Updated Analysis of NEJ009: Gefitinib-Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated EGFR

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Background

- NEJ002 in advanced mNSCLC with EGFR mutations
  - Gefitinib vs platinum based chemotherapy
  - Improved PFS, QoL
  - No significant improvement in OS
  - High cross-over rates
  - 30% on Gefitinib arm did not receive chemotherapy

- NEJ005
  - Concurrent vs sequential use of same agents
  - No difference in PFS
  - Median OS :41m vs 30.7 months (p=0.036)

Hence concurrent combination of gefiitnib & chemotherapy was selected for NEJ009 study

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

- Chemotherapy-naïve
- IIIB/IV or recurrent nonsquamous NSCLC
- *EGFR* mutation +
- exon 18, 19, 21
- ECOG PS ≤ 2
- asymptomatic CNS mets allowed

(N = 350)

Gefitinib 250 mg QD + **Carboplatin/Pemetrexed**

Gefitinib 250 mg QD

Treatment continued until PD

Stratified by ECOG PS and EGFR mutation subtype

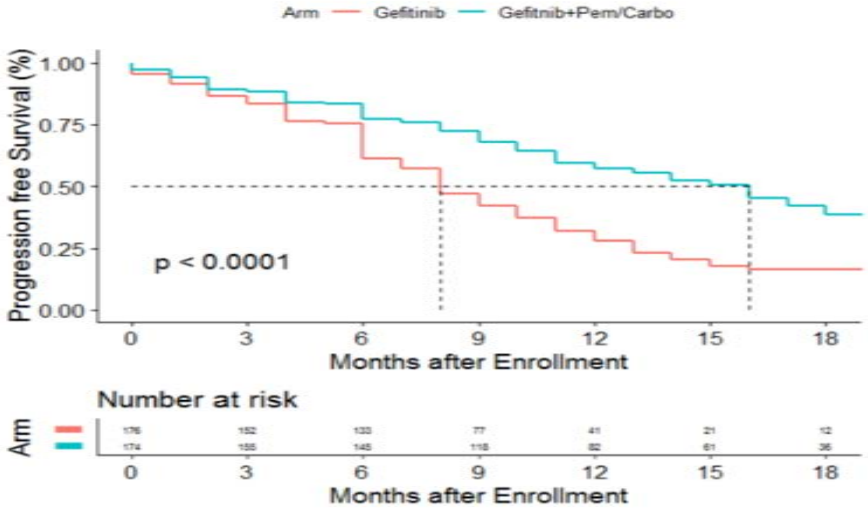
- PFS
- Secondary endpoints: OS, toxicity, QoL

