Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Beyond Progressive Disease

A Retrospective Analysis for Japanese Patients with Activating EGFR Mutations

Kenichi Nishie, MD,† Tomoya Kawaguchi, MD,* Akihiro Tamiya, MD,* Tomoyasu Mimori, MD,* Naoko Takeuchi, MD,* Yoshinobu Matsuda, MD,* Naoki Omachi, MD,* Kazuhiro Asami, MD,* Kyoichi Okishio, MD,* Shinji Atagi, MD,* Tomohisa Okuma, MD,* Akihito Kubo, MD,‡ Yoshihito Maruyama, PhD,§ Shinzoh Kudoh, MD,|| and Minoru Takada, MD¶*

Introduction: It is not determined whether the continuous use of epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKI) is reasonable for patients with activating *EGFR* mutations, who have progressed with the drug.

Methods: We retrospectively analyzed the data from 2002 to 2010 of consecutive patients who had advanced non–small-cell lung cancer (NSCLC) harboring activating *EGFR* mutations and showed radiological disease progression after EGFR-TKI treatment as the first-line or second-line setting. We classified them into two groups: continuous EGFR-TKI and switching to chemotherapy, and compared the clinical outcomes. Multivariate analysis for survival was performed including age, sex, Eastern Cooperative Oncology Group performance status (0–1/ 2–4), brain metastasis, *EGFR* mutations (deletions in exon 19 versus L858R), continuous EGFR-TKI (yes/no), and initiation of EGFR-TKI (first versus second).

Results: A total of 551 NSCLC patients were screened for *EGFR* mutations in the period, and 186 patients had activating *EGFR* mutations. To explore the potential use of EGFR-TKI beyond progressive disease (PD), 64 patients were selected and analyzed. There were 13 men and 51 women, and median age was 65.5 years (range, 42–86). Among them, 31 patients had deletions in exon 19, and 33 had point mutation of L858R in exon 21. Thirty-nine patients were continuing *EGFR*-TKI beyond PD; 25 patients were switched to cytotoxic chemotherapy alone. The median overall survival was 32.2 months in the patients continuing *EGFR*-TKI, and 23.0 months in the patients switching to chemotherapy, presenting a significant difference between the two groups ($p = 0.005$). Cox analysis showed that continuous EGFR-TKI after PD (hazards ratio 0.42, 95% confidence interval: 0.21–0.83, $p = 0.013$) was associated with improved survival.

Conclusion: Continuous use of EGFR-TKI beyond PD may prolong overall survival compared with switching to cytotoxic chemotherapy in patients with activating *EGFR* mutations. A prospective study will be needed to confirm our results.

Key Words: Advanced non–small-cell lung cancer, Epidermal growth factor receptor mutation, Epidermal growth factor receptor tyrosine kinase inhibitor.

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Lung cancer represents the leading cause of death from cancer in Japan as well as in the European Union and the United States, and non–small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers.[1–3] Many patients with NSCLC have advanced disease at diagnosis and a poor prognosis with median survival time of 8 to 10 months. However, the clinical course and survival have changed dramatically after epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKI) were introduced to a subgroup of patients.[4,5] Somatic mutations in the *EGFR* have been demonstrated as the most important biomarker in predicting the clinical outcome treated with EGFR-TKI. The activating *EGFR* mutations including deletions in exon 19 and L858R in exon 21 encompass most of the tyrosine kinase-binding domain of *EGFR*.[6] A couple of phase III studies showed that gefitinb or erlotinib provided a significant clinical benefit in NSCLC patients with activating *EGFR* mutations, with a response of more than 70% in NSCLC patients harboring activating *EGFR* mutations, with progression-free survival (PFS) ranging from 9.2 to 13.1 months and median overall survival (OS) from 21.0 to 30.9 months.[5,7–11]

*National Hospital Organization (NHO) Kinki-Chuo Chest Medical Center, Sakai, Osaka, Japan; †Sakai Municipal Hospital, Sakai, Osaka, Japan; ‡Aich Medical University School of Medicine, Nagakute, Aichi, Japan; §Keio University, Minato-ku, Tokyo, Japan; ||Osaka City University Hospital, Osaka City, Osaka, Japan; and ¶Sakai Hospital Kinki University Faculty of Medicine, Sakai, Osaka, Japan.

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Address for correspondence: Tomoya Kawaguchi, MD, Department of Internal Medicine, National Hospital Organization (NHO) Kinki-Chuo Chest Medical Center, Sakai, Osaka 591–8555, Japan. E-mail: t-kawaguchi@kch.hosp.go.jp

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However, NSCLC develops resistance to EGFR-TKI, with the eventual appearance of progressive disease (PD).[12,13] Although guidelines recommend that EGFR-TKI should be changed to cytotoxic chemotherapy including platinum doublet after failure,[14,15] the result of this treatment strategy after acquiring resistance to EGFR-TKI is not clear in a practical setting. Rapid tumor increase after stopping EGFR-TKI after PD has been reported, and there are some suggestions that continuing EGFR-TKI after PD is a reasonable option for patients with activating *EGFR* mutation.[16,17] To date there are no studies examining the efficacy of continuing EGFR-TKI treatment after PD in patients with activating *EGFR* mutation, and we explored the potential of allowing the continuation of EGFR-TKI after the failure of EGFR-TKI.

PATIENTS AND METHODS

Patients

Clinical information was retrospectively obtained from the NSCLC patients treated from June 2002 to February 2010 through a database from the National Hospital Organization Kinki-chuo Chest Medical Center, Japan, and the data was updated in December 2011. We examined patients with advanced NSCLC harboring activating *EGFR* mutations (deletions in exon 19 or L858R), who were treated with EGFR-TKI in first- or second-line setting, and showed radiological progression after treatment with EGFR-TKI. We confirmed PD using the Response Evaluation Criteria in Solid Tumors 1.0. One radiologist (OT) reviewed all the patients and determined all the responses to EGFR-TKI independently. We then classified the patients into two groups based on the following treatment: continuous EGFR-TKI and switching to chemotherapy. We defined beyond PD as continuing EGFR-TKI after confirming PD. The patients who were readministrated EGFR-TKI after the cytotoxic chemotherapy were excluded in this study. A genetic analysis had been performed to detect EGFR mutations from exons 18 to 21. The nucleotide sequence of the kinase domain of the *EGFR* gene had been determined using polymerase chain reaction INVADER assay of the individual exons.

Statistical Analysis

Associations among clinical characteristics were analyzed by Fisher's exact test or Mann–Whitney *U* test. OS was defined as a period from the start of first-line treatment of chemotherapy or *EGFR*-TKI to the date of death by any cause, or the date when the patient was last known to be alive. This was analyzed by the Kaplan–Meier method. The differences between the two groups were tested using the log-rank test. Multivariate analysis for survival was performed with Cox regression model using the following covariates: age, sex, Eastern Cooperative Oncology Group performance status (PS), histology, stage, brain metastasis, *EGFR* mutations (deletions in exon 19 versus L858R), continuous EGFR-TKI, and initiation of using EGFR-TKI (first versus second). Statistical analysis was performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC). This study was approved by the Institutional Review Boards of the National Hospital Organization Kinki-Chuo Chest Medical Center.

RESULTS

Patient Characteristics

EGFR mutations were screened in 551 patients (Fig. 1). Activating *EGFR* mutations were detected in 186 of 551 patients (33.8%). One hundred and thirty-five patients with activating *EGFR* mutations were treated with EGFR-TKI. Of the 135 patients who received EGFR-TKI, 112 patients received EGFR-TKI as first line or second line; 23 patients received EGFR-TKI at first time after second line. Among the

