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

Part II

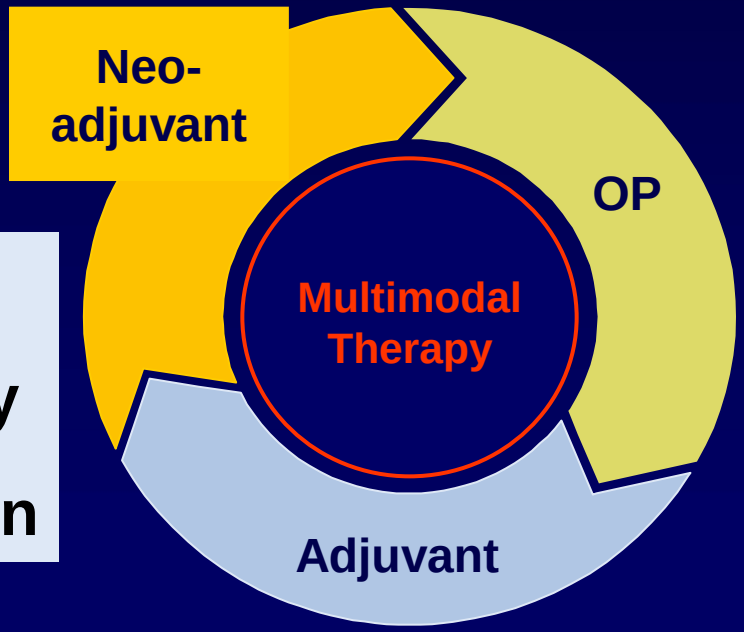
Niels Reinmuth, MD, PhD
Hospital Grosshansdorf
Grosshansdorf, Germany

Stage III
A Heterogeneous Disease

Stage IIIA	Stage IIIB
18% to 20%	
T3 N1 M0	Tx N3 M0
T4 N0/N1 M0	T4 N2 M0
T1-3 N2 M0	

Surgery at Stage IIIa (N2-Level)

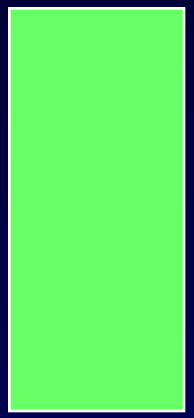
- Potential cure / incurable
- Dissectable / not dissectable
- Neoadjuvant / adjuvant therapy



Mediastinal staging and graduation of the multimodal therapy are adjusted to the individual situation

Crinò L, et al. *Ann Oncol.* 2010;21(Suppl 5):103-121. Goeckenjan G, et al. *Pneumologie.* 2011;65(1):39-59.

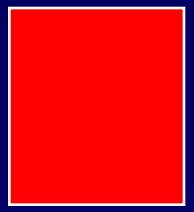
N2: Should Surgery Be Done?



- $IIIA_1$ Incidental nodal metastases found on final pathology examination of the resection specimen
- $IIIA_2$ Nodal (single station) metastases recognized intraoperatively

?

- $IIIA_3$ Nodal metastases (single or multiple station) recognized preoperatively (eg, mediastinoscopy, EBUS)



- $IIIA_4$ Bulky or fixed multistation N2 disease
- IIIB

EBUS, endobronchial ultrasound

Robinson LA, et al. *Chest.* 2007;132(3 Suppl):243S-265S.

Perioperative Chemotherapy

NSCLC I-IIIA (Incidential)

Lung Adjuvant Cisplatin Evaluation (LACE)

- 4584 patients eligable from 5 trials (ALPI, BLT, IALT, JBR 10, ANITA)
- Follow-up 62 months (median)
- 9% of pts ≥70 year
- Pneumonectomy: 29%

Stage (pTNM)	Total	IA (8%)	IB (29%)	II (35%)	IIIA (28%)
HR (OS)	0.89	1.40	0.93	0.83	0.83
P value	.005				

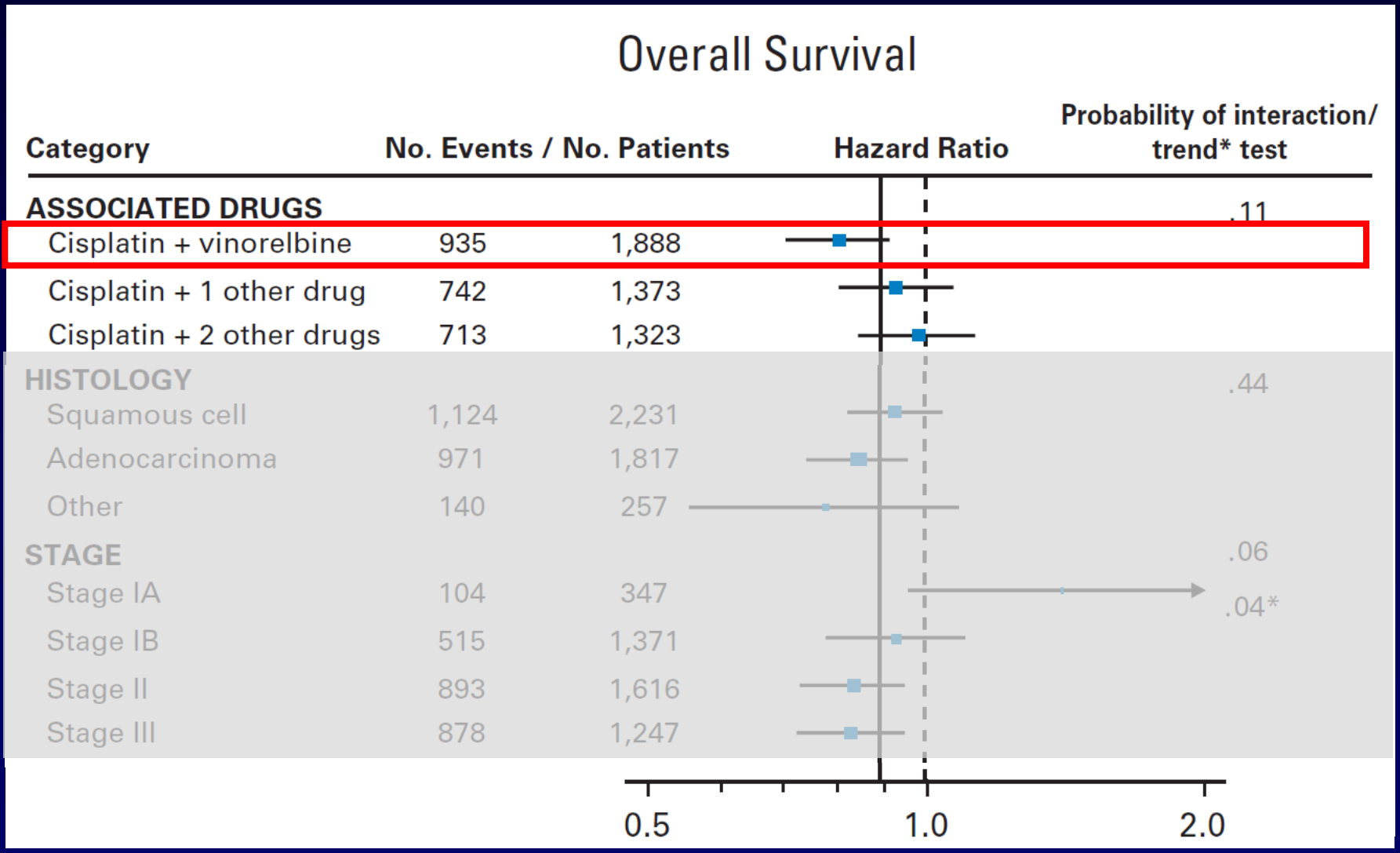
Absolute OS benefit at 5 years 5.4% ± 1.6%

