# First generation TKI plus something in EGFR mutant NSCLC

Dr. Akhil Kapoor

Associate Professor, Medical Oncology

Tata Memorial Hospital (HBCH &MPMMCC), Varanasi

# Background

- We all love to give Osimertinib in EGFR mutant NSCLC.

Reasons:

- Well tolerated
- Oral treatment
- Very good outcomes (usually)

- Issue: Affordability
- Generic not going to come, Patent till 2035 !!!!!!

# Alternative Strategies

- Gefitinib plus Chemotherapy
- TKI plus Metformin
- TKI plus Bevacizumab

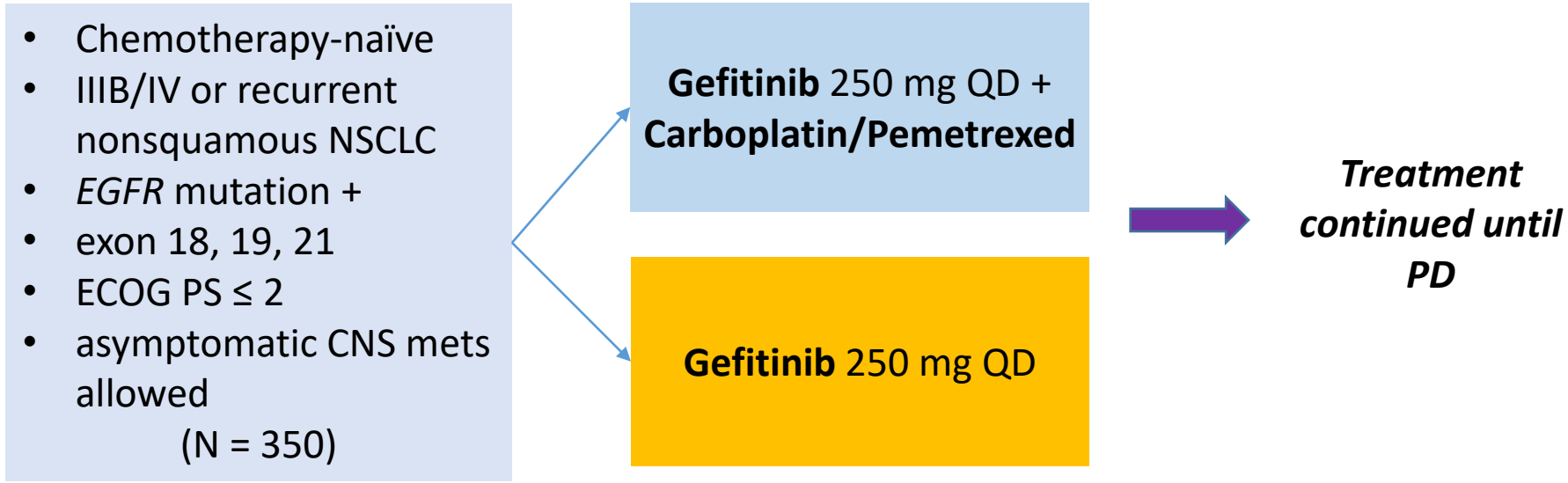
# Gefitinib plus Chemotherapy

original report

## Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in *EGFR*-Mutated Lung Cancer

Vanita Noronha, MBBS, MD, DM[1]; Vijay Maruti Patil, MBBS, MD, DM[1]; Amit Joshi, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1]; Anuradha Chougule, PhD[1]; Abhishek Mahajan, MBBS, MD, MRes[1]; Amit Janu, MBBS, DMRD, DNB[1]; Nilendu Purandare, MBBS, DNB[1]; Rajiv Kumar, MBBS, MD[1]; Sucheta More, BAMS, MSc[1]; Supriya Goud, BAMS[1]; Nandkumar Kadam, BSc[2]; Nilesh Daware, HSc[2]; Atanu Bhattacharjee, MSc, PhD[1]; Srushti Shah, BHMS, PDCR[1]; Akanksha Yadav, MSc[1]; Vaishakhi Trivedi, MSc[1]; Vichitra Behel, MTech[1]; Amit Dutt, PhD[3]; Shripad Dinanath Banavali, MBBS, MD[1]; and Kumar Prabhash, MBBS, MD, DM[1]

# Gefitinib ± Carboplatin/Pemetrexed As First-Line Therapy for EGFR-Mutant NSCLC




- Primary endpoint: PFS
- Secondary endpoints: OS, toxicity, QoL

*Stratified by ECOG PS and EGFR mutation subtype*

Noronha et al. ASCO 2019

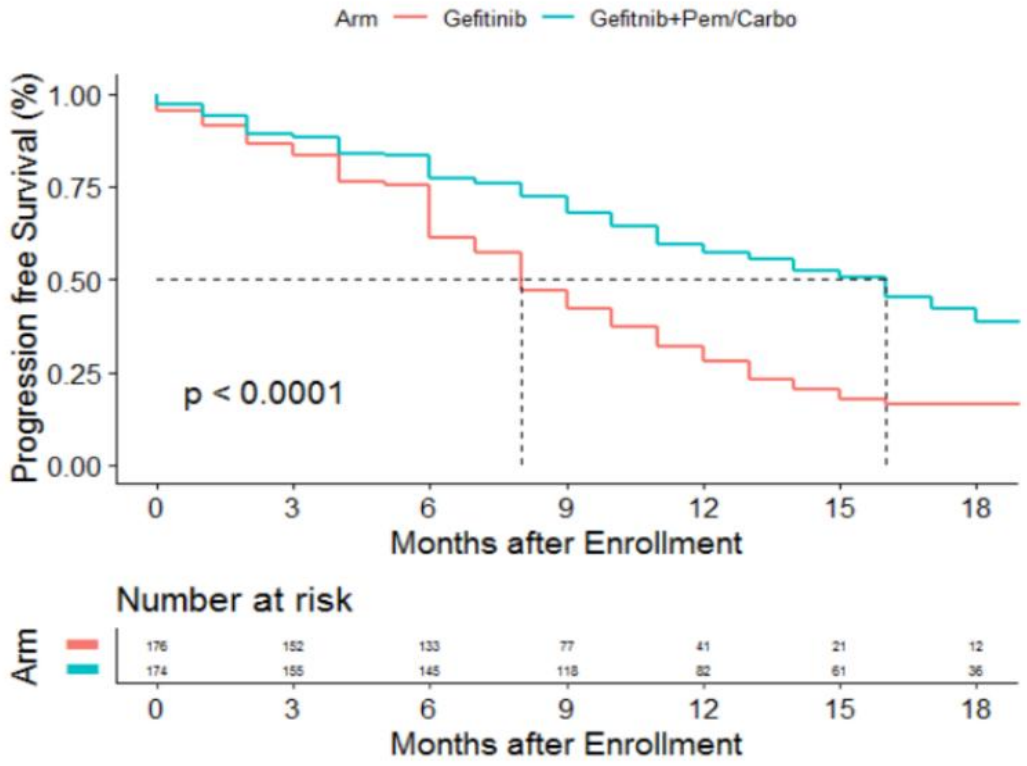
# Included rare mutations as well: Real world Scenario

| Characteristic | Gef+C (n = 174) | Gef (n = 176) |
|---|---|---|
| Presence of brain metastases[e] | 30 (17) | 34 (19) |
| Presence of pulmonary embolism[f] | 7 (4) | 2 (1) |
| *EGFR* mutation type | | |
| Exon 19 in-frame deletion | 107 (62) | 109 (62) |
| Exon 21 (L858R/L861Q) | 60 (35) | 60 (34) |
| Exon 18 (G719X) | 1 (1) | 2 (1) |
| Exon 20 (T790M) with additional sensitizing mutation[g] | 4 (2) | 2 (1) |
| Dual sensitizing mutation[h] | 2 (1) | 3 (2) |

# Gefitinib  vs Gefitinib + chemotherapy TMH

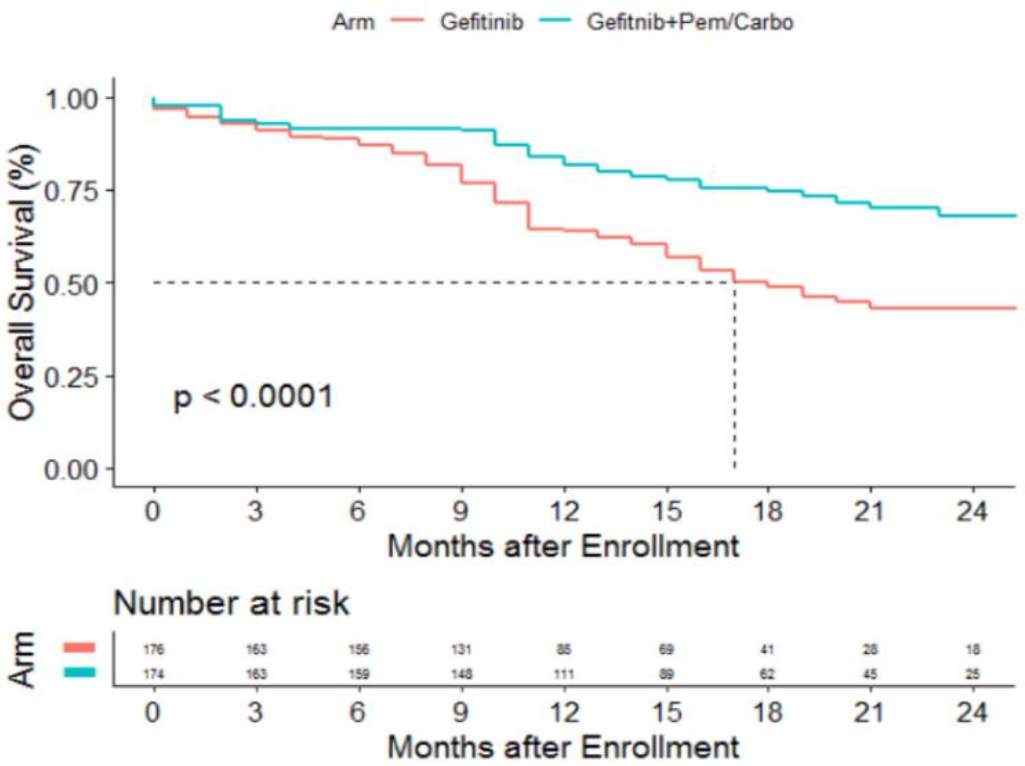
## Panel A

| Arm | Number of patients | Number of events | Median PFS (95%CI) |
|---|---|---|---|
| Gefitinib | 176 | 138 | 8 months (7.0 to 9.0) |
| Gefitinib + pemetrexed/carboplatin | 174 | 99 | 16 months (13.5 to 18.5) |
| Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66 | | | |




