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

Part II

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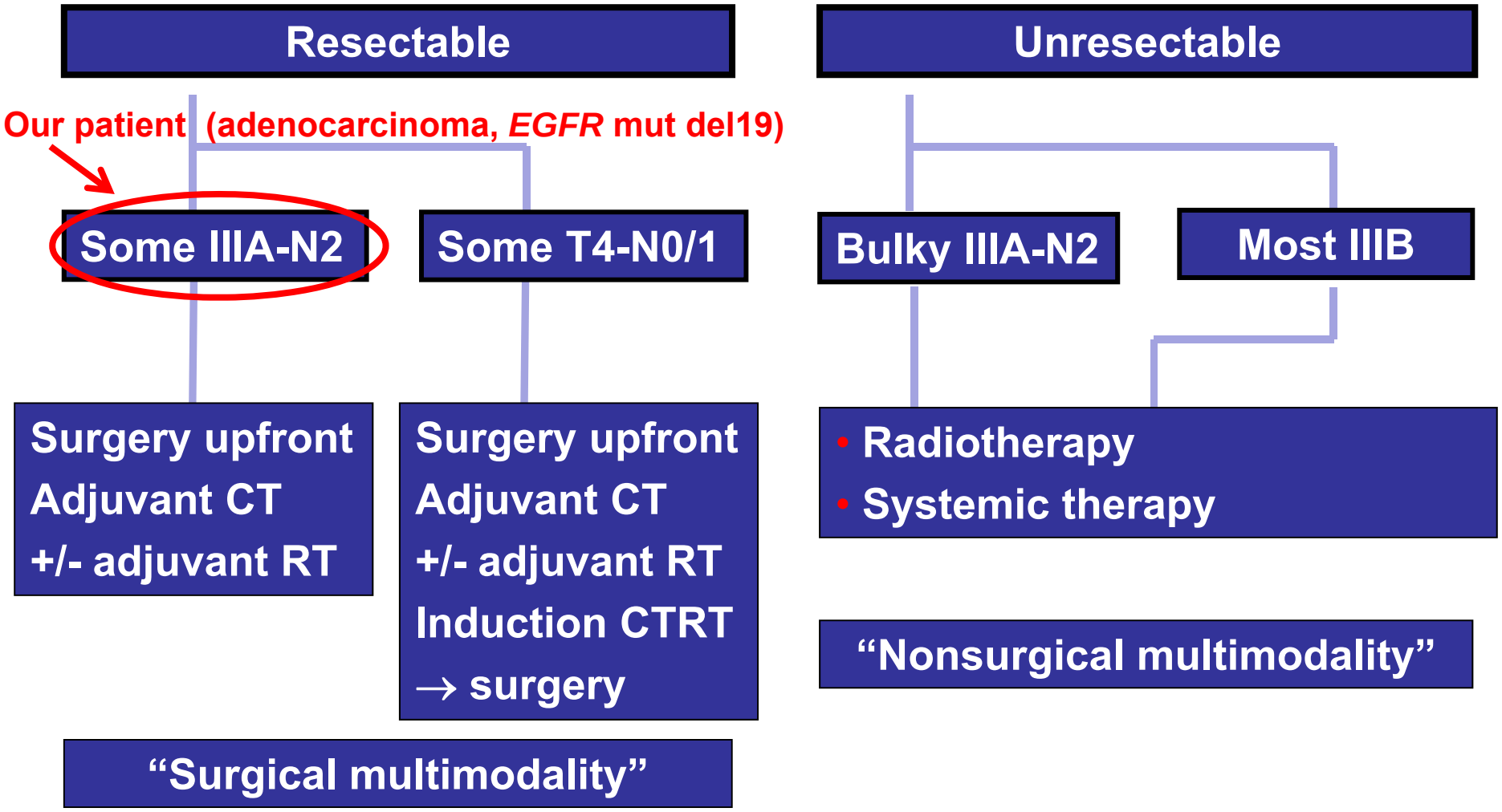
Locally Advanced (Stage III) NSCLC: A Heterogeneous Group: Gustave Roussy Policy



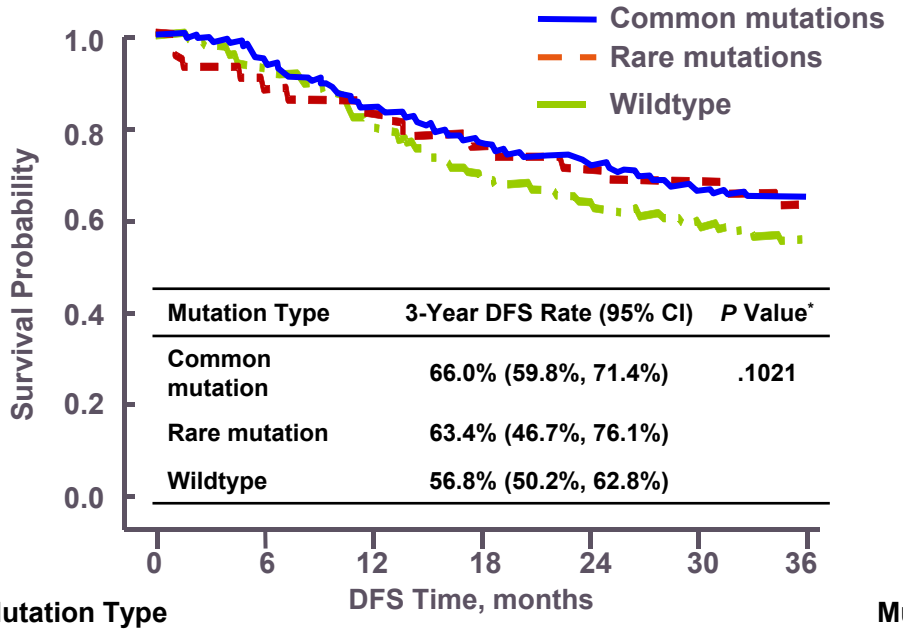
CT, chemotherapy; NSCLC, non-small cell lung cancer; RT, radiation therapy

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

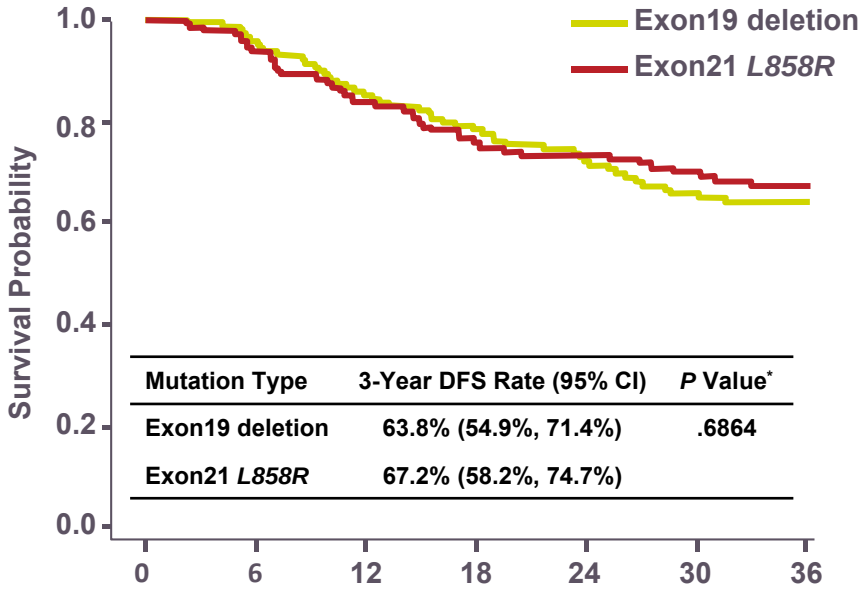
3-Year DFS (Common Mut vs Rare Mut vs Wildtype)



Mutation Type	3-Year DFS Rate (95% CI)	*P* Value*
Common mutation	66.0% (59.8%, 71.4%)	.1021
Rare mutation	63.4% (46.7%, 76.1%)	
Wildtype	56.8% (50.2%, 62.8%)	

Mutation Type							
Common	271	257	227	201	182	166	134
Rare	42	38	35	32	28	26	23
Wildtype	255	234	197	166	149	136	106

3-Year DFS (Exon19Del vs Exon21 *L858R*)



Mutation Type	3-Year DFS Rate (95% CI)	*P* Value*
Exon19 deletion	63.8% (54.9%, 71.4%)	.6864
Exon21 *L858R*	67.2% (58.2%, 74.7%)	

Mutation Types							
Exon19 deletion	139	133	117	103	91	80	67
Exon21 *L858R*	128	120	106	94	87	82	63

*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.

