

Case # 1

Early-Stage NSCLC: The Role of Adjuvant Systemic Therapy

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Case # 1: 68-year-old male smoker with adenocarcinoma of the right upper lobe

- ❑ CT Scan: 2.6 cm right upper lobe mass – no obvious hilar or mediastinal adenopathy. Upper abdomen normal.
- ❑ Bronchoscopy/mediastinoscopy: Submucosal tumour RUL bronchus. Mediastinoscopy showed minimally enlarged right hilar nodes.
- ❑ Pathology: poorly differentiated adenocarcinoma from bronchial biopsy. Two hilar lymph nodes show metastatic adenocarcinoma.
- ❑ Staging: FDG-PET shows uptake in the right upper lobe mass and in the right hilum only. MRI of brain is normal.

Case # 1 (cont): 68-year-old male smoker with adenocarcinoma of the right upper lobe

- ❑ Pre-operative evaluation: PFTs satisfactory for surgery. All laboratory studies are normal. ECG unremarkable.
- ❑ Medical history: hypertension and type II diabetes (both medically controlled)
- ❑ Surgery: right upper lobectomy and lymph node dissection is performed. Margins of resection are clear and 3 hilar lymph nodes contained metastatic adenocarcinoma with no extra-capsular spread.
- ❑ Postoperative performance status =1

Case # 1: Which postoperative strategy would you recommend for this patient?

1. Close observation only
2. Adjuvant chemotherapy
3. Concurrent chemoradiotherapy
4. Sequential chemoradiotherapy
5. Clinical trial of vaccine therapy
6. Clinical trial of zoledronic acid

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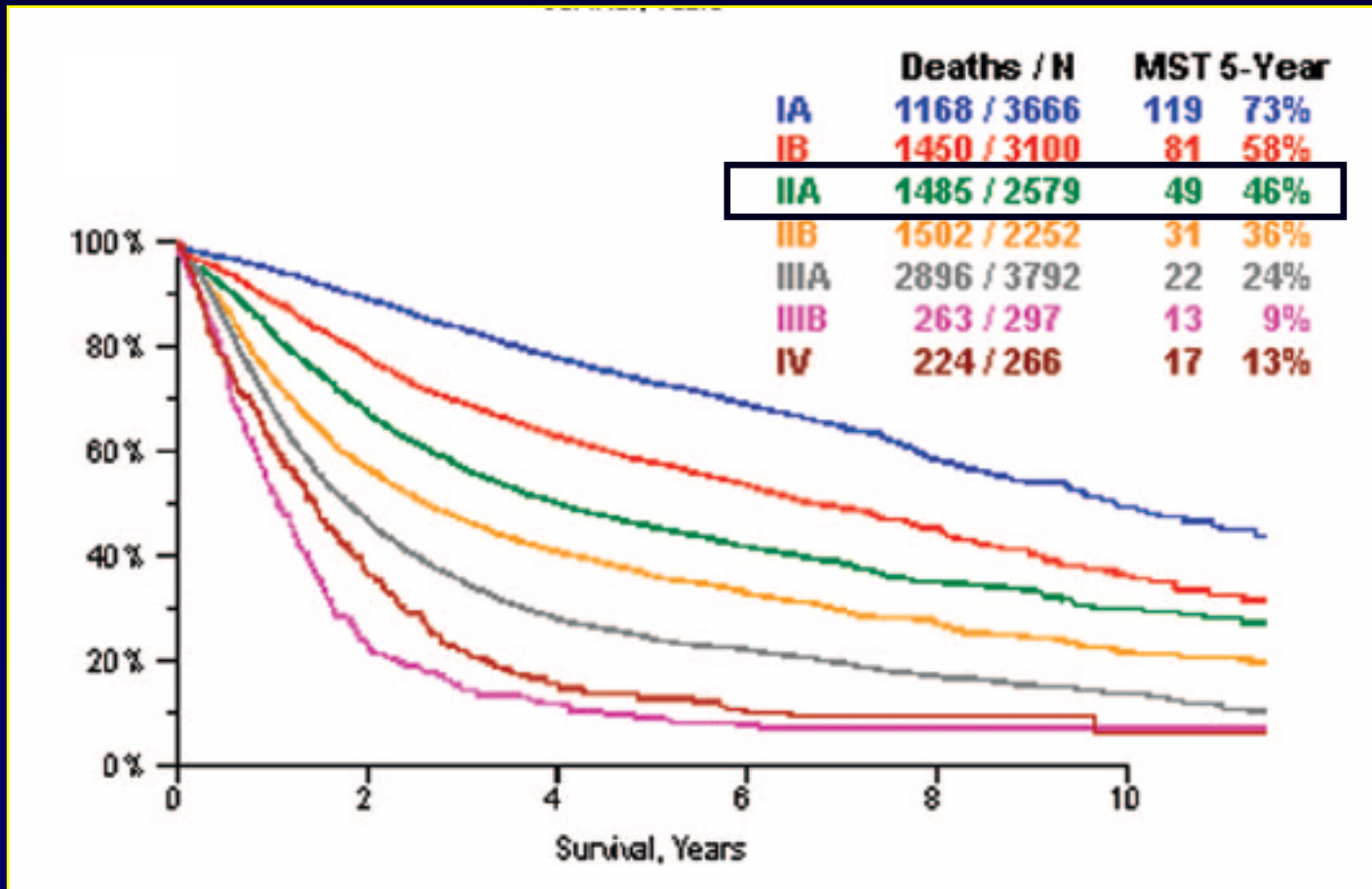
Case # 1

> Relevant data

- Tumour characteristics
 - o poorly differentiated adenocarcinoma
 - o pT1N1 (stage IIA) – complete resection
- Patient characteristics
 - o male
 - o 68 years
 - o co-morbidity: hypertension – diabetes
 - o PS: 1

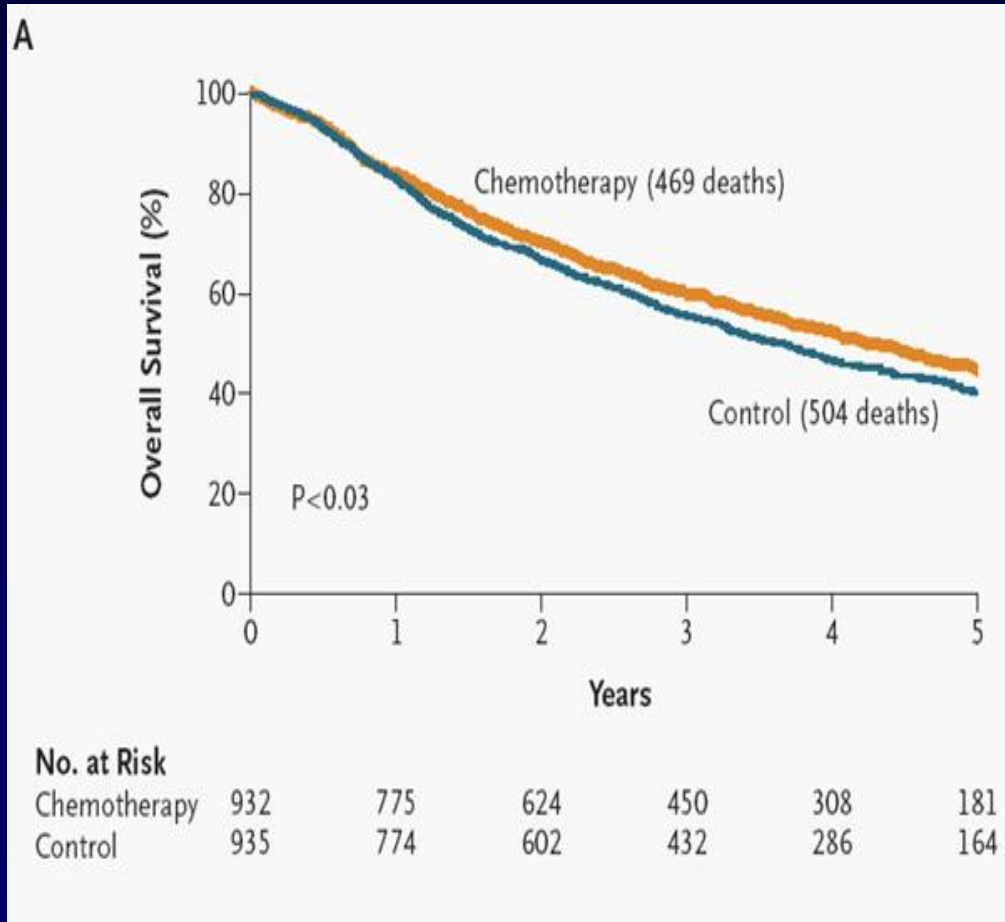
Case # 1

> pT1N1 (stage IIA) adenocarcinoma



Early stage NSCLC

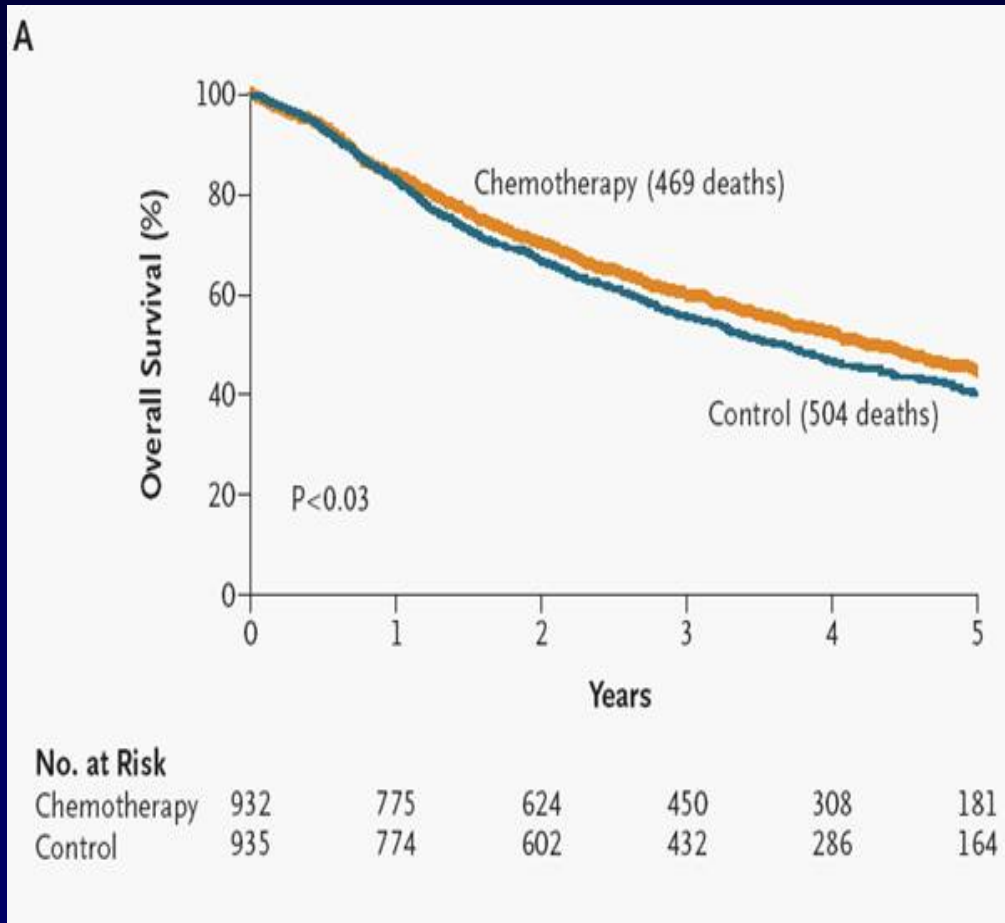
> Role of adjuvant chemotherapy: IALT



International Adjuvant Lung cancer Trial
14% reduction risk of death
4.1% better 5-year survival