Toxic death 0.8% to 2%

pTNM, pathologic TNM stage; HR, hazard ratio; OS, overall survival

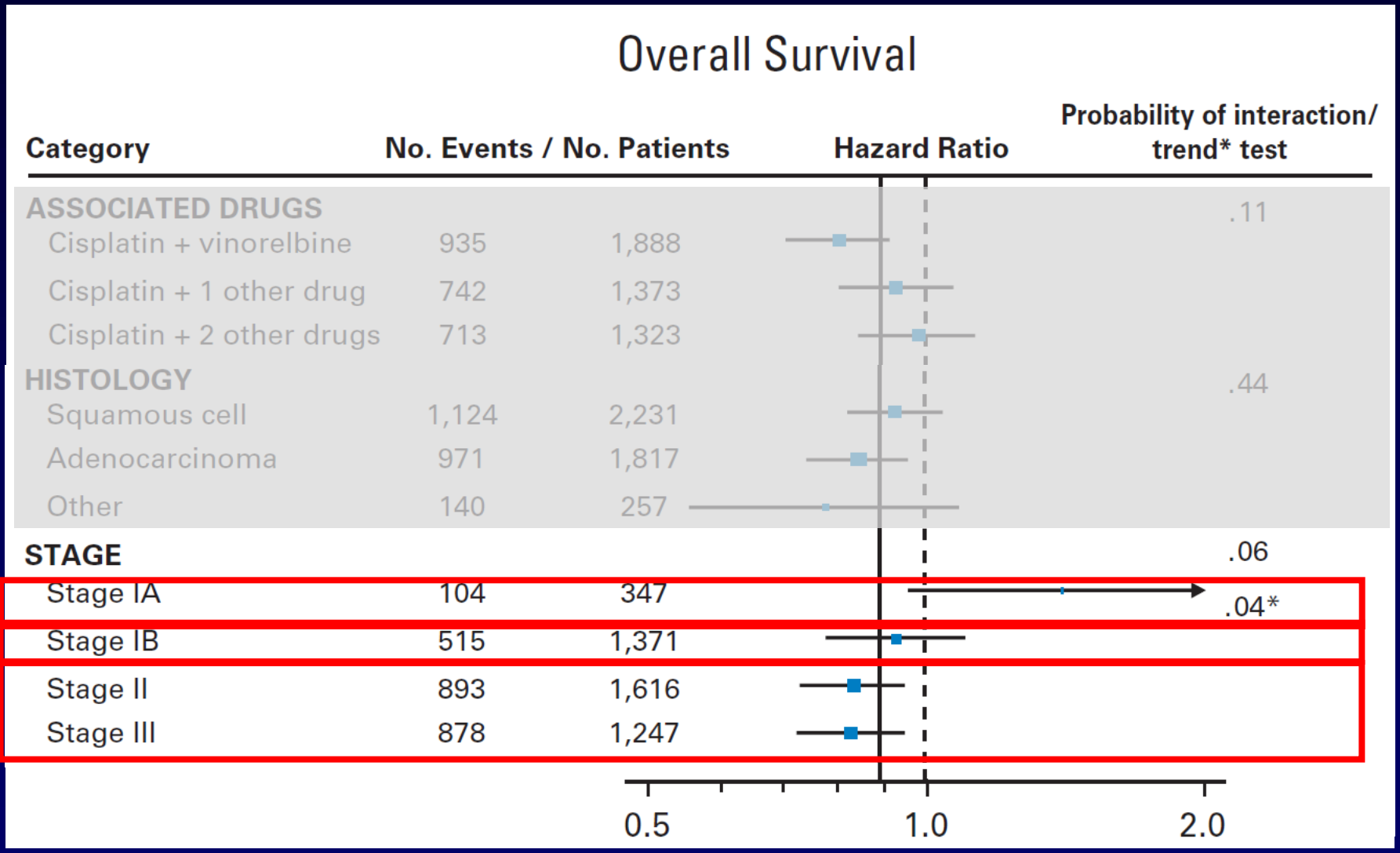
Pignon JP, et al. *J Clin Oncol.* 2008;26(21):3552-3559.

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.