Noronha et al. ASCO 2019

Gefitinib vs Gefitinib + chemotherapy TMH

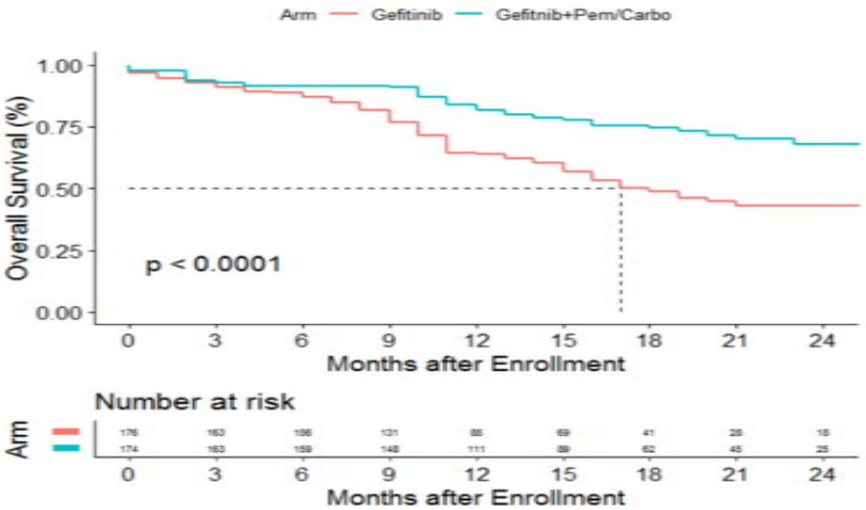
Panel A

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

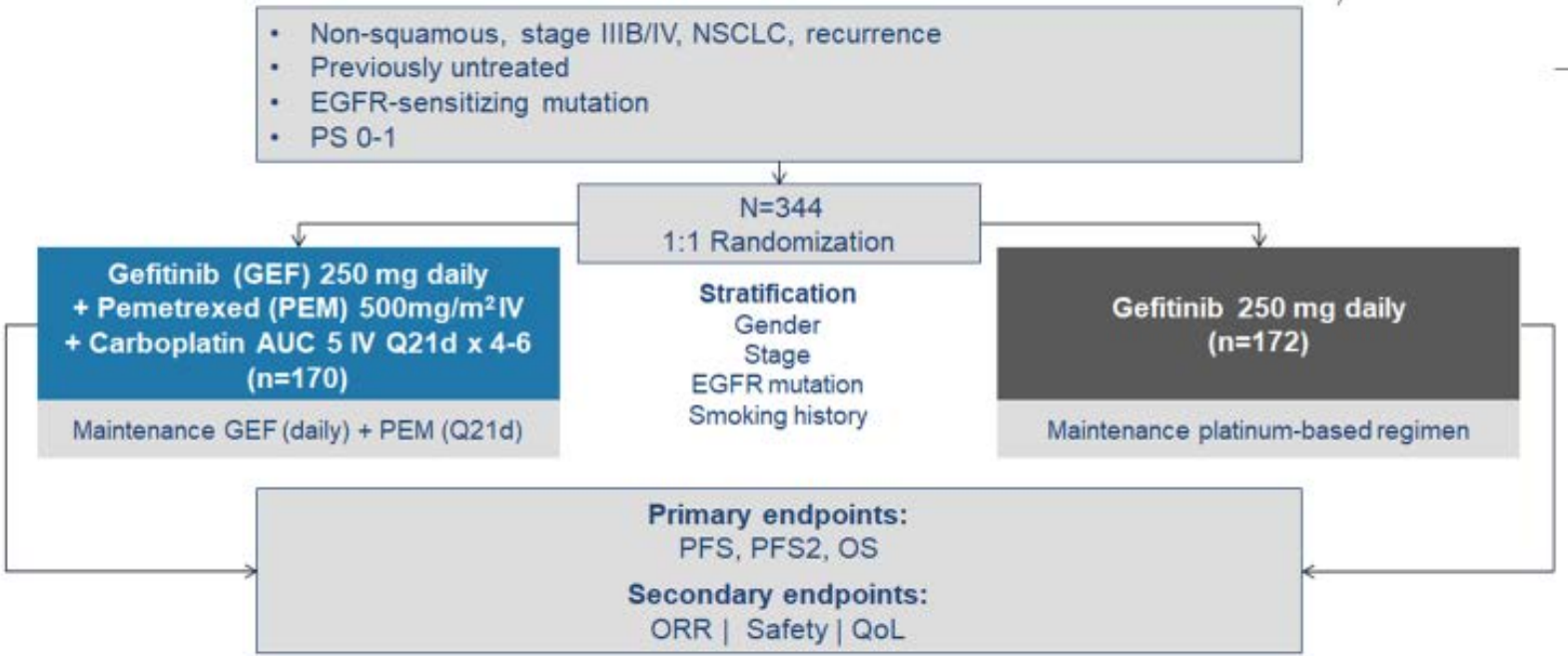
Arm	Number of patients	Number of events	Median OS (95%CI)
Gefitinib	176	80	17 months (13.5 to 20.5)
Gefitinib + pemetrexed/carboplatin	174	42	NC (NC to NC)
Hazard ratio for disease progression or death, 0.51; 95% CI, 0.39 to 0.66			



NEJ009 : Study design

- Randomized phase III design
- Inclusion criteria (all of the following)
  - Chemotherapy naive, stage IIIB or IV or relapsed nonsquamous NSCLC
  - EGFR mutations (exon 19 deletion, L858R, G719A, G719C, G719S, and L861Q)
  - Age 20 to 75 years
  - ECOG PS 0 to 1
  - adequate organ function
- Exclusion criteria
  - serious concomitant systemic disorders, interstitial pneumonia, another primary malignancy
  - preexistence of T790M mutation
  - symptomatic brain metastases
  - pregnancy

