Optimal Adjuvant Treatment for Resected NSCLC

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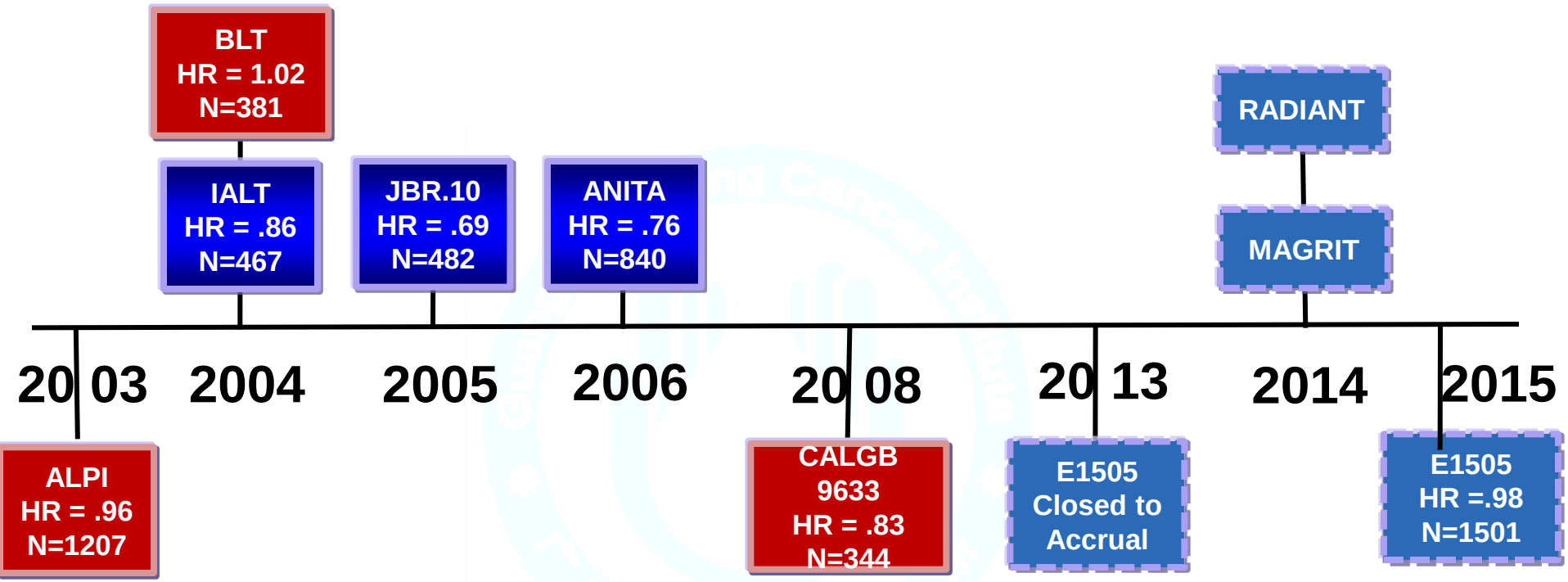
Disclosure

- Conducting research sponsored by Roche, Boehringer-ingelheim, AstraZeneca, Pfizer, Novartis, BMS;

- Received the honorarium from Roche, AstraZeneca, Eli Lilly, Sanofi.

Adjuvant Therapy Timeline



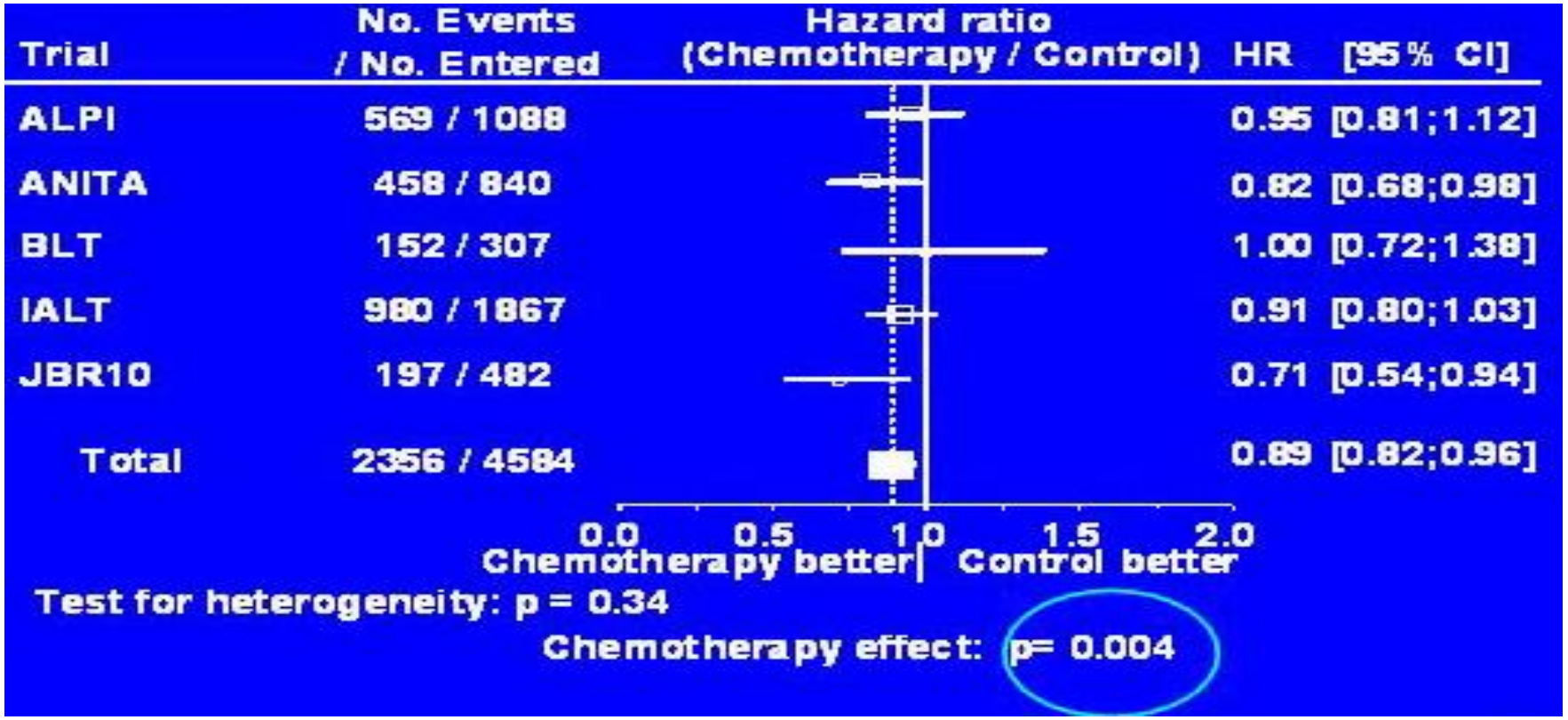
ALPI–MVP vs OBS Stage I-IIIA Scagliotti GV et al. J Natl Cancer Inst 2003; 95: 1453-61
BLT-CPPP-based vs OBS Stage I-III Waller D et al. Eur J Cardiothorcic Surg 2004;26:173-182
IALT–CDDP-based vs OBS Stage I-IIIA Arriagada R et al. N Engl J Med 2004; 350: 350-61
JBR.10–CDDP-VNR vs OBS Stage IB-II Winton T et al. N Engl J Med 2005; 352:2589-97
ANITA–CDDP-VNR vs OBS Stage IB-IIIA Douilland JY et al. Lancet Oncol 2006; 7: 719-27
CALGB 9633–PAC-CARBO vs OBS Stage IB Strauss GM et al. J Clin Oncol 2008; 26: 5043-51

The NEW ENGLAND JOURNAL of MEDICINE

IALT was first trial that confirmed ADJ in NSCLC,2004

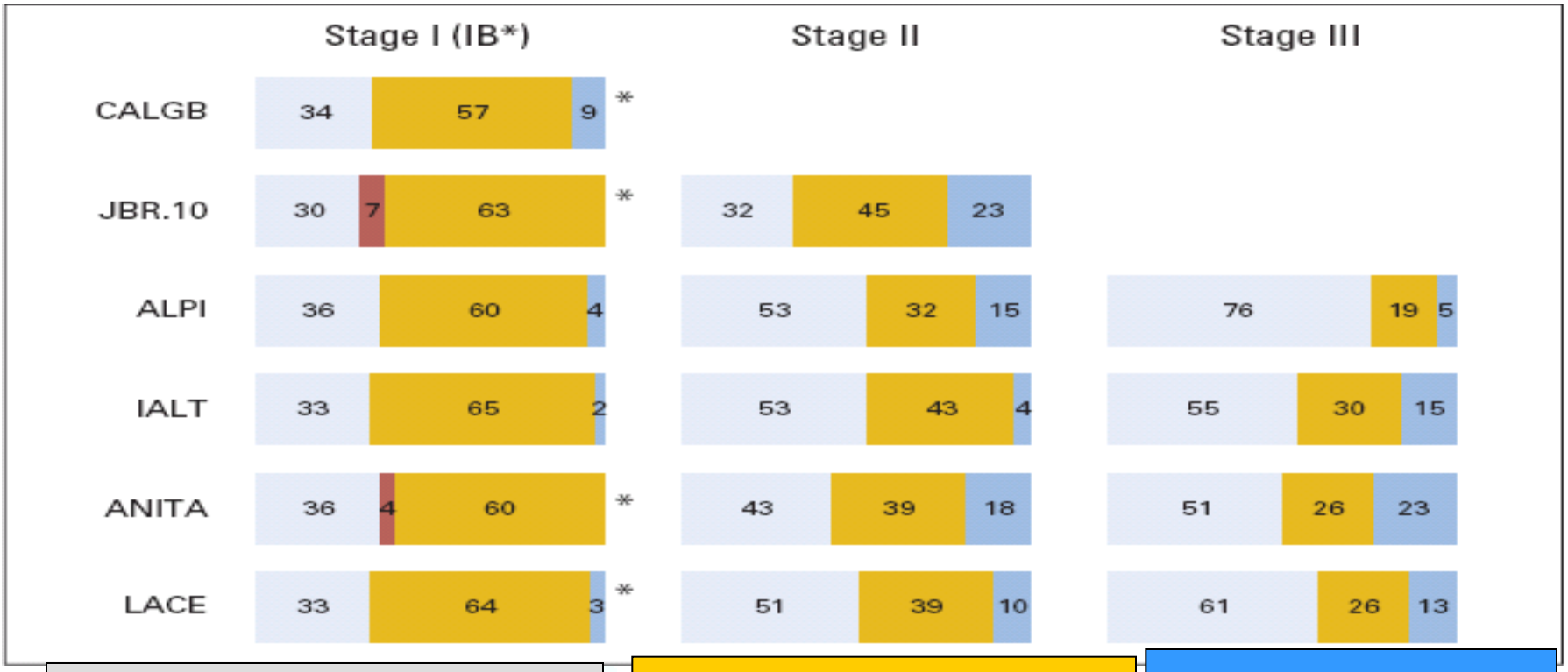
Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer

The International Adjuvant Lung Cancer Trial Collaborative Group*



LACE IPD SR: 4584 cases from 5 trials（JCO 2008,26:3552）

CCO & ASCO guideline 2007



Pts die within 5 years whether they receive chemotherapy or not

Pts live without receiving chemotherapy

Pts live because of chemotherapy

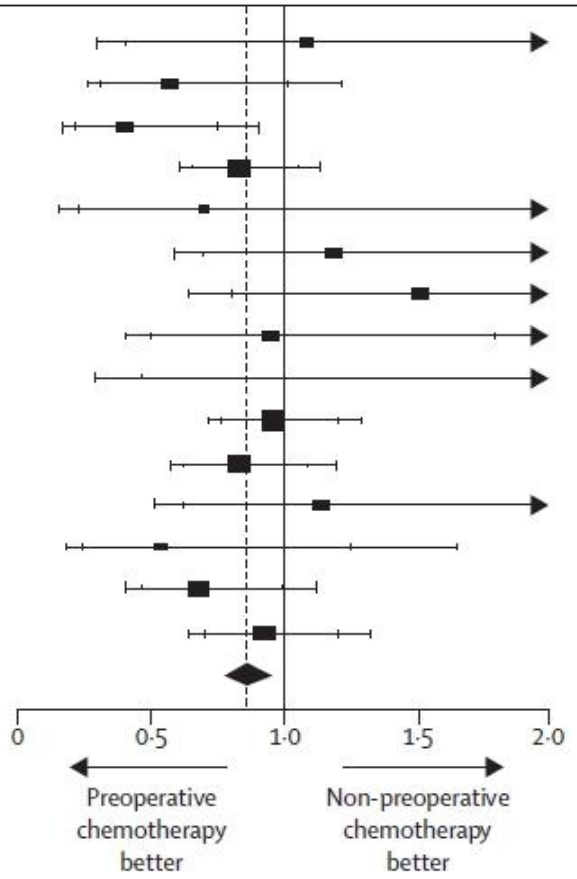
Estimated absolute risk and benefit for 100 patients with NSCLC

Ⅱ、Ⅲ期: To prevent one death at 5 years for every 15 patients treated.

Ⅰ期: To treat 43 patients to prevent one death

Neo-adjuvant: Overall survival
15 trials, 2385 patients, 1427 deaths

	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=0·007**



Overall effect

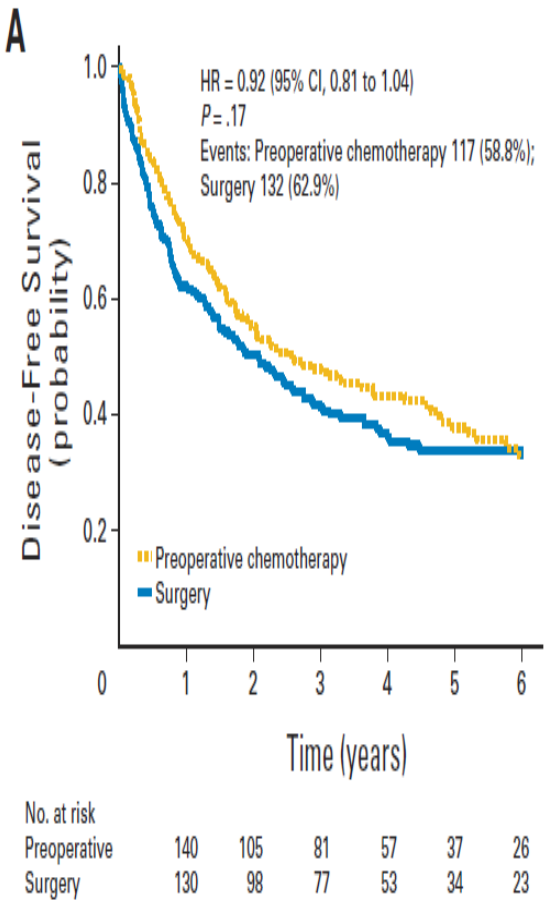
HR=0.87 (95% CI 0.78-0.96), p=0.007

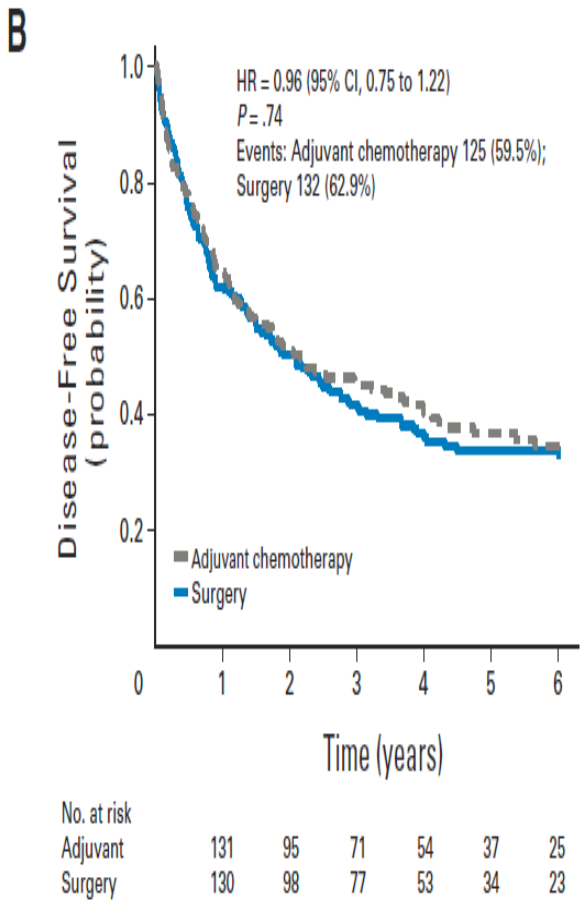
5% survival improvement at 5 years

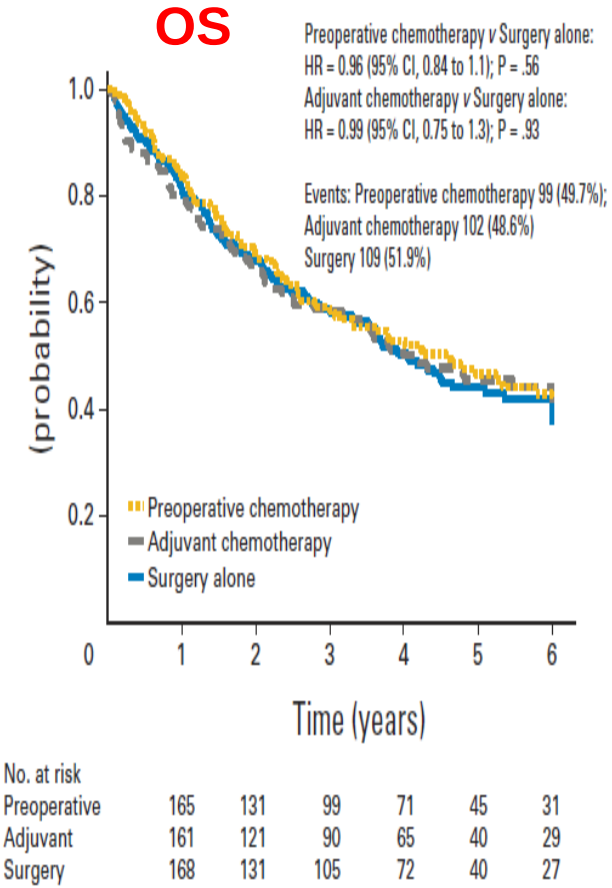
Heterogeneity: chi-square=18.75, df=14, p=0.175, I^2=25.35

