Response Rate Is Associated with Prolonged Survival in Patients with Advanced Non-small Cell Lung Cancer Treated with Gefitinib or Erlotinib

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Introduction: Gaining a higher response rate (RR) has usually been determined as a primary end point in phase II trials evaluating the efficacy of new molecular targeted drugs. However, a relationship between clinical response and survival benefit has not been well studied in the patients treated with molecular targeted agents.

Methods: Prospective trials of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) monotherapy in non-small cell lung cancer were extracted from MEDLINE, EMBASE, and the annual meetings in 2007 of the American Society of Clinical Oncology, European Cancer Conference, and World Conference on Lung Cancer.

Correlation between clinical response and survival was examined using linear regression analysis. We also tried to compare the significance of RR as surrogate markers for survival with that of disease control rate (DCR) by calculating the area under their receiver operating characteristic (ROC) curves.

Results: We identified 24 phase II trials and 4 phase III trials with a total of 6171 patients and 30 treatment arms, including 22 arms for the gefitinib group and 8 arms for the erlotinib group. Both RR and DCR strongly correlated with median survival time (MST; $p < 0.0001$ and $p = 0.003$, respectively). In an ROC analysis, the area under the ROC curve predicting MST prolongation by RR was 0.918, which was higher than the area under the ROC curve by DCR.

Conclusions: We found a significant relationship between RR and MST in clinical trials with EGFR-TKIs. RR could be an independent surrogate marker for MST in the current response criteria in the clinical trials of EGFR-TKIs.

Key Words: Non-small cell lung cancer, Gefitinib, Erlotinib, EGFR, Response rate.

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The small-molecule inhibitors of epidermal growth factor receptor (EGFR), gefitinib (Iressa, AstraZeneca Pharmaceuticals, Wilmington, DE), and erlotinib (Tarceva, Genentech, South San Francisco, CA) have shown antitumor activity in patients with non-small cell lung cancer (NSCLC). These drugs are orally bioavailable synthetic anilinoquinazolines that selectively and reversibly prevent ATP binding and autophosphorylation of the EGFR tyrosine kinase.

Gaining a higher response rate (RR) has usually been determined as a primary end point in phase II trials evaluating the efficacy of new molecular targeted drugs[1,2] and often in the correlative studies that have been conducted to find out the molecular and clinical predictors of survival in the treatment of EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, a relationship between clinical response and survival benefit has not been well studied to date in the patients treated with molecular targeted agents, such as EGFR-TKIs, although survival benefit is usually the most reliable index to be tested.

Furthermore, the same objective tumor response criteria as cytotoxic agents, which are mainly known as World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors Group (RECIST) criteria, have been used in phase II trials of molecular targeted agents, although they seemed to be different from cytotoxic agents in their tumor killing mechanism. It has not been well investigated whether these criteria are appropriate for evaluating the potential antitumor effect of molecular targeted agents. Disease stabilization, not tumor shrinkage, may be the main impact of molecular targeted agents on tumor growth, because many of these agents may affect tumor cells by reducing proliferation rather than by causing cell death. In the analysis of a randomized, placebo-controlled, double-blind trial conducted by Shepherd et al.,[3] the patients treated with erlotinib have been

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TABLE 1. Definition of Each Endpoint[4,5]

Abbreviation	TTP	PFS	TTF
Written in full	Time to progression	Progression-free survival	Time to treatment failure
Definition[a]	The time elapsed between treatment initiation and tumor progression	The time elapsed between treatment initiation and tumor progression or death from any cause	The time elapsed between treatment initiation and treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death

[a] PFS differs from TTP in that PFS includes death as a result of any cause in its definition in addition to tumor progression. TTF uses treatment discontinuation as a result of any cause instead of tumor progression in its definition.

PFS, progression-free survival; TTP, time to progression; TTF, time to treatment failure.

shown to have a survival advantage compared with those given a placebo even if we censor the patients who have responded. These results may suggest that RR is not an adequate end point for phase II studies of EGFR-TKIs.

The purpose of this study was to clarify through a systematic review of publications the significance of RR, stable disease rate (SDR), and disease control rate (DCR) in the current criteria as a surrogate end point for survival in the treatment of advanced NSCLC with EGFR-TKIs, gefitinib, and erlotinib. It will be worthwhile to examine such a relationship, because molecular targeted agents are expected to play a more important role than ever for cancer treatments, and the clinical predictors of outcome in NSCLC patients will be required in clinical trials using molecular targeted agents.