NEJ009 – Study design



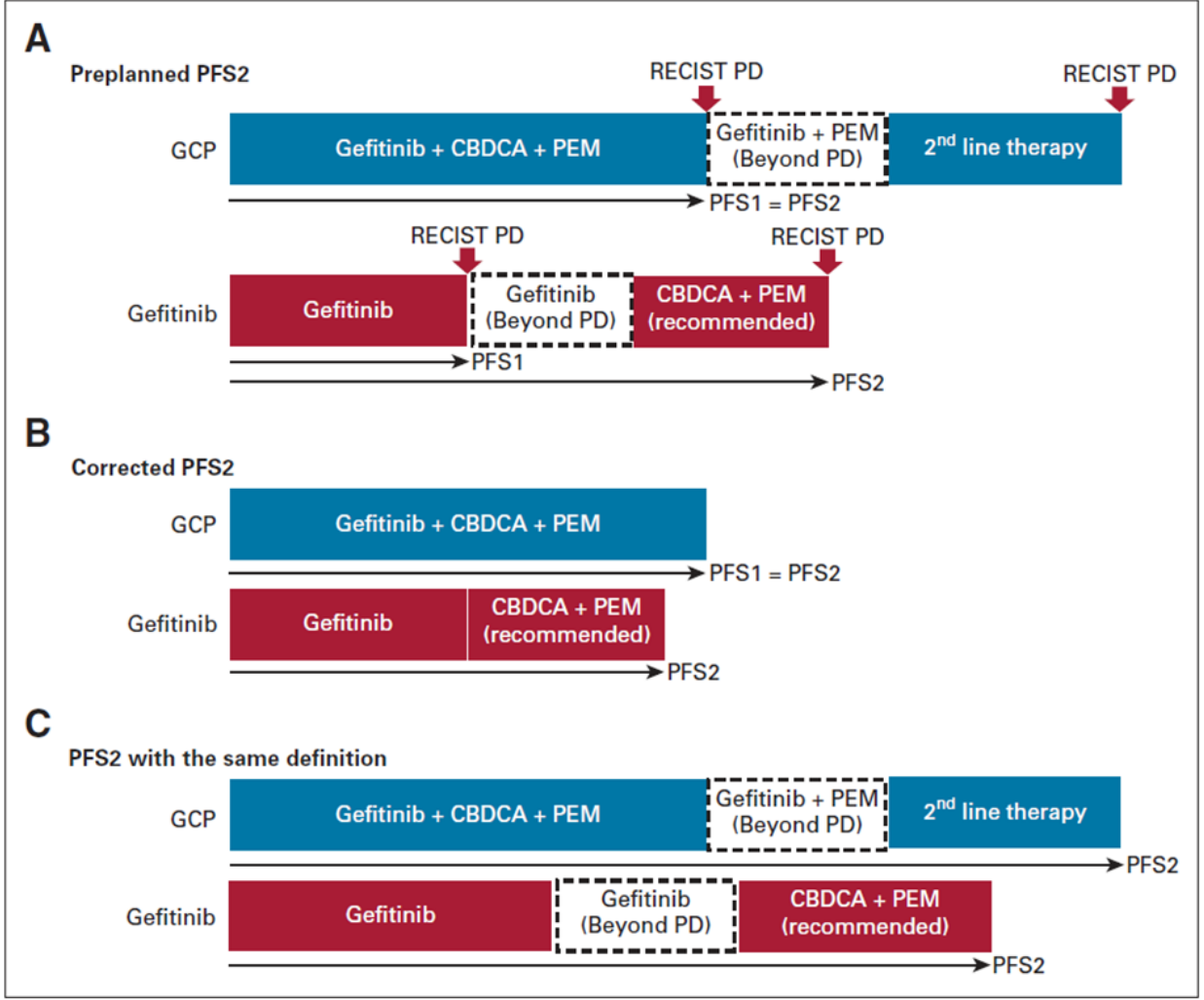
EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; OS, overall survival; QoL, quality of life; PS, performance status.

1. Nakamura A et al. J Clin Oncol. 2018;36:15 (suppl; abstr 9005).

Methods

- Radiographic assessments at baseline and then every 2 months for the first year and every 3 months thereafter until PD.
- Toxicity assessment - CTCAE 4.0
- QoL assessment - before treatment, at 8 weeks, and then once every 6 months for the next 3 years
- Primary endpoints : PFS, PFS2, OS
- Secondary endpoints : ORR, safety and QoL
- Statistical analysis by hierarchical sequential testing (superiority for PFS ● PFS2 ● OS)

NEJ009 : Updated PFS2 definition



Sample size calculation

- Study period - 4 years
- A two-sided log-rank test with 80% power
- HR 0.7 for the primary endpoints
- Sample size required - 168 patients in each arm to show a 5% significance.

