Defining the role of targeted therapies in early stage NSCLC

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Disclosures

I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack, Merck Serono, MSD, Amgen, Clovis, Astellas and Tesaro, for which I received honoraria.

I declare no conflict of interest.

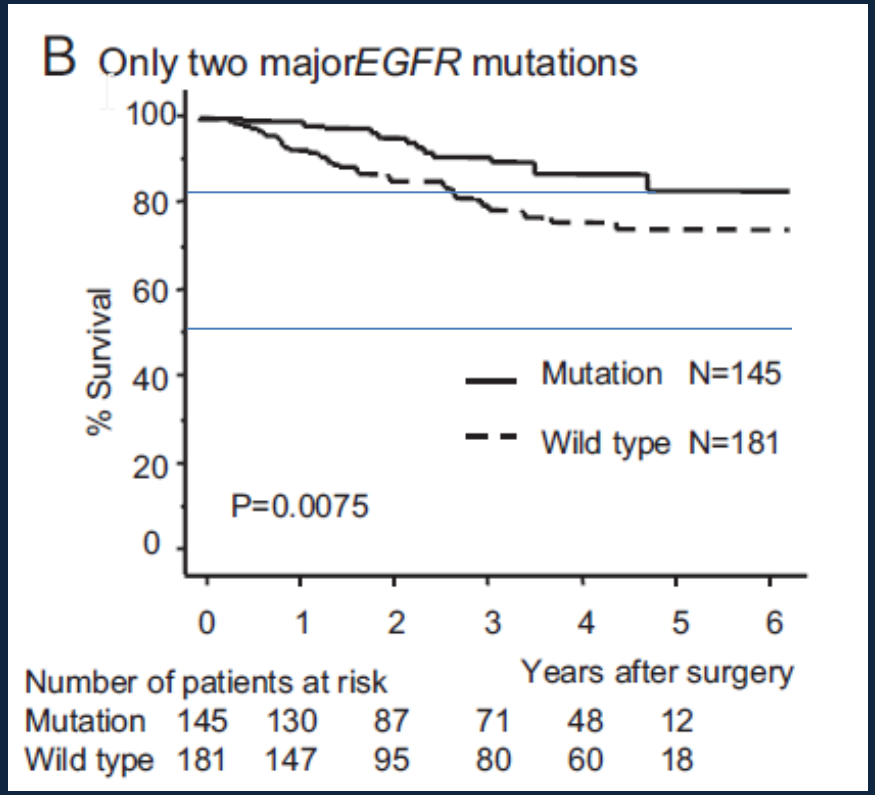
Defining the role of targeted therapies in early stage NSCLC

Adjuvant EGFR TKI in early EGFR M+ NSCLC?

Biomarker-driven treatment: EGFR TKI in stage IV

Study	EGFR TKI	n	Median PFS in TKI arm (months)	P value	HR
OPTIMAL	Erlotinib	154	13.1	<0.0001	0.16
First Signal	Gefitinib	42	8.4	0.084	0.61
IPASS	Gefitinib	261	9.5	<0.0001	0.48
WJTOG 3405	Gefitinib	177	9.2	<0.001	0.48
NEJSG 002	Gefitinib	200	10.8	<0.001	0.36
Ensure	Erlotinib	217	11	<0.0001	0.34
EURTAC	Erlotinib	174	9.4	<0.0001	0.42
LUX-3	Afatinib	308	13.6	<0.0001	0.47
LUX-6	Afatinib	364	11.0	<0.0001	0.28

What is the expected 5-years survival rate of patients with EGFR mutation?



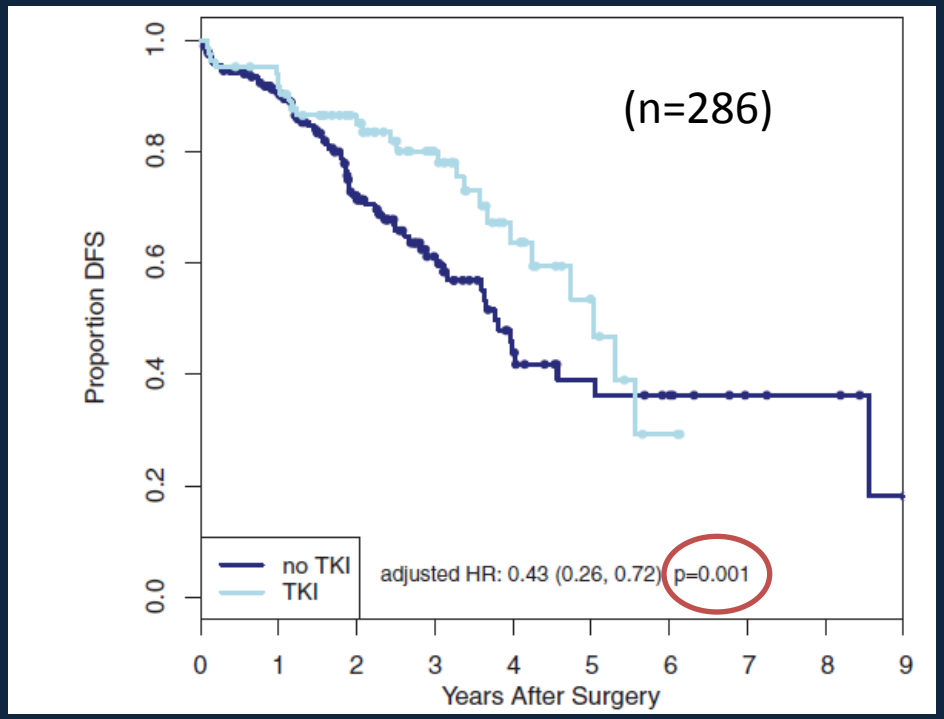
- Radically resected NSCLC
- Survival reported in 145 EGFR TKI-not exposed NSCLC patients
- EGFR M+ 65% stage I, 35% stages II-IV

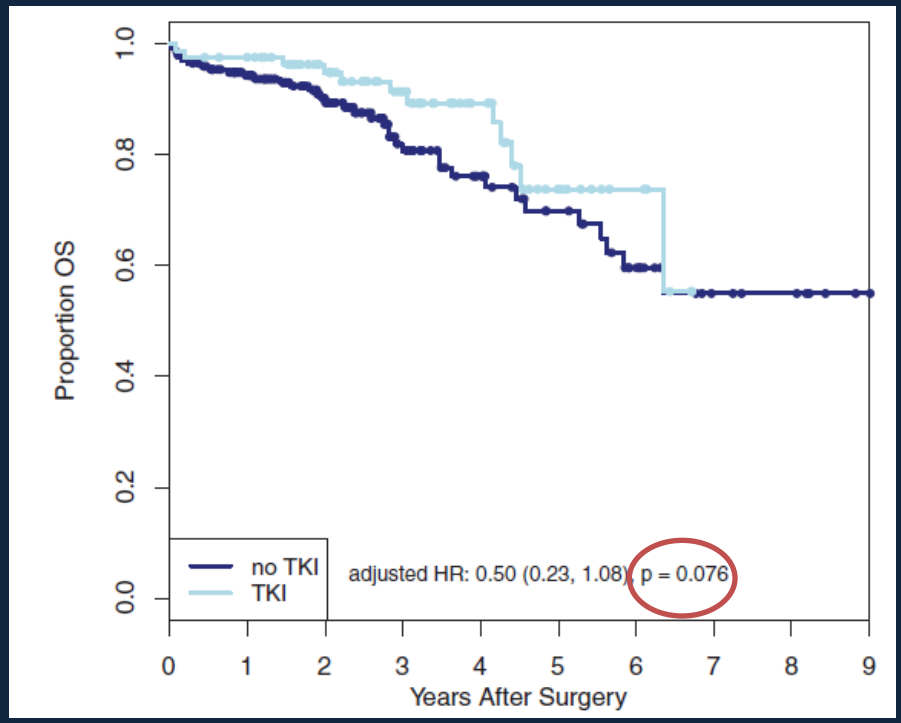
Kosaka et al JTO 9:27, 2009; discussion Mok ASCO 2014

Retrospective look: Adjuvant TKI for EGFR M+ NSCLC (1)

	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 analysis of adjuvant EGFR TKI (2)