MATERIALS AND METHODS

Literature Search and Data Extraction

Prospective trials of EGFR-TKIs monotherapy in NSCLC, published by December 31, 2007, were identified from MEDLINE, EMBASE, using the keywords "nonsmall cell lung cancer" and "gefitinib," "ZD1839," "Iressa," "erlotinib," or "tarceva." A manual search was performed for abstracts presented at the annual meetings of the American Society of Clinical Oncology, European Cancer Conference, and World Conference on Lung Cancer in 2007. All results were limited to phase II trial or phase III trial and those written in the English language. In consideration of the accuracy of data, reports of trials with a sample size of at least 30 patients per arms were included if they contained mature data on RR and median survival time (MST). Trials using the agents in combination were excluded.

For each trial, data on sample size, kind of EGFR-TKIs, RR, SDR, DCR, MST, and median time to progression (MTTP) or median progression-free survival (MPFS) were collected. Such patient characteristics of each study as gender, performance status (PS), clinical stage, number of prior chemotherapy, ethnicity, response criteria, and age were also extracted. MST, MTTP, or MPFS on each study was determined using published data or survival curves.

Statistical Analysis

Correlation between clinical response (RR and DCR) and survival (MST and MPFS) was examined in each study using linear regression analysis. We also tried to compare the significance of RR as surrogate markers for survival with that of DCR by calculating the area under their receiver operating characteristic (ROC) curves. In this model, ROC curves examined the accuracy of each surrogate marker to predict whether MST of each study arm was longer than 7.6 months or not, which was the median MST among every study arm. An index of 0.5 indicates no discrimination ability, whereas a value of 1 indicates perfect discrimination.

In linear regression analysis, we analyzed not only MST but also MPFS, because MPFS has often been used as a primary end point, which is not affected by effective subsequent therapies, instead of MST in the studies of clinical oncology. If data about MPFS were not mentioned and only MTTP or median time to treatment failure (MTTF) was available in published data or survival curves, they were calculated the same as MPFS when examining correlation between clinical response and MPFS. As some differences were seen in their definition[4,5] (Table 1), we checked whether there was not a major difference among them when correlated with RR by calculating the linear regression line in the figure.

There could be some correlations among RR, SDR, and DCR, and they might influence the result of our analyses. Accordingly, we examined a relation between them by linear regression analysis.

Moreover, this analysis was performed on many heterogeneous studies with different kinds of patient characteristics, and these differences might possibly lead to false conclusions. Therefore, we investigated the influence of such patient characteristics on MST, MPFS, and RR as gender, PS, histologic subtypes of cancer, number of prior chemotherapies, ethnicity, and types of EGFR-TKIs using Student *t* test.

A p value <0.05 was considered statistically significant, and all reported p values were two sided. All statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Study Characteristics

We identified 28 trials of EGFR-TKIs monotherapy with a total of 6171 patients and 30 treatment arms, including 22 arms for the gefitinib group and 8 arms for the erlotinib group. There were 24 phase II trials and 4 phase III trials. The baseline characteristics of the 28 trials with 30 treatment arms are shown in Table 2.[3,6–32] Nine studies were identified from the abstracts presented at the conference meetings. Among them, four studies[29–32] have been published already, and all the data of these studies were collected from final publications.