NSCLC Meta-analysis group Lancet 2014;383:1561

Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non–Small-Cell Lung Cancer



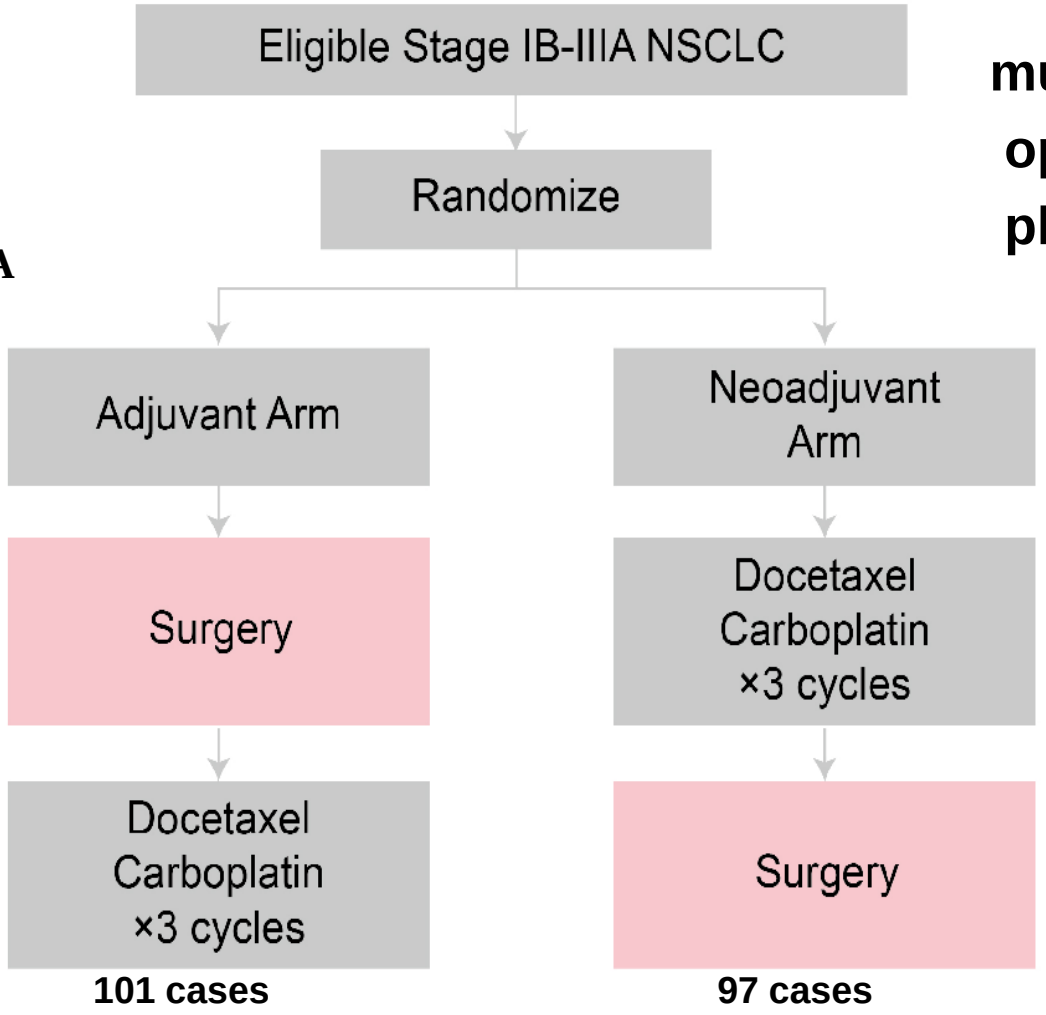




Felip JCO 2010

CSLC 0501: Neo vs adj in resected NSCLC

Stratification:
Center
IB *VS* II *VS* IIIA



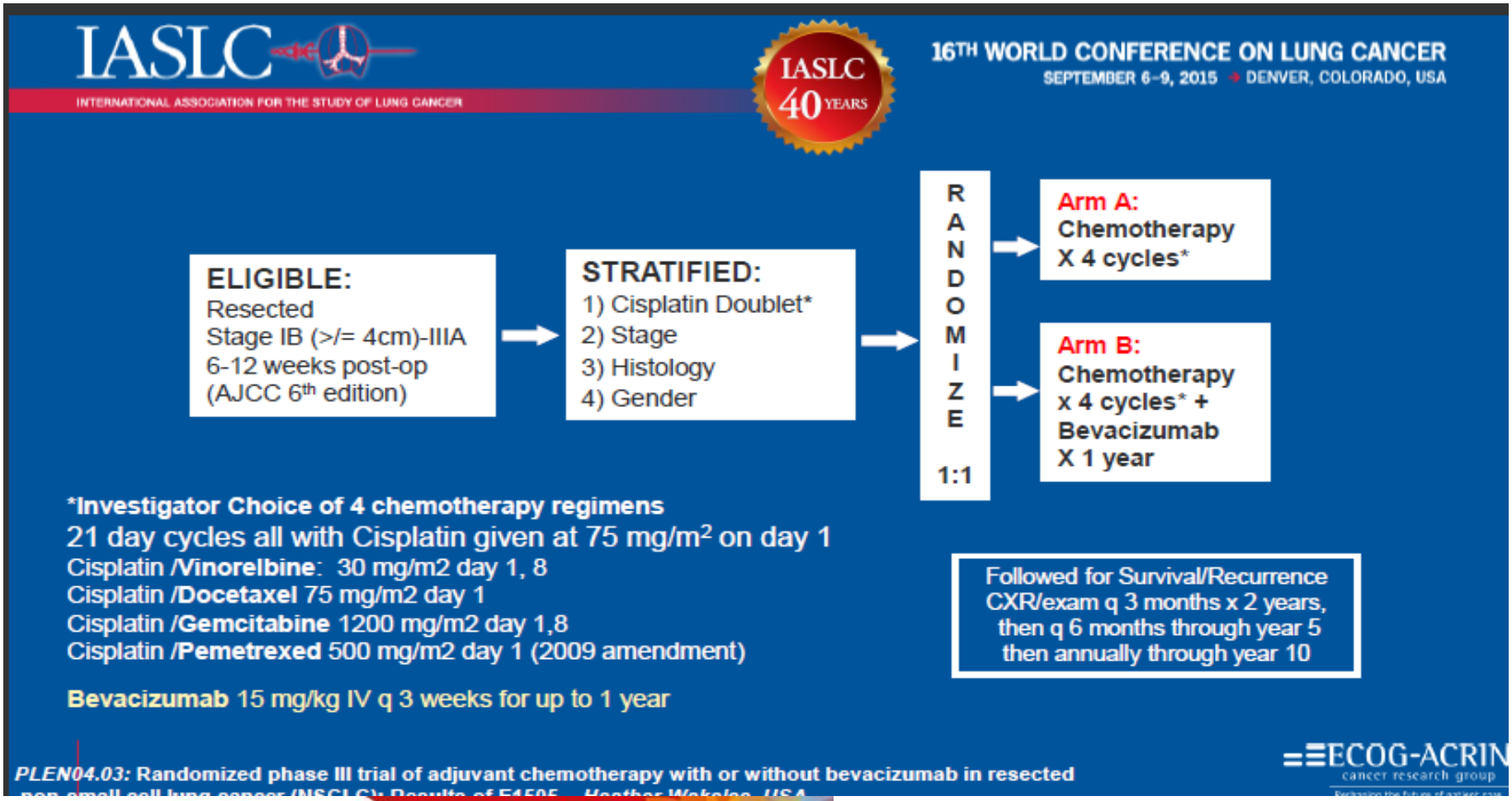
101 cases **97 cases**

multi-center
open label
phase 3 trial

Estimated Enrollment :410

Start : Mar. 2006
Dec. 2010 (early closed)

Could we add a new drug in chemo double to improve survival?



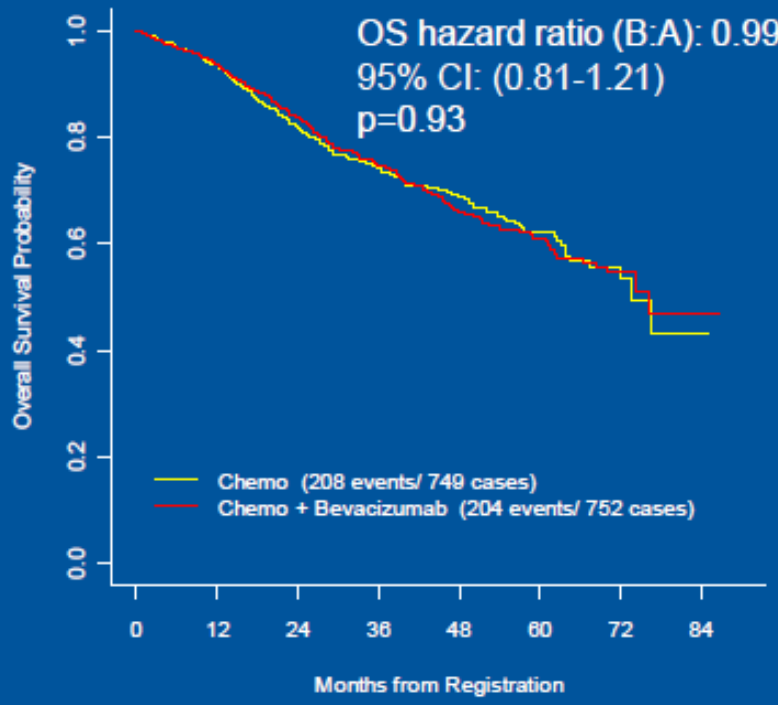
E1505 not met its primary end point

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

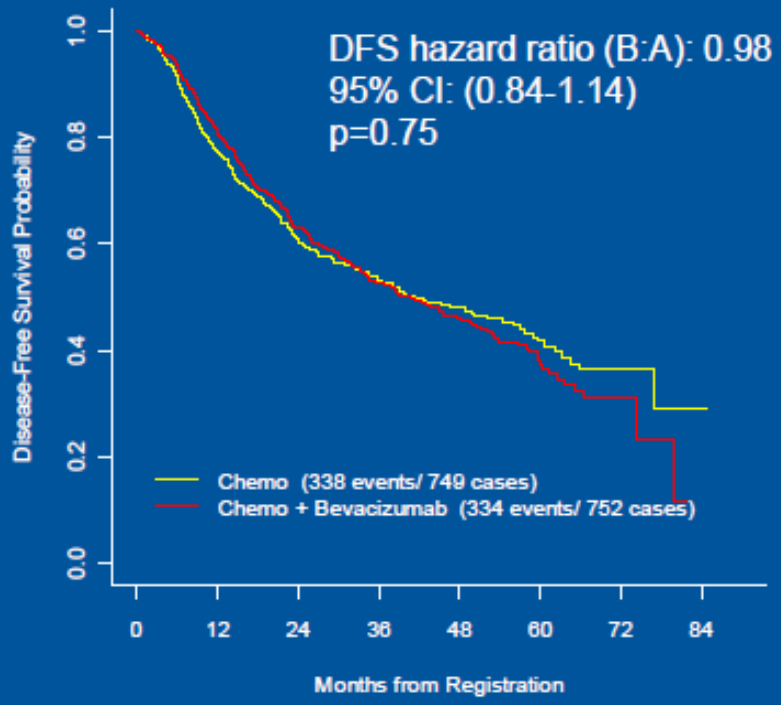
IASLC 40 YEARS

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 ✈ DENVER, COLORADO, USA

Overall Survival



Disease Free Survival



PLEN04.03: **Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected non-small cell lung cancer (NSCLC): Results of E1505 – *Heather Wakelee, USA***

ECOG-ACRIN cancer research group
Reshaping the future of patient care

MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)

- **Study objective**
  - To determine if recMAGE-A3 + AS15 cancer immunotherapeutic (MAGE-A3 CI) as adjuvant therapy over 27 months improves DFS in patients with resected NSCLC

Key patient inclusion criteria

- **Stages IB, II, IIIA NSCLC**
- **Completely resected tumour**
- **MAGE-A3-positive**
- **PS 0–2**

(n=2,272)

R
2:1

13 IM injections of MAGE-A3 CI (n=1,515) → **PD**

Stratification
- **Chemotherapy**

13 IM injections of placebo (n=757) → **PD**

Primary endpoint

- **DFS**

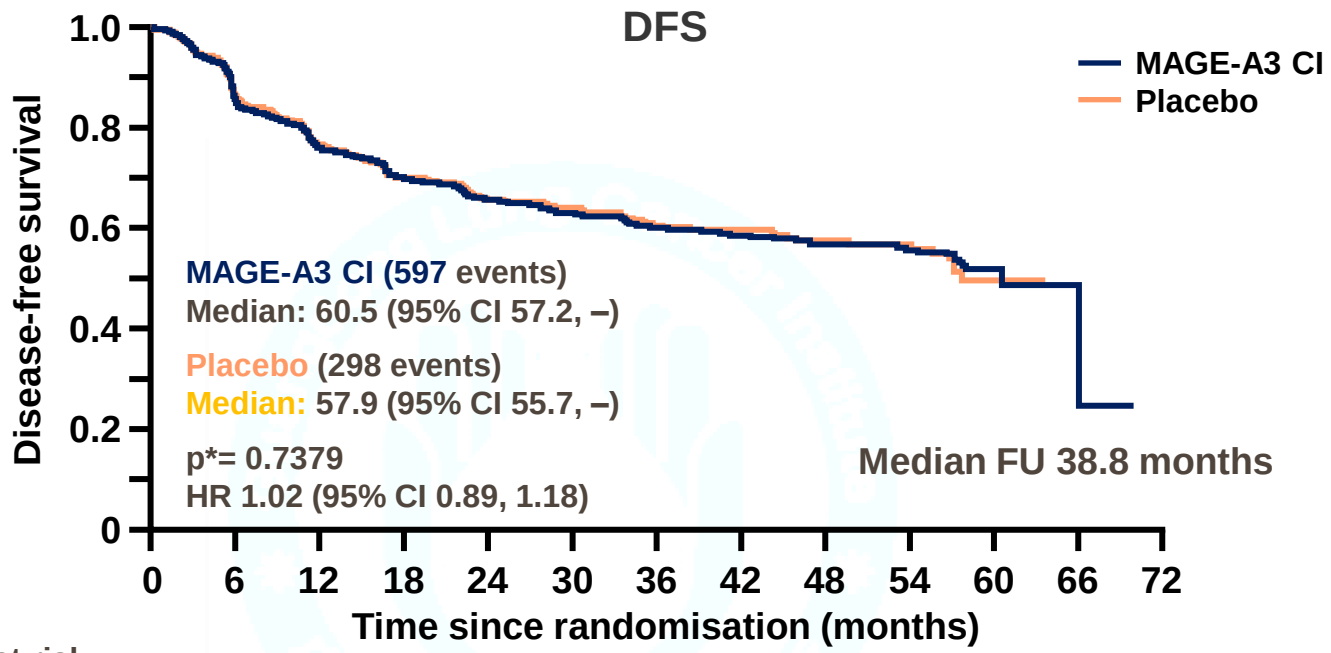
Secondary endpoints

OS, lung cancer specific survival, immunogenicity

Safety, health-related QoL

Vansteenkiste et al. Ann Oncol 2014; 25 (suppl 4): abstr 1173O

MAGRIT trial: Adjuvant vaccine therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)



