

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-57. DOI: 10.1056/NEJMoa0810699.

(PDF updated September 3, 2009.)

## **SUPPLEMENTARY APPENDIX**

### **INVESTIGATOR AND SPONSOR ROLES**

The first draft of the manuscript was written by Professor T. Mok, with Miss E. Duffield and Miss C. Watkins providing information for inclusion in the Methods and Results sections, and Professor T. Mok prepared the final draft. The Steering Committee made the decision to submit for publication. An agreement was in place between the study sponsor and the authors, which established the authors' rights to publish the study and have access to the data. The study sponsor was permitted a period of 30 days for review of the proposed final manuscript to allow for filing of any relevant patent applications. Responsibility for opinions, conclusion and interpretation of the data lies with the authors.

### **ADDITIONAL ELIGIBILITY CRITERIA**

World Health Organization performance status 0 to 2, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria<sup>18</sup> with at least 1 measurable lesion not previously irradiated, adjuvant chemotherapy permitted if not platinum-based and completed > 6 months previously, absolute neutrophil count > 2.0 x 10<sup>9</sup>/L, and adequate hepatic function.

### **SECONDARY ANALYSES OF PROGRESSION-FREE SURVIVAL-**

Supportive secondary analyses of progression-free survival were conducted in the per protocol population, unadjusted for covariates (P-value equivalent to a log rank test), censoring events occurring >12 weeks after the last evaluable RECIST assessment at the time of the last evaluable RECIST assessment prior to the  $\geq$ 12-week interval, and

censoring events that occurred after the start of additional cancer therapy at the last evaluable RECIST assessment prior to the start of additional therapy.

## INTERIM ANALYSIS

One interim analysis was planned. The purpose of this analysis was to detect inferiority of gefitinib compared with carboplatin/paclitaxel in terms of progression-free survival. The analysis was performed by an independent statistician with no involvement in the study. The timing of the planned analysis was to be event driven, with a data cut-off set to coincide as near as possible to the time at which 150 confirmed objective progressions (via RECIST) had been identified.

Progression-free survival was analyzed as per protocol for the primary analysis. Consideration was given to stop the study early if progression-free survival for gefitinib was inferior to carboplatin/paclitaxel at a 2-sided 10% significance level, i.e., if the lower 90% CI for the HR was  $>1.0$ . There was no adjustment of significance level for the primary analysis of progression-free survival as there was no opportunity in the interim analysis to accept the hypothesis of non-inferiority for progression-free survival.

The interim analysis was performed using data derived from a data cutoff of January 22, 2007, when 173 patients had progressed from the 501 patients already randomized to the study. The recommendation of the Independent Data Monitoring Committee was that the study should continue as planned and without change until completion.

Supplemental Table 1. Key Demographic and Baseline Characteristics for Patients by EGFR Mutation Status

	Number (%) of Patients							ITT Population (n=1217)
	EGFR Mutation-Positive		EGFR Mutation-Negative		Unknown EGFR Mutation Status			
	Gefitinib (n=437)	Carboplatin/paclitaxel (n=129)	Gefitinib (n=91)	Carboplatin/paclitaxel (n=85)	Gefitinib (n=386)	Carboplatin/paclitaxel (n=394)		
Female	335 (76.7)	108 (81.8)	103 (79.8)	67 (73.6)	57 (67.1)	309 (80.1)	321 (81.5)	965 (79.3)
Age <65 years	326 (74.6)	95 (72.0)	90 (69.8)	75 (82.4)	66 (77.6)	277 (71.8)	296 (75.1)	899 (73.9)
WHO PS 0 or 1	402 (92.0)	119 (90.2)	122 (94.6)	85 (93.4)	76 (89.4)	344 (89.1)	345 (87.6)	1091 (89.6)
Never-smoker	405 (92.7)	124 (93.9)	122 (94.6)	82 (90.1)	77 (90.6)	365 (94.6)	370 (93.9)	1140 (93.7)

EGFR, epidermal growth factor receptor; ITT, intent to treat; WHO, World Health Organization; PS, performance status.

Supplemental Table 2. Baseline EGFR Mutation Status.

EGFR Mutation Status	Number (% of all patients) <sup>a</sup>			
	[% of patients with known EGFR mutation status] <sup>b</sup>			
	Gefitinib (n=609)		Carboplatin/Paclitaxel (n=608)	
Negative (no mutation detected)	91 (14.9)	[40.8]	85 (14.0)	[39.7]
Positive	132 (21.7)	[59.2]	129 (21.2)	[60.3]
Exon 19 deletions <sup>c</sup>	66 (10.8)	[29.6]	74 (12.2)	[34.6]
Exon 21 L858R <sup>c</sup>	64 (10.5)	[28.7]	47 (7.7)	[22.0]
Exon 20 T790M <sup>c</sup>	5 (0.8)	[2.2]	6 (1.0)	[2.8]
Other <sup>c,d</sup>	3 (0.5)	[1.3]	7 (1.2)	[3.3]
Unknown <sup>e</sup>	386 (63.4)	NA	394 (64.8)	NA

<sup>a</sup>Percentage calculated using the total number of randomized patients in each treatment group as denominator.

