

Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part I

Wolfgang Jungraithmayr, MD, PhD
University Hospital Zurich
Zurich, Switzerland

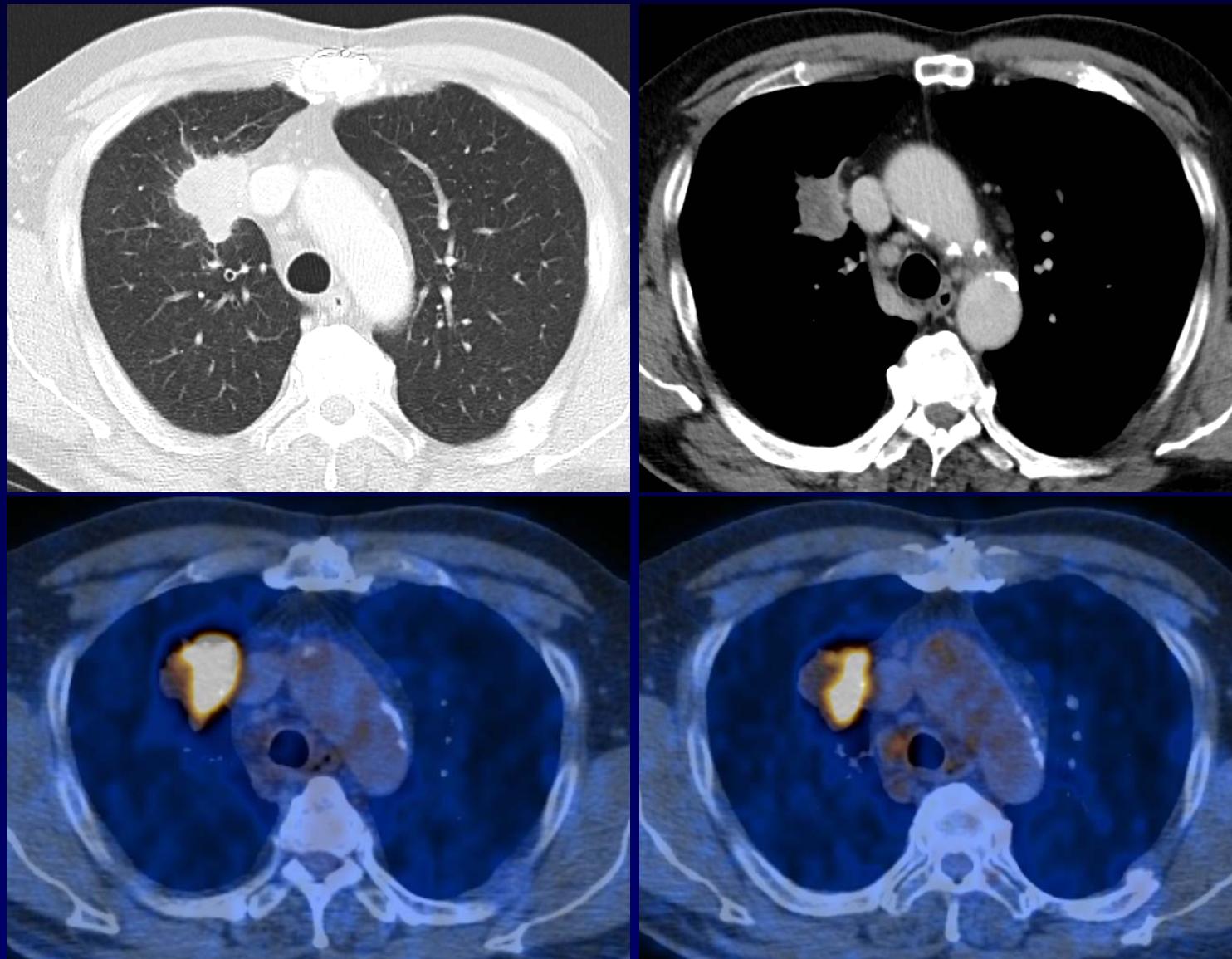
www.prIMEoncology.org



Our Patient

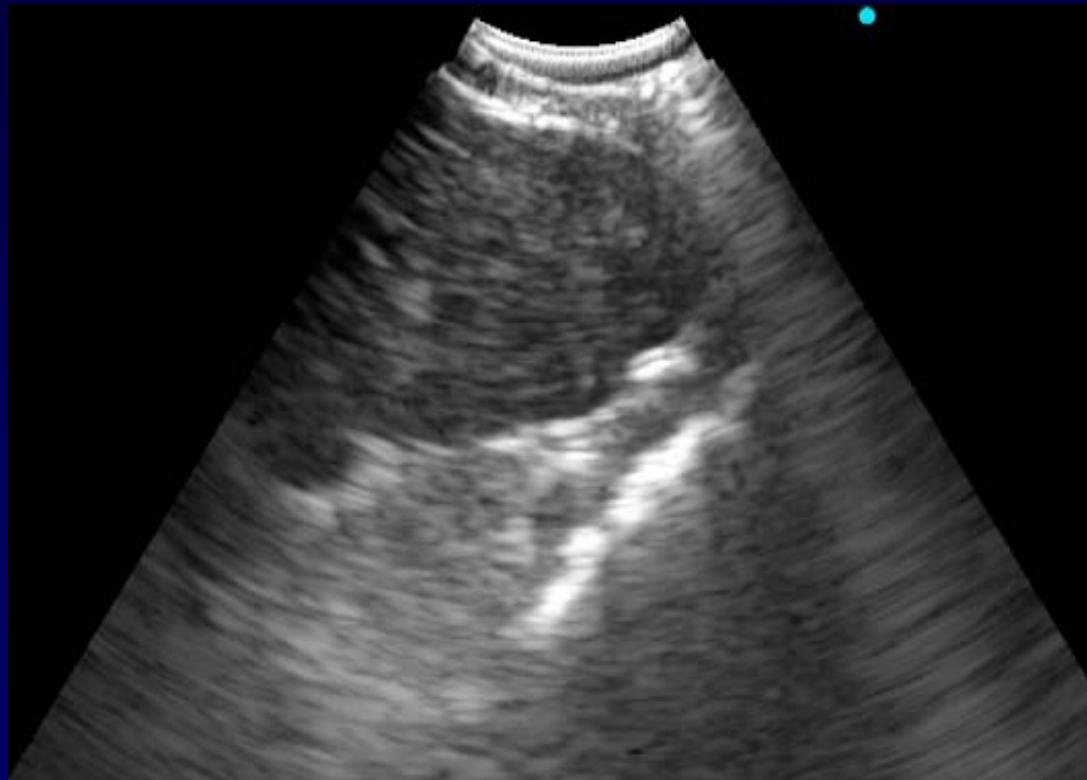


Our Patient



Our Patient

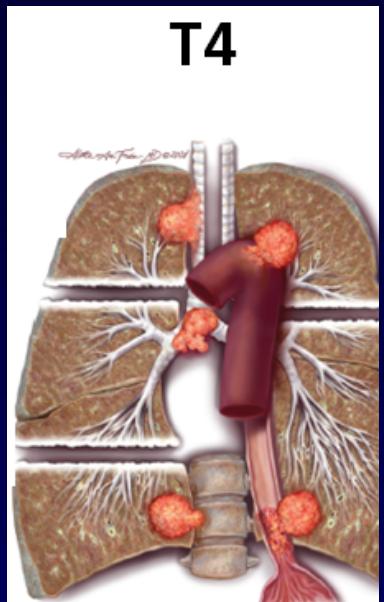
Clinical Stage: **T2aN2M0 (IIIA-N2)**



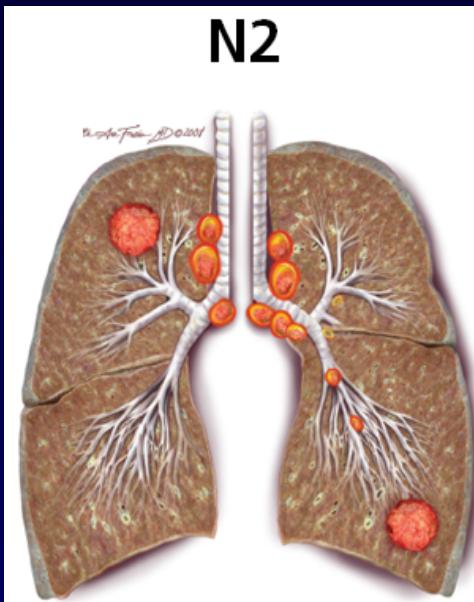
MULTIDISCIPLINARY THORACIC TUMOR BOARD

Stage III NSCLC

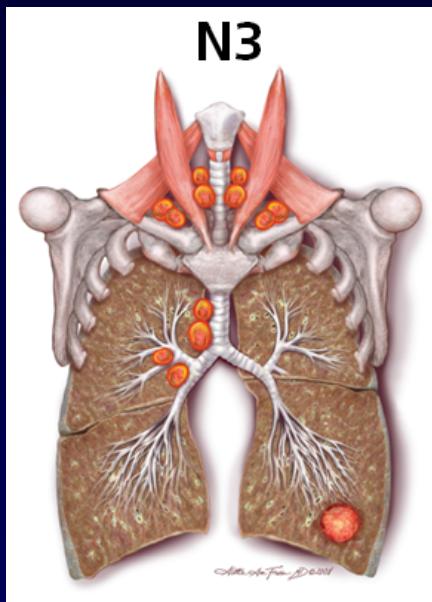
T4



N2



N3



T₄, N₀₋₁

T₁₋₃, N₂

any T, N₃

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 >7	IIb	IIIa	IIIa	IIIb
	T3 Inv	IIb	IIIa	IIIa	IIIb
	T3 Satell	IIb	IIIa	IIIa	IIIb
T4	T4 Inv	IIIa	IIIa	IIIb	IIIb
	T4 ipsi Nod	IIIa	IIIa	IIIb	IIIb
M1	M1a Contra Nod	IV	IV	IV	IV
	M1a Pl Disem	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Stage groups according to TNM descriptor and subgroups

Question 1: What treatment approach would you suggest for this patient with clinical stage IIIA-N2 (single node 1.7-cm) NSCLC?

- 1. Surgical resection with mediastinal LN dissection → chemotherapy +/- radiotherapy**
- 2. Neoadjuvant systemic therapy → surgery if no progression**
- 3. Induction chemoradiotherapy (CRT) → surgery if no progression**
- 4. Definitive concurrent CRT**

Which Patients Are Candidates for Surgery?

- Is a complete resection possible?
- Does the patient tolerate pulmonary resection?
- What is the mortality/morbidity?

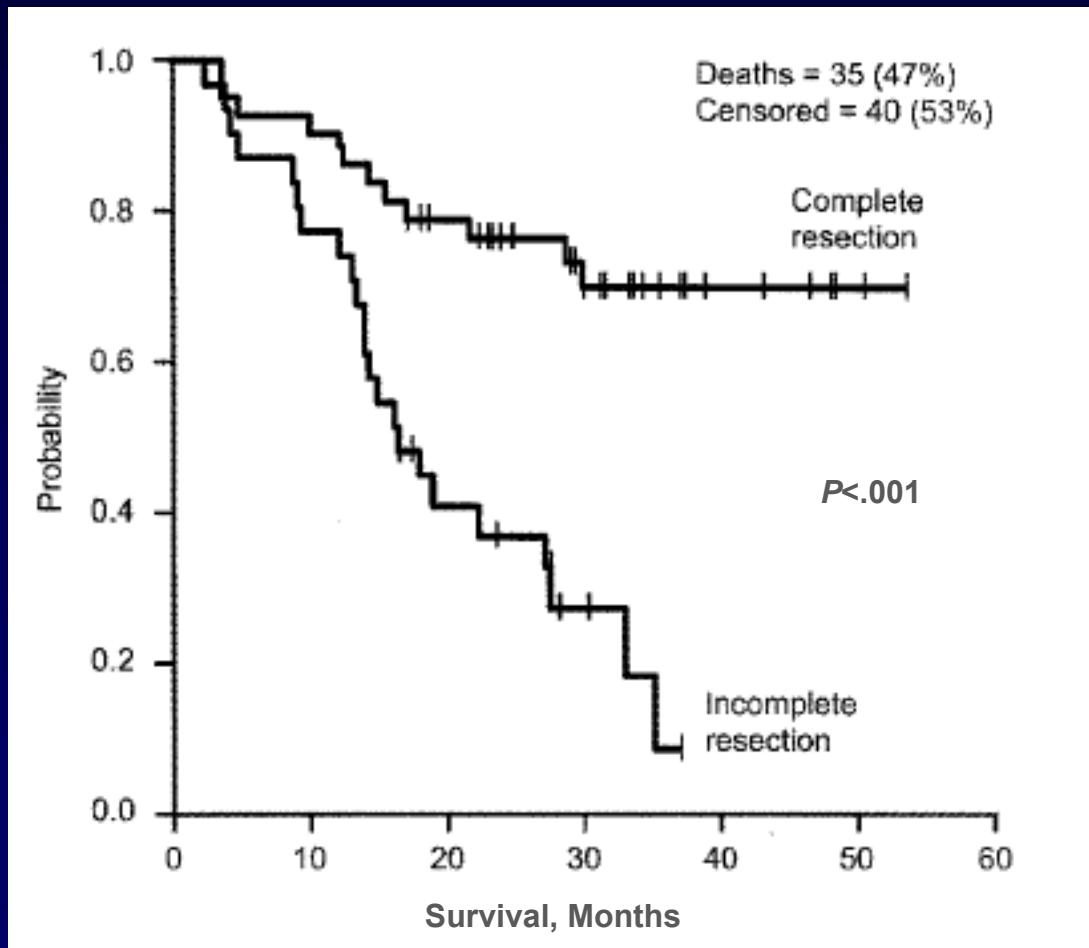
→ Risk-benefit ratio

Individualized Treatment

Complete Resection in Lung Cancer Surgery

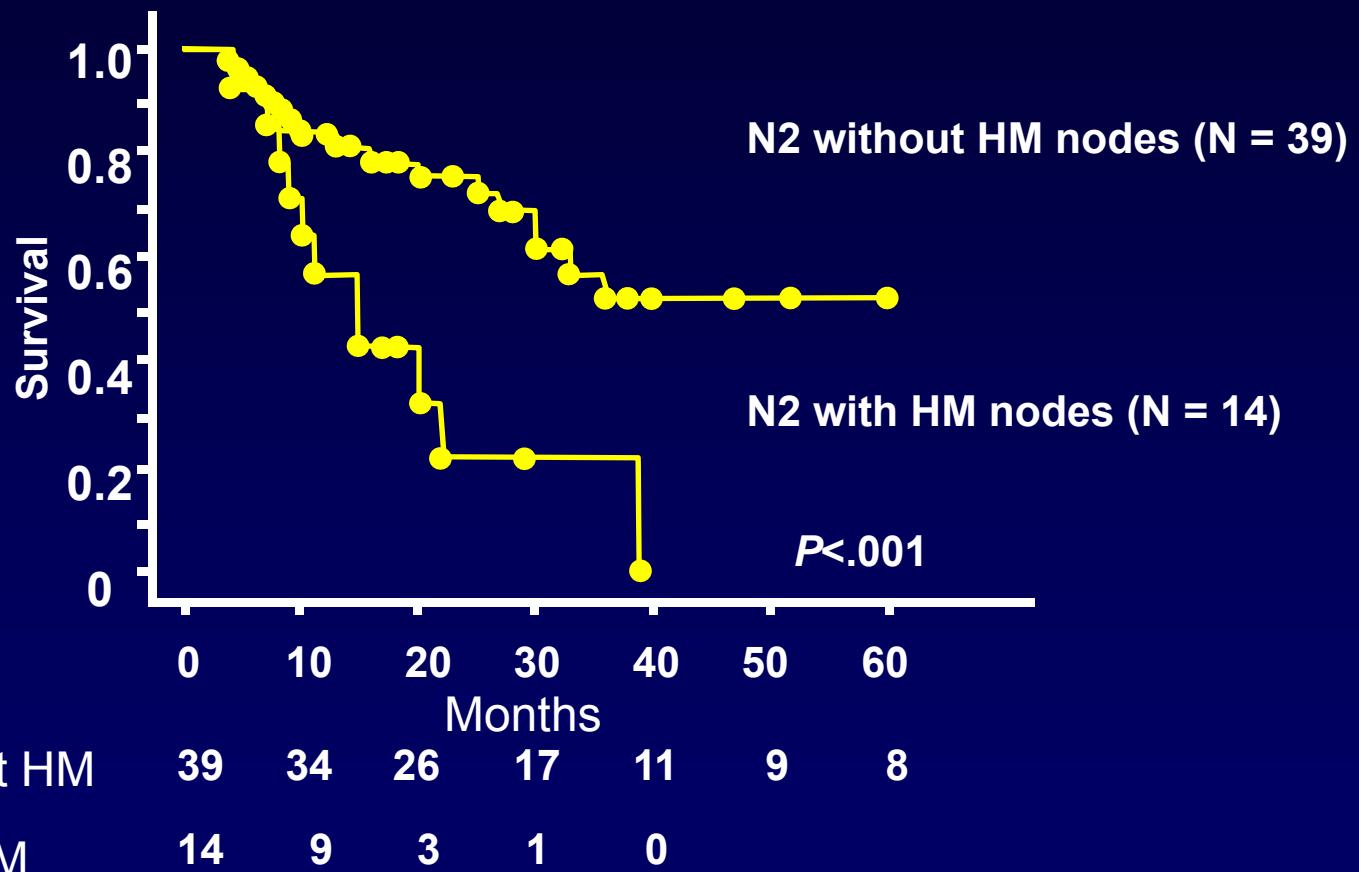
- Free resection margins (proved microscopically)
- No extra capsular nodal extension
- Highest mediastinal LN removed is negative

Overall Survival Dependent on Complete Resection



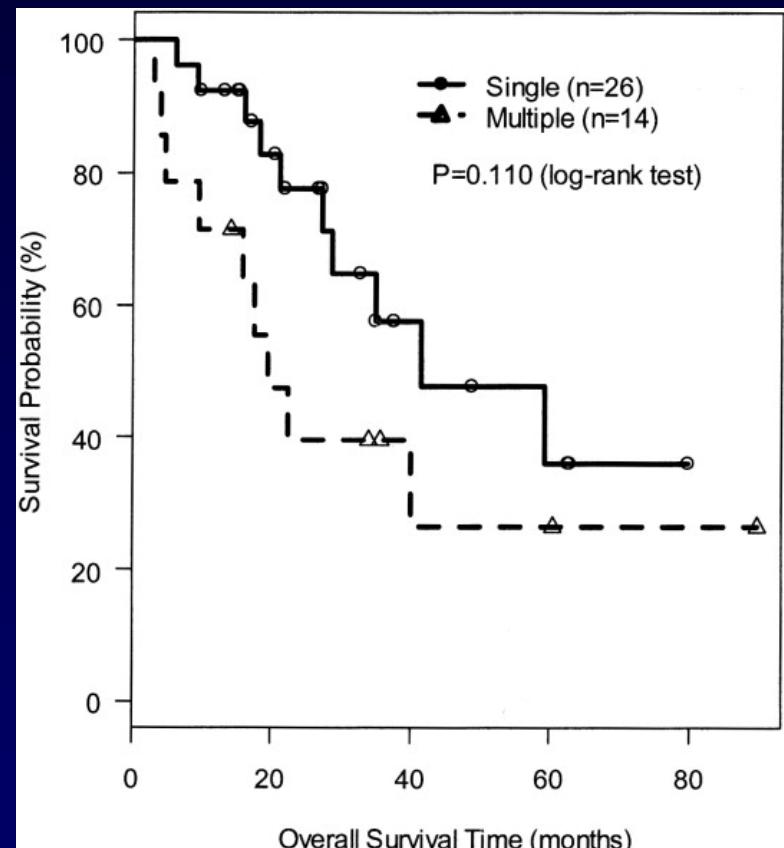
Betticher DC, et al. *J Clin Oncol*. 2003;21(9):1752-1759.

Role of Highest Level N2 Node

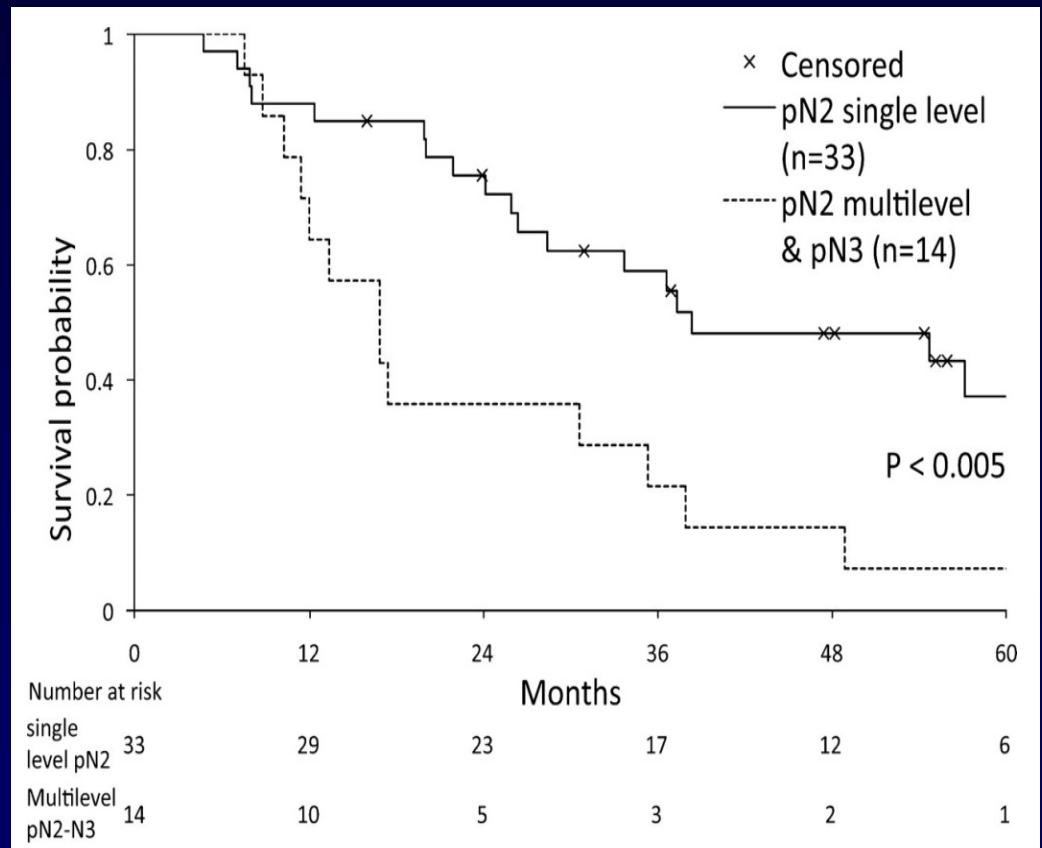


Sakao Y, et al. *Ann Thorac Surg*. 2006;81(1):292-297.

Single Versus Multilevel N2: Overall Survival



Uy KL, et al. *J Thorac Cardiovasc Surg.* 2007;134(1):188-193.



Decaluwe H, et al. *Eur J Cardiothorac Surg.* 2009;36(3):433-439.