Number at risk												
MAGE-A3 CI	1,515	1,257	1,115	1,013	887	656	476	339	220	127	19	2
Placebo	757	639	562	514	448	328	253	180	114	62	6	0

*Likelihood ratio test from Cox regression model stratified by chemotherapy and adjusted for baseline variables used as minimisation factors

Vansteenkiste et al. Ann Oncol 2014; 25 (suppl 4): abstr 1173O

Summary: Current status of Adjuvant treatment

- Adjuvant and neo-adjuvant chemotherapy give 5% survival benefit for patients with resected stage 2-3A NSCLC
- Adjuvant chemo in stage 1b is controversy
- Adjuvant vaccine immunotherapy don’t work in resected NSCLC
- New adjuvant therapy paradigm is an option

EGFR-TKI vs Chemotherapy in 1L EGFR-mu NSCLC

Trial	Patient Population	TKI	Pts No.	PFS (months)			OS (months)		
				TKI	Chemo	HR(95%CI)	TKI	Chemo	HR(95%CI)
EGFR mutation+ subgroup analysis in phase III trials									
IPASS	Asia, non-smoker	Gefitinib	261	9.5	6.3	0.48 (0.36-0.64)	21.6	21.9	0.78 (0.50-1.20)
First Signal	Korea, non-smoker	Gefitinib	42	8.4	6.7	0.61 (0.31-1.22)	30.6	26.5	0.82 (0.352-1.922)
Phase III trials in EGFR mutation+ patients									
NEJ002	Japan	Gefitinib	228	10.8	5.4	0.322 (0.236-0.438)	27.7	26.6	0.88 (0.634-1.241)
WJTOG3405	Japan	Gefitinib	172	9.6	6.6	0.520 (0.378-0.715)	35.5	38.8	1.185 (0.767-1.829)
OPTIMAL	China	Erlotinib	154	13.1	4.6	0.16 (0.10-0.26)	32.1	37.5	1.065
EURTAC	Caucasian	Erlotinib	174	9.7	5.2	0.37 (0.25-0.54)	22.9	18.8	0.80 (0.47-1.37)
LUX-Lung3	Asia, non-Asia	Afatinib	345	11.1	6.9	0.58 (0.43-0.78)	27.3	24.3	0.81 （0.66-0.99）
LUX-Lung6	Asia	Afatinib	364	11.0	5.6	0.28 (0.20-0.39)			
ENSURE	China	Erlotinib	210	11.0	5.6	0.42 (0.27-0.66)	26.3	25.5	0.91 (0.63-1.31)

1. Mok, et al. NEJM 2009; 2. Han et al. JCO 2012. 3. Maemondo, et al. NEJM 2010; 4. Mitsudomi, et al. Lancet Oncol 2010;
5. Zhou, et al. Lancet Oncol 2011; 6. Rosell et al. Lancet Oncol 2012. 7. Sequist, et al. JCO 2013. 8. Wu et al. Lancet Oncol 2014
9. Wu et al. Ann Oncol 2015.

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LUX-Lung3	Asia, non-Asia	Afatinib	345	11.1	6.9	0.58 (0.43-0.78)	Exon19 31.7	20.7	0.59 (0.45-0.77)
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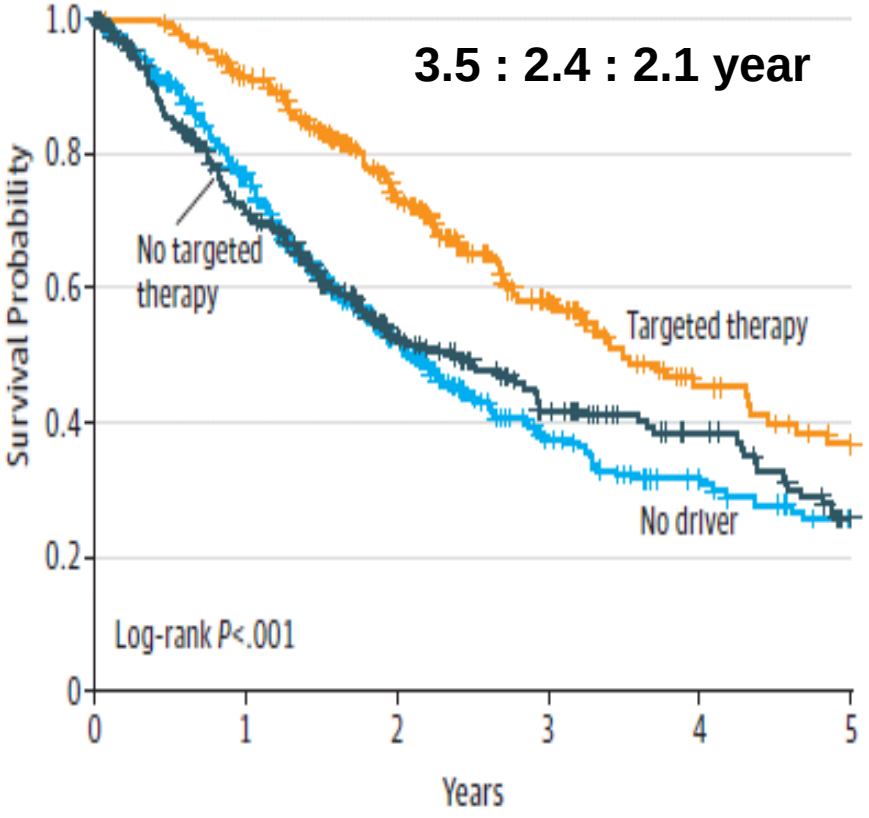
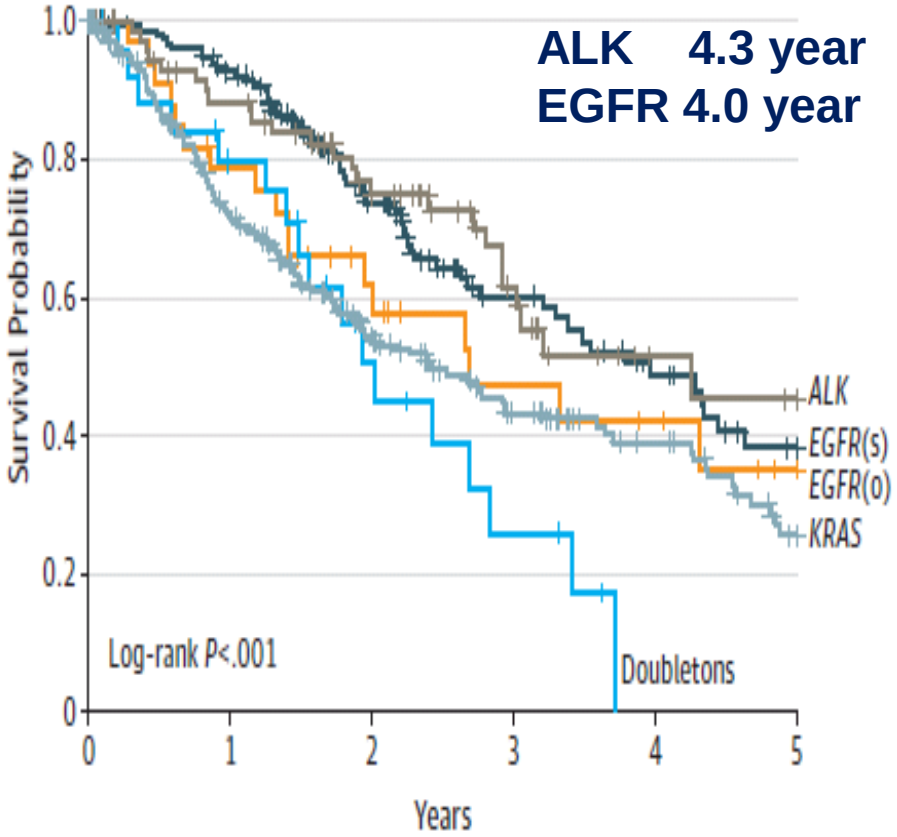
9. Wu et al. Ann Oncol 2015.

Target therapy has improved OS for advanced NSCLC with driver genes





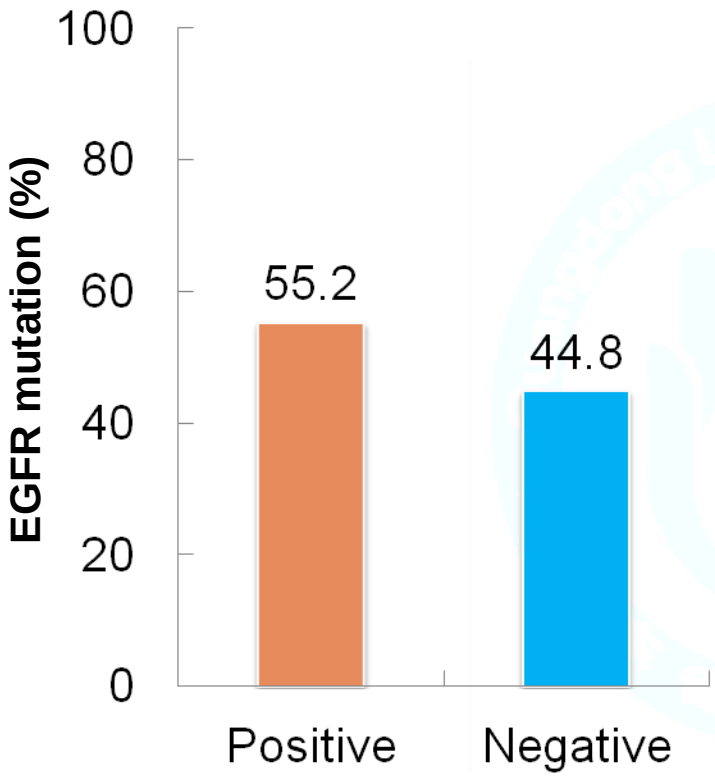
Kris MG,et al. JAMA. 2014 May 21;311(19):1998-2006.

Knowledge Gaps

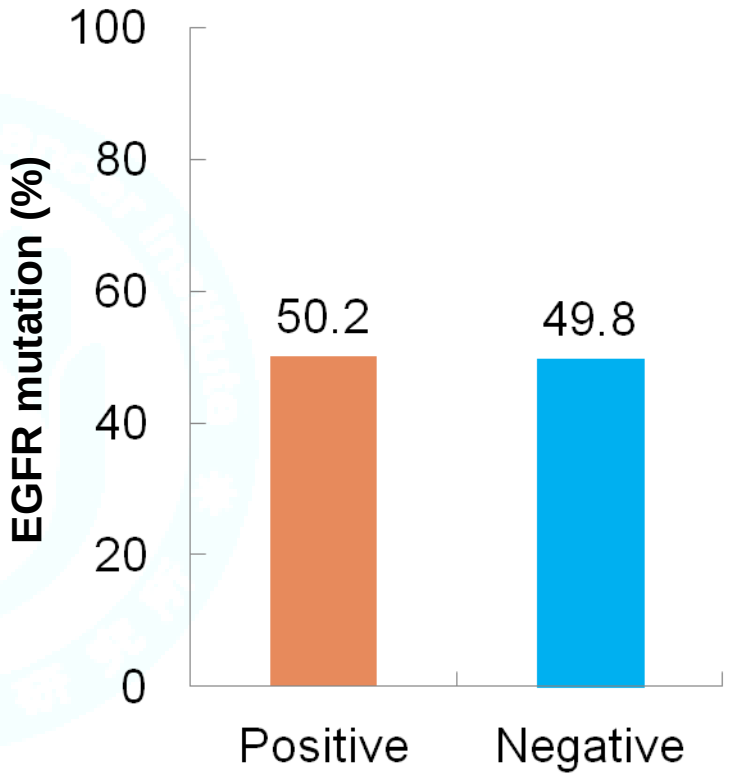
- **Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?**
  - **Is EGFR mutation rate different between early stage and advanced NSCLC?**
  - **Heterogeneity in resected NSCLC**
- **What novel treatment strategies are being pursued?**

EGFR mutation between early and advanced NSCLC

2013 ASCO Early stage NSCLC
ICAN

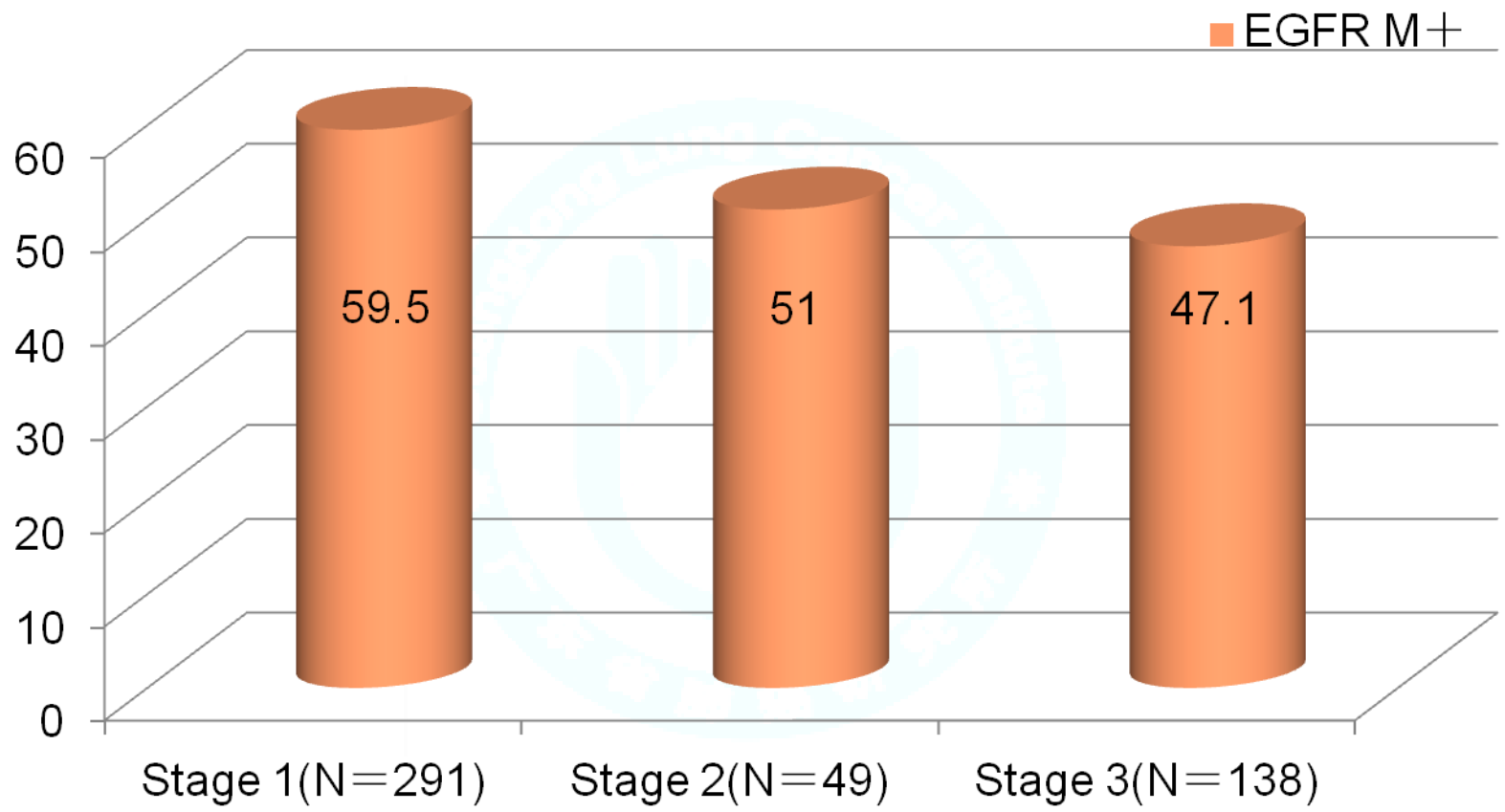


2012 ASCO Advanced NSCLC
PIONEER



Zhang X, et al. 2013 ASCO Abstract 1547.
Yang PC, et al. 2012 ASCO Abstract 1534.

