Survival Outcome Assessed According to Tumor Response and Shrinkage Pattern in Patients with EGFR Mutation–Positive Non–Small-Cell Lung Cancer Treated with Gefitinib or Erlotinib

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Introduction: Somatic mutations in the epidermal growth factor receptor gene (EGFR) are associated with a marked therapeutic response to EGFR–tyrosine kinase inhibitors (TKIs) in patients with advanced non–small cell lung cancer (NSCLC). Clinical indicators of the likely survival benefit of EGFR-TKI treatment in NSCLC patients with EGFR mutations have not been identified, however. We therefore evaluated progression-free survival (PFS) and overall survival (OS) according to tumor response and tumor shrinkage pattern in such patients.

Methods: Among 145 EGFR mutation–positive NSCLC patients treated with EGFR-TKIs, 68 individuals were selected for analysis.

Results: Of the 68 selected patients, 6 achieved a complete response (CR), 42 a partial response (PR), and 14 stable disease (SD). Both PFS and OS were significantly longer in patients who achieved a CR or PR than in those who experienced SD. Multivariate analysis showed that a response (CR or PR) to EGFR-TKIs was significantly associated with both PFS and OS. Among the CR/PR group, the median maximal tumor shrinkage relative to baseline was 56%, and the median time to response (TTR) was 4.2 weeks. The subsets of these patients who experienced rapid tumor regression (TTR of ≤4.2 weeks) or a high degree of tumor shrinkage (≥56%) did not show a more favorable PFS or OS compared with those who experienced slow tumor regression or a low degree of tumor shrinkage.

Conclusion: Response (CR or PR) may represent the optimal surrogate for efficacy among EGFR mutation–positive NSCLC patients treated with EGFR-TKIs.

Key Words: Epidermal growth factor receptor, Non–small cell lung cancer, Tyrosine kinase inhibitor, Tumor shrinkage, Response, Mutation, Survival.

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Patients and Methods

We screened 145 consecutive patients with EGFR mutation–positive NSCLC who were treated with EGFR-TKIs between May 2003 and July 2012 at Kinki University Hospital or Kishiwada City Hospital. Criteria for use of a patient’s data included the provision of signed informed consent for EGFR mutation analysis, a diagnosis of stage IIIb or IV or recurrent NSCLC with a proven EGFR mutation, the presence of at least one tumor lesion that could be accurately measured by...
computed tomography according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1., and treatment with gefitinib or erlotinib. All patients were evaluated at least every 8 weeks until response confirmation by RECIST. Maximal tumor shrinkage was defined as the greatest tumor shrinkage achieved at any follow-up assessment. Time to response (TTR) was defined as the time from the start of treatment with an EGFR-TKI to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR. OS and PFS were assessed from the first day of EGFR-TKI therapy to the date of death from any cause and the date of objective disease progression, respectively. The study protocol was approved by the institutional review board at each study site.

RESULTS

Patient Characteristics
Among 145 EGFR mutation–positive NSCLC patients treated with EGFR-TKIs, 68 individuals were selected for analysis (Fig. 1). There were no substantial differences in patient characteristics between eligible (n = 68) and ineligible (n = 77) patients (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/JTO/A497). Demographics of the eligible 68 patients are shown in Table 1. Fifty-seven (84%) of these individuals were treated with gefitinib and 11 (16%) with erlotinib. Fifty-two patients (76%) were women and 52 (76%) were never-smokers, with the median age of all patients being 69 years (range, 39–87). Sixty-seven patients (99%) had adenocarcinoma, and 59 (87%) had disease of stage IIIb or IV. Most patients (90%) had a good Eastern Cooperative Oncology Group performance status (0 or 1), and 38 (56%) received EGFR-TKI treatment as first-line chemotherapy. With regard to the type of EGFR mutation, 34 patients (50%) had a deletion in exon 19, 31 (46%) had a missense mutation in exon 21 (L858R or L861Q), and three (4%) had a G719A mutation in exon 18.

Analysis of PFS and OS According to Response to EGFR-TKI Treatment
According to the RECIST criteria, six patients experienced a CR, 42 patients a PR, 14 patients SD, and six patients progressive disease (PD) (Table 1). The response rate (CR + PR) and disease control rate (CR + PR + SD) were thus 71% (48 of 68 patients) and 91% (62 of 68 patients), respectively. For the entire cohort, the median PFS was 11.3 months (95% confidence interval [CI], 7.5–15.2) and the median OS was 24.9 months (95% CI, 8.8–40.9). Analysis of PFS according to response to EGFR-TKI treatment revealed a significant benefit for the CR/PR group compared with the SD group (median of 15.9 versus 8.5 months, p = 0.009) (Fig. 2A). Kaplan–Meier curves for OS also revealed a significant benefit for the CR/PR group compared with the SD group (median of 44.4 versus 12.2 months, p = 0.004) (Fig. 2B).