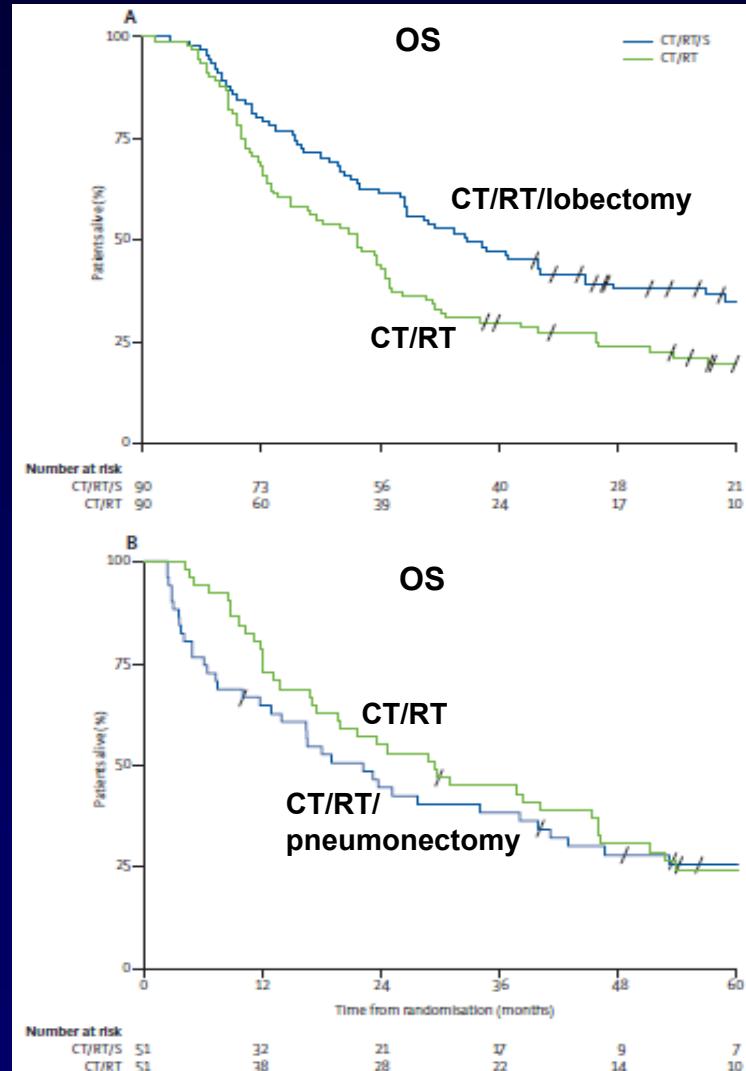
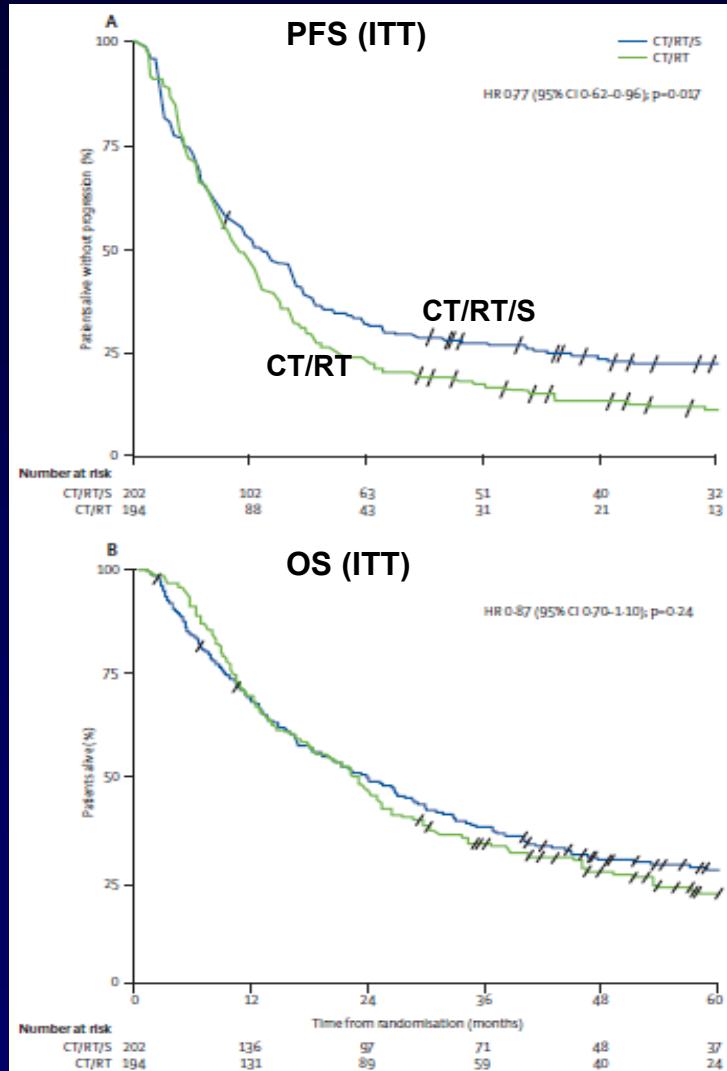
Role of Induction Chemotherapy Followed by Surgical Resection

Table 1
Studies of induction chemotherapy and surgical resection for stage III (N2) disease

Authors, Ref.	Year	Phase	Disease	Patients (N)	Resected (n)	Resected (%)	pCR (%)	5-y Survival (%)	N2 Downstaging
Burkes et al, ⁷⁷	1992	II	IIIA-N2	39	22	56	5	26 (3-y)	36
Sugarbaker et al, ⁸	1995	II	IIIA-N2	74	46	62	NS	23 (3-y)	22
Rosell et al, ^{6,78}	1994, 1999	III	44/60 (N2)	60	23/27	85	3	17 (induction), 0 (no induction)	32
Roth et al, ^{4,5}	1994, 1998	III	IIIA	60	17/28	61	4	36 (induction), 15 (no induction)	NS
Van Zandwijk et al (EORTC), ⁷⁹	2000	II	IIIA-N2	47 (17 surgery)	16/17	94 (induction)	6 (1/17)	NS for surgical group	53
Betticher et al, ⁸⁰	2003	II	IIIA-N2	90	75	83	NS	34 (3-y)	61
Nagai et al, ⁸¹	2003	III	IIIA-N2	62	20/31	65 (induction)	0 (0/31)	22 (induction), 10 (no Induction)	NS
O'Brien et al (EORTC), ⁸²	2003	II	IIIA-N2	52 (15 surgery)	12/15	80 (induction)	2	NS for surgical group	17
Garrido et al, ⁸³	2007	II	IIIA (N2)-B (T4N0-1)	69 (N2)	46 (N2)	67	2 (N2)	32 (N2 resected)	27

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; NS, not stated; pCR, complete pathologic response.

Radiotherapy Plus Chemotherapy With or Without Surgical Resection



Albain KS, et al. *Lancet.* 2009;374(9687):379-386.

ITT, intention-to-treat population

Randomized Trials in Stage IIIA N2 NSCLC

Study (reference)	EORTC 08941 [55]		Intergroup 0139 [56]	
	Treatment arm	Induction chemotherapy + surgery	Induction chemotherapy + radiotherapy	Induction chemoradiotherapy + surgery
Number of patients with IIIA–N2	167		166	202
Chemotherapy regimen	Platinum based	–	Cisplatin–etoposide	–
Radiotherapy total dose (Gray)	–	60	45	61
Rate of pneumonectomy/ (bi-)lobectomy/exploratory thoracotomy (%)	47/38/14	–	27/49/4	–
R0 resection rate(%)	50	–	71	–
Treatment related mortality rate (%)	4	<1	8	2
Pathological nodal downstaging rate (%)	41 (pN0–1)	–	38 (pN0)	–
Pathological complete response rate (%)	5	–	15	–
Median PFS (months)	9.0	11.3	12.8	10.5
Locoregional failure rate (%)	32	55	10	22
Median OS (months) with 95% CI	16.4 (13.3–19.0)	17.5 (15.8–23.2)	23	22.2
5 year SR (%) with 95% CI	15.7 (10–22)	14 (9–20)	27.2	20.3

Crino L, et al. *Ann Oncol.* 2010;21(Suppl 5):v103-v115.

- Equivalence in overall survival between surgery and RT
- Better local control in surgery
- Choose the safest approach for each patient
 - If lobectomy is possible → surgery

Operative Risk of Pneumonectomy: Influence of Induction Therapy

- **Single institution study, 1993-2007**
- **183 pneumonectomy: 46 with induction chemoradiotherapy (45 Gy)**
- **Mortality 2/46 (4.3%) after preoperative therapy vs 9/137 (6.6%) after resection only $P = .73$**
- **Morbidity was not different**

Risk of Pneumonectomy After Induction Therapy for Locally Advanced NSCLC

- Multi-institutional study 1989-2004
- 315 pneumonectomies, median age 64 years (25-82)
 - 200 right sided (63%)
 - 68 patients with induction chemotherapy (22%)
- Mortality: 9.2% and 21% after induction

Mortality of Pneumonectomy After Chemotherapy or Chemo Radiotherapy for Advanced NSCLC (Stage III)

- 176 pneumonectomies (78% extended) performed after chemotherapy or chemoradiotherapy (80%) in Essen or Zurich in 1998-2007
- → Perioperative mortality 3%
3-year and 5-year overall survival were 55% and 38%
- Meta-analyses between 1990-2010: peri-operative mortality
 - right vs left pneumonectomy, 11% vs 5%

Author	N	Induction		Mortality
		CT	CT-RT	
d'Amato '09	68	X		21%
Stamatis, '02	127	X		7%
Albain '05	24		x	27%
Sonett, '04	40		X (>59)	0%
Weder, '09	176	X	X	3%

Weder W, et al. *J Thorac Cardiovasc Surg.* 2010;139(6):1424-1430; Kim AW, et al. *J Thorac Cardiovasc Surg.* 2012;143(1):55-63

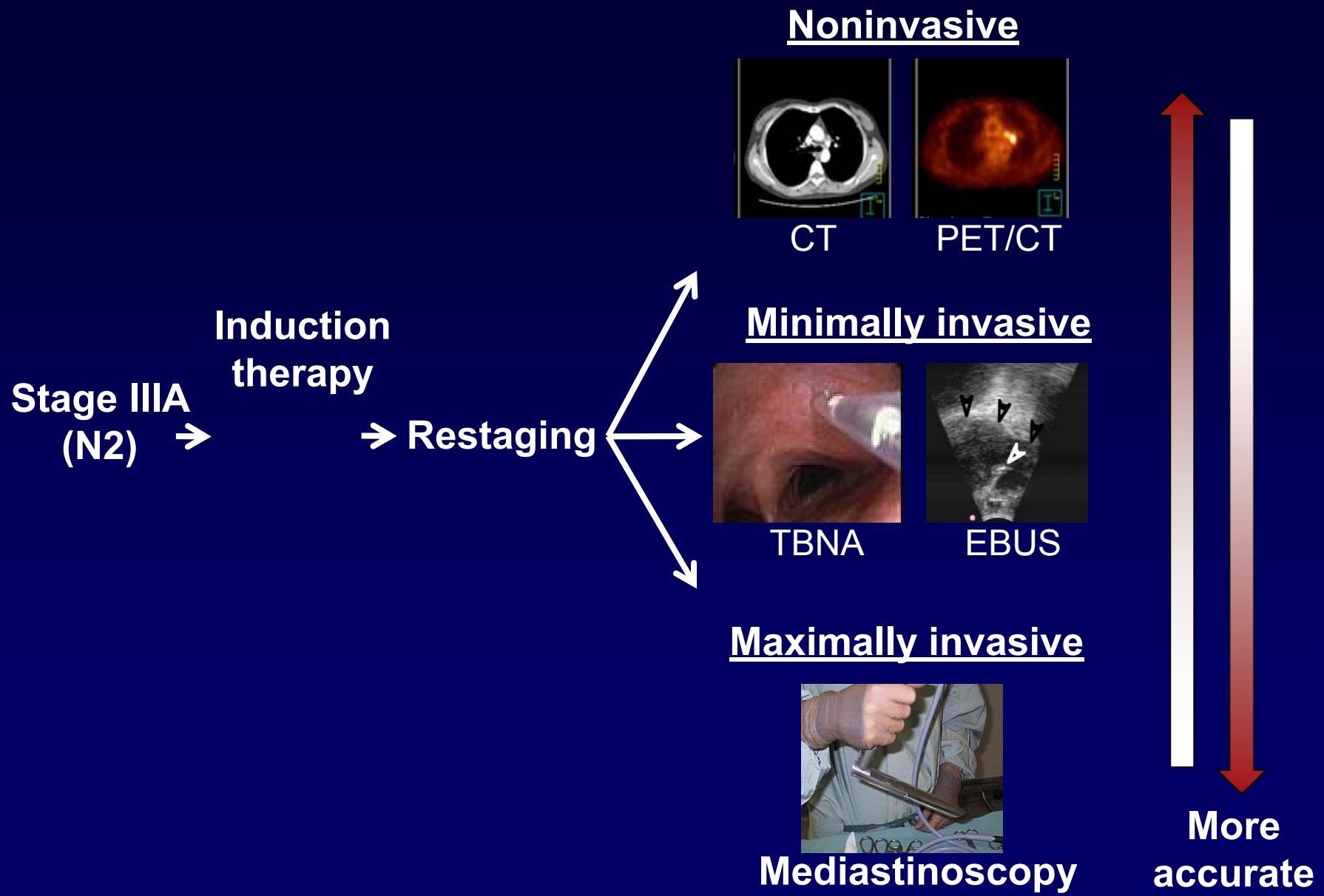
Conclusions

- **Surgery is indicated as part of multimodality treatment in selected patients with N2 disease (nonfixed, single zone)**
- **N2 (bulky, fixed) or N3 disease can be considered for radical multimodality treatment preferentially in a study protocol**
- **Surgical resection after induction chemoradiotherapy should be limited to a lobectomy, whenever possible**
- **T4 tumors should be considered for multimodality treatment including surgery when complete resection can be achieved**

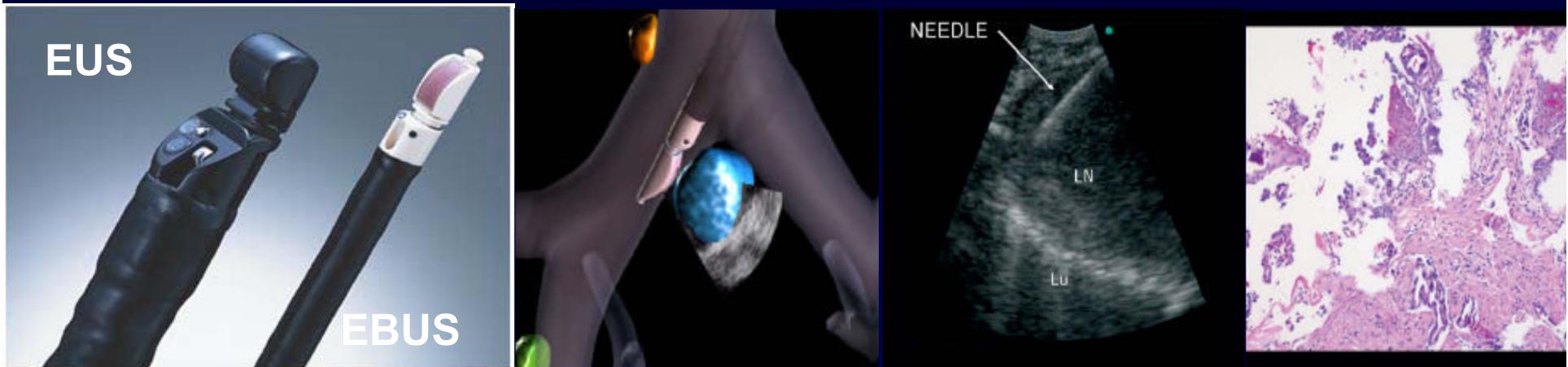
Q2: Would you consider mediastinoscopy after preoperative therapy if evaluation PET/CT showed partial response?

- 1. Yes**
- 2. No, I would consider EBUS for restaging after neoadjuvant chemotherapy**
- 3. No, evaluation with PET/CT is adequate**
- 4. Uncertain**

Restaging: Choices



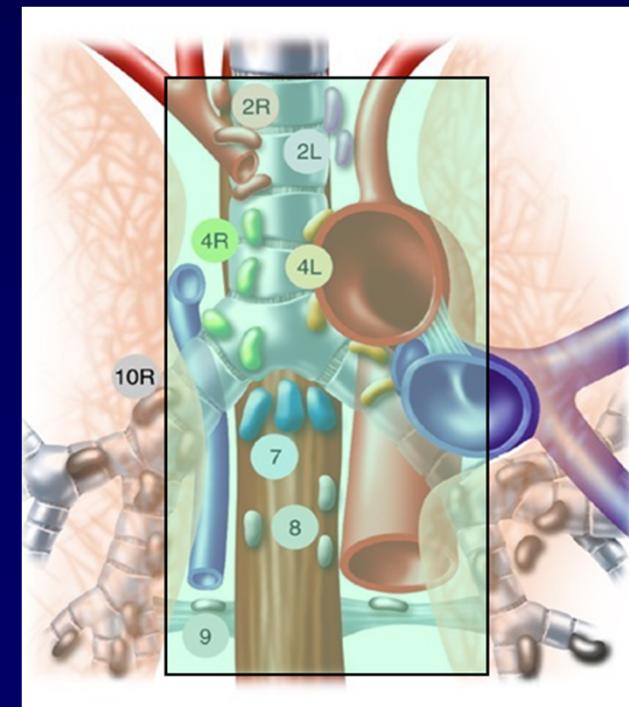
(Re-) Staging Techniques



- ATS 1, 2, 3, 4, 5, 6, 7, (EUS: 8, 9), 10, 11
- Visually assisted (doppler)
- Outpatient setting possible
- Re-staging

Technique	Pat. No.	Sensitivity	Specificity
TBNA	910	0.76	0.96
EUS-FNA	215	0.88	0.91
Mediast	5.687	0.81	1.00

Toloza EM, et al. *Chest*. 2003;123(1 Suppl): 157S-166S.



Restaging: CT

Study	N	CRT	CT	Sens	Spec	FN	FP
Trodella et al.	56	+	-	92	77	9	8
De Leyn et al	30	-	+	59	62	47	34
Mateu-Navarro et al.	24	-	+	42	75	44	38
Lardionois et al.	24	-	+	56	73	27	44
Ohtsuka et al	22	+	+	67	62	27	45
All sites				63	70	31	34

- Overall false negative rate of ~30%
- Generally not recommended

FN, false negative rate; FP, false positive rate

de Cabanyes Candela S, et al. *J Thor Oncol.* 2010;5(3):389-398.

Restaging: PET-CT

Study	N	PET	PET/CT	Sens	Spec	FN	FP
Cerfolio et al.	93	-	+	62	88	20	25
Eschmann et al.	56	+	-	77	68	29	25
Hellwig et al.	33	+	-	50	88	15	43
Akhurst et al.	54	+	-	67	61	21	54
De Leyn et al.	30	-	+	77	92	25	7
All sites				63	70	26	34

- Overall false negative rate of ~25%
- Generally not recommended

Restaging: Needle Techniques

Study	N	Tech	Sens	Spec	FN	FP
Herth et al.	124	EBUS-NA	76	100	80	0
Annema et al.	17	EUS-NA	67	100	33	0
Varadarajulu et al.	14	EUS-NA	86	100	14	0
Stigt et al.	25	EUS-NA	96	100	8	0
Kunst et al.	11	TBNA	100	100	0	0
All sites			84	100	14	0

- Overall false negative rate of ~15%
- Only large study of EBUS had FN rate of 80%!
- EUS / TBNA studies very small (inconclusive)
- Not recommended given lack of solid evidence

Restaging: Primary Mediastinoscopy

Study	N	CRT	CT	Sens	Spec	FN	FP
Zielinski et al.	63	+	+	96	100	3	0
Lardinois et al.	22	-	+	82	100	15	0
All sites				89	100	9	0

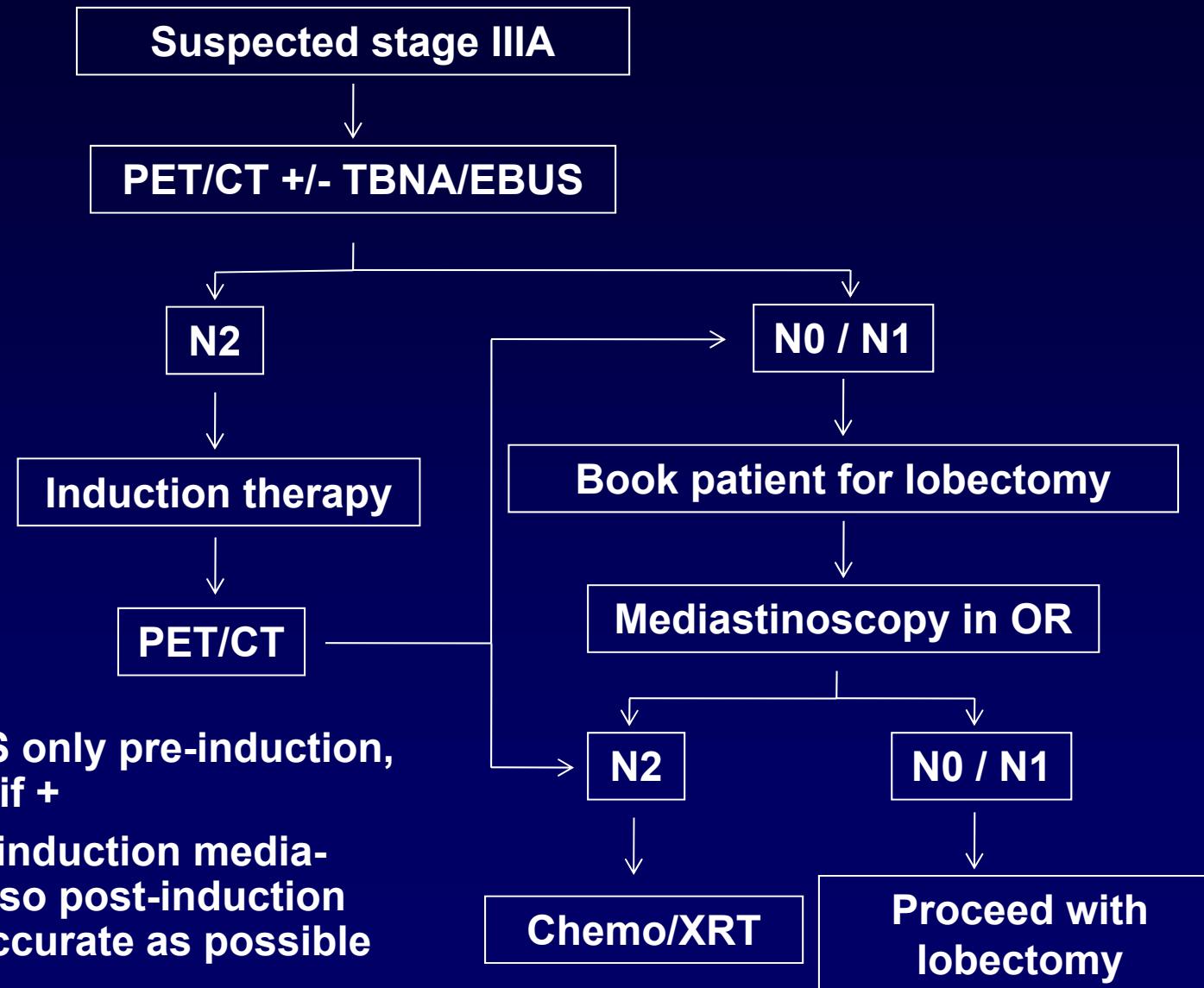
- Overall false negative rate of ~10%
- Best option

Restaging: Repeat Mediastinoscopy

Study	N	CRT	CT	Sens	Spec	FN	FP
Stamatis et al.	165	+	-	74	100	14	0
Meerschaut et al.	112	n/a	n/a	71	100	9	0
Marra et al.	104	+	-	51	100	21	0
De Waele et al.	104	+	+	70	100	27	0
De Leyn et al.	30	-	+	50	100	38	0
All sites				63	100	22	0

- Overall false negative rate of ~20%
- Technically feasible but difficult
- Recommended over noninvasive imaging

Stage IIIA N2 Disease: Algorithm



Features

1. TBNA/EBUS only pre-induction, only useful if +
2. Avoids pre-induction mediastinoscopy so post-induction will be as accurate as possible

Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

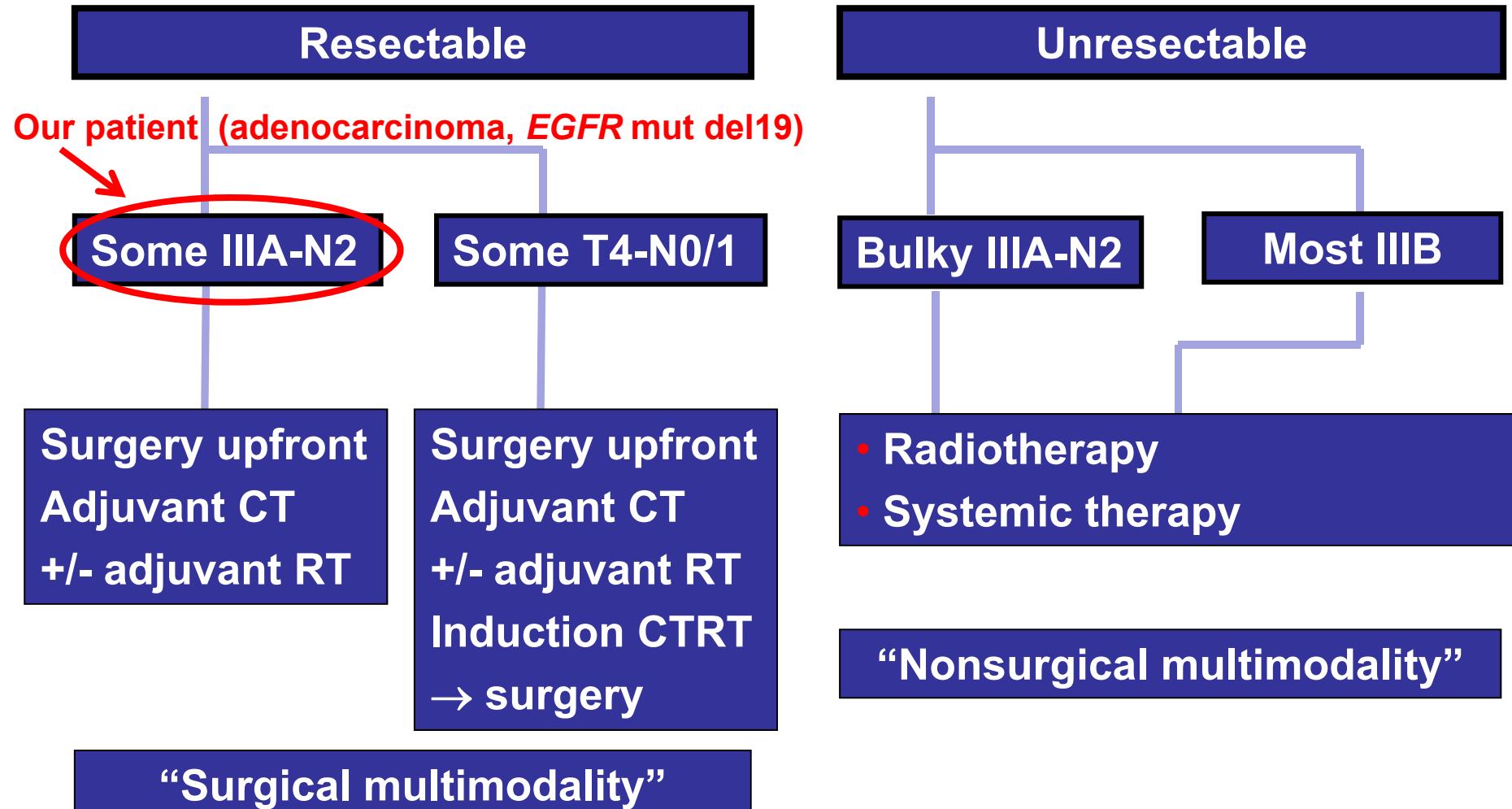
Part II

Benjamin Besse, MD, PhD

Gustave Roussy
Villejuif, France



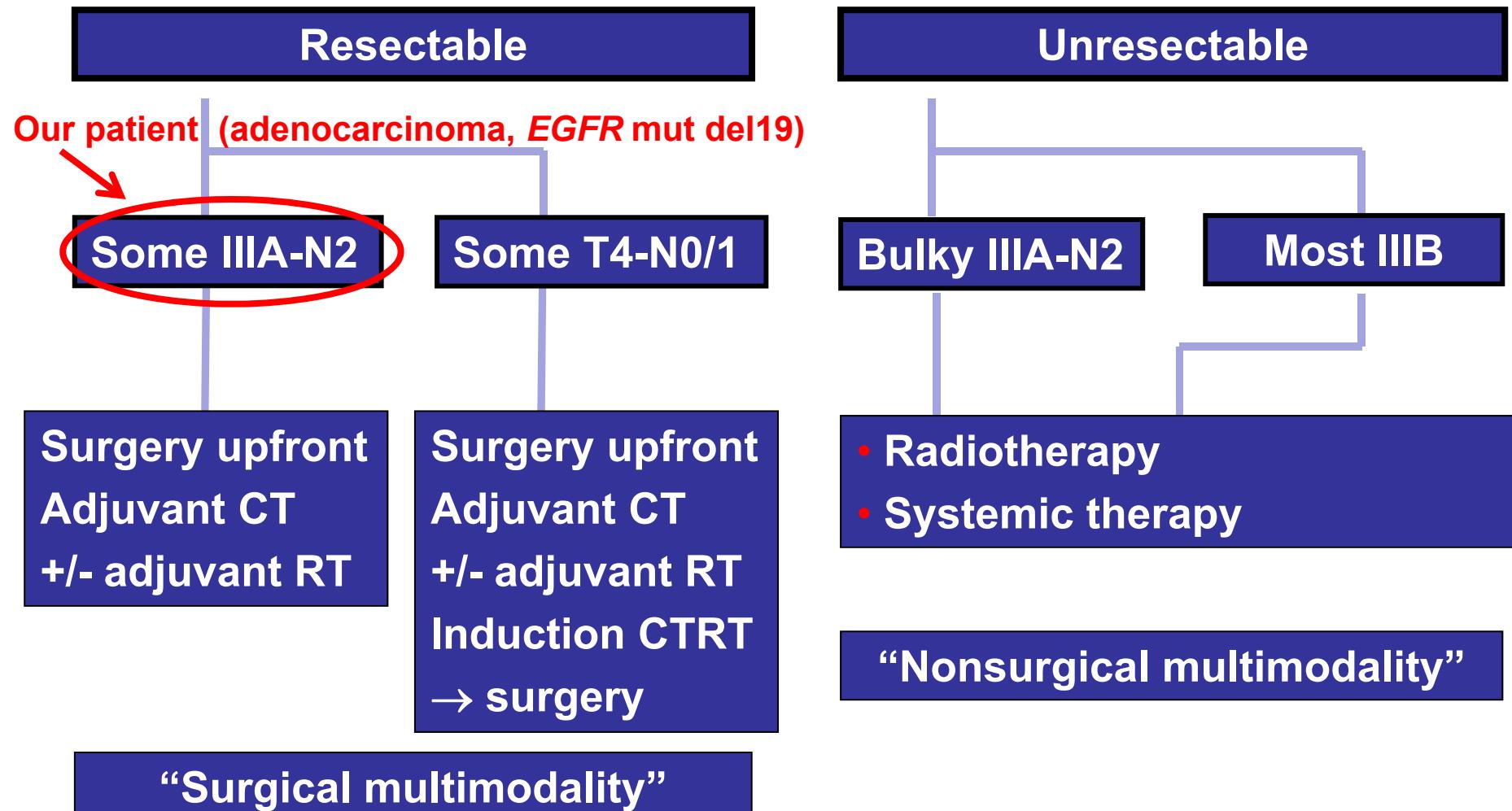
Locally Advanced (Stage III) NSCLC: A Heterogeneous Group: Gustave Roussy Policy



CT, chemotherapy; NSCLC, non-small cell lung cancer; RT, radiation therapy

Modified from Vansteenkiste J, Presented at: 2008 ERS School Course on State of the Art for Non Small Cell Lung Cancer; November 27-30, 2008; Leuven, Belgium.