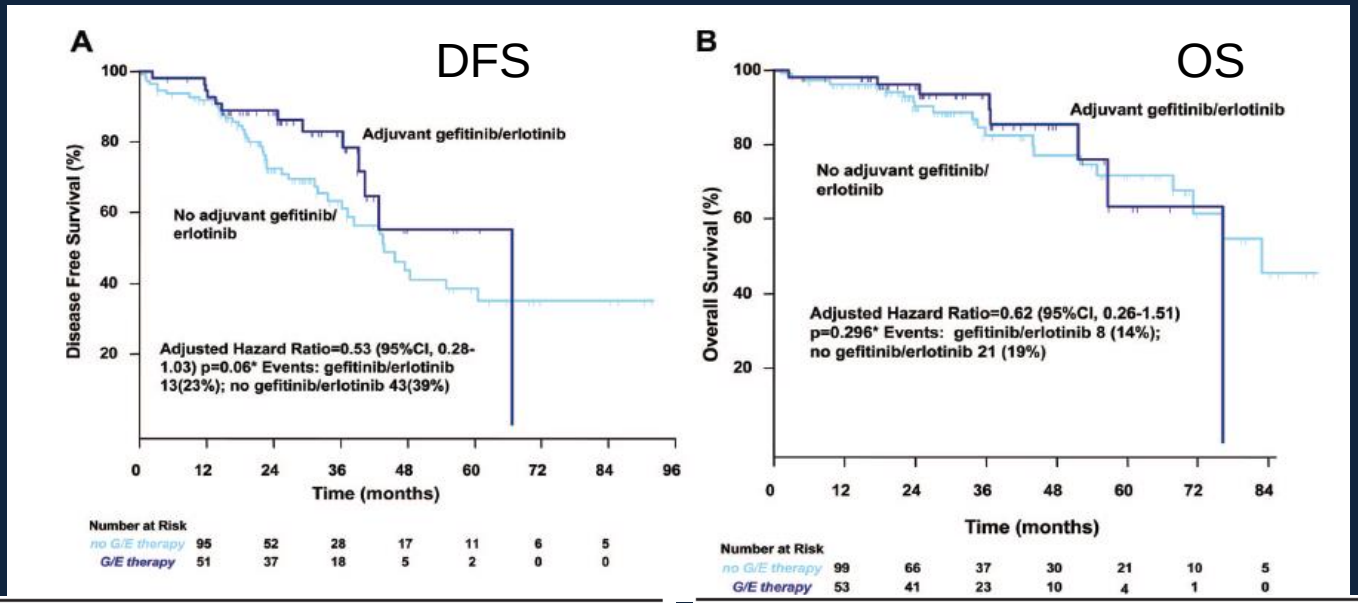


TABLE 3. Multivariate Disease-Free Survival Analysis

n = 167	*N* (Event *N*)	2-yr Survival (95% CI)	Adjusted Hazard Ratio[a] (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)		

[a] 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[a] (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)		

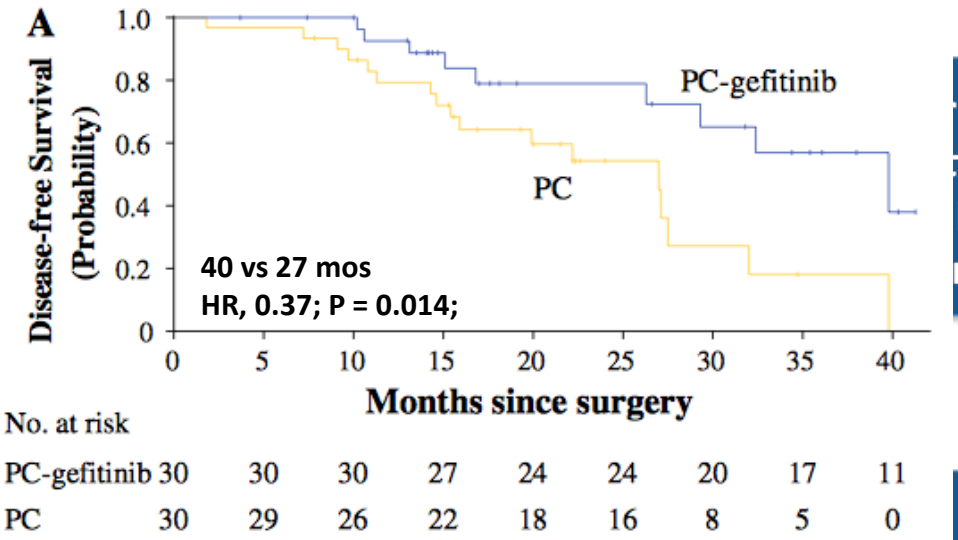
[a] Adjusted for sex, type of surgery, stage, and adjuvant cisplatin chemotherapy; hazard ratio less than 1.00 indicates improved survival.

- 167 EGFR M+ patients with completely resected stages I to III adenocarcinoma.
- 33% received perioperative TKI
- Small power (number of events low)

Janjigian , JTO 2010

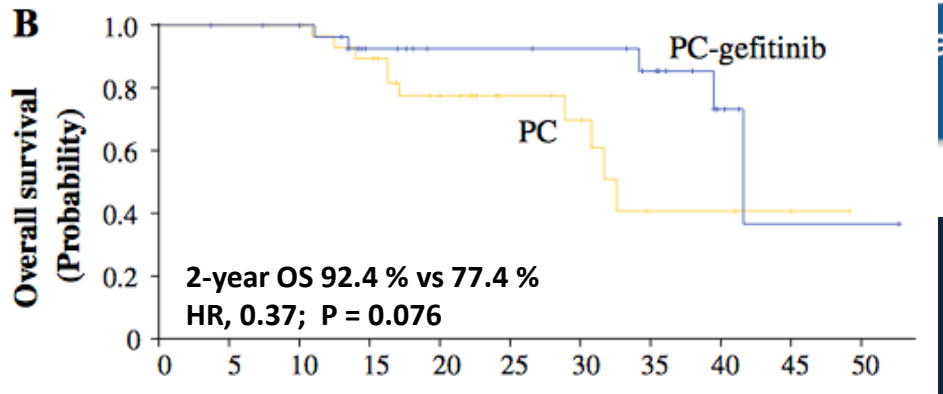
Adjuvant gefitinib in resected stage IIIA-N2 EGFR M+ : prospective phase 2 trial

Resecte
stage III
N2
EGFR M



No. at risk

PC-gefitinib	30	30	30	27	24	24	20	17	11
PC	30	29	26	22	18	16	8	5	0

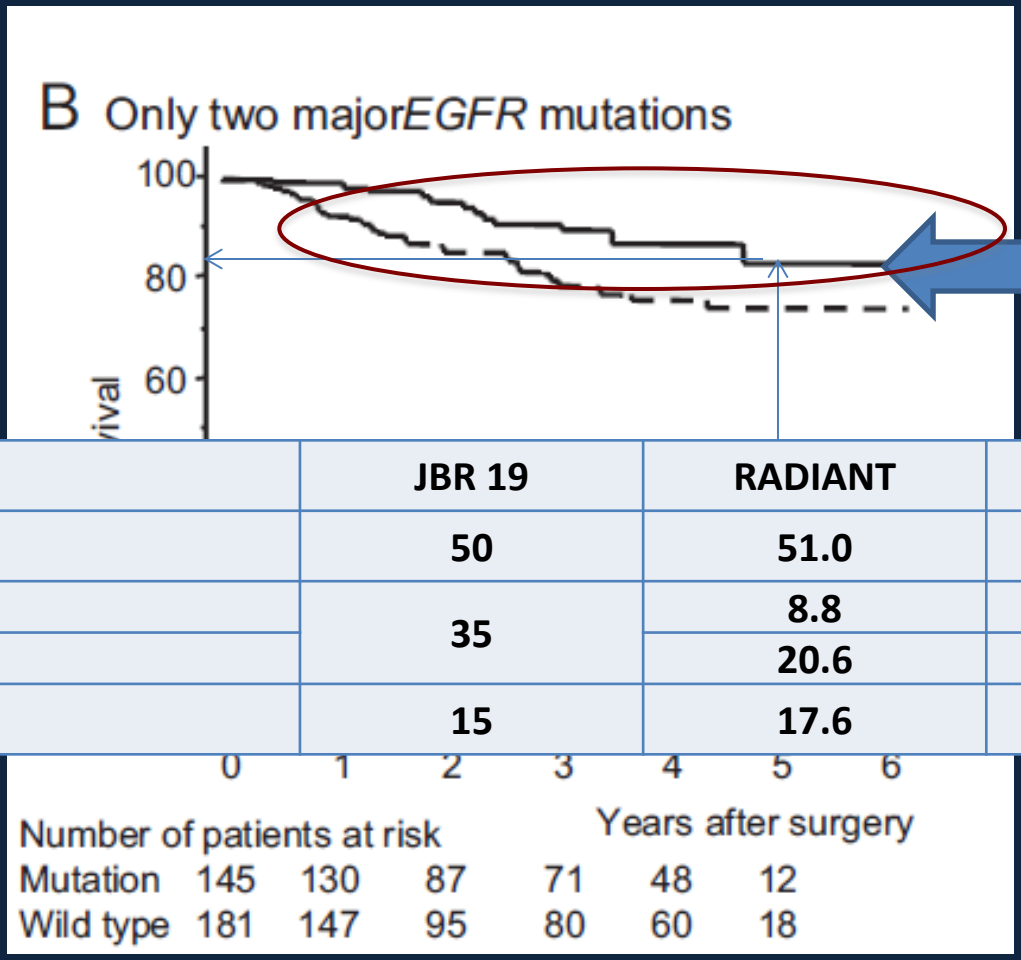


No. at risk

PC-gefitinib	30	30	30	28	28	28	28	26	22	11	11
PC	30	30	30	27	23	23	21	12	12	12	12