## Panel B

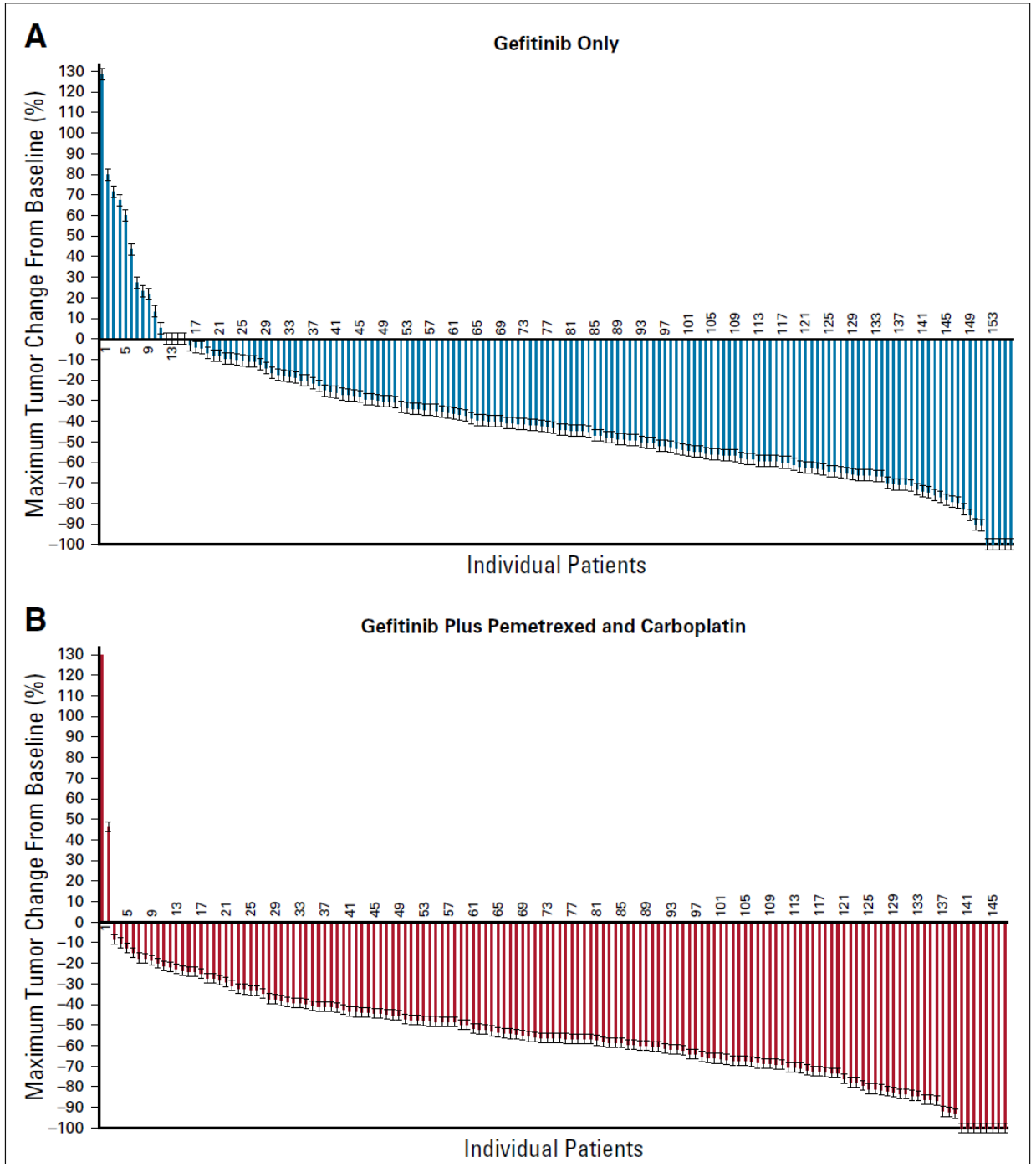
| Arm | Number of patients | Number of events | Median OS (95%CI) |
|---|---|---|---|
| Gefitinib | 176 | 80 | 17 months (13.5 to 20.5) |
| Gefitinib + pemetrexed/carboplatin | 174 | 42 | NC (NC to NC) |
| Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66 | | | |

