the response to gefitinib [10,11]. The *EGFR* gene mutation has also been shown to be frequently observed in females, never-smokers, adenocarcinoma, and individuals of Asian origin [12–14]. However, what factors influence the prognosis of the patients who yielded a response to the treatment with gefitinib remains unclear.

In the present study, we reviewed the gefitinib-treated NSCLC patients who had been previously treated with one or more chemotherapy regimens to evaluate the prognostic factors in those patients with and without a response to gefitinib treatment.

2. Patients and methods

A total of 145 consecutive patients without operation for lung cancer, who were cytologically or histologically diagnosed to have advanced NSCLC, were treated with gefitinib from July 2002 to December 2005 at the National Kyushu Cancer Center. Of these 145 patients, 14 patients were excluded from the present study because gefitinib was used as a first-line treatment.

Among the 131 patients analyzed, 8 patients were not assessable for their response to gefitinib due to the following reasons: 3 suffered from drug-induced interstitial pneumonia before confirmation of a tumor response, 1 patient had no measurable lesion, 2 patient refused gefitinib treatment in 2 weeks, and the data of 2 patients' responses were missing.

Those 8 non-assessable patients were classified as non-responders to gefitinib treatment. The median age was 62 years (ranging from 26 to 80 years) and 99 patients (75%) were younger than 70 years old. Seventy-seven patients (58%) were male, 111 patients (85%) had performance status (PS) (ECOG) 0–1, 112 patients (85%) had adenocarcinoma, and 113 patients (87%) had stage IV disease. Seventy-seven patients (59%) received chemotherapy with one regimen prior to treatment with gefitinib while 54 received two or more regimens. Sixty-one patients (47%) had a response to first-line chemotherapy while 70 were non-responders to the chemotherapy.

A response was evaluated according to the response evaluation criteria in solid tumors [15]. Patients with either a complete response (CR) or a partial response (PR) were defined as responders. In contrast, those with stable disease (SD), progressive disease (PD) or non-assessable for response were defined as non-responders.

The differences between the proportions of patient characteristics were estimated by the χ^2 test. The survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The multivariable analyses with the Cox proportional hazards model were used to estimate the simultaneous effects of the prognostic factors on survival. All statistical analyses were performed using the Dr. SPSS II software program (SPSS Inc., Chicago, IL). The differences were considered to be statistically significant when the p-value was 0.05 or less.

3. Results

3.1. Patient characteristics of gefitinib responders

Out of 131 patients, 1 (1%) and 38 patients (29%) yielded a CR and a PR to gefitinib treatment, respectively. Therefore, the objective response rate was 30% (95% confidence interval: 22–38%). Thirty-four patients (26%) had SD, resulting in a disease control rate (objective responses plus SD) of 55%. A comparison of the patient characteristics between the gefitinib responders and the non-responders is shown in Table 1. A good performance status, never-smoker, stage IV, and a histology of adenocarcinoma were more frequently observed in the gefitinib responders than in the non-responders.

Table 1
Patient characteristics.

Characteristics	Treatment with gefitinib		p-Value
	Responder (n=39)	Non-responder (n=92)	
Age, yrs	59.8 (34–76)	61.5 (26–78)	0.3952
Gender			
Male	18 (46%)	59 (64%)	0.0560
Female	21 (54%)	33 (36%)	
ECOG PS			
0	19 (49%)	22 (24%)	0.0179
1	18 (46%)	52 (57%)	
2	2 (5%)	12 (13%)	
3–4	0	6 (6%)	
Smoking status			
Smoker	12 (31%)	55 (60%)	0.0002
Never-smoker	27 (69%)	27 (29%)	
Unknown		10 (11%)	
Tumor histology			
Adenocarcinoma	37 (95%)	75 (82%)	0.0313
Others	2 (5%)	17 (18%)	
Stage			
IIIB	2 (5%)	16 (17%)	0.0437
IV	37 (95%)	76 (83%)	
Prior chemotherapy regimens			
1	27 (69%)	50 (54%)	0.2343
2	7 (18%)	29 (32%)	
3≤	5 (13%)	13 (14%)	
Response to first-line chemotherapy			
Responder	19 (49%)	42 (46%)	0.7478
Non-responder	20 (51%)	50 (54%)	

The response to first-line chemotherapy did not predict the response to subsequent treatment with gefitinib, since 49% of the responders and 46% of the non-responders to gefitinib treatment showed a response to the first-line chemotherapy.