Li, Ann Surg Oncol 2014

PROSPECTIVE TRIALS : BR19, RADIANT, SELECT

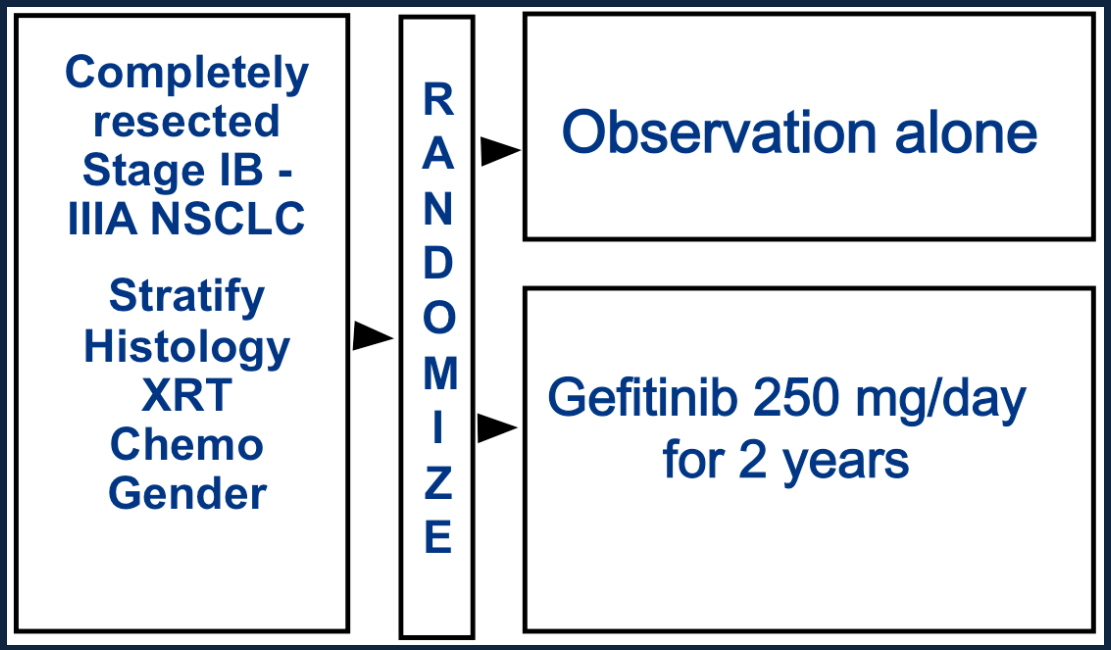


65% stage I
35% stage II-IV

5	JBR 19	RADIANT	SELECT
Stage : I	50	51.0	45.0
IIA	35	8.8	11
IIB		20.6	16
IIIA	15	17.6	28

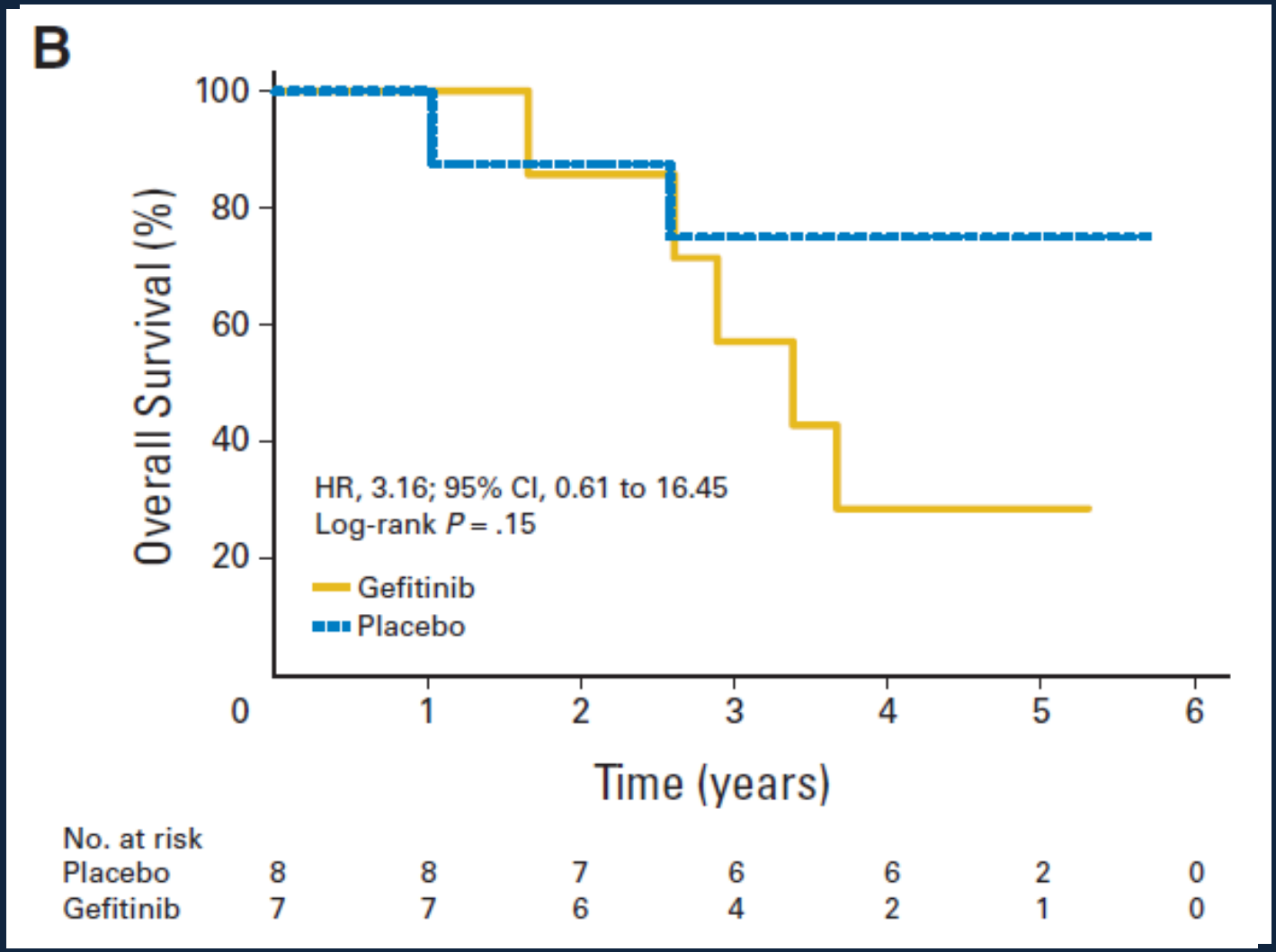
Kosaka et al JTO 9:27, 2009; discussion Mok ASCO 2014

JBR.19 Adjuvant Gefitinib in Completely Resected NSCLC



Outcome (years)	Gefitinib (n=251)	Placebo (n=252)	HR (95% CI)	P value
Median OS	5.1	NR	1.23 (0.94-1.64)	0.136
Median PFS	4.2	NR	1.22 (0.93-1.61)	0.152