Locally Advanced (Stage III) NSCLC: A Heterogeneous Group: Gustave Roussy Policy

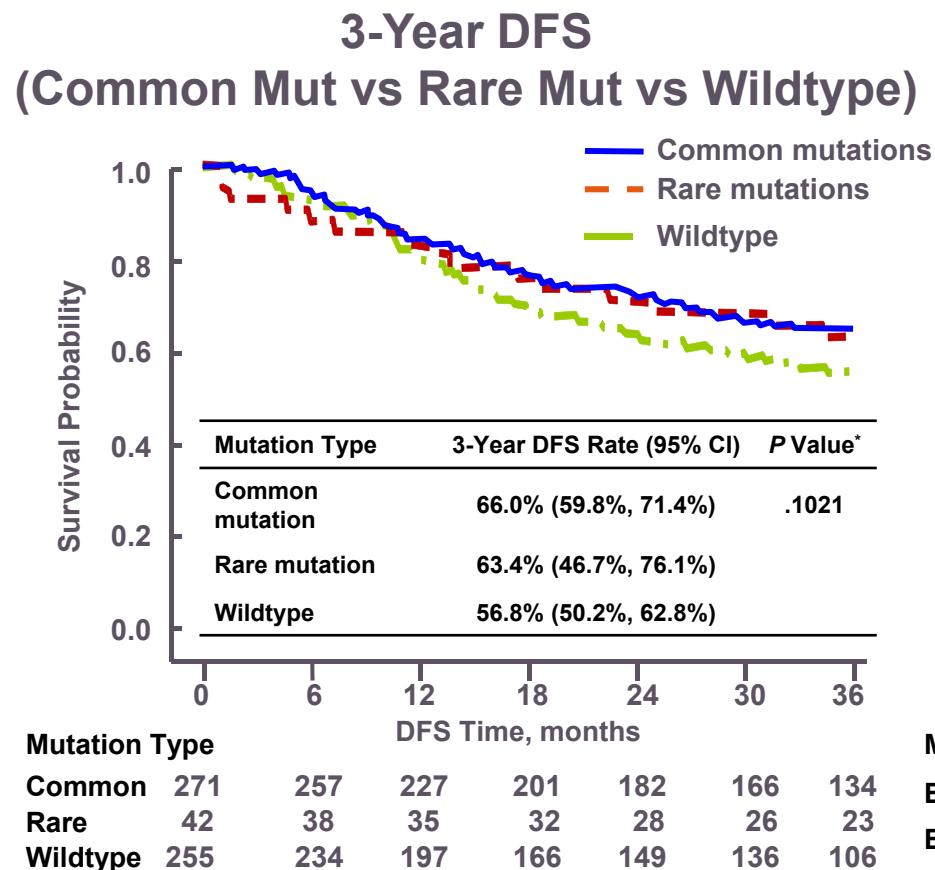


CT, chemotherapy; NSCLC, non-small cell lung cancer; RT, radiation therapy

Modified from Vansteenkiste J, Presented at: 2008 ERS School Course on State of the Art for Non Small Cell Lung Cancer; November 27-30, 2008; Leuven, Belgium.

Prognostic/Predictive Role of *EGFR* Mutations in Resected Patients With NSCLC

ICAN: DFS in Chinese Patients With Resected Lung Adenocarcinoma According to *EGFR* Mutations

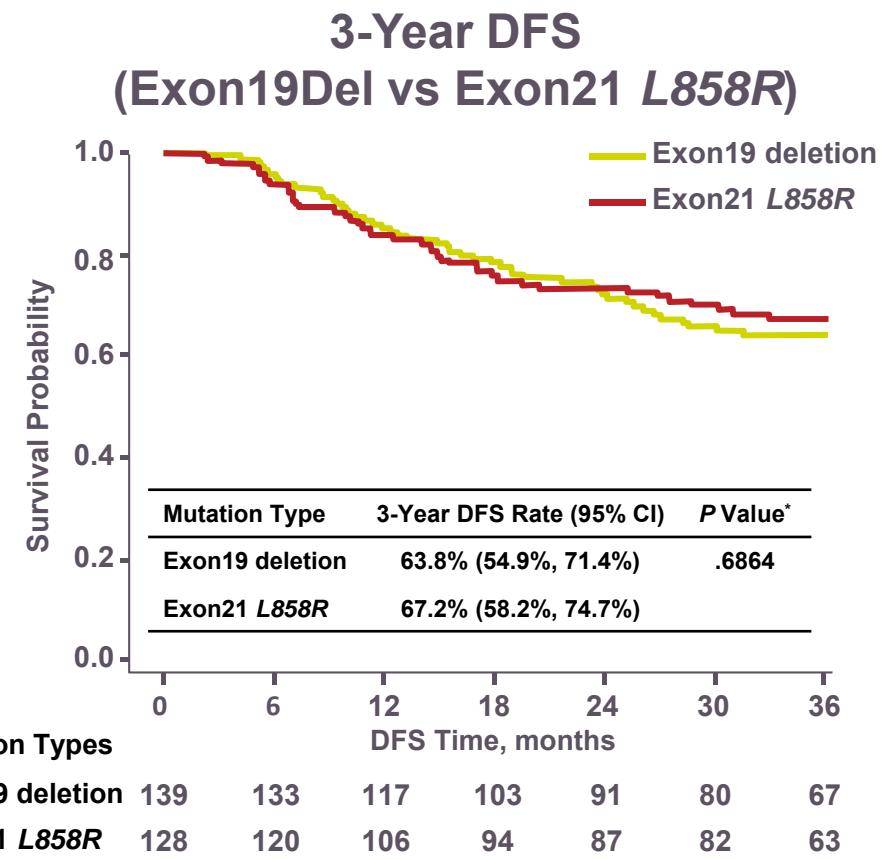


*Log-Rank test

Common mutation (sensitive mutation) include deletion, *L858R*deletion + *L858R*, rare mutation include unknown mutation and other types, 4 patients with both *L858R* and deletion were excluded in Exon19Del vs Exon21 *L858R* comparison.

CI, confidence interval; DFS, disease-free survival

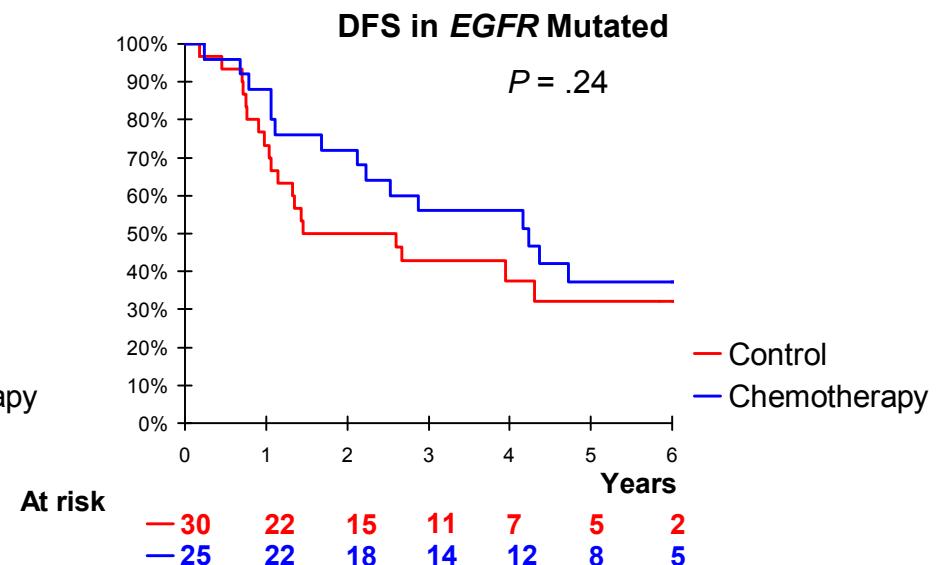
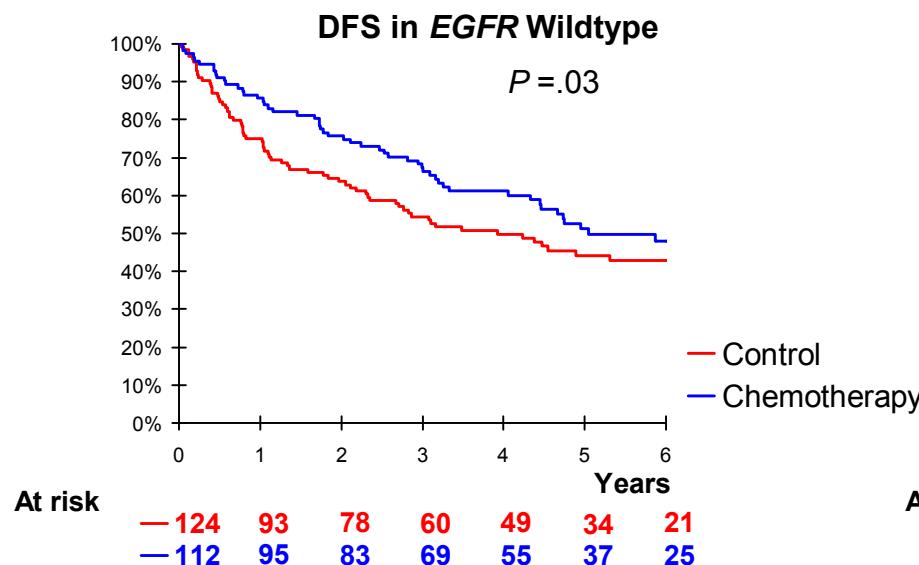
Wu Y, et al. Ann Oncol. 2014;25(Suppl 4): Abstract 1175O.



LACE-bio: EGFR Prognostic Value in KRAS Wildtype Patients

Pooled analysis of IALT, JBR10, and CALGB-9633 trials

- Lack of predictive value on DFS (n = 291)



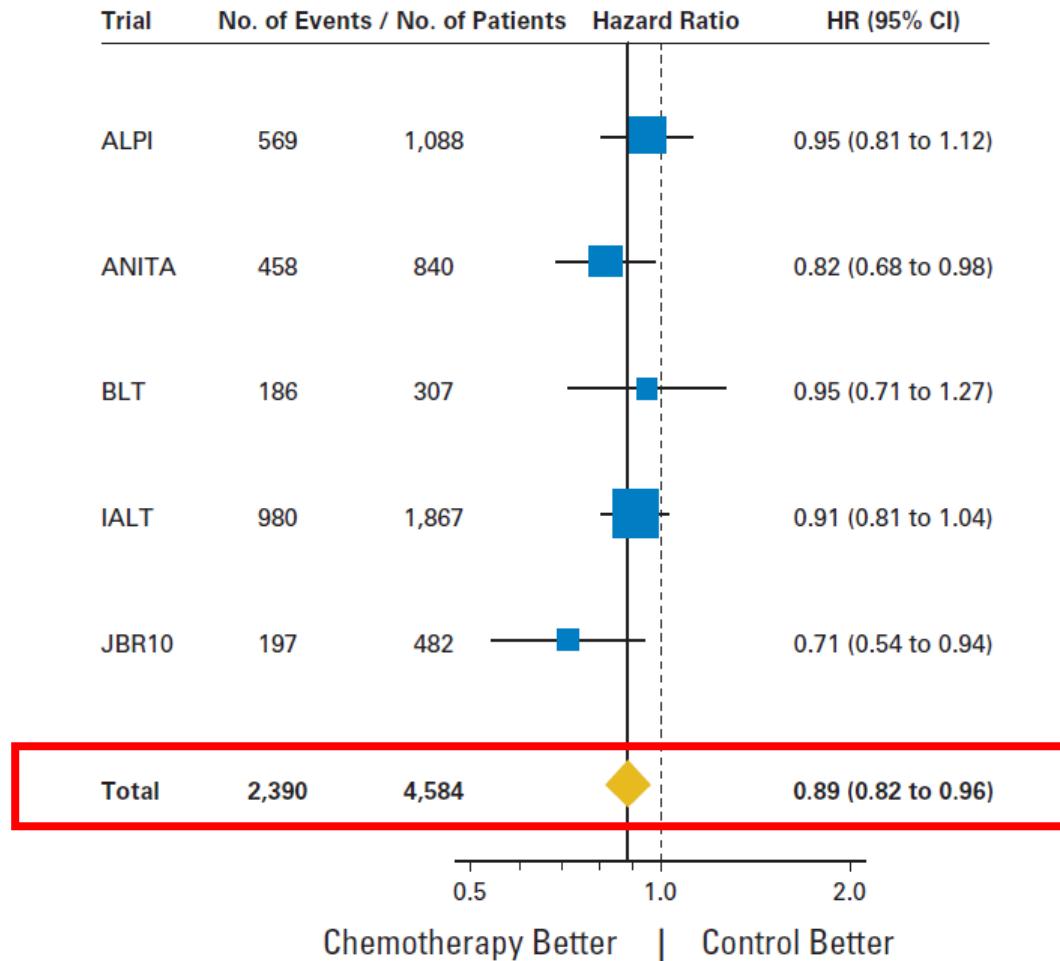
Interaction test
 $P = .97$

IN LACE (MOSTLY CAUCASIANS),
BOTH GROUPS HAVE A BENEFIT OF CHEMOTHERAPY

Perioperative Chemotherapy

LACE: 5 Adjuvant Cisplatin-Based Regimens

Overall Survival



**Absolute OS benefit
at 5 years
 $5.3\% \pm 1.6\%$**

**Toxic death
0.8% to 2%**

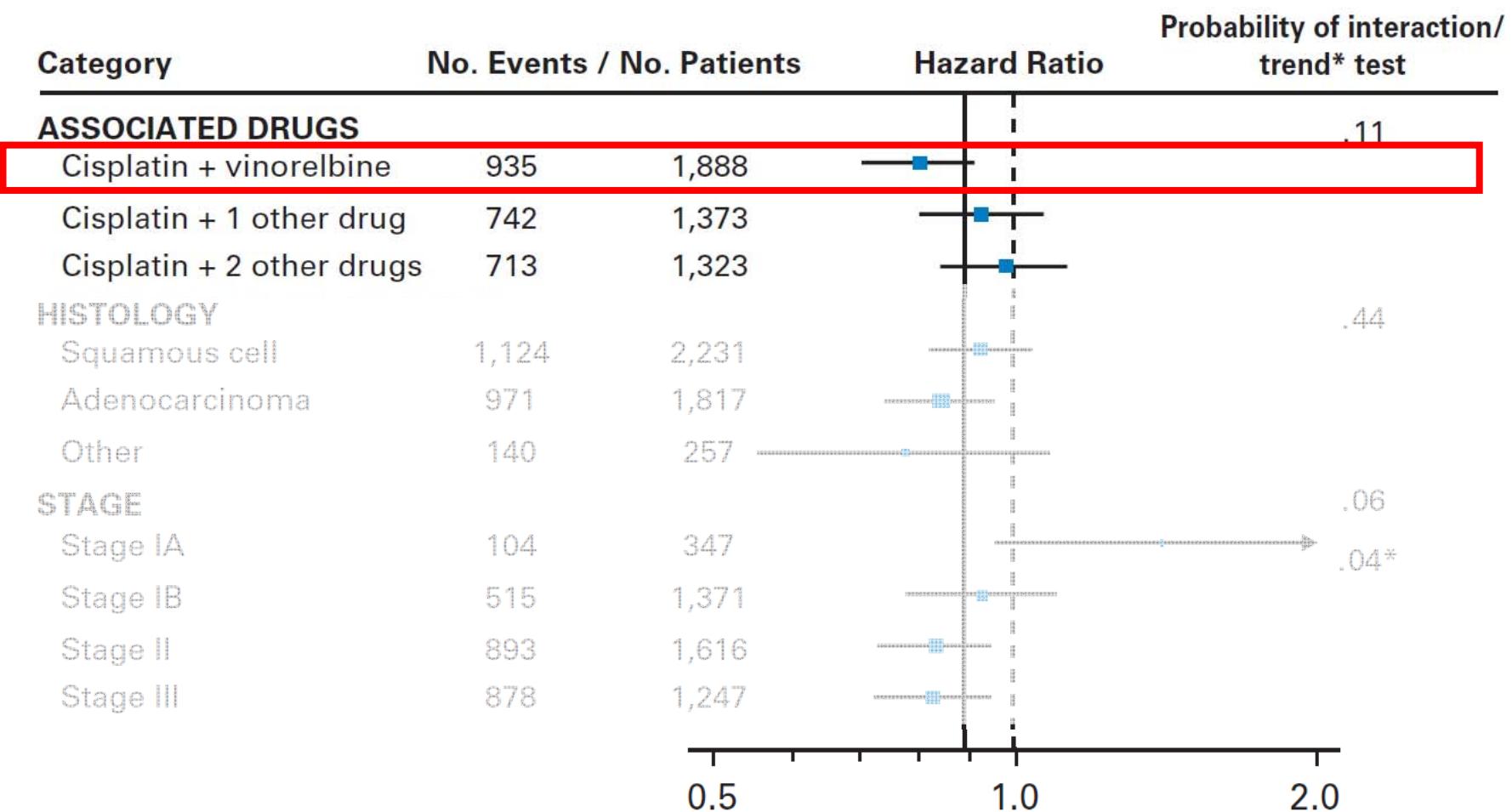
Chemotherapy effect: Logrank statistic = 8.5, P = .005

Test for heterogeneity: $\chi^2_4 = 4.25$, P = .37, I² = 6%

HR, hazard ratio; OS, overall survival

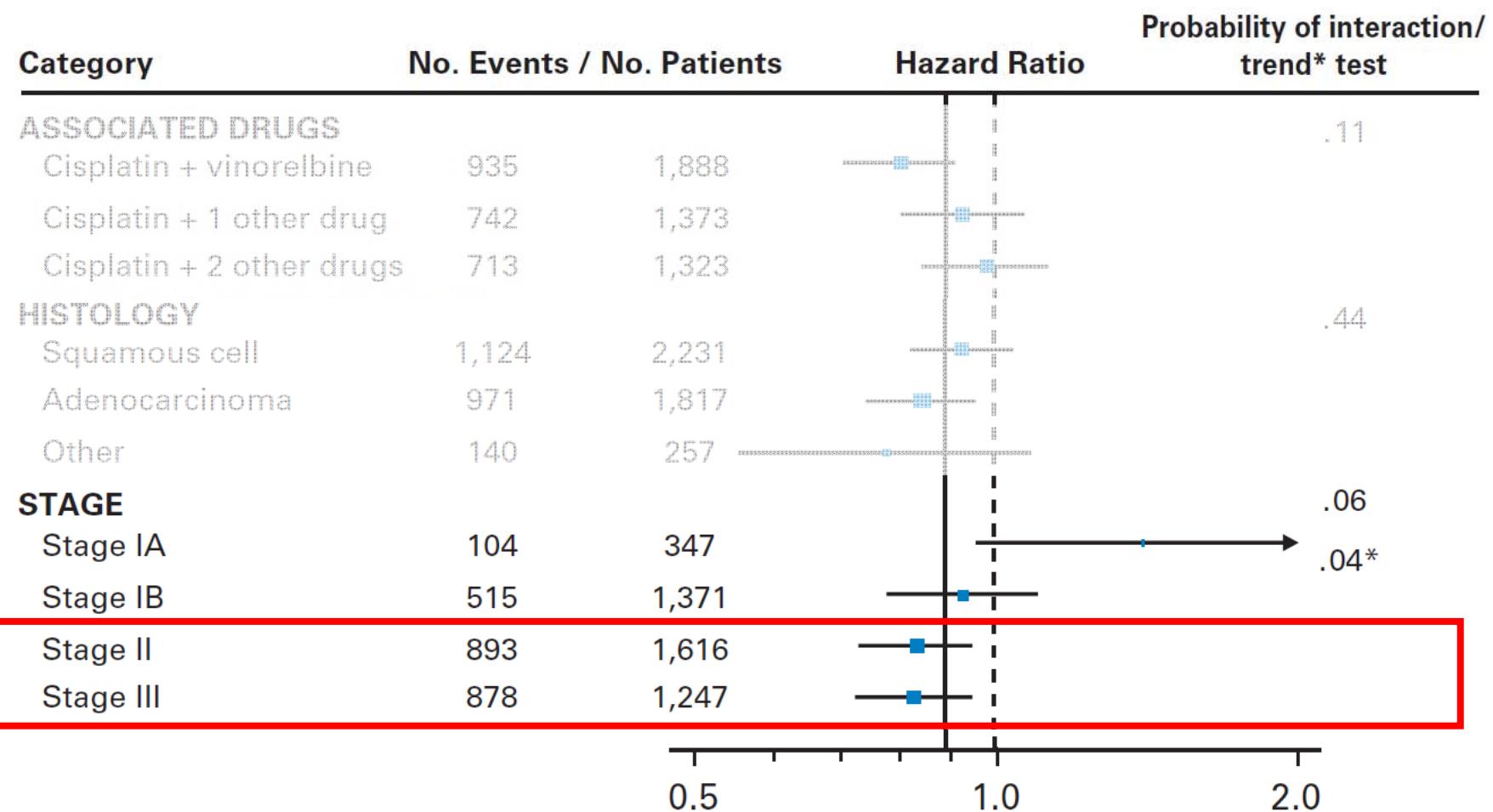
Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

