

Supplementary Appendix

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

Supplement to: Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.

Supplementary Table 1. Eligibility Criteria and Exclusion Criteria of NEJ002

Eligibility Criteria

- 1) First-stage registration: Cases that have been histologically or cytologically diagnosed as having non-small cell lung cancer or cases that are suspected of having non-small cell lung cancer.
Second-stage registration: Cases that have been histologically or cytologically diagnosed as having non-small cell lung cancer.
- 2) First-stage registration: Cases that have stage IIIB or stage IV non-small cell lung cancer, or cases that have recurrent disease after operation and are considered to lack an indication for operation or curative radiation therapy.
Second-stage registration: Cases that have stage IIIB or stage IV non-small cell lung cancer, or cases that have recurrent disease after operation and are confirmed to lack an indication for operation or curative radiation therapy.
- 3) First-stage registration: Cases in which lung cancer sample is available for the EGFR mutation test performed by the PNA-LNA PCR clamp method. Lung cancer samples include cytological samples that are considered to contain cancer cells and paraffin-embedded tissues.
Second-stage registration: Cases in which lung cancer was confirmed to have sensitive EGFR mutations (exon 19 deletions, L858R, L861Q, G719A, G719C, or G719S).
- 4) Cases that have lesions that can be evaluated by RECIST criteria. The lesions include those with a diameter of 20 mm or larger as measured using conventional CT images that are taken with a slice thickness of 10 mm or less, or lesions with a diameter of 10 mm or larger as measured using helical CT images that are reconstructed using an algorithm that provides images with a slice thickness of 5 mm or less.
- 5) Chemotherapy-naïve cases. Previous treatment with UFT or OK-432 is permitted.
- 6) Cases aged between 20 years old and 75 years old.
- 7) Cases with PS 0 or 1 according to the ECOG criteria
- 8) Cases with normal bone marrow, liver, and renal function as judged by the laboratory data listed below.

White blood cell count	$\geq 4,000/\text{mm}^3$
Platelet count	$\geq 100,000/\text{mm}^3$
Hemoglobin	$\geq 9.0 \text{ g/dl}$
AST, ALT	\leq twice of the upper normal limit defined at each institution
Serum total bilirubin	$\leq 1.5 \text{ mg/dl}$
Creatinine clearance	≥ 40 (calculated value)
PaO ₂	$\geq 70 \text{ Torr}$

- 9) Cases with prognosis more than 3 months
- 10) Cases with written informed consent

Exclusion Criteria

- 1) Cases that have interstitial pneumonia or pulmonary fibrosis as revealed by chest CT that is suspected to cause a serious clinical problem during the treatment.
- 2) Second-stage registration process: cases in which lung cancer is positive for the resistant EGFR mutation, T790M.
- 3) Cases with symptomatic brain metastasis. Cases in which symptoms are resolved by radiation therapy are eligible.
- 4) Cases that have received radiation therapy for primary lesions. Cases that received palliative radiation therapy for their brain/or bone metastases more than two weeks previously are eligible.
- 5) Cases with severe complications such as uncontrolled heart, lung, liver, or kidney diseases or diabetes mellitus.
- 6) Pregnant or lactating women, and women who are likely to be or want to become pregnant
- 7) Cases with severe malabsorption syndrome or with diseases affecting digestive function, as exemplified by post-total gastrectomy and active inflammatory bowel disease.
- 8) Cases that have received systemic administration of steroids for 4 weeks or longer
- 9) Cases with pleural effusion, pericardial effusion and/or peritoneal effusion requiring tube drainage. Cases that have been clinically stable after drainage at least for 2 weeks are eligible.
- 10) Cases that are considered to be contra-indicated for gefitinib, carboplatin, or paclitaxel.
- 11) Cases with active double cancers. Intramucosal carcinomas are not considered to be an independent cancer.
- 12) Cases judged by attending physicians to be inappropriate for enrollment.

Supplementary Table 2. Assessment before Entry to NEJ002

The items described below are assessed for each case before registration.

Patient's background: sex, birth date, histological type, clinical stage, smoking history, and PS (ECOG)

Major medical history: illnesses that coexist, surgical history, and previous history of treatment for lung cancer such as radiotherapy

Assessment of the tumor: chest/abdominal CT and brain MRI taken within 1 month before the registration

Bone scintigram or PET are not indispensable for cases with asymptomatic bone disease.