Early stage NSCLC

> Role of adjuvant chemotherapy: IALT



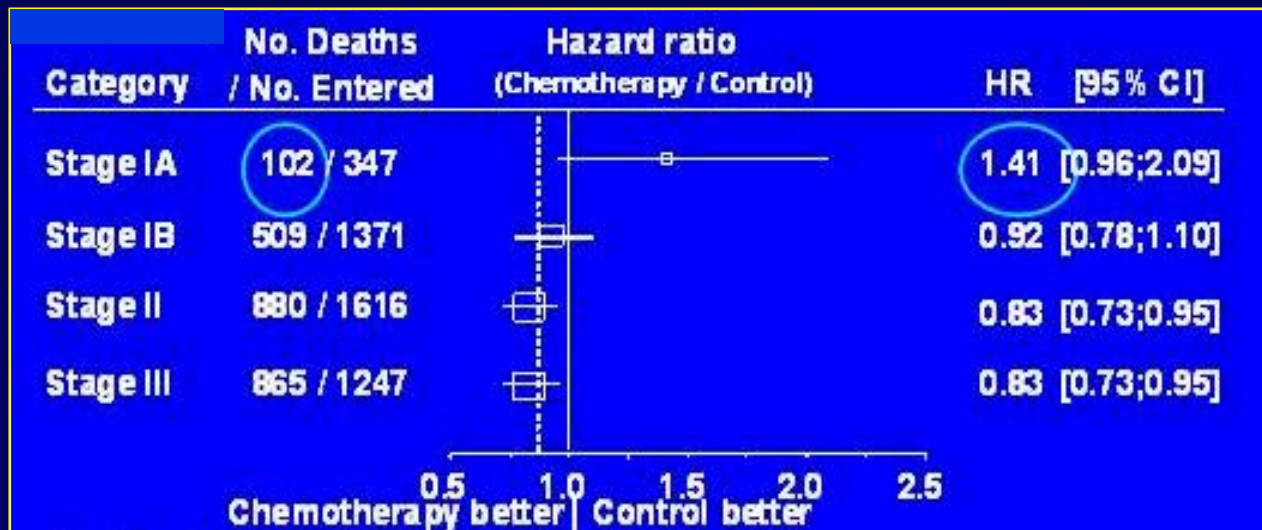
International Adjuvant Lung cancer Trial
14% reduction risk of death
4.1% better 5-year survival

Later chemotherapy trials
30% reduction risk of death
10% better 5-year survival

Case # 1

> pT1N1 (stage IIA) adenocarcinoma

- LACE meta-analysis [Lung Adjuvant Cisplatin Evaluation]
- Pooling of IP data from ALPI, IALT, NCI-C, BLT and ANITA
- Pooled HR 0.89 [0.82-0.96]; $P < 0.005$; 5YS 43 → 49%



Case # 1

> pT1N1 (stage IIA) adenocarcinoma

No direct evidence
yet

Case # 1

> pT1N1 (stage IIA) adenocarcinoma

No direct evidence
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Indirect evidence from
advanced NSCLC

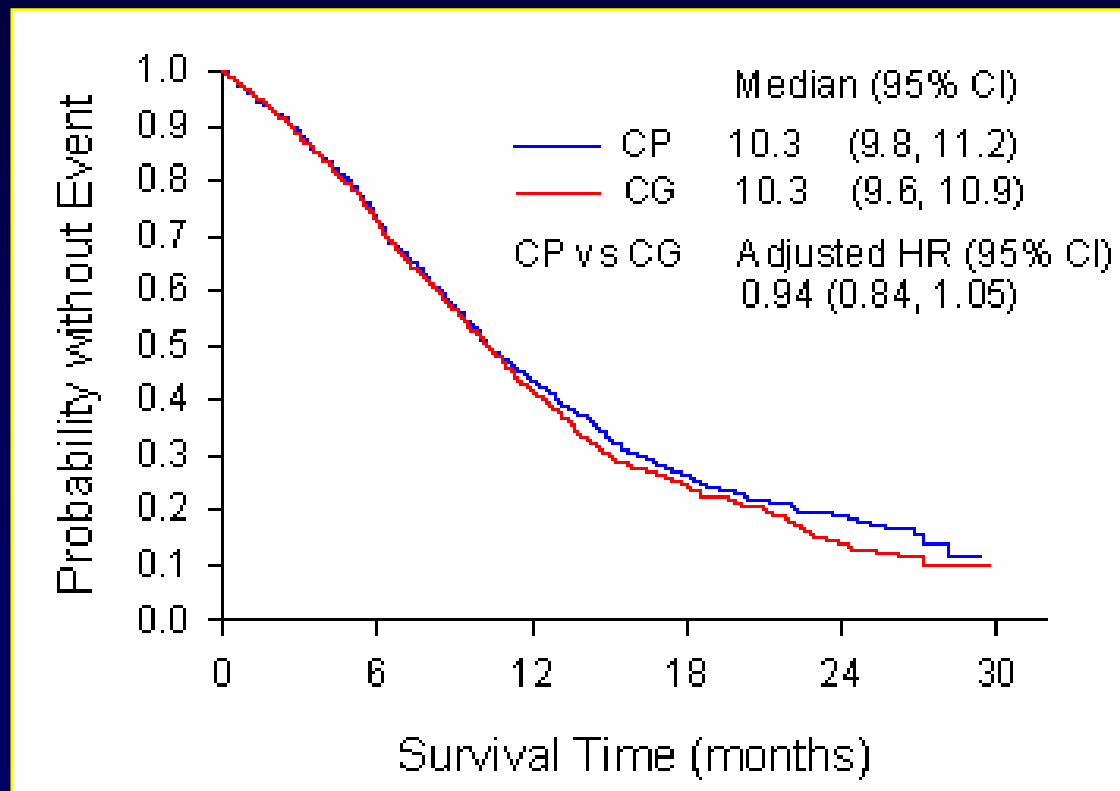
**A Randomized Phase III Trial of
Cisplatin and Pemetrexed versus
Cisplatin and Gemcitabine in Patients
with Locally Advanced or Metastatic
Non-Small Cell Lung Cancer**

Scagliotti GV, Parikh P, von Pawel J, Biesma B,
Vansteenkiste J, Manegold C, Simms L,
Sugarman K, Obasaju C & Blatter J

on behalf of JMDB investigators

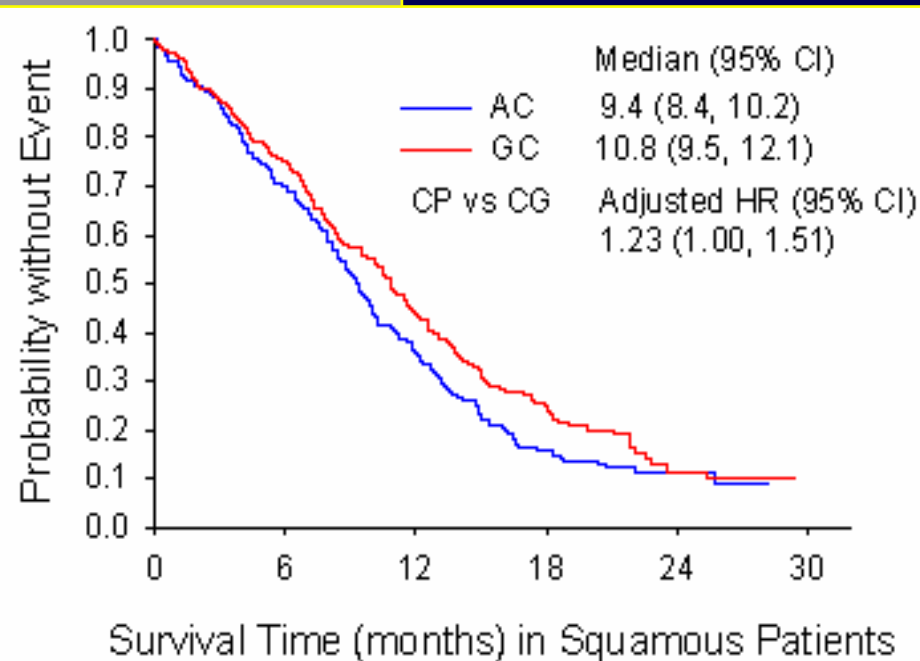
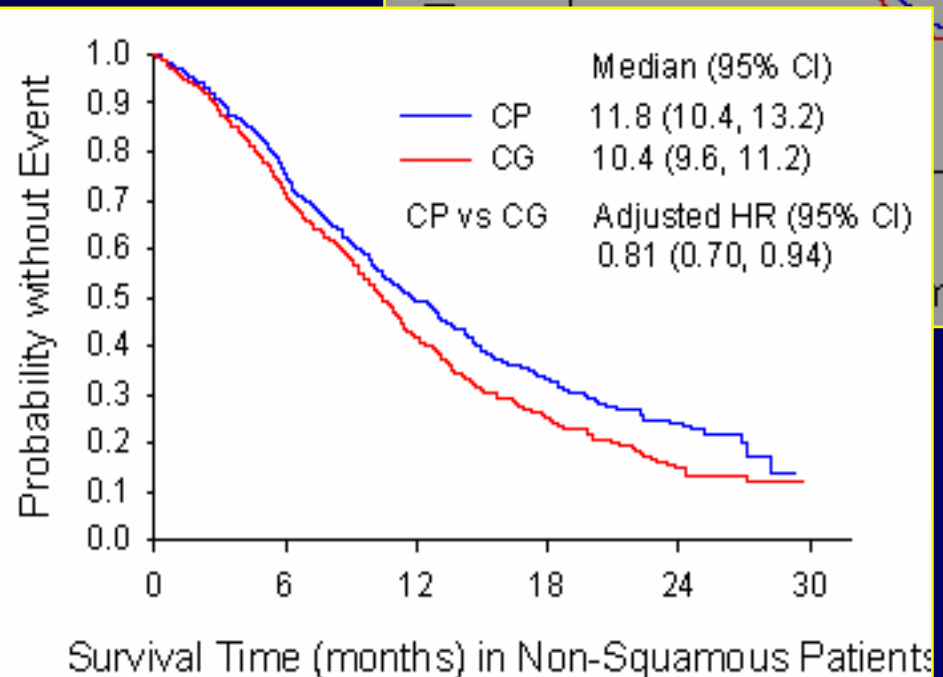
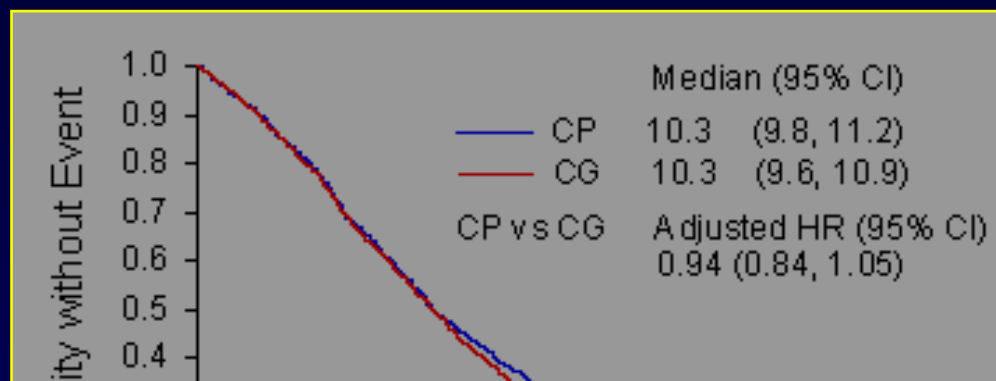
Advanced NSCLC