LACE: OS According to Chemotherapy Regimen

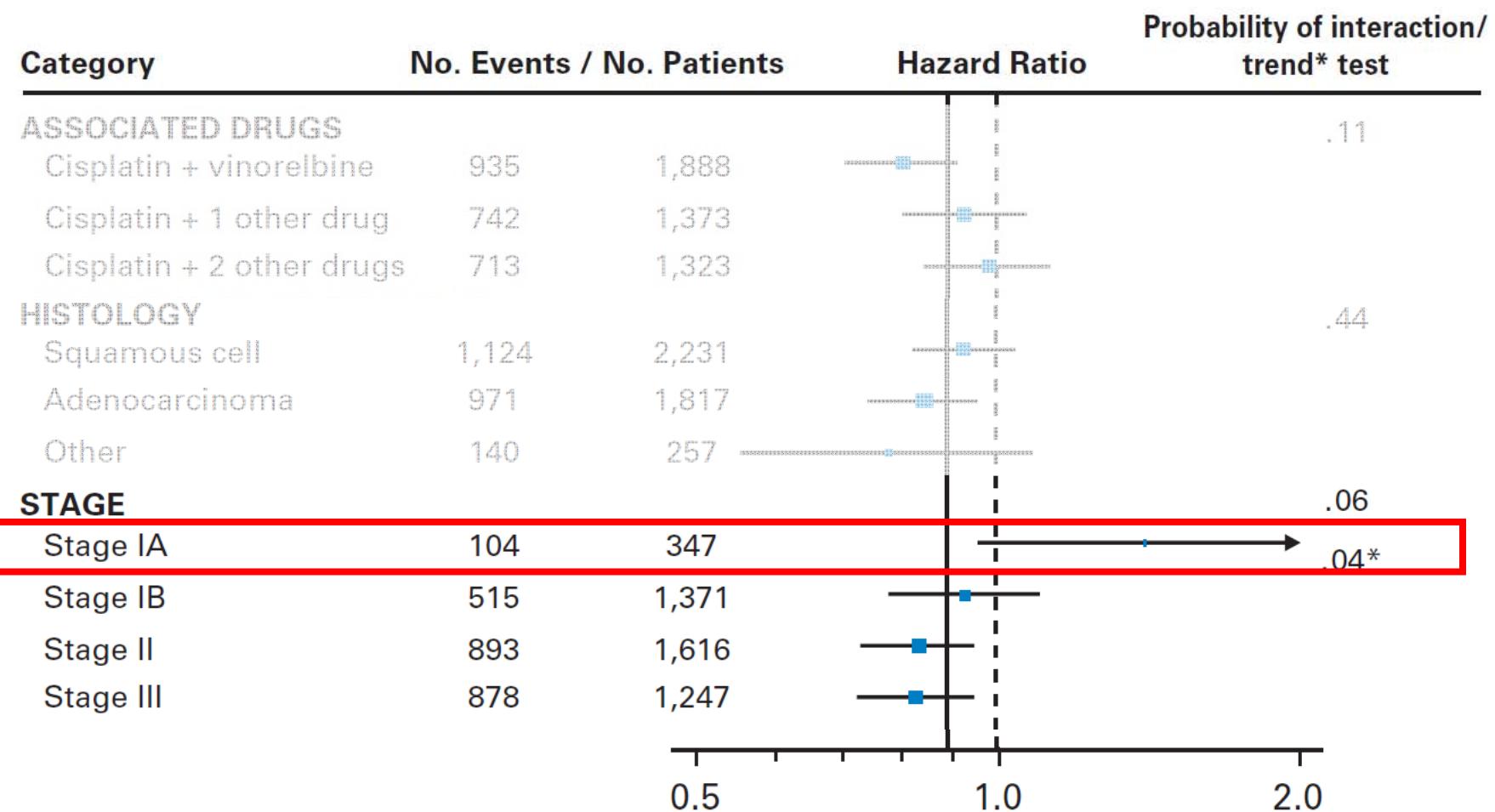


Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

LACE: OS Analysis by Stage

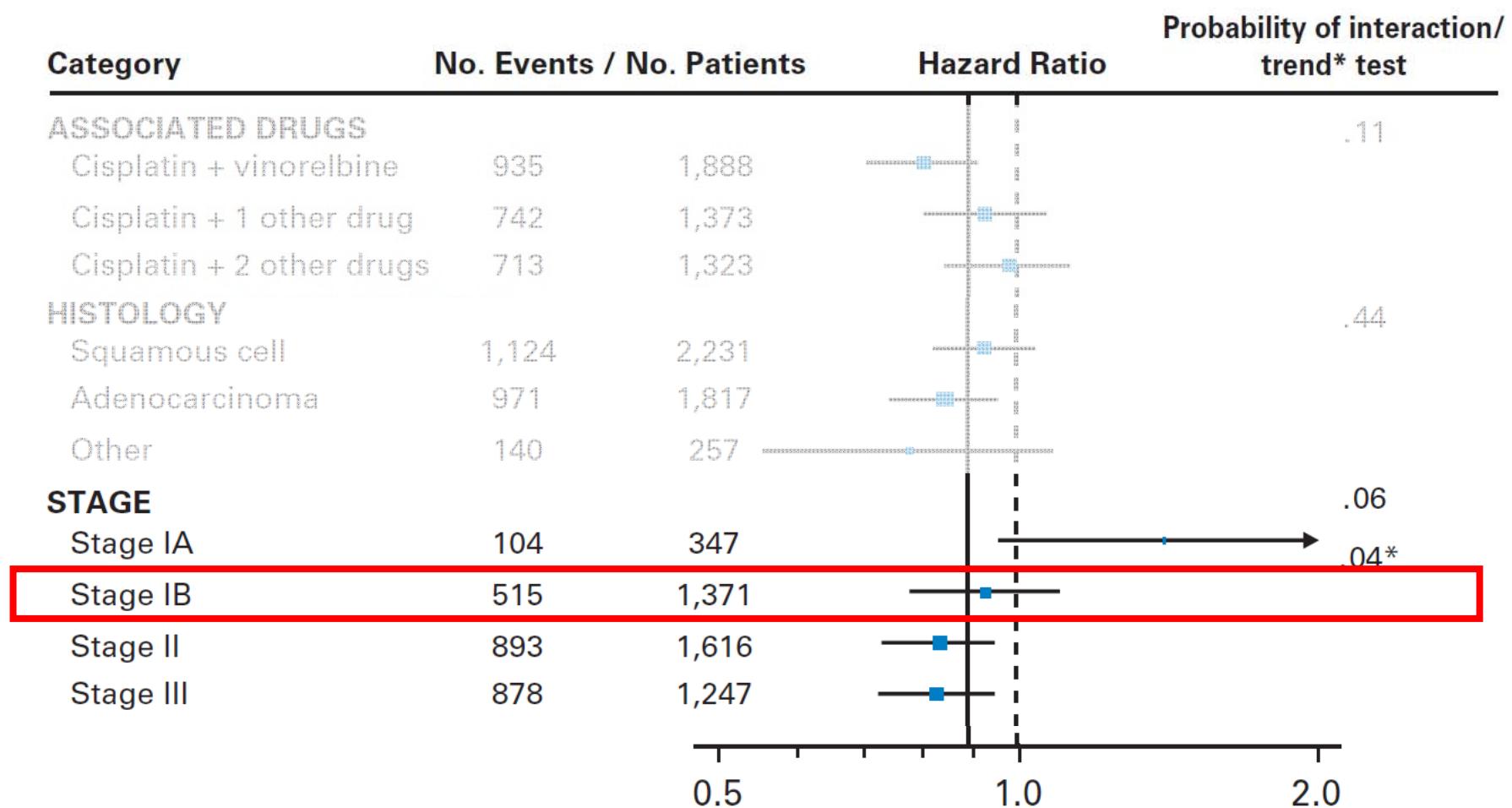


LACE: OS Analysis by Stage



Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

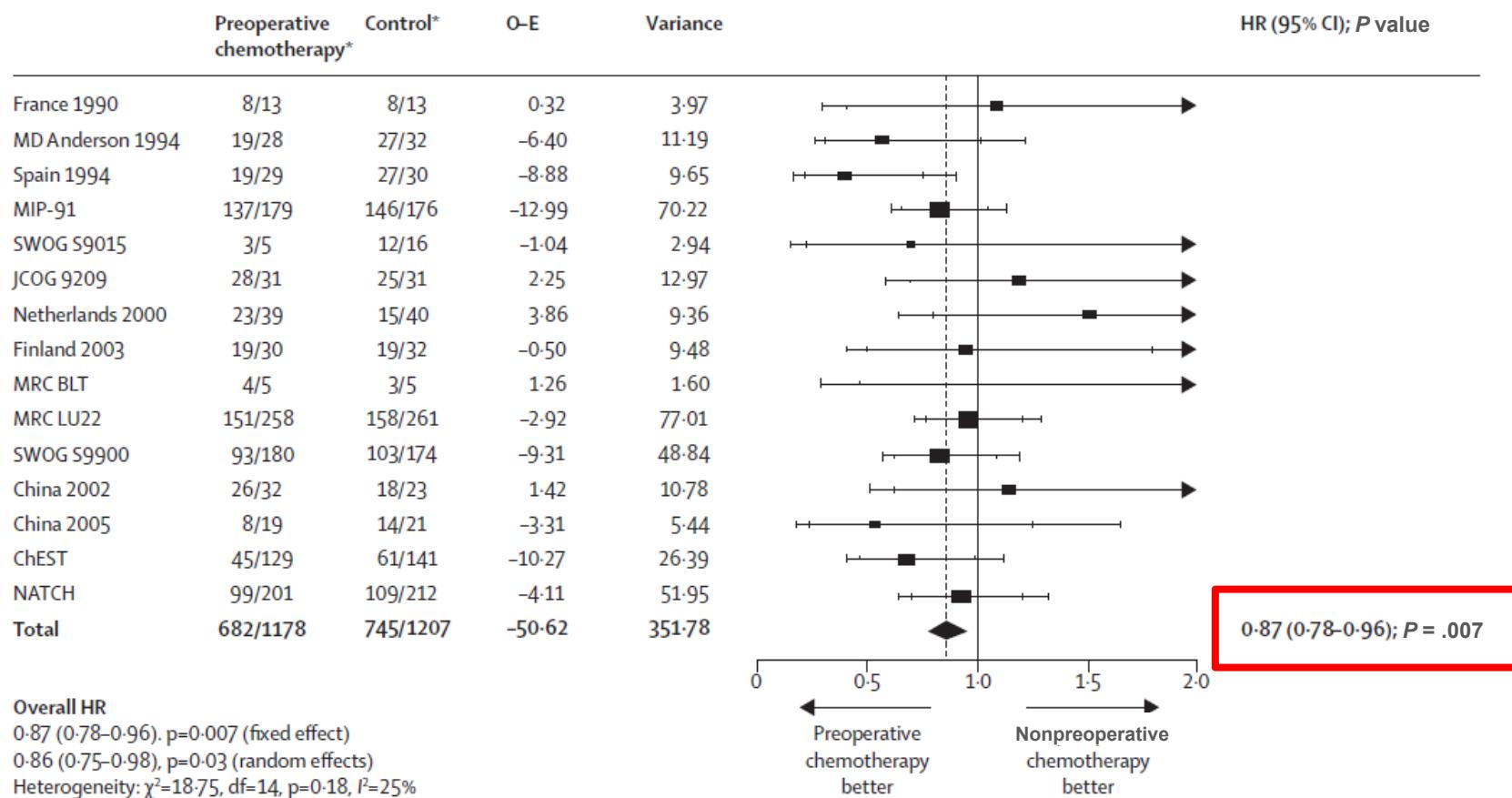
LACE: OS Analysis by Stage



Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559.

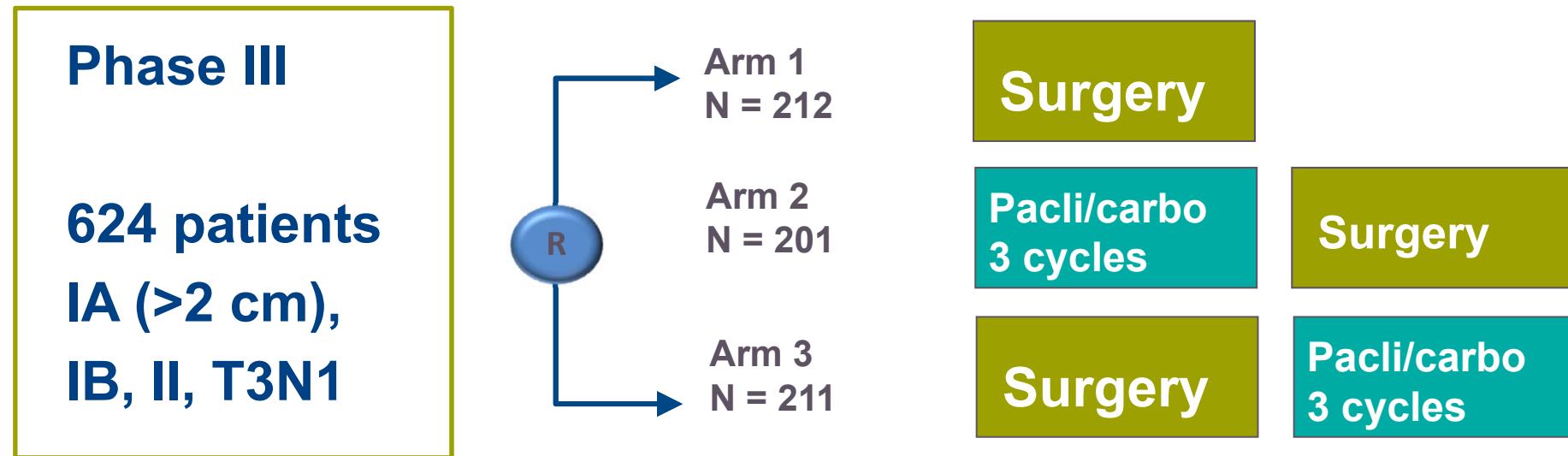
Survival Benefit of Preoperative Chemotherapy: Meta-Analysis of 15 Randomized Controlled Trials

N = 2385



NSCLC Meta-Analysis Collaborative Group. *Lancet.* 2014;383(9928):1561-1571.

NATCH Trial

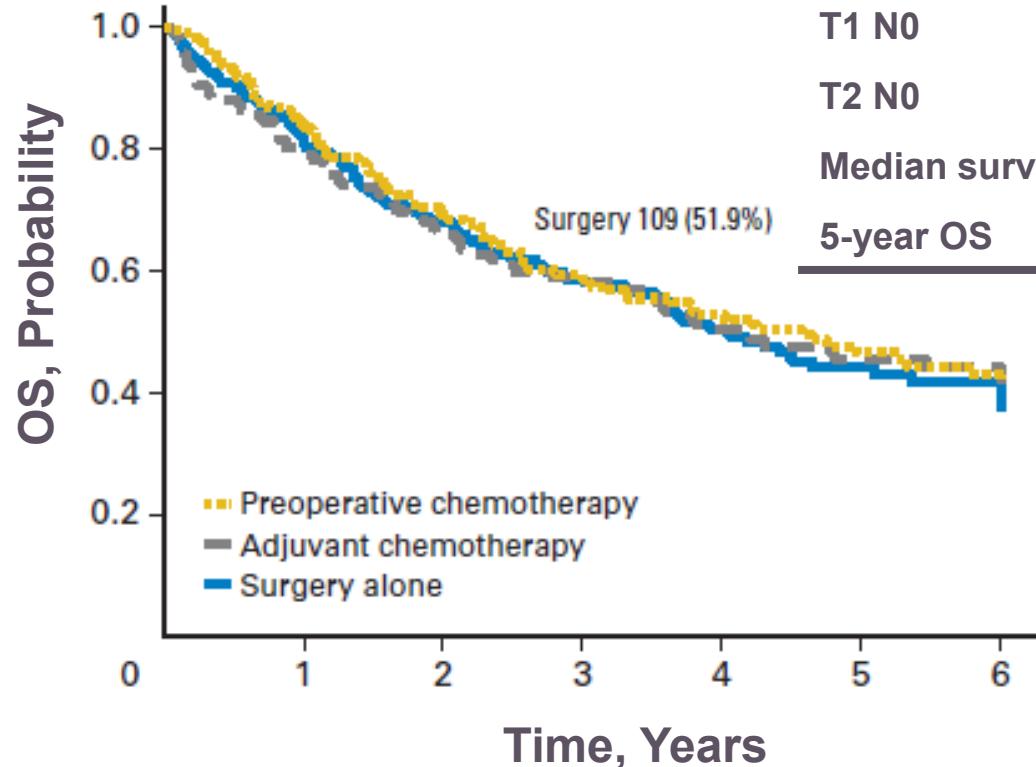


Paclitaxel 200 mg/m² + carboplatin AUC 6 /3 weeks

AUC, area under the curve

Felip E, et al. *J Clin Oncol.* 2010;28(19):3138-3145.

NATCH Trial: OS



	Preop	Adj	Surg
T1 N0	8%	14%	10%
T2 N0	66%	63%	64%
Median survival, months	55.2	50.3	48.8
5-year OS	46.6%	45.5%	44%

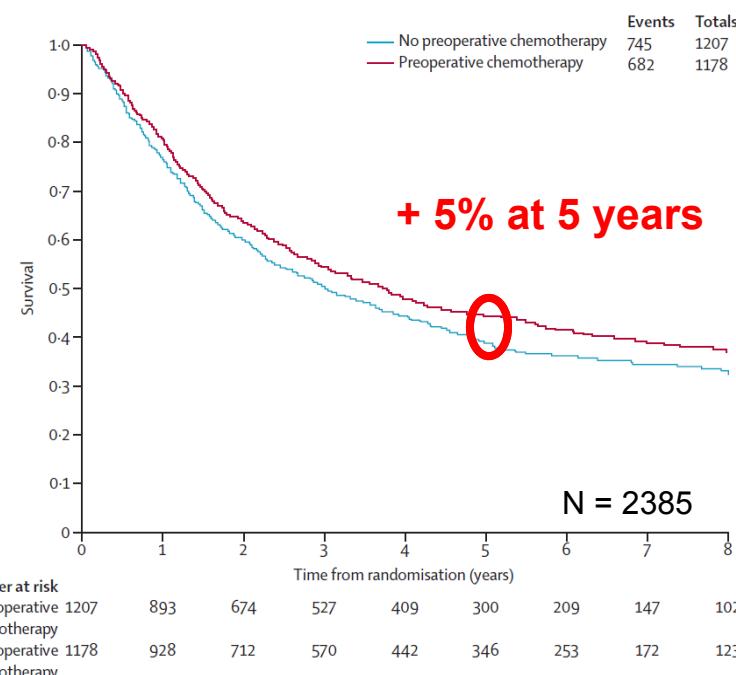
No. at risk	1	2	3	4	5	6
Preoperative	165	131	99	71	45	31
Adjuvant	161	121	90	65	40	29
Surgery	168	131	105	72	40	27

Surg vs Adj: HR = 0.99 (0.75-1.3); P = .93 - Surg vs Preop: HR = 0.96 (0.84-1.1); P = .56

Felip E, et al. J Clin Oncol. 2010;28(19):3138-3145.

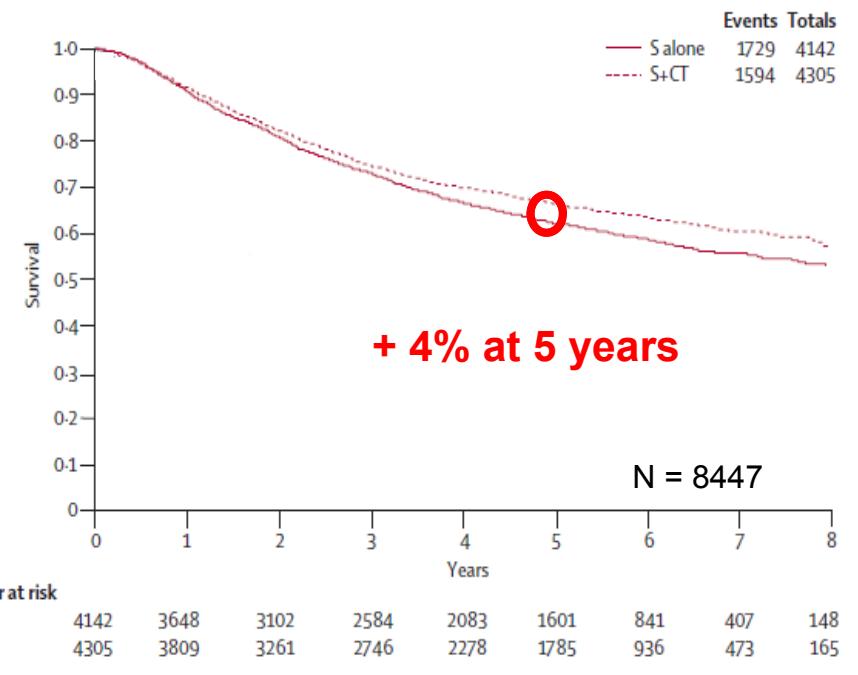
Survival Benefit of Neoadjuvant and Adjuvant Chemotherapy

Neoadjuvant CT¹



HR = 0.87, 95% CI 0.78-0.96; P = .007

Adjuvant CT²



HR = 0.87 95% CI 0.81-0.93; P<.000001

1. NSCLC Meta-Analyses Collaborative Group. *Lancet*. 2014;383(9928):1561-1571. 2. NSCLC Meta-Analyses Collaborative Group. *Lancet*. 2010;375(9722):1267-1277.

BEACON Trial: Bevacizumab Perioperative

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

Nonsquamous: Bevacizumab (BEV) + CIS-Docetaxel (DC) x 4 → surgery → BEV (15 mg/kg x 3 week/1 year)

Squamous: DC x 4 → surgery → BEV (15 mg/kg x 3 week/1 year)

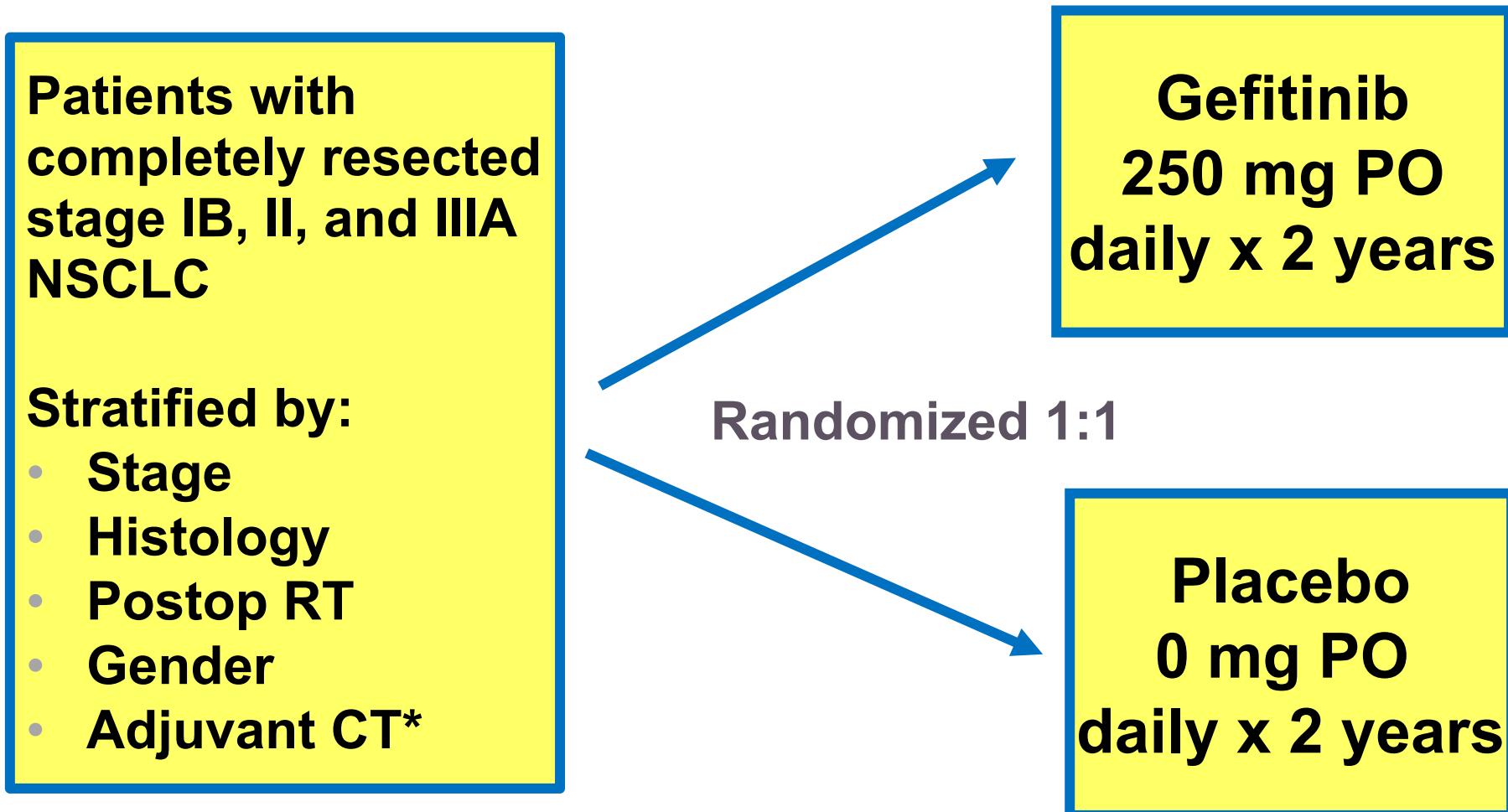
	BEV+DC (n = 36)	DC (n = 11)
ORR	58%	40%
Downstaging	44%	27%
Postop toxicity Grade 3/4	16%	9%

ORR, overall response rate

Price K, et al. *J Clin Oncol.* 2009;27(15S): Abstract 7531.

Adjuvant EGFR TKI

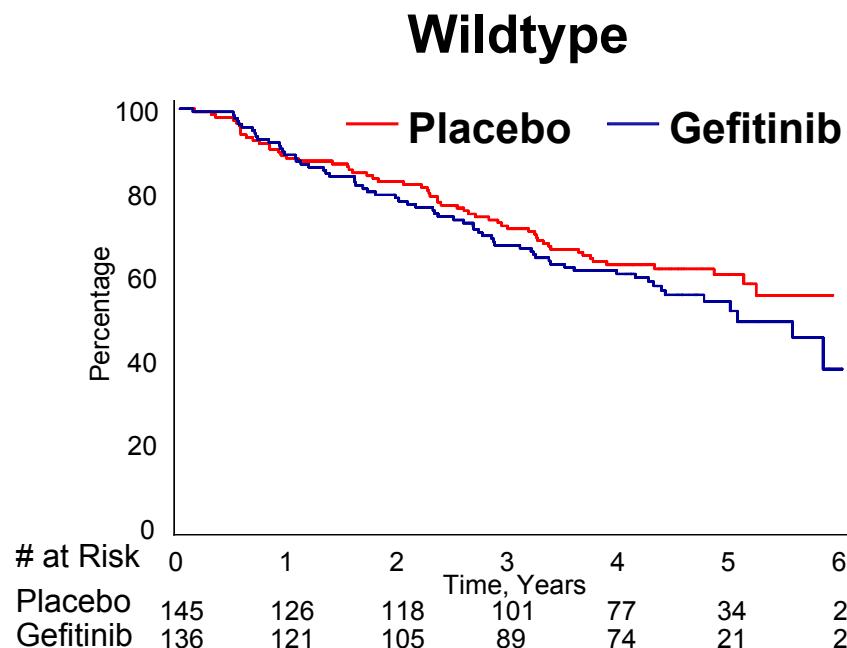
BR.19: Trial Design



*Protocol amended January 2003 to allow adjuvant chemotherapy which became a stratification factor

Goss GD, et al. *J Clin Oncol.* 2010;28(15S): Abstract LBA7005.