TABLE 2. Characteristics of the Trials Included in the Analysis

Trial	Phase	Treatment Regimens	No. of Patients	RR (%)	SDR (%)	TTP (mo)	PFS (mo)	MST (mo)	Response Criteria
Cappuzzo et al.[6]	II	G 250 mg	63	15.9	42.8	3.3	—	4.1	R
Fukuoka et al.[7a]	II	G 250 mg	103	17.5	35.9	—	2.7	7.6	W
		G 500 mg	109	19.1	32.4	—	2.8	8	W
Kris et al.[8a]	II	G 250 mg	106	11.8	30.4	—	—	7	W
		G 500 mg	115	8.8	27.2	—	—	6	W
Cappuzzo et al.[9]	II	G 250 mg	40	5	45	3	—	5	R
Cappuzzo et al.[10]	II	G 250 mg	106	14.4	26.8	3.4	—	9.4	R
Ceresoli et al.[11]	II	G 250 mg	41	9.8	17.1	—	3	5	R
Perez-Soler et al.[12]	II	E 150 mg	57	12.3	35.1	—	2.1	8.4	W
Chen et al.[13]	II	G 250 mg	36	33.3	38.9	4.7	—	9.5	W
Chiu et al.[14]	II	G 250 mg	76	33.3	35.1	—	5	9.9	R
Han et al.[15]	II	G 250 mg	90	23.3	30	2.7	—	7.4	W
Shepherd et al.[3a]	III	E 150 mg	488	8.9	36.1	—	2.2	6.7	R
Spigel et al.[16]	II	G 250 mg	72	5.7	60.4	—	3.7	6.3	W
Thatcher et al.[17a]	III	G 250 mg	1129	8	32	—	3[b]	5.6	R
Giaccone et al.[18]	II	E 150 mg	54	22.7	30.2	2.8	—	13	R
Lee et al.[19]	II	G 250 mg	72	55.6	11.1	—	5.5	19.7	W
Lin et al.[20]	II	G 250 mg	53	32.1	20.7	—	3.2	9.4	R
Niho et al.[21]	II	G 250 mg	42	30	40	—	—	13.9	R
Jackman et al.[22]	II	E 150 mg	82	10	41	3.5	—	10.9	R
Wu et al.[23]	II	G 250 mg	40	32	45	—	9	15	R
Goss et al.[24a]	II	G 250 mg	100	6	—	—	1.2	3.9	R
Nishimura et al.[25]	II	G 250 mg	30	23	27	—	3.2	11.9	R
Paz-Ares et al.[26]	II	E 150 mg	879	18.8	39	3.9	—	6.1	R
Tamura et al.[27]	II	E 150 mg	108	28.3	20.8	2.5	—	13.8	R
Tan et al.[28]	II	E 150 mg	264	14	30	—	2.6	7.6	R
Crinò et al.[29a]	II	G 250 mg	97	3.1	40.2	—	2.6	5.9	R
Kim et al.[30a]	III	G 250 mg	733	9.1	—	—	2.2	7.6	R
Maruyama et al.[31a]	III	G 250 mg	245	22.5	34	—	2	11.5	R
Hesketh et al.[32]	II	E 150 mg	81	8	34	—	2.1	5	R

[a] Randomized controlled trial.
[b] Time to treatment failure.
G, gefitinib; E, erlotinib; RR, response rate; SDR, stable disease rate; TTP, time to progression; PFS, progression free survival; MST, median survival time; R, RECIST criteria; W, WHO criteria.

The sample size of each arm ranged from 30 to 1129 patients, with a median sample size of 86 patients. Nine treatment arms reported MTTP, 17 reported MPFS, 1 reported MTTF, and 3 did not report either. RR and MST were reported in all the treatment arms, whereas SDR was not reported in two treatment arms. Nine arms were intended only for chemotherapy-naive patients, 14 arms were only for chemotherapy-received patients, and 7 arms contained both of them. The cancer histology type was restricted to adenocarcinoma in four arms, whereas no arms restricted patients' eligibility in those found to have EGFR mutations in their tumors. Eleven arms had been conducted in Asian countries, including four arms in Japan, two in China, two in Korea, two in Taiwan, and one in Singapore. Evaluation for response was conducted according to RECIST criteria in 21 treatment arms and WHO criteria in 9 arms. RR and MST in the treatment arms ranged from 3.1 to 55.6% (median: 15.2%) and from 3.9 to 19.7 months (median: 7.6 months), respectively.

Correlations among Clinical Response

RR and SDR were shown to have negative relationships with each other by linear regression analysis, whereas RR and DCR had positive relationships (Figure 1). Thus, it seemed that there were some limitations in evaluating the true meaning of correlation between SDR and MST, because they could have been influenced strongly by these negative relationships. We, therefore, analyzed DCR, rather than SDR, when investigating the correlation between disease stabilization and survival in further analyses.