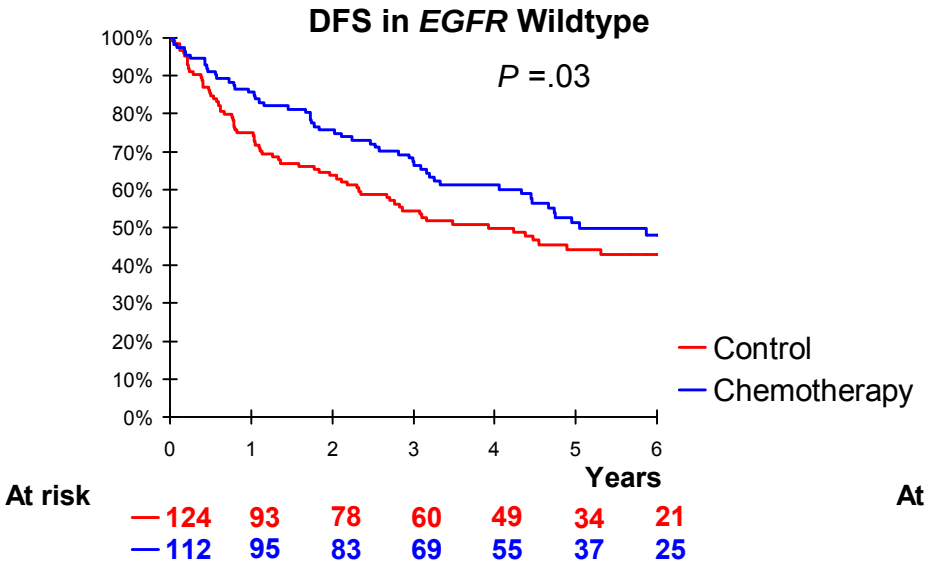
CI, confidence interval; DFS, disease-free survival

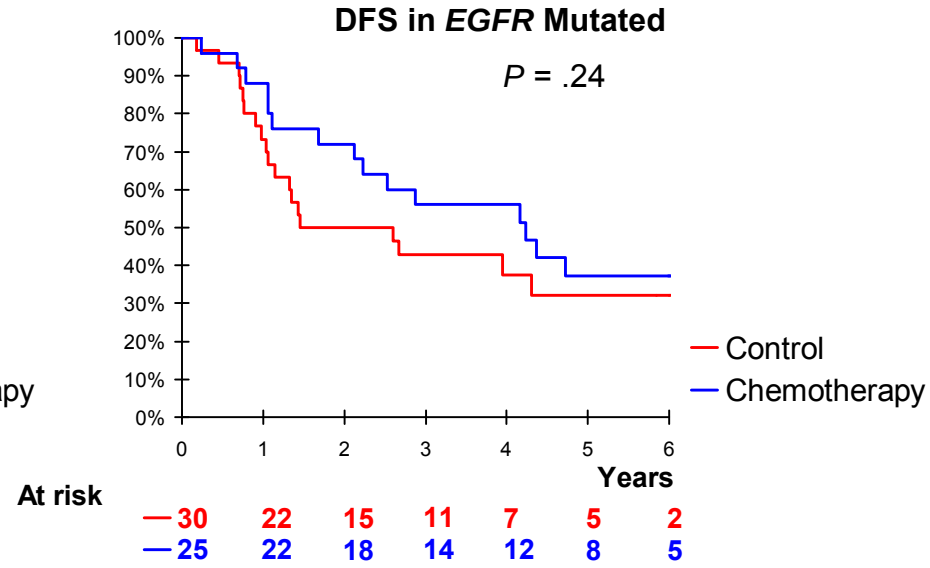
Wu Y, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1175O.

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)**





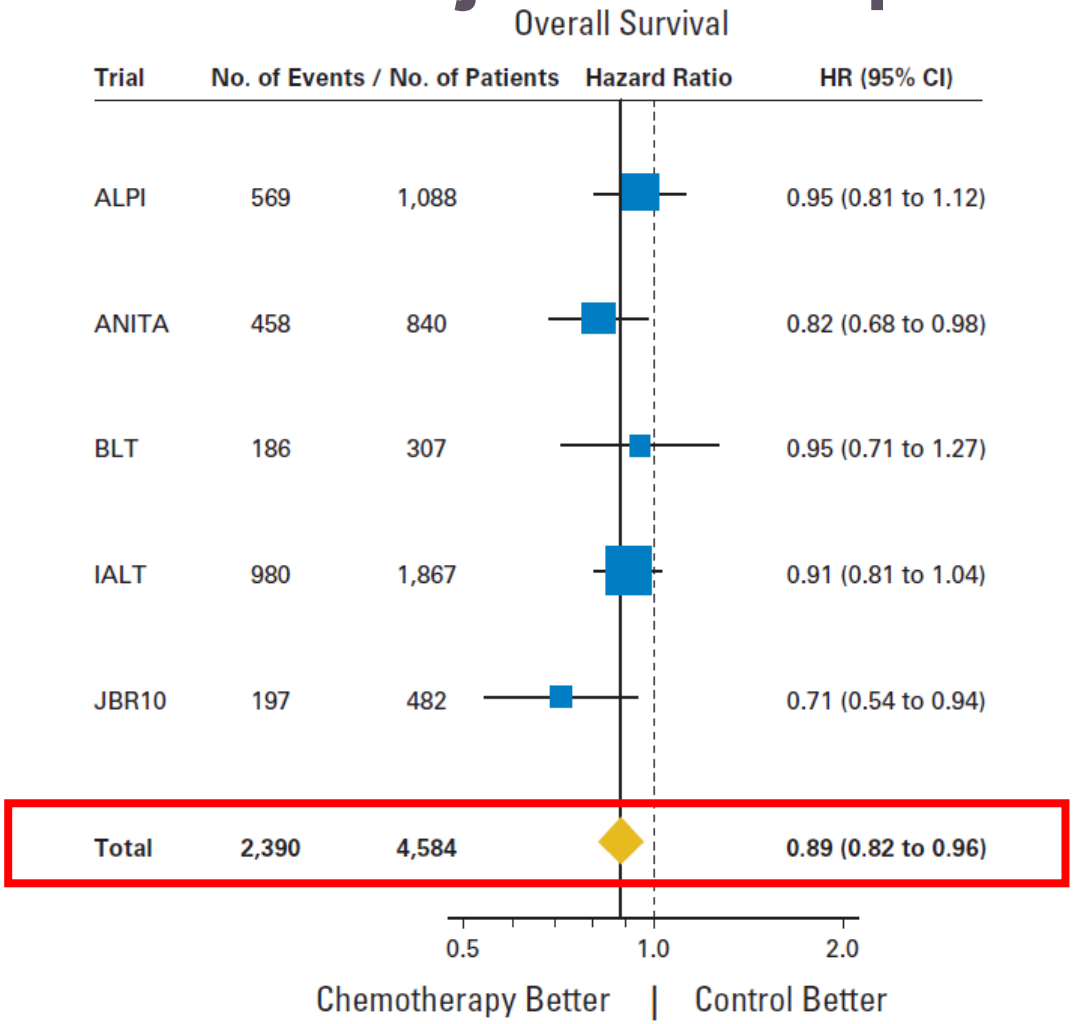
Interaction test
***P* = .97**

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

Soria J, et al. *J Thorac Oncol.* 2011;6(Suppl 2): Abstract MO16.06.

Perioperative Chemotherapy

LACE: 5 Adjuvant Cisplatin-Based Regimens



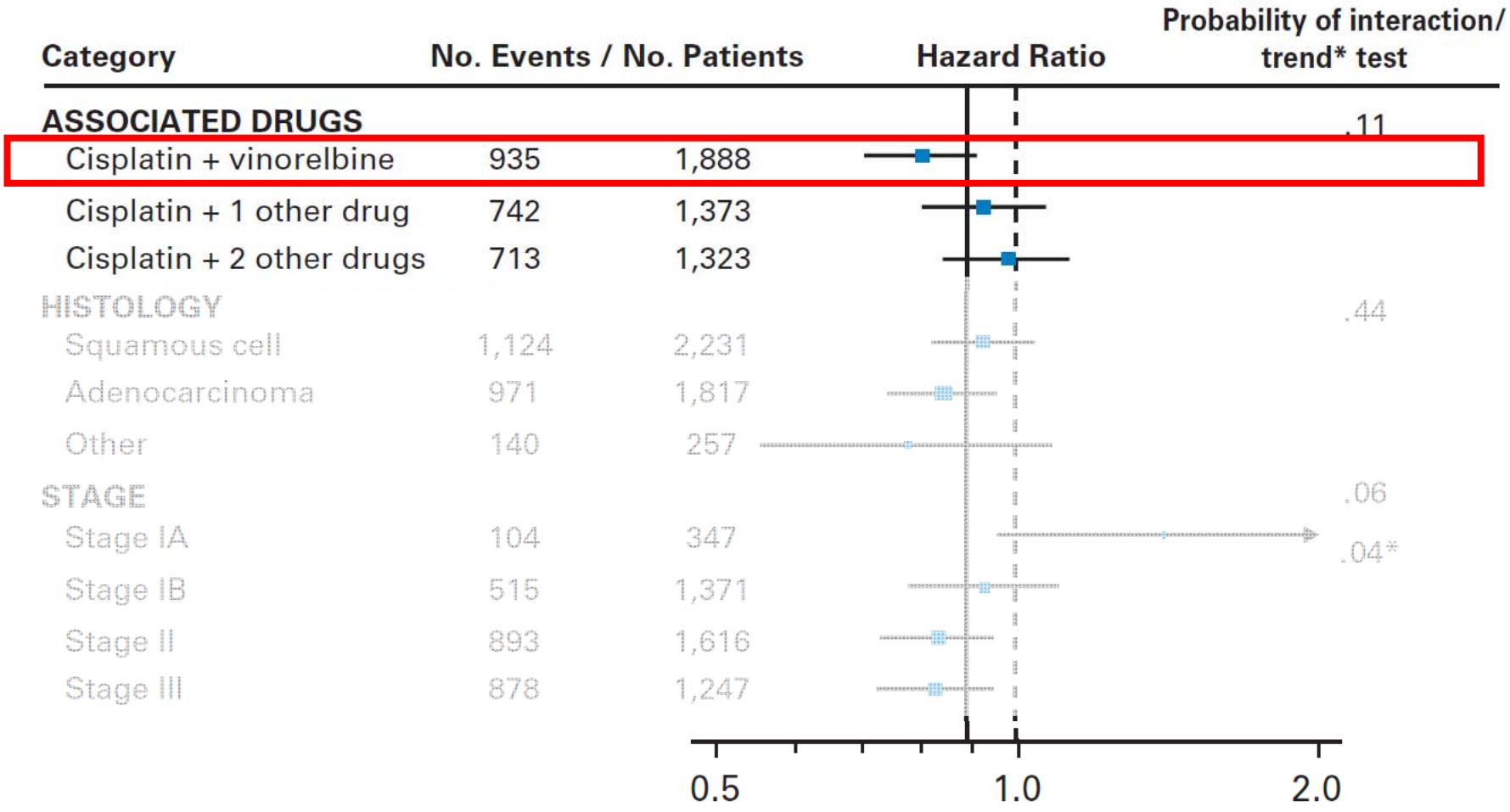
Absolute OS benefit at 5 years
5.3% ± 1.6%