Baseline characteristics

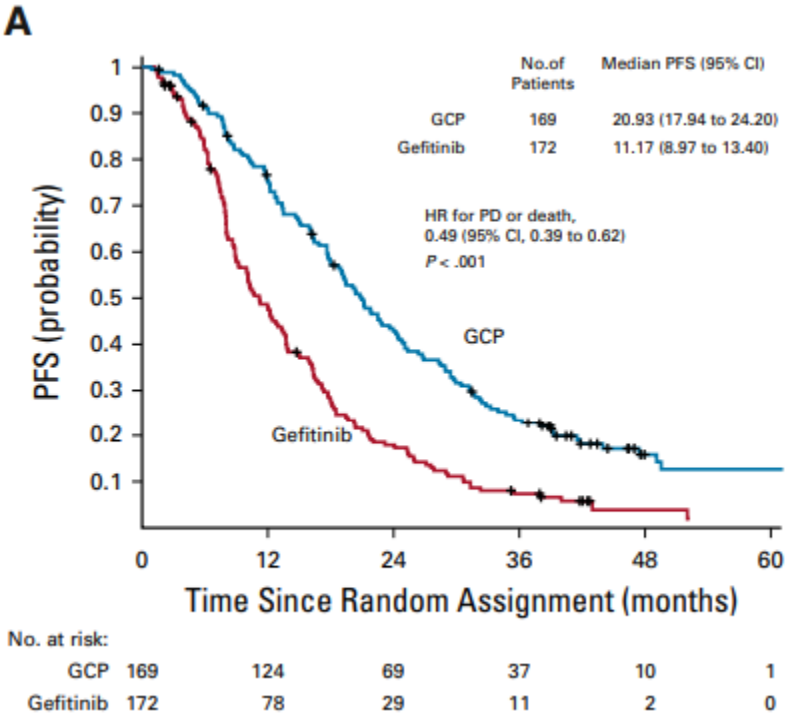
Characteristic	Gefitinib, No. (%)	GCP, No. (%)
No. of patients	172	170
Sex		
Male	64 (37.2)	56 (32.9)
Female	108 (62.8)	114 (67.1)
Age, years		
Mean ± standard deviation	64.0 ± 8.4	64.8 ± 7.8
Range	37-75	34-75
Smoking status		
Never	97 (56.4)	96 (56.5)
Previous or current smoker	75 (43.6)	73 (42.9)
ECOG PS		
0	107 (62.2)	98 (57.6)
1	65 (37.8)	72 (42.4)
Histologic diagnosis		
Adenocarcinoma	170 (98.8)	168 (98.8)
Other	2 (1.2)	2 (1.2)
Clinical stage		
IIIA	1 (0.6)	0 (0.0)
IIIB	4 (2.3)	6 (3.5)
IV	137 (79.7)	139 (81.8)
Postoperative relapse	30 (17.4)	24 (14.7)
CNS metastasis		
Yes	38 (22.1)	50 (29.4)
Did not received irradiation	23 (13.4)	33 (19.4)
Pretreated with irradiation	15 (8.7)	17 (10.0)
No	134 (77.9)	120 (70.6)
Type of EGFR mutation		
Exon 19 deletion	95 (55.2)	93 (54.7)
L858R	67 (39.0)	69 (40.6)
Others	10 (5.8)	8 (4.7)