BR.19 Trial: OS by EGFR Mutation Status and Treatment

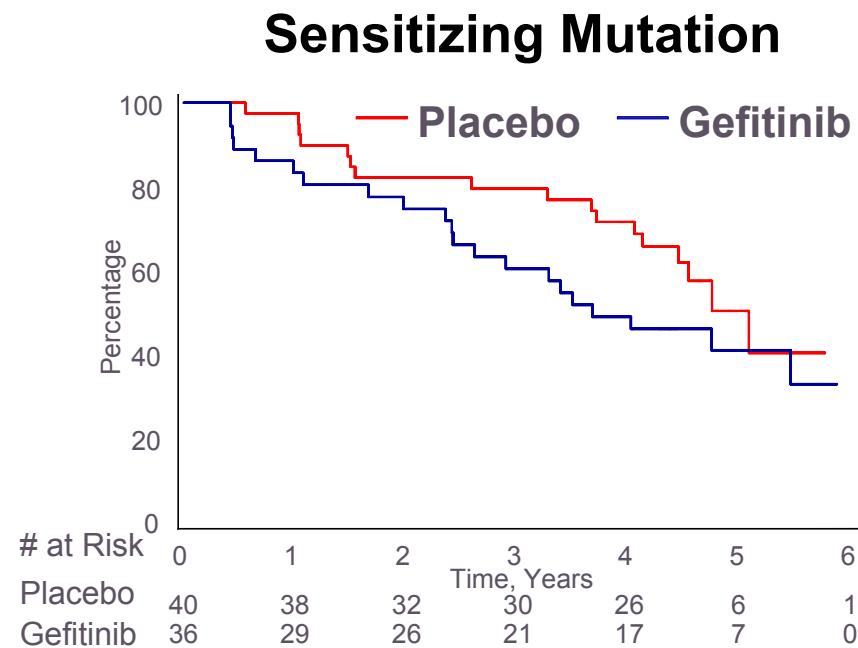


HR (95% CI)

Gefitinib/Placebo: 1.21 (0.84, 1.73)
Log Rank: $P = .301$

Median (95% CI)

- Placebo: Not reached (5.1, inf.)
- Gefitinib: 5.0 (4.3, inf.)



HR (95% CI)

Gefitinib/Placebo: 1.58 (0.83, 3.00)
Log Rank: $P = .160$

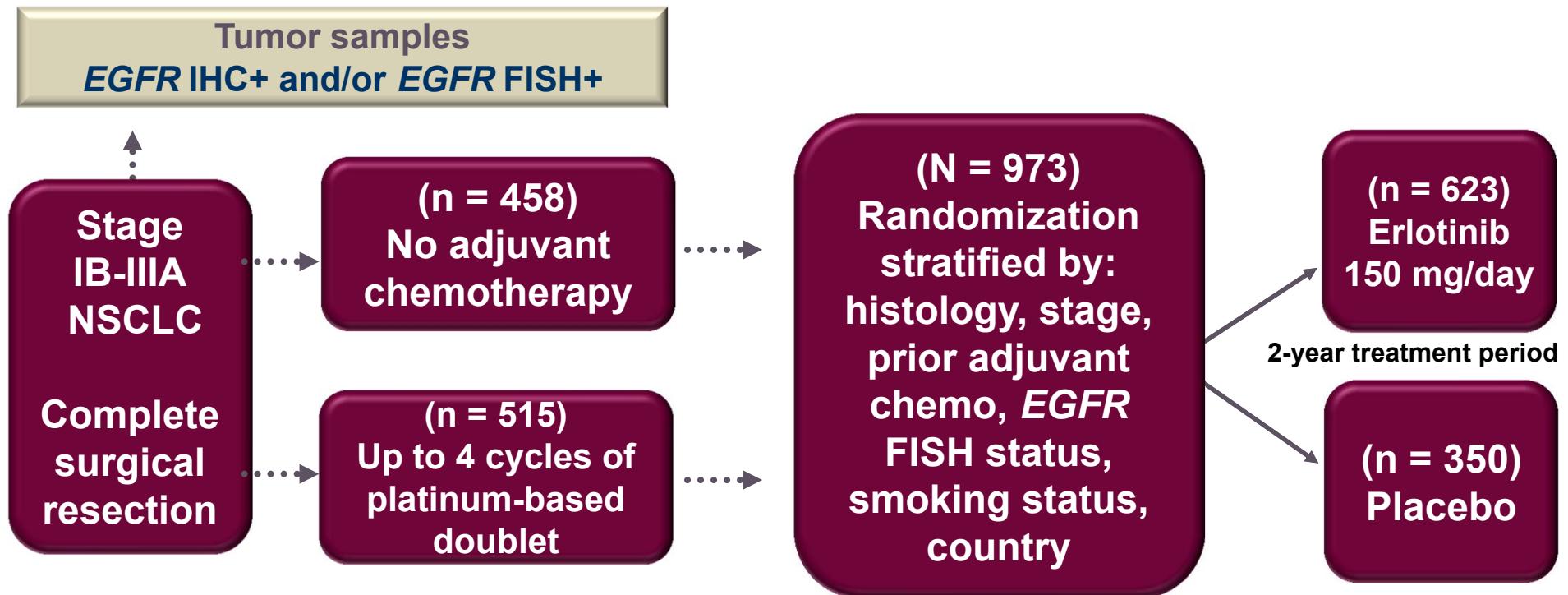
Median (95% CI)

- Placebo: 5.1 (4.4, inf.)
- Gefitinib: 3.7 (2.6, inf.)

Goss GD, et al. J Clin Oncol. 2010;28(15S):Abstract LBA7005.

Goss asco 2010

RADIANT: Trial Design



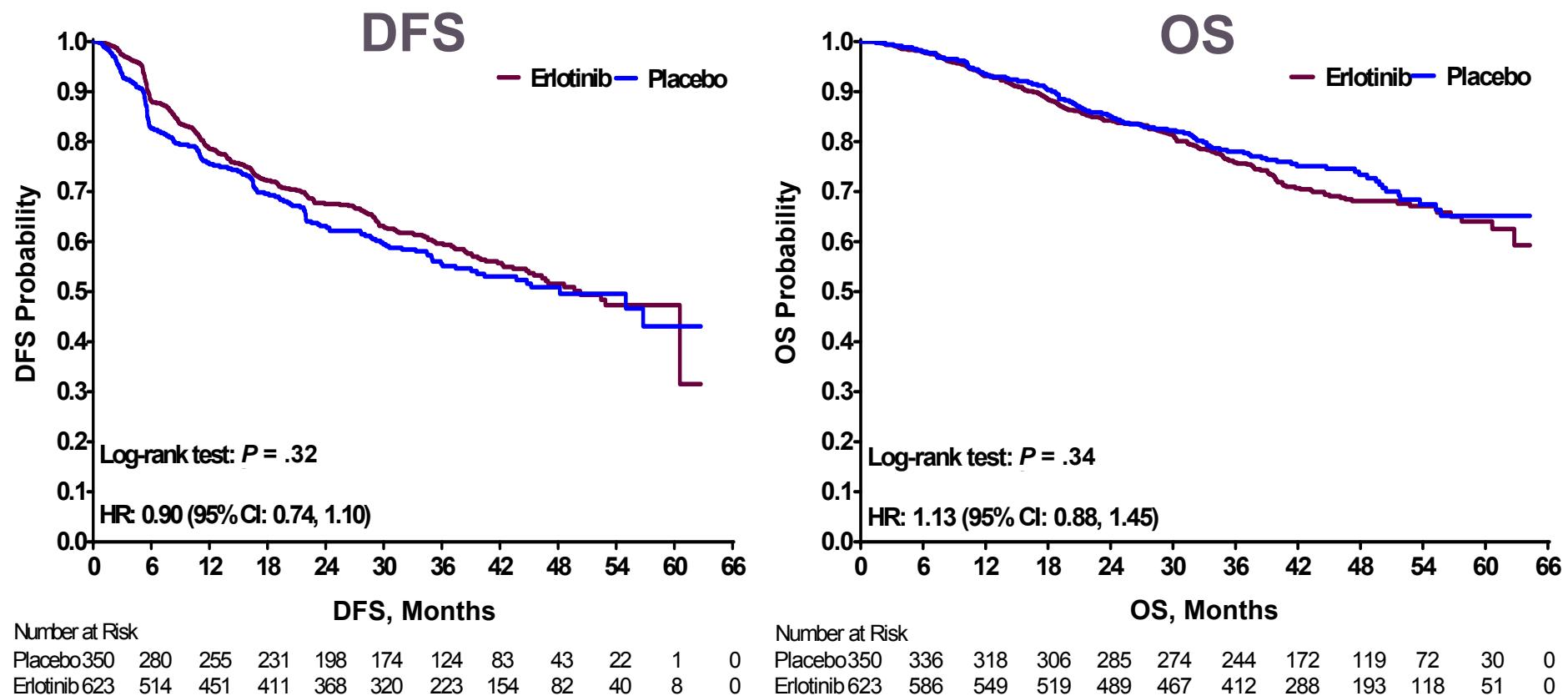
- **Radiology assessment:** Every 3 months on treatment and yearly during long-term follow up
- **Primary endpoint:** DFS
- **Secondary endpoints:** OS; DFS and OS in patients with del19/L858R (*EGFR M+*)

Data cut-off date: 8 Apr 2013

EGFR M+, *EGFR*-activating mutations; FISH, fluorescent *in situ* hybridization
Shepherd FA, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1174O.

RADIANT: DFS and OS

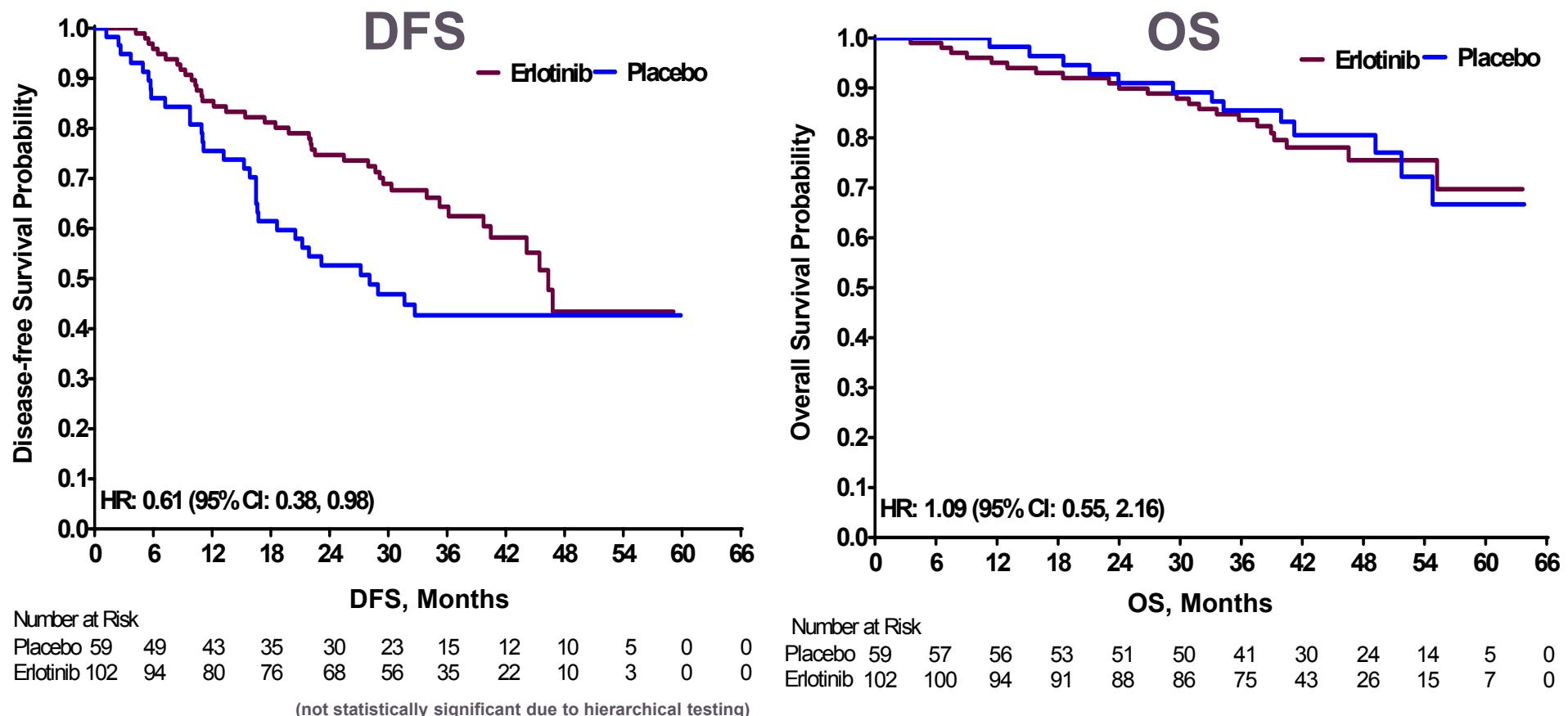
All Randomized Patients



Shepherd FA, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1174O.

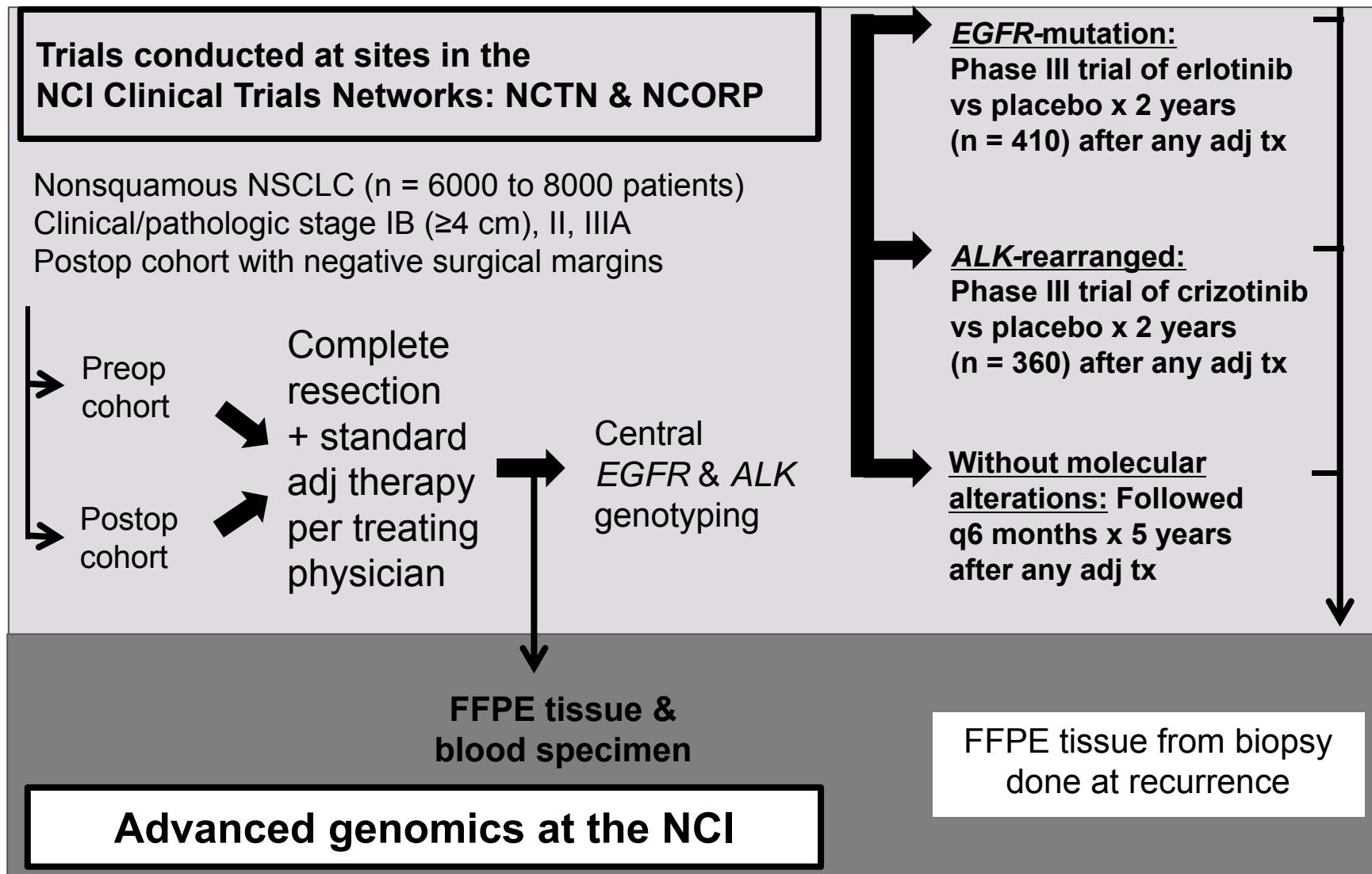
RADIANT: DFS and OS

EGFR M+ Subgroup



Shepherd FA, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1174O.

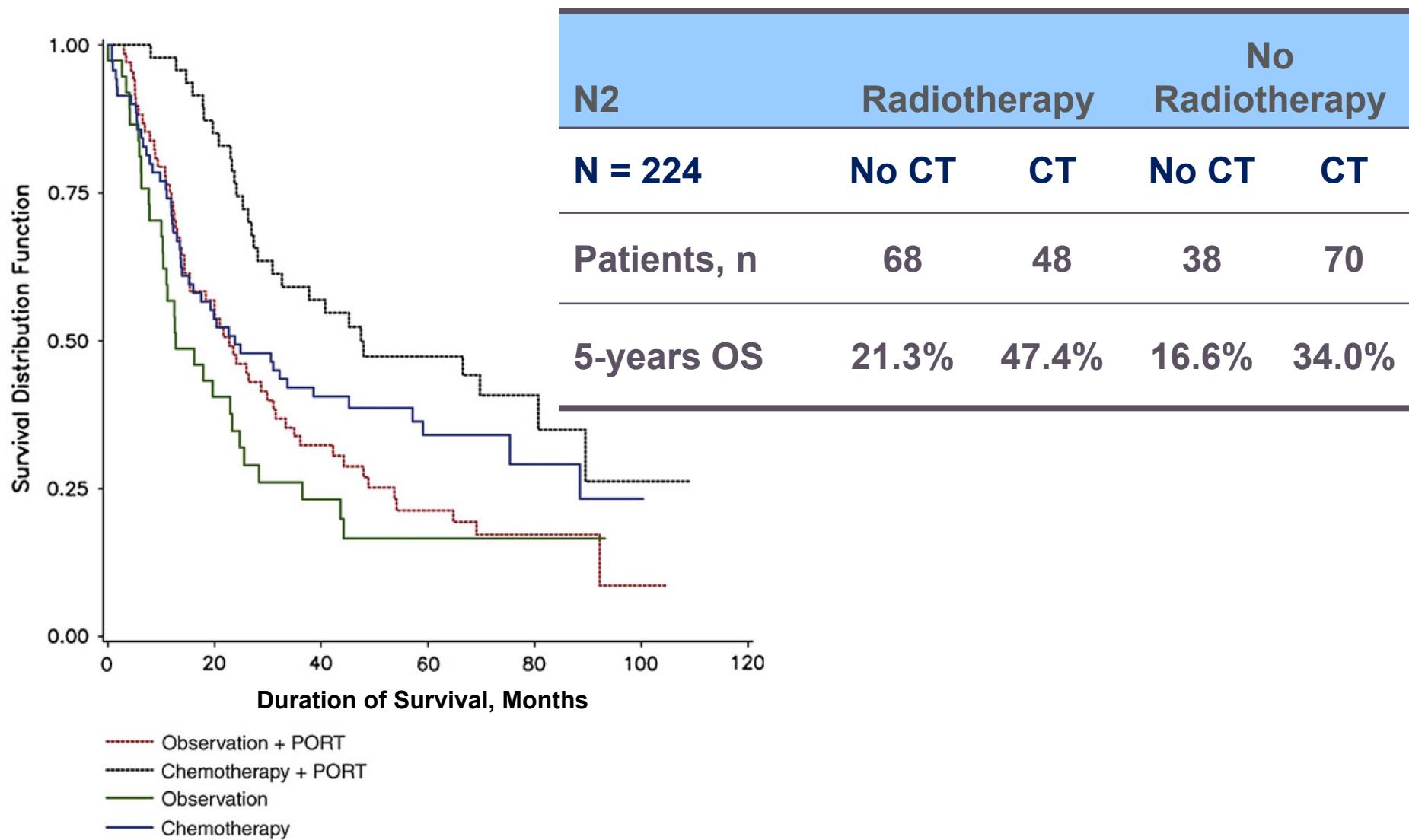
Ongoing Initiative: ALCHEMIST Trial



1. National Institutes of Health. Available at: <http://clinicaltrials.gov/ct2/show/NCT02194738>. Accessed 10 December 2014.
2. National Institutes of Health. Available at: <http://clinicaltrials.gov/ct2/show/NCT02193282>. Accessed 10 December 2014.
2. National Institutes of Health. Available at: <http://clinicaltrials.gov/ct2/show/NCT02201992>. Accessed 10 December 2014.

Adjuvant Radiotherapy

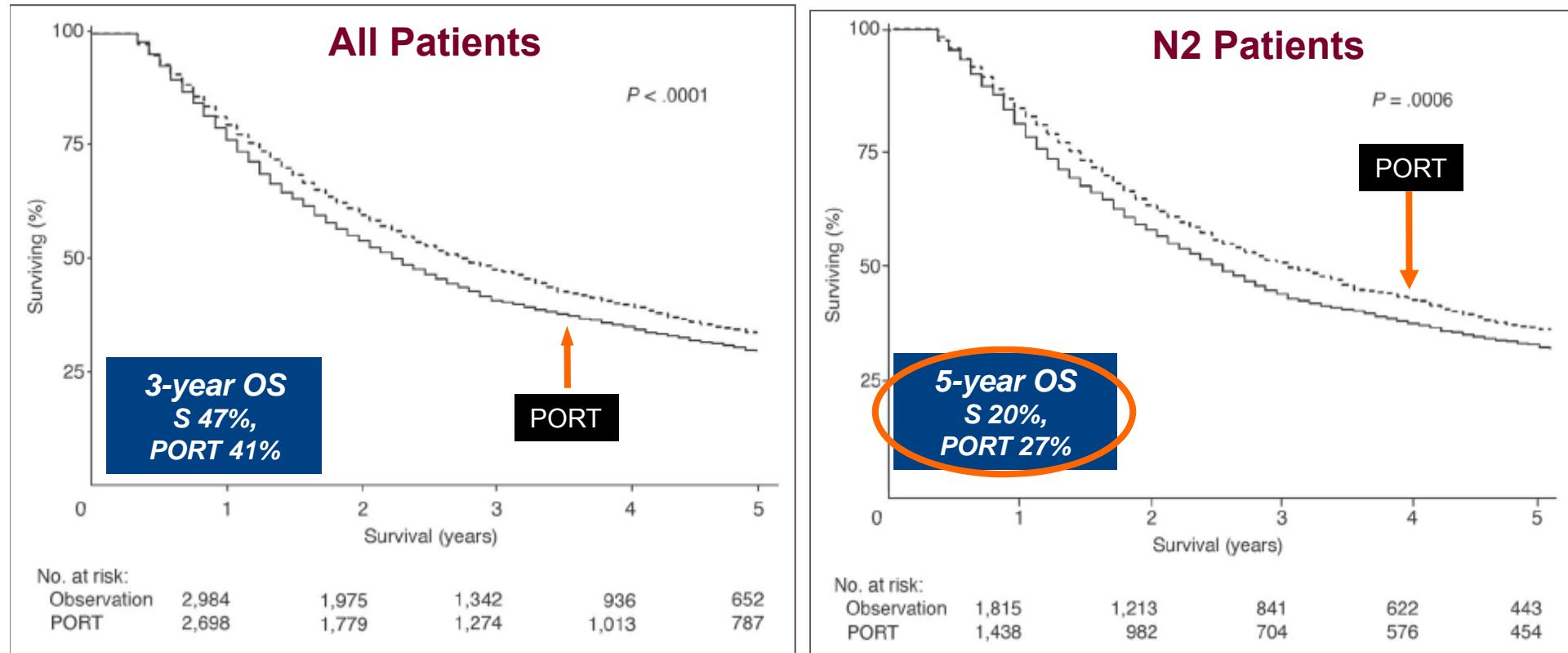
PORT in N2 Patients



Douillard JY, et al. *Int J Radiat Oncol Biol Phys.* 2008;72(3):695-701.