Toxic death
0.8% to 2%

HR, hazard ratio; OS, overall survival

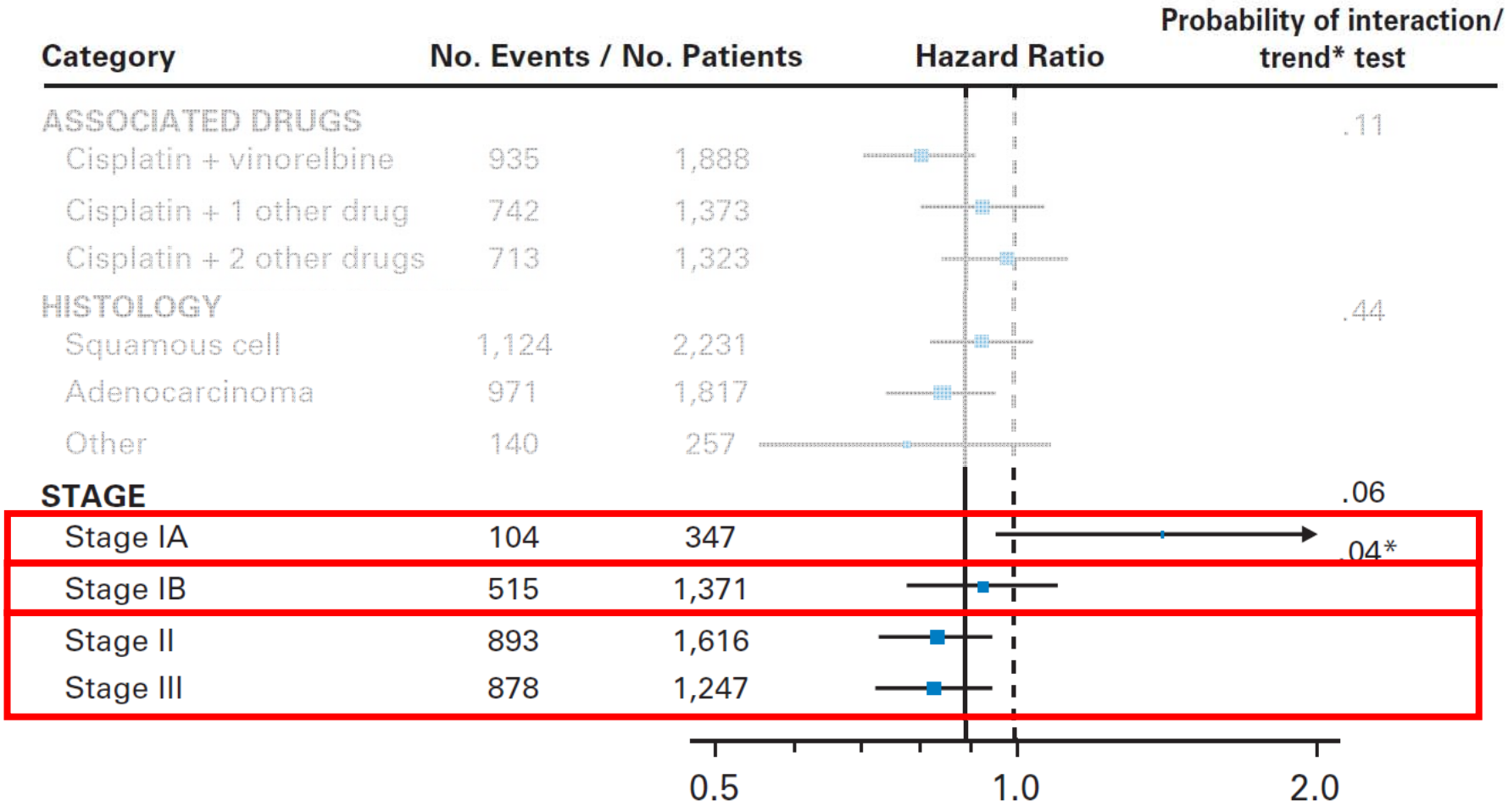
Pignon JP, et al. *J Clin Oncol.* 2008;26(21):3552-3559.

LACE: OS According to Chemotherapy Regimen



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

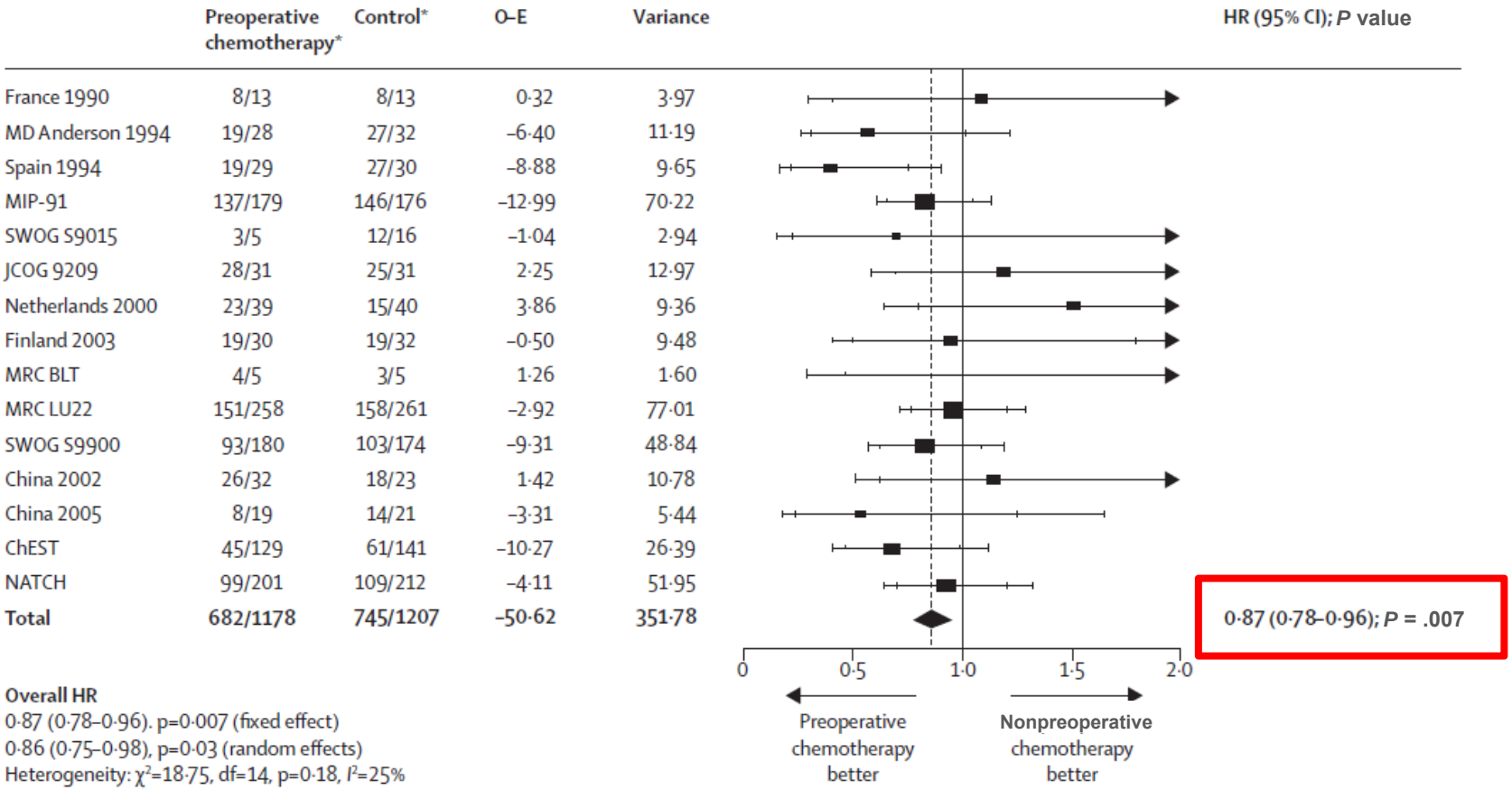
LACE: OS Analysis by Stage



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



	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); *P* value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG S9900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); *P* = .007**