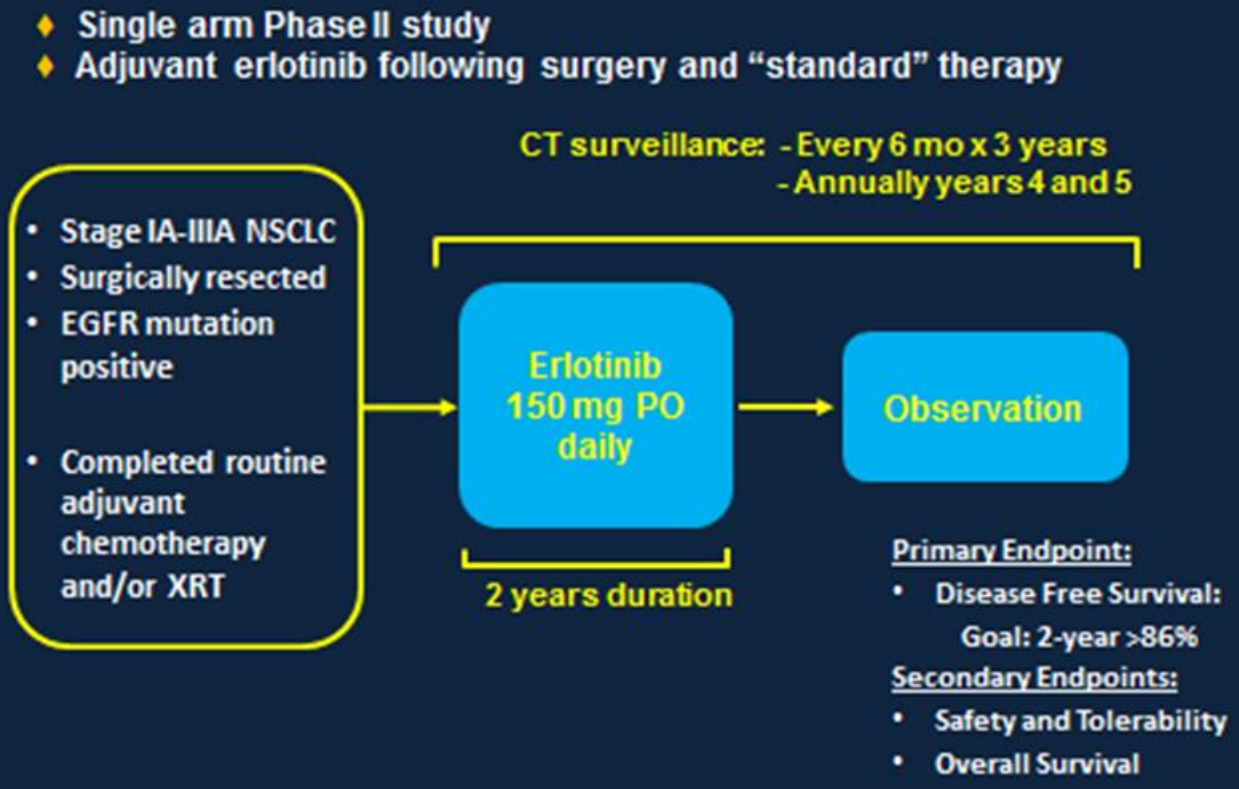
Goss, ASCO 2010, LBA7005



- Data reported on 15 EGFR M+ patients

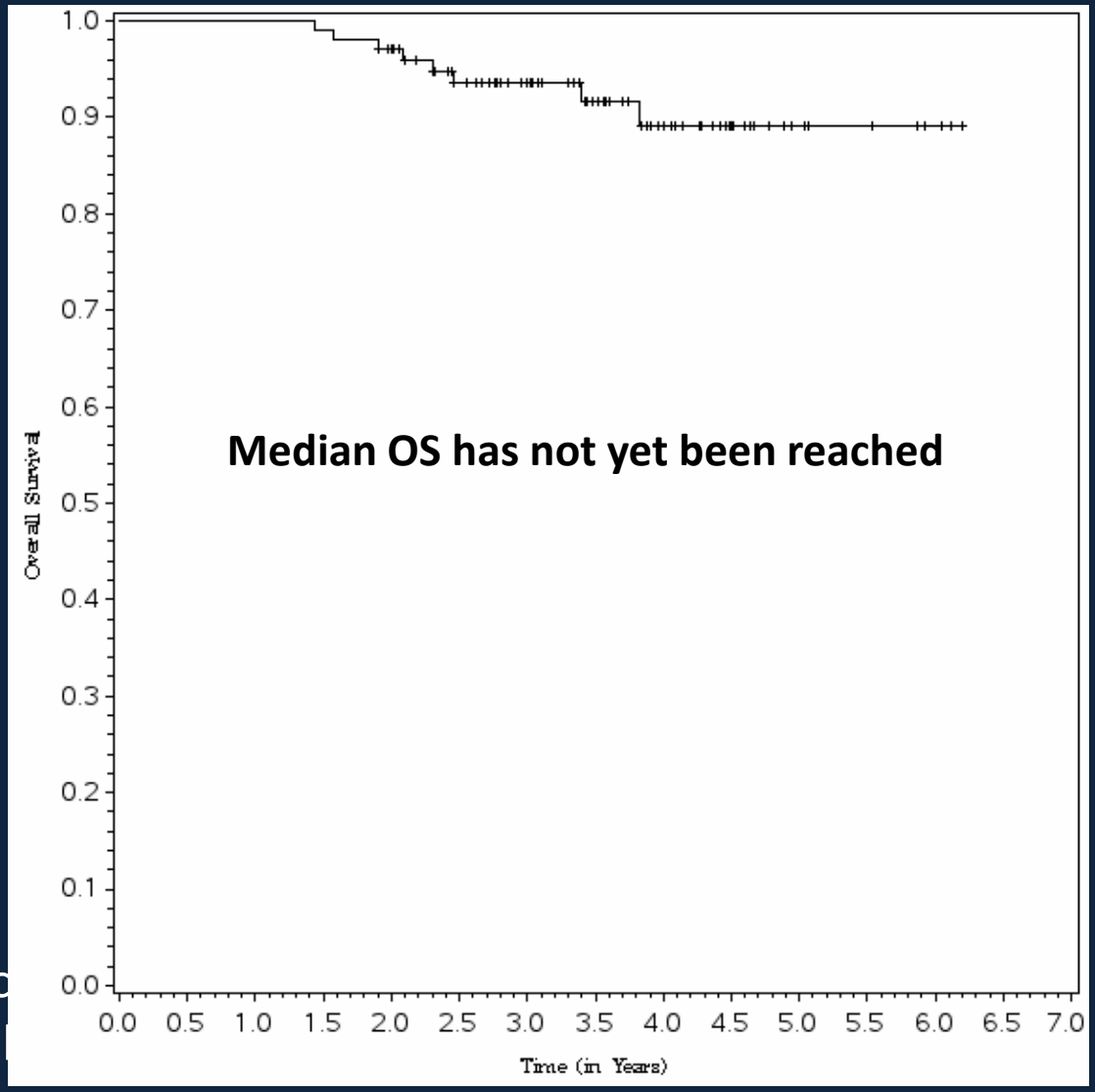
Goss, JCO 2013

Phase II Select Trial



- Initial N=36
- Expanded to n=100

SELECT : DFS & OS



- 2/3 rec
- 24 pts

Neal , ASCO 2012 and Pennell, ASCO 2014

RADIANT Adjuvant Erlotinib in EGFR positive NSCLC

Key inclusion criteria

- Completely resected
- IB – IIIA
- EGFR positive by IHC or FISH
- Adjuvant chemotherapy allowed

Erlotinib

2 years trial treatment
Randomisation 2 : 1 *

Placebo

Primary Endpoint

- DFS

Secondary Endpoints

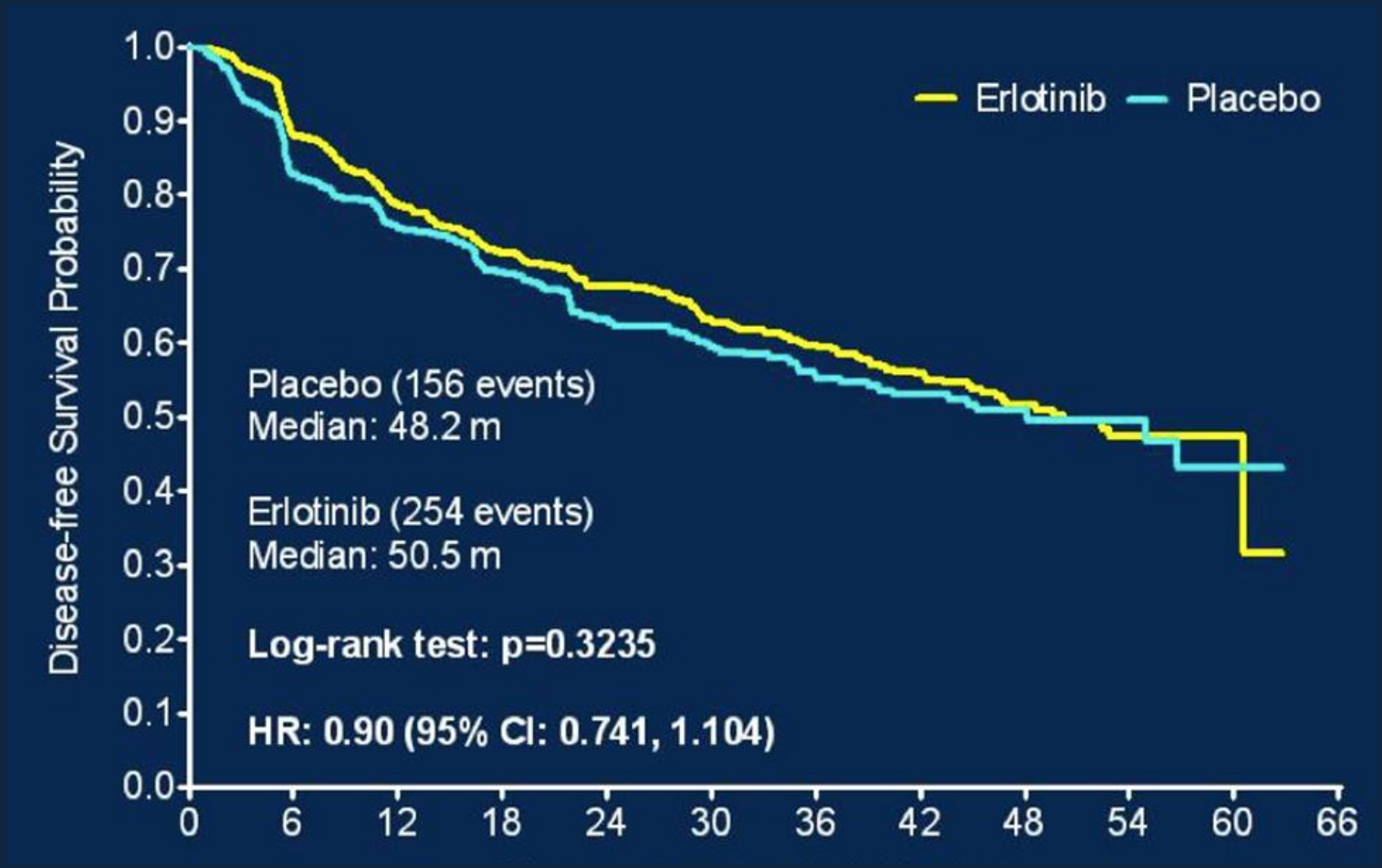
- OS
- DFS and OS in patients with del19/L858R

n= 973

*Stratification by histology, stage, adjuvant chemotherapy, smoking status, country, EGFR FISH status