<sup>b</sup>Percentage of patients with a positive or negative status calculated using number of patients with known EGFR mutation status in each treatment group as denominator.

<sup>c</sup>Eleven patients had multiple mutations and are counted once for each type of mutation they had: four patients with exon 19 deletions and exon 21 L858R, four patients with exon 19 deletions and exon 20 T790M mutations, and three patients with exon 21 L858R and exon 20 T790M mutations.

<sup>d</sup>Other mutations were three patients with exon 18 G719X, five patients with exon 20 S768I, and two patients with exon 21 L861Q.

<sup>c</sup>Unknown included patients who declined consent for biomarker analysis, had no available tumor sample or had samples of insufficient quality for EGFR mutation analysis (118 cytologic samples and 128 histologic samples of insufficient quality).

Supplemental Table 3. Best Overall Response in the Overall Population, EGFR Mutation-Positive Patients, EGFR Mutation-Negative Patients, and Patients with Unknown EGFR Mutation Status (Intent-to-Treat Population).

	Number (%) of Patients							
	Overall Population		EGFR Mutation-Positive Patients		EGFR Mutation-Negative Patients		Unknown EGFR Mutation Status	
	Gefitinib (n=609)	Carboplatin/ paclitaxel (n=608)	Gefitinib (n=132)	Carboplatin/ paclitaxel (n=129)	Gefitinib (n=91)	Carboplatin/ paclitaxel (n=85)	Gefitinib (n=386)	Carboplatin/ paclitaxel (n=394)
Best Overall Response								
CR	5 (0.8)	1 (0.2)	3 (2.3)	1 (0.8)	0	0	2 (0.5)	0
PR	257 (42.2)	195 (32.1)	91 (68.9)	60 (46.5)	1 (1.1)	20 (23.5)	165 (42.7)	115 (29.2)

SD	182 (29.9)	286 (47.0)	27 (20.5)	52 (40.3)	35 (38.5)	51 (60.0)	120 (31.1)	183 (46.4)
Progression	129 (21.2)	70 (11.5)	10 (7.6)	14 (10.9)	47 (51.6)	10 (11.8)	72 (18.7)	46 (11.7)
Not Evaluable	36 (5.9)	56 (9.2)	1 (0.8)	2 (1.6)	8 (8.8)	4 (4.7)	27 (7.0)	50 (12.7)
Objective Tumor Response (CR+PR)	262 (43.0)	196 (32.2)	94 (71.2)	61 (47.3)	1 (1.1)	20 (23.5)	167 (43.3)	115 (29.2)
Disease Control (CR+PR+SD)	444 (72.9)	482 (79.2)	121 (91.7)	113 (87.6)	36 (39.6)	71 (83.5)	287 (74.4)	298 (75.6)

Analysis of Objective Tumor Response

Odds Ratio (95% CI)	1.59 (1.25 to 2.01)	2.75 (1.65 to 4.60)	0.04 (0.01 to 0.27)	1.88 (1.39 to 2.53)
------------------------	---------------------	---------------------	---------------------	---------------------

P-value

0.0001

0.0001

0.0013

<0.0001

---

EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval

Supplemental Table 4. Analysis of Specific Safety Events (Evaluable-for-Safety Population).<sup>a</sup>

Event <sup>b</sup>	Number (%) of Patients		
	Gefitinib (n=607)	Carboplatin/Paclitaxel (n=589)	Adjusted P-value <sup>c</sup>
Rash/acne <sup>d</sup>	398 (65.6)	132 (22.4)	<0.0001
Diarrhea	274 (45.1)	128 (21.7)	<0.0001
Nausea	74 (12.2)	260 (44.1)	<0.0001
Vomiting	59 (9.7)	193 (32.8)	<0.0001
Elevated Liver Transaminases (CTC ≥ Grade 3) <sup>e</sup>	57 (9.4)	6 (1.0)	<0.0001
Neurotoxicity <sup>d</sup>	30 (4.9)	411 (69.8)	<0.0001
Neutropenia (CTC ≥ Grade 3) <sup>e</sup>	4 (0.7)	385 (65.4)	<0.0001
Leukopenia (CTC ≥ Grade 3) <sup>e</sup>	1 (0.2)	202 (34.3)	<0.0001
Anemia (CTC ≥ Grade 3) <sup>e</sup>	11 (1.8)	56 (9.5)	<0.0001
Thrombocytopenia (CTC ≥ Grade 3) <sup>e</sup>	5 (0.8)	29 (4.9)	0.0001

<sup>a</sup>Specified events anticipated to be more common with gefitinib: rash/acne, diarrhea, nausea, vomiting, elevated liver transaminases. Specified events anticipated to be

more common with carboplatin/paclitaxel: neurotoxicity, neutropenia, leucopenia, anemia, thrombocytopenia.