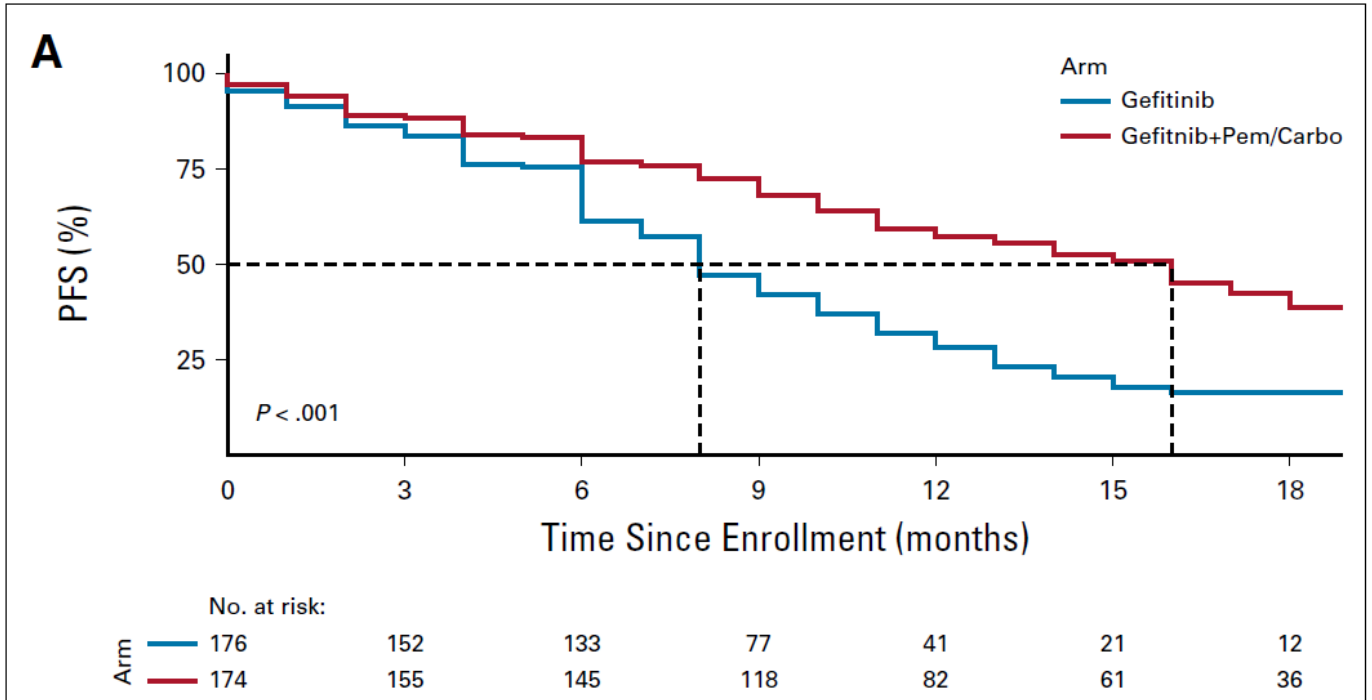


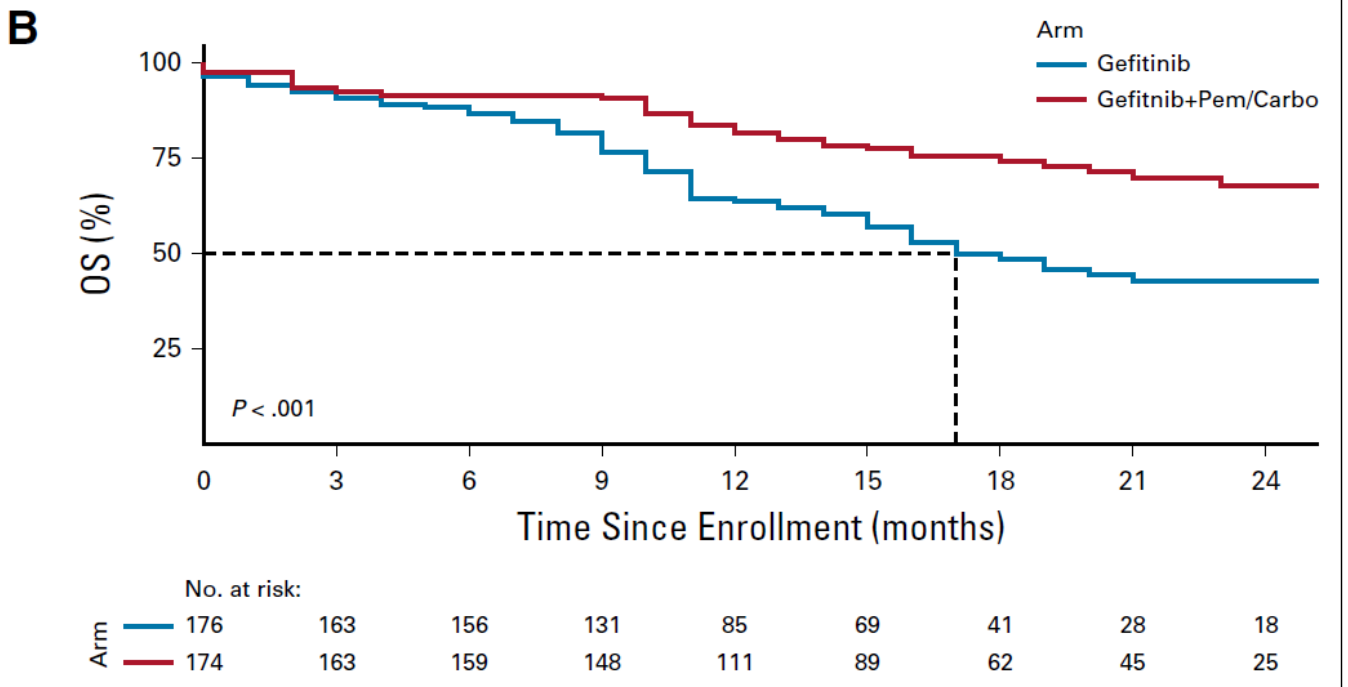
# ORR

75% versus 62%

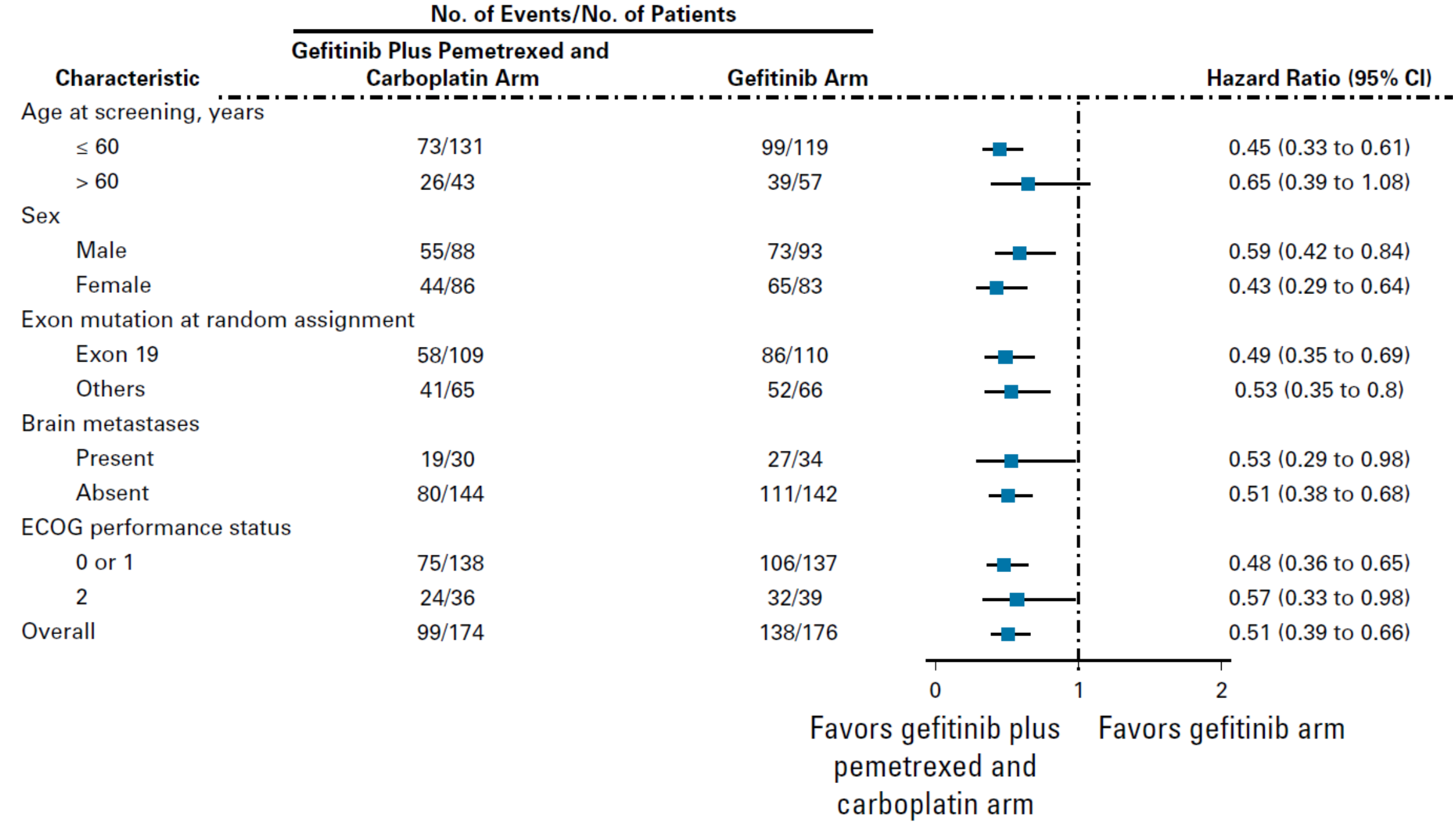
P=0.01






- PFS time: 8 m Vs. 16 m
- OS: 18-month OS rates were 48.7% and 74.3%
- PFS2 time was 14 months and 23 months.


No. of Events/No. of Patients
Characteristic
Gefitinib Plus Pemetrexed and Carboplatin Arm
Gefitinib Arm
Hazard Ratio (95% CI)
Age at screening, years
≤ 60 73/131 99/119 0.45 (0.33 to 0.61)
> 60 26/43 39/57 0.65 (0.39 to 1.08)
Sex
Male 55/88 73/93 0.59 (0.42 to 0.84)
Female 44/86 65/83 0.43 (0.29 to 0.64)
Exon mutation at random assignment
Exon 19 58/109 86/110 0.49 (0.35 to 0.69)
Others 41/65 52/66 0.53 (0.35 to 0.8)
Brain metastases
Present 19/30 27/34 0.53 (0.29 to 0.98)
Absent 80/144 111/142 0.51 (0.38 to 0.68)
ECOG performance status
0 or 1 75/138 106/137 0.48 (0.36 to 0.65)
2 24/36 32/39 0.57 (0.33 to 0.98)
Overall 99/174 138/176 0.51 (0.39 to 0.66)
0
1
2
Favors gefitinib plus pemetrexed and carboplatin arm
Favors gefitinib arm

# Toxicities

- Benefit came at the price of a doubling of serious clinically relevant toxicities, from 25% to 51%.
- Chemotherapy-induced myelosupression and nephrotoxicity.
- FN rates 11%, 1 death
- Fatigue not statistically different, but in clinical practice seems to be higher constantly

rapid communications

# Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study

**Yukio Hosomi, MD, PhD[1]; Satoshi Morita, PhD[2]; Shunichi Sugawara, MD, PhD[3]; Terufumi Kato, MD[4]; Tatsuro Fukuhara, MD, PhD[5]; Akihiko Gemma, MD, PhD[6]; Kazuhisa Takahashi, MD, PhD[7]; Yuka Fujita, MD, PhD[8]; Toshiyuki Harada, MD, PhD[9]; Koichi Minato, MD[10]; Kei Takamura, MD[11]; Koichi Hagiwara, MD, PhD[12]; Kunihiko Kobayashi, MD, PhD[13]; Toshihiro Nukiwa, MD, PhD[14]; and Akira Inoue, MD, PhD[15] for the North-East Japan Study Group**

abstract

**PURPOSE** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor combined with cytotoxic chemotherapy is highly effective for the treatment of advanced non–small-cell lung cancer (NSCLC) with EGFR mutations; however, little is known about the efficacy and safety of this combination compared with that of standard therapy with EGFR- tyrosine kinase inhibitors alone.

**METHODS** We randomly assigned 345 patients with newly diagnosed metastatic NSCLC with EGFR mutations to gefitinib combined with carboplatin plus pemetrexed or gefitinib alone. Progression-free survival (PFS), PFS2, and overall survival (OS) were sequentially analyzed as primary end points according to a hierarchical sequential