> Cis-Pem vs Cis-Gem: Histology based outcomes



Advanced NSCLC

> Cis-Pem vs Cis-Gem: Histology based outcomes



Case # 1

> pT1N1 (stage IIA) adenocarcinoma

Ongoing RCTs in Europe

- ❑ Adjuvant Cis-Pemetrexed vs. Carbo-Pemetrexed [PI C. Manegold, recruited]
- ❑ Adjuvant Cis-Pemetrexed vs. Cis-Vinoreline [PI Thomas–Vansteenkiste]
- ❑ Adj. Cis-Pemetrexed +/- LMW heparin in PET selected patients [NVALT]
- ❑ PGx-driven vs. standard adjuvant chemotherapy [PI Scagliotti]
- ❑ Neo-adjuvant vs. adjuvant Cis-Pemetrexed [EORTC, closed low accrual]

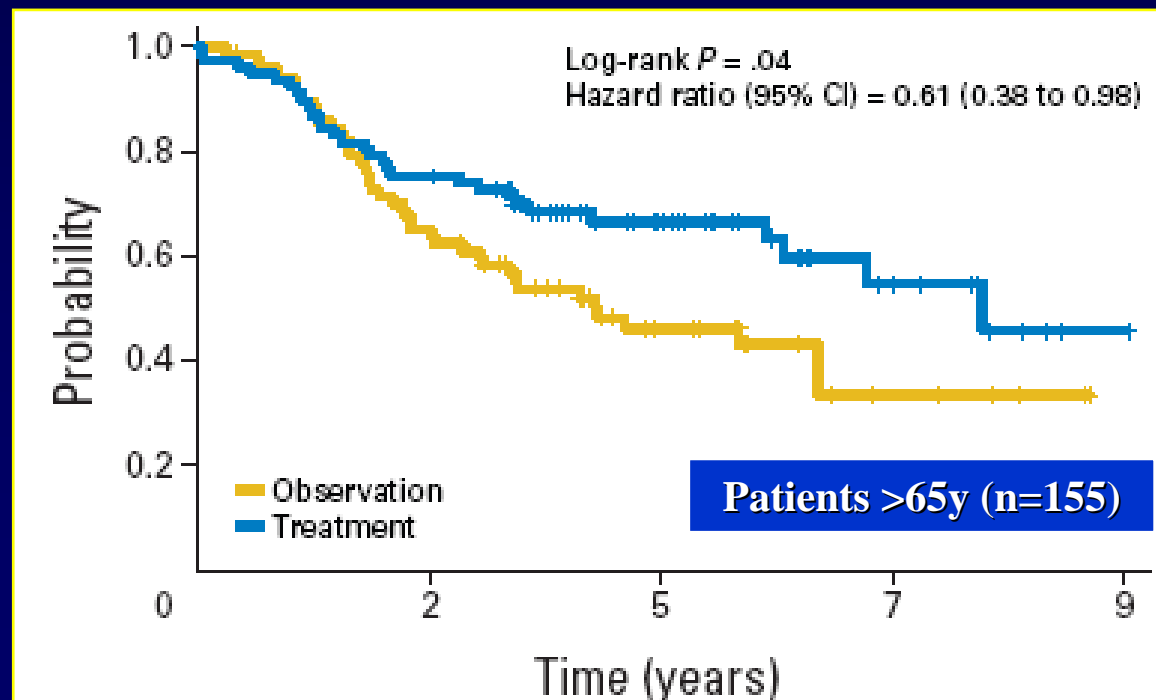
Non-randomised trials in Europe

- ❑ Neo-adjuvant Cis-Pemetrexed with PGx [Poland]
- ❑ Neo-adjuvant Cis-Pemetrexed with PGx [PI Rosell]

Case # 1

> male 68 years / hypertension-diabetes /
PS=1

- Retrospective analysis of BR.10: <65y (n=327) vs. >65y (n=155)
 - o elderly have more dose reduction/omission but similar benefit
- Therapy should not be withheld because of age 65-75



Case # 1

> male 68 years / hypertension-diabetes /
PS=1

□ LACE meta-analysis

- o adjuvant chemotherapy = cisplatin-based

□ Carboplatin can be an alternative in special situations

- o cardiovascular disease impeding hydration

- o diabetic neuropathy

- o diabetic nephropathy

Case # 1: Which postoperative strategy would you recommend for this patient?

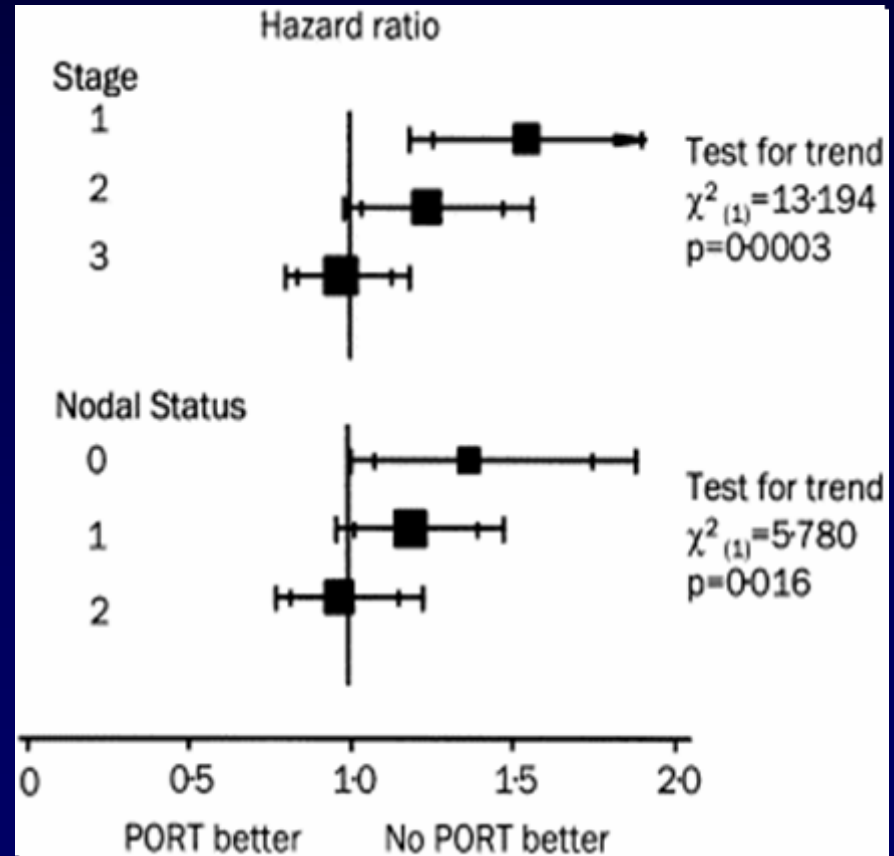
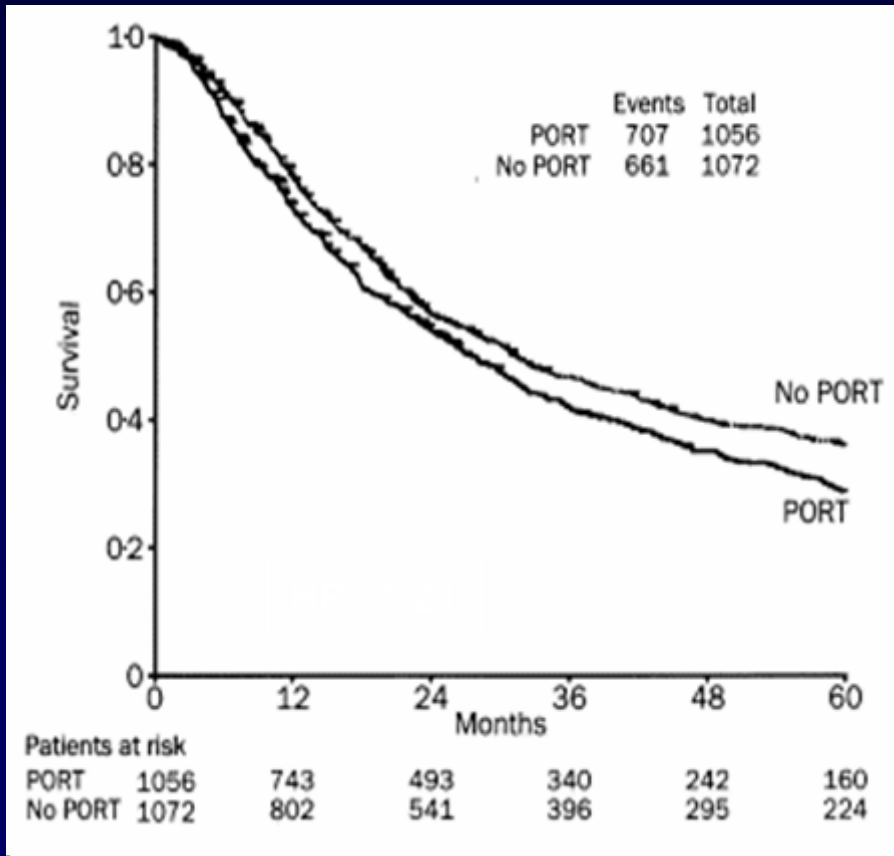
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Early Stage NSCLC

> Recurrence after “curative resection”

First Author (Year)	Locoregional	Brain	Systemic
Mountain (1980)			
-Squamous	24%	-	76%
-Non-squamous	17%	-	83%
Feld (1984)			
-Squamous	39%	20%	41%
-Non-squamous	25%	25%	50%
Holmes (1986)	17%	17%	66%
Lad (1988)			
-Squamous	24%	19%	57%
-Non-squamous	16%	26%	58%
Ohta (1993)	20%		80%