Median Survival Time

RR had a strong correlation with MST in the simple linear regression analysis (Figure 2*A*, $p < 0.0001$). Similarly, DCR had a positive correlation with MST (Figure 2*B*, $p = 0.003$). In terms of relationship between RR and MST, there seemed to be no differences between gefitinib arms and erlotinib arms, and between arms using WHO

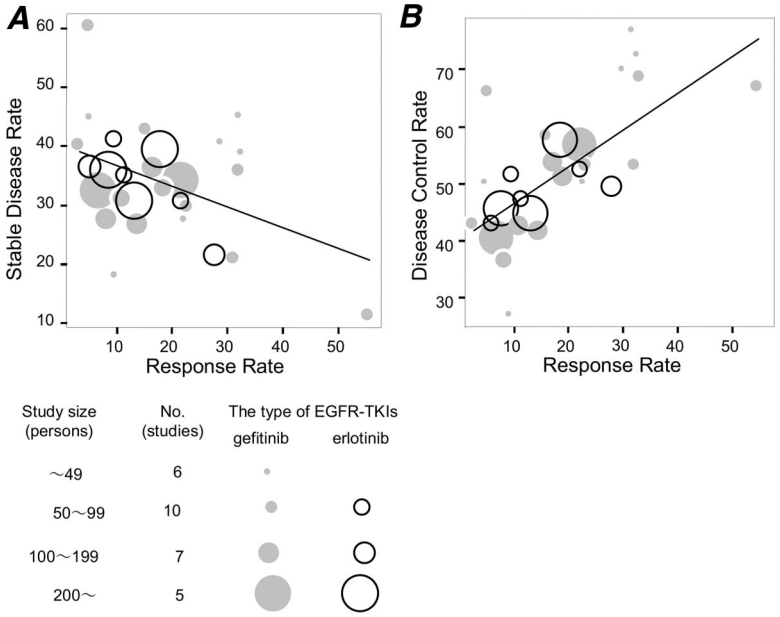

FIGURE 1. *A,* Correlation between stable disease rate and response rate. *B,* Correlation between disease control rate and response rate. Each scatterplot is shown separately by study size and the type of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). The linear regression lines are shown.

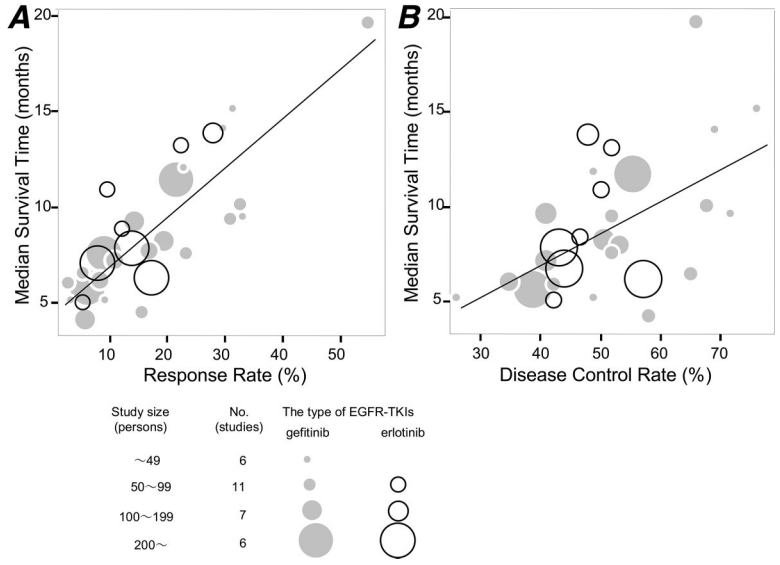

FIGURE 2. *A,* Correlation between median survival time and response rate. *B,* Correlation between median survival time and disease control rate. Each scatterplot is shown separately by study size and the type of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). The linear regression lines are shown.

criteria and RECIST criteria (Figure 2*A*). The coefficient 0.258 for RR indicated that MST increased 0.258 month with each 1% increase in RR. Similarly, each 1% increase of DCR was associated with an increase of 0.170 month in MST.

The influence of study characteristics on MST and RR are summarized in Table 3. Study arms with a larger proportion of females had a significantly longer MST than those with a lower proportion of females ($p = 0.021$). Study groups, which had a larger proportion of patients with adenocarcinoma histology, showed significantly longer MST compared with a lower proportion of patients with adenocarcinoma histology ($p = 0.005$). Study groups with a larger proportion of never smokers showed significantly longer MST than those with a lower proportion of never smokers ($p = 0.004$). Study arms conducted in Asian countries had a statistically longer MST than those conducted in non-Asian countries ($p < 0.001$), indicating Asian ethnicity was correlated with survival prolongation in the treatment of EGFR-TKIs. Moreover, all these four study groups, which showed longer MST, also had a higher RR compared with those with shorter MST ($p = 0.026$, <0.001, <0.001, and 0.001, respectively), which were similar to previous published data on the treatment of EGFR-TKIs. In contrast, study arms with a larger proportion of patients with PS 2 to 4 showed a significantly shorter MST than those with a lower proportion of poor PS ($p = 0.047$). No significant differences on MST were shown between gefitinib arms and erlotinib arms, arms using WHO criteria and those using RECIST criteria, and arms intended only for chemotherapy-naive patients and those intended only for chemotherapy-received patients.