# Inclusion Criteria

Age 20-75years

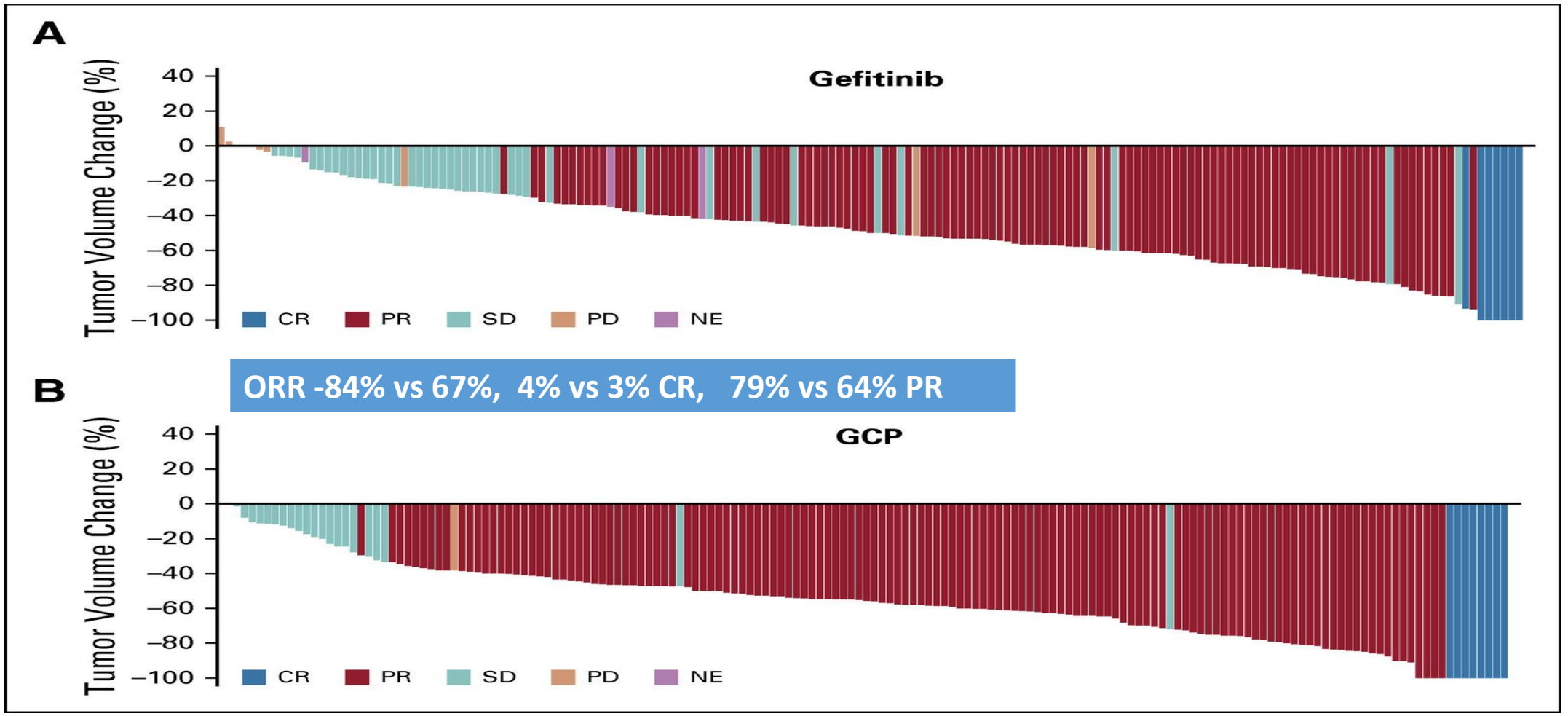
PS-0, 1

Normal marrow, renal, liver function

# Exclusion Criteria

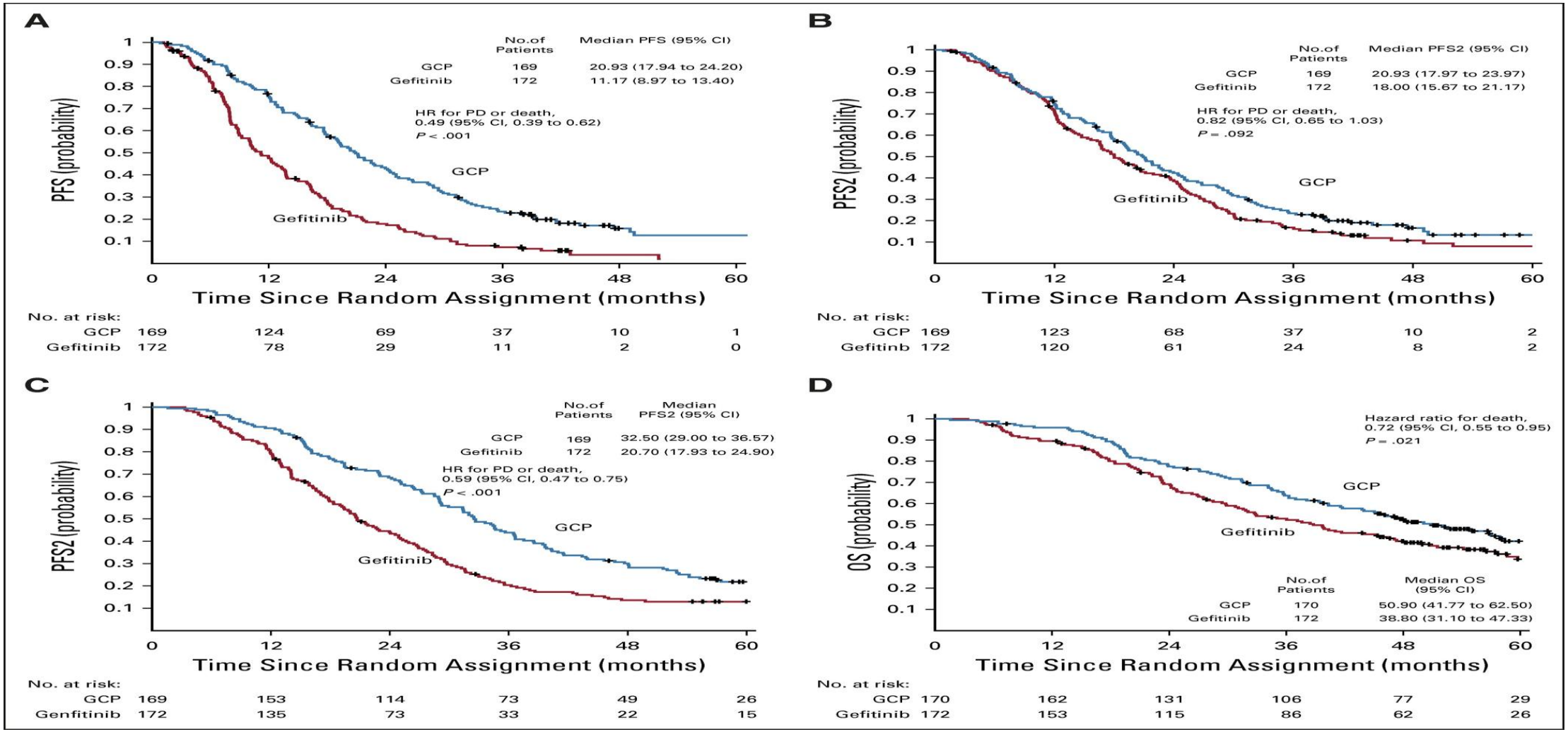
- Interstitial pneumonia or pulmonary fibrosis
- EGFR T790M Mutation
- Geftinib or pemtrexed as pre- or postoperative adjuvant therapy
- Symptomatic brain metastasis (enrollment accepted if symptoms disappear after RT)
- RT for the primary lesion
- Serious complications (poorly controlled psychiatric, pulmonary, hepatic or renal disease, DM)
- Marked malabsorption syndrome, diseases affecting GI function (post gastrectomy, gastric and duodenal ulcers, active IBD)