Early Stage NSCLC > Adjuvant radiotherapy

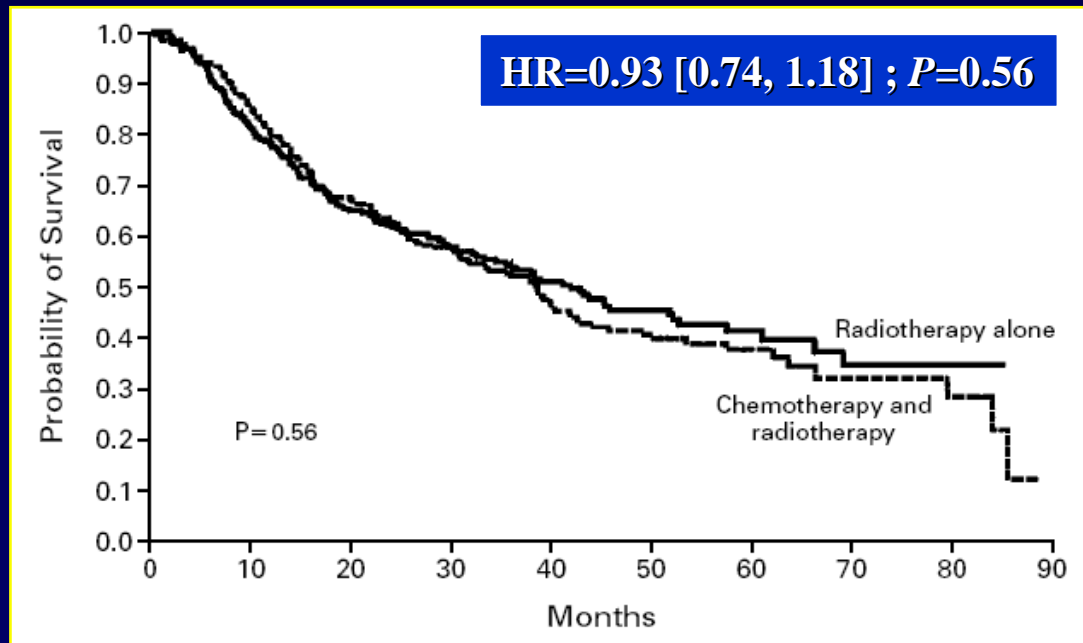


PORT Meta-analysis', *Lancet* 352:257, 1998
Burdet et al, *Lung Cancer* 47:81-83,2005

Early Stage NSCLC

> Adjuvant chemoradiotherapy (ECOG 3590)

- Completely resected stage II or IIIA NSCLC
 - o chemo plus thoracic RT vs. thoracic RT alone (n=488)



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Early Stage NSCLC > Adjuvant chemotherapy

LACE meta-analysis

5-year survival
43% -> 49%



Room for further
improvement

Early Stage NSCLC > Adjuvant chemotherapy

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Room for further
improvement

Cisplatin-based
chemotherapy

<u>Trial</u>	<u>N cycles</u>	<u>Compliance</u>
IALT	3-4 cycles	74%
ALPI	3 cycles	69%
NCI-C	4 cycles	50%
BLT	3 cycles	64%
BR 10	4 cycles	50%

Room for better
tolerated therapy

Early Stage NSCLC

> Adjuvant chemotherapy

LACE meta-analysis

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Room for further
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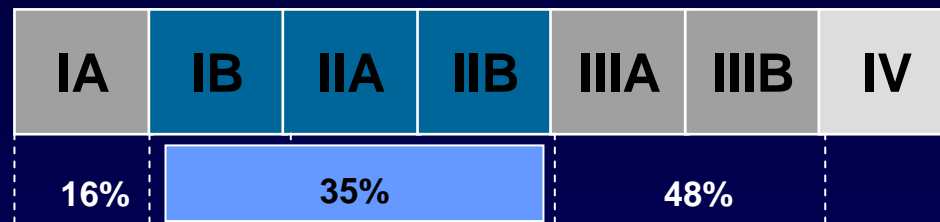
Room for better tolerated
therapy

Vaccine therapy
Angiogenesis / EGFR inhibition
Zoledronic acid

Early Stage NSCLC

> Adjuvant MAGE-A3 vaccine therapy

□ MAGE-A3 antigen: expressed in NSCLC



- No expression in normal cells, genuinely tumour-specific
- Post-operative MAGE-A3 immunotherapy might be a tumour-specific, well tolerated, effective adjuvant treatment

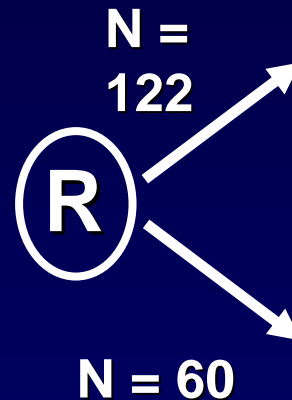


Early Stage NSCLC

> Adjuvant MAGE-A3 vaccine therapy

- p-stage IB or II NSCLC
 - MAGE-A3 (+) tumours
 - complete resection
 - PS 0-1
- Stratification
 - stage
 - histology
 - lymph node procedure

double-blind



MAGE-A3 immunotherapy

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

Placebo

- Same schedule

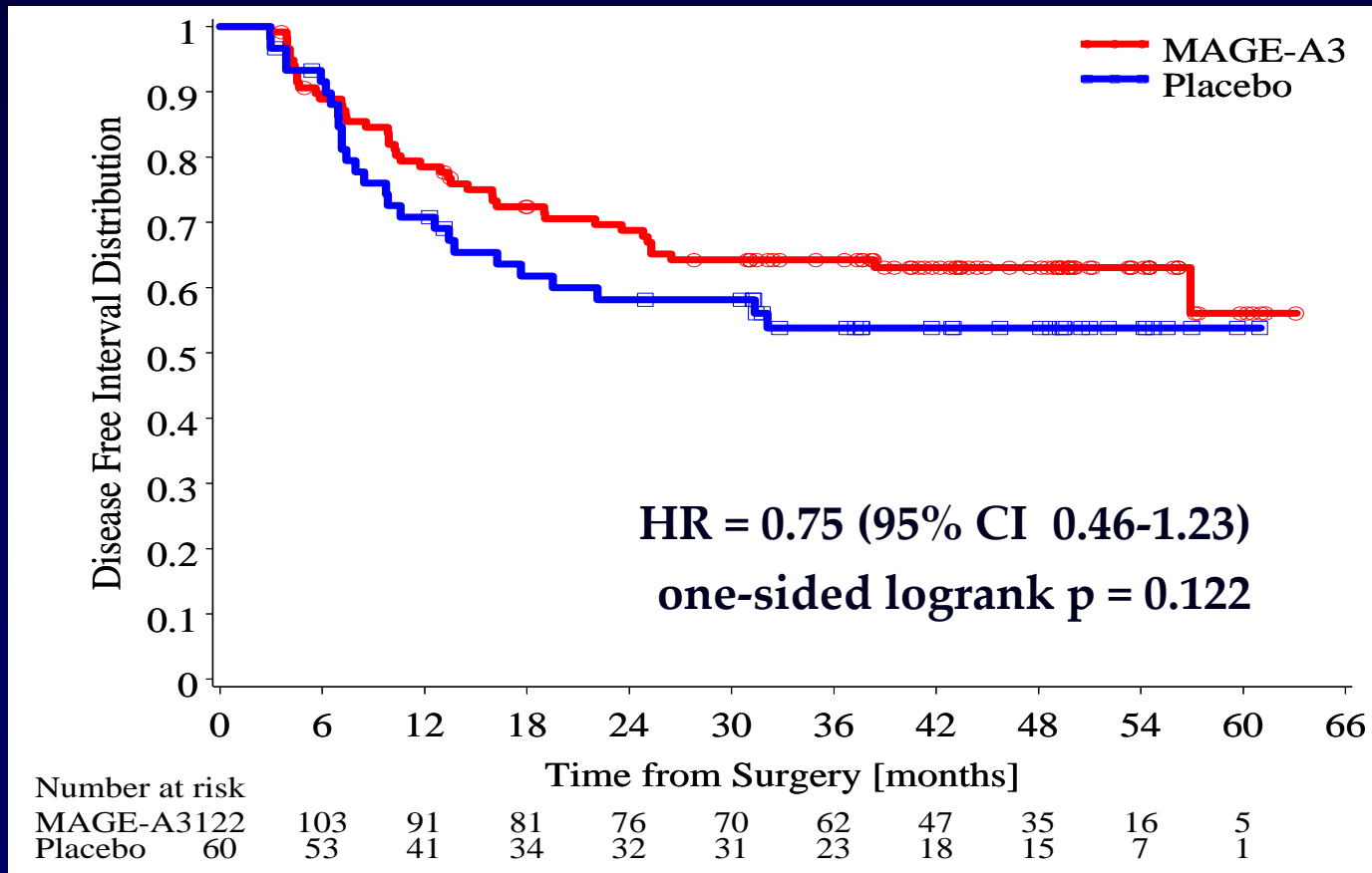
Early Stage NSCLC

> Adjuvant MAGE-A3: tolerability

- ❑ 182 patients (122 MAGE-A3, 60 placebo)
- ❑ 1214 MAGE-A3 doses administered
- ❑ MAGE-A3 immunotherapeutic overall well tolerated
 - Mild: grade 1 or 2
 - Local or systemic reactions
- ❑ Grade 3 or 4 events: 9.6% of the total MAGE-A3 doses administered (117/1214) in 48 patients
 - Only three grade 3 events, possibly related to MAGE-A3
 - Leading to withdrawal of 1 patient (COPD exacerbation)