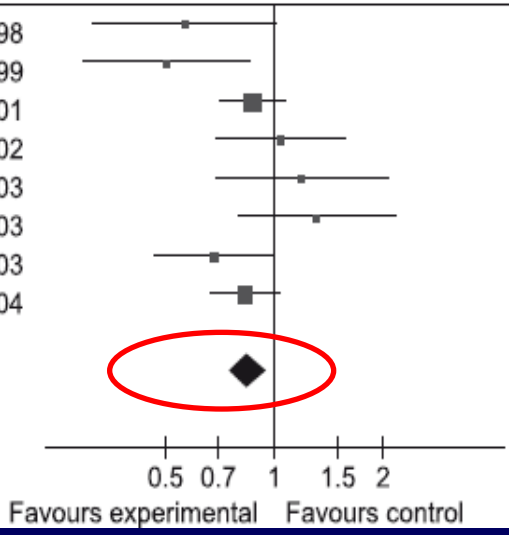
Metaanalysis: Survival in Stage III

Neoadjuvant CHT+Surgery is superior to surgery alone

Study or Subgroup	NC Events	NC Total	SUR Events	SUR Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI	Year
Roth	19	28	27	32	-6.38	11.15	4.1%	0.56 [0.31, 1.01]	1998
Rosell	25	30	30	30	-9.38	13.64	5.0%	0.50 [0.30, 0.85]	1999
Zhou	206	314	235	310	-12.24	89.77	33.0%	0.87 [0.71, 1.07]	2001
Depierre	51	72	40	50	0.89	22.42	8.2%	1.04 [0.69, 1.57]	2002
JCOG	28	31	24	31	2.26	12.92	4.7%	1.19 [0.69, 2.05]	2003
Liao	32	37	24	28	4.144	15.31	5.6%	1.31 [0.79, 2.16]	2003
Li	59	77	47	60	-10.03	26.2	9.6%	0.68 [0.46, 1.00]	2003
Yao	154	234	171	222	-15.19	81.03	29.7%	0.83 [0.67, 1.03]	2004
Total (95% CI)		**823**		**763**			**100.0%**	**0.84 [0.75, 0.95]**	
Total events	574		598						

Heterogeneity: $Chi^2 = 12.27$, $df = 7$ ($P = 0.09$); $I^2 = 43\%$

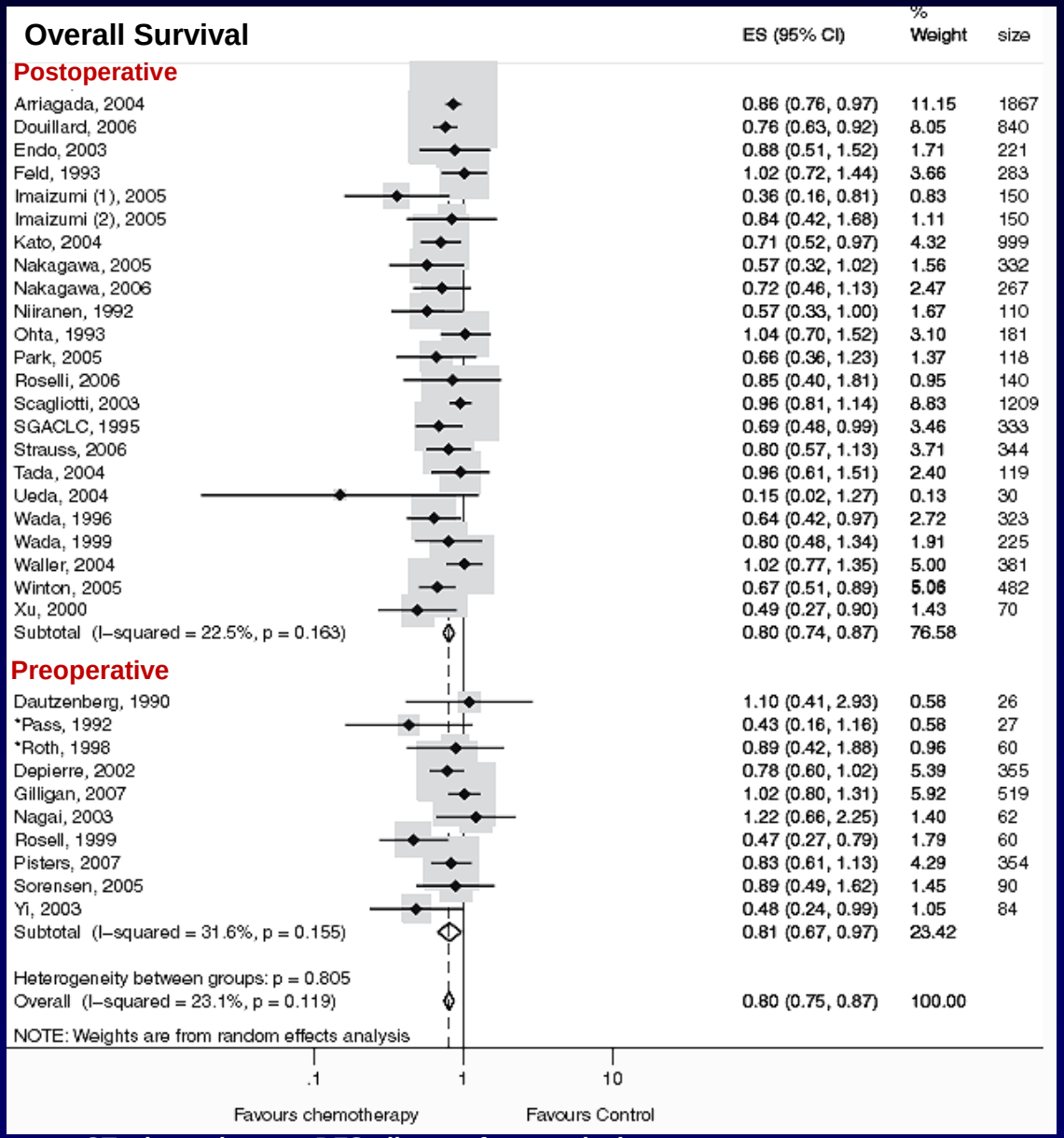
Test for overall effect: $Z = 2.78$ ($P = 0.005$)



HR 0.84 (0.75-0.95); *P* = .005

Song WA, et al. *J Thorac Oncol.* 2010;5(4):510-516.

Neoadjuvant vs Adjuvant Chemotherapy Meta-Analysis



CT, chemotherapy; DFS, disease-free survival

Lim E, et al. *J Thorac Oncol.* 2009;4(11):1380-1388.