3.2. Survival from gefitinib treatment

The median follow-up time of the survivors from gefitinib treatment was 22.6 months, ranging from 3.6 to 62.3 months. The median survival time from gefitinib treatment of all of the 131 patients was 18 months while that of the 39 gefitinib responders and 92 non-responders was 24.3 months and 5.8 months, respectively, as shown in Fig. 1.

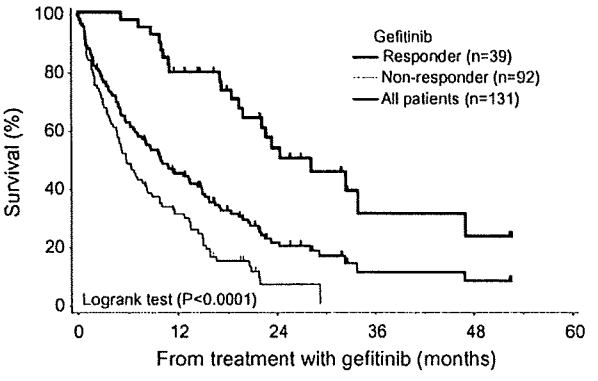

Fig. 1. The overall survival according to response to gefitinib.

Table 2
Univariate analysis on survival from gefitinib treatment.

Characteristics	Responder (n = 39)			Non-responder (n = 92)			All (n = 131)		
	No.	HR (95% IC)	p-Value	No.	HR (95% IC)	p-Value	No.	HR (95% IC)	p-Value
Age, yrs									
<60	19	1.128 (.475–2.678)	.7847	41	1.140 (.730–1.788)	.5650	60	1.103 (.744–1.634)	.6266
≥61	20	1		51	1		71	1	
Gender									
Female	21	0.752 (0.316–1.786)	.5182	33	0.633 (0.396–1.013)	.0569	54	0.620 (0.414–0.929)	.0207
Male	18	1		59	1		77	1	
ECOG PS									
0	19	0.669 (0.281–1.595)	.3650	22	0.191 (0.096–0.380)	<.0001	41	0.308 (0.192–0.495)	<.0001
1–4	20	1		70	1		90	1	
Smoking status									
Never-smoker	27	1.099 (.424–2.847)	.8455	27	0.861 (0.524–1.414)	.5539	54	0.600 (0.395–0.912)	.0167
Smoker	12	1		55	1		67	1	
Prior chemotherapy regimens									
1	27	0.822 (0.331–2.041)	.6720	50	0.681 (0.432–1.072)	.0967	77	0.612 (0.412–0.910)	.0151
≥2	12	1		42	1		54	1	
Response to first-line chemotherapy									
Responder	19	0.362 (0.144–0.908)	.0303	42	0.947 (0.606–1.479)	.8105	61	0.740 (0.496–1.104)	.1404
Non-responder	20	1		50	1		70	1	

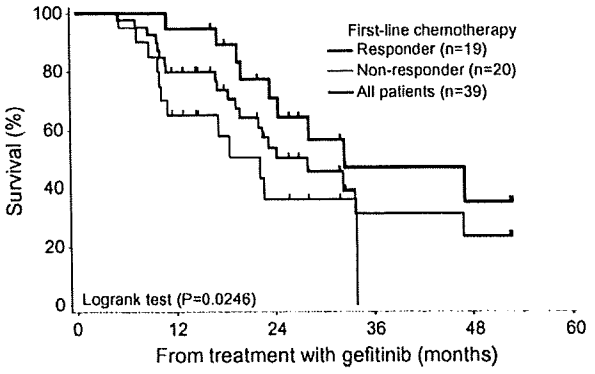

Fig. 2. The overall survival of gefitinib responders according to their response to first-line chemotherapy.