Survival analysis

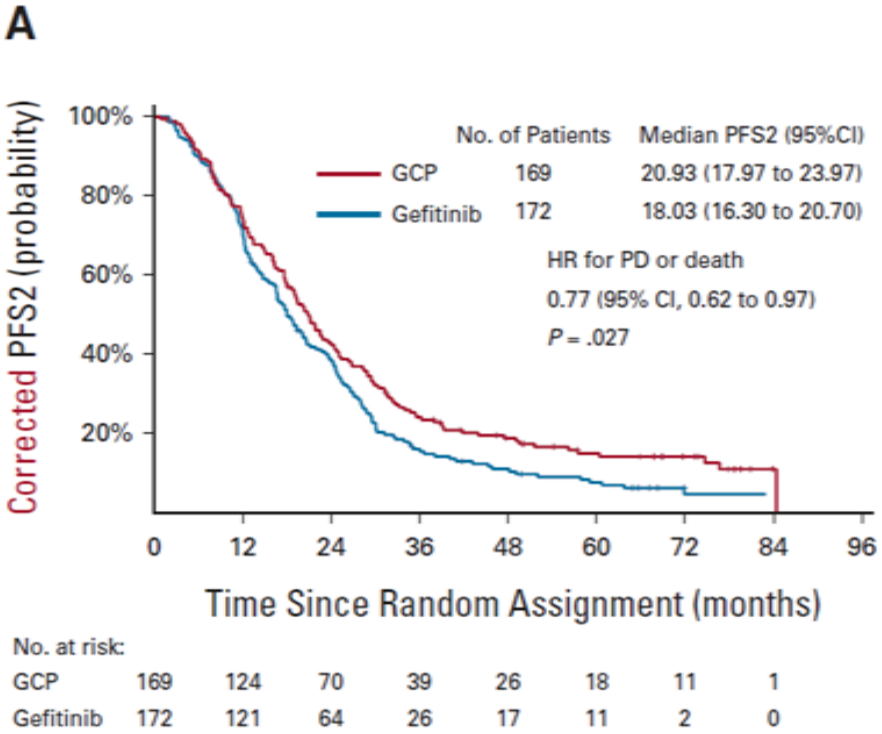
- Survival analysis in the update was calculated as RMST (Restricted mean survival time)
- RMST up to 5 and 7 years as a complementary to the log-rank test for OS.
- RMST between the GCP and gefitinib groups represents the average gain in survival time within a time window from 0 to a specific threshold time point
- The time was based on the areas under the survival curves for each group
- Median Follow up 84 months

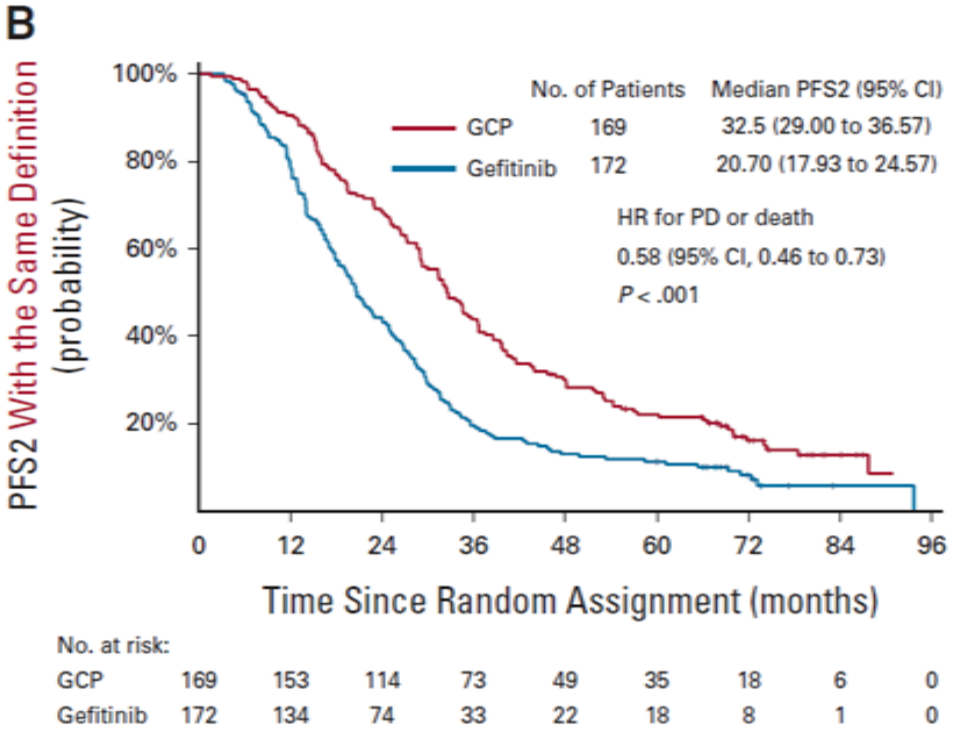
Progression-free survival

Response Rate (%)		
	Gefitinib	combo
CR	3.5	4.7
PR	64.0	79.3
SD	25.0	13.6
PD	4.7	1.2
ORR	67.4	84.0