To rule out potential confounding interaction between response and other factors, we performed multivariate analysis for PFS and OS (Table 2). Response (CR or PR) to EGFR-TKI treatment (hazard ratio [HR], 0.33; 95% CI, 0.17–0.62; p = 0.001) and a favorable performance status (HR, 0.25; 95% CI, 0.10–0.65; p = 0.004) were significantly associated with PFS, whereas response (CR or PR) to EGFR-TKI treatment (HR, 0.29; 95% CI, 0.13–0.68; p = 0.004), a favorable performance status (HR, 0.18; 95% CI, 0.05–0.65; p = 0.008), and female sex (HR, 0.22; 95% CI, 0.06–0.79; p = 0.021) were

![FIGURE 1.](image_url) Flowchart of patient selection. EGFR-TKI, epidermal growth factor receptor gene tyrosine kinase inhibitor; NSCLC, non–small-cell lung cancer.
significantly associated with OS. Other covariables (smoking history, age, **EGFR** genotype, and type of mutation) did not affect PFS or OS.

**Relation of Maximal Tumor Shrinkage to PFS**

Given that a response to EGFR-TKI treatment was found to be associated with a longer PFS and OS, we investigated the impact of a marked reduction in tumor size on survival outcome among patients who achieved a CR or PR. The maximal decrease in tumor size over time ranged from 30% to 100% for this group, with a median value of 56% (Fig. 3). No significant correlation was detected between maximal tumor shrinkage and PFS ($R^2 = 0.0008$), however (Fig. 4A).

We divided this group of patients into two subgroups according to maximal tumor shrinkage (low shrinkage, $<56$%; high shrinkage, $\geq 56$%), but no trend toward a more favorable PFS ($p = 0.87$) (Fig. 4B) or OS ($p = 0.55$) (Fig. 4C) was apparent in the subset of patients who experienced a more pronounced change in tumor size in response to EGFR-TKI therapy.

**PFS According to TTR**

We next investigated the impact of rapid tumor shrinkage, as reflected by TTR, on survival outcome among patients who achieved a CR or PR. The median TTR was 4.2 weeks (95% CI, 3.9–4.5), with most patients (97%) achieving a CR or PR within 2 months after initiation of EGFR-TKI treatment. No correlation was apparent between TTR and PFS ($R^2 = 0.0084$; Fig. 4D). We divided this group of patients into two subgroups according to TTR (long TTR, >4.2 weeks; short TTR, $\leq 4.2$ weeks), but there was no significant difference in PFS ($p = 0.29$; Fig. 4E) or OS ($p = 0.58$; Fig. 4F) between patients with a long or a short TTR.

**DISCUSSION**

EGFR-TKIs such as erlotinib and gefitinib are highly effective for the treatment of NSCLC patients harboring activating **EGFR** mutations.4–7 The efficacy of EGFR-TKI treatment varies, however, even among **EGFR** mutation–positive NSCLC patients, with no studies to date having evaluated

### TABLE 2. Multivariate Analysis for Survival after Initiation of EGFR-TKI Treatment in NSCLC Patients with **EGFR** Mutations ($n = 68$)

| Factor                        | Progression-Free Survival | Overall Survival |
|-------------------------------|---------------------------|-----------------|
|                              | HR   | 95% CI   | $p$  | HR   | 95% CI   | $p$  |
| Sex (female/male)             | 0.37 | 0.14–1.03 | 0.056 | 0.22 | 0.06–0.79 | 0.021 |
| ECOG PS (0–1/2–3)$^a$         | 0.25 | 0.10–0.65 | 0.004 | 0.18 | 0.05–0.65 | 0.008 |
| Smoking history (never-smoker/smoker) | 1.19 | 0.48–2.96 | 0.716 | 2.20 | 0.74–6.59 | 0.156 |
| Age ($\leq 69$/>70 years)      | 1.00 | 0.52–1.92 | 0.999 | 0.96 | 0.43–2.14 | 0.917 |
| **EGFR** mutation (E19del/other) | 0.66 | 0.35–1.23 | 0.190 | 0.49 | 0.21–1.14 | 0.096 |
| EGFR-TKI (erlotinib/gefitinib) | 0.96 | 0.38–2.42 | 0.928 | 1.59 | 0.53–4.82 | 0.409 |
| Response ([CR + PR]/[SD + PD]) | 0.33 | 0.17–0.62 | 0.001 | 0.29 | 0.13–0.68 | 0.004 |

$^a$At initiation of EGFR-TKI treatment.