Postoperative Radiotherapy (PORT) in 7465 Resected Stage II-III NSCLC Patients

SEER Database

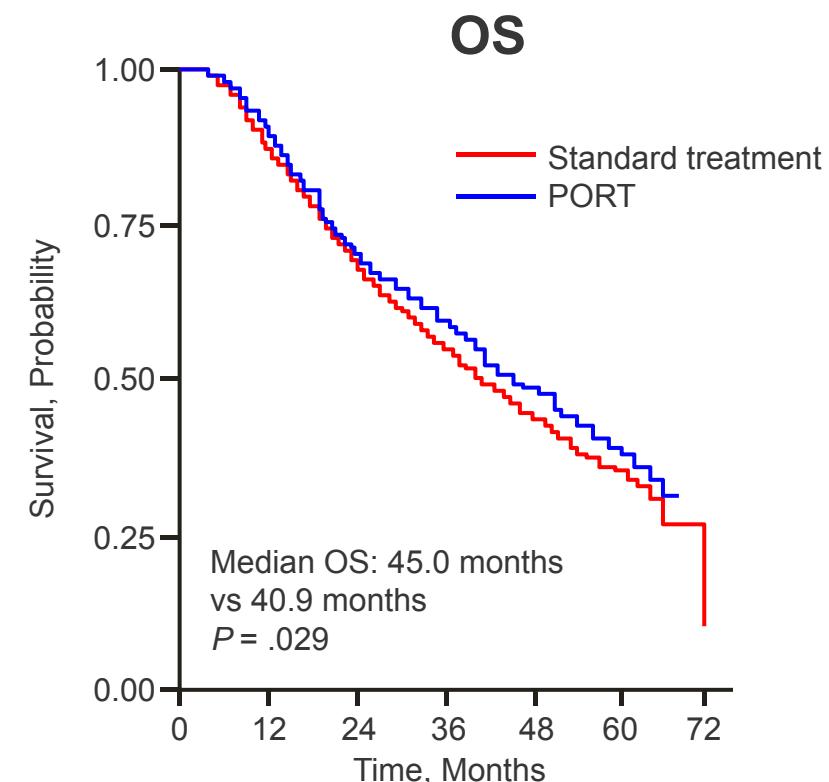


Surg + PORT: Increased survival in N2 patients ($P < .04$)
No adjuvant CT in most patients

PORT in pN2 Patients Treated With Adjuvant Chemotherapy

Key results

- In multivariate analysis, younger age, treatment at an academic facility, higher income, lower Charlson score, smaller tumor, lobectomy, and use of PORT (HR for PORT 0.89 [95% CI 0.80, 0.99]; $P = .029$) were predictive of improved OS for the entire group
- Use of PORT was associated with a significant increase in median OS (figure)

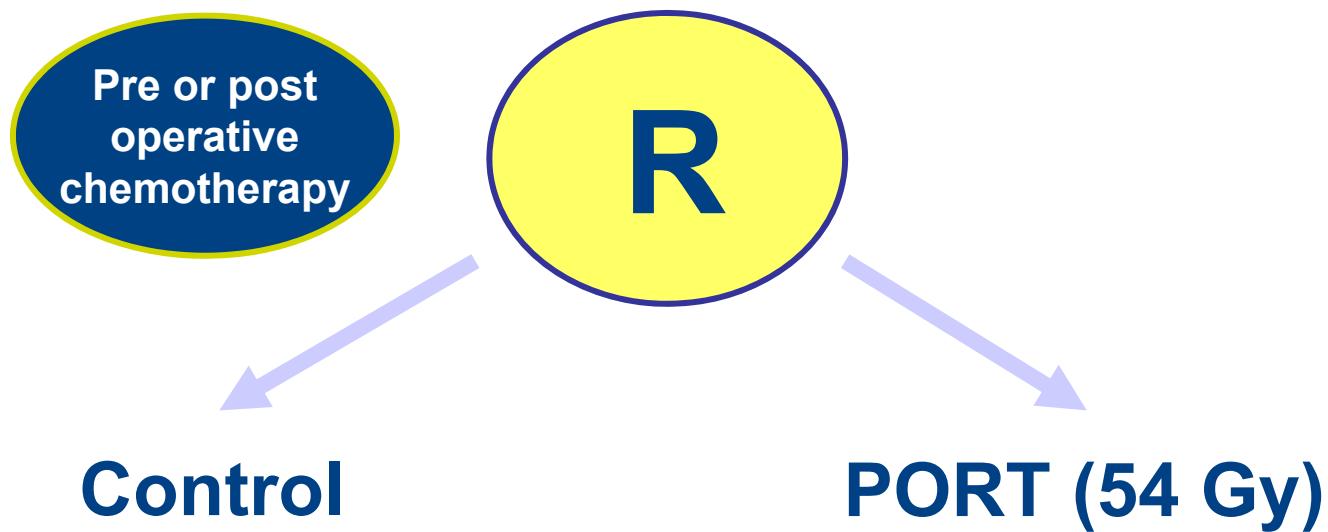


Conclusion

- Modern PORT may confer an additional 5% survival advantage in NSCLC patients after complete resection beyond that achieved with adjuvant CT alone

Lung ART IFCT 05-03 EORTC 22055-08053

Patients With Resected pN2 NSCLC



Ongoing study: Enroll patients!

Principal Investigator: Cécile Le Pechoux (cecile.lepechoux@igr.fr)

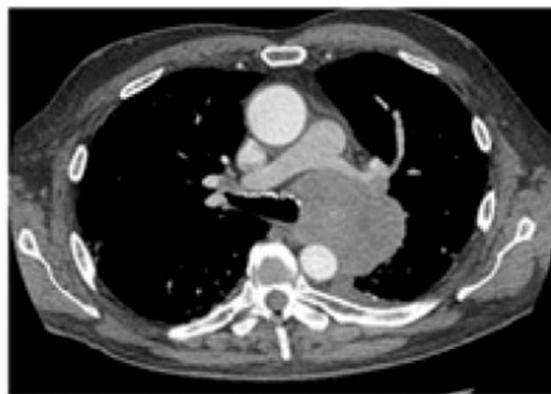
My Options

- **Surgery upfront**
- **Adjuvant chemotherapy**
 - 4 cycles, q4w
 - Vinorelbine 25 mg/m² d1, d8, d15, d21
 - Cisplatin 100 mg/m² d1
- **Inclusion in LungART for adjuvant RT**
- **No impact of *EGFR* mut on the strategy in this setting**
- **Follow-up for 5 years at least**
 - Chest CT scan, each 6 months for 3 years than each year
 - Discuss brain imaging in the follow-up

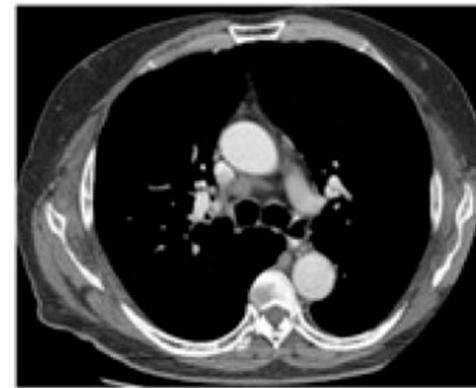
Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part III

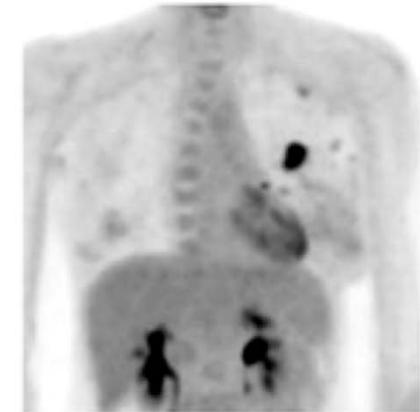
Umberto Ricardi, MD, PhD
University of Turin
Turin, Italy



Mediastinal Infiltration

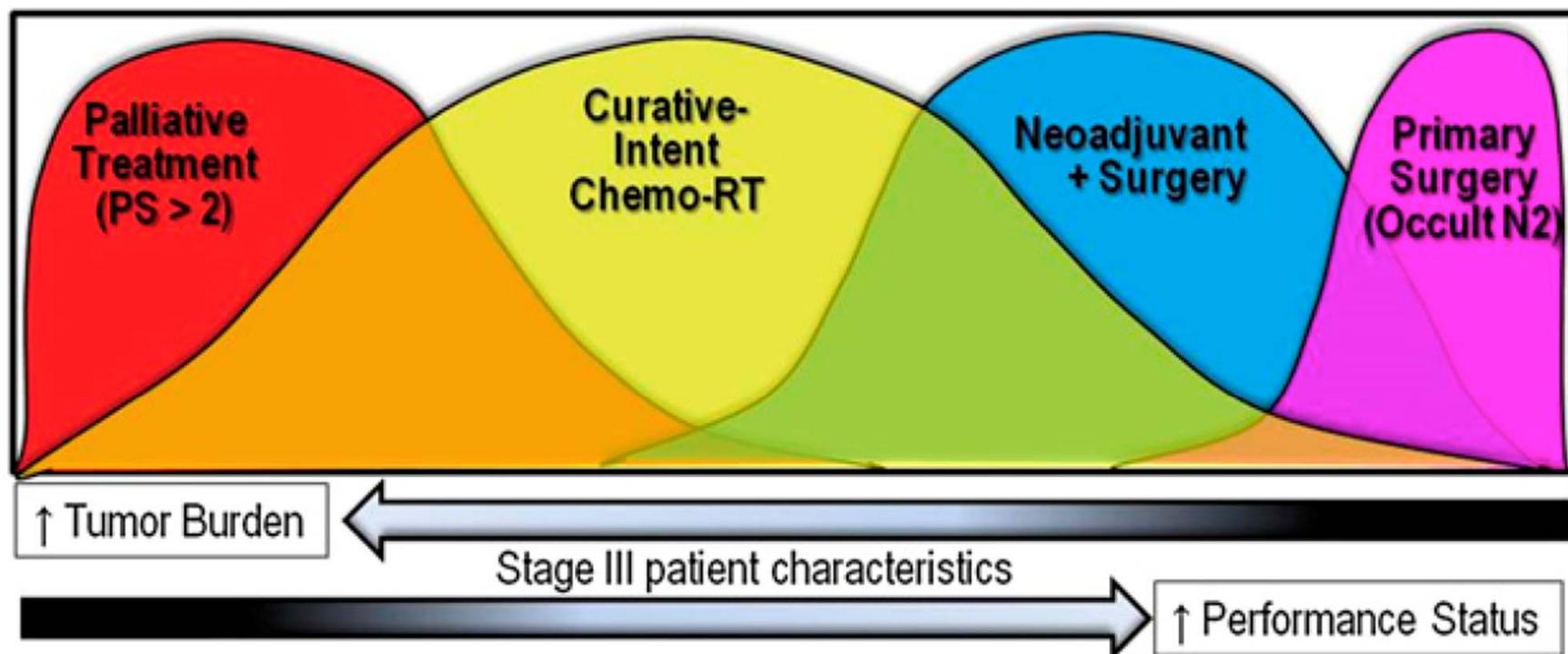


Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches



Good PS Stage III NSCLC

What Positive Level 1 Evidence Do We Have?

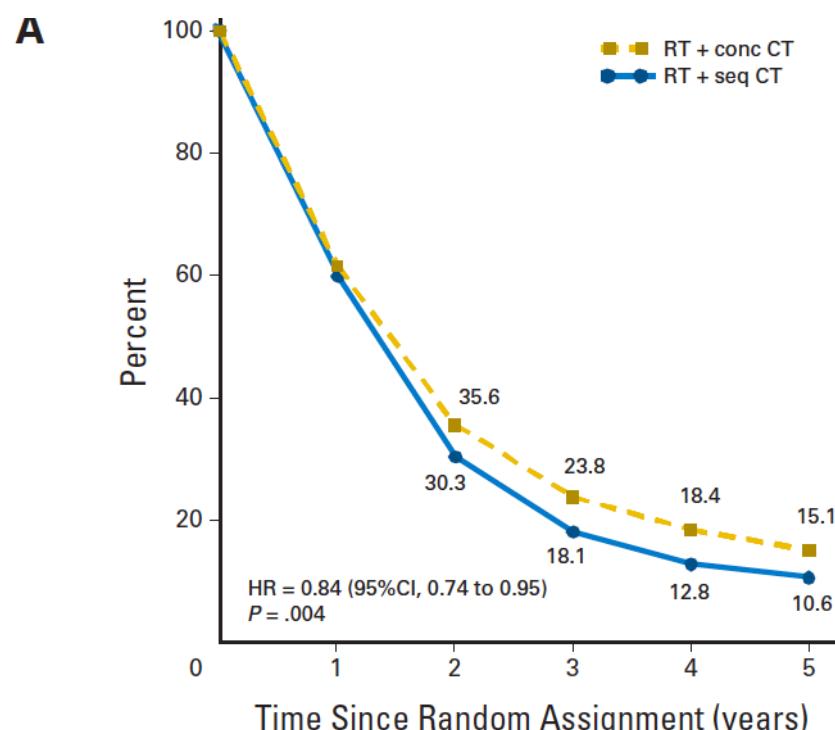
- Chemo-RT:
 - Better survival than RT alone
- Concurrent chemo-RT:
 - Better survival than sequential chemo-RT

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

Absolute survival benefit with concomitant chemoradiotherapy:

- **5.7% at 3 years**
- **4.5% at 5 years**

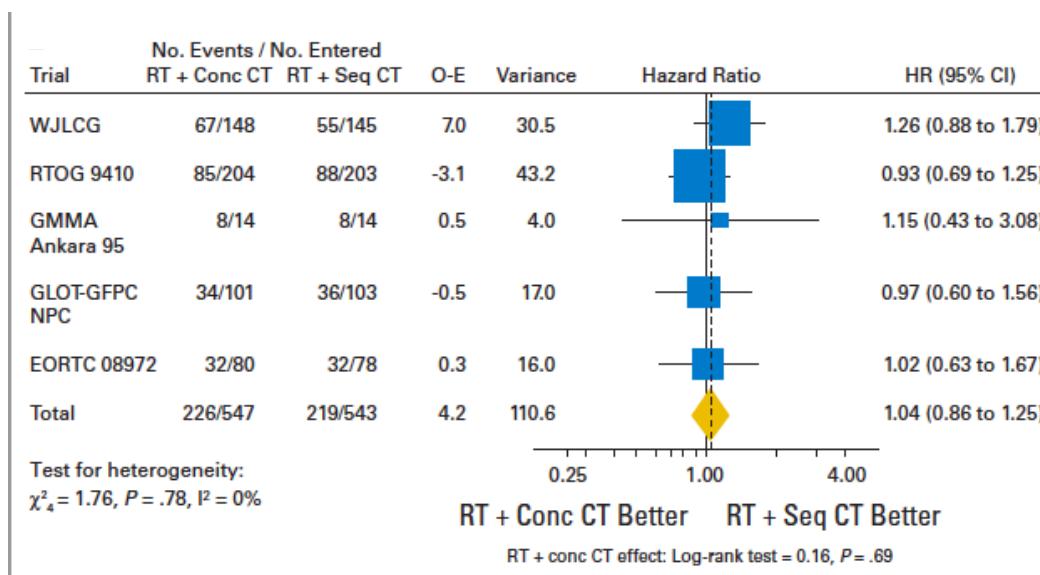
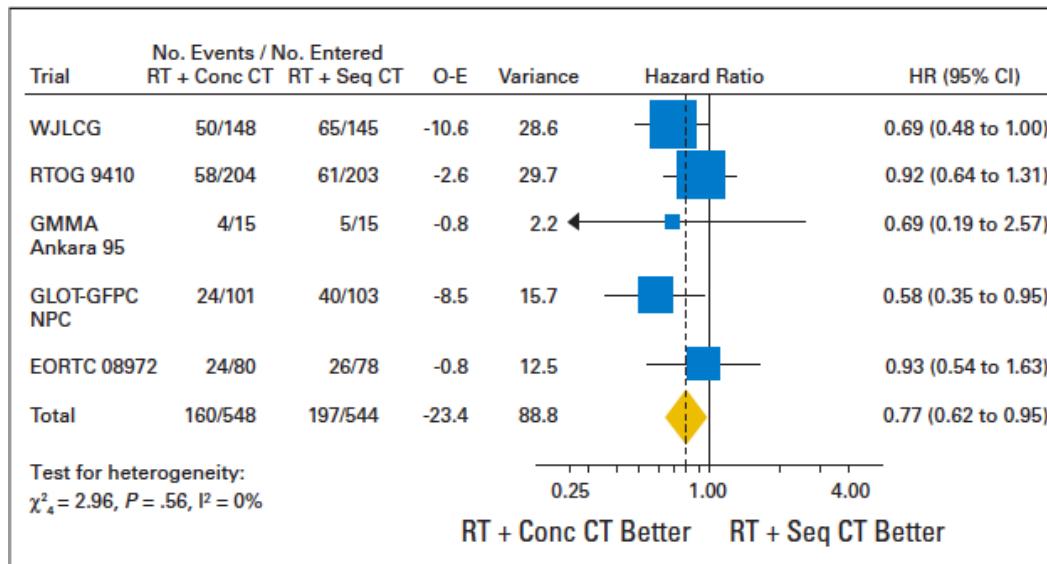


CI, confidence interval; CT, chemotherapy; HR, hazard ratio

Aupérin A, et al. *J Clin Oncol*. 2010;28(13):2181-2190.

	0y-1y	1y-2y	2y-3y	3y-4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/83	23/126

Hazard Ratio Plots for Local Progression and Distant Progression



Results

Of seven eligible trials, data from six trials were received (1,205 patients, 92% of all randomly assigned patients). Median follow-up was 6 years. There was a significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; $P = .07$). Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; $P = .01$); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; $P = .69$).

Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; $P < .001$). There was no significant difference regarding acute pulmonary toxicity.

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

- The preferred treatment of unresectable LA-NSCLC is definitive concurrent chemotherapy and radiotherapy [I, A]
- Definitive thoracic radiotherapy should be no less than the biological equivalent of 60 Gy in 2.0 Gy fractions [I, A]
- In patients who are unfit to receive concurrent chemotherapy and radiotherapy, the sequential approach should be offered as an alternative treatment with curative intent [I, A]

Concurrent CT-RT Is Not the Standard Treatment in Locally Advanced NSCLC, Unless Treating Only:



Highly “FIT” patients

- Age
- Performance status
- Weight loss
- Pulmonary function tests
- Stage/tumor burden
- Dose to critical organs

Dutch Statistics on Lung Cancer
Sobering Experience for a New Approach

Matjaz Zwitter, MD, PhD

- Half of patients with NSCLC did not receive treatment according to the well accepted guidelines
- EBM is based on selected series of patients and is not applicable to an average patient in clinical practice
- Stage III NSCLC: The gap between an ideal patient from the guidelines and the average patient from clinical practice is especially wide
- Vast majority of patients present bulky tumors and/or suffer from significant comorbidity

Current Standard Concurrent Chemoradiotherapy

Induction
Chemo
?



Concurrent
Chemo/RT

Concurrent
Chemo/RT

Concurrent
Chemo/RT



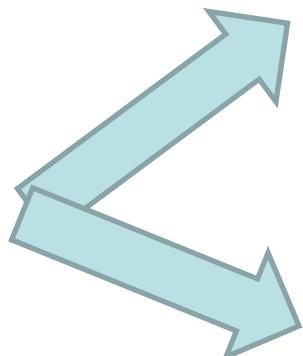
Consolidation
Chemo
?

Good PS Stage III NSCLC: What Negative/Null Evidence Do We Have?

- Induction chemotherapy
 - No advantage when added to concurrent chemo-RT
- Consolidation chemotherapy
 - No advantage when added to concurrent chemo-RT

CALGB 39801: Trial Design

R
E
G
I
S
T
E
R



A (Concurrent Chemo/RT)

Paclitaxel 50 mg/m² IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total)

B (Induction → Concurrent Chemo/RT)

Paclitaxel 200 mg/m² IV/3h
Carboplatin AUC 6 IV/30 min
q 21 days for a total of 2 cycles

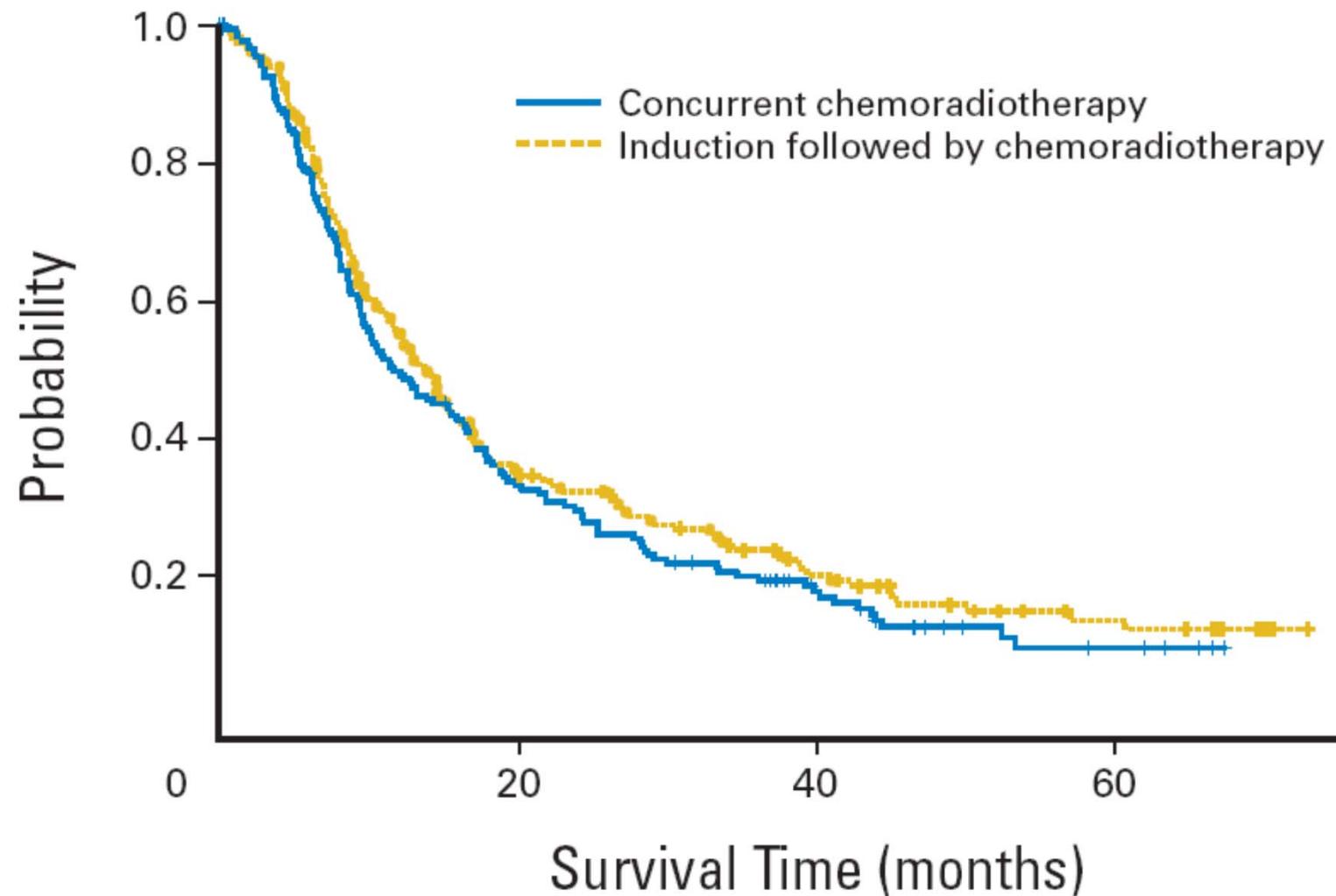


Paclitaxel 50 mg/m² IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total) (d 43)

AUC, area under the curve

Vokes EE, et al. *J Clin Oncol*. 2007;25(13):1698-1704.

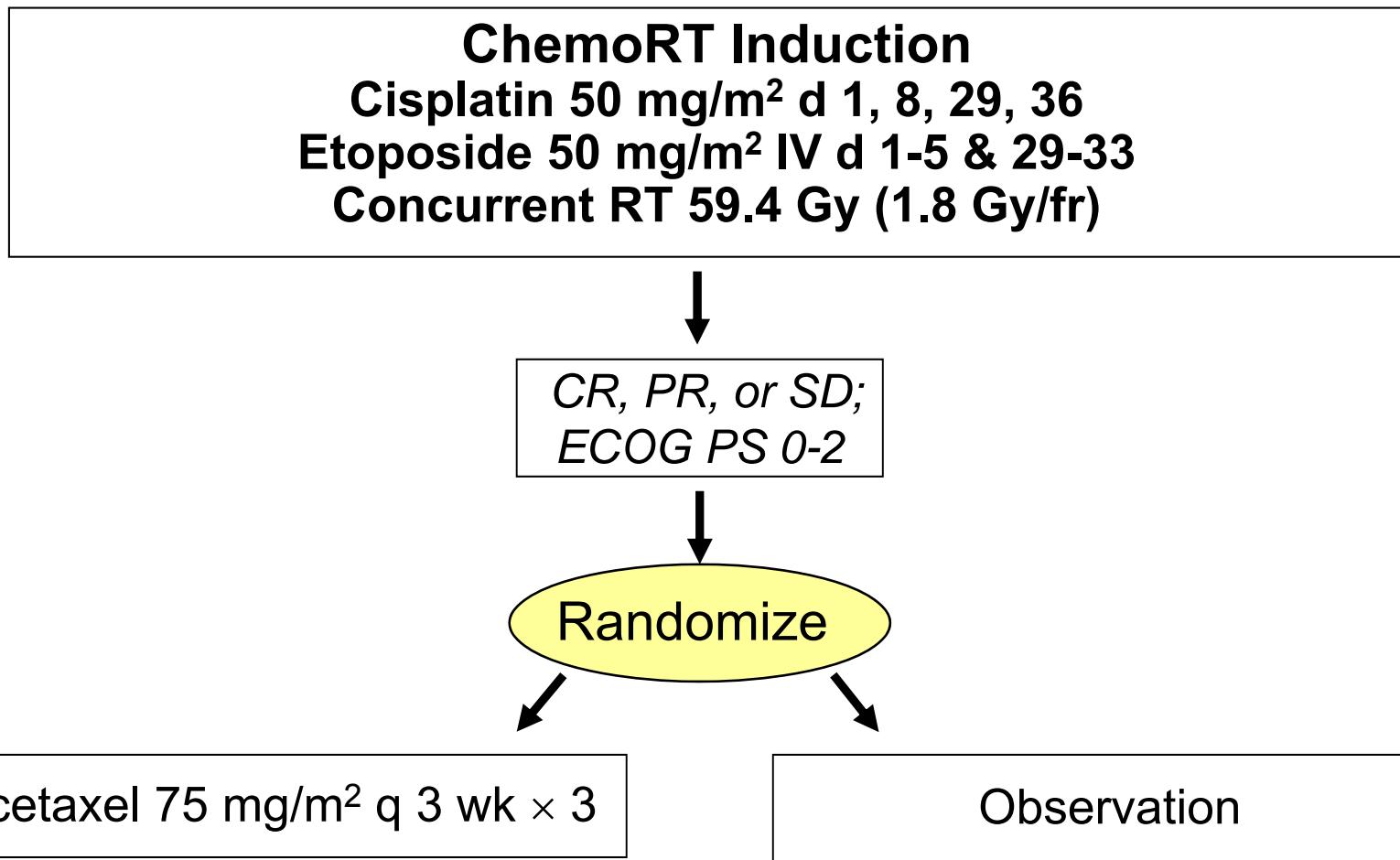
CALGB 39801: Overall Survival (OS) Intent-to-Treat (ITT)



ITT, intent-to-treat

Vokes EE, et al. *J Clin Oncol*. 2007;25(13):1698-1704.