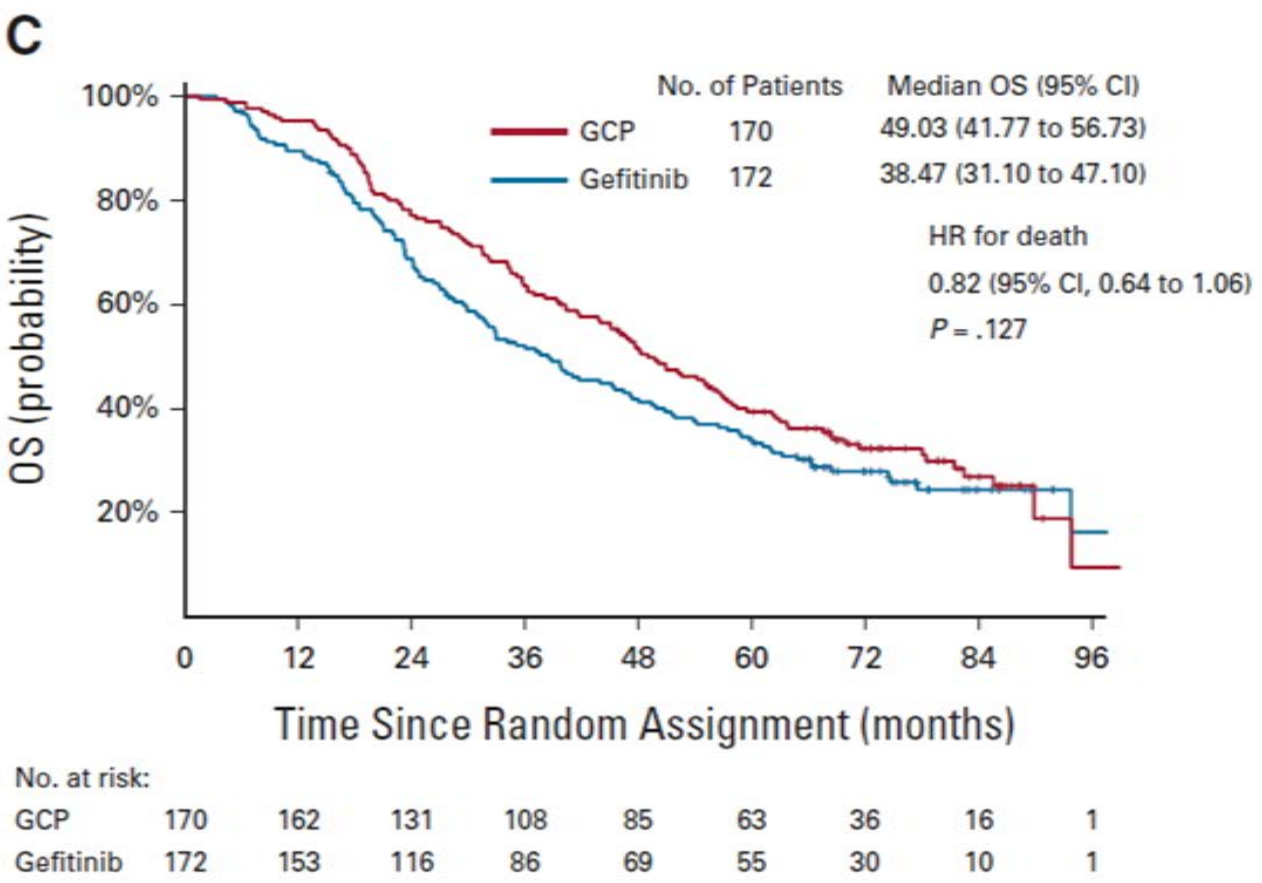


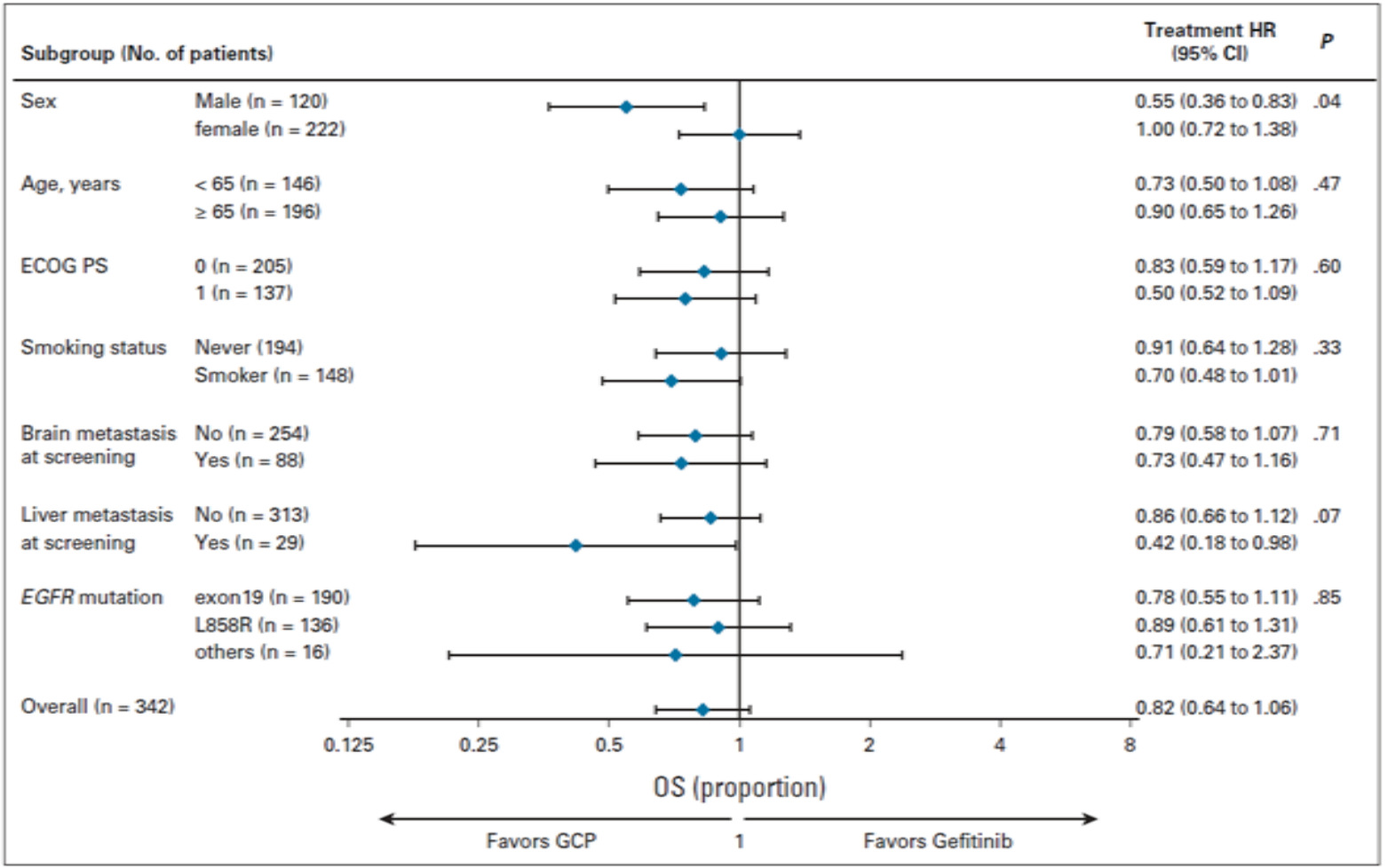
Progression-free survival- 2





Overall survival




Subgroup (No. of patients)
Treatment HR (95% CI)
P
Sex
Male (n = 120)
0.55 (0.36 to 0.83)
.04
female (n = 222)
1.00 (0.72 to 1.38)
Age, years
< 65 (n = 146)
0.73 (0.50 to 1.08)
.47
≥ 65 (n = 196)
0.90 (0.65 to 1.26)
ECOG PS
0 (n = 205)
0.83 (0.59 to 1.17)
.60
1 (n = 137)
0.50 (0.52 to 1.09)
Smoking status
Never (194)
0.91 (0.64 to 1.28)
.33
Smoker (n = 148)
0.70 (0.48 to 1.01)
Brain metastasis at screening
No (n = 254)
0.79 (0.58 to 1.07)
.71
Yes (n = 88)
0.73 (0.47 to 1.16)
Liver metastasis at screening
No (n = 313)
0.86 (0.66 to 1.12)
.07
Yes (n = 29)
0.42 (0.18 to 0.98)
EGFR mutation
exon19 (n = 190)
0.78 (0.55 to 1.11)
.85
L858R (n = 136)
0.89 (0.61 to 1.31)
others (n = 16)
0.71 (0.21 to 2.37)
Overall (n = 342)
0.82 (0.64 to 1.06)
0.125
0.25
0.5
1
2
4
8
OS (proportion)
Favors GCP
1
Favors Gefitinib