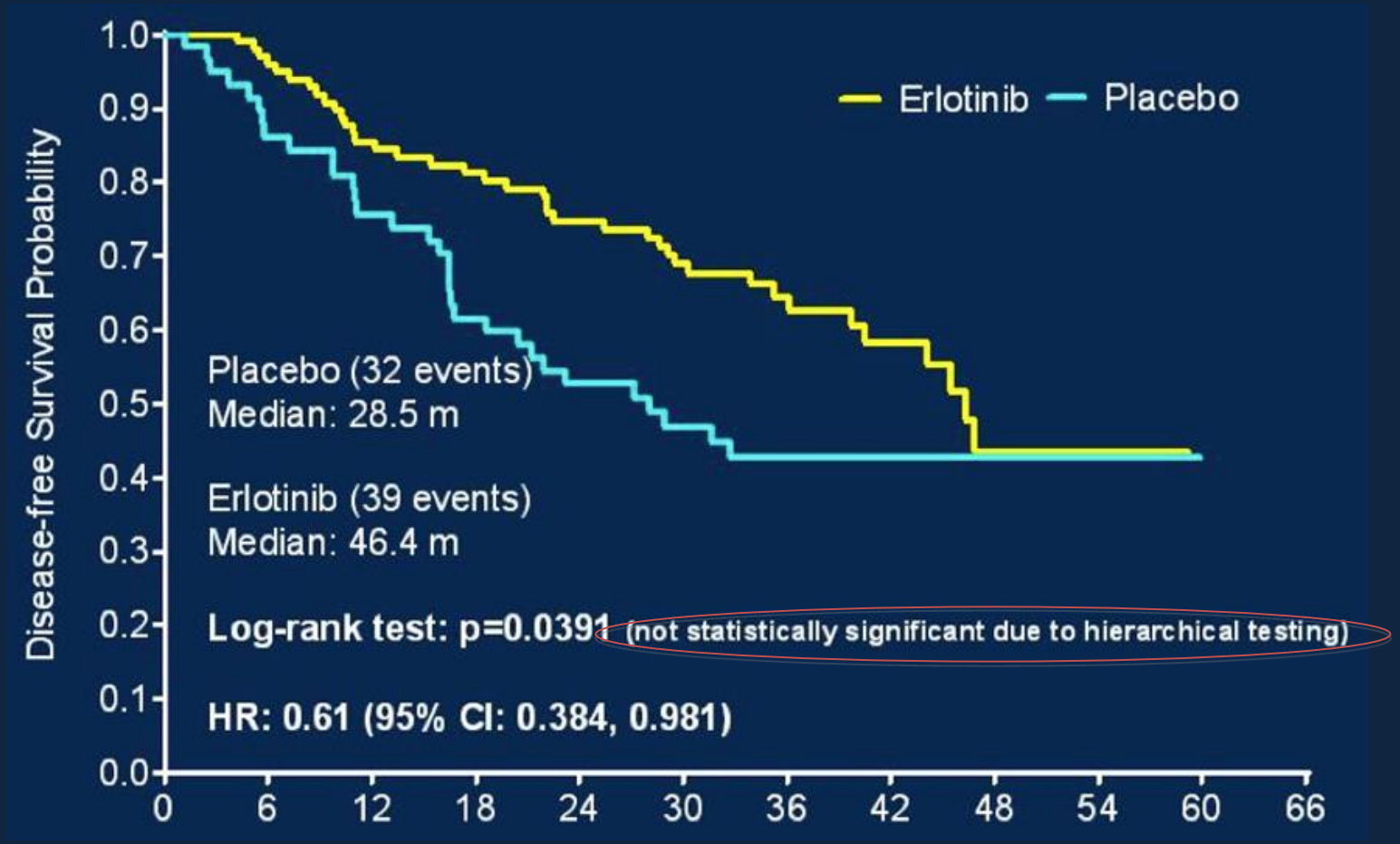
Shepherd, ASCO 2014

RADIANT:
unselected patient population



Kelly, ASCO 2014

RADIANT: EGFR M+ DFS



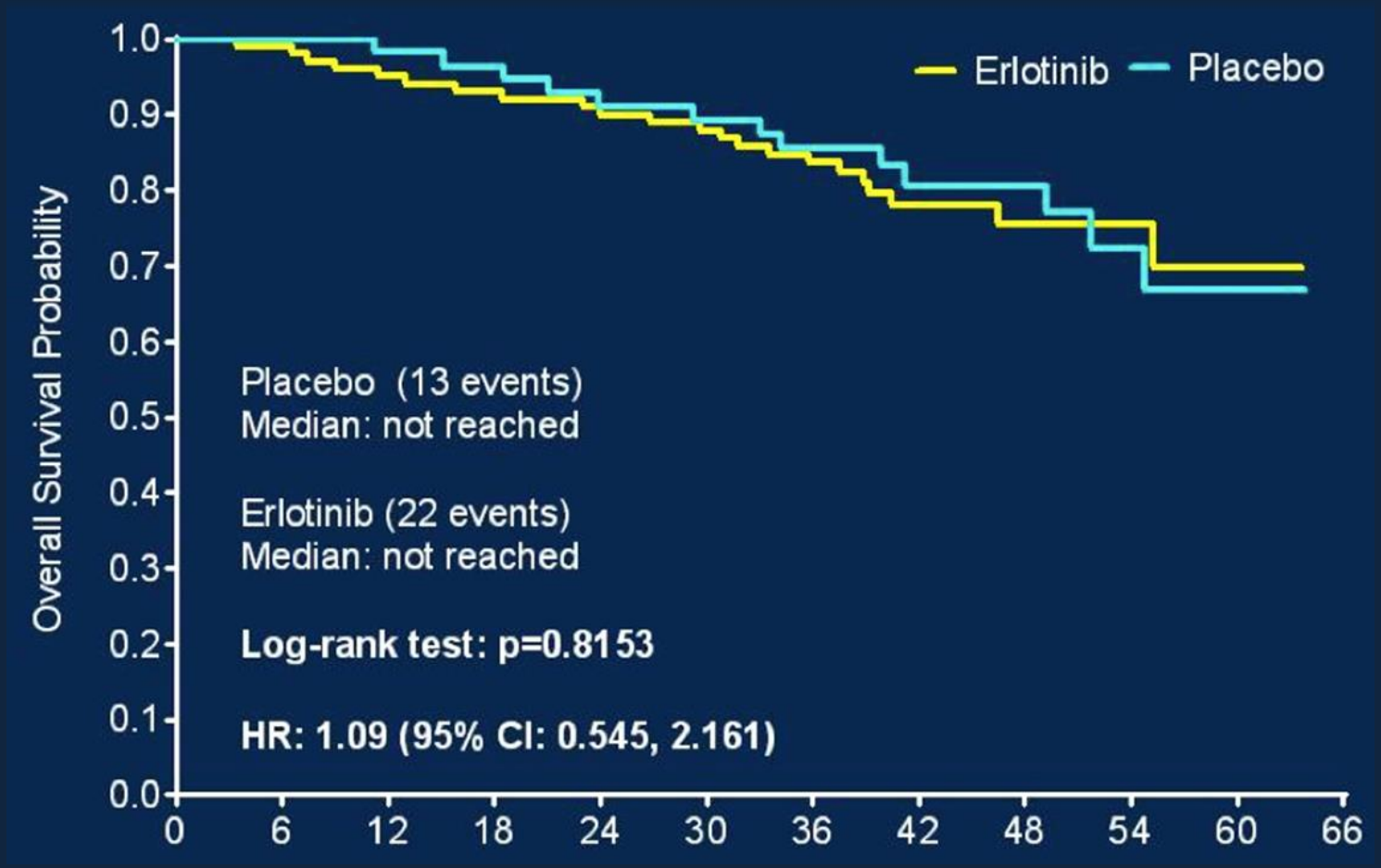
RADIANT: EGFR M+

Question 1: Are we speaking about adjuvant treatment
to reach cure?