EGFR-TKI, epidermal growth factor receptor gene tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PS, performance status; E19del, exon-19 deletion.

$p$ values $<0.05$ are shown in bold.
survival according to tumor response among such individuals. We have now shown that PFS and OS were significantly longer in such patients who achieved a CR or PR than in those who manifested SD. Multivariate analysis also revealed that a response (CR or PR) to EGFR-TKI treatment was associated with a longer PFS and OS, suggesting that response might represent the optimal surrogate for efficacy in patients with EGFR mutation–positive tumors treated with EGFR-TKIs.

Although SD is a relatively more complex category than CR or PR, ranging from a minor decrease to a minor increase in tumor size, we found that most EGFR mutation–positive NSCLC patients who experienced SD with EGFR-TKI therapy showed some tumor shrinkage, ranging from 4% to 27% relative to baseline, and the median PFS in this group of patients was 8.5 months, which seems better than that of individuals who experienced SD among unselected NSCLC

FIGURE 3. Waterfall plot of the maximal decrease in tumor size over time relative to the pretreatment baseline for individual patients treated with epidermal growth factor receptor gene tyrosine kinase inhibitor who achieved a partial response or complete response. The median decrease of 56% was used to define patient subgroups characterized by low or high tumor shrinkage.

FIGURE 4. Relation between survival and either maximal tumor shrinkage or time to response for patients treated with EGFR-TKIs who achieved a complete response or partial response. A, Correlation between maximal tumor shrinkage and PFS. Progression-free survival (B) and overall survival (C) according to the maximal tumor shrinkage (low shrinkage, <56%; high shrinkage, ≥56%). D, Correlation between time to response and progression-free survival. Progression-free survival (E) and overall survival (F) according to the time to response (long, >4.2 weeks; short, ≤4.2 weeks). EGFR-TKI, epidermal growth factor receptor gene tyrosine kinase inhibitor.
patients treated with EGFR-TKIs.\textsuperscript{3} Given that patients who achieved a CR or PR showed a significantly longer survival after EGFR-TKI treatment than did those who experienced SD in our study, SD might reflect an insufficient survival benefit for such treatment in \textit{EGFR} mutation–positive patients. Further studies are therefore warranted to elucidate the molecular mechanism responsible for SD, with several candidates having been identified.\textsuperscript{8–11} Analysis of pretreatment tumor specimens from NSCLC patients harboring \textit{EGFR} mutations revealed that a high level of expression of hepatocyte growth factor, a ligand of the receptor tyrosine kinase MET, occurred more frequently in tumors with intrinsic EGFR-TKI resistance (SD or PD) than in sensitive tumors (PR or CR).\textsuperscript{9} In addition, the T790M mutation of EGFR, which has been associated with acquired resistance to EGFR-TKIs in NSCLC patients harboring activating \textit{EGFR} mutations, was recently shown to be present in some patients before treatment with EGFR-TKIs. Among \textit{EGFR} mutation–positive NSCLC patients treated with EGFR-TKIs, those with a de novo T790M mutation were found to have a significantly shorter PFS than those without it.\textsuperscript{10,11} New treatment strategies are thus needed to improve outcome for patients in whom these candidate mechanisms for SD are operative.

Oncogene-addicted tumors have clinical features associated with rapid and marked tumor shrinkage after administration of a corresponding molecularly targeted drug. Such clinical features are considered to reflect early improved quality of life.\textsuperscript{12,13} However, the impact of rapid and pronounced tumor shrinkage on survival outcome in EGFR-TKI–treated NSCLC patients who harbor an \textit{EGFR} mutation and who show a CR or PR has remained unknown. We have now shown that neither the maximal extent of tumor shrinkage nor TTR was related to PFS or OS in such patients. Patients who harbor \textit{EGFR} mutations eventually develop resistance to TKIs through the acquisition of additional genetic changes, such as the T790M mutation of EGFR or MET amplification. Our findings suggest that time to acquired resistance (disease progression) after initiation of EGFR-TKI therapy is defined by the duration of EGFR-TKI exposure, regardless of the time to onset of tumor response or the extent of tumor shrinkage.

The limitations of the present study include a retrospective design and a relatively small number of patients. Although all patients enrolled for this analysis were evaluated at least every 8 weeks until response confirmation, they underwent computed tomographic imaging at different time points.

In conclusion, response (CR or PR) may represent the optimal surrogate for survival among \textit{EGFR} mutation–positive NSCLC patients treated with EGFR-TKIs. Moreover, our results suggest that the survival benefit of EGFR-TKI treatment in patients who achieve a CR or PR is not influenced by the pattern of tumor shrinkage.

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