# Results-ORR

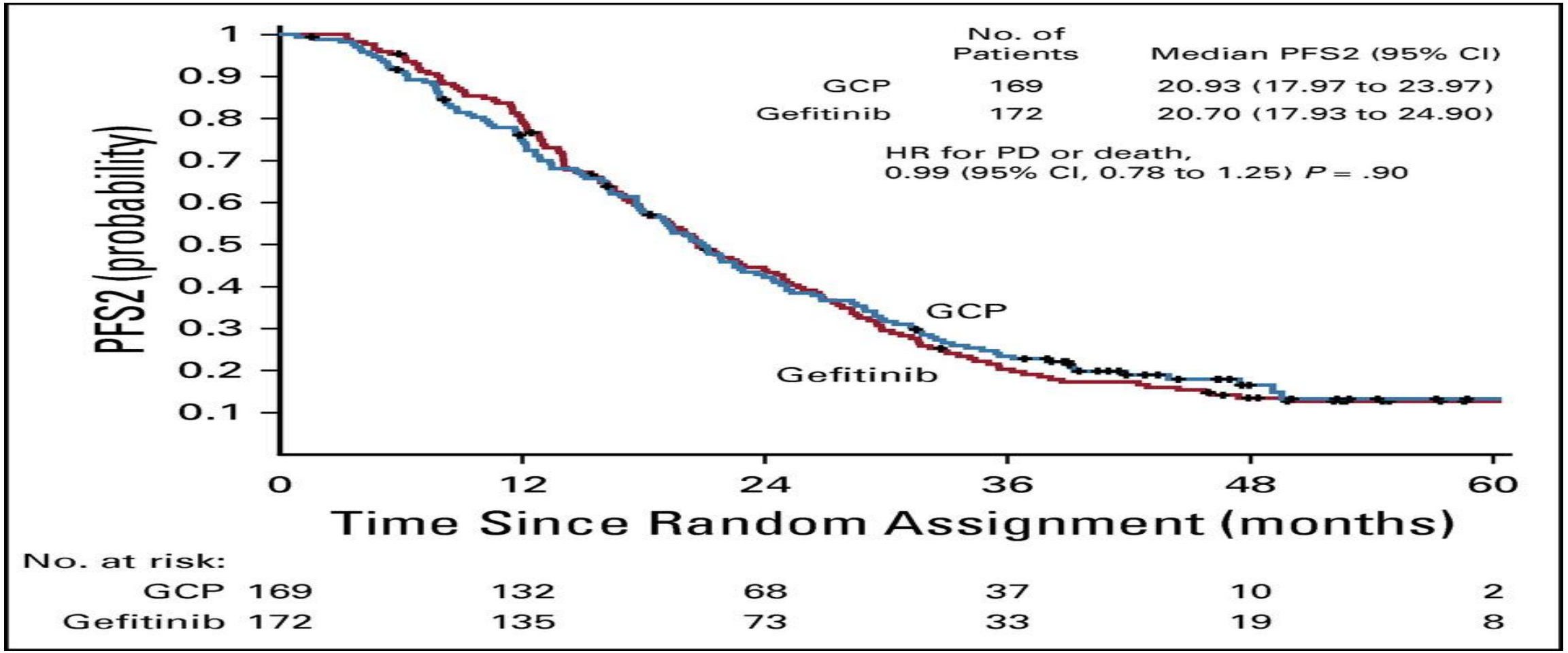


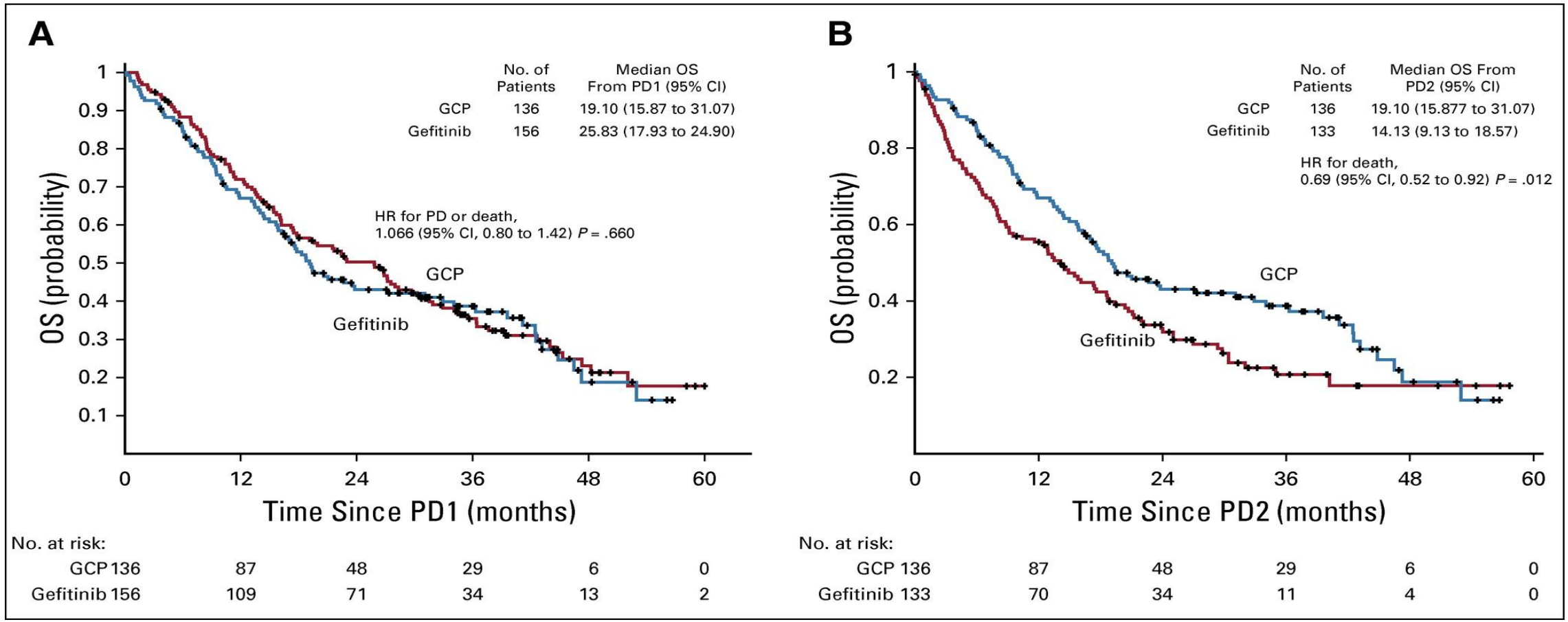

**ORR -84% vs 67%, 4% vs 3% CR, 79% vs 64% PR**

# Results-PFS/PFS2/OS



# Results-


No. of Patients
Median PFS2 (95% CI)
GCP 169 20.93 (17.97 to 23.97)
Gefitinib 172 20.70 (17.93 to 24.90)
HR for PD or death, 0.99 (95% CI, 0.78 to 1.25) P = .90
PFS2 (probability)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
GCP
Gefitinib
0
12
24
36
48
60
Time Since Random Assignment (months)
No. at risk:
GCP 169 132 68 37 10 2
Gefitinib 172 135 73 33 19 8

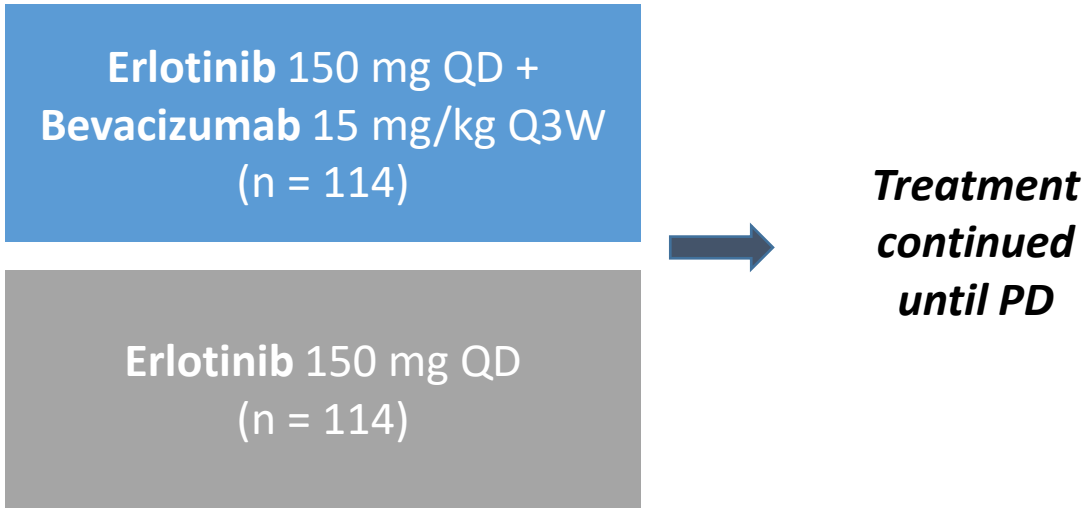

A
No. of Patients
Median OS From PD1 (95% CI)
GCP 136 19.10 (15.87 to 31.07)
Gefitinib 156 25.83 (17.93 to 24.90)
HR for PD or death, 1.066 (95% CI, 0.80 to 1.42) P = .660
GCP
Gefitinib
OS (probability)
Time Since PD1 (months)
No. at risk:
GCP 136 87 48 29 6 0
Gefitinib 156 109 71 34 13 2
B
No. of Patients
Median OS From PD2 (95% CI)
GCP 136 19.10 (15.877 to 31.07)
Gefitinib 133 14.13 (9.13 to 18.57)
HR for death, 0.69 (95% CI, 0.52 to 0.92) P = .012
GCP
Gefitinib
OS (probability)
Time Since PD2 (months)
No. at risk:
GCP 136 87 48 29 6 0
Gefitinib 133 70 34 11 4 0

# Clinical status at PD1 and PD2

| | Gefitinib (n=172) | Gefitinib+CBDCA+PEM (n=169) |
|---|---|---|
| PD1 | n=153 | n=135 |
| ECOG PS, n (%)<br>0-1 / 2 / 3-4 | 134 (87.6) / 8 (5.2) / 3 (2.0) | 116 (85.9) / 12 (8.9) / 4 (2.9) |
| Number of metastatic organs<br>median (range) | 1 (0-5) | 1 (0-7) |
| Brain metastasis, n (%) | 38 (24.8) | 48 (35.6) |
| PD2 | n=128 | |
| ECOG PS, n (%)<br>0-1 / 2 / 3-4 | 88 (68.8) / 19 (14.8) / 11 (8.6) | |
| Number of metastatic organs<br>median (range) | 2 (0-6) | |
| Brain metastasis, n (%) | 38 (29.7) | |

# Phase III NEJ026: Erlotinib ± Bevacizumab in *EGFR*-Mutated Advanced NSCLC

- Chemotherapy-naive patients IIIB/IV or recurrent nonsquamous NSCLC
- *EGFR* mutation +ve (exon 19 deletion or L858R, no T790M)
- ECOG PS ≤ 2
- asymptomatic CNS mets allowed
- (N = 228)

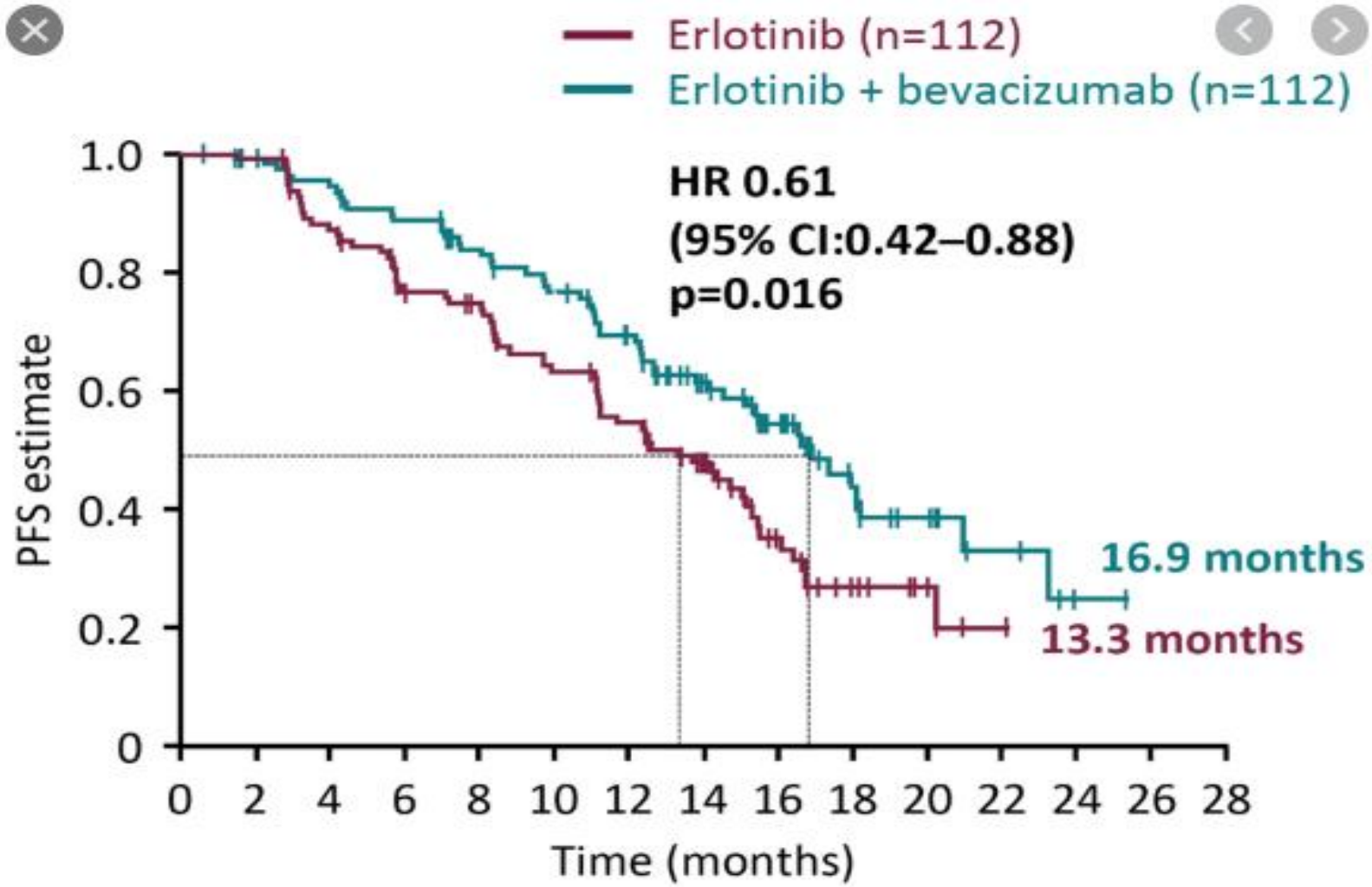



*Stratified by sex, stage,* EGFR *mutation, and smoking history*

- Primary endpoint: PFS by independent review
- Secondary endpoints: OS, tumor response, DoR, QoL, safety

Saito. Lancet Oncol. 2019;20:625.