Table 2. DFS Summary: *EGFR* M+ Subgroup

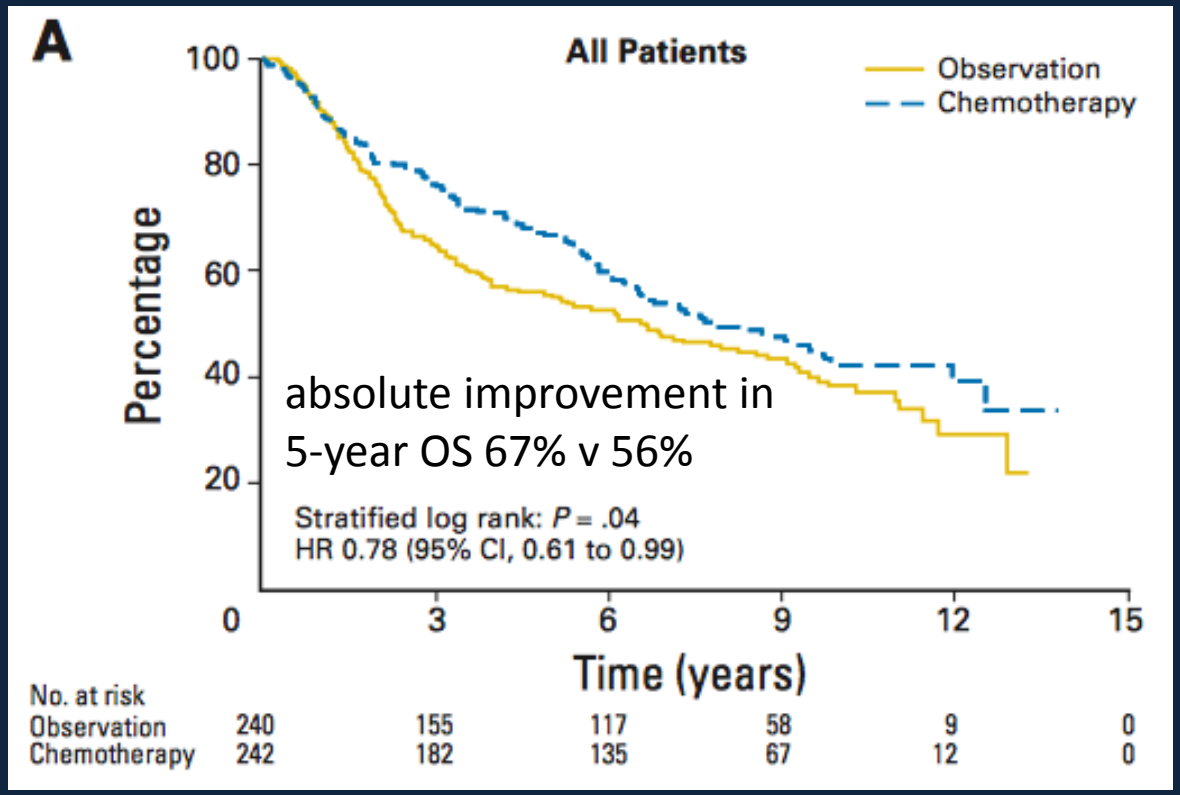
	Erlotinib (n=102)	Placebo (n=59)
DFS rate (95% CI)		
2-y	0.75 (0.66, 0.83)	0.54 (0.42, 0.67)
4-y	0.43 (0.28, 0.59)	0.43 (0.30, 0.56)

OS EGFR M+


Erlotinib
Placebo
Overall Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
66
Placebo (13 events)
Median: not reached
Erlotinib (22 events)
Median: not reached
Log-rank test: p=0.8153
HR: 1.09 (95% CI: 0.545, 2.161)

RADIANT: EGFR M+
Example of another adjuvant trial

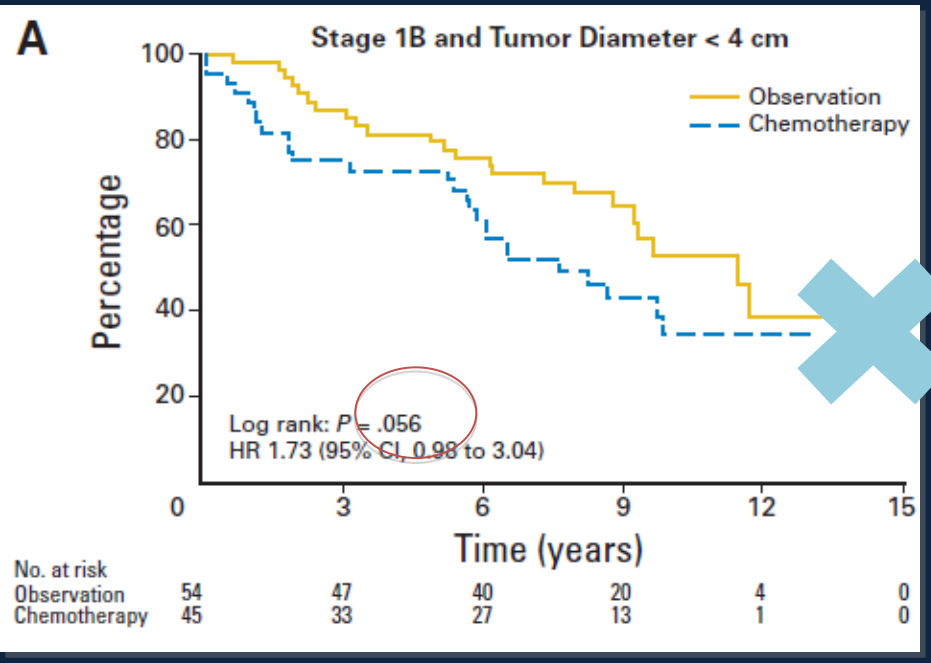
Question 2: Is the number of events large enough to conclude about adjuvant benefit in this unplanned subgroup?

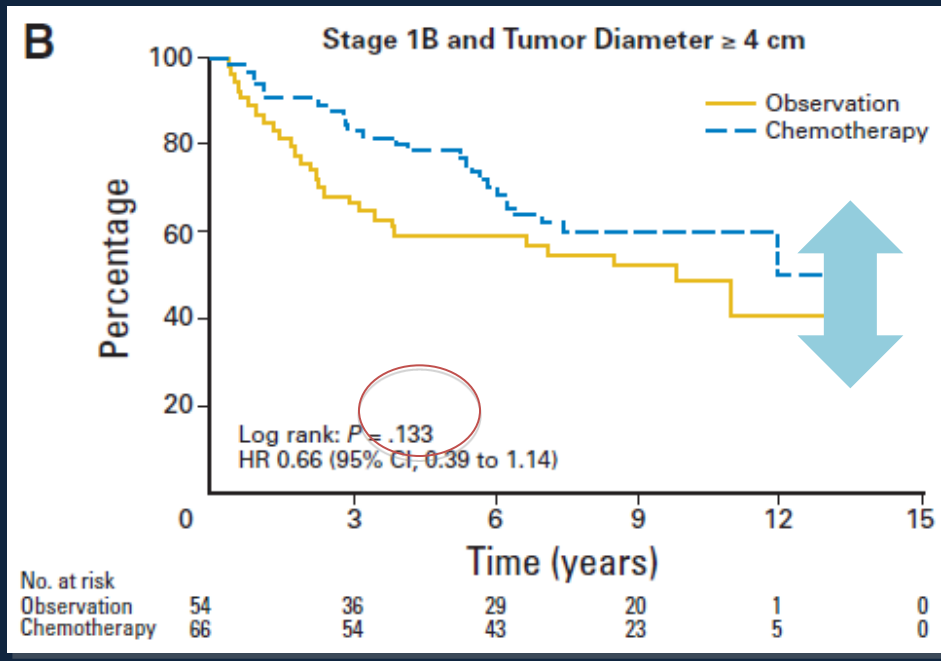


RADIANT: EGFR M+

Question 2: Is the number of events large enough to conclude about adjuvant benefit in this unplanned subgroup?

JBR.10: OS tumors ≥4cm





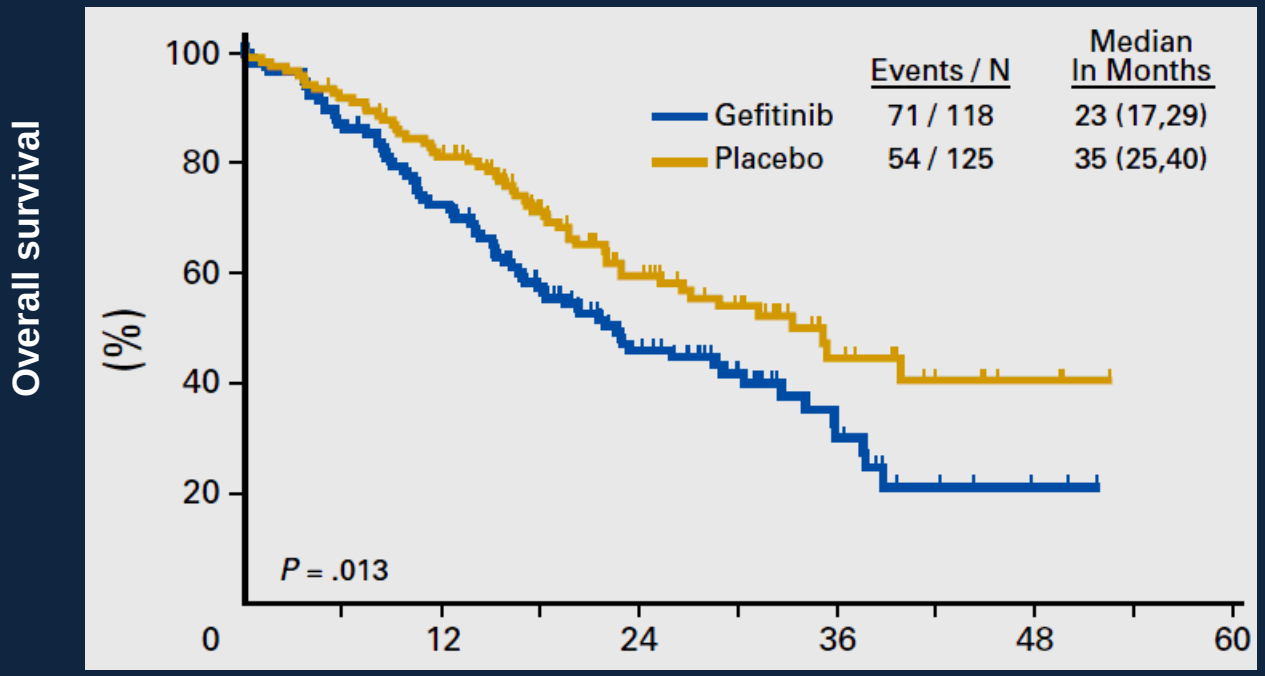
RADIANT: EGFR M+

Question 3: Are we maybe modifying tumour biology/course

MORE CNS RELAPSE?