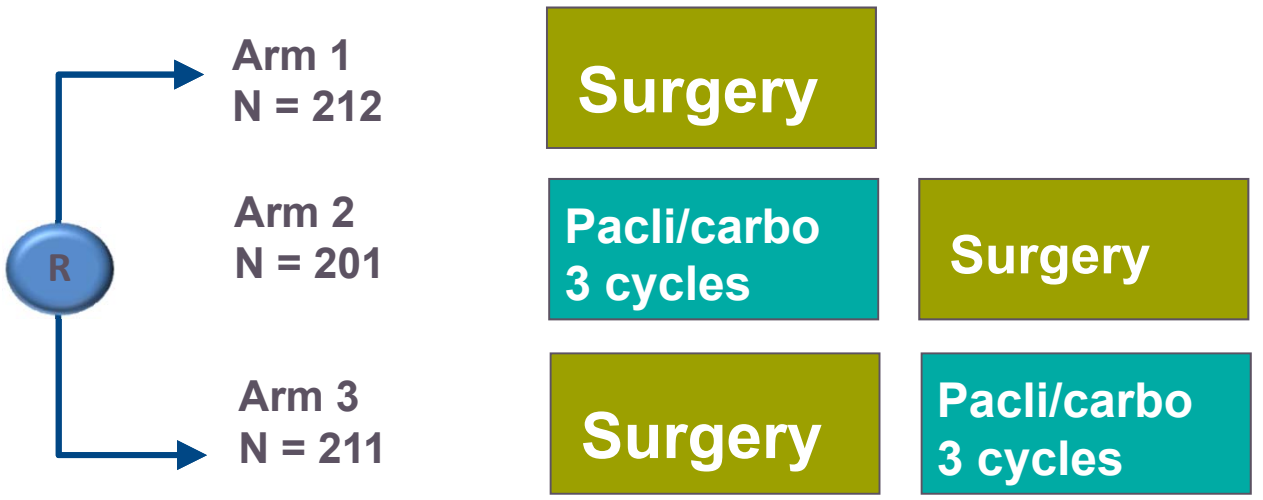
Overall HR
0·87 (0·78–0·96). p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

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

NATCH Trial

Phase III

624 patients
IA (>2 cm),
IB, II, T3N1



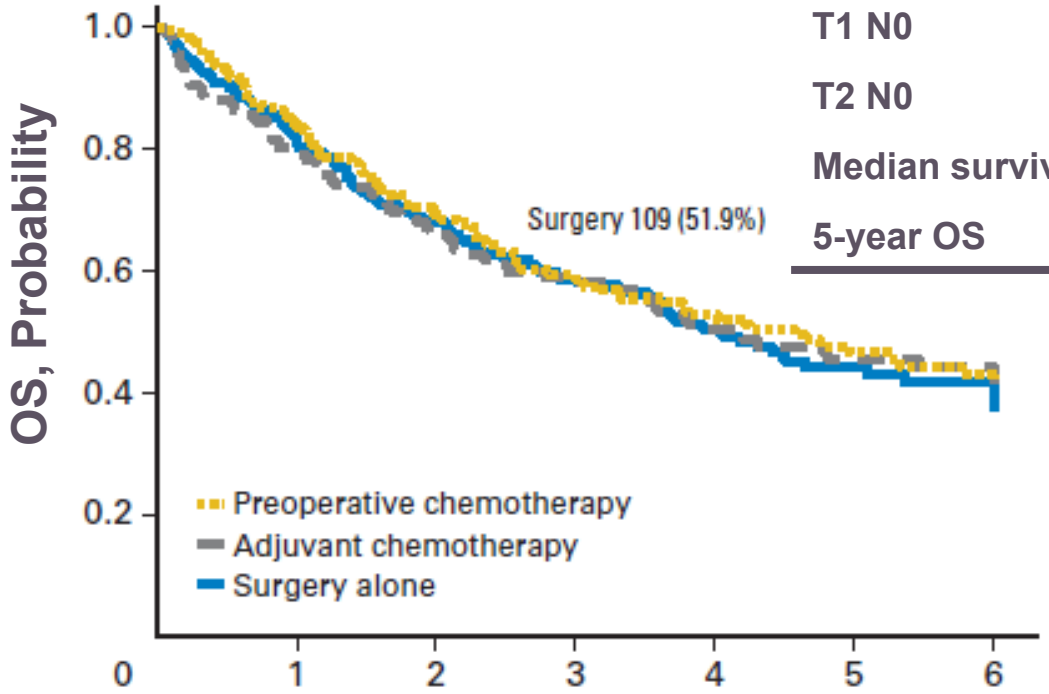
Paclitaxel 200 mg/m² + carboplatin AUC 6 /3 weeks

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%



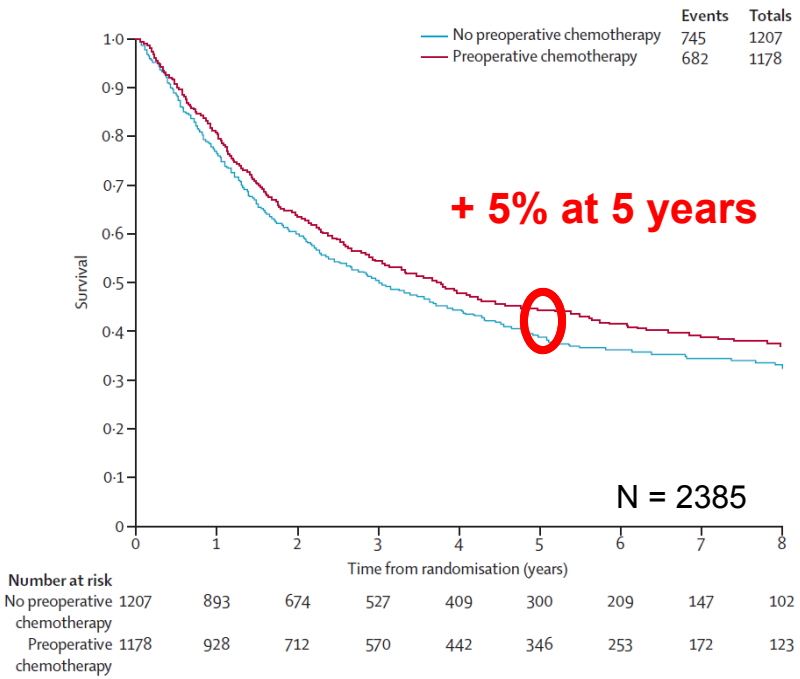
No. at risk						
Preoperative	165	131	99	71	45	31
Adjuvant	161	121	90	65	40	29
Surgery	168	131	105	72	40	27

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.

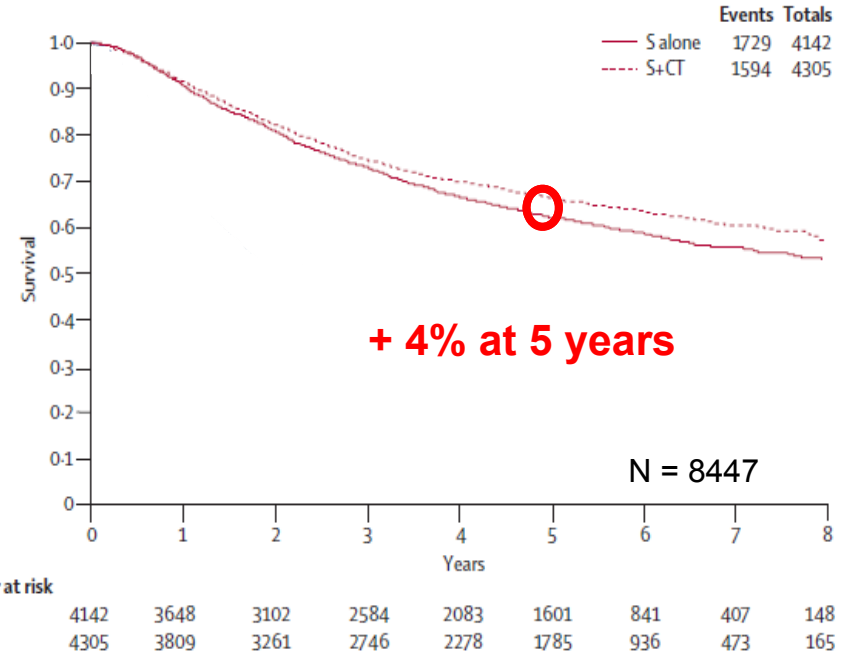
Survival Benefit of Neoadjuvant and Adjuvant Chemotherapy

Neoadjuvant CT[1]



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

Adjuvant CT[2]



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)