TABLE 3. The Influence of Study Characteristics on RR, MST, and PFS or TTP[3,6–32]

		MST (mo)		PFS/TTP (mo)		RR (%)	
Characteristics of Studies	**Number**	**Mean ± SD**	***p***	**Mean ± SD**	***p***	**Mean ± SD**	***p***
Proportion of female (%)[a]							
<40	15	7.19 ± 2.72	0.021	2.69 ± 0.65	0.026	13.36 ± 7.09	0.026
≥40	15	10.22 ± 3.97		3.95 ± 1.93		22.73 ± 13.77	
Type of EGFR-TKIs							
Gefitinib	22	8.62 ± 3.90	0.838	3.48 ± 1.68	0.217	19.06 ± 13.00	0.443
Erlotinib	8	8.94 ± 3.27		2.70 ± 0.68		15.35 ± 7.41	
Proportion of patients with PS 2–4 (%)[a,b]							
<20	14	9.99 ± 4.14	0.047	2.98 ± 0.94	0.411	19.60 ± 12.63	0.465
≥20	15	7.28 ± 2.76		3.49 ± 1.89		16.27 ± 11.45	
Proportion of patients with adenocarcinoma (%)[a]							
<65	16	7.03 ± 2.47	0.005	2.80 ± 0.72	0.077	11.14 ± 5.61	<0.001
≥65	14	10.62 ± 3.98		3.82 ± 1.98		25.93 ± 12.12	
Patients type included in studies[c]							
Only chemotherapy-naïve patients	14	8.27 ± 3.20	0.665	3.30 ± 1.94	0.489	16.61 ± 9.29	0.803
Only chemotherapy-received patients	9	8.91 ± 3.72		2.78 ± 0.83		15.51 ± 11.38	
Proportion of never smokers (%)[a,d]							
<25	12	7.38 ± 2.87	0.004	2.64 ± 0.76	0.062	10.04 ± 7.02	<0.001
≥25	11	11.70 ± 3.60		3.93 ± 2.03		29.10 ± 10.67	
Country where a study was conducted[e]							
Non-Asian country	14	6.91 ± 2.65	0.001	2.85 ± 080	0.085	11.29 ± 5.15	<0.001
Asian country	11	11.78 ± 3.64		4.04 ± 2.11		29.76 ± 10.46	

[a] Studies were divided into two groups with the median by each characteristics, and then they were compared with each other.
[b] One study[25] was excluded because it did not have detail information about performance status.
[c] Seven studies[10,11,14,15,19,26,28] were excluded because they contained both chemotherapy-naïve patients and chemotherapy-received patients.
[d] Five studies[6–8,11,26] including seven arms were excluded because they did not have detail information about smoking status.
[e] Four studies[7,17,29,30] including five arms were excluded because they were undertaken in many countries across Asia and non-Asia.
MST, median survival time; TTP, time to progression; PFS, progression free survival; SD, standard division.

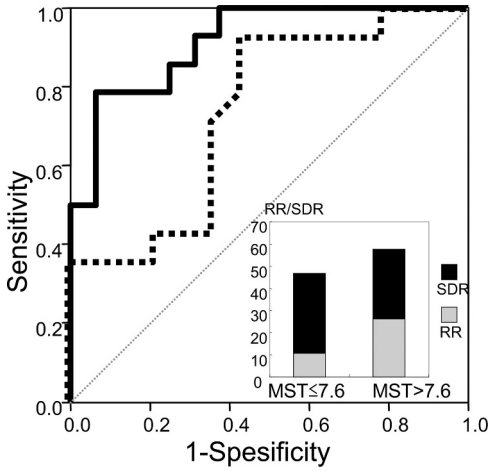

FIGURE 3. Receiver operating characteristic (ROC) curves examining whether median survival time (MST) was more than 7.6 months or not by RR (solid line) and disease control rate (DCR; dotted line). A diagonal line stands for expected ROC curve for random guessing of MST prolongation. The area under the ROC curves for RR and DCR were 0.918 and 0.737, respectively. RR, response rate; SDR, stable disease rate.