		Placebo (n=59)
Number of		31 (52.5%)
Disease Sit		
Bone		29.0%
Brain†		12.9%
Liver	5.7%	6.5%
Lung	45.7%	54.8%
Mediastinum	5.7%	9.7%
Peripheral lymph node	5.7%	6.5%
Pleura	11.4%	6.5%
Pleural effusion	2.9%	6.5%

Gefitinib after local CT-RT in unselected NSCLC (+/- docetaxel consolidation)



Deaths are due to progressive disease !

Kelly, JCO 2010

RADIANT: EGFR M+

Question 4: Treatment/drug exposure sufficient?

Treatment duration In RADIANT (m)	Erlotinib (n=100)
Median	21.2
Range	(0.2–22.9)
≤3	21.0%
>3 to 6	5.0%
>6 to 12	15.0%
>12 to 18	2.0%
>18 to 22	23.0%
>22	34.0%

RADIANT: EGFR M+

Question 4: Treatment/drug exposure sufficient?

Treatment duration In RADIANT (m)	Erlotinib (n=100)
Median	21.2
>18 to 22	23.0%
>22	34.0%

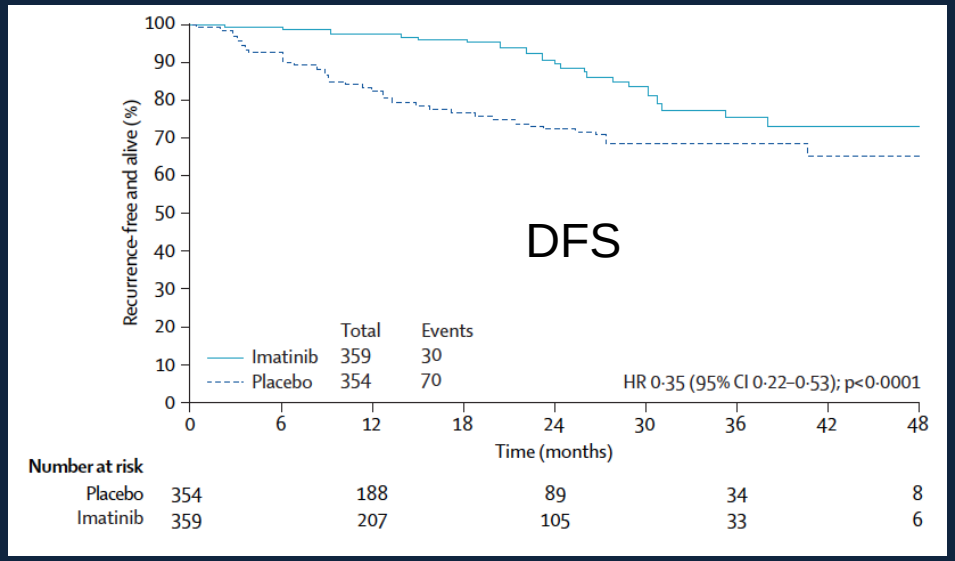
Duration of treatment ?

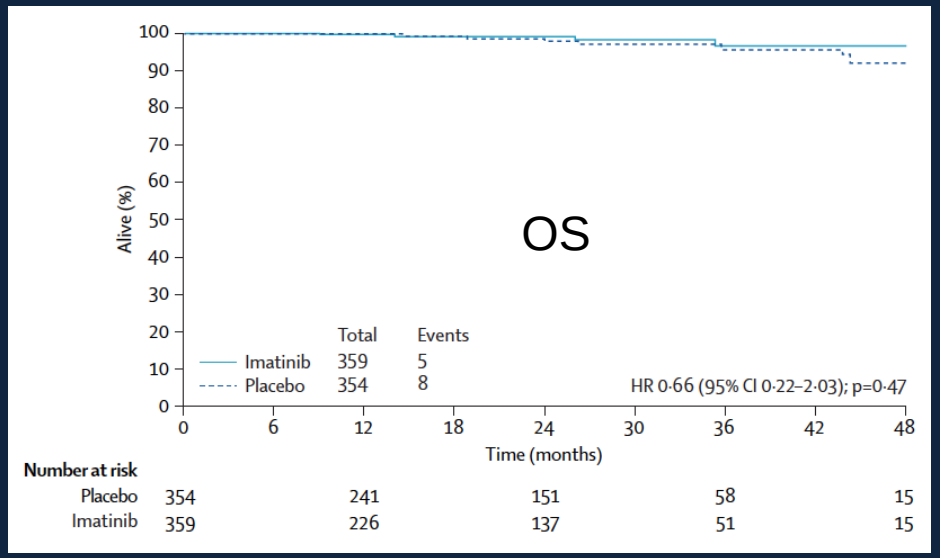
RADIANT: EGFR M+

Question 4: Treatment/drug exposure sufficient?

Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial

Ronald P DeMatteo, Karla V Ballman, Cristina R Antonescu, Robert G Maki, Peter W T Pisters, George D Demetri, Martin E Blackstein, Charles D Blanke, Margaret von Mehren, Murray F Brennan, Shreyaskumar Patel, Martin D McCarter, Jonathan A Polikoff, Benjamin R Tan, Kouros Owzar, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team