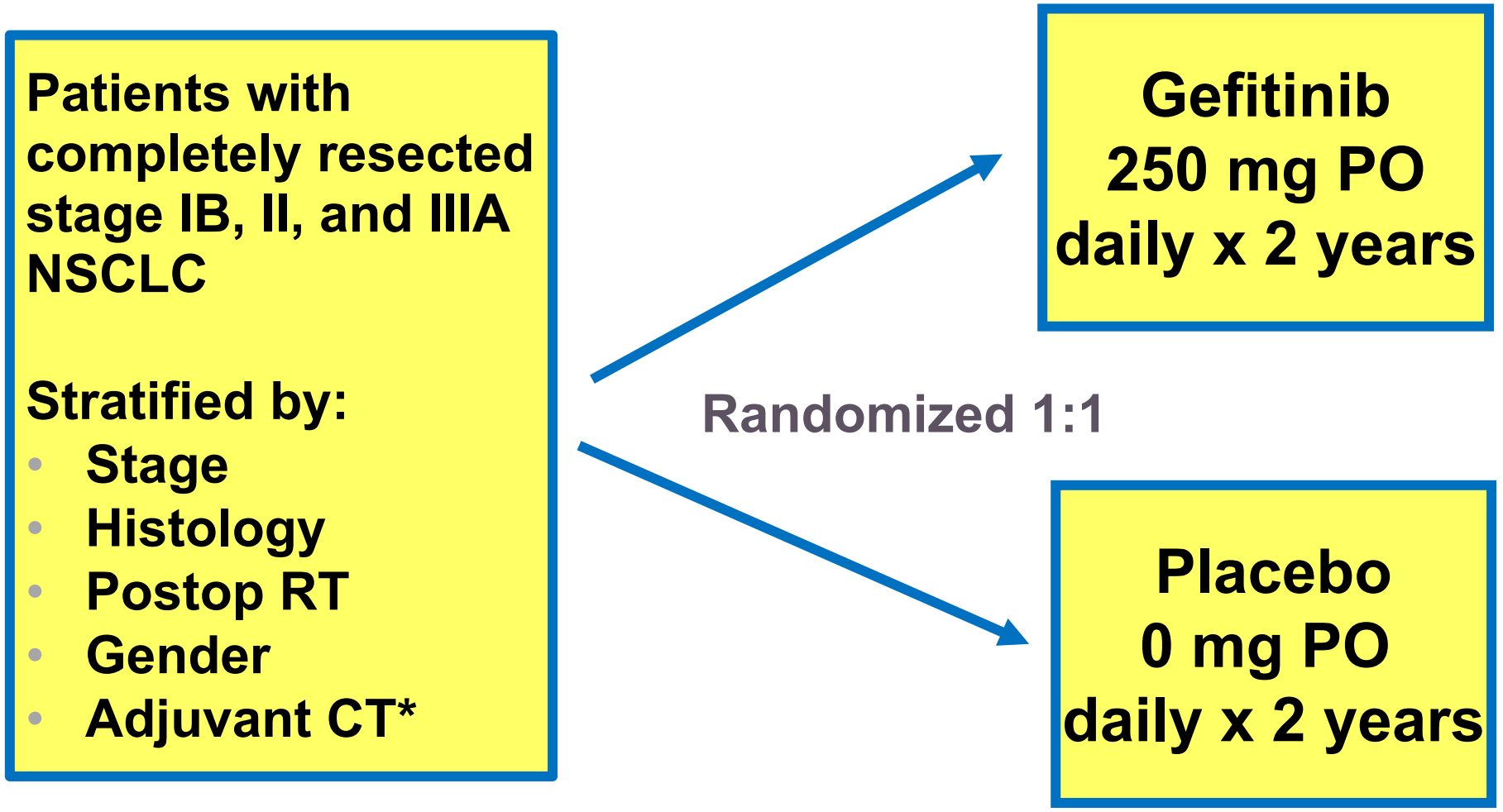
	BEV+DC (n = 36)	DC (n = 11)
ORR	58%	40%
Downstaging	44%	27%
Postop toxicity Grade 3/4	16%	9%

ORR, overall response rate

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

Adjuvant EGFR TKI

BR.19: Trial Design

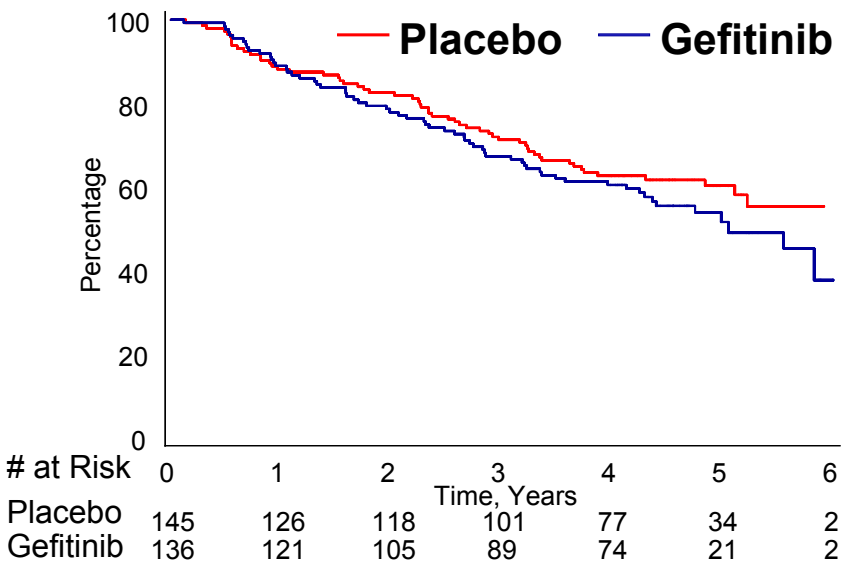


*Protocol amended January 2003 to allow adjuvant chemotherapy which became a stratification factor

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

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

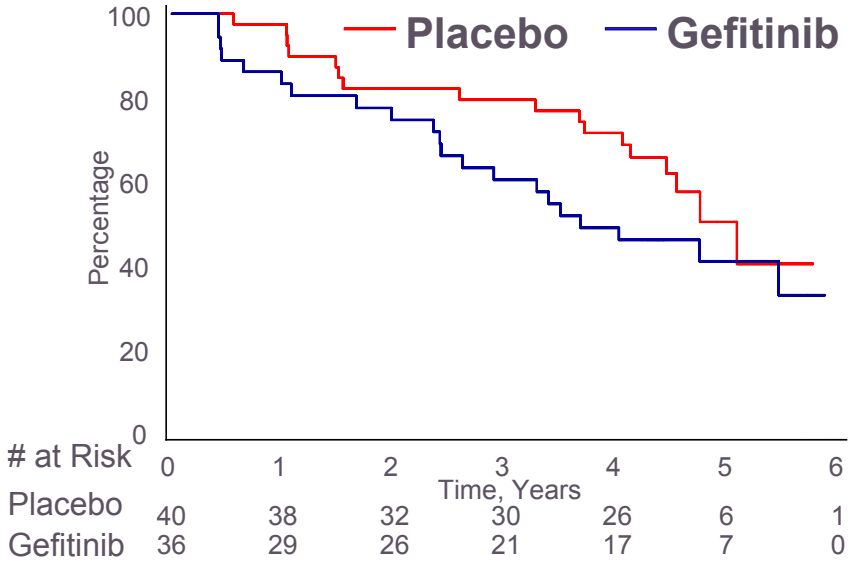
Wildtype



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.)

Sensitizing Mutation

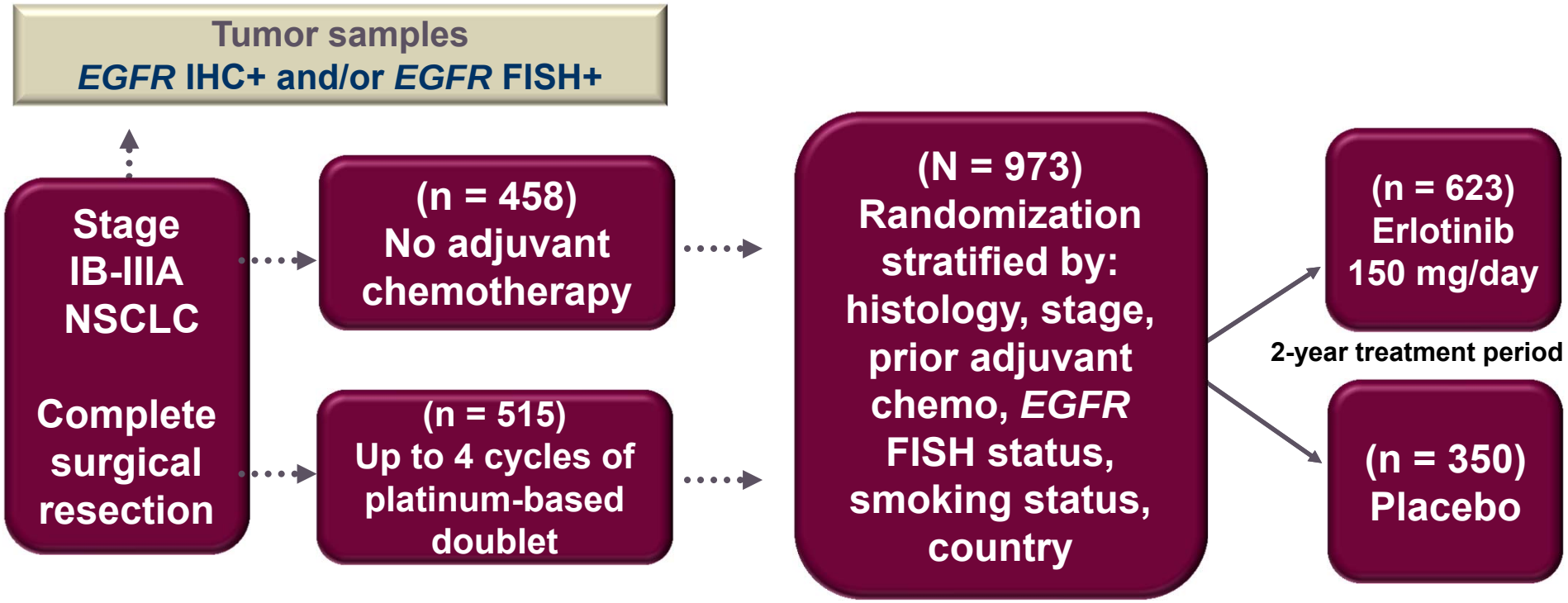


HR (95% CI)
Gefitinib/Placebo: 1.58 (0.83, 3.00)
Log Rank: *P* = .160

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.