Early Stage NSCLC

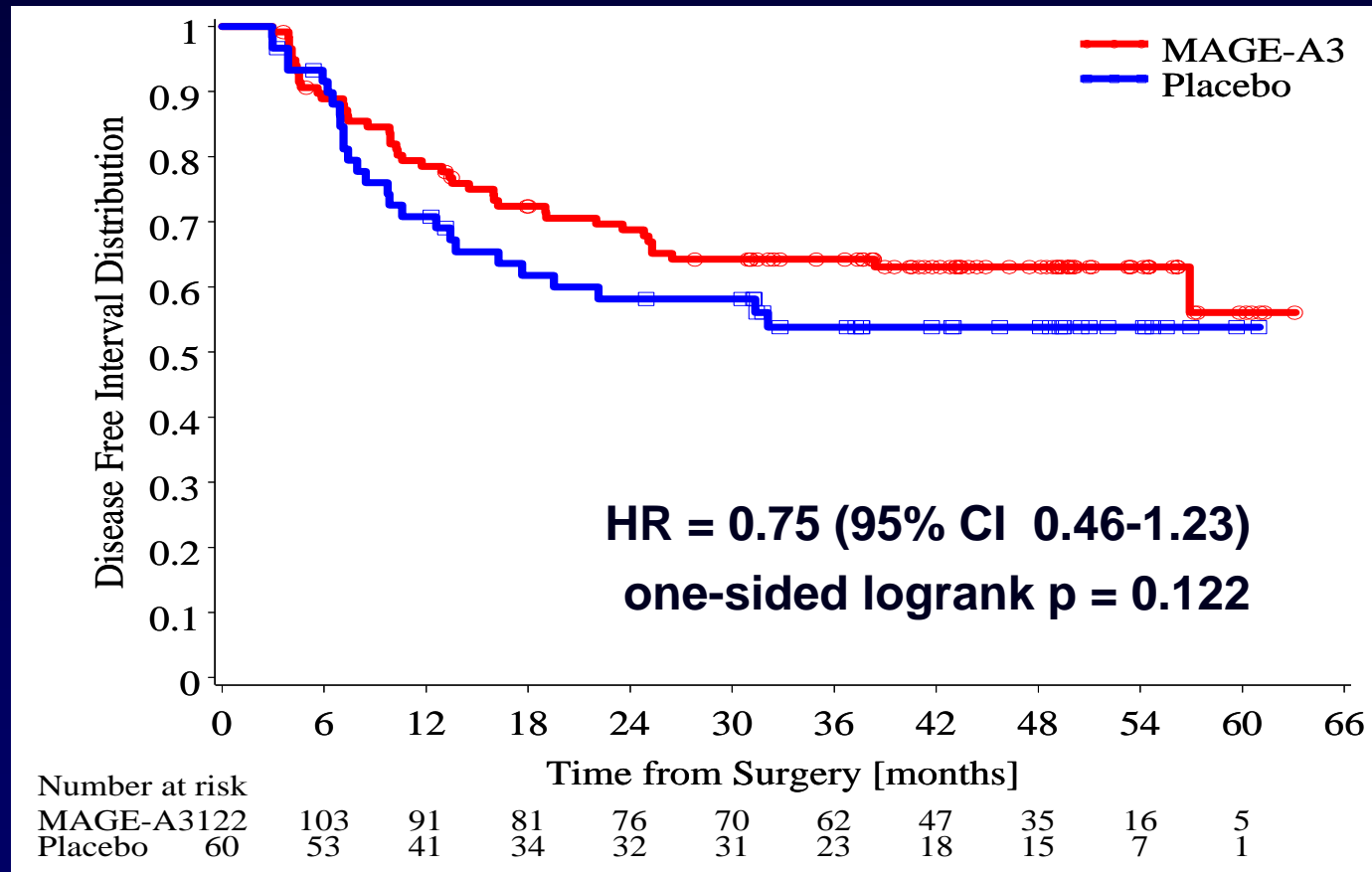
> Adjuvant MAGE-A3: Overall survival



Early Stage NSCLC

> Adjuvant MAGE-A3: Overall survival

Direct
evidence

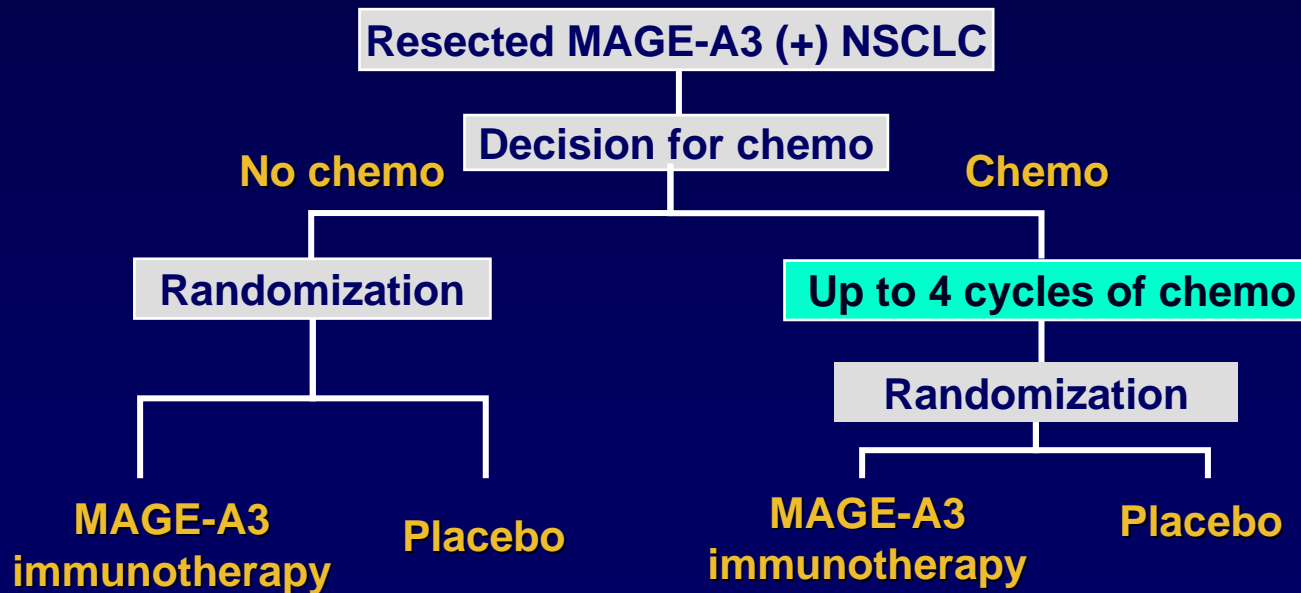


Early Stage NSCLC

> Adjuvant MAGE-A3: Phase III MAGRIT

MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy

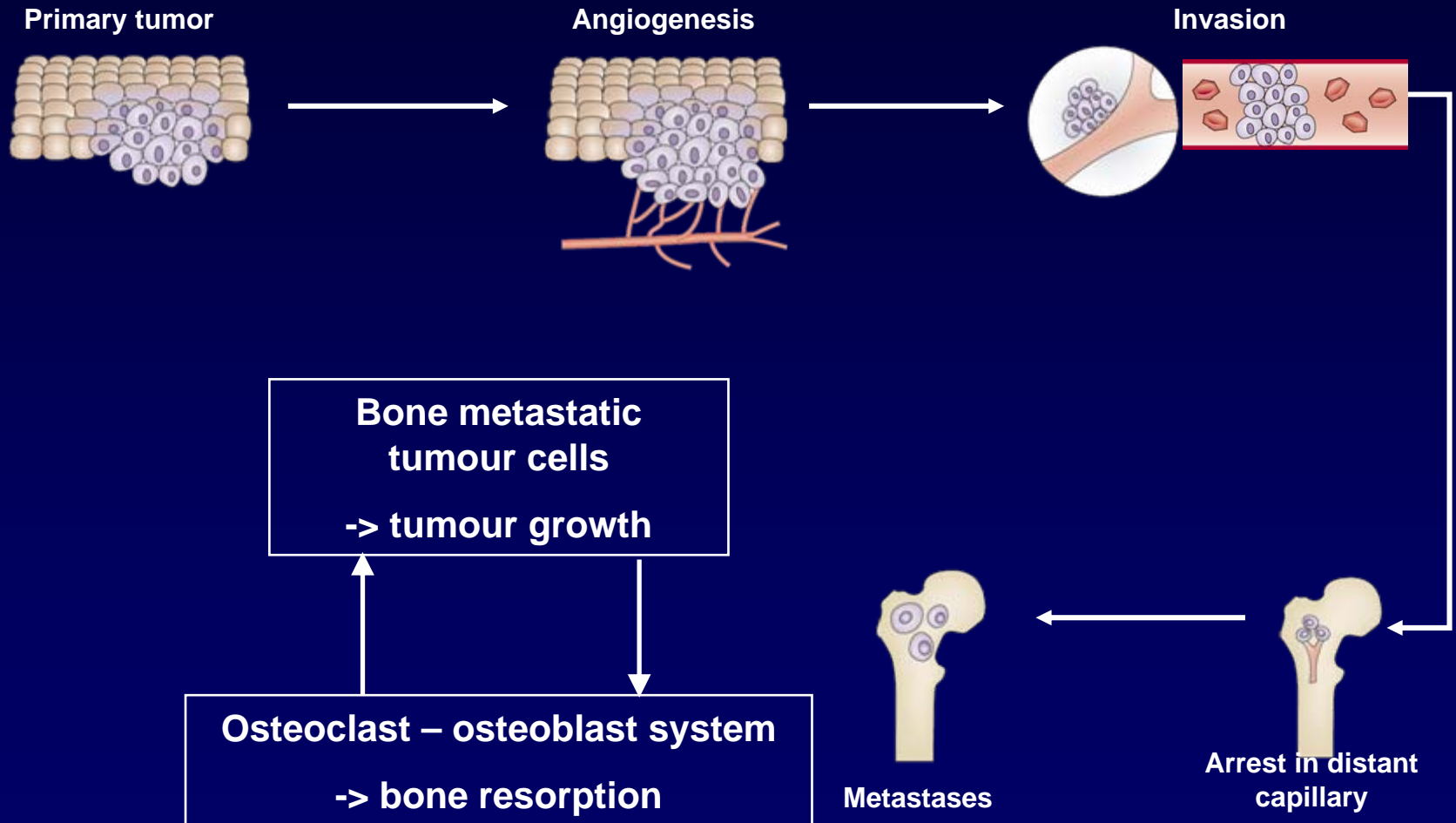
- worldwide multicenter, randomized, double-blind, placebo-controlled ph III trial
- n = 2270 patients
- primary endpoint: disease-free survival



Open for recruitment

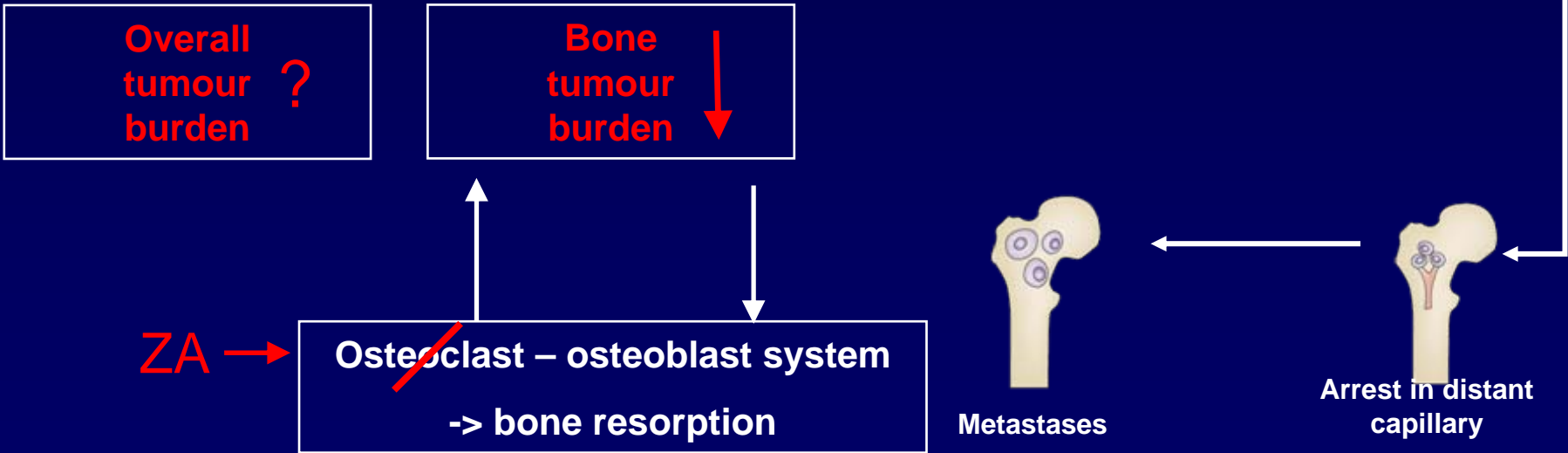
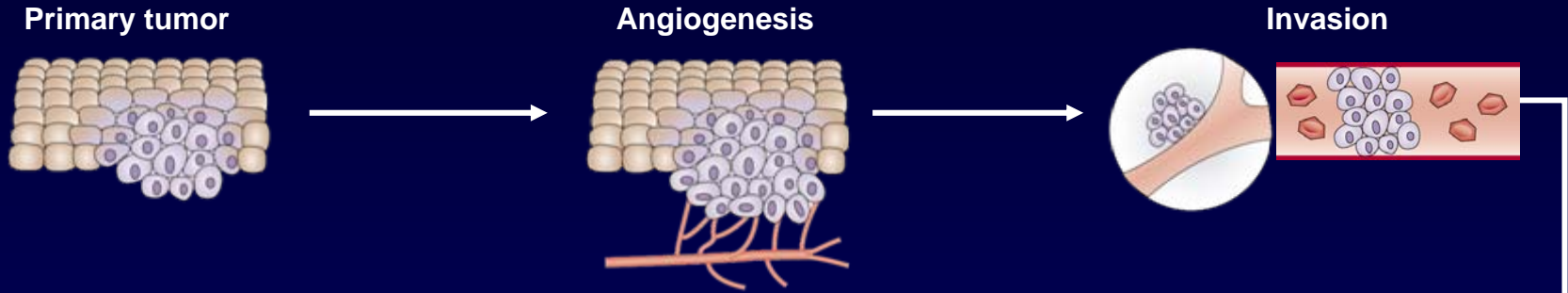
Early Stage NSCLC

> Zoledronic acid? Improvement of outcome?