The relationships between RR and MST were conspicuous when study arms were divided into two categories by MST: study arms of which MST was more than 7.6 months or not (Figure 3). In an ROC analysis, the area under the ROC curve predicting MST prolongation by RR was 0.918, which was higher than the area under the ROC curve by DCR, even though both of them performed significantly better than random guessing of MST prolongation (Figure 3, $p < 0.001$ and 0.033, respectively).

Progression-Free Survival

Both RR and DCR significantly correlated with MPFS ($p = 0.001$ and <0.001, respectively). There seemed to be no major difference among MPFS, MTTP, and MTTF when correlated with RR (Figure 4). Among each study characteristics, only a proportion of females was significantly correlated with MPFS prolongation, whereas a proportion of patients with adenocarcinoma histology, proportion of never smokers, or Asian countries' studies tended to have relationships with MPFS without statistical significance (Table 3). The coefficient for RR was 0.072, indicating that a 1% increase in the RR prolonged MPFS by 0.072 month. Similarly, each 1% increase in DCR was associated with an increase of 0.093 month in MPFS.

DISCUSSION

The most commonly used end point for phase III trials and for the regulatory approval of new anticancer drugs is overall survival (OS). The OS is clinically meaningful and

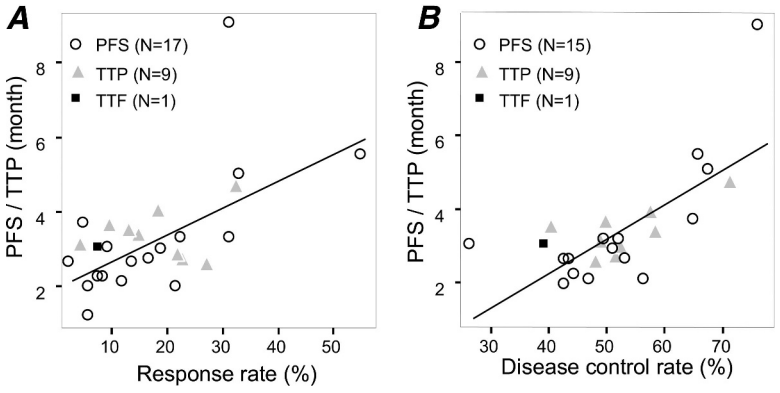

FIGURE 4. *A*, Correlation between progression-free survival or time to progression and response rate. *B*, Correlation between progression-free survival, time to progression, or time to treatment failure and disease control rate. The linear regression lines are shown. PFS, progression-free survival; TTP, time to progression; TTF, time to treatment failure.

objectively measured but can be influenced by effective sequential therapies. Furthermore, these phase III studies are laborious, time consuming, and costly.[33] A validated shorter term surrogate end point would reduce drug development costs and allow for more rapid completion of randomized controlled trials. From such a point of view, some investigators[34,35] have already examined the relationships between surrogate end points including clinical response and survival in the treatment of neoplasm with cytotoxic agents. However, EGFR-TKIs, kinds of molecular targeted agents, seemed to be different with cytotoxic agents in tumor killing mechanism, and it was unclear how large an impact on survival the clinical response with EGFR-TKIs had. To our knowledge, this was the first analysis investigating the relationships between clinical response and survival benefit in cancer treatments with molecular targeted agents.

In this analysis, the MST prolongation for a 1% increase in RR is higher than for a 1% increase in DCR, although both RR and DCR were significantly related to MST and MPFS. Additionally, the area under the ROC curve for assessment of survival indicated that RR was a more accurate marker than DCR when predicting MST prolongation. These results suggest that it is more important to increase RRs than to achieve stable disease to improve OS in the treatment of EGFR-TKIs, although there may be some importance in achieving stable disease.