Note that once bone scintigram or PET are not taken in such cases, they should not be taken as long as the case stays asymptomatic of bone disease.

Others: ECG, height, body weight, vital signs, blood biochemistry, urinalysis, PaO₂, and QOL

Supplementary Table 3. Common Toxicity

Toxicity	Gefitinib (n = 114)					Carboplatin-Paclitaxel (n = 113)					P value
	1	2	3	4	≥ Grade 3	1	2	3	4	≥ Grade 3	
Constipation	6	2	0	0	0.0%	13	10	0	1	0.9%	0.002
Diarrhea	32	6	1	0	0.9%	7	0	0	0	0.0%	<0.001
Stomatitis	8	3	0	0	0.0%	3	1	0	0	0.0%	0.066
Appetite loss	7	4	6	0	5.3%	39	18	7	0	6.2%	<0.001
Vomiting	6	0	1	0	0.9%	9	8	1	0	0.9%	0.017
Fatigue	8	1	3	0	2.6%	19	11	1	0	0.9%	0.002
Rash	38	37	6	0	5.3%	8	14	3	0	2.7%	<0.001
Pruritus	0	2	0	0	0.0%	0	0	0	0	0.0%	0.161
Alopecia	4	2	0	0	0.0%	28	33	0	0	0.0%	<0.001
Nail changes	5	3	3	0	2.6%	0	0	0	0	0.0%	<0.001
Edema	1	0	0	0	0.0%	0	1	0	0	0.0%	0.995
Fever	1	0	0	0	0.0%	1	0	0	0	0.0%	1.000
Hypersensitivity	0	0	0	0	0.0%	1	0	1	0	0.9%	0.158
Dyspnea	4	1	1	0	0.9%	1	0	0	0	0.0%	0.058
Neuropathy: motor	0	0	0	0	0.0%	1	1	2	0	1.8%	0.045
Neuropathy: sensory	0	1	0	0	0.0%	28	27	7	0	6.2%	<0.001
Arthralgia	1	2	1	0	0.9%	25	21	8	0	7.1%	<0.001
Pain	0	1	0	0	0.0%	1	1	0	0	0.0%	0.564
Pneumonitis	3	0	2	1**	2.6%	0	0	0	0	0.0%	0.015

Infection	1	0	2	0	1.8%	0	2	3	1	3.5%	0.299
AST/ALT elevation	20	13	29	1	26.3%	31	5	0	1	0.9%	<0.001
Bilirubin elevation	9	1	0	0	0.0%	11	6	1	0	0.9%	0.086
ALP elevation	2	2	0	0	0.0%	0	0	0	0	0.0%	0.047
Creatinine elevation	3	0	0	0	0.0%	12	1	0	0	0.0%	0.010
Albumin depression	2	0	0	0	0.0%	1	0	0	0	0.0%	0.571
Potassium elevation	7	0	0	0	0.0%	11	0	0	0	0.0%	0.319
Potassium depression	4	0	0	0	0.0%	0	0	0	0	0.0%	0.047
Sodium depression	5	0	0	0	0.0%	15	0	2	0	1.8%	0.007
Vertigo	0	1	2	0	1.8%	0	0	0	0	0.0%	0.086
Hiccup	0	0	0	0	0.0%	0	2	0	0	0.0%	0.158
Cerebral infarction	0	0	0	1	0.9%	0	0	0	0	0.0%	0.325
Convulsion	0	0	0	0	0.0%	0	0	0	1	0.9%	0.321
Bowel obstruction	0	0	0	0	0.0%	0	0	0	1	0.9%	0.321
Leukocytopenia	8	5	0	0	0.0%	18	36	29	2	27.4%	<0.001
Neutropenia	5	1	0	1	0.9%	4	9	37	37	65.5%	<0.001
Febrile neutropenia	0	0	0	0	0.0%	0	0	0	1	0.9%	0.321
Anemia	19	2	0	0	0.0%	35	32	6	0	5.3%	<0.001
Thrombocytopenia	8	0	0	0	0.0%	25	3	3	1	3.5%	<0.001
Any toxicity	17	44	43	4**	41.2%	4	25	41	40	71.7%	<0.001