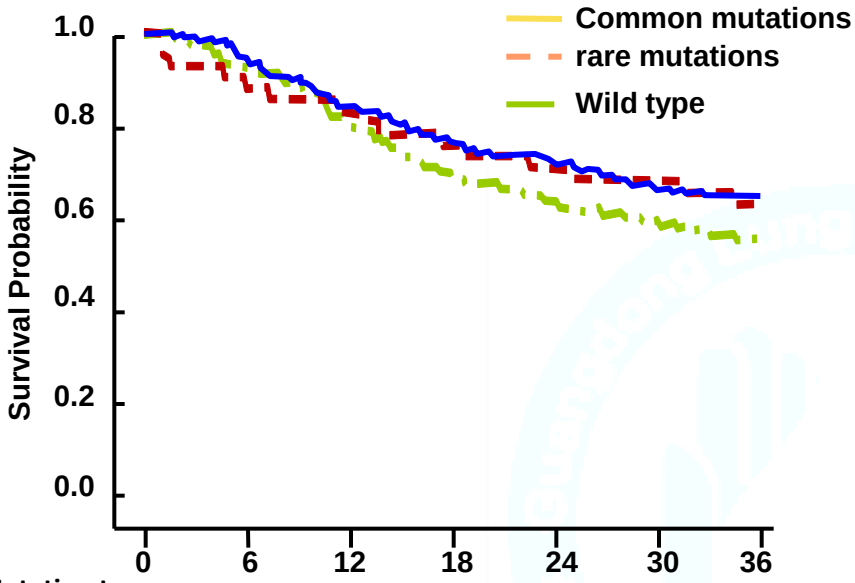
EGFR Mutation Rate by pStage



Wu et al. ICAN study ESMO 2014

Results: 3-yr DFS rate

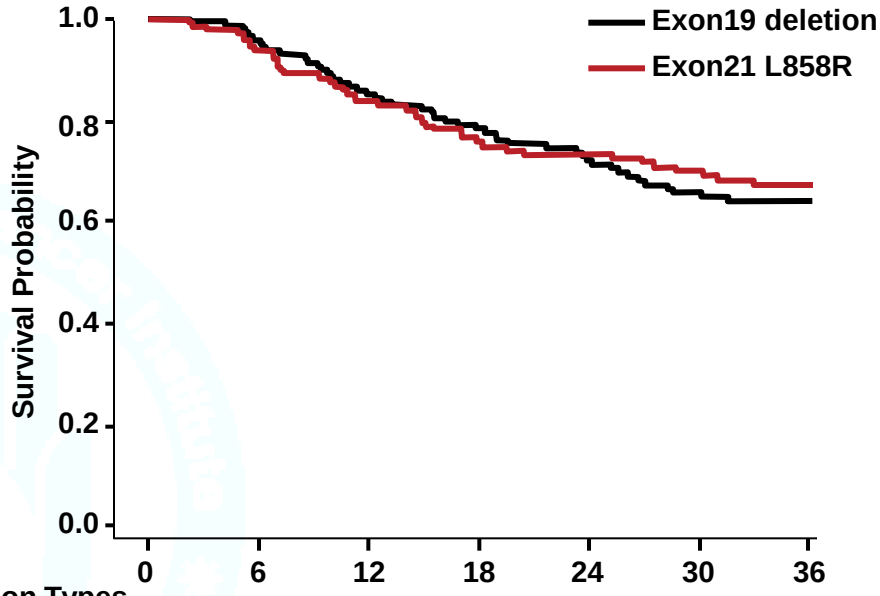
3-yr DFS (Common Mut. vs. rare Mut. vs. wild type)



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

Mutation type	3-yr DFS rate(95% CI)	P Value*
Common mutation	66.0% (59.8%, 71.4%)	0.1021
Rare mutation	63.4% (46.7%, 76.1%)	
Wild type	56.8% (50.2%, 62.8%)	

3-yr DFS (Exon19Del vs. Exon21 L858R)



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

Mutation type	3-yr DFS rate(95% CI)	P Value*
exon19 deletion	63.8% (54.9%, 71.4%)	0.6864
exon21 L858R	67.2% (58.2%, 74.7%)	

*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.

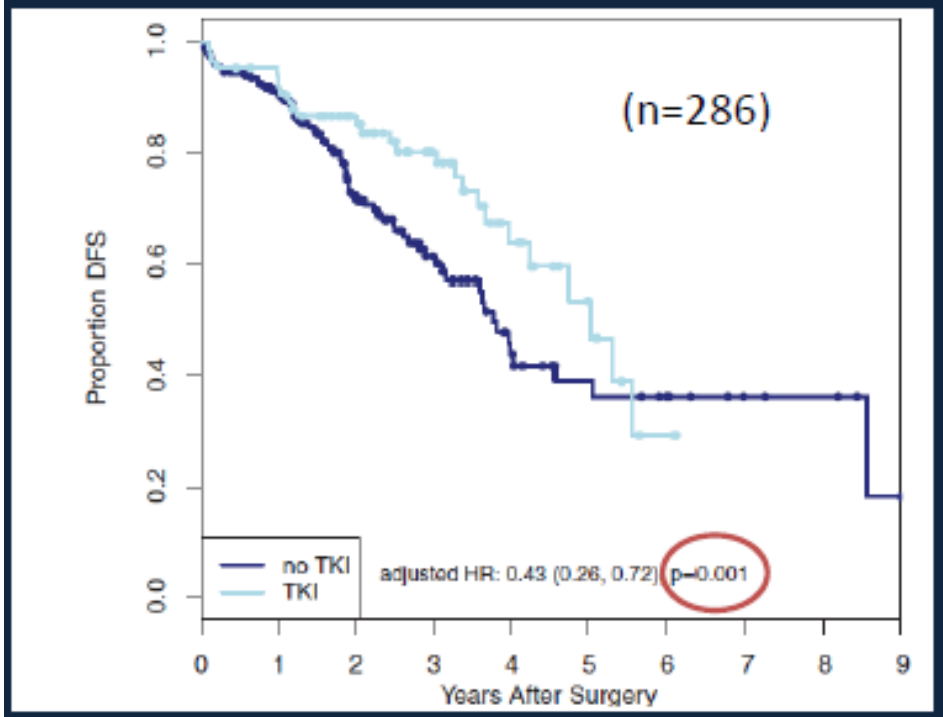
Knowledge Gaps

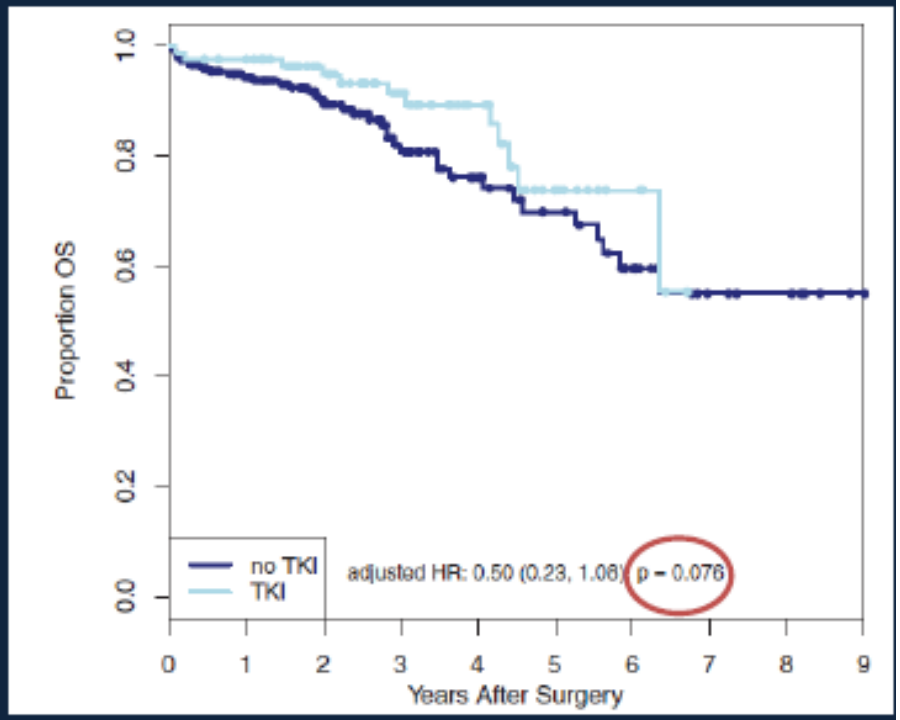
- **Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?**
  - Is EGFR mutation rate different between early stage and advanced NSCLC?
  - Heterogeneity in resected NSCLC
  - What novel treatment strategies are being pursued?

Retrospective study:
Adjuvant TKI for EGFR+ NSCLC

	No Adjuvant Gefitinib/ Erlotinib (n=202)	Adjuvant Gefitinib/ Erlotinib (n=84)
Stage I	84%	52%
Stage II	8%	17%
Stage III	8%	31%

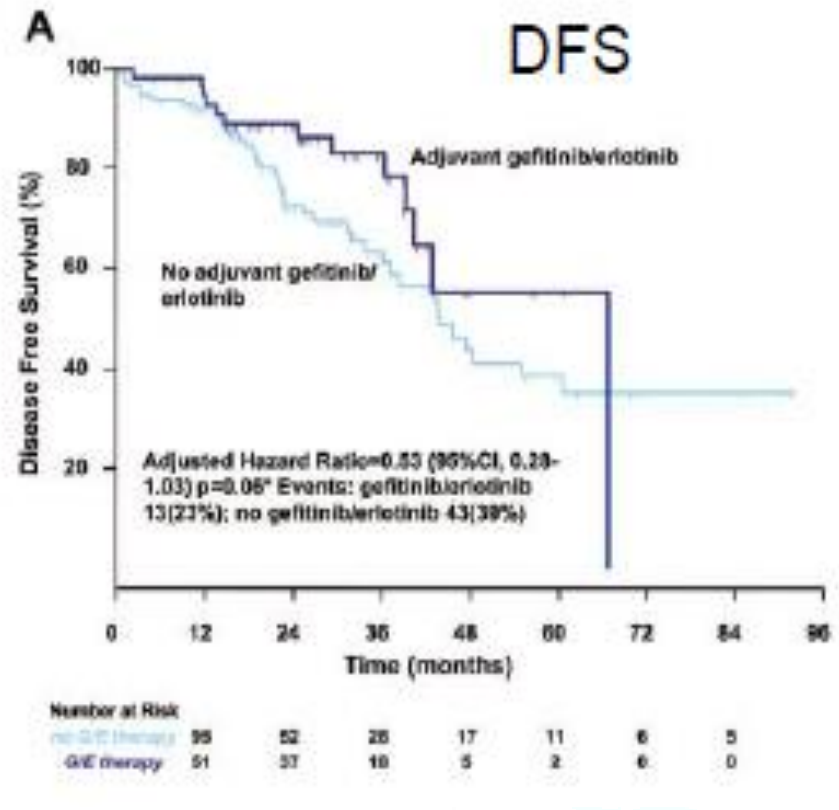
"Difficult to distinguish the prognostic from the predictive impact of *EGFR mutations in a retrospective study where EGFR TKI is preferably administered to higher stage diseases*"





D' Angelo JTO 2012

Retrospective study:
Adjuvant TKI for EGFR＋ NSCLC



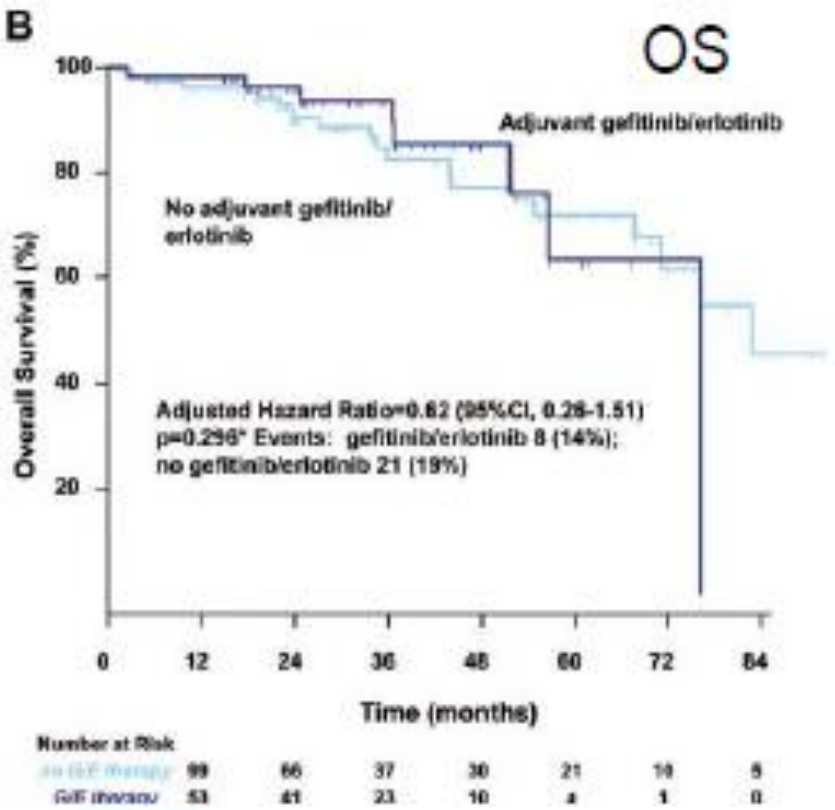


TABLE 3. Multivariate Disease-Free Survival Analysis

n = 167	N (Event N)	2-yr Survival (95% CI)	Adjusted Hazard Ratio* (95% CI)	Adjusted p
Adjuvant erlotinib/gefitinib	56 (13)	89% (77–95)	0.53 (0.28–1.03)	0.06
No adjuvant erlotinib/gefitinib	111 (43)	72% (61–80)		

* Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.

TABLE 4. Multivariate Overall Survival Analysis

n = 167	N (Event N)	2-yr Survival (95% CI)	Adjusted Hazard Ratio* (95% CI)	Adjusted p
Adjuvant erlotinib/gefitinib	56 (8)	96% (85–99)	0.62 (0.26–1.51)	0.296
No adjuvant erlotinib/gefitinib	111 (21)	90% (82–95)		

* Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.

Janjigian JTO 2010

Adjuvant Gefitinib: JBR.19

- Path stage IB - III NSCLC
- Complete surgical resection
- PS 0-2
- Adjuvant chemo and /or XRT allowed

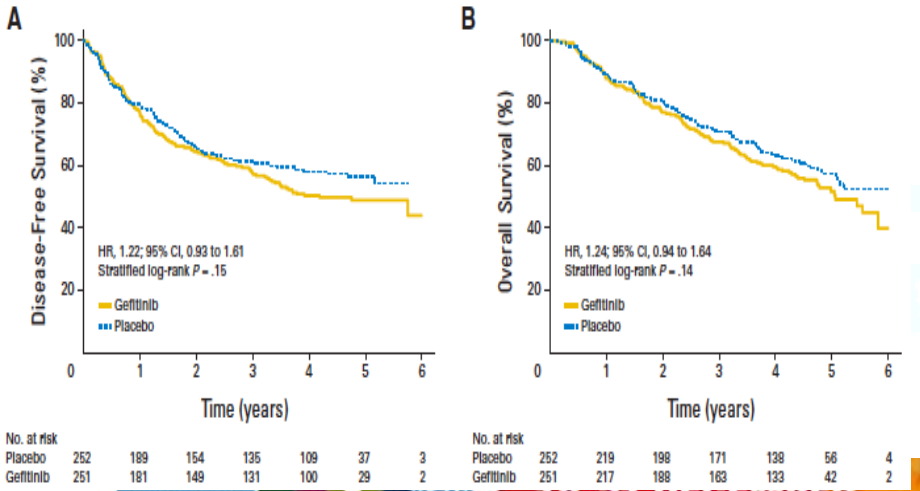
N = 503

R

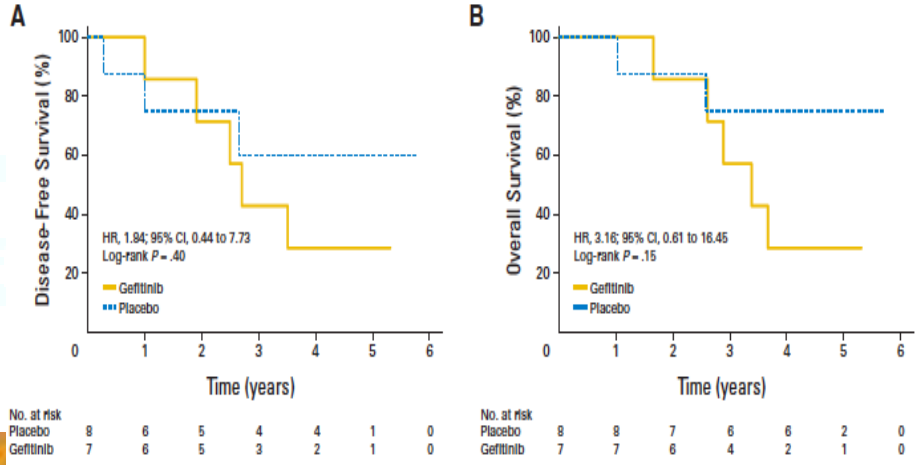
Gefitinib
250 mg po qd
x 2 years

Placebo
PO qd
x 2 years

All patients



EGFR Mutated



Goss GD, et al. J Clin Oncol 2013; 31: 3320-26

SELECT: Study Design

- Single arm, open-label Phase II study
- Adjuvant erlotinib following standard therapy