3.3. *Prognostic factors in responders and non-responders to the subsequent treatment with gefitinib*

Next, which factors, including age (<60 vs >60), gender (female vs male), performance status (0 vs 1–4), smoking status (never-smoker vs smoker), number of prior regimens (1 vs >2), and response to a first-line chemotherapy (responder vs non-responder), influenced the survival of the gefitinib responders and non-responders, respectively, were analyzed. As shown in Table 2, a statistically significant difference of the hazard ratio (HR) on survival was observed in the effectiveness of the first-line chemotherapy among the 39 gefitinib-responders and in the PS among the 92 gefitinib non-responders.

The results of a multivariate analysis with the use of a stepwise procedure were the same as those of the univariate analysis and show that the predominant prognostic factor was the effectiveness of the first-line chemotherapy (HR = 0.362, $p = 0.030$) in gefitinib responders and the PS (HR = 0.195, $p < 0.0001$) in the gefitinib non-responders. As shown in Fig. 2, the MST, 1- and 2-year-survival rates were 32.4 months, 94.7% and 70.8% in the responders to both the first-line chemotherapy and gefitinib treatment and 22.2 months, 65.0% and 36.1% in the gefitinib responders who had not responded to the first-line chemotherapy, respectively. Fig. 3 shows that the MST, 1- and 2-year-survival rates were 15 months, 71.6% and 25.5% in the gefitinib non-responders with a good PS and 4.0 months, 17.7% and 0% in the gefitinib non-responders with a poor PS, respectively.

In terms of survival from gefitinib treatment in all 131 patients, the prognostic factors determined by a univariate analysis were

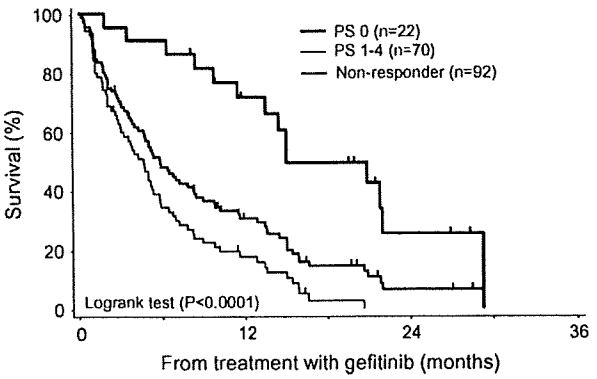

Fig. 3. The overall survival of gefitinib non-responders according to performance status.

gender, PS, smoking status and the number of prior chemotherapy regimens (Table 2). The results of a multivariate analysis revealed the predominant prognostic factor to be the PS (HR = 0.319, $p < 0.0001$) and smoking status (HR = 0.600, $p = 0.0167$).

4. Discussion

In the present retrospective study, the effectiveness of the first-line chemotherapy was found to be a prognostic factor in the gefitinib responders with previously treated NSCLC. Weiss et al. reported that the best response to first-line chemotherapy significantly influenced the overall survival from second-line chemotherapy [16]. In addition, a subset analysis of a phase III trial of comparing erlotinib as EGFR-TKI to a placebo control in NSCLC patients previously treated with chemotherapy revealed that the patients with a positive response to prior chemotherapies had a significantly better survival benefit from the erlotinib treatment than those treated with placebo, while patients without a response to prior chemotherapy (SD or PD) had a marginal survival benefit from the erlotinib [17]. The results of a subset analysis of a phase III trial comparing gefitinib to a placebo control in those patients were also similar to those of the erlotinib trial [7]. However, precisely which group of patients treated with EGFR-TKI may have their survival influenced by the effectiveness of prior chemotherapy remains to be elucidated in these phase III trials. In the present study, the effectiveness of the first-line chemotherapy was not a prognostic factor when the subjects consisted of either patients treated with gefitinib or gefitinib non-responders. On the other hand, the effectiveness of the first-line chemotherapy was a prognostic factor in gefitinib responders. Therefore, it is of interest to clarify whether these observations were seen in the subset analysis of those phase III trials.