RMST

TABLE A2. Restricted Mean Survival Time

Group	Gefitinib (n = 172)	GCP (n = 170)	*P*
5-Year RMST			
Mean (95% CI)	38.6 (35.6 to 41.6)	43.6 (40.8 to 46.3)	
SE	1.5	1.4	
Difference in RMST (95% CI)	Reference	5.0 (0.9 to 9.0)	.017
7-Year RMST			
Mean (95% CI)	45.3 (41.0 to 49.5)	51.6 (47.5 to 55.6)	
SE	2.2	2.1	
Difference in RMST (95% CI)	Reference	6.3 (0.4 to 12.2)	.037

Abbreviations: GCP, gefitinib and carboplatin plus pemetrexed; RMST, restricted mean survival time.

NEJ009 : Subsequent line of treatment

Chemotherapy Regimen	Second-Line Therapy		Third-Line Therapy	
	Gefitinib (n = 172), No. (%)	GCP (n = 170), No. (%)	Gefitinib (n = 172), No. (%)	GCP (n = 170), No. (%)
Any treatment	153 (89.0)	125 (73.5)	114 (66.3)	88 (51.8)
Platinum-based with or without bevacizumab	102 (59.3)	16 (9.4)	18 (10.5)	6 (3.5)
Pemetrexed	0 (0.0)	0 (0.6)	6 (3.5)	2 (1.2)
Docetaxel with or without ramucirumab	4 (2.3)	37 (21.8)	26 (15.1)	13 (7.6)
Tegafur, gimeracil, and oteracil	0 (0.0)	1 (0.6)	4 (2.3)	4 (2.4)
Osimertinib	10 (5.8)	11 (6.5)	6 (3.5)	9 (5.3)
Gefitinib or erlotinib	22 (12.8)	29 (17.1)	20 (11.6)	21 (12.4)
Afatinib	3 (1.7)	15 (8.8)	15 (8.7)	19 (11.2)
Immune checkpoint inhibitors	0 (0.0)	3 (1.8)	6 (3.5)	8 (4.7)
Others	12 (7.0)	13 (7.6)	13 (7.6)	6 (3.5)
Response rate (95% CI)	34.0 (26.5 to 41.5)	20.8 (13.7 to 27.9)	16.7 (9.8 to 23.5)	19.3 (11.1 to 27.6)
Disease control rate (95% CI)	72.5 (65.5 to 79.6)	66.4 (58.1 to 74.7)	64.0 (55.2 to 72.8)	58.0 (47.6 to 68.3)

Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.

NEJ009 : Adverse events

Event	Gefitinib (n = 171) Grade ≥ 3 (n = 53), No. (%)	GCP (n = 170) Grade ≥ 3 (n = 113), No. (%)
Leukopenia	1 (0.6)	36 (21.2)
Neutropenia	1 (0.6)	53 (31.2)
Anemia	4 (2.3)	36 (21.2)
Thrombocytopenia	0 (0.0)	29 (17.1)
Liver dysfunction	38 (22.2)	21 (12.4)
Blood bilirubin increased	1 (0.6)	0 (0.0)
Hyponatremia	1 (0.6)	5 (2.9)
Diarrhea	2 (1.2)	7 (4.1)
Vomiting	1 (0.6)	4 (2.4)
Stomatitis	0 (0.0)	1 (0.6)
Rash	5 (2.9)	7 (4.1)
Nail changes	2 (1.2)	5 (2.9)
Anorexia	2 (1.2)	12 (7.1)
Edema limbs	0 (0.0)	3 (1.8)
Fatigue	0 (0.0)	8 (4.7)
Infection	0 (0.0)	8 (4.7)
Pneumonia	2 (1.2)	3 (1.8)

Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.

Conclusions

- First study to evaluate efficacy and safety of TKI + chemotherapy vs TKI alone
- Combination delayed development of resistance and had higher response rate
- This study showed improvement in PFS and corrected PFS2 with the GCP group
- However, it did not translate to significant improvement in OS
- Lack of CNS protection in both the arms
- Only 22% of patients received Osimertinib post PD
- No new long-term safety signals

THANK YOU