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+)**

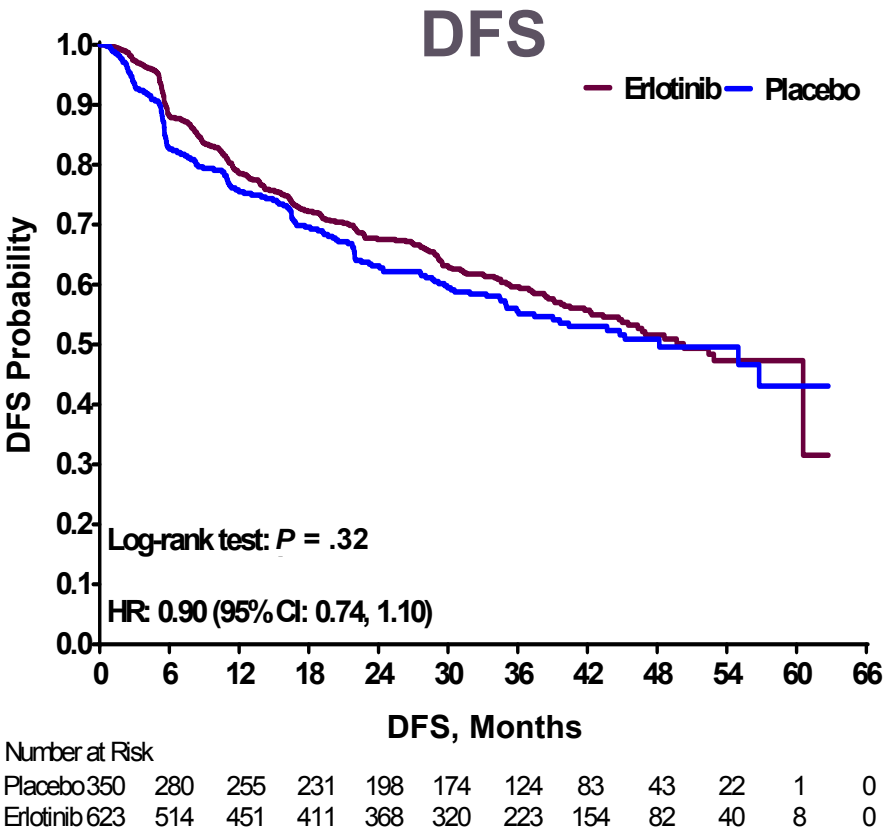
Data cut-off date: 8 Apr 2013

***EGFR* M+, *EGFR*-activating mutations; FISH, fluorescent *in situ* hybridization**

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

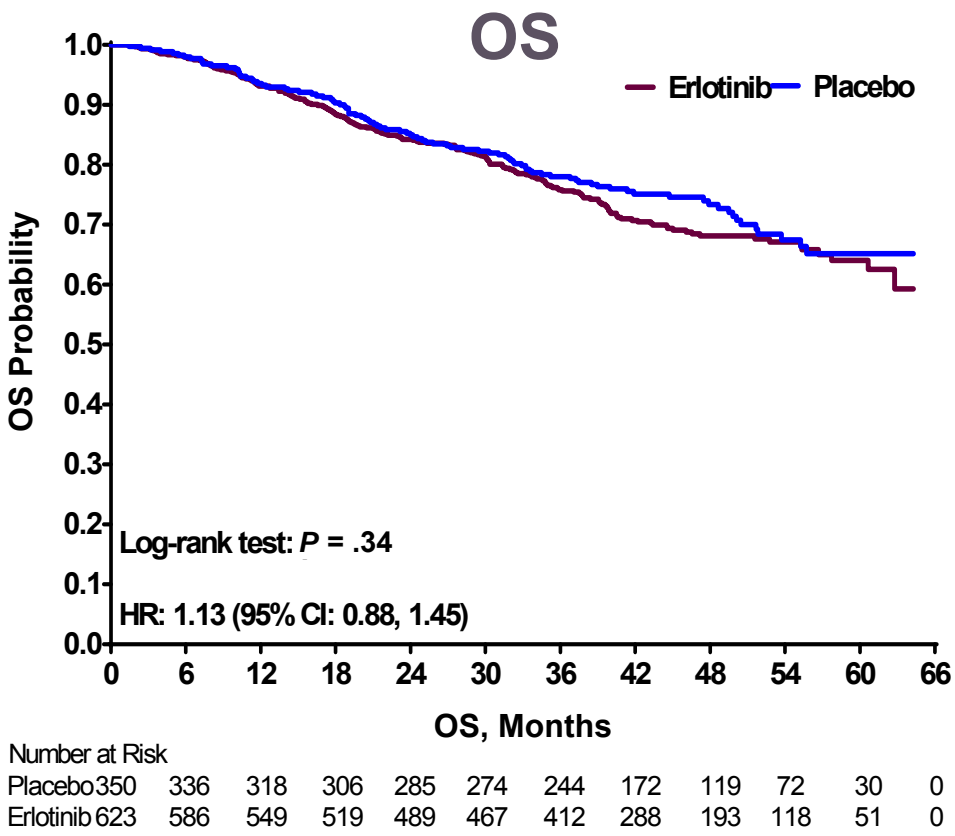
RADIANT: DFS and OS

All Randomized Patients



Number at Risk

Placebo	350	280	255	231	198	174	124	83	43	22	1	0
Erlotinib	623	514	451	411	368	320	223	154	82	40	8	0



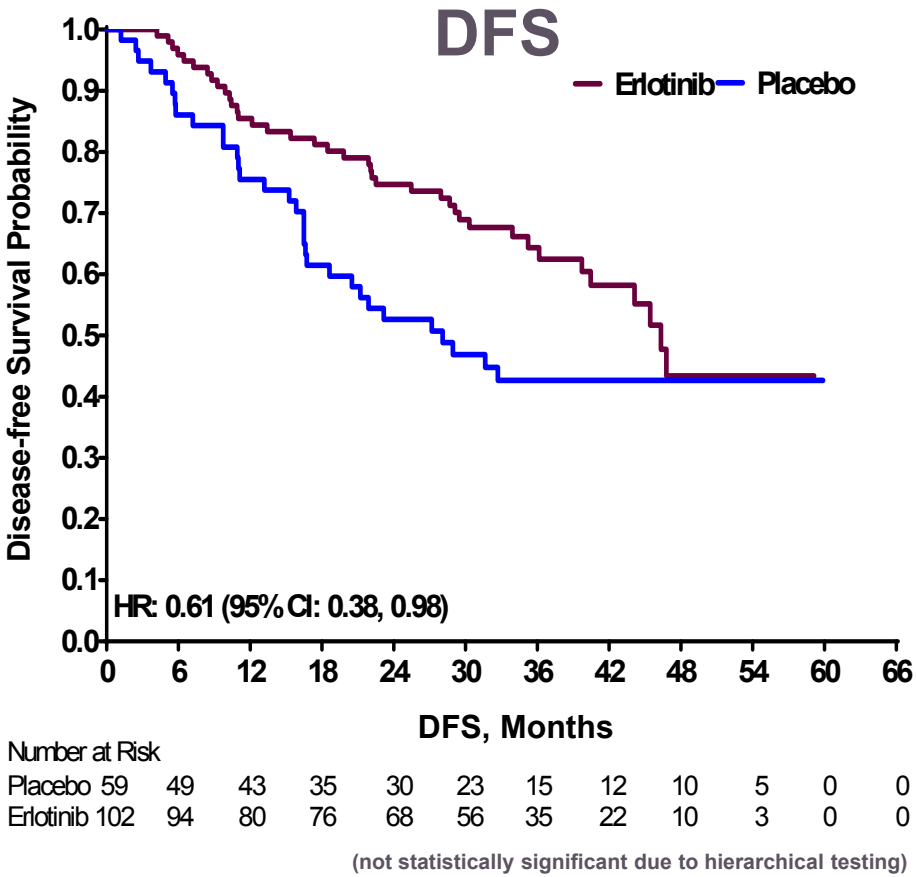
Number at Risk

Placebo	350	336	318	306	285	274	244	172	119	72	30	0
Erlotinib	623	586	549	519	489	467	412	288	193	118	51	0