<sup>b</sup>Data derived from adverse events and laboratory data reported on-treatment.

<sup>c</sup>Calculated using the method of Westfall and Young.<sup>24</sup>

<sup>d</sup>Grouped term (sum of high-level and preferred terms).

<sup>e</sup>Worsening in laboratory value (ALT or AST for liver transaminases, absolute neutrophil count for neutropenia, white blood cell count for leukopenia, hemoglobin for anemia, and platelets for thrombocytopenia) from baseline to CTC grade 3-4. CTC, Common Terminology Criteria; ALT, alanine transaminase; AST, aspartate aminotransferase.

## SUPPLEMENTARY FIGURE LEGENDS

### **Supplemental Figure 1. Progression-Free Survival in Pre-Planned Clinical Subgroups.**

Intent-to-treat population

Cox analysis with covariates (performance status [0-1, 2], smoking history [never, ex-smoker], and gender).

PFS, progression-free survival; WHO, World Health Organization; PS, performance status; HR, hazard ratio; CI, confidence interval.

**Supplemental Figure 2. Kaplan-Meier Curves for Overall Survival (Follow-Up Ongoing) in (A) the Overall Population, and Post-Hoc Analyses in (B) EGFR Mutation-Positive Patients, (C) EGFR Mutation-Negative Patients, and (D) Patients with Unknown EGFR Mutation Status.**

Intent-to-treat population

<sup>a</sup>Cox analysis with covariates (performance status [0-1, 2], smoking history [never, ex-smoker], and gender).

EGFR, epidermal growth factor receptor; OS, overall survival; HR, hazard ratio; CI, confidence interval.

**Supplemental Figure 3. Quality of Life and Symptom Improvement Rates by EGFR Mutation Status (Post-Hoc Analyses).**

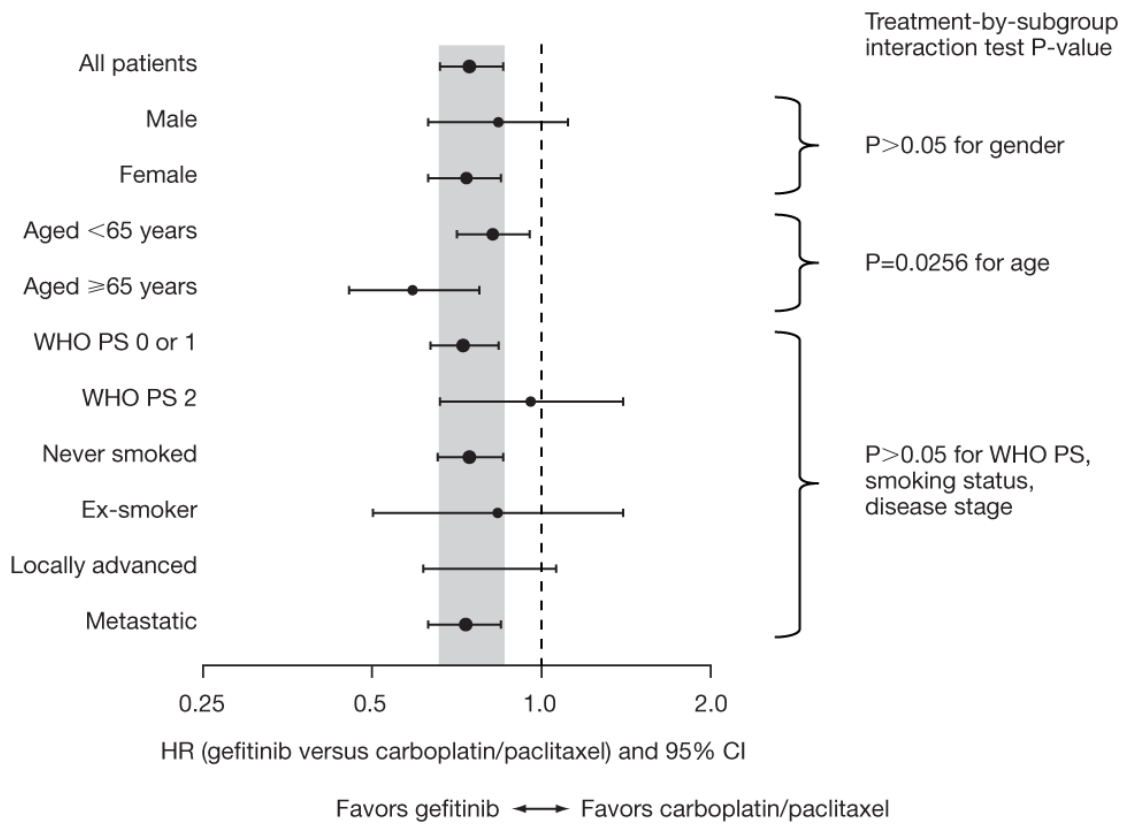
Evaluable-for-quality of life population.