- Surgically resected Stage IA-IIIA NSCLC
- EGFR mut
- Surgically resected
- Completed routine adjuvant chemotherapy and/or XRT

CT surveillance q 6 mo x 3 years
q12 mo years 4 and 5

Erlotinib 150 mg PO daily → **Observation**

2 years duration

Primary Endpoint:

- 2-year Disease Free Survival >86%

Secondary Endpoints:

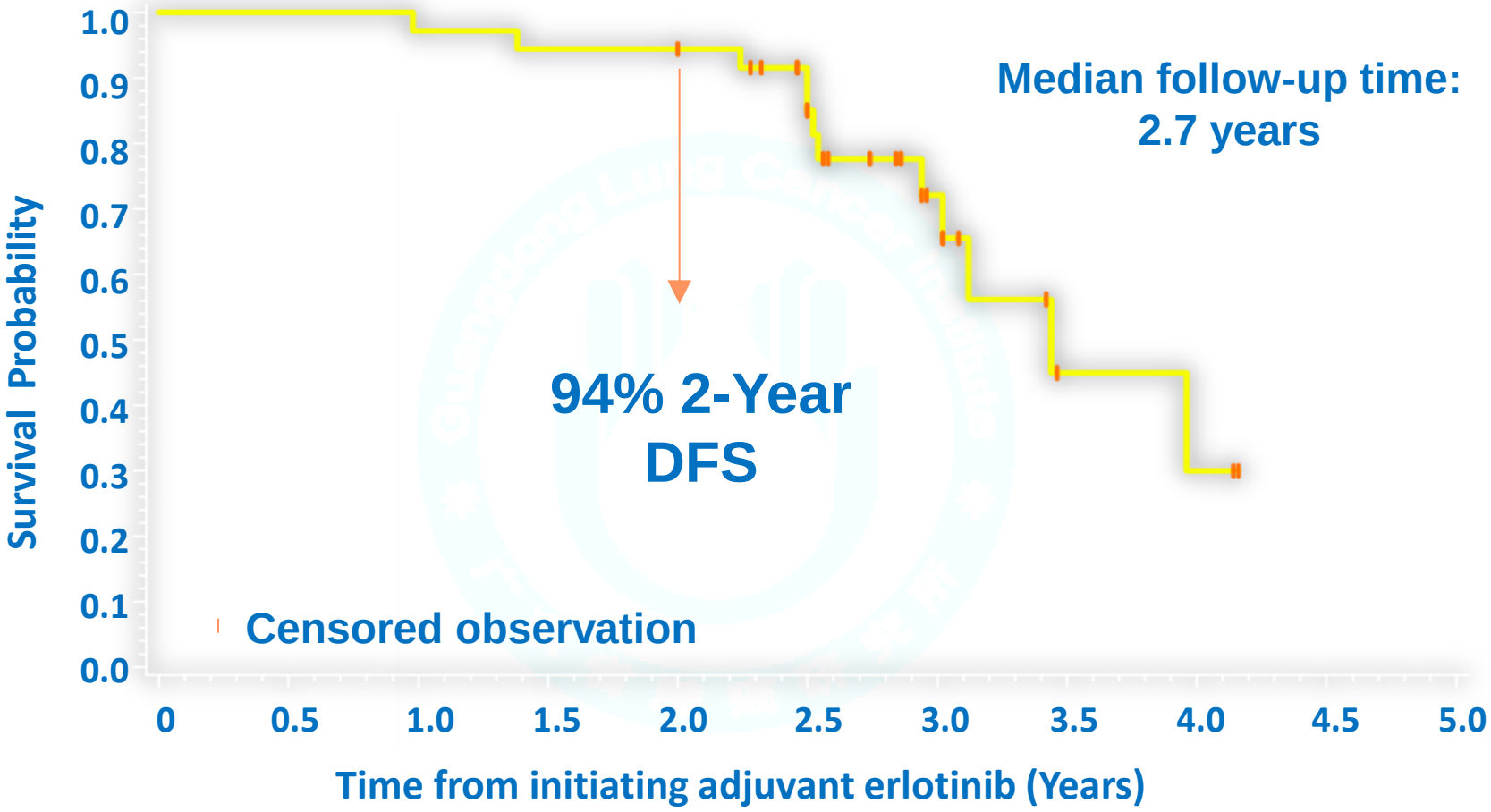
- Safety and Tolerability
- Median Disease Free Survival
- Overall Survival

Neal ASCO 2012; Abstr 7010.

SELECT: Disease-Free Survival

69% of patients completed >90% of therapy

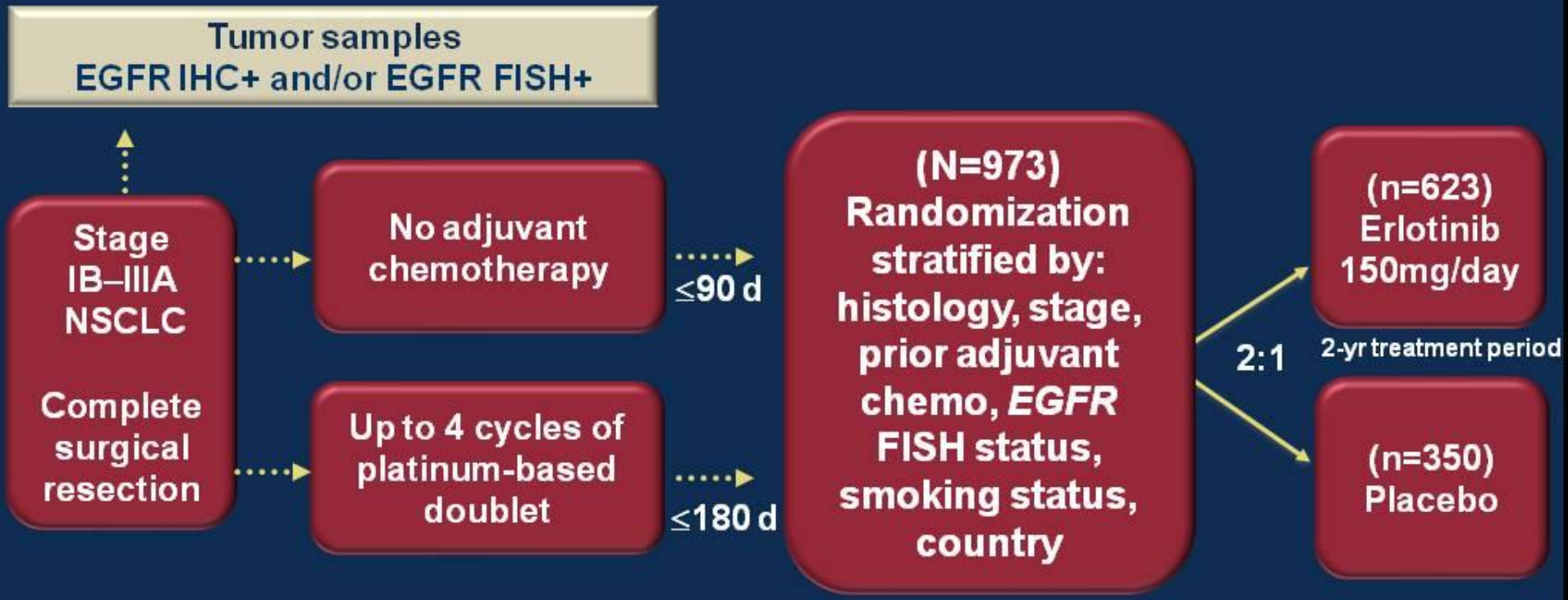
39% of patients had 1+ dose reductions



Patients at Updated 2yr DFS with N=100 is 89%

Neal ASCO 2012; Abstr 7010 updated Pennell ASCO 2014.

RADIANT Trial Design

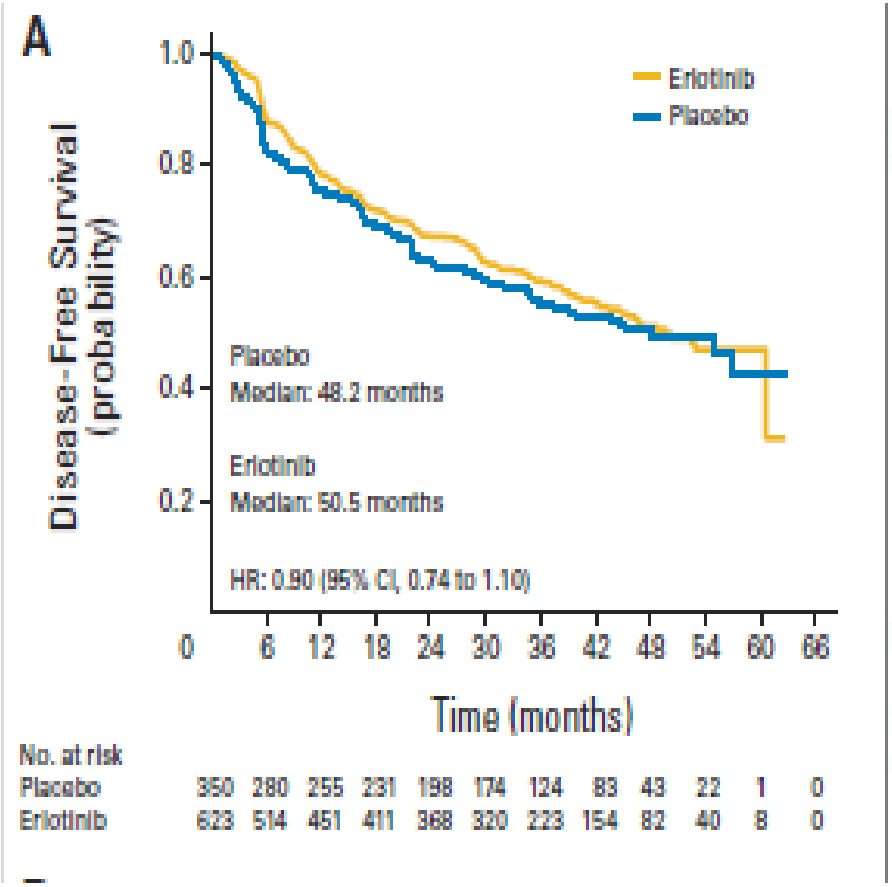


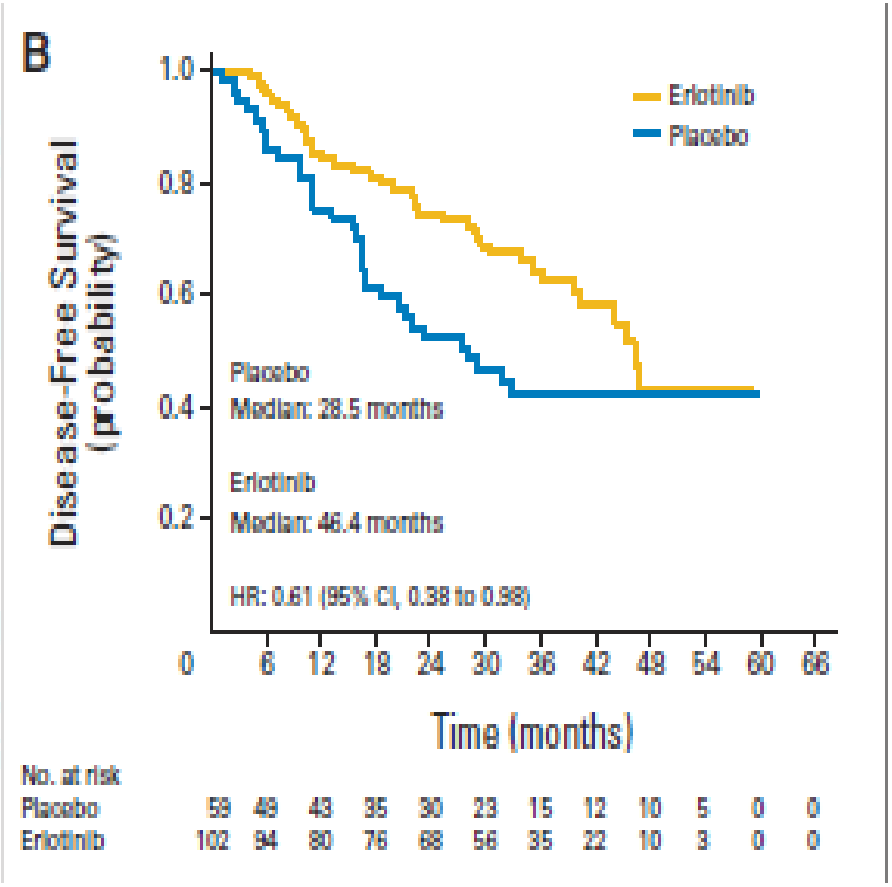
- **Radiology assessment:** every 3 months on treatment and yearly during long-term follow up

- **Primary endpoint: DFS**
- **Secondary endpoints: Overall survival (OS); DFS and OS in patients with del19/L858R (*EGFR* M+)**

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

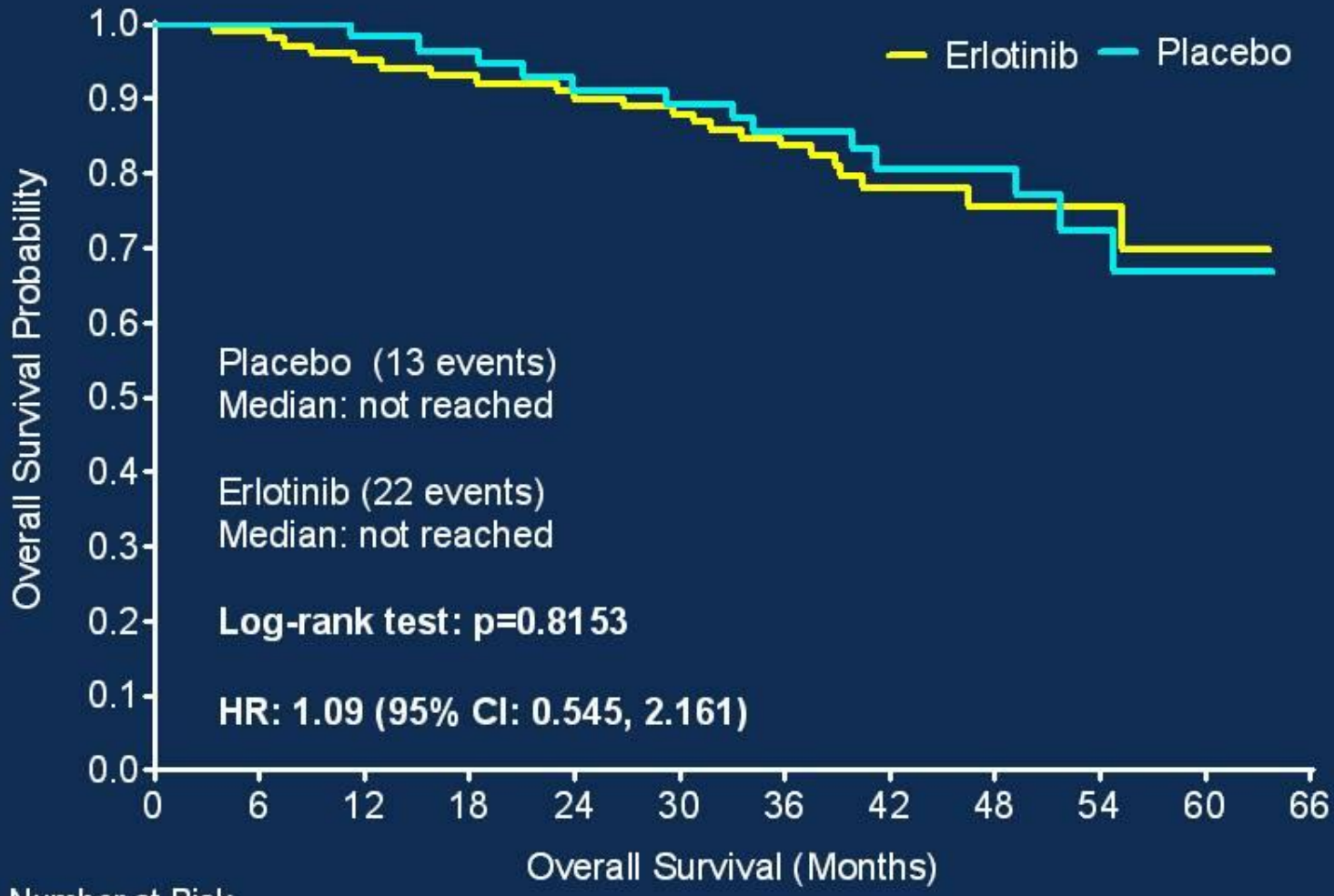
Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non–Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial





Kelly JCO 2015

Overall Survival: *EGFR* M+



Number at Risk

Placebo	59	57	56	53	51	50	41	30	24	14	5	0
Erlotinib	102	100	94	91	88	86	75	43	26	15	7	0

RADIANT Conclusions

- **Erlotinib following resection and adjuvant chemotherapy did NOT prolong DFS in patients with EGFR expressing tumors**
- **In the subset of patients whose tumors had del19 and L858R mutations, DFS favored erlotinib.**
  - **Not statistically significant due to hierarchical testing.**
- **No Overall Survival benefit noted, even in EGFRmut**

Kelly JCO 2015

Knowledge Gaps

- **Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?**
  - **Is EGFR mutation rate different between early stage and advanced NSCLC?**
  - **Heterogeneity in resected NSCLC**
- **What novel treatment strategies are being pursued?**

Resected NSCLC is heterogeneity:

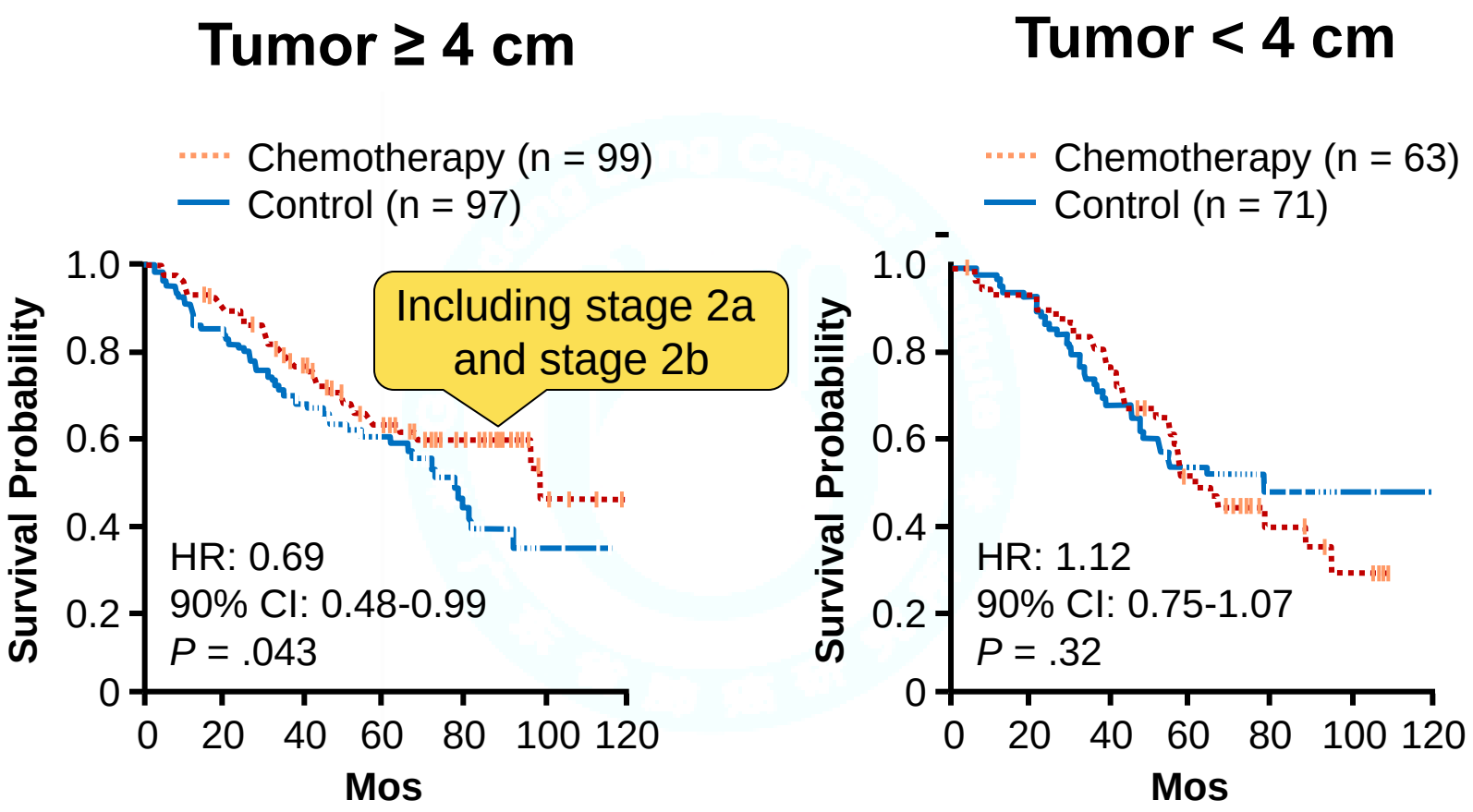
Major Changes in Stage 1B Classification

6th Edition TNM (CALGB 9633)	7th Edition TNM		
Stage 1B	Stage 1B	Stage 2A	Stage 2B
T2 (>3cm)	T2A (>3-5cm)		
		T2B (>5-7cm)	
			T3 (>7cm)

13% stage 1B in IASLC database with 58% 5-y survival

Goldstraw, JTO 2007

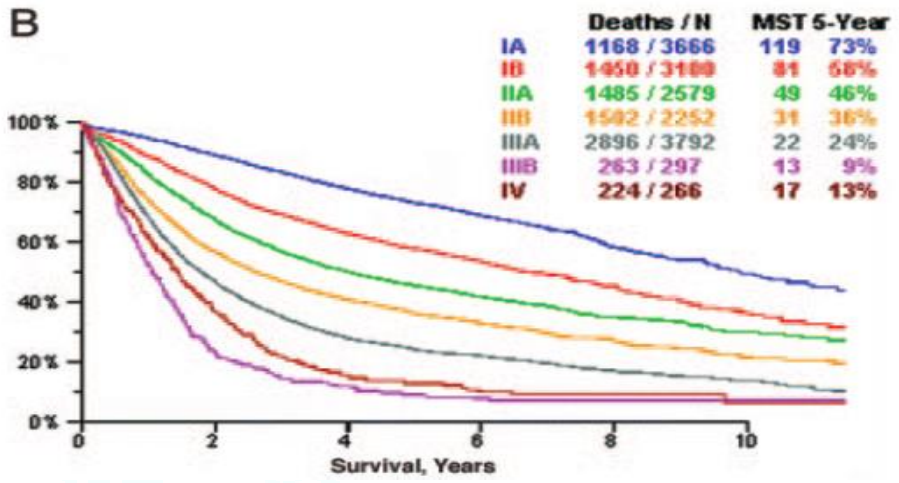
CALGB 9633: Adjuvant chemo for stage 1B Survival by Tumor Size



Strauss GM, et al. J Clin Oncol. 2008;26:5043-5051

Resected NSCLC is heterogeneity

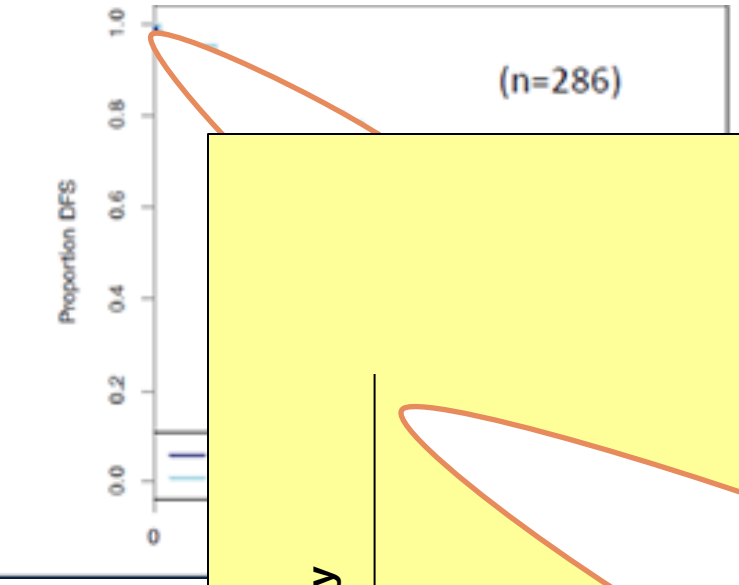
Stage	MST
Stage 1A	119
Stage 1B	81
Stage 2A	49
Stage 2B	31
Stage 3A	22

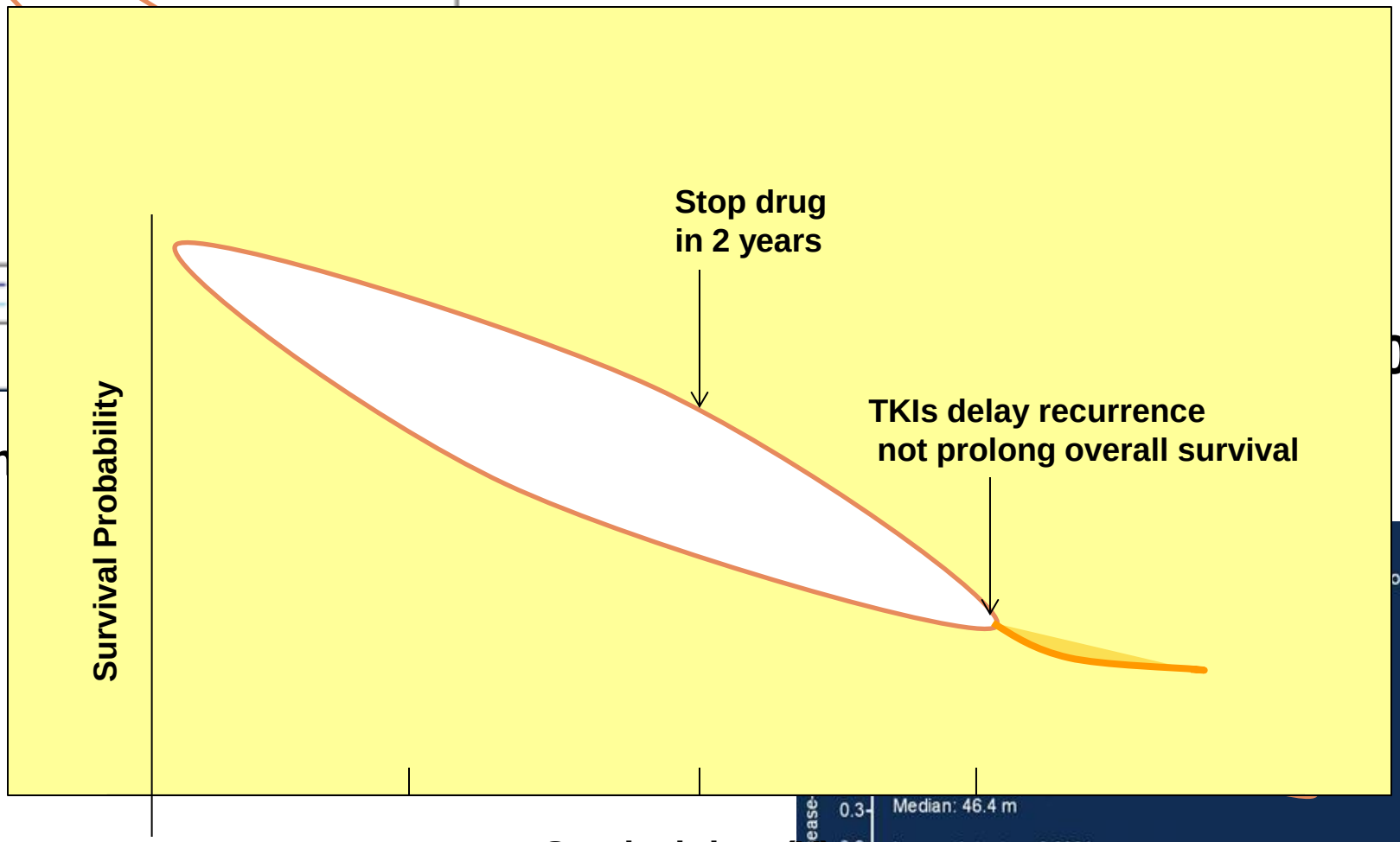


Type	Reference	Stage 1 (%)	Stage 2 (%)	Stage 3(%)
Retrospective	Janjigian 2010	54	20	27
	D'Angelo 2012	52	17	31
Prospective	BR.19 2013	53	35	12
	Select 2014	44	27	28
	Radian 2014	51	33	16

Goldstraw, JTO 2007

What secret behind PFS from retrospective and prospective





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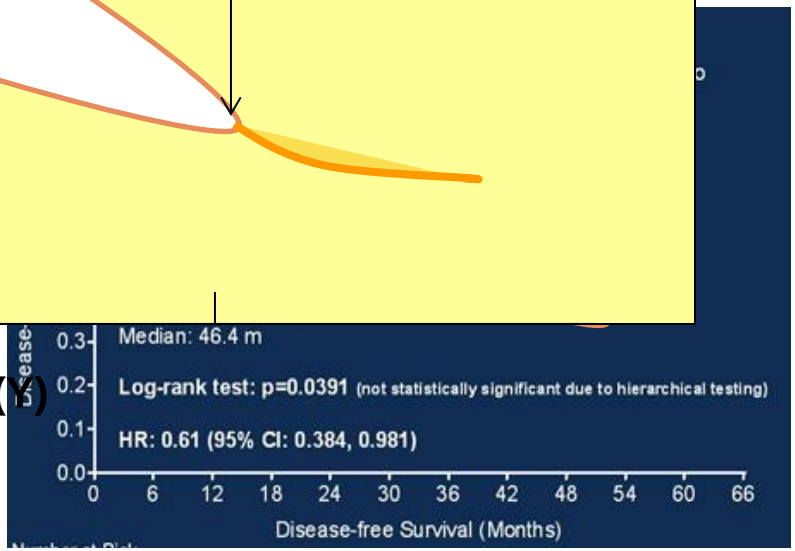


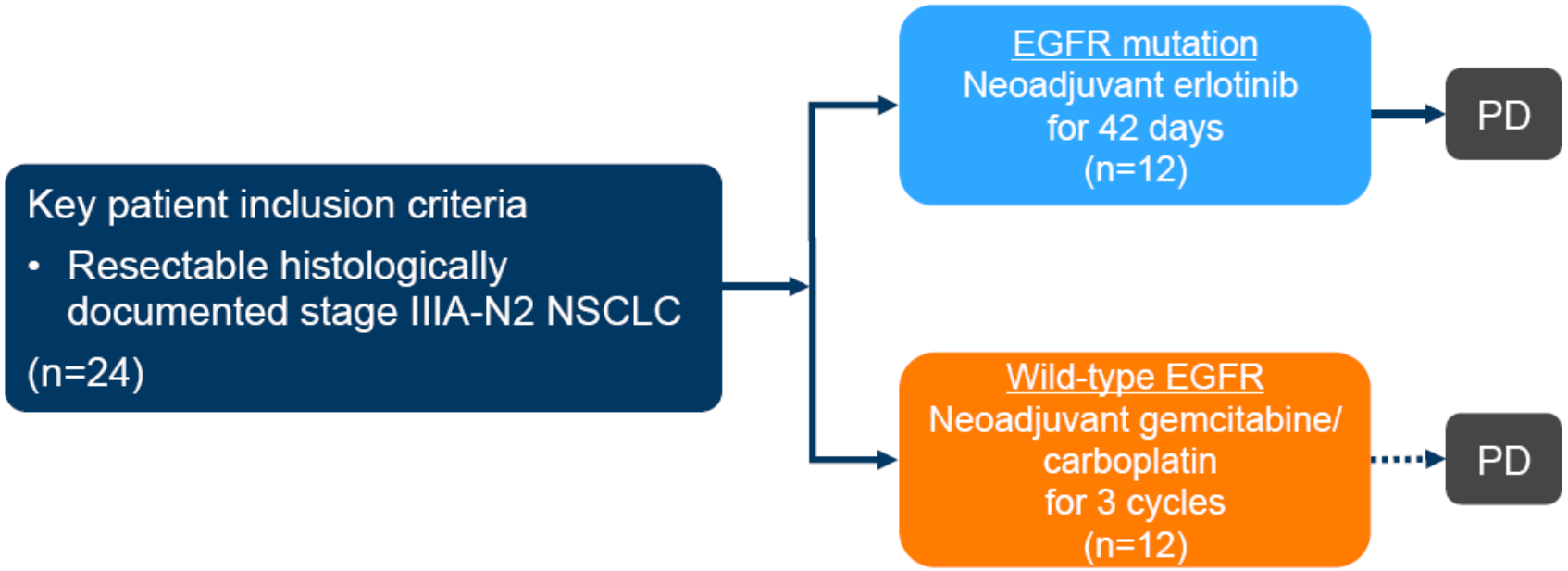
Knowledge Gaps

- Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?
- Is EGFR mutation rate different between early stage and advanced NSCLC?
- Heterogeneity in resected NSCLC