Early Stage NSCLC

> Zoledronic acid? Improvement of outcome?



Abstract LBA4: M. Gnant, B. Mlineritsch, W. Schippinger, G. Luschin-Ebengreuth, S. Poestlberger, C. Menzel, R. Jakesz, E. Kubista, C. Marth, R. Greil, on behalf of the ABCSG

Adjuvant Ovarian Suppression Combined With Tamoxifen or Anastrozole, Alone or in Combination With Zoledronic Acid, in Premenopausal Women With Hormone-Responsive, Stage I and II Breast Cancer: First Efficacy Results From ABCSG-12

Michael Gnant

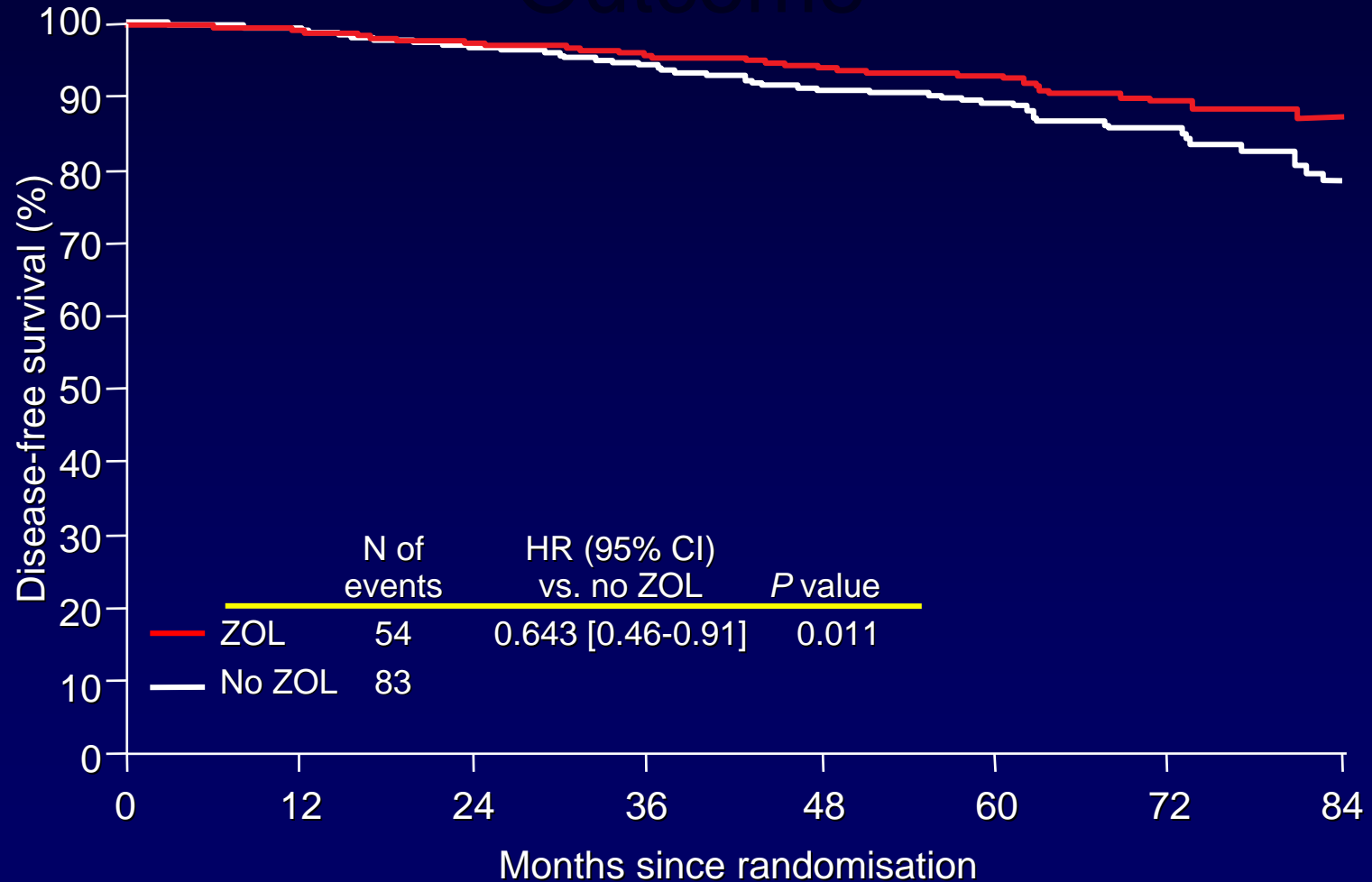
Professor of Surgery, Medical University of Vienna
Austrian Breast & Colorectal Cancer Study Group



ASCO 2008 Annual Meeting
Chicago, Illinois; June 1, 2008

Early Breast Cancer

> Zoledronic acid - Improvement of Outcome



Early Stage NSCLC > Zoledronic acid? Studies in (locally) advanced

Tumour setting	Study / Region	Design / Objectives	Timing	Status
NSCLC Stage IIIA/B <ul style="list-style-type: none"> • non-progressive after primary combination treatment 	CZOL 446G2419 EU/Asia	Zoledronic acid 24 mo vs. follow-up only Time to bone metastases Rate of bone mets, TTP, risk of SREs, time to SRE, survival	Mar-05 Dec-09	Planned= 446 Enrolled= 273
NSCLC Stage IIIBwet, IV, or recurrent <ul style="list-style-type: none"> • no prior 1st line • no bone metastases 	CZOL 446GUS85 US	1st line + Zoledronic acid vs. 1st line only Time to bone metastases TTP, overall survival	Mar-09 Mar-11	Planned= 584 Enrolled= 0

Case # 1: Adenocarcinoma pT1N1 (stage IIA)
male – 68 years – hypertension/diabetes – PS 1

- ❑ Adjuvant cisplatin-based chemotherapy indicated
 - o carboplatin = compromise in some situations
- ❑ No place for adjuvant radiotherapy
- ❑ Room for improvement

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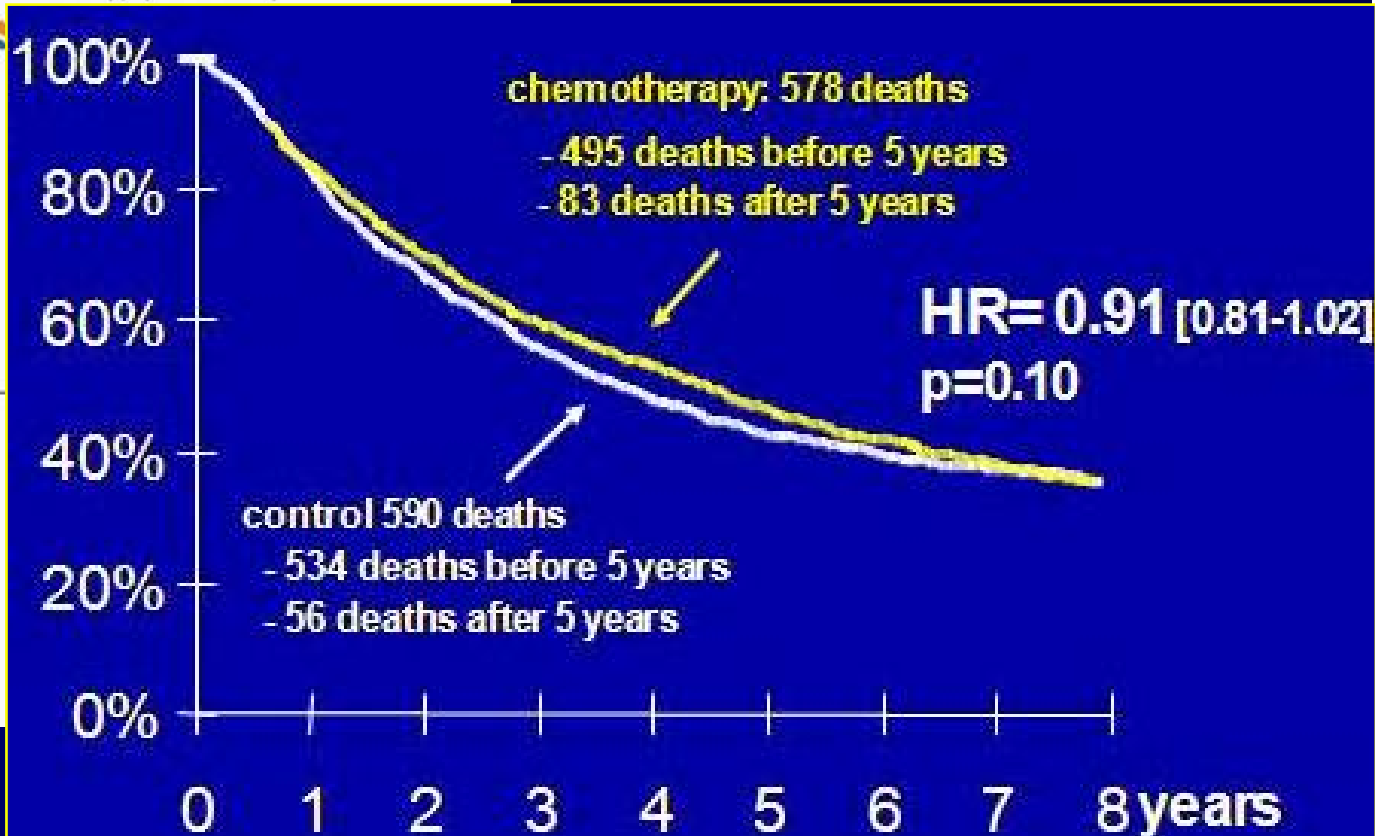
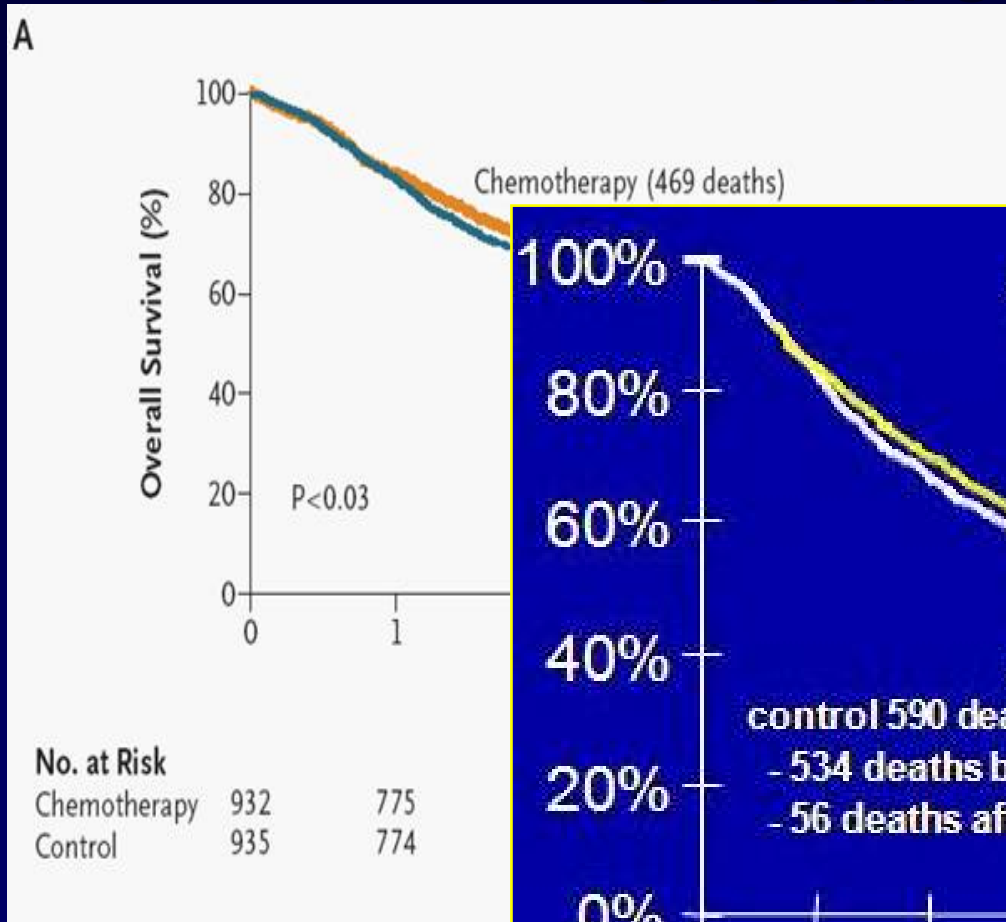
- ❑ Adjuvant cisplatin-based chemotherapy indicated
 - carboplatin = compromise in some situations
 - **MAGE-A3 potential alternative if non chemo eligible?**
- ❑ No place for adjuvant radiotherapy
- ❑ Room for improvement
 - **cisplatin-pemetrexed if non-squamous?**
 - **add MAGE-A3 immunotherapeutic?**
 - **add molecular agents?**