# PFS


Erlotinib (n=112)
Erlotinib + bevacizumab (n=112)
HR 0.61
(95% CI:0.42–0.88)
p=0.016
16.9 months
13.3 months
PFS estimate
1.0
0.8
0.6
0.4
0.2
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Time (months)

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PDF [1 MB]

# Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial

Prof Kazuhiko Nakagawa, MD • Edward B Garon, MD • Takashi Seto, MD • Makoto Nishio, MD • Santiago Ponce Aix, MD • Prof Luis Paz-Ares, MD • et al. Show all authors • Show footnotes

Published: October 04, 2019 • DOI: https://doi.org/10.1016/S1470-2045(19)30634-5 • Check for updates


## Summary

### Background

Dual blockade of the EGFR and VEGF pathways in *EGFR*-mutated metastatic non-small-cell lung cancer (NSCLC) is supported by preclinical and clinical data, yet the approach is not widely implemented. RELAY assessed erlotinib, an EGFR tyrosine kinase

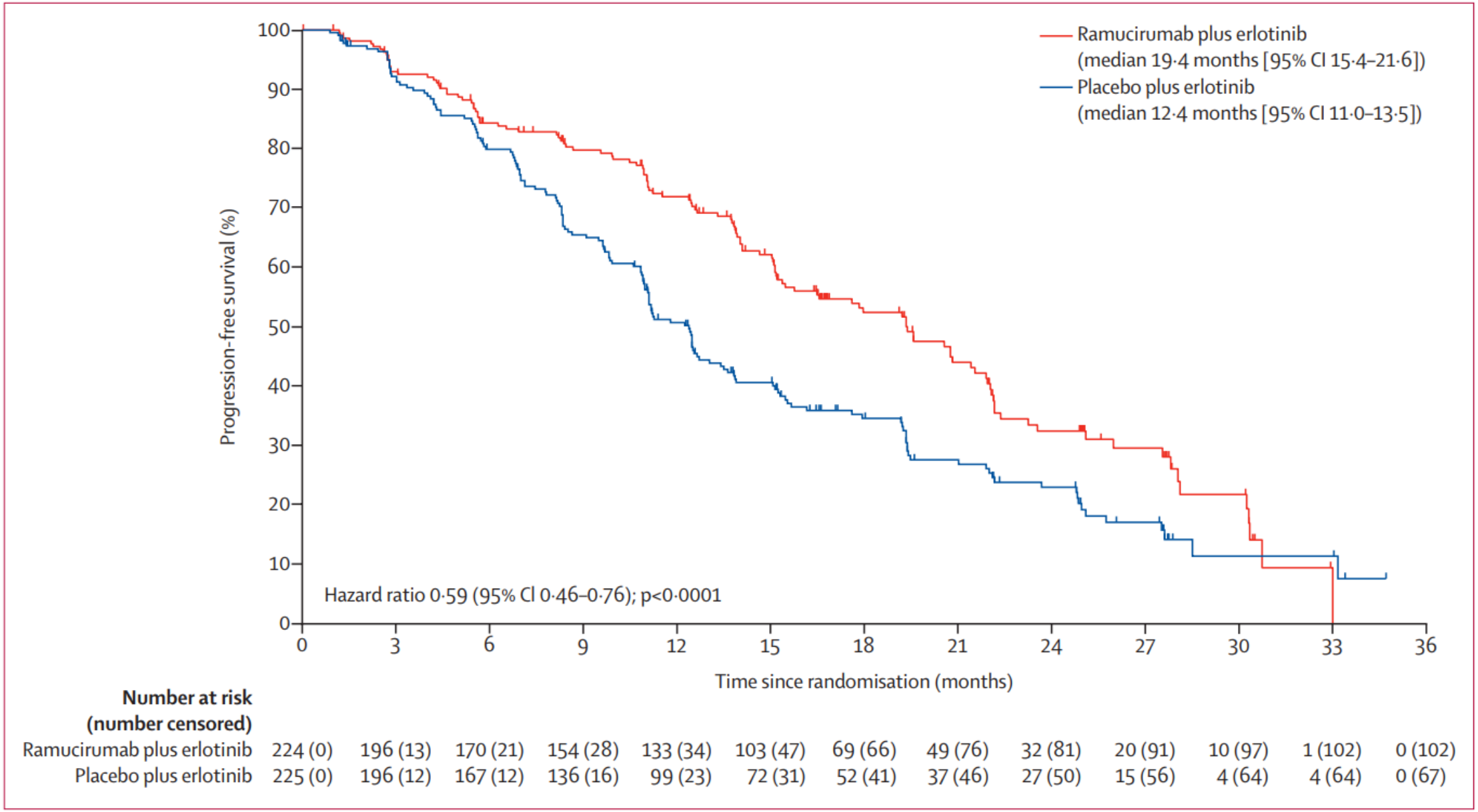



***Figure 2:*** **Kaplan-Meier estimates of investigator-assessed progression-free survival**

## What Information will help improve our treatment decisions?
## Are all EGFR mutations equal?

# Patients with Exon 19 Deletion Were Associated with Longer Progression-Free Survival Compared to Those with L858R Mutation after First-Line EGFR-TKIs for Advanced Non-Small Cell Lung Cancer: A Meta-Analysis

**Indirect comparison of EGFR exon 19 deletion versus EGFR exon 21 L858R mutation in TKI therapy cohort in terms of HR for PFS**

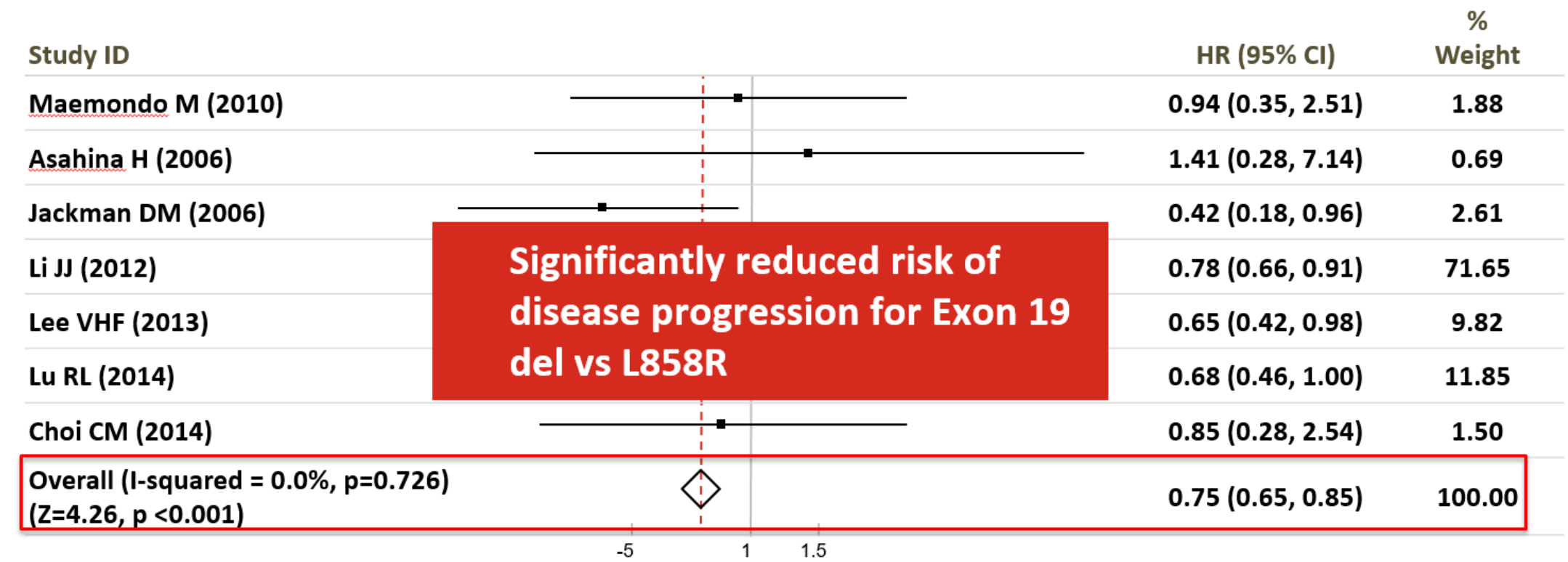
| TKI | $HR_{19/21}$ of TKI[a] for PFS (95% CI) | P-value |
|---|---|---|
| Gefitinib | | |
| Erlotinib | | |
| Afatinib | | |
| Overall | 0.59 (0.38-0.92) | 0.019 |

**Significantly reduced risk of disease progression for Exon 19 del vs L858R**

[a]$HR_{19/21}$ of TKI represent $HR_{19}$ exon deletion/exon 21 L858R mutation in TKI therapy cohort

| | | | |
|---|---|---|---|
| Indirect meta-analysis | 6 studies | 1382 patients | EGFR TKI (monotherapy - 1st or 2nd generation) vs CT |

# Patients with Exon 19 Deletion Were Associated with Longer Progression-Free Survival Compared to Those with L858R Mutation after First-Line EGFR-TKIs for Advanced Non-Small Cell Lung Cancer: A Meta-Analysis