- **What novel treatment strategies are being pursued?**

Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status

- **Study objective**
  - To evaluate the role of biomarker-guided neoadjuvant treatment strategy in patients with IIIA-N2 NSCLC stratified by EGFR mutation status



Primary endpoint

- RR

Secondary endpoints:

- PFS and OS

Zhong & WU JHO, 2015

RR for erlotinib and GC regimen

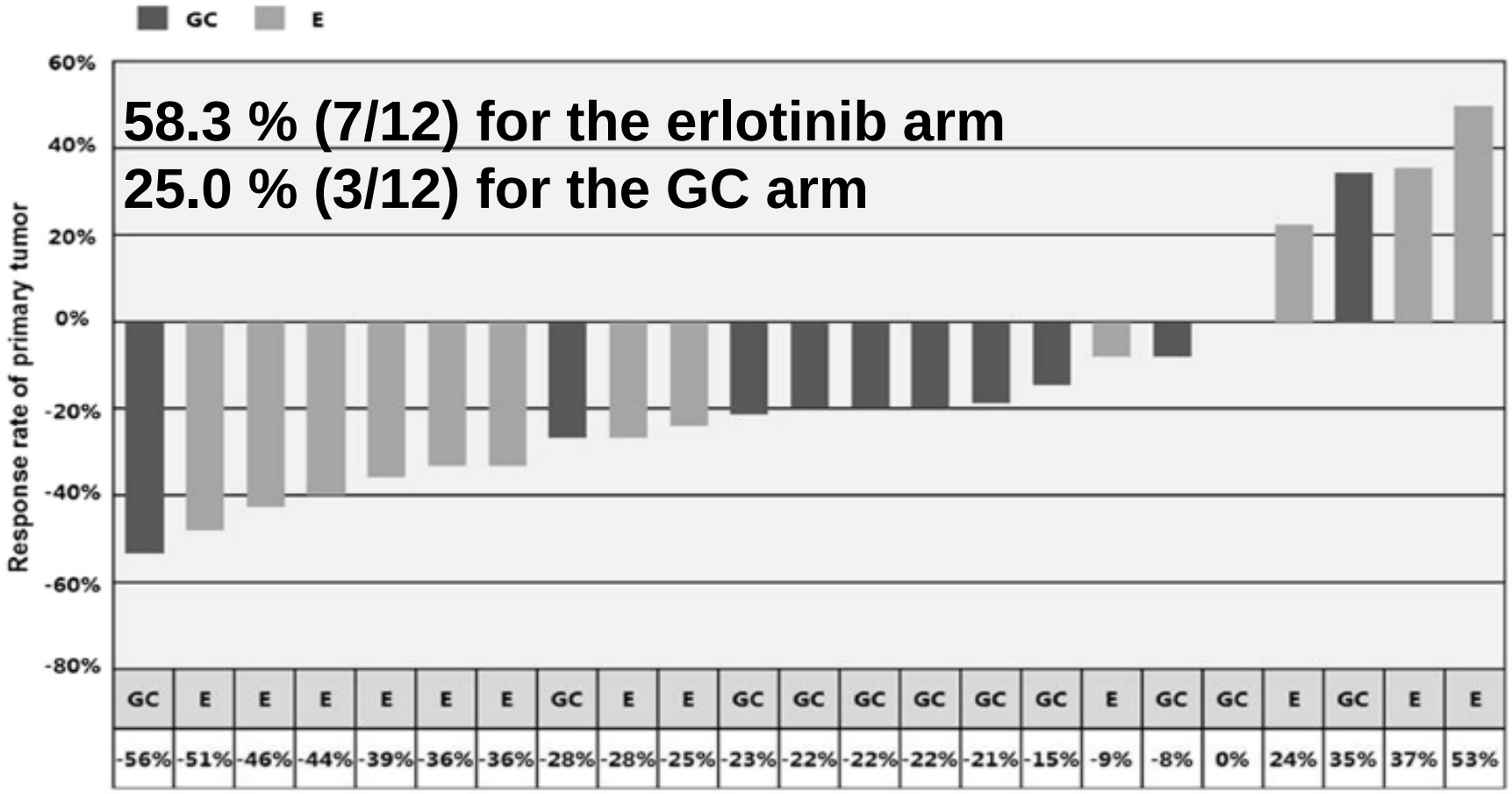
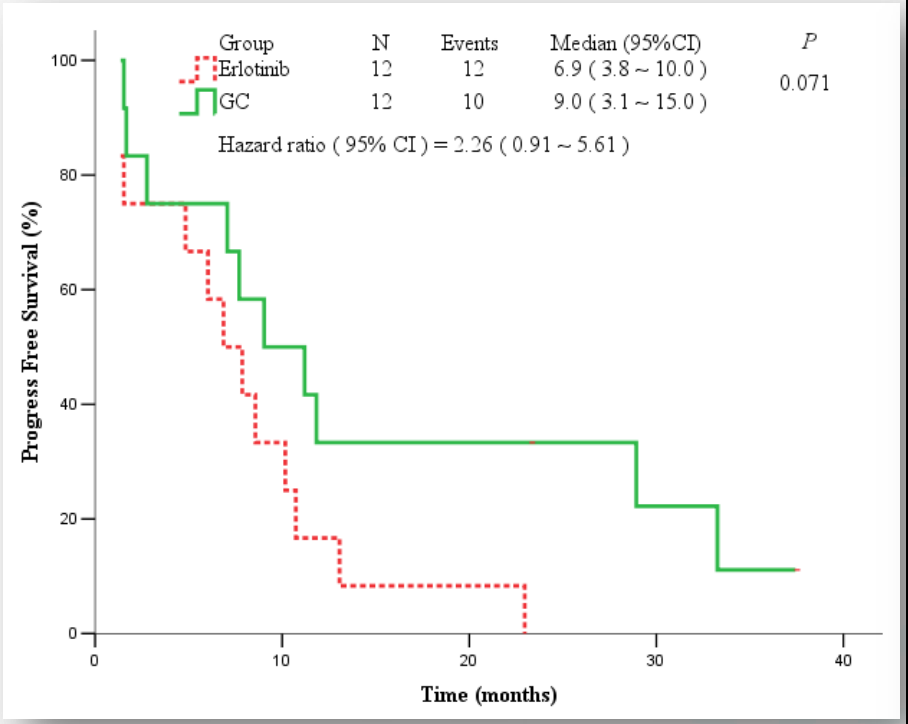


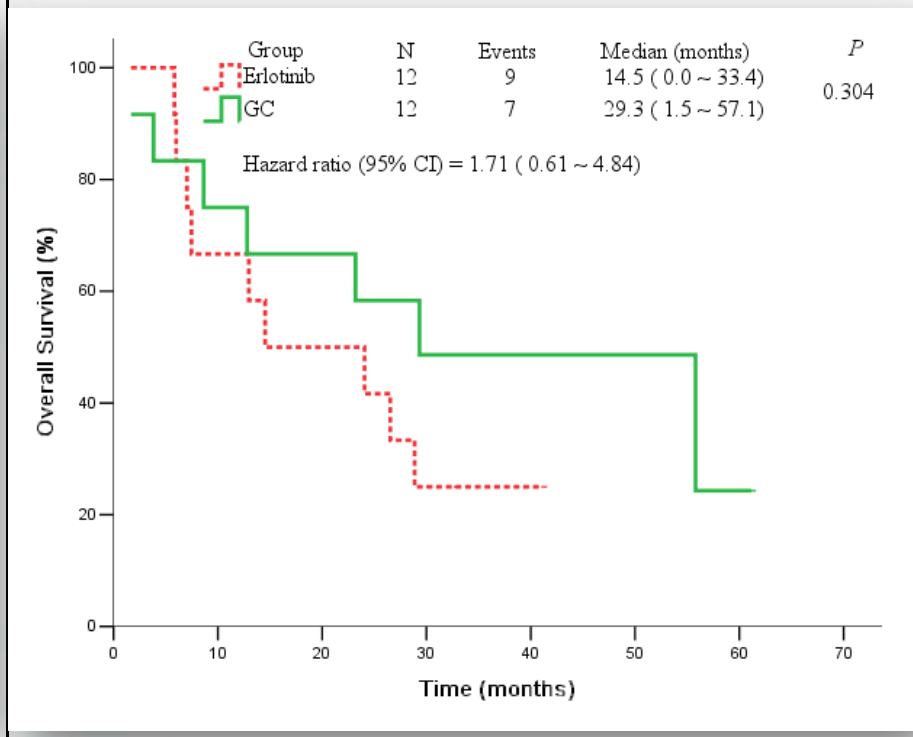
Fig. 1 Waterfall plot of response to neoadjuvant treatment. Abbreviations: GC, gemcitabine/carboplatin; E, erlotinib. Note: The response rate of one case in the GC arm was not available

Zhong & WU JHO, 2015

PFS and OS comparison

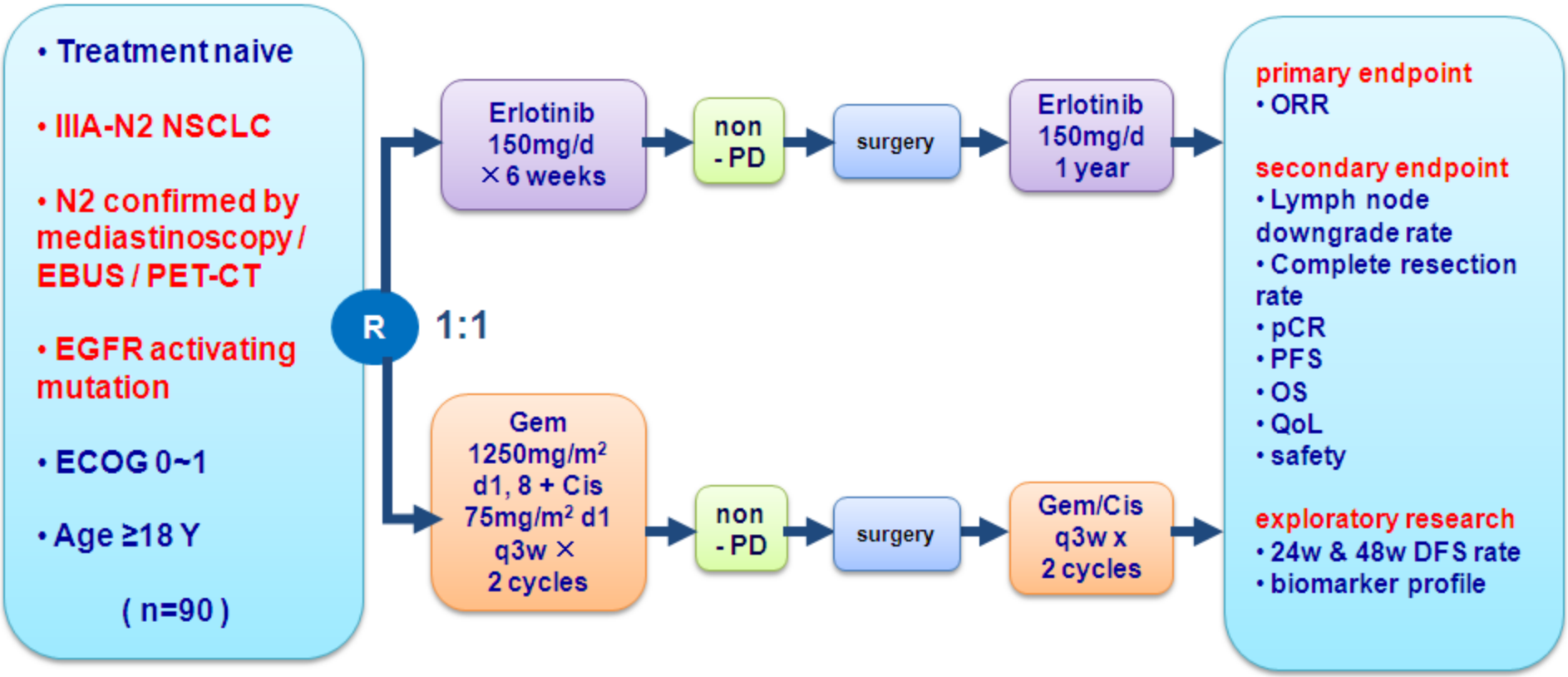


B:PFS comparison between the 2 arms



C:OS comparison between the 2 arms

CTONG 1103 （EMERGING）
2011-2018



China：CTONG 1104 (ADJUVANT)
Japan：WJOG 6401L

- Completely resected
- Pathological stage II-IIIA(N1-N2) NSCLC
- *EGFR* Act Mut+ (exon 19 deletion or exon 21 L858R mutation)
- PS 0–1, ≥18 yrs, < 75 yrs

(n=220-230)

R

1:1

Gefitinib 250mg/day
24 months or disease progression or unacceptable toxicity.

Vinorelbine (25 mg/m^2 d1,8)
Cisplatin 75mg/m2 d1)
q3w, up to 4 cycles

Primary endpoint

- Disease-free survival (PFS)

Secondary endpoints

- Overall survival (OS), 3 yeas DFS rate, 5 years DFS rate, 5 years OS rate, Safety, HRQoL (FACT-L, LCSS), exploratory biomarker analyses

Stratification factors

- Mutation type
- N stage
- Smoking status

Efficacy assessment

- Every 3 months

China: 222 cases
FPI: Sep. 15, 2011
LPI: Apr. 24, 2014

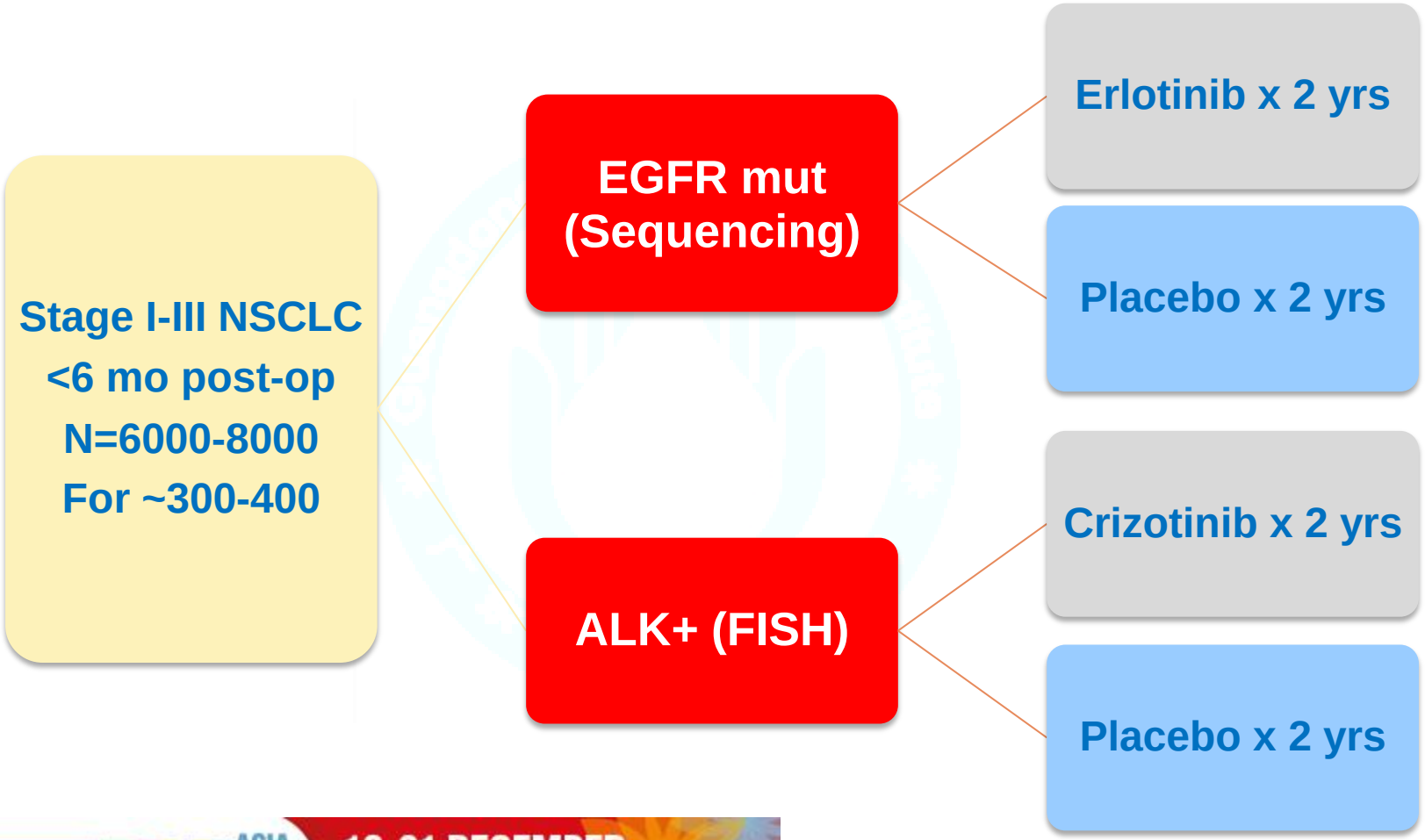
JAPAN: 230 cases
LPI: Dec 2015

Act Mut+ = activating mutations; ECOG = Eastern Cooperative Oncology Group; PS = performance status
HRQoL = health-related quality of life; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCSS = lung cancer symptom scale