P values from logistic regression with covariates (performance status [0-1, 2], smoking history [never, ex-smoker], and gender).

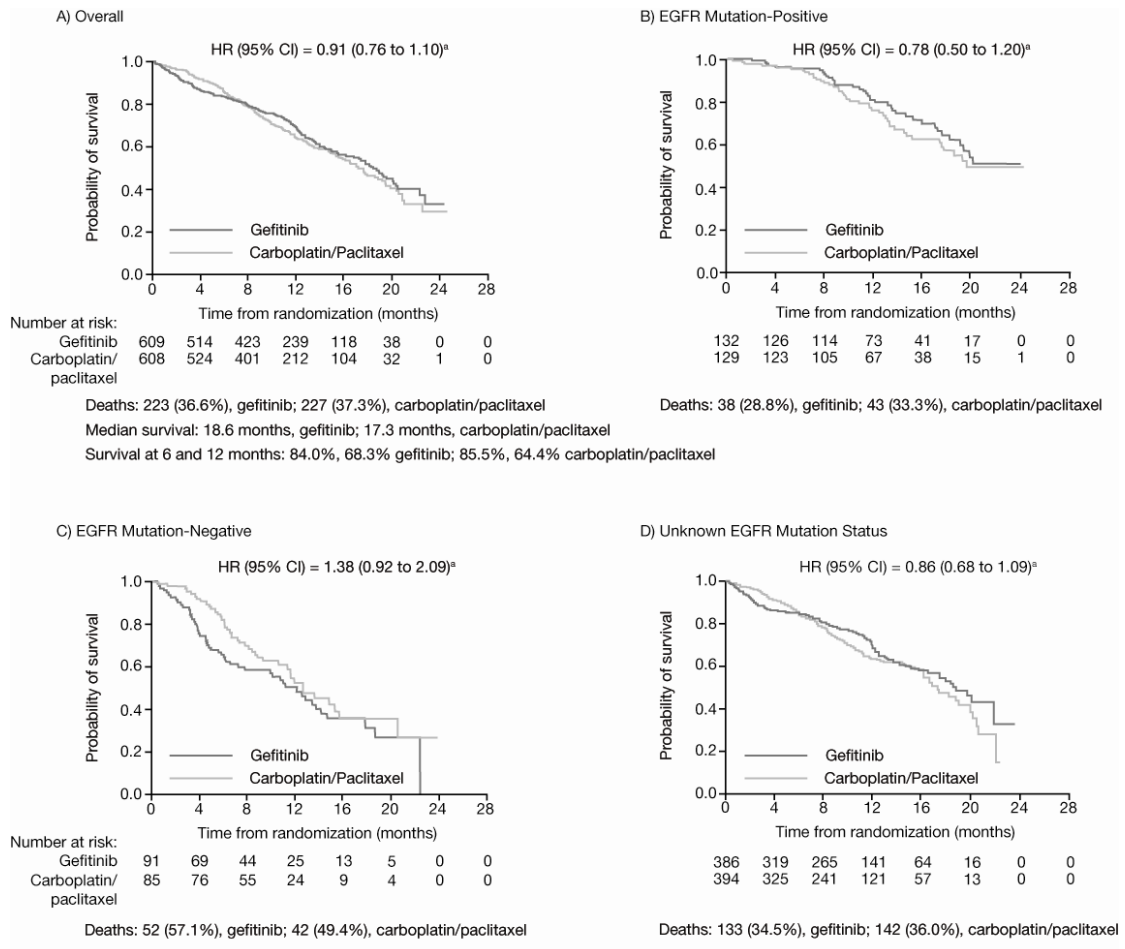
Clinically relevant improvement predefined as  $\geq 6$ -point improvement for FACT-L and TOI;  $\geq 2$ -point improvement for LCS, maintained for at least 21 days.

M+, EGFR mutation-positive; M-, EGFR mutation-negative; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale; OR, odds ratio; CI, confidence interval.

Supplemental Figure 1.



## Supplemental Figure 2.



Supplemental Figure 3