Case # 1: Do IALT results about late adjuvant-chemo-related mortality influence your view?

1. No
2. Yes
3. I do not know these data

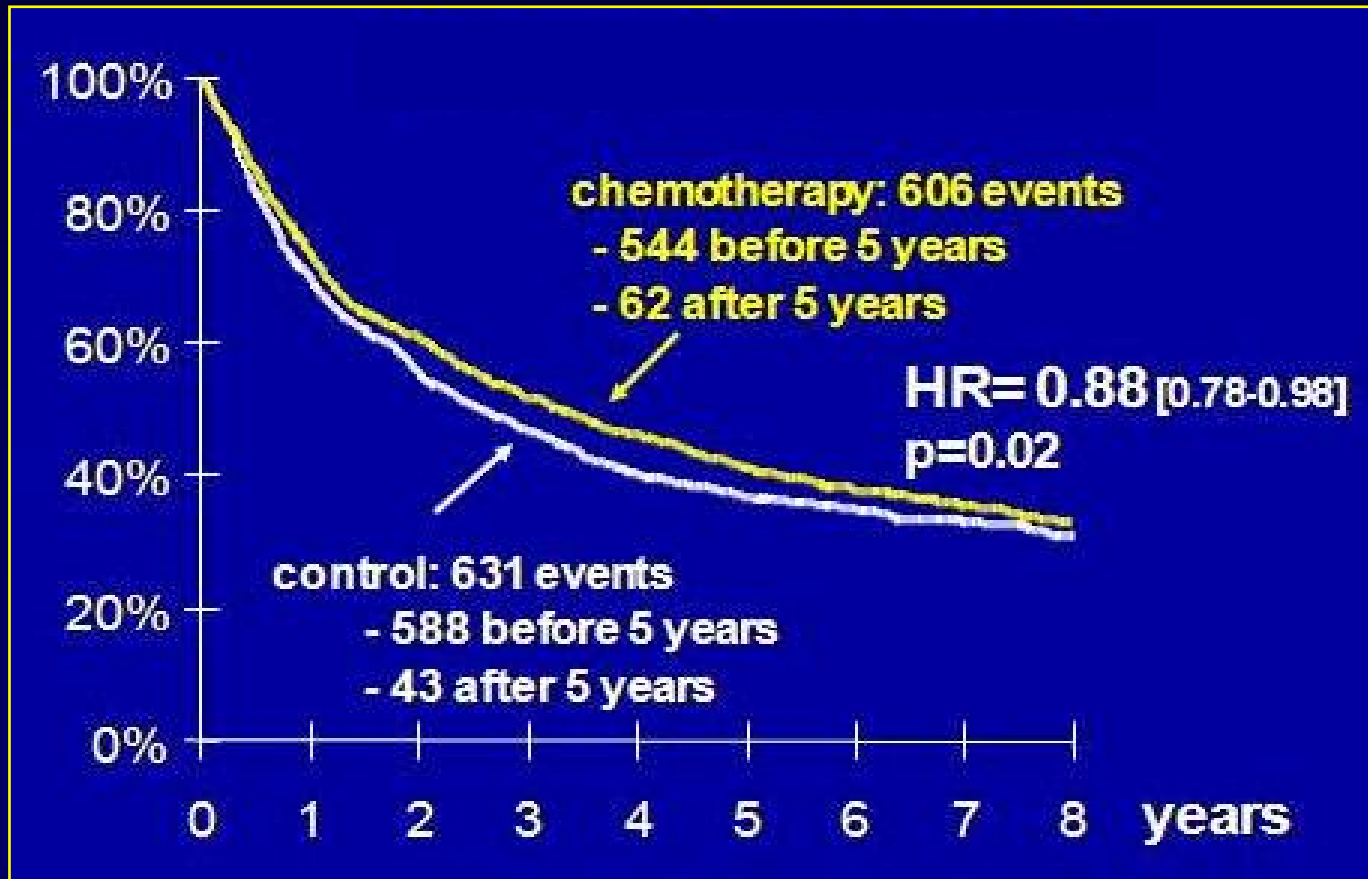
Early Stage NSCLC

> Long-term follow-up IALT: Overall survival



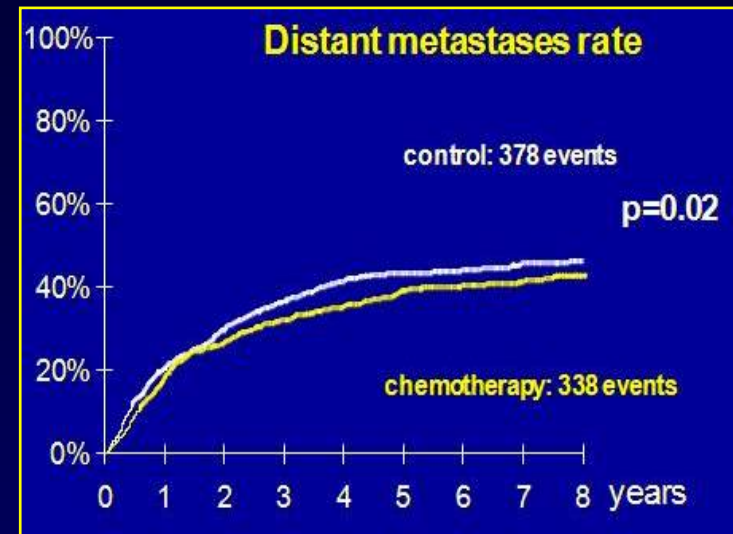
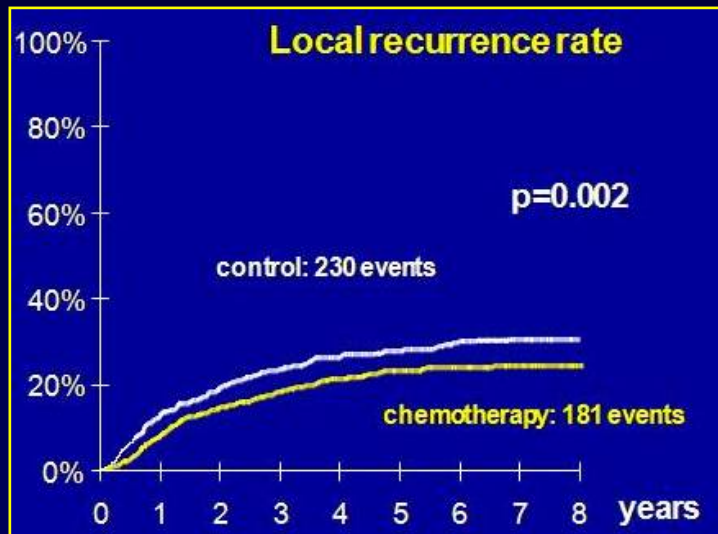
Early Stage NSCLC