ICOTINIB Phase III Adjuvant trials

- **Completely resected stage II-IIIA NSCLC with EGFR mutations (Exon 19 or 21)**
  - **NCT01996098**
    - **AFTER 4 cycles adjuvant platinum chemotherapy**
    - **Randomized to Icotinib (125 mg po tid) x 6 or 12 mo vs Observation**
    - **DFS primary endpoint, N=477**
    - **PI: SY Wang – Sun Yat-sen University Cancer Center**
  - **Pending: NCT02125240**
    - **NO prior adjuvant therapy**
    - **Randomized to Icotinib (125 mg po tid) vs placebo**
    - **2 yr DFS primary endpoint, N= 300**
    - **PI:YK Shi – Cancer Hospital, Chinese Academy of Medical Sciencesb**

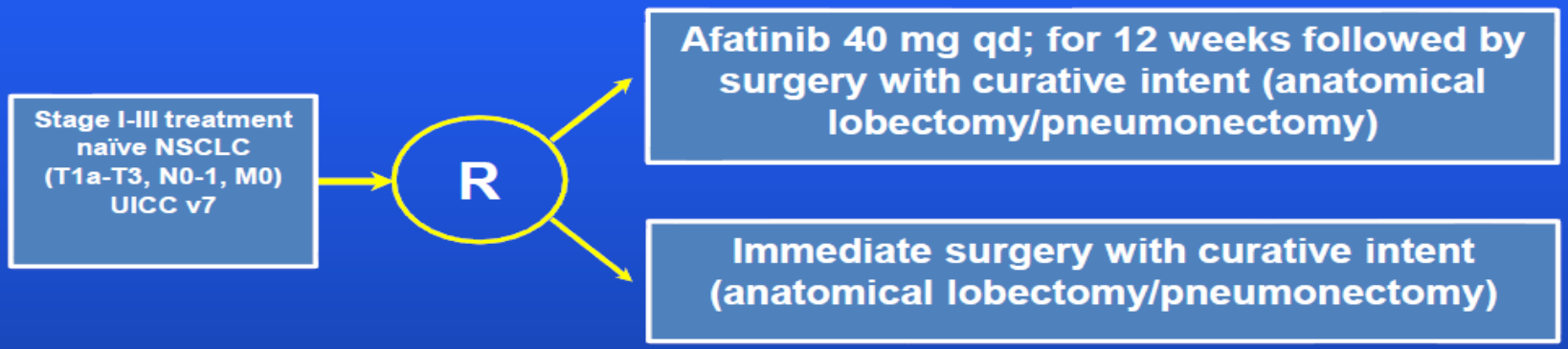
US ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial



Adjuvant Therapy: Molecular Selection

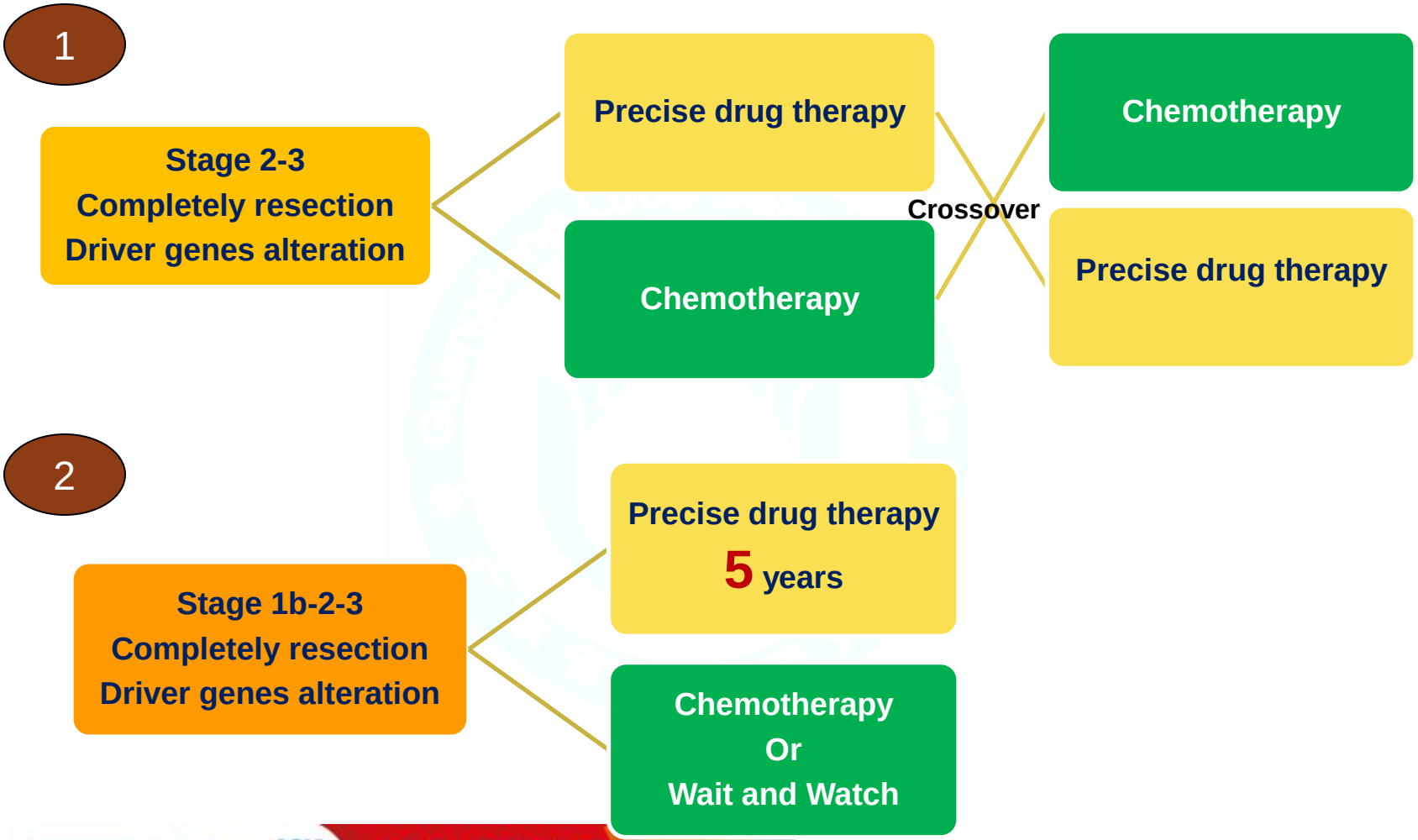
EORTC 08115-REMNANT: NEOadjuvant Afatinib (BIBW2992) in EGFR Mutant Operable NSCLC; a study of the EORTC Lung Cancer Group

Study coordinator: Dr Sanjay Popat, Royal Marsden Hospital



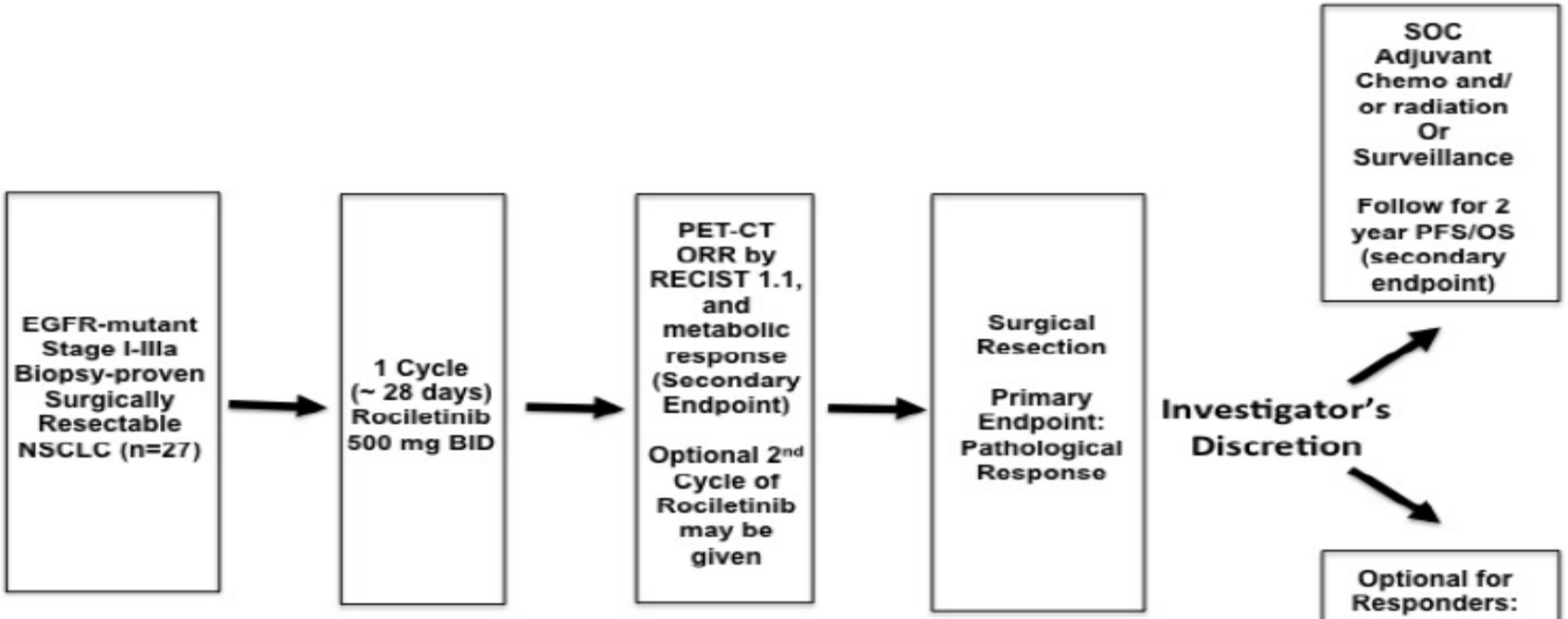
- There will be a minimum of 1 week between the last dose of afatinib and surgery.
- The first 5 patients will form a safety run-in to check that afatinib treatment doesn't delay surgery
- Endpoints and statistical considerations under discussion

Key Trials in Future



3rd generation EGFR TKI in Neoadjuvant setting

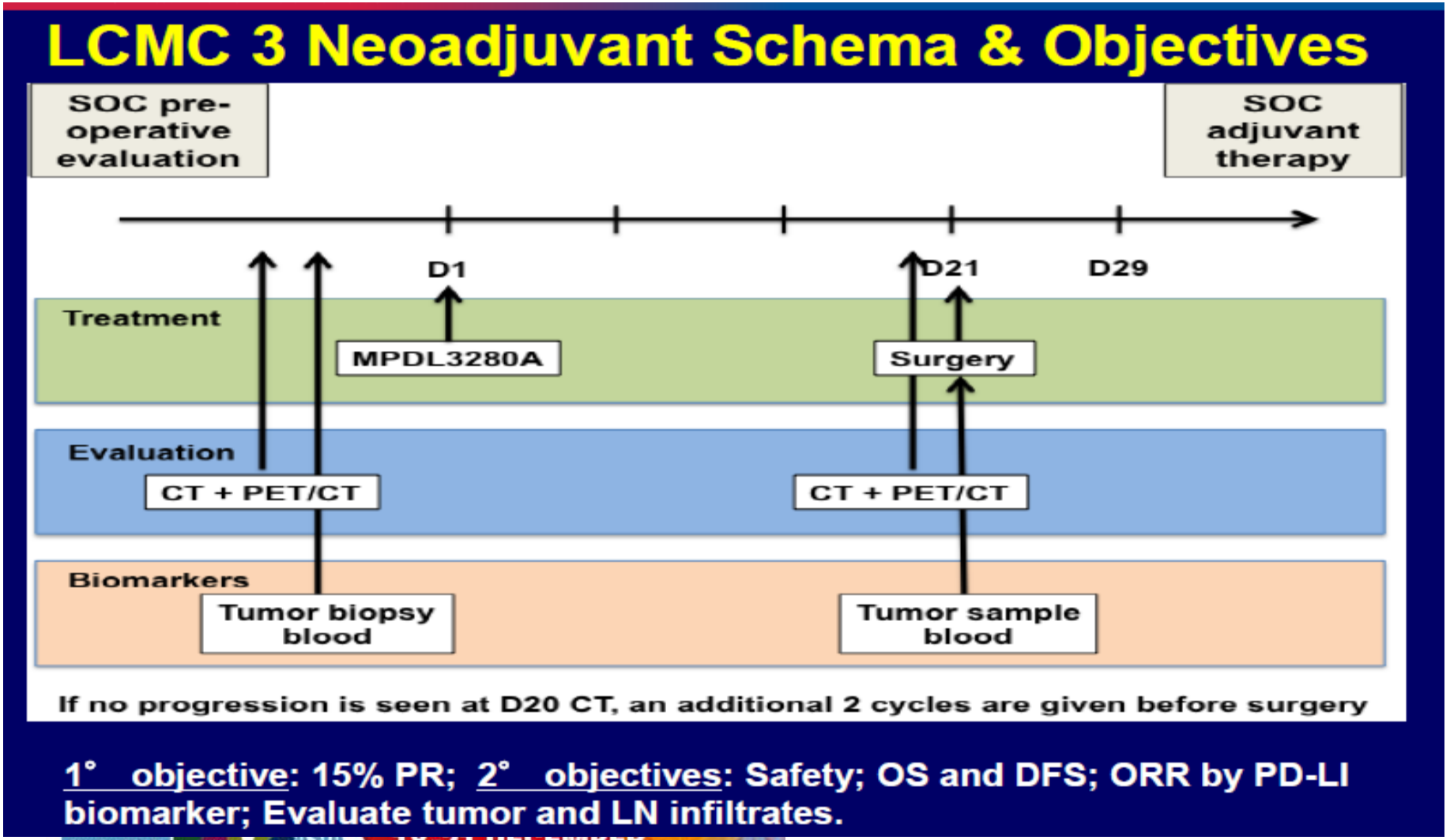
Neoadjuavant Rocilitinib Trial: UCSF & UCD



1° objective: pathologic response rate (<50% viable tumor cells)

2° objectives: ORR; complete pathologic response; 2 year PFS; 2 year OS; Tissue and blood biomarkers; Safety and tolerability

Checkpoint Inhibitor in Neoadjuvant Setting



Conclusions

- **Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?**
  - **Is EGFR mutation rate different between early stage and advanced NSCLC?**
  - **Heterogeneity in resected NSCLC**
- **What novel treatment strategies are being pursued?**
- **Is There a Role for Adjuvant EGFR TKIs in Early NSCLC?**

Conclusions

- **Could advantage of EGFR TKIs in advanced NSCLC translate to early NSCLC?** **Maybe**
  - **Is EGFR mutation rate different between early stage and advanced NSCLC?** **No**
  - **Heterogeneity in resected NSCLC** **Yes**
- **What novel treatment strategies are being pursued?** **Waiting**
- **Is There a Role for Adjuvant EGFR TKIs in Early NSCLC?** **Maybe**

What is the optimal adjuvant treatment for resected NSCLC?

Adjuvant chemotherapy for Stage 2-3 NSCLC

2004

2015

HARMONIOUS FAMILY
相亲相爱的一家人 >>

感谢肺研所团队
每一个人的贡献

Acknowledge my team!

广东省肺癌研究所
Guangdong Lung Cancer Institute