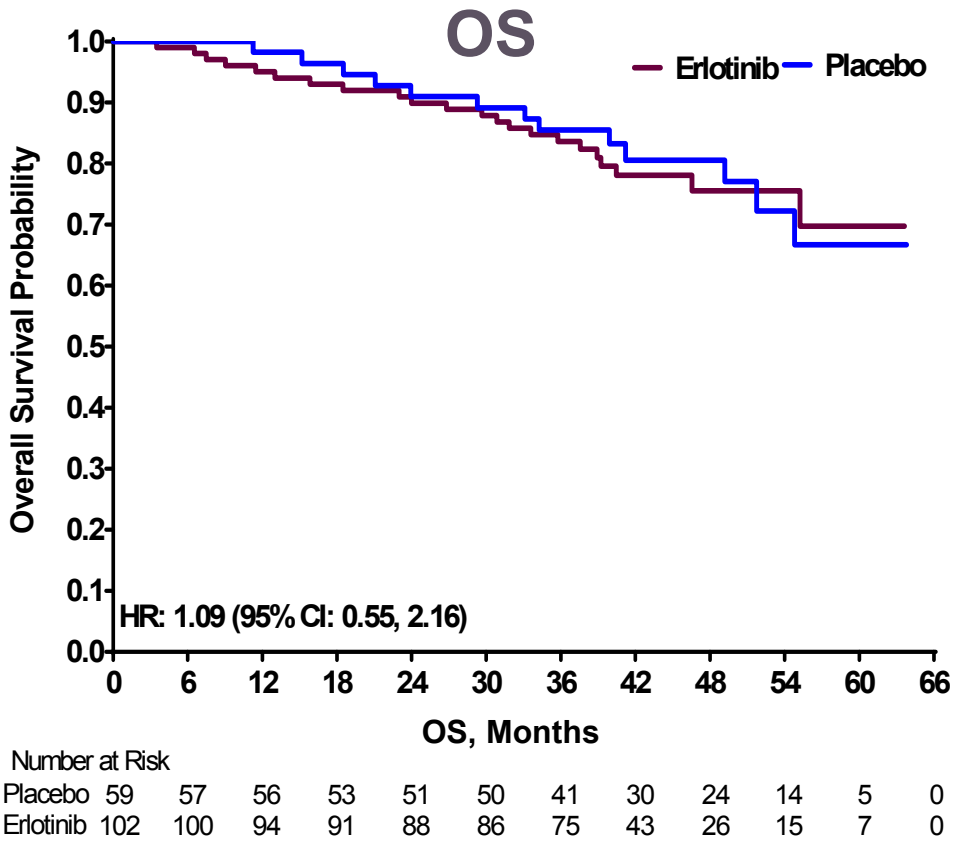
Shepherd FA, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1174O.

RADIANT: DFS and OS

EGFR M+ Subgroup

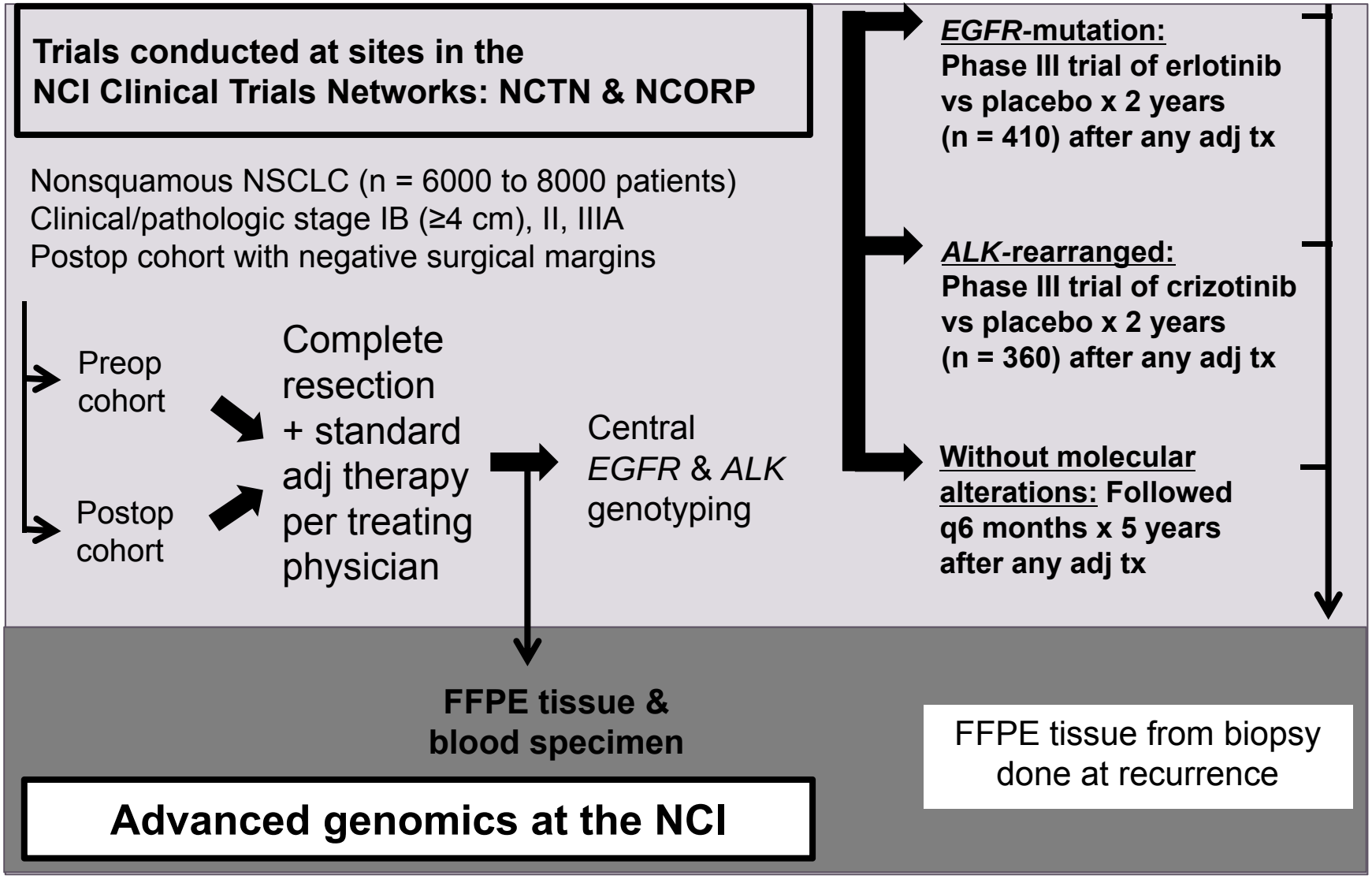


(not statistically significant due to hierarchical testing)