*Grade of National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0, **One Grade 5 included

Supplementary Fig. 1

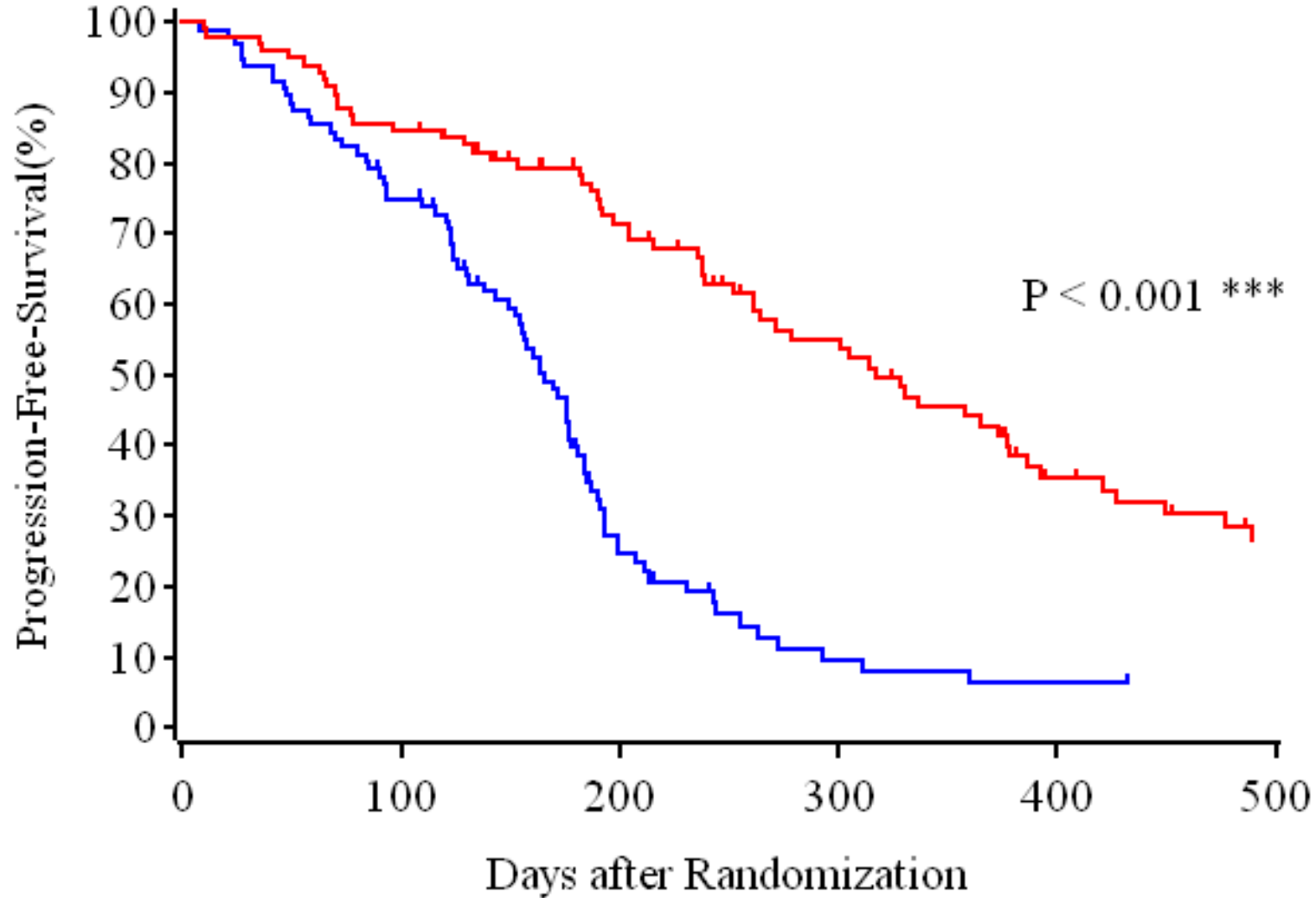


Figure legend. Progression-Free Survival at the interim analysis.

Kaplan-Meier curves for progression-free survival at the interim analysis (n=194) of patients treated with gefitinib (red line) and those treated with standard chemotherapy (blue line) are shown.