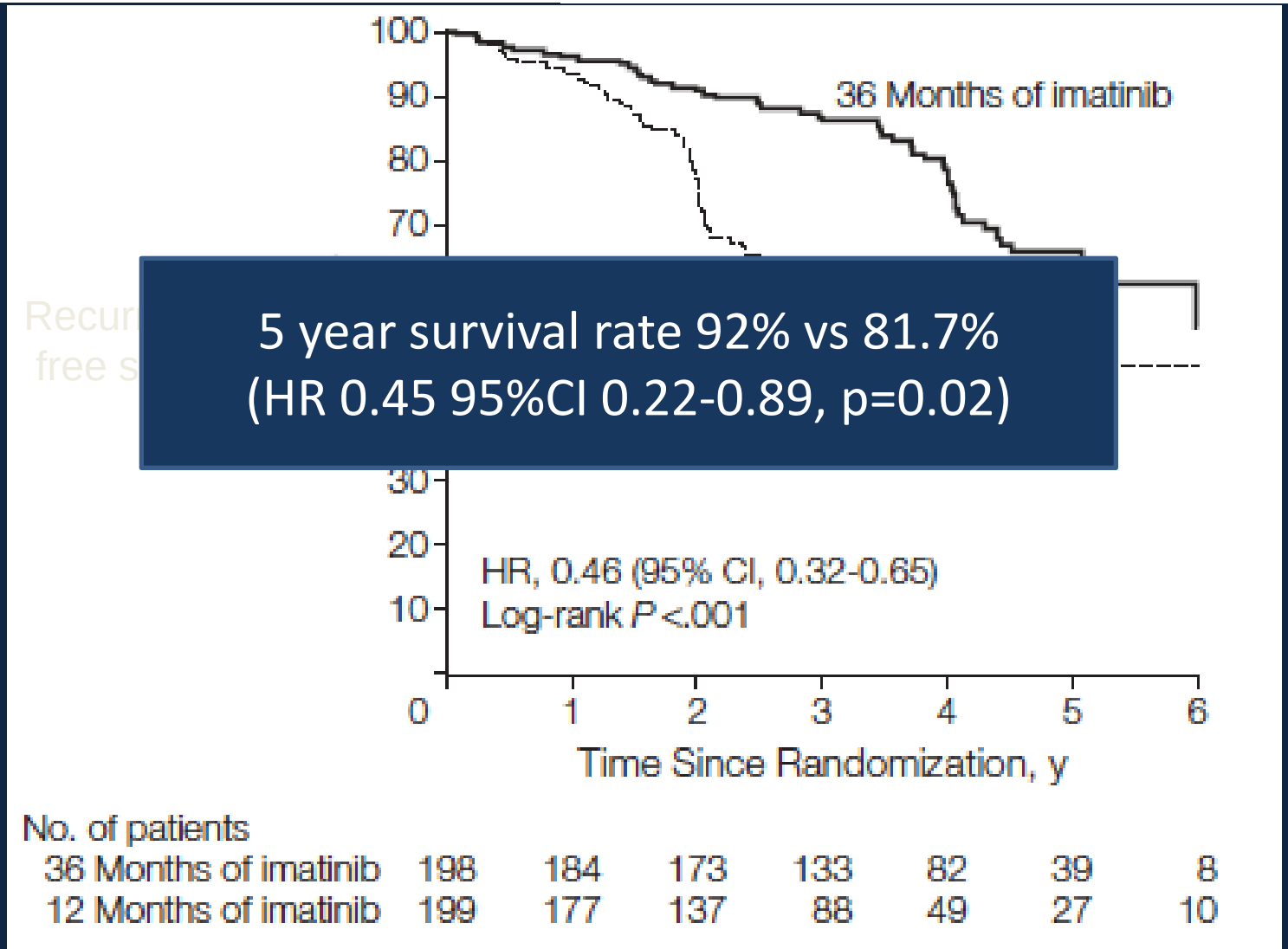




One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor

A Randomized Trial

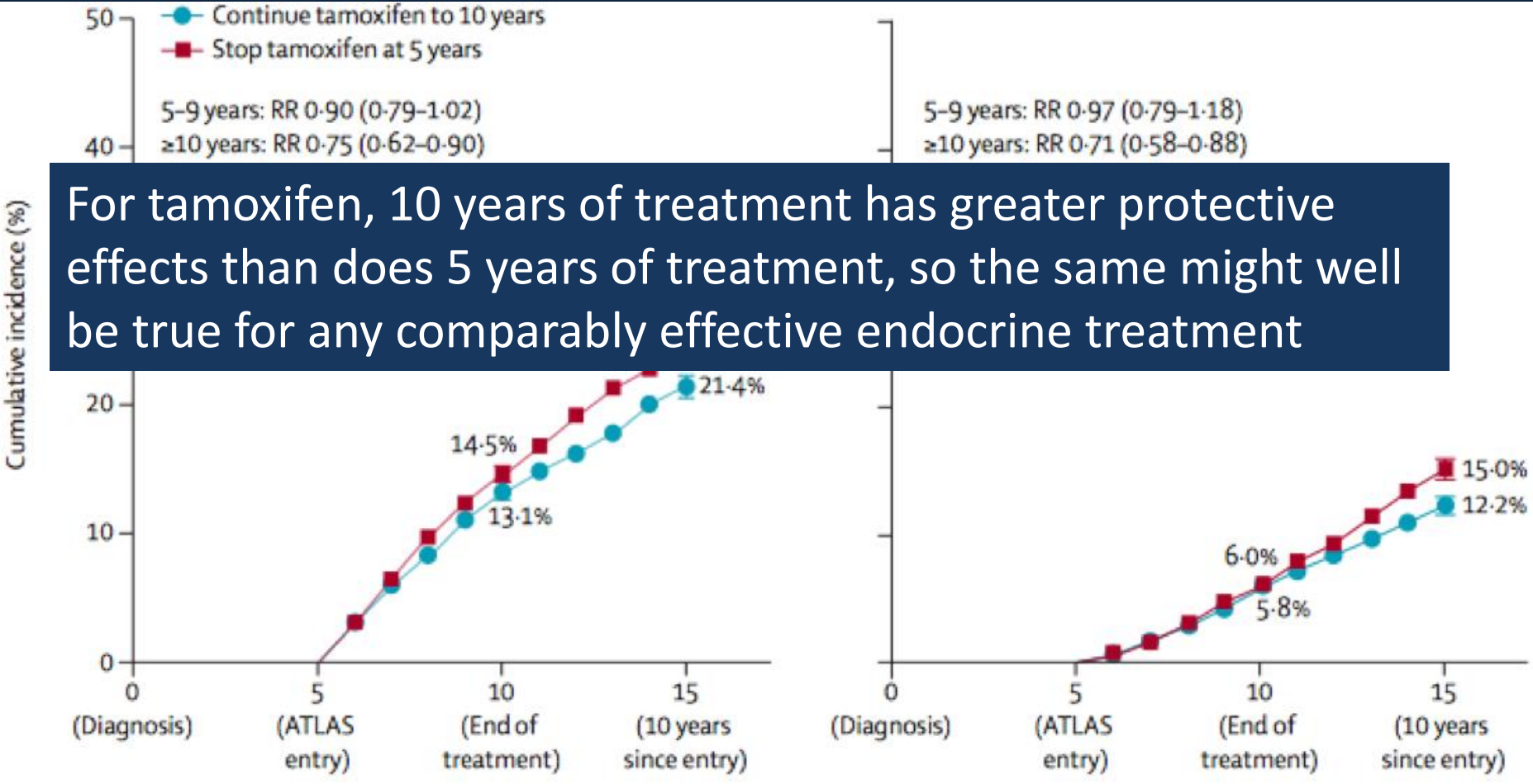
JAMA, March 28, 2012—Vol 307, No. 12 1265



5 year survival rate 92% vs 81.7%
(HR 0.45 95%CI 0.22-0.89, p=0.02)

Adjuvant EGFR TKI – Conclusions (2) Opened Questions

- How long to treat?



For tamoxifen, 10 years of treatment has greater protective effects than does 5 years of treatment, so the same might well be true for any comparably effective endocrine treatment

Davies, Lancet 2013

RADIANT: EGFR M+

Question 5: Which TKI?

Which EGFR TKI would be the best?

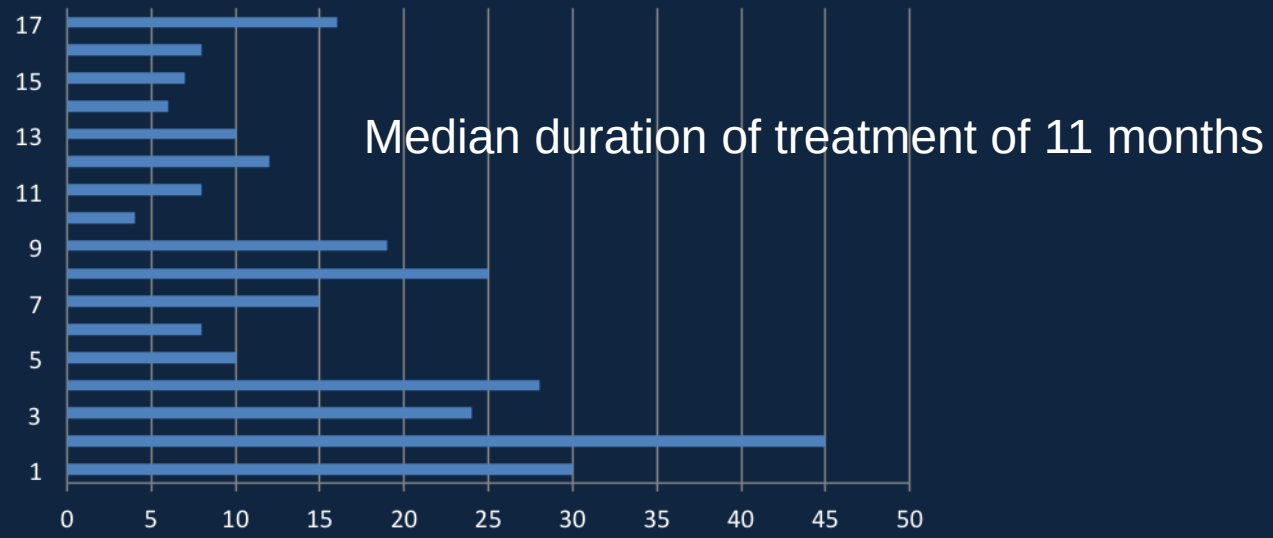
- Resistance
- Toxicity
- Compliance

gefitinib or erlotinib
Or afatinib
Or dacomitinib
Or
3rd generation TKI (AZD 9291 or CO-1686)

RADIANT: EGFR M+

Question 6: Crossover to EGFR TKI jeopardizing observed benefit?

- Cross-over to TKI upon progression
  - No data from RADIANT
  - SELECT is a single arm study
    - Re-treatment with EGFR TKI after relapse after adjuvant TKI is relatively effective



Ongoing trials
Molecular Targeted Adjuvant Trials

- NCI/Cooperative Group Trials: ALCHEMIST
  - Adjuvant erlotinib vs placebo for EGFR mutant NSCLC (n=410)
  - Adjuvant crizotinib vs placebo for ALK positive NSCLC (n=336)

- Japan: WJOG6410L (IMPACT)
  - Stage II-III: surgery -> cisplatin/vinorelbine vs gefitinib (n=230)

- China: CTONG1104 (ADJUVANT) - recruited
  - Stage II-IIIA: surgery -> cisplatin/vinorelbine vs gefitinib (n=220)

- Phase II adjuvant afatinib

Adjuvant E nclusions (1)
s

ALCHEMIST – EGFR A081105
EGFRmut
~10%
430 (5% ineligible)
Overall Survival
85%
0.05
0.67

- 2 prospective E Asian trials <u>eagerly awaited</u>

-> All with 2

- However, poter both Asian studies:

1. DFS as primary e
2. Not powered fo

Adjuvant EGFR TKI – Conclusions (2) Available Data

- Trials reported thus far look at unselected patient populations and/or are small

- In RADIANT, adjuvant TKI may have delayed systemic recurrence, and could have increased the chance of CNS relapse

- TKI at relapse (“crossover”) - not reported - might dramatically impact OS endpoint

Adjuvant EGFR TKI – Conclusions (3) Available Data

- Magnitude of DFS consistent in SELECT, RADIANT and retrospective trials

- DFS improvement looks impressive, but does not translate into OS benefit - which remains the strict aim of adjuvant therapy

- A well conducted prospective trial is needed to settle adjuvant TKI as a standard of care

Thanks for your attention…