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

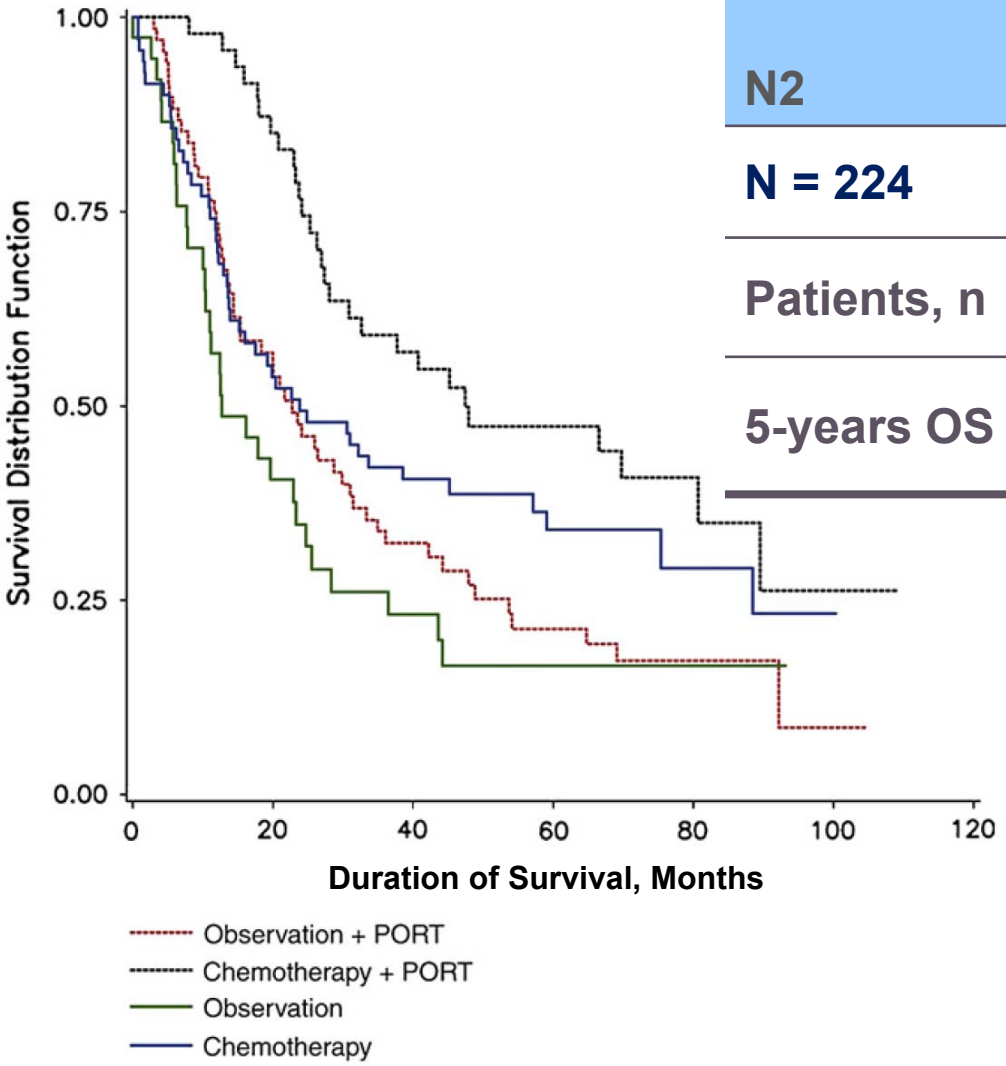
Ongoing Initiative: ALCHEMIST Trial



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

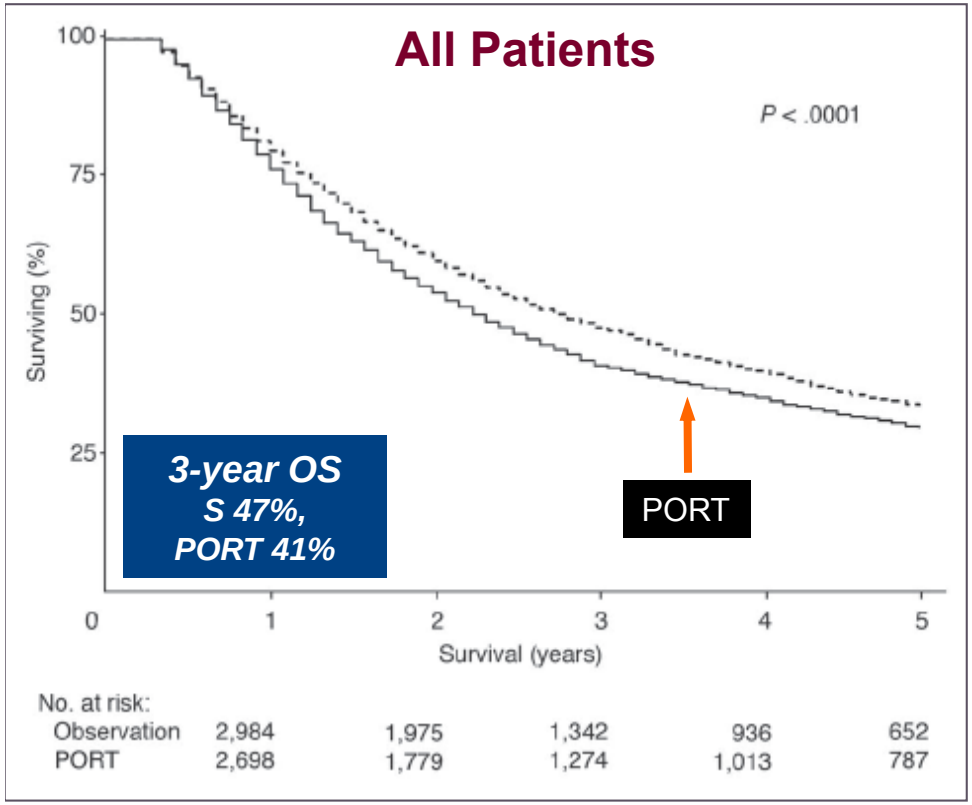


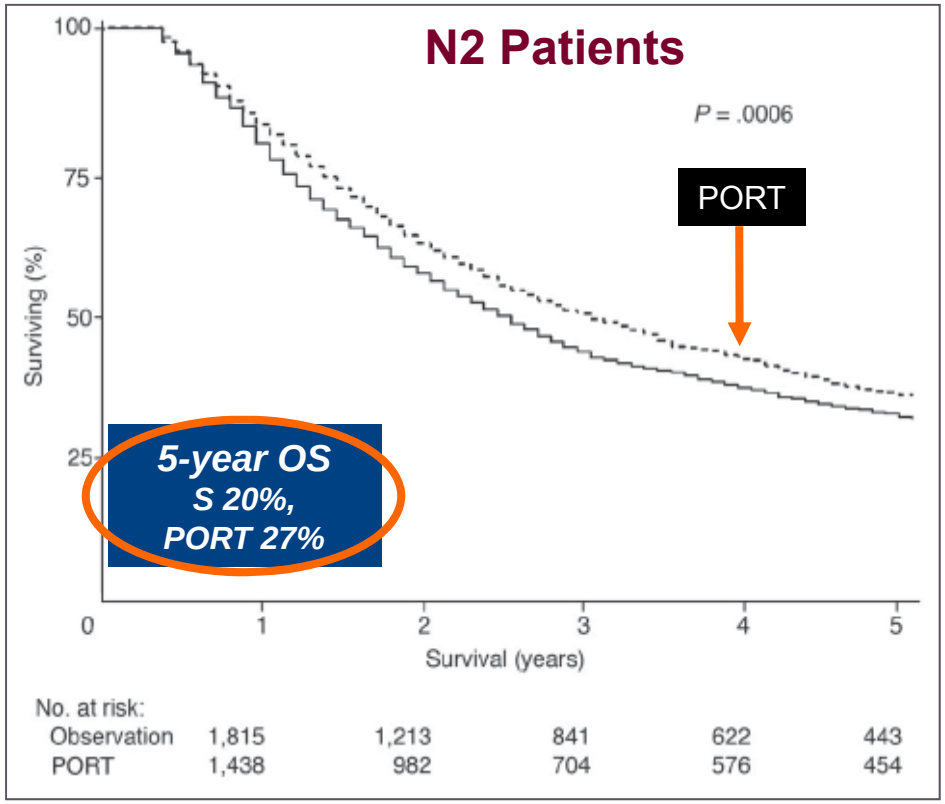
N2	Radiotherapy		No Radiotherapy	
N = 224	No CT	CT	No CT	CT
Patients, n	68	48	38	70
5-years OS	21.3%	47.4%	16.6%	34.0%

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)

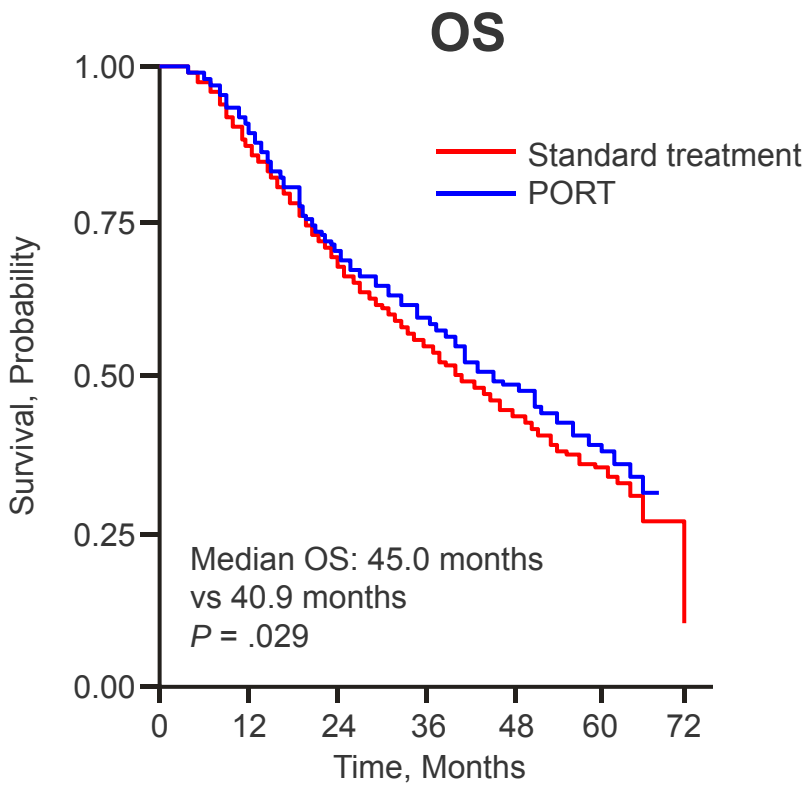
No adjuvant CT in most patients

Lally BE, et al. *J Clin Oncol.* 2006;24(19):2998-3006.

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)



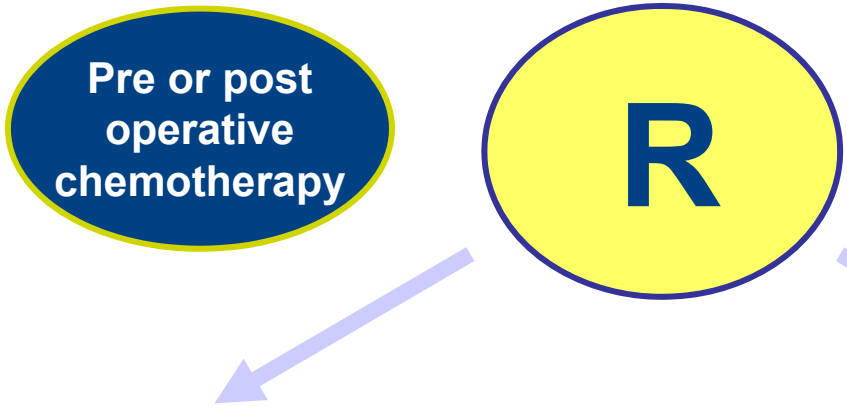
Conclusion

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

Robinson et al. *J Clin Oncol* 2014;32(5S); Abstract 7509.

Lung ART IFCT 05-03 EORTC 22055-08053

Patients With Resected pN2 NSCLC



Control **PORT (54 Gy)**

Ongoing study: Enroll patients!

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

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00410683. Assessed on 26 November 2014.

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