- 32 randomized trials
  - 22 postop CT
  - 10 preop CT
- >10,000 participants

Postop vs preop CT:

- OS: HR 0.99 (0.81-1.21)
  - *P* value = .91
- DFS: HR 0.96 (0.77-1.20)
  - *P* value = .70

Radiotherapy vs Concurrent Radiochemotherapy Stage III

	Median OS, months		2-Year-Survival, %		*P* Value
	RT	RCT	RT	RCT	
Dillmann 1996	9.6	13.7	13	26	.01
Sause 2000	12.2	13.7	21	33	.05
Jeremic 1996	14	22	9*	22*	.02
Schaake-K 1992	12	12	9	26	.04

* 4-Year OS

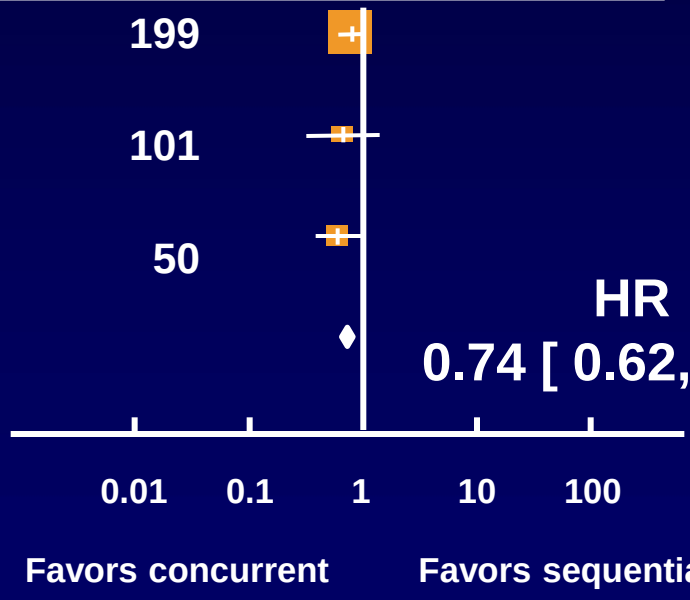
Meta-analysis 2010: HR = 0.71 [0.64, 0.80]

RT, radiotherapy; RCT, radiochemotherapy

O'Rourke N, et al. *Cochrane Database Syst Rev.* 2010;16(6):CD002140.

Concurrent vs Sequential Chemoradiotherapy Overall Survival

Study or Subgroup	Concurrent ChemoRT N	Sequential ChemoRT N	Hazard Ratio IV, Random, 95% CI
Curran 2003	200	199	
Fournel 2001	100	101	
Zatloukal 2003	52	50	
Total (95% CI)			HR 0.74 [0.62, 0.89]

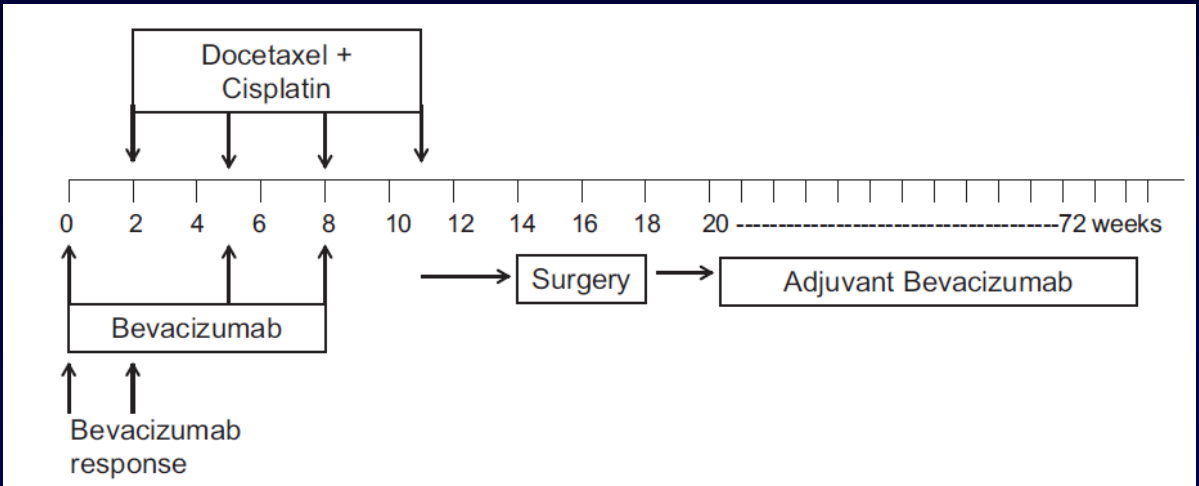


O'Rourke N, et al. *Cochrane Database Syst Rev.* 2010;16(6):CD002140.

Adjuvant Therapy With *EGFR* or VEGF Targeting Agents

BEACON Trial: Bevacizumab Perioperative

Phase II single institution, 50 patients, IB-IIIA nonsquamous



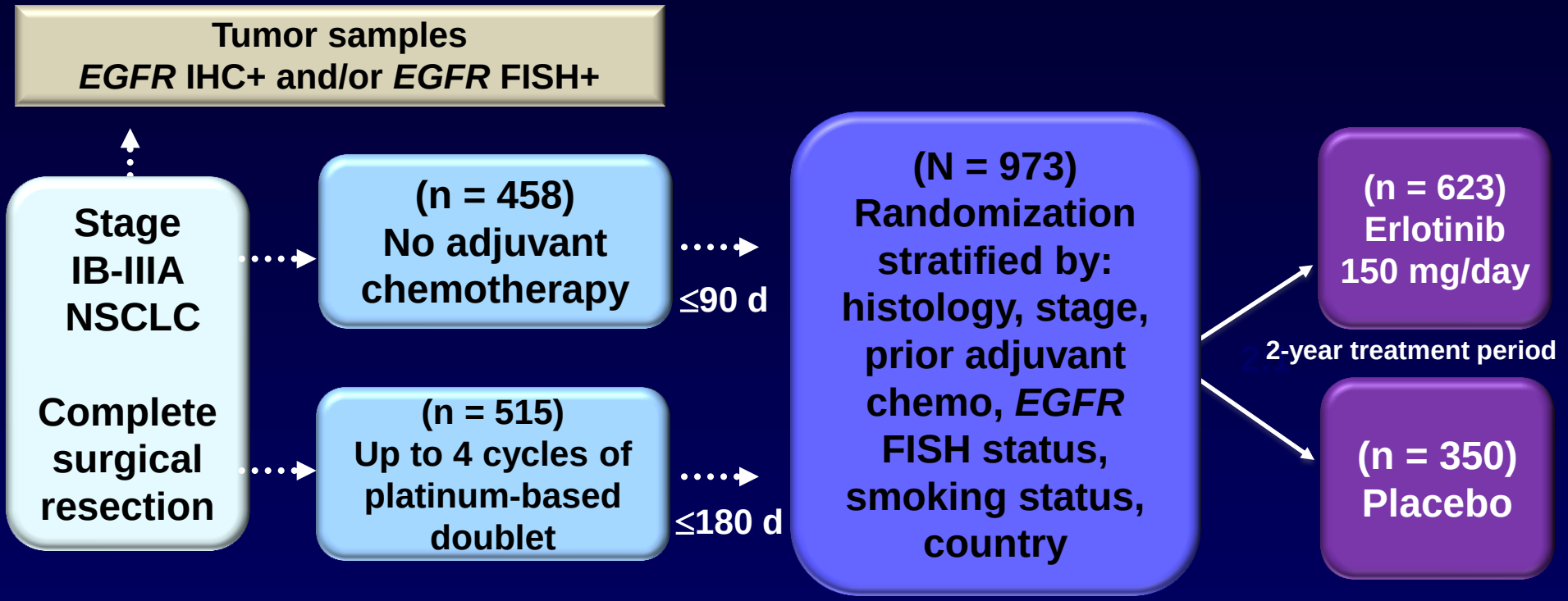
Primary endpoint: Improvement of downstaging (published) 33% → 50%