It has not been well understood whether clinical response obtained by EGFR-TKIs has similar impacts on survival benefit to that obtained by cytotoxic agents. Previously, we reported[36] an analysis examining the correlation between clinical response and survival in the second-line treatment of NSCLC using studies about cytotoxic agents and a small number of studies about EGFR-TKIs. Although the results indicated that there were some relationships between clinical response and survival, there were very few studies of EGFR-TKIs monotherapy in those days, and therefore we could not detect the differences of these relationships between cytotoxic agents and EGFR-TKIs. The 0.0744-month increase of MST by each 1% increase of RR in our previous report was similar to published data of other cytotoxic agents studies in NSCLC.[34,37] However, the 0.258-month increase of MST by each 1% increase of RR for EGFR-TKIs in this study was about three times longer than that in previous studies of cytotoxic agents. These findings suggest that the clinical response of EGFR-TKIs could have a more close relationship with survival prolongation than that of cytotoxic agents, although further investigation will be necessary.

There are some limitations to our analysis. First, we relied on summary data from many published trials to assess the validity of surrogate end points. Trial-level surrogacy as described here is not necessarily linked to individual-level surrogacy,[38] and so our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. For instance, we may sometimes feel in clinical practice that some patients continue to benefit from gefitinib or erlotinib even after episodes of localized relapse. Our analyses could not include such specific cases, although it may be an important issue whether there is "clinical benefit beyond progression" in some patients treated with gefitinib or erlotinib.[39] Further studies that are based on individual patient data will be required to assess the real meaning of responsiveness to EGFR-TKIs on an NSCLC patient in clinical practice. Furthermore, the value of response on survival calculated in this study is based on EGFR-TKIs trials, and we do not know whether the same relations will hold for other molecular targeting agents, such as antibodies.

Second, there was potential bias in this study. Our analysis contained many heterogeneous phase II studies with different patient characteristics, and the method of evaluating end points such as response, stable disease, and progression-free survival (PFS) may not be exactly the same in each study. Indeed, patients came from extended access programs in some studies.[9–16] Therefore, the quality of the results is different from other closely monitored studies in terms of PFS and RR. These differences might possibly lead to false conclusions. In addition, we have no detailed information on whether the evaluation of response and stable disease was performed by physicians or others. In particular, the evaluation method of the response is important as time to progression and PFS are the end points, which are influenced by the value of the response. Moreover, several studies[9–11] came from the same center with overlapping selecting criteria. It was not known whether there was some overlapping of the analyzed patients.

In addition, patients registered in phase II studies are generally required to have measurable lesions, whereas this is not always required in phase III studies. This shows that the higher RRs and selection bias tend to increase in phase II studies.

In terms of patient characteristics, our investigation suggests that female gender, adenocarcinoma histology, smoking status, ethnicity, and PS might have an influence on MST. However, all of these characteristics except PS have already been reported to be associated with RR, which was confirmed in our analysis as well. Thus, we postulate that these patient groups gained higher RRs by the treatment of EGFR-TKIs, leading to higher MST in this study.

Third, our analysis did not contain an untreated control arm for comparison. Therefore, strictly speaking, the results of the analyses are unable to determine whether these findings were caused by a differential effect of treatment on the cancers in responded patients or by the indolent behavior of cancers in responded patients. It is well known that the presence of the EGFR mutation predicts a high RR after treatment with gefitinib or erlotinib.[40] In addition, some investigators[41,42] suggested that the presence of the EGFR mutation was associated with longer survival, irrespective of treatment. Therefore, the high RR of groups of patients after receiving gefitinib or erlotinib may serve only as a surrogate marker of their good prognosis after whatever systemic treatments they received. Appropriate control, such as chemotherapy or placebo, should be selected to evaluate the efficacy of novel EGFR-TKI in drug evaluation studies.

Despite these limitations, a strong relationship was seen between RR and MST in this study. These findings suggest that RR could be a primary end point as a surrogate marker of survival in the phase II trials and in the correlative studies conducted to find out the molecular and clinical predictors of survival in NSCLC treated with EGFR-TKIs. Furthermore, they may allow researchers and oncologists to use clinical response as a surrogate marker of survival in clinical trials of NSCLC with a more objective estimate of how long an EGFR-TKIs therapy with a known RR may, on average, prolong life. Further analyses will be needed to assess whether these findings could be applied to other types of cancer or other kinds of molecular targeted agents.

In summary, using a systematic review of publications, we found a significant relationship between RR and MST in clinical trials with EGFR-TKIs using a linear regression model. RR could be an independent surrogate marker for MST in the current response criteria in clinical trials of EGFR-TKIs. These findings may be supportive as further trials for lung cancer and EGFR-TKIs are developed in the future.

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