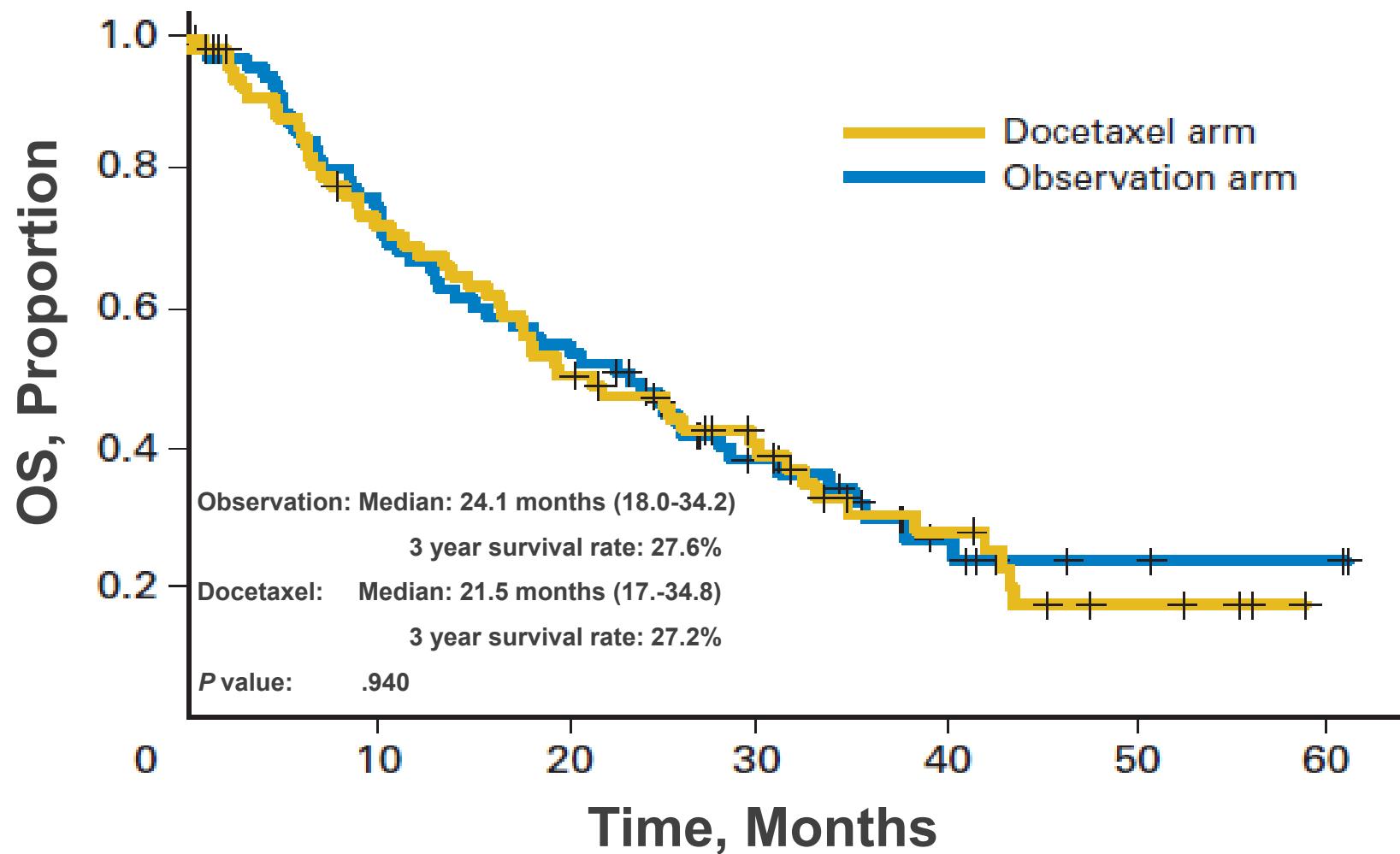
Optimizing Chemotherapy: Confirmation Study for Consolidation Hoosier Oncology Group (LUN 01-24)



CR, complete response; PR, partial response; SD, stable disease
Hanna N, et al. J Clin Oncol. 2008;26(35):5755-5760.

LUN 01-24: OS (ITT)

Randomized Patients (n = 147)



Hanna N, et al. *J Clin Oncol*. 2008;26(35):5755-5760.

Treatment Algorithm For Locally Advanced NSCLC: 2014

Locally Advanced Stage NSCLC & PS 0-1



Unresectable Stage III NSCLC

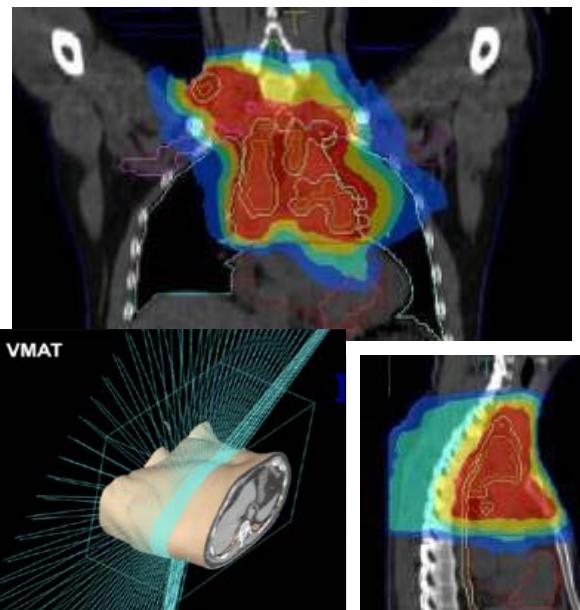
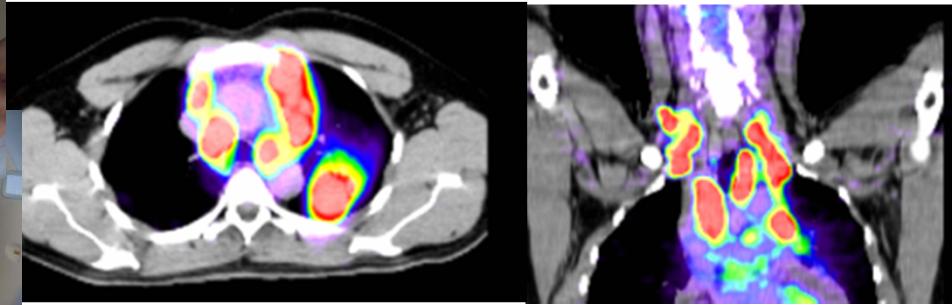
Optimal Radiation Dose

- Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemoradiation**

Image Guided, PET-Assisted Radiotherapy of Lung Cancer

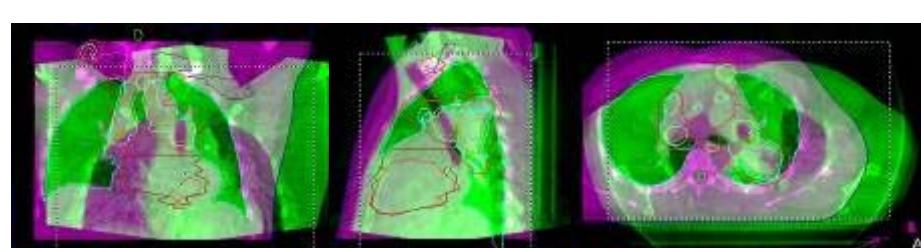
Target Volume Reduction and RT-Optimization for Critical Tumor-to-Lung Ratio

1. **Use of 4D-CT:** Accounting for tumor motion during breathing
2. **CTV-Definition:** Minimization based on functional Imaging (PET-CT) and shift to smaller volumes

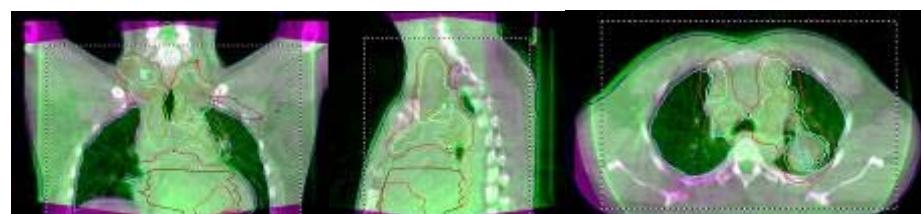


2. **Treatment Planning as IMRT** based on Monte-Carlo dose calculation (dose-painting)

CT, computed tomography



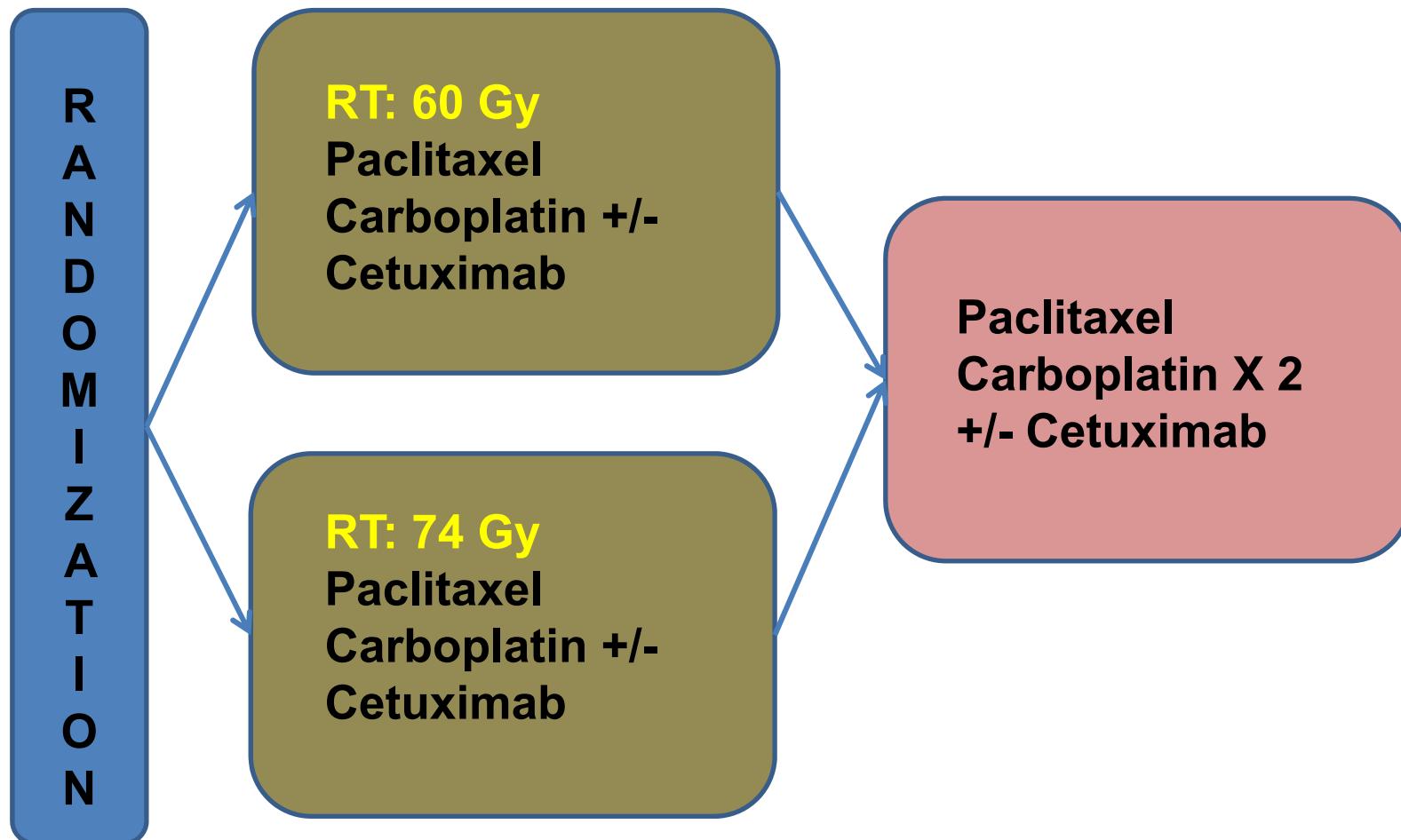
Suboptimal Positioning



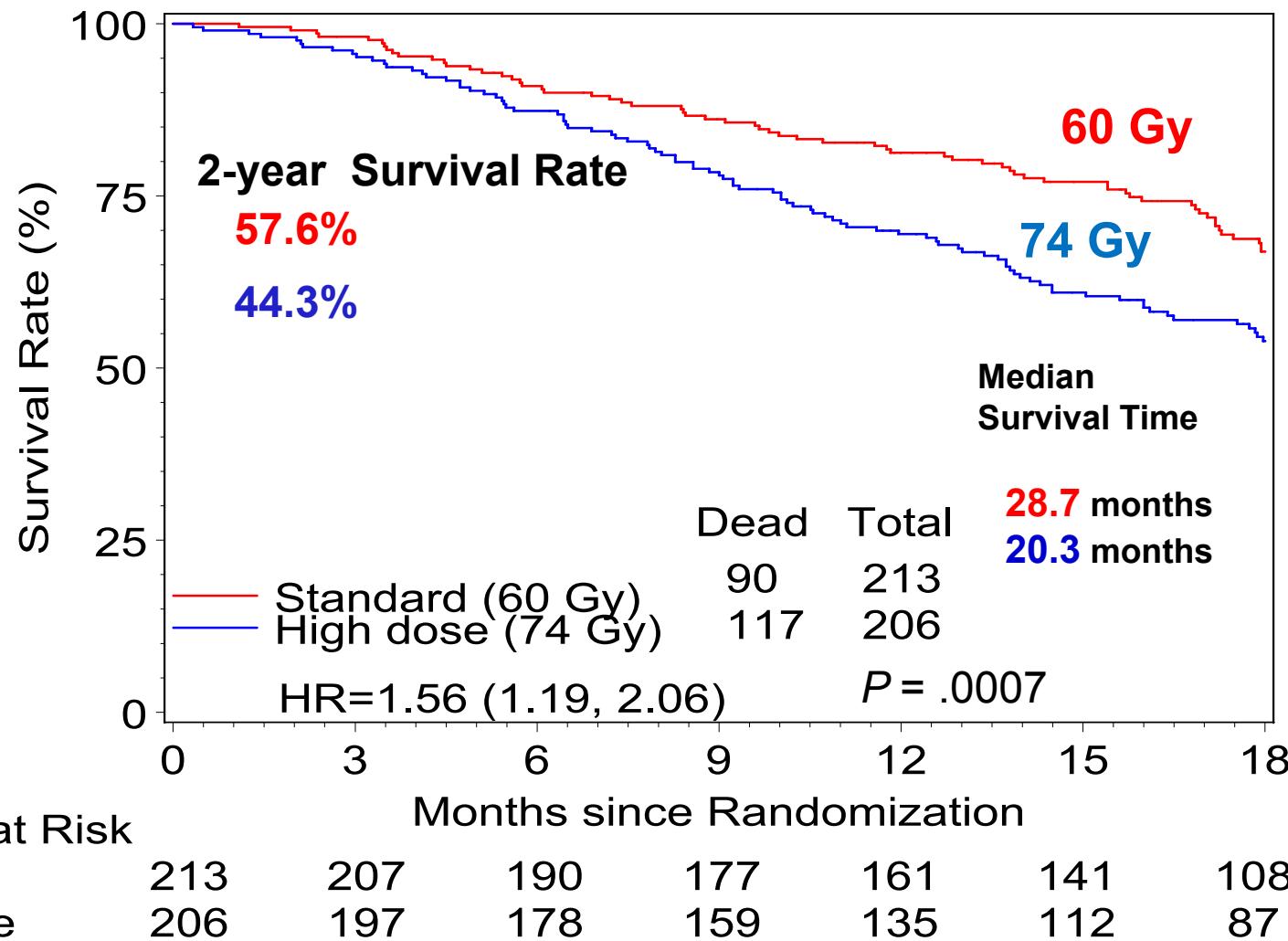
Optimal Positioning

3. **Image Guided Radiotherapy Treatment**
with Cone-Beam-CT at Linac for margins reduction

RTOG 0617, NCCTG N0628, CALGB 30609: Conventional vs High=Dose RT



RTOG 0617: OS

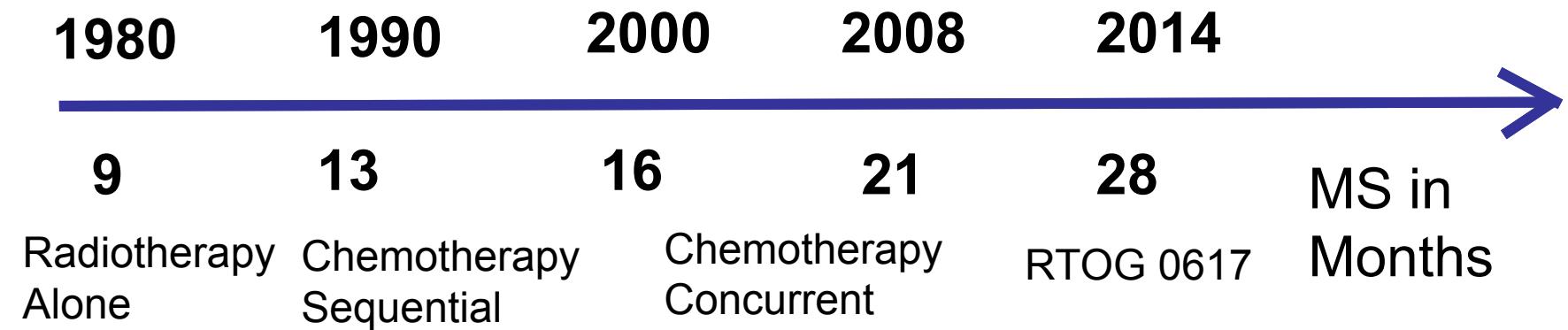


Bradley J, et al. Presented at the American Society for Therapeutic Radiology and Oncology Annual Meeting. Atlanta, Georgia, United States; September 21-25, 2013.

Unresectable Stage III NSCLC

- At present, concurrent chemotherapy with radiotherapy to a dose of 60 Gy in 30 daily fractions is considered to be the standard treatment**

Survival of Stage III NSCLC:



- 1. Stage Migration**
- 2. Concurrent Chemoradiation Therapy**
- 3. Improved Radiation Technology**

Good PS Stage III NSCLC: Lack of Evidence

- Use of any advanced technology RT tools
- **Selection of best chemo to give concurrently with RT**
- Role of induction or consolidation therapy in the context of chemobeam
- Use of targeted agents concurrent with chemo-RT



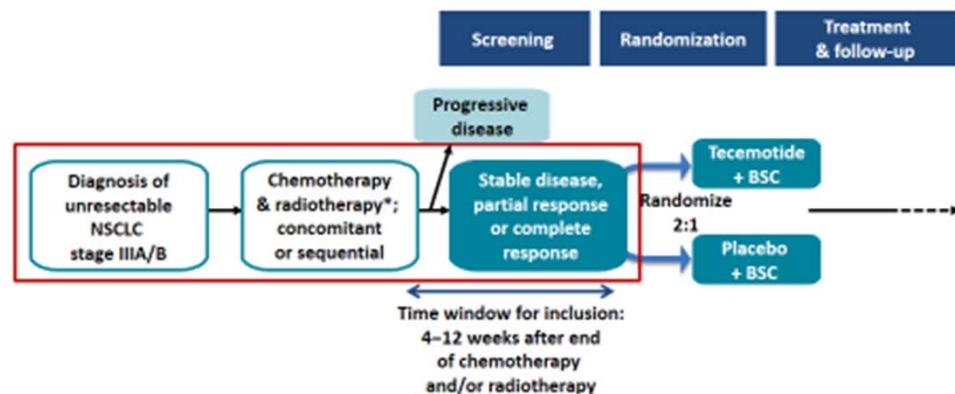
Treatment of Stage III Non-small Cell Lung Cancer

**Diagnosis and Management of Lung Cancer,
3rd ed: American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines**

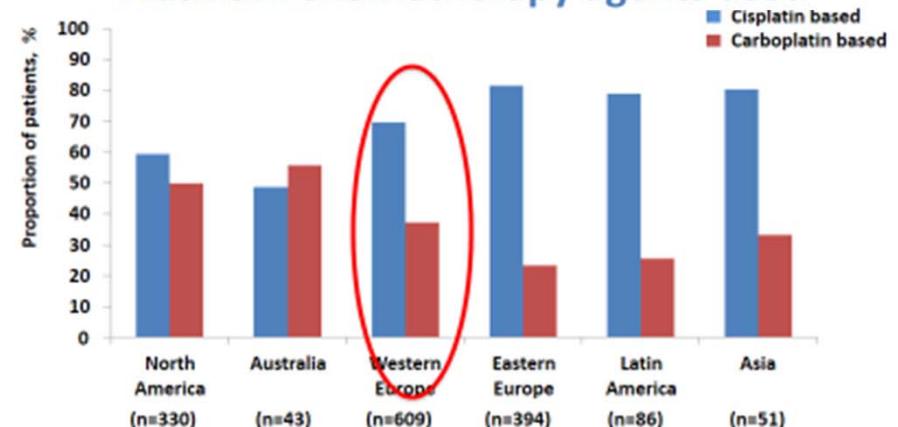
2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (Grade 2C).

Remark: An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC.

Geographic Differences in the Combined-Modality Treatment of Stage III Unresectable NSCLC: Results From a Global Phase III Trial of Tecemotide (L-BLP25)



Platinum chemotherapy agents used



	North America (N=330) n (%)	Australia (N=43) n (%)	Western Europe (N=609) n (%)	Eastern Europe (N=394) n (%)	Latin America (N=86) n (%)	Asia (N=51) n (%)
Carboplatin-based doublet therapy						
Gemcitabine	11 (3.3)	0	43 (7.1)	12 (3.0)	3 (3.5)	2 (3.9)
Paclitaxel	106 (32.1)	21 (48.8)	97 (15.9)	16 (4.1)	13 (15.1)	8 (15.7)
Vinorelbine	8 (2.4)	1 (2.3)	61 (10.0)	55 (14.0)	3 (3.5)	2 (3.9)
Cisplatin-based doublet therapy						
Docetaxel	5 (1.5)	3 (7.0)	63 (10.3)	4 (1.0)	1 (1.2)	14 (27.5)
Etoposide	164 (49.7)	19 (44.2)	57 (9.4)	46 (11.7)	28 (32.6)	3 (5.9)
Gemcitabine	3 (0.9)	0	83 (13.6)	42 (10.7)	11 (12.8)	3 (5.9)
Vinorelbine	22 (6.7)	0	187 (30.7)	211 (53.6)	11 (12.8)	7 (13.7)

Thatcher N, et al. *J Thorac Oncol*. 2013;8(Suppl 2): Abstract O02.01.