- **44 patients underwent surgery, 3 patients unresectable disease**
- **ORR 45%**
- **Downstaging 38%**
- **3-year OS 70% vs 56% in the group without downstaging, *P* = .24**
- **Toxicity: Perioperative complications 12%, potentially attributable to preoperative bevacizumab 9%**

ORR, overall response rate

Chaft JE, et al, *J Thoracic Oncol.* 2013:8(8):1084-1090

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+)

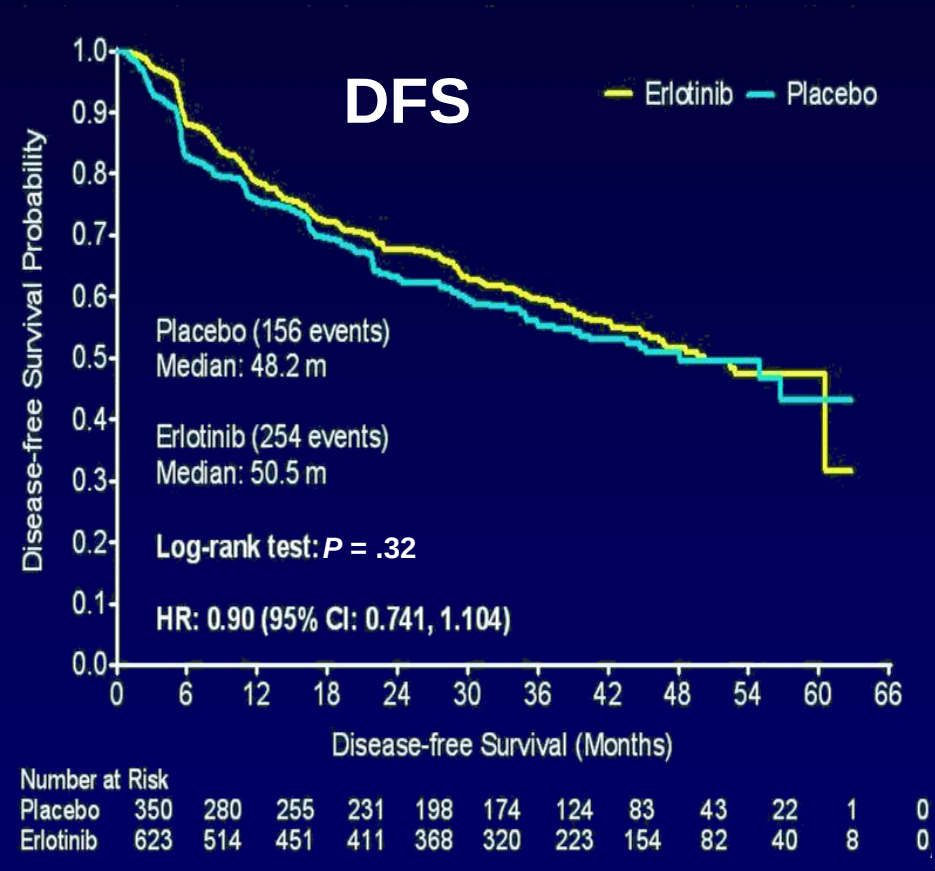
EGFR M+, *EGFR*-activating mutations; FISH, fluorescent *in situ* hybridization

