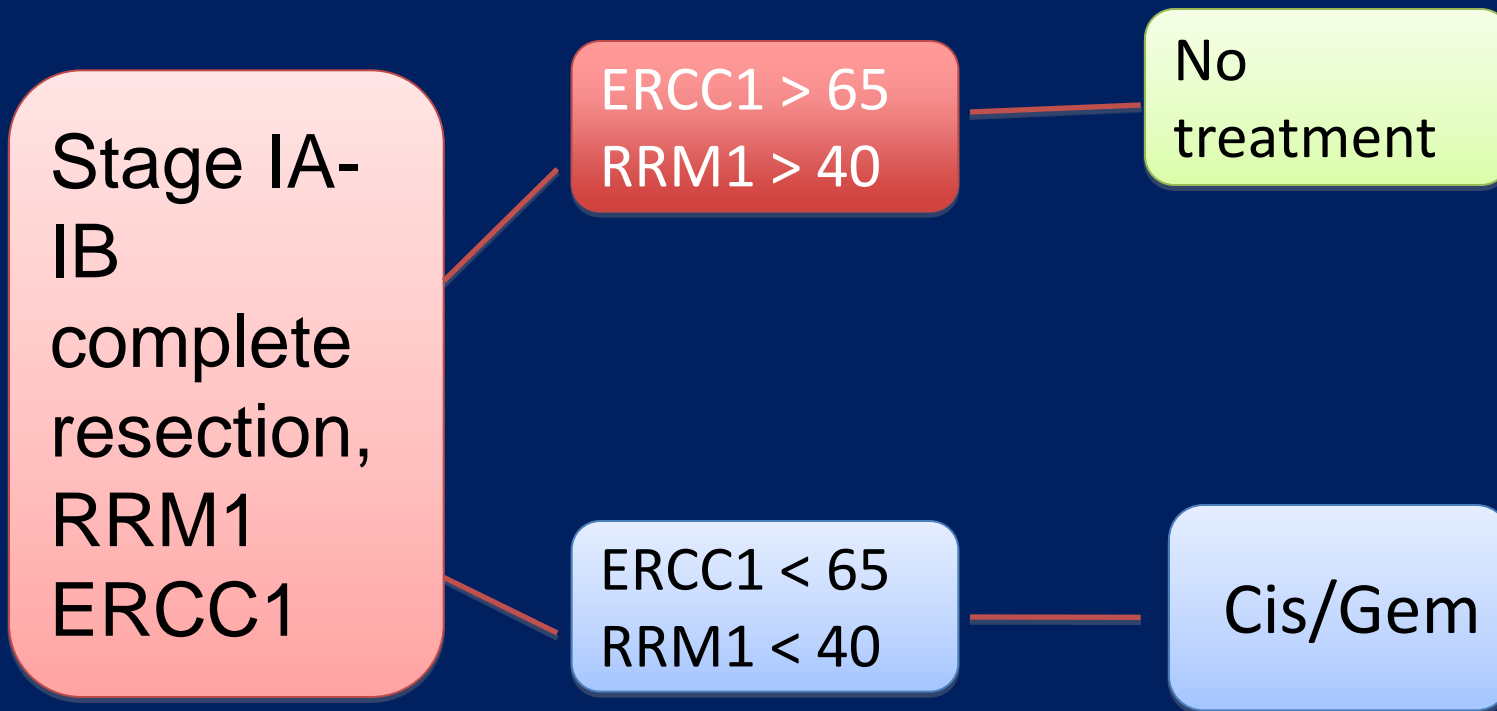


# NSCLC (WJOG6410L): tailored (EGFR mut.) adjuvant therapy - Gefitinib vs. CT



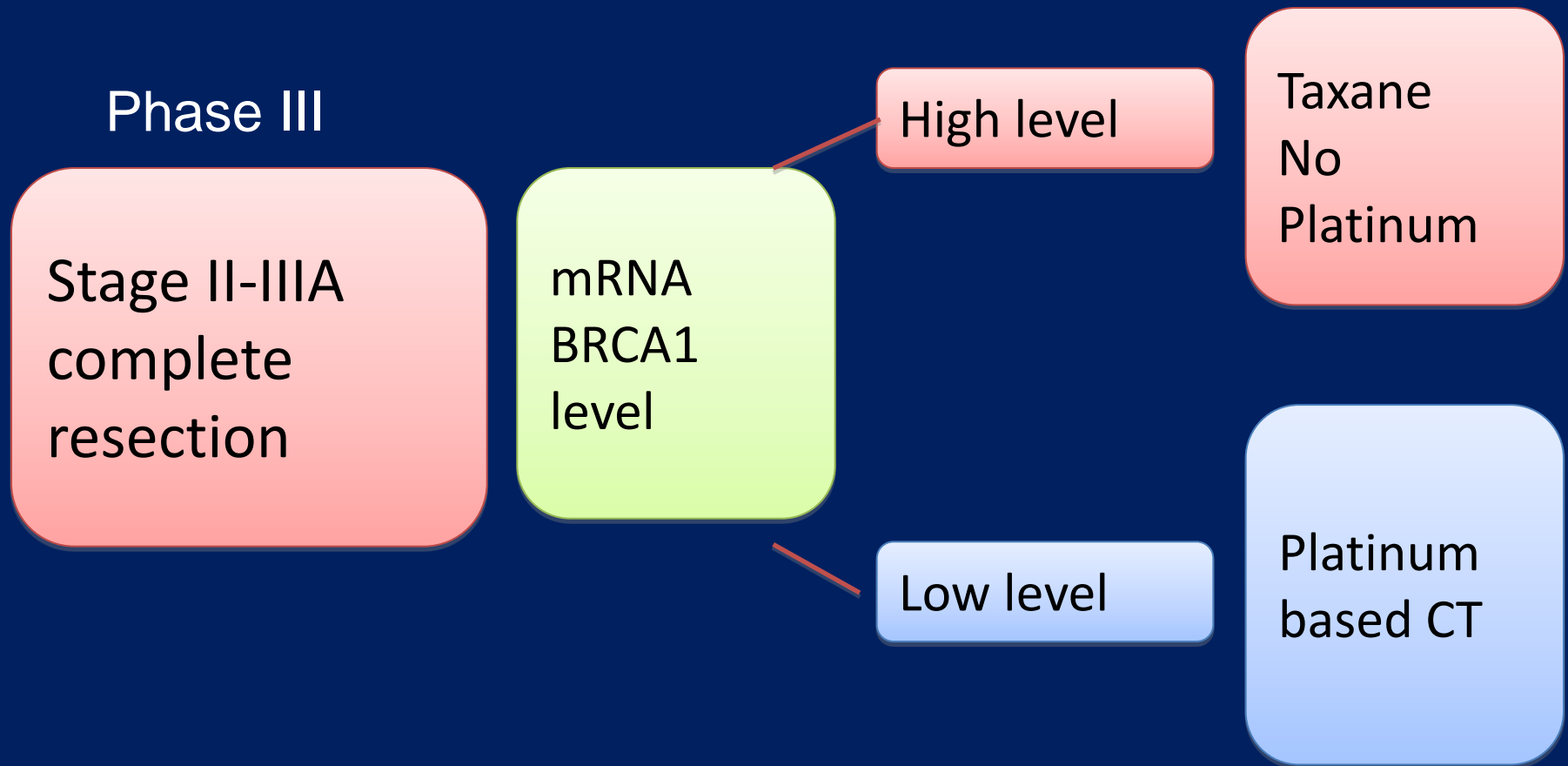
# NSCLC (SWOG 0720): tailored (ERCC1, RRM1) adjuvant Chemotherapy

## Phase II



# NSCLC (SCAT): tailored (BRCA1) adjuvant chemotherapy

Spanish customized adjuvant treatment according BRCA1



# CONCLUSIONS

- **Cisplatin-based adjuvant CT improves overall and disease-free survivals of patients with NSCLC**
- **Cisplatin-based chemotherapy is certainly effective for stage II & III**
- **No variation of chemotherapy effect with other factors**