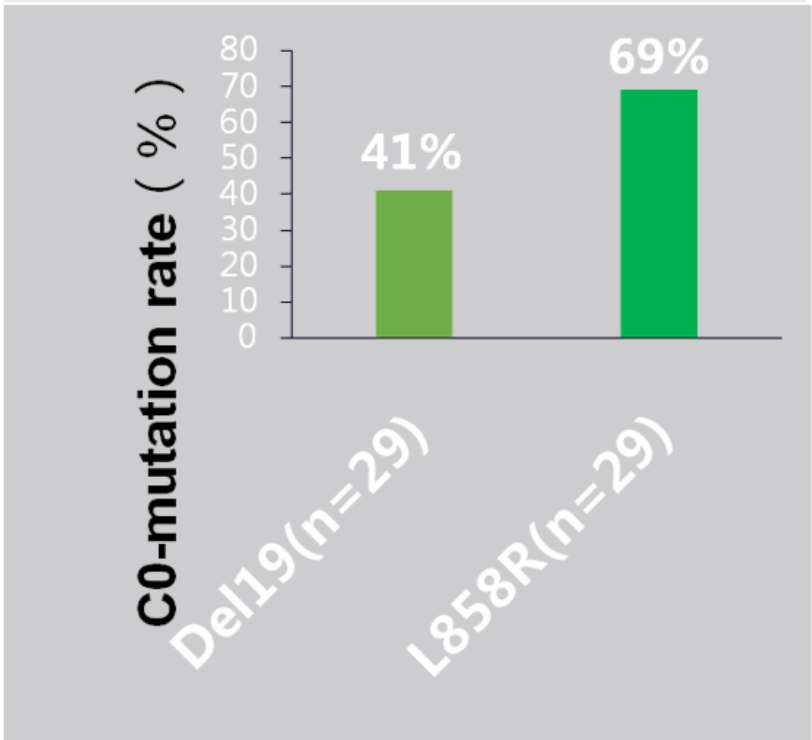



Direct meta-analysis | 7 studies | 549 patients | EGFR TKI (monotherapy - 1st or 2nd generation) vs CT

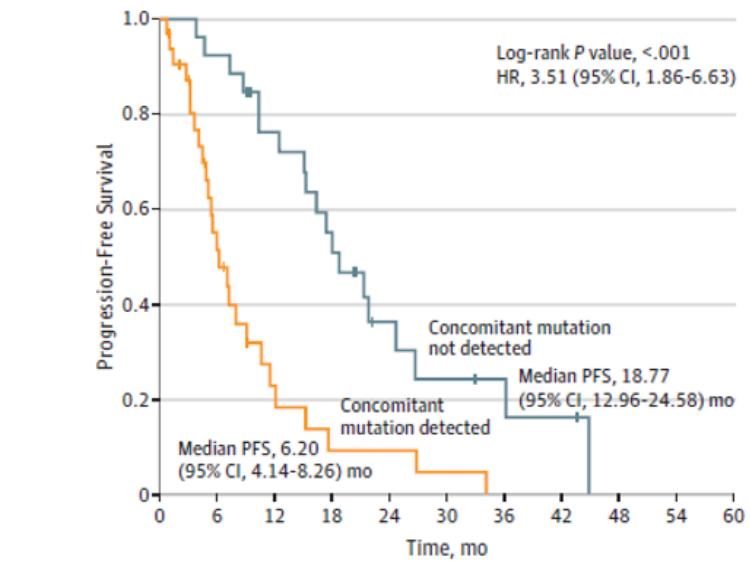
# L858R: Higher Incidence of Concomitant Mutation and Poor outcome

**Retrospective cohort study1 from Sun Yat-sen University Cancer Center, China, 2012-2014, 58 cases with EGFRm advanced NSCLC. Cell-free DNA obtained before treatment was subjected to NGS of 49 cancer-related genes**

**Co-mutation rate: L858R vs Del19: 69% vs 41%, *p*=0.04**



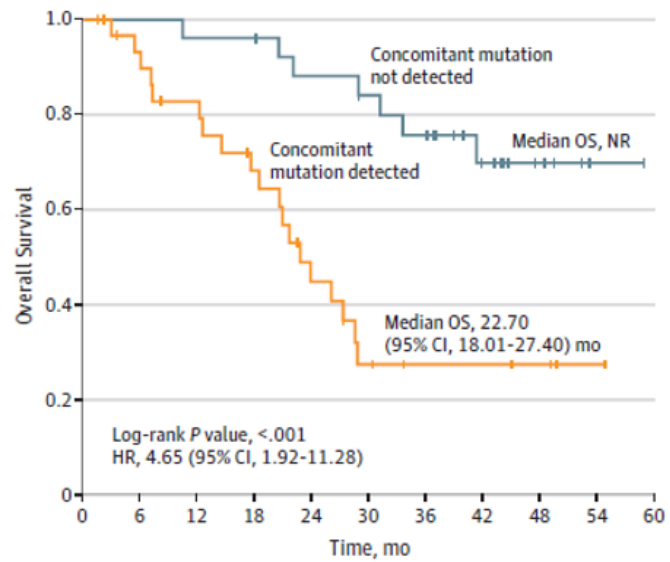

**PFS: 18.77 vs 6.2 months (*p*<0.001)**




No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Not detected | 26 | 24 | 18 | 13 | 6 | 4 | 3 | 2 |
| Detected | 32 | 14 | 5 | 2 | 2 | 1 | | |

**OS: NR vs 22.7 months (*p*<0.001)**



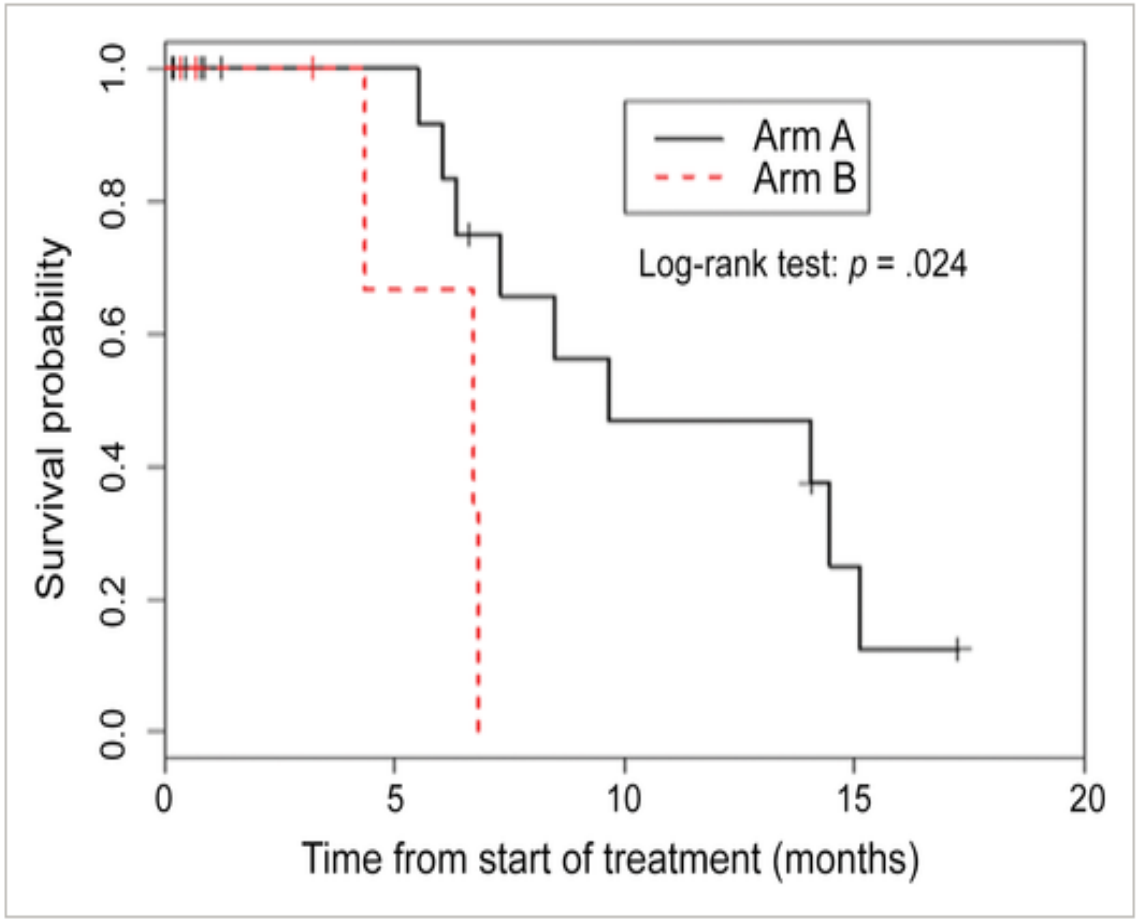

No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Not detected | 26 | 26 | 25 | 25 | 22 | 20 | 18 | 11 | 5 | 1 |
| Detected | 32 | 26 | 23 | 18 | 11 | 6 | 4 | 4 | 3 | 1 |

# A Randomized Phase II Study of Metformin plus Paclitaxel/Carboplatin/Bevacizumab in Patients with Chemotherapy-Naïve Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer

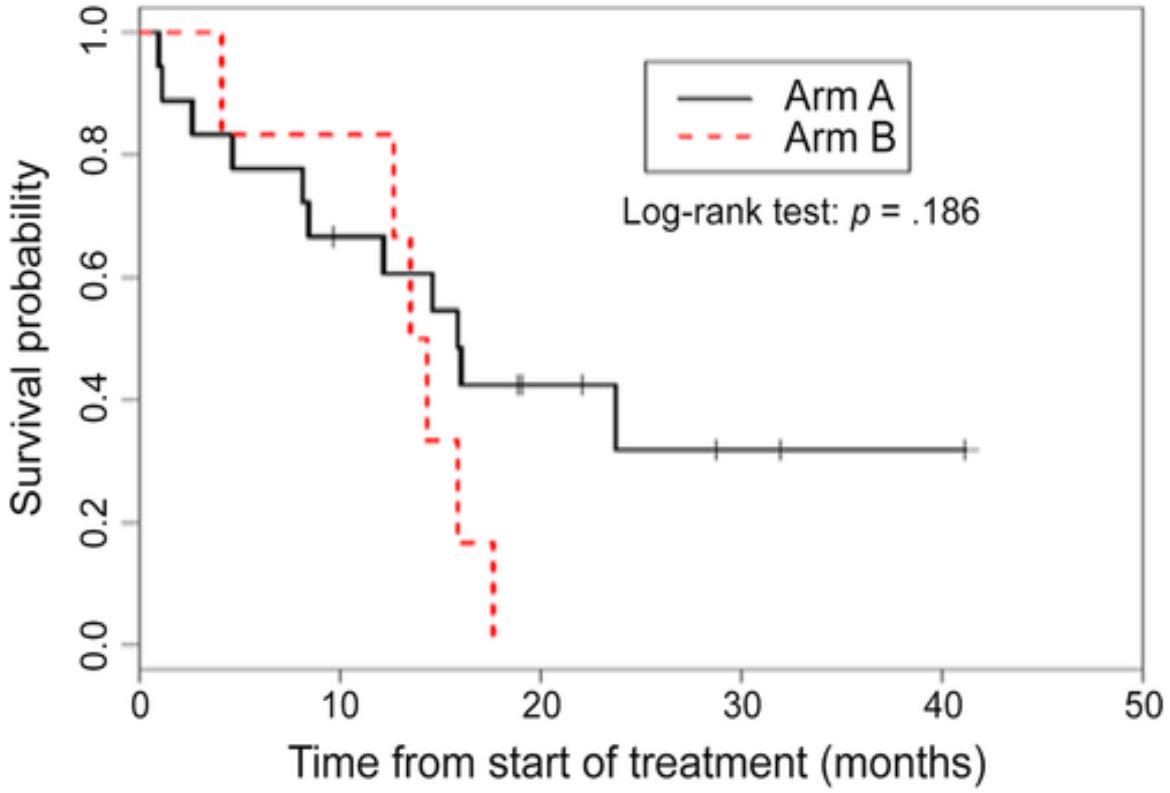
Kristen A. Marrone, Xian Zhou, Patrick M. Forde, Michael Purtell, Julie R. Brahmer, Christine L. Hann, Ronan J. Kelly, Barbara Coleman, Edward Gabrielson, Gary L. Rosner, David S. Ettinger