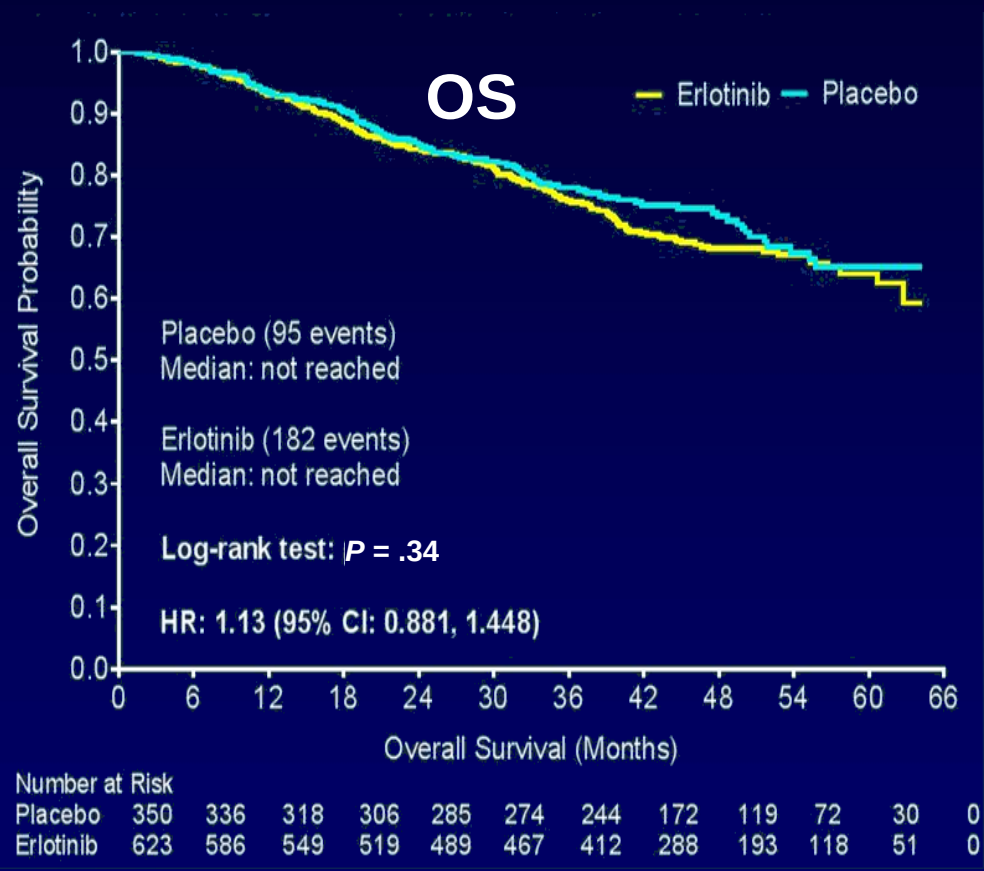
Data cut-off date: 8 Apr 2013

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

RADIANT: DFS and OS

All Randomized Patients

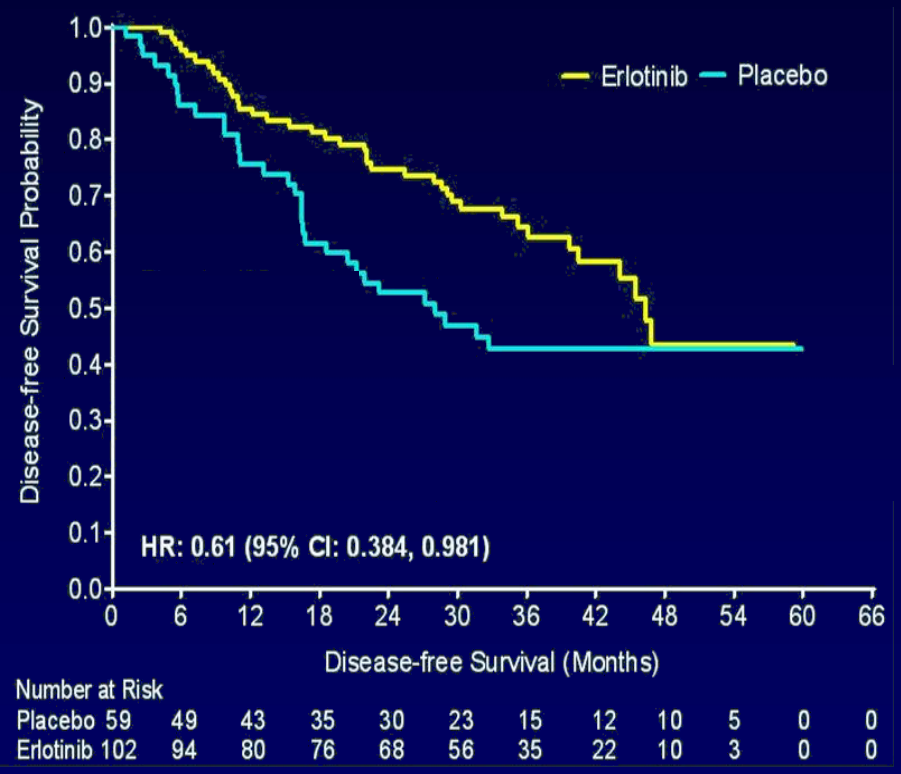




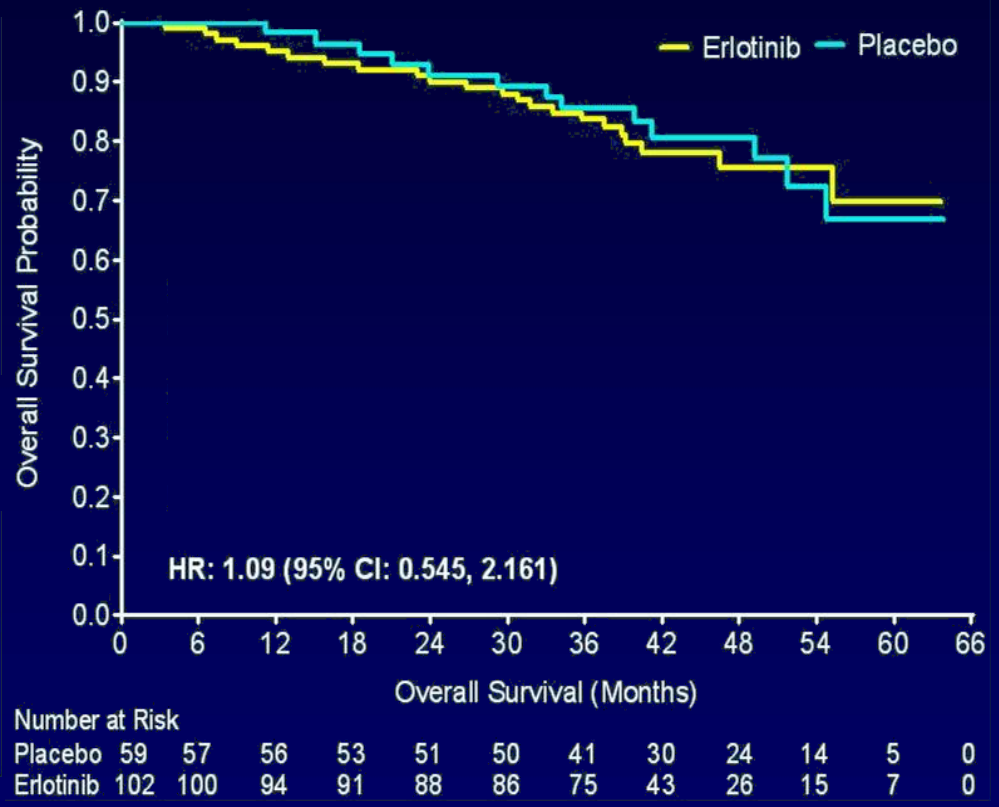
Shepherd FA, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1174O.