> Long-term follow-up IALT: DFS



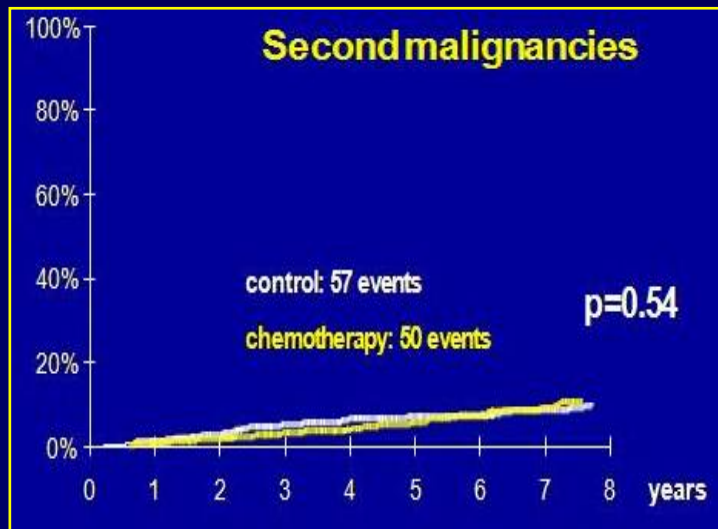
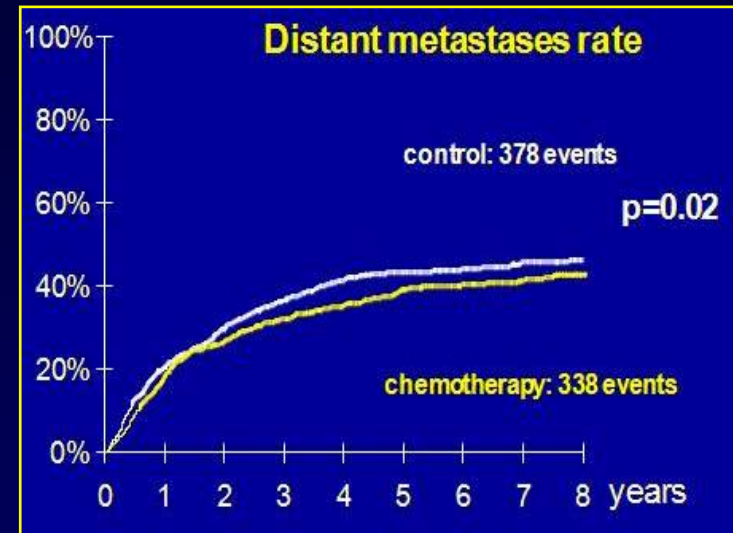
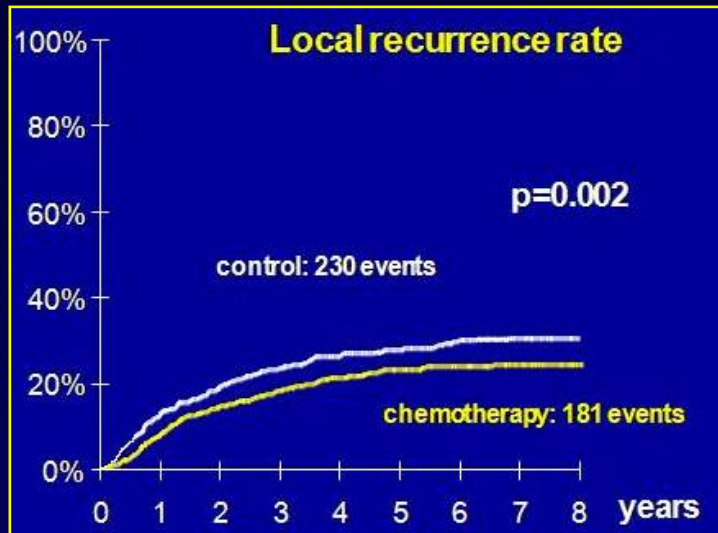
Early Stage NSCLC

> Long-term follow-up IALT



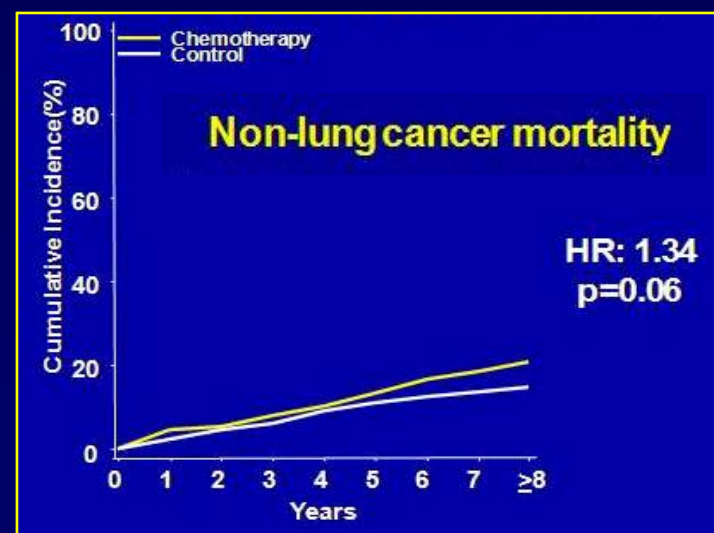
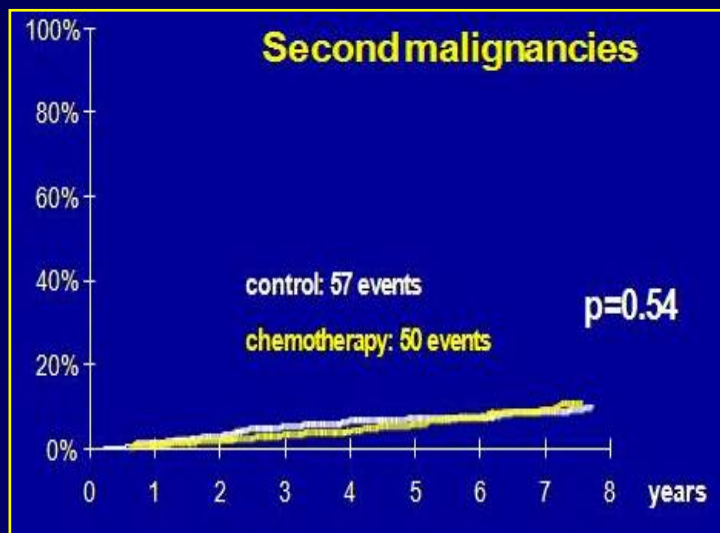
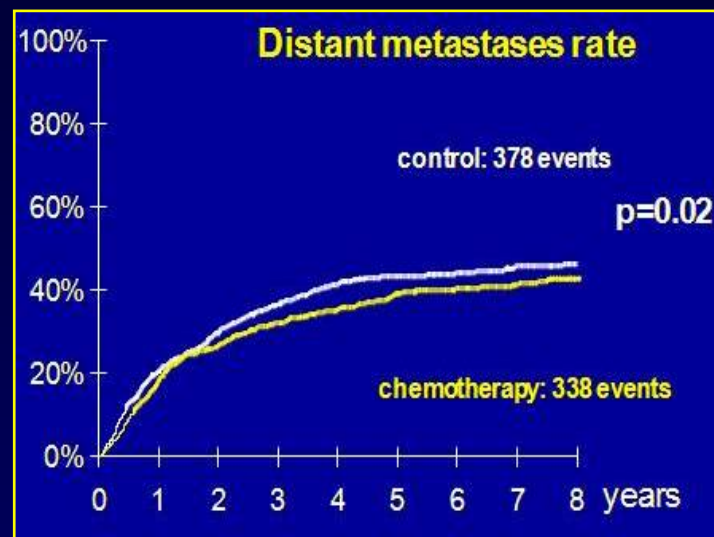
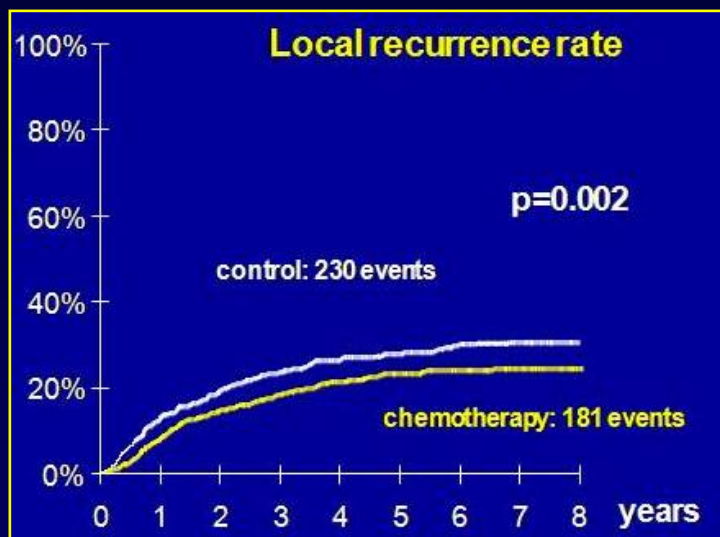
Early Stage NSCLC

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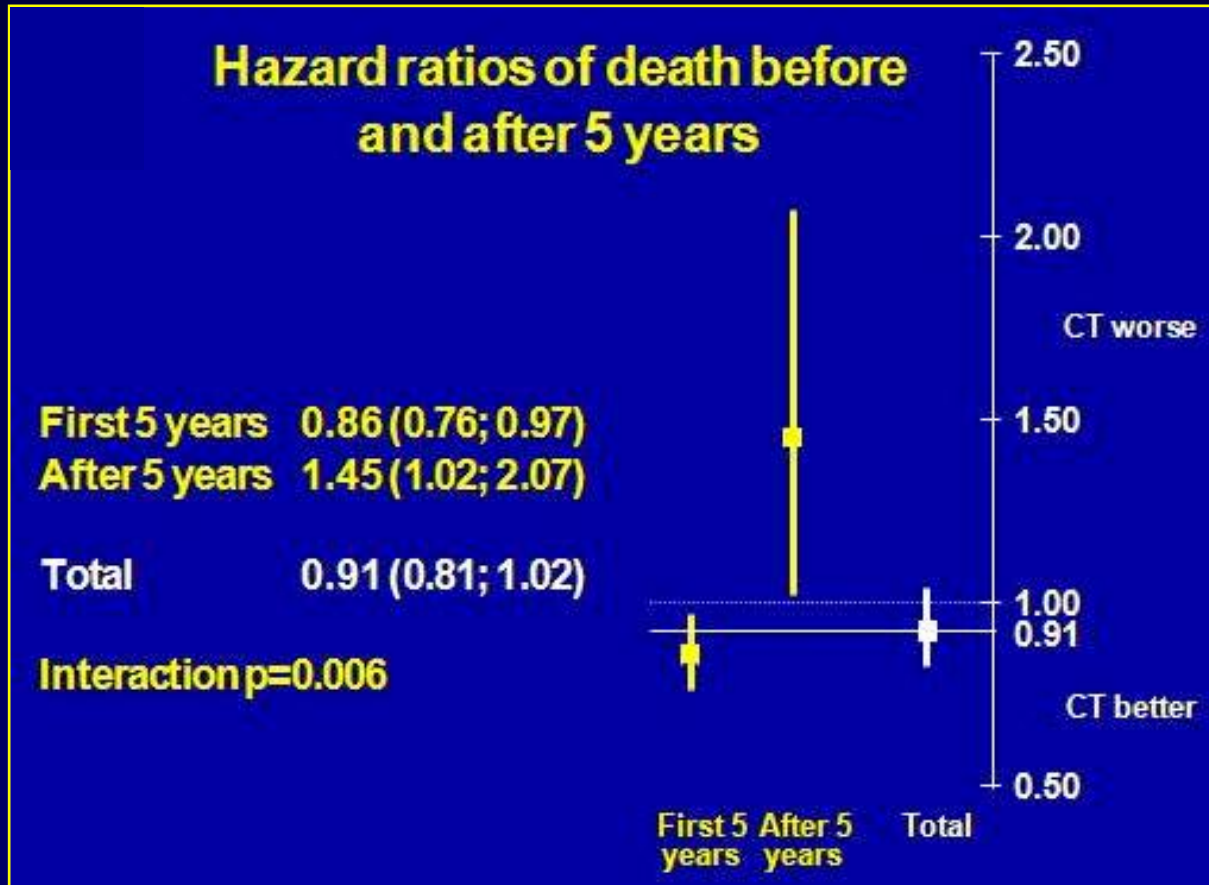


Early Stage NSCLC

> Long-term follow-up IALT



Early Stage NSCLC > Long-term follow-up IALT



Case # 1: Do IALT results about late adjuvant chemo-related mortality influence your view?

1. No

- o adjuvant chemotherapy improves the 5-year post-surgery survival
- o both locoregional and distant recurrence remain lower after 5 years
- o reasons for late non-cancer mortality are unclear
 - o effect not seen in other study (e.g. ANITA)
 - o deserves further study. Drug-related? ...?



Thank you for your
kind attention

Leuven, Gothic Town Hall (1448)