First published: 27 February 2018 | https://doi.org/10.1634/theoncologist.2017-0465 | Citations: 4




- The 1-year PFS on Arm A was 47% (95% CI: 25%–88%), with the 95% lower confidence bound greater than 15%, the hypothesized 1-year PFS without metformin.

- The median PFS was 9.6 months (95% CI: 7.3–not applicable [NA]) for Arm A and 6.7 months (95% CI: 4.4–NA) for Arm B




- The 1-year OS on Arm A was 68% (95% CI: 48%–92%), compared with the historical probability of 51%.

- Median OS of patients treated on Arm A was 15.9 months (95% CI: 8.4–NA) and 13.9 months (95% CI: 12.7–NA) on Arm B; the difference was not statistically significant (p = .186).

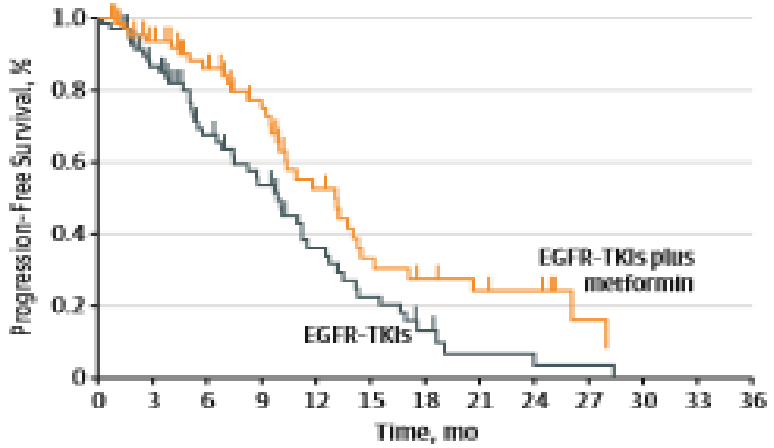
JAMA Oncology | Original Investigation

# Effect of Metformin Plus Tyrosine Kinase Inhibitors Compared With Tyrosine Kinase Inhibitors Alone in Patients With Epidermal Growth Factor Receptor–Mutated Lung Adenocarcinoma

## A Phase 2 Randomized Clinical Trial

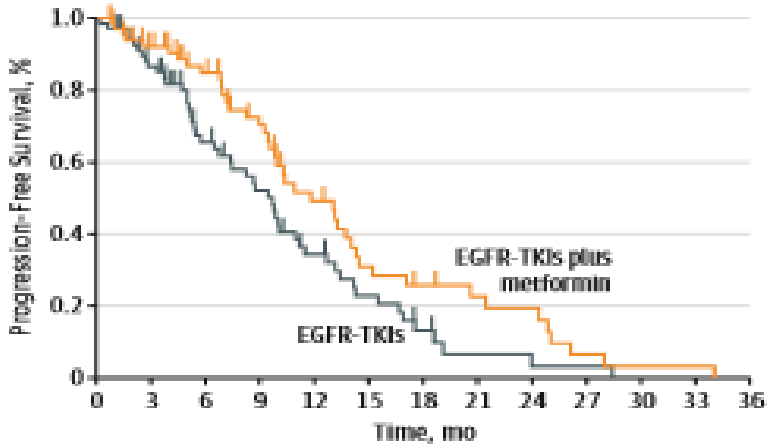
Oscar Arrieta, MD, MSc; Feliciano Barrón, MD; Miguel-Ángel Salinas Padilla, MD; Alejandro Avilés-Salas, MD; Laura Alejandra Ramírez-Tirado, MD, MSc; Manuel Jesús Arguelles Jiménez, MD; Edgar Vergara, MD, PhD; Zyanya Lucia Zatarain-Barrón, MD, MSc; Norma Hernández-Pedro, PhD; Andrés F. Cardona, MD, PhD; Graciela Cruz-Rico, PhD; Pedro Barrios-Bernal, BBs; Masao Yamamoto Ramos, MD; Rafael Rosell, MD, PhD

A Progression-free survival (radiooncologist 1)



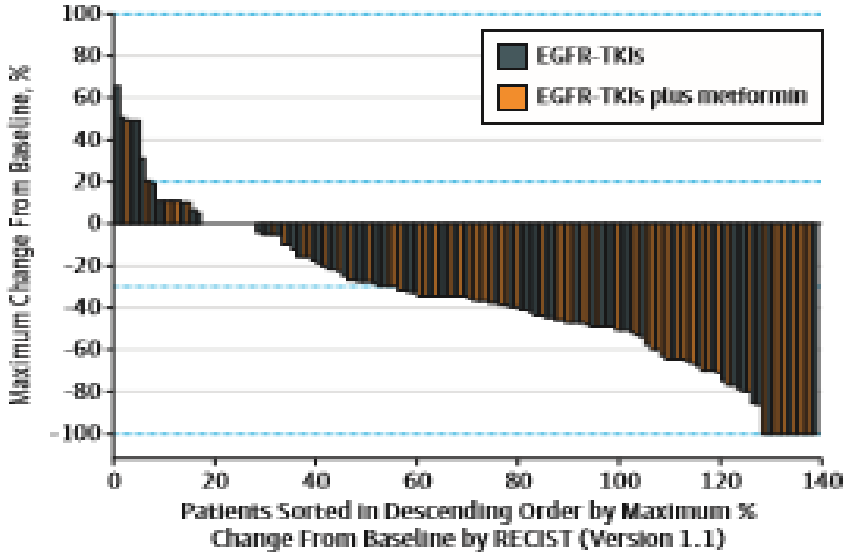

| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| EGFR-TKIs | 70 | 55 | 36 | 27 | 16 | 10 | 5 | 2 | 1 | 1 | 0 |
| EGFR-TKIs plus metformin | 69 | 55 | 44 | 33 | 20 | 12 | 9 | 7 | 6 | 2 | 1 |

B Progression-free survival (radiooncologist 2)

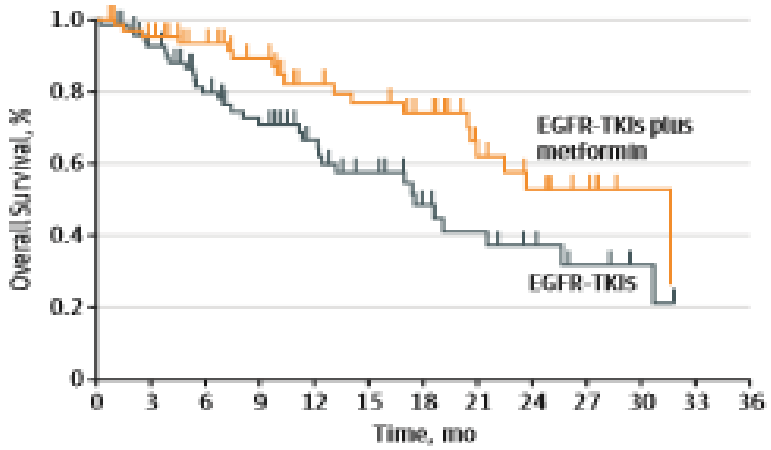



| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EGFR-TKIs | 70 | 55 | 36 | 27 | 16 | 10 | 5 | 2 | 1 | 1 | 0 | 0 | 0 |
| EGFR-TKIs plus metformin | 69 | 55 | 44 | 33 | 20 | 12 | 9 | 7 | 6 | 2 | 1 | 1 | 0 |

C Waterfall plot of the maximum percentage change from baseline in tumor dimension




D Overall survival comparison




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| EGFR-TKIs | 70 | 61 | 48 | 39 | 30 | 22 | 14 | 11 | 8 | 5 | 3 |
| EGFR-TKIs plus metformin | 69 | 58 | 50 | 41 | 32 | 28 | 24 | 15 | 11 | 6 | 2 |

Clinical Trials: Targeted Therapy

Clinical Cancer Research

# Combination of Metformin and Gefitinib as First-Line Therapy for Nondiabetic Advanced NSCLC Patients with EGFR Mutations: A Randomized, Double-Blind Phase II Trial

Li Li[1], Liyan Jiang[2], Yubo Wang[1], Yizhuo Zhao[2], Xiao-Ju Zhang[3], Guoming Wu[4], Xiangdong Zhou[5], Jianguo Sun[6], Jun Bai[7], Biyong Ren[8], Kun Tian[9], Zhi Xu[4], Hua-liang Xiao[10], Qi Zhou[11], Rui Han[1], Hengyi Chen[1], Haidong Wang[12], Zhenzhou Yang[13], Chan Gao[14], Shangli Cai[14], and Yong He[1]

# Results

- n=224

- Median PFS (10.3 months vs. 11.4 months)
- Median OS (22.0 months vs. 27.5 months) were numerically lower in the metformin group
- ORRs were similar between the two arms (66% vs. 66.7%).


CHOOSING WISELY REMAINS THE KEY

# THANKS and GREETING FROM TMH VARANASI