RADIANT: DFS and OS
EGFR M+ Subgroup

***EGFR* mutations in 161 patients (55% exon 19 del, 45% exon 21 L858R)**



(not statistically significant due to hierarchical testing)



There were slight imbalances in baseline characteristics:

- **Erlotinib group had less chemotherapy and lower stage**
- **Placebo group had smaller tumor size**

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

Ongoing Initiative: ALCHEMIST Trial

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

Nonsquamous NSCLC (n = 6000 to 8000 patients)
Clinical/pathologic stage IB (≥4 cm), II, IIIA
Postop cohort with negative surgical margins

Preop cohort
Postop cohort

→ Complete resection + standard adj therapy per treating physician

→ Central *EGFR* & *ALK* genotyping

→ ***EGFR*-mutation:** Phase III trial of erlotinib vs placebo x 2 years (n = 410) after any adj tx

→ ***ALK*-rearranged:** Phase III trial of crizotinib vs placebo x 2 years (n = 360) after any adj tx

→ **Without molecular alterations:** Followed q6 months x 5 years after any adj tx

FFPE tissue & blood specimen

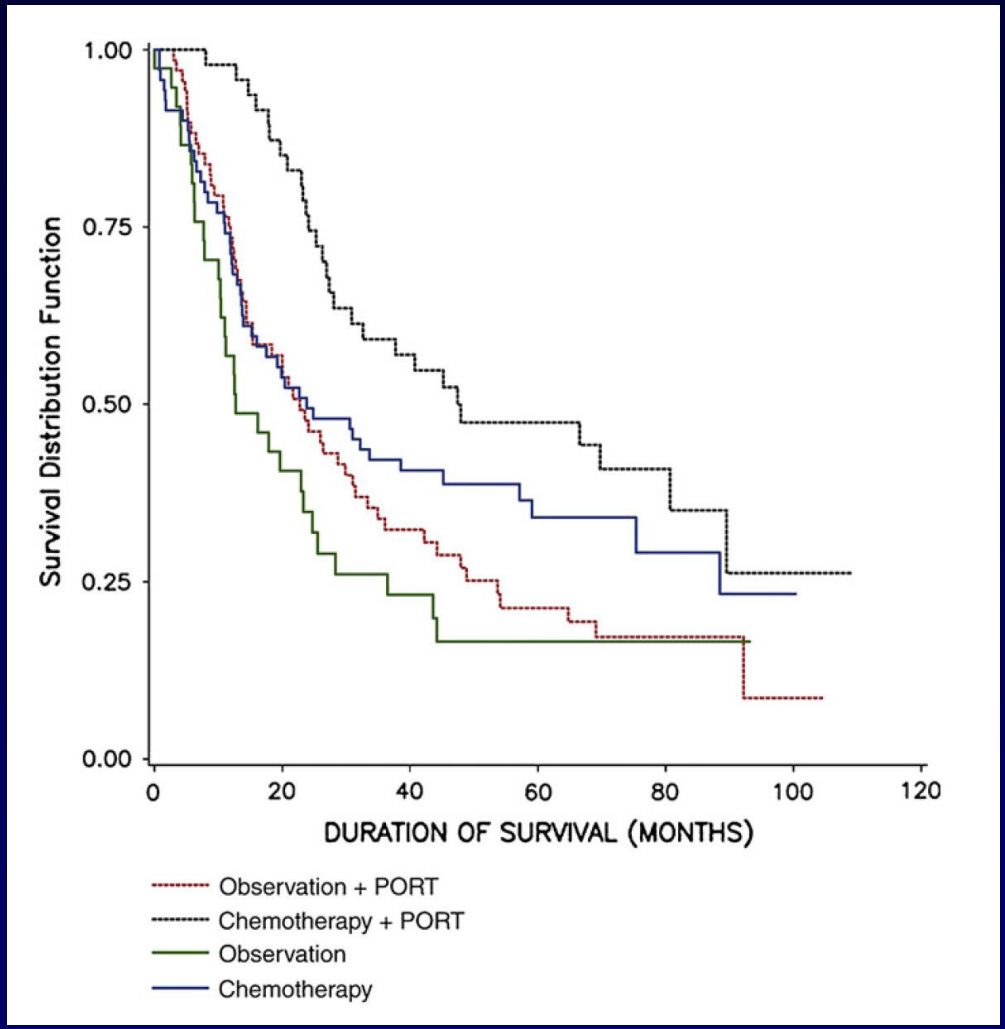
Advanced genomics at the NCI

FFPE tissue from biopsy done at recurrence

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. 3. National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02201992. Accessed 10 December 2014.

Adjuvant Radiotherapy

PORT in N2 Patients



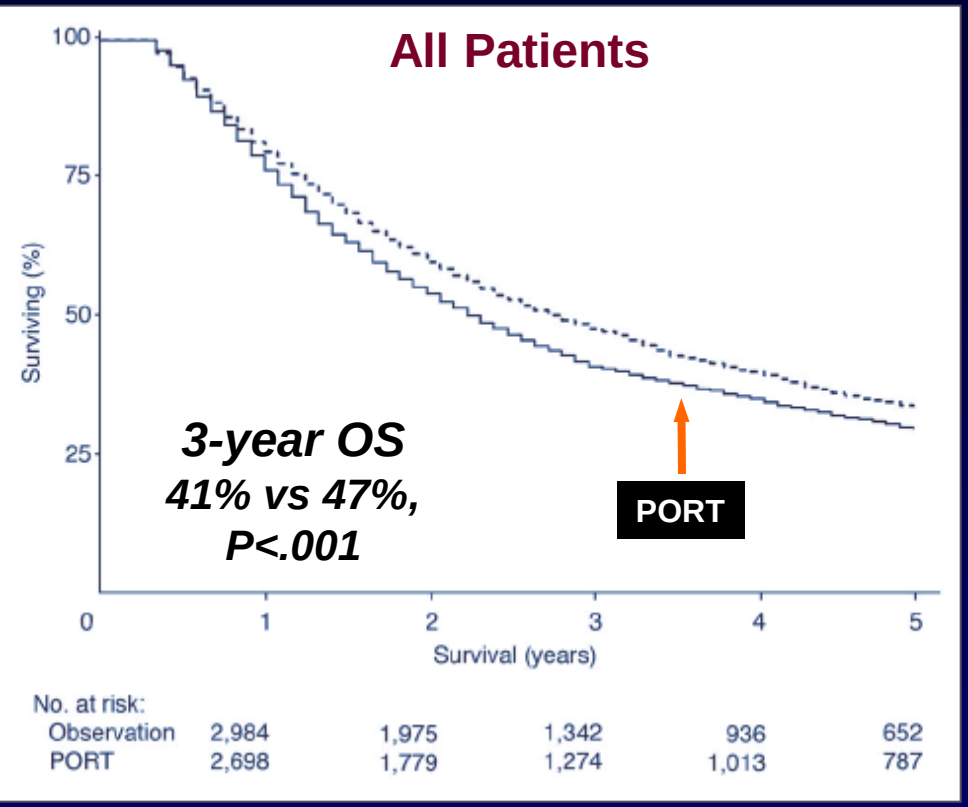
N2	Radiotherapy		No Radiotherapy	
N = 224	No CT	CT	No CT	CT
Patients, n	68	48	38	70
5-years OS	21.3%	47.4%	16.6%	34.0 %