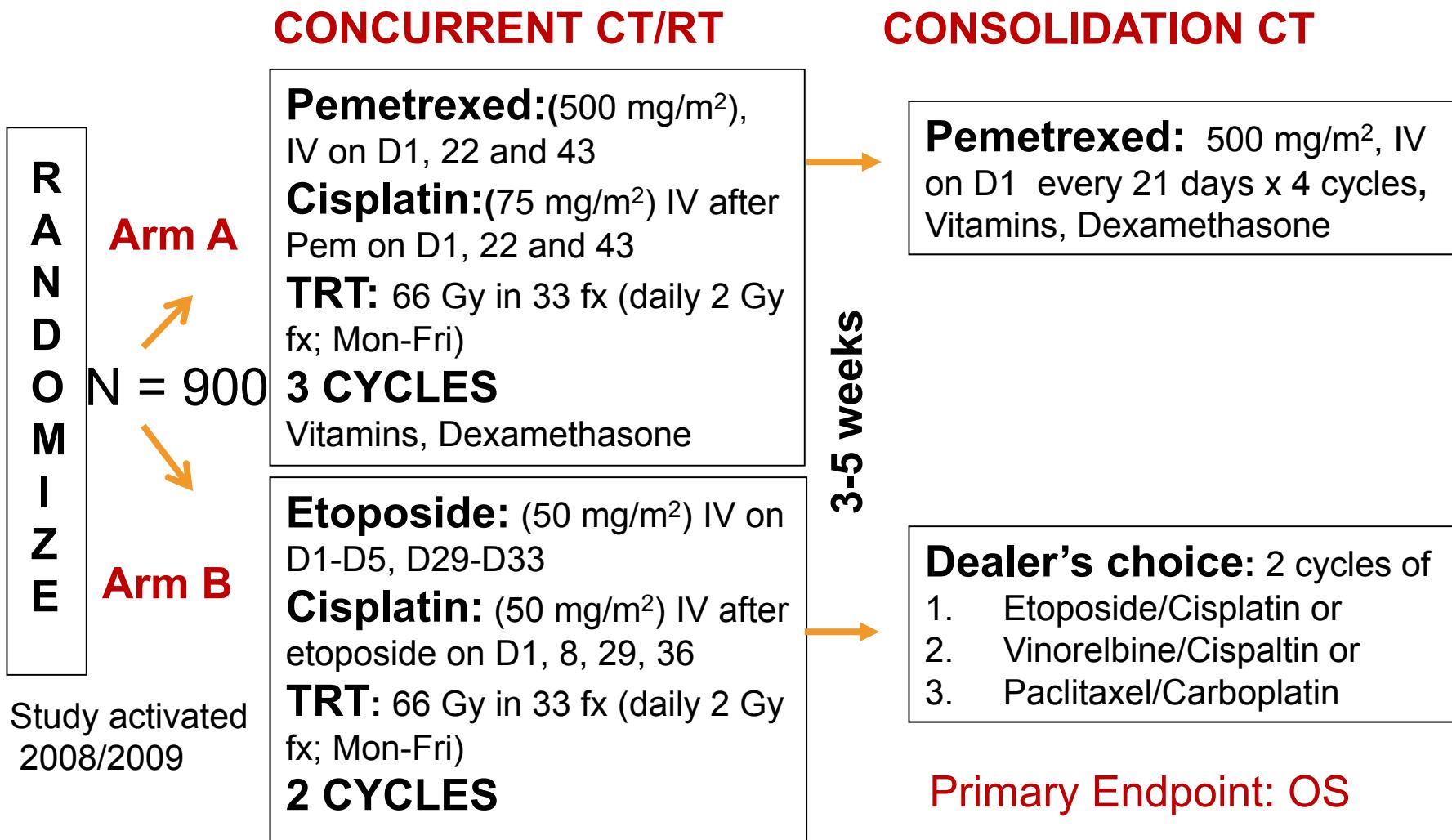
Locally Advanced NSCLC

Future Directions

- Better staging and stratification
- **Improved systemic therapy**
 - New chemotherapy platform
 - Patient selection
- Continued improvement of radiation therapy
- Careful integration of molecularly targeted therapy
- Good supportive care and pulmonary rehabilitation
- Post therapy risk stratification

PROCLAIM: Phase III International Trial

Stage III NSCLC (Closed)



Locally Advanced NSCLC

Future Directions

- Better staging and stratification
- Improved systemic therapy
 - New chemotherapy platform
 - Patient selection
- Continued improvement of radiation therapy
- **Careful integration of molecularly targeted therapy**
- Good supportive care and pulmonary rehabilitation
- Post therapy risk stratification

Role of targeted therapy remains unclear and is yet unproven

SWOG 0023: Gefitinib vs Placebo After Chemoradiation Followed by Docetaxel in Stage IIIA (N2) or IIIB

Study Schema

Definition TX

CDDP (50 mg/m²
d 1,8,29,36)

VP-16 (50 mg/m²
d 1-5, 29-33)

RT (1.8-2 Gy/d
61 Gy)

Consolidation

Docetaxel
(70 mg/m²
x 3 cycles)

Maintenance

Placebo

Gefitinib
500 mg/day
250 mg/day
(5-1-03)

R
A
N
D
O
M
I
Z
E

1° Endpoint: OS

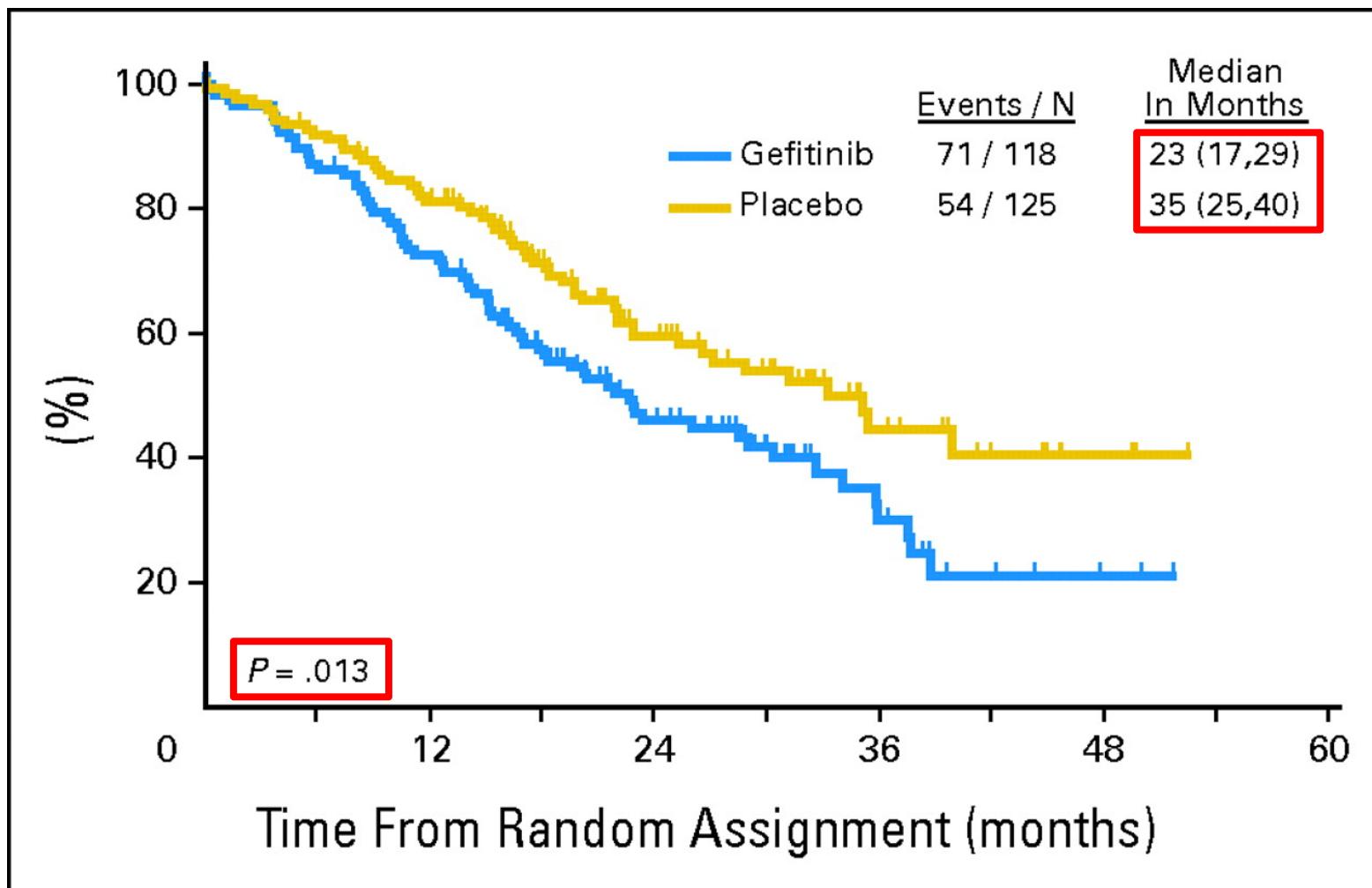
2° Endpoint: PFS, toxicity, and correlative science

Maintenance therapy could continue for a maximum of 5 years

Stratification factors: IIIA vs IIIB; measurable vs nonmeasurable disease; squamous vs nonsquamous

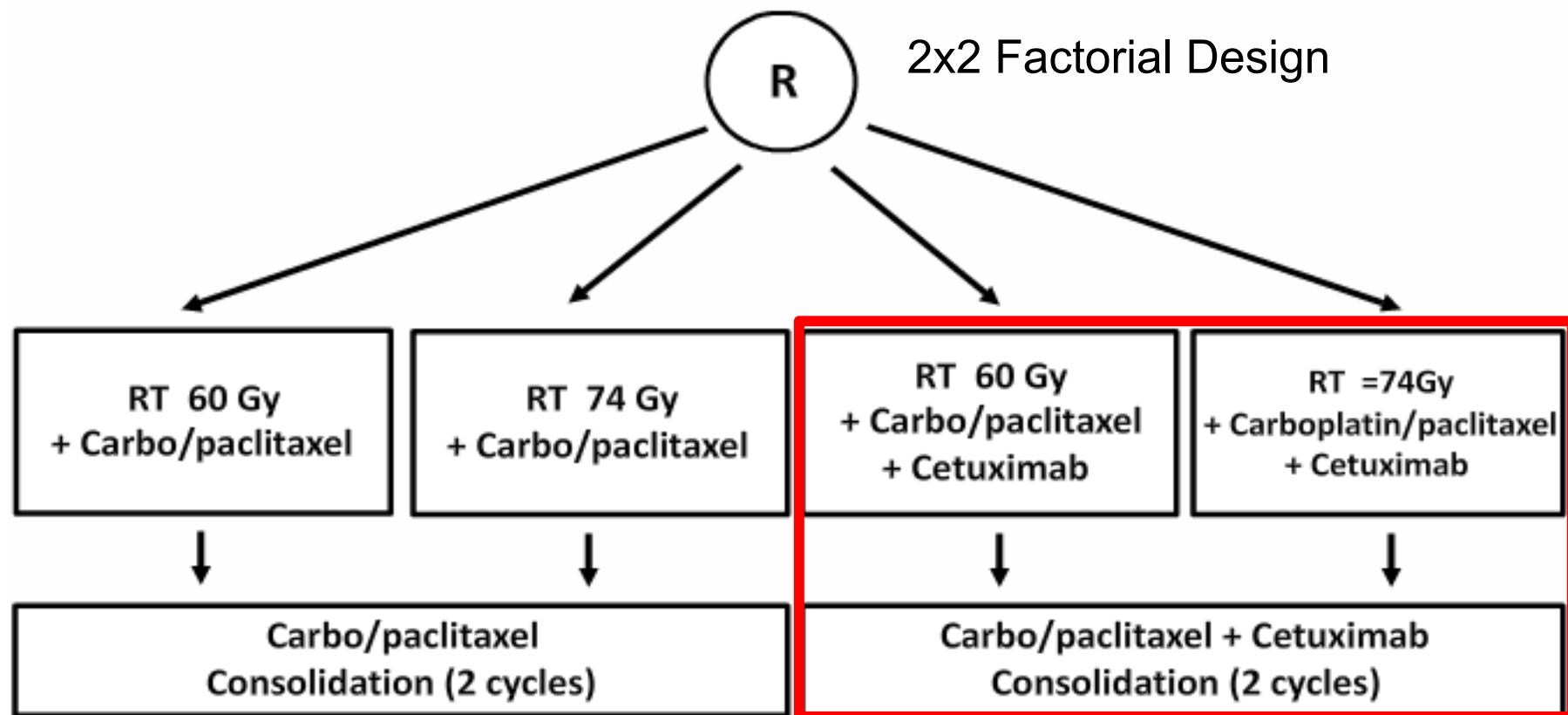
Kelly K, et al. *J Clin Oncol.* 2007;25(18S): Abstract 7513. Kelly K, et al. *J Clin Oncol.* 2008;26(15):2450-2456.

SWOG 0023: OS for Patients Receiving Maintenance Gefitinib or Placebo



Kelly K, et al. *J Clin Oncol*. 2008;26(15):2450-2456.

Phase III RTOG 0617/US Intergroup Trial: Chemoradiation + Cetuximab

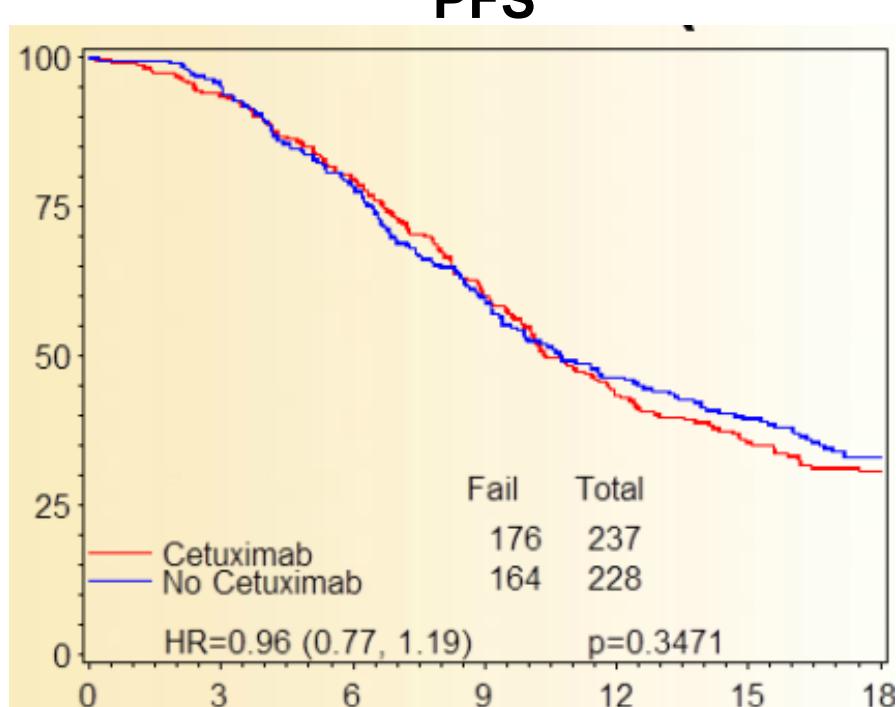
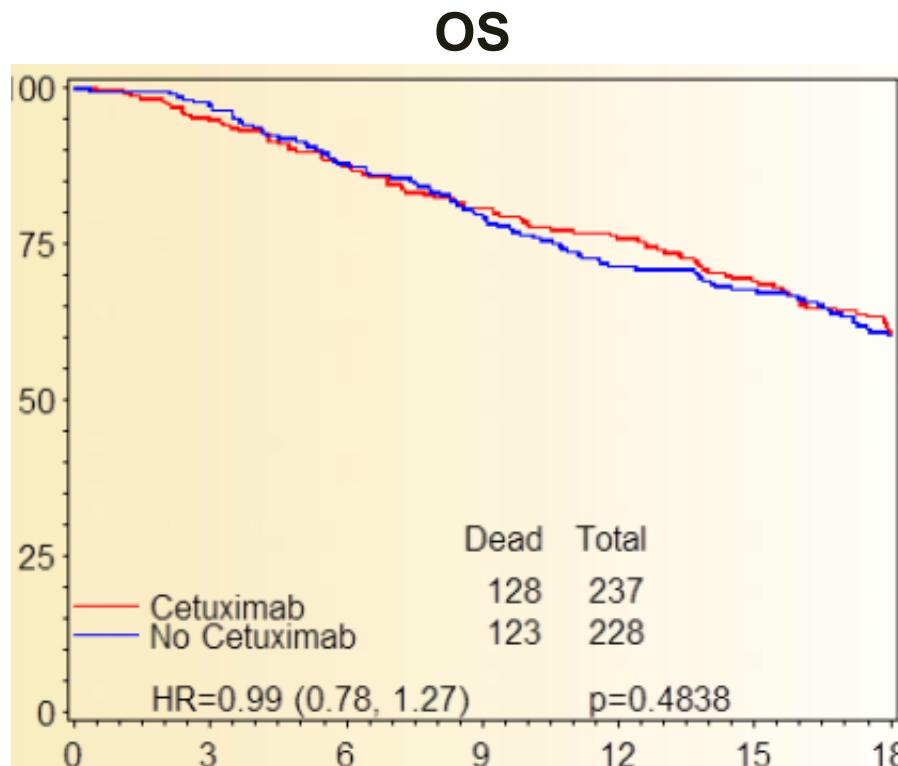


Co-primary Objective:

- Compare the OS of patients treated with concurrent CT-RT plus cetuximab versus CT-RT alone

Bradley J, et al *J Thorac Oncol.* 2013;8(Suppl 2): Abstract PL03.05

Chemoradiation + Cetuximab: OS and PFS



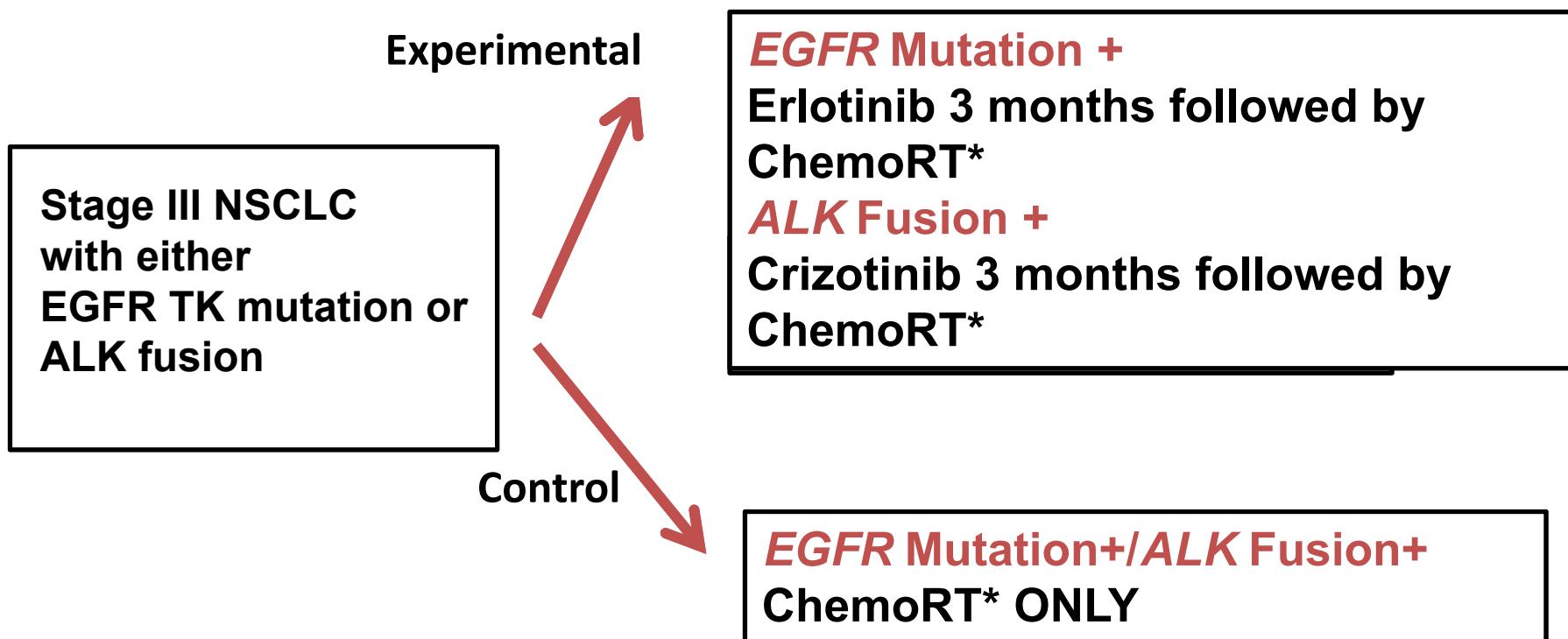
- Cetuximab did not improve overall survival or PFS in the overall population, when added to standard chemoradiotherapy for unresectable stage III NSCLC
- Cetuximab increases overall grade 3-5 toxicities (85% vs 69%, $P<.0001$), and grade 3-5 nonhematologic toxicities (70.5% vs 50.7%, $P<.0001$) when added to standard chemoradiotherapy

Bradley J, et al *J Thorac Oncol.* 2013;8(Suppl 2): Abstract PL03.05

RTOG 1210/ Alliance 31101

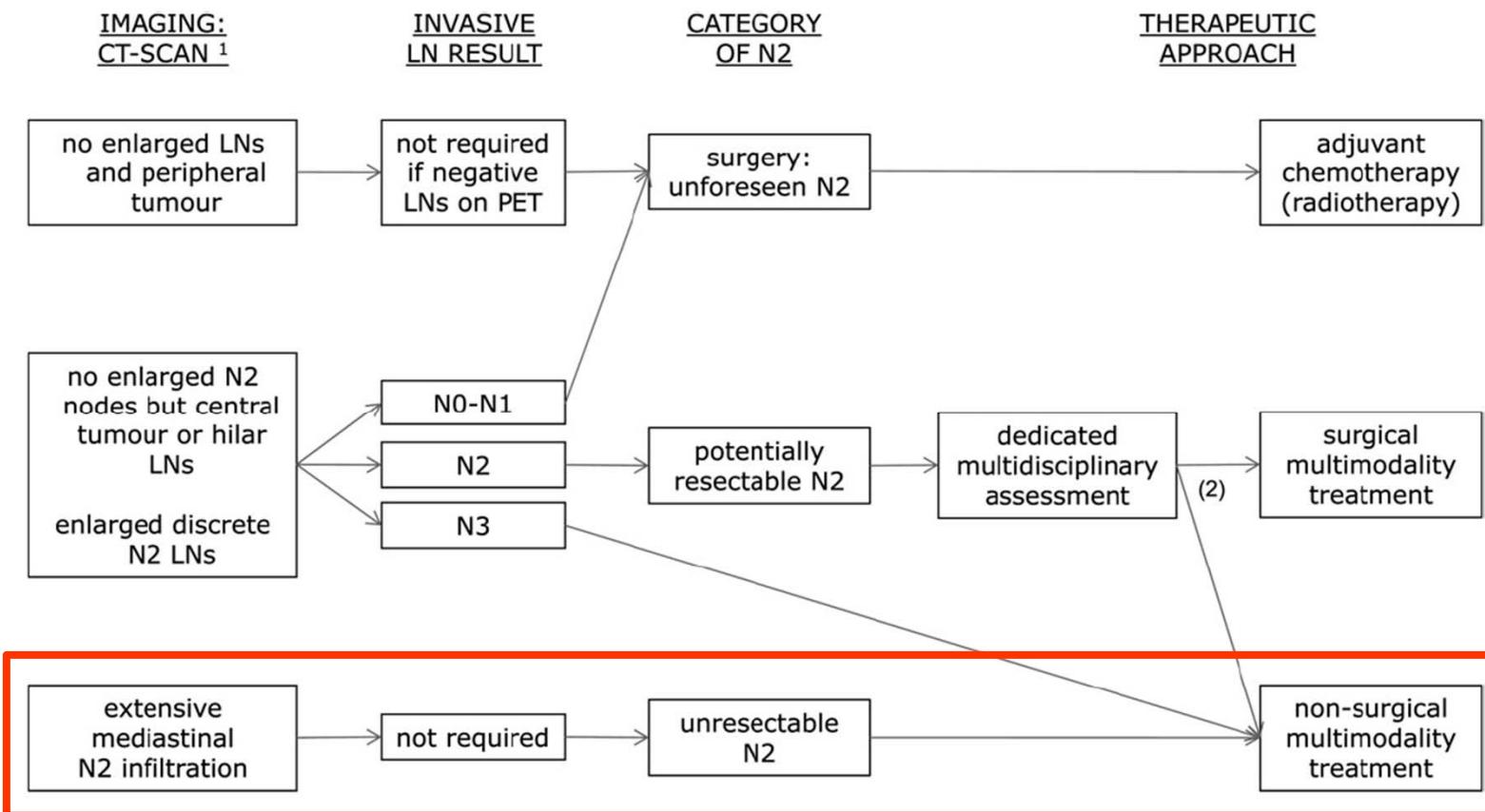
Submitted to NCI

A Randomized Phase II Trial



*Pemetrexed 500 mg/m² q 3 weekly x 4 carboplatin AUC 5 (4 cycles) with thoracic radiation 64 Gy

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

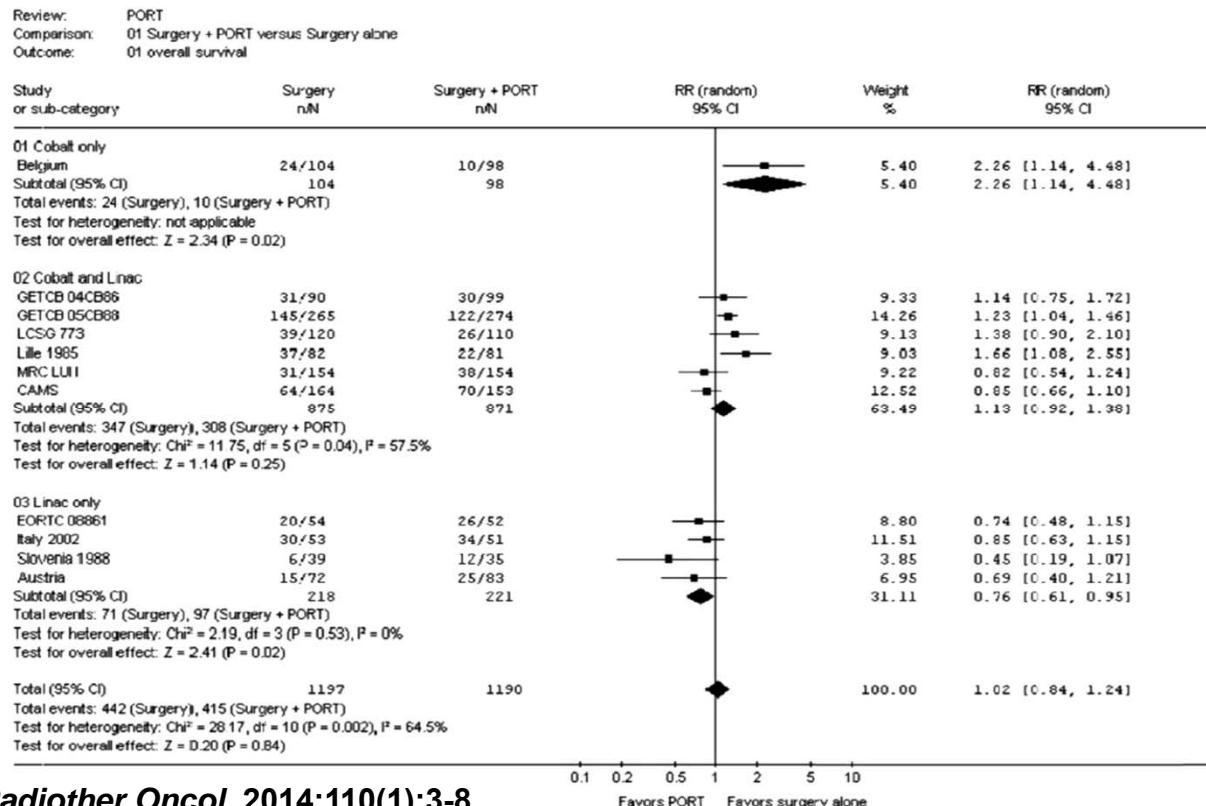


55-year-old man, T2aN2M0 (IIIN2); 5 cm tumor in RUL and 1.7-cm LN, 4R region; adenocarcinoma, EGFR mutation (deletion 19), PS 0

- Induction chemotherapy (carboplatin-pemetrexed)
- Surgery, if responding
- PORT, if pN2

Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: A meta-analysis

Abbreviation	# Patients	Stage	Beam quality	Dose/fraction (Gy)	EQD ₂ (tumor) (Gy)	EQD _{2,T} (Gy)
Belgium [23]	224	I-III	Cobalt only	60/30	60	50.76
CAMS [24]	317	II, III	Cobalt and Linac	60/30	60	50.76
GETCB 04CB86 [25]	189	I-III	Cobalt and Linac	60/24-30	60	50.76
GETCB 05CB88 [26]	539	I-III	Cobalt and Linac	60/24-30	62.50	57.88
LCSG 773 [27]	230	II, III	Cobalt and Linac	50/25-28	50	45.38
Lille 1985 [28]	163	I	Cobalt and Linac	45-60/22-30	45	43.68
MRC LUI I [29]	308	II, III	Cobalt and Linac	40/15	42.23	42.23
Slovenia 1988 [30]	74	III	Linac only	30/10-12	32.50	32.50
Austria [31]	155	III	Linac only	50-56/28	50	45.38
EORTC [32]	106	II, III	Linac only	56/28	55.07	48.47
Italy [33]	104	I	Linac only	50.40/28	49.56	42.96



**Same patient, but with multiple sites N2 disease
(size of the lymph nodes 1.5-3.5 cm)?**

- **Definitive concurrent chemoradiotherapy**
- **CDDP-ETO or CARBO-PACLI as chemo regimen**
- **60-66 Gy in 2 Gy daily fractions**