Most patients with a positive response to gefitinib are thought to have *EGFR* gene mutated tumors according to the results of various studies [10,11,13,18]. Since the *EGFR* gene mutation is frequently seen in the never-smoker, histology of adenocarcinoma, and female subject, those factors are considered to be predictive factors for a response to EGFR-TKI. The present study confirmed that the PS, smoking status, histology, and stage were significantly predictive factors of a gefitinib response, as previously reported [5,9,19]. Gender was a marginally significant predictive factor ($p = 0.056$). *In vitro* studies using lung cancer cell lines showed that gefitinib induced apoptosis to cell lines with an *EGFR* gene mutation, and that those gefitinib-sensitive cell lines tended to be refractory to cytotoxic chemotherapeutic agents [20,21]. Although those findings do not seem to support the present results, it is unknown whether or not mutated tumors with a positive response to conventional chemotherapy are refractory to EGFR-TKI. In the present study, the effectiveness of the first-line chemotherapy was found to not be a predictive factor for the response to subsequent gefitinib treatment.

The most important prognostic factor in gefitinib non-responders was found to be the PS. This result seems to be reasonable as shown in many studies. However, the PS was not related with the prognosis of gefitinib responders, thus implying that a poor PS improved in gefitinib responders.

5. Conclusions

The present study in 131 previously treated NSCLC patients who received gefitinib subsequently revealed the effectiveness of the first-line chemotherapy to be a prognostic factor in the gefitinib responders, while the PS was shown to be a prognostic factor in the gefitinib non-responders. If the former finding is confirmed in larger, other cohort studies, elucidating the mechanism of this phenomenon will thus be worthy of study to improve the survival of NSCLC patients.

Conflict of interest

None declared.

Acknowledgements

We would like to thank Mr. Brian Quinn for his critical review and Ms. Yumiko Oshima for her help in preparing the manuscript.

References

[1] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710–7.
[2] Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. J Thorac Oncol 2007;2:845–53.
[3] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.
[4] Massarelli E, Andre F, Liu DD, Lee JJ, Wolf M, Fandi A, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. Lung Cancer 2003;39:55–61.
[5] Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard J-Y, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol 2003;21:2237–46.
[6] Kris M, Natale R, Herbst Rea. A phase II trial of ZD 1839 ('Iressa') in advanced non-small-cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimen (IDEAL 2). Proc Am Soc Clin Oncol 2002;21:p292a.
[7] Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527–37.
[8] Douillard JY, Kim E, Hirsh V, Mok T, Socinski M, Gervais R, et al. Gefitinib (IRESSA) versus docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer pre-treated with platinum-based chemotherapy: a rondomized, open-label Phase III study (INTEREST). J Thorac Oncol 2007;2:S305 (PRS-02).
[9] Kaneda H, Tamura K, Kurata T, Uejima H, Nakagawa K, Fukuoka M. Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer. Lung Cancer 2004;46:247–54.
[10] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
[11] Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
[12] Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA 2004;101:13306–11.
[13] Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol 2005;23:2513–20.
[14] Bell DW, Lynch TJ, Haserlat SM, Harris PL, Okimoto RA, Brannigan BW, et al. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. J Clin Oncol 2005;23:8081–92.
[15] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[16] Weiss G, Rosell R, Fossella F, Perry M, Stahel R, Barata F, et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. Ann Oncol 2007;18:453–60.
[17] Tsao M-S, Sakurada A, Cutz J-C, Zhu C-Q, Kamel-Reid S, Squire J, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. N Engl J Med 2005;353:133–44.
[18] Taron M, Ichinose Y, Rosell R, Mok T, Massuti B, Zamora L, et al. Activating mutations in the tyrosine kinase domain of the epidermal growth factor recep-

tor are associated with improved survival in gefitinib-treated chemorefractory lung adenocarcinomas. Clin Cancer Res 2005;11:5878–85.
[19] Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 2006;24:2549–56.
[20] Sordella R, Bell DW, Haber DA, Settleman J. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science 2004;305: 1163–7.
[21] Tracy S, Mukohara T, Hansen M, Meyerson M, Johnson BE, Janne PA. Gefitinib induces apoptosis in the EGFRL858R non-small-cell lung cancer cell line H3255. Cancer Res 2004;64:7241–4.