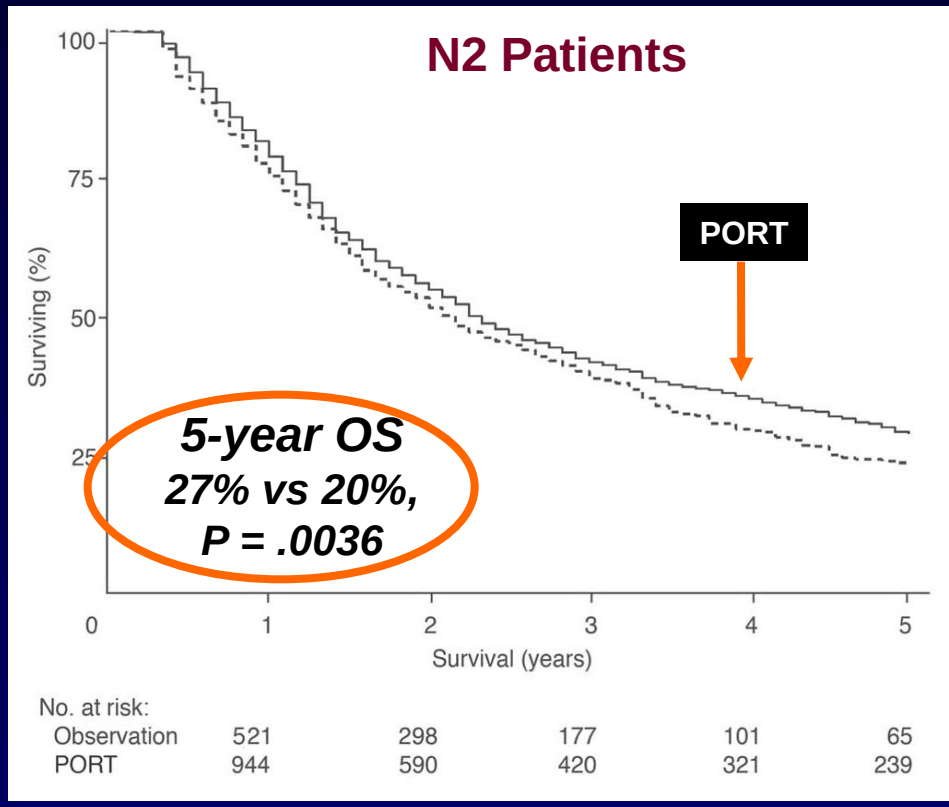
ANITA Trial, N = 840
232 (27.6%) received PORT
116 pN2, 85 pN1

PORT, Post-Operative Radiotherapy

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

PORT in 7465 Resected Stage II-IIIA NSCLC Patients (SEER Database)





Surgery + 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.

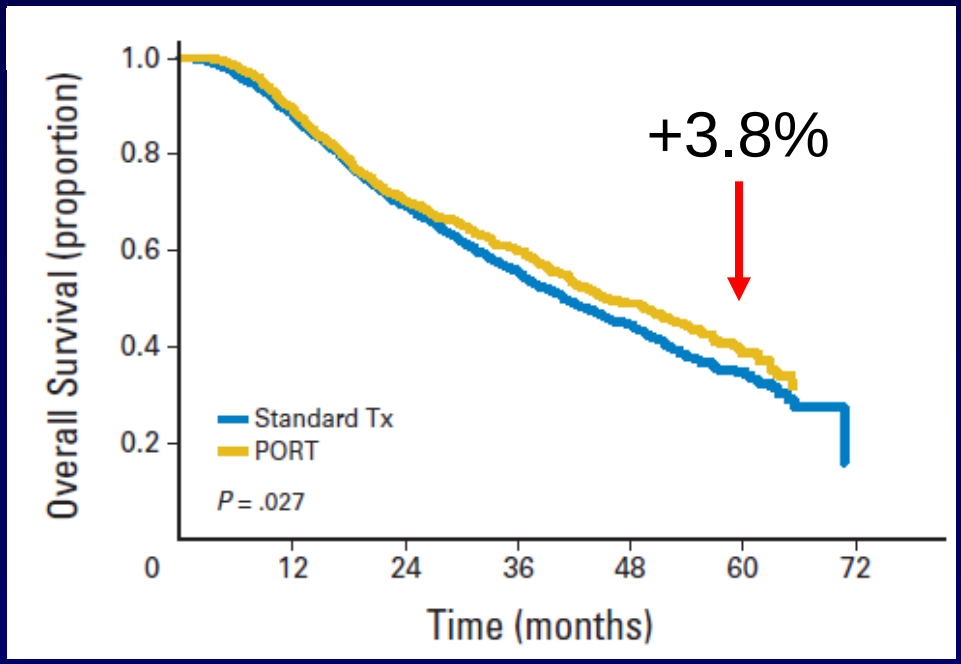
PORT in pN2 Patients Treated With Adjuvant Chemotherapy

- 4483 patients, pN2 NSCLC, R0 resection, adjuvant CT
- 2006-2010, National Cancer Data Base
- PORT n = 1850; no PORT n = 2633

Key results:

- Improved OS remained independently predicted by younger age, female sex, urban population, lower Charlson score, smaller tumor size, multi-agent chemotherapy, resection with at least a lobectomy, and PORT (HR = 0.886; 95% CI, 0.798 to 0.988)
- Median OS (45.2 months vs 40.9 months; 5-year OS, 38.4% vs 34.6%; *P* = .027

Adjusted OS



Robinson CG, et al. *J Clin Oncol.* 2015;33(8):870-876.

Stage III (N2)

What Do We Know?

- Neoadjuvant/adjuvant chemotherapy is beneficial
- Local treatment (radiation, surgery) is beneficial
- Concurrent chemoradiation is better than sequential therapy
- No benefit of EGFR TKI proven so far
- No benefit of neoadjuvant bevacizumab

What Do We Not Know?

- Timepoint of surgery

How I Would Treat This Patient

Pulmonary Adenocarcinoma

Stage T2aN2 (single, 4R) M0 (IIIA-N2);
55years, ECOG 0

Surgery technically feasible?

Surgery upfront

Adjuvant chemotherapy for 4 cycles
Cisplatin 75 mg/m² d1+ vinorelbine 25 mg/m² d1, d8; Q3W

Chemo

Surgery

Adjuvant radiotherapy

Follow-up: Every 3 months for 2 years; every 6 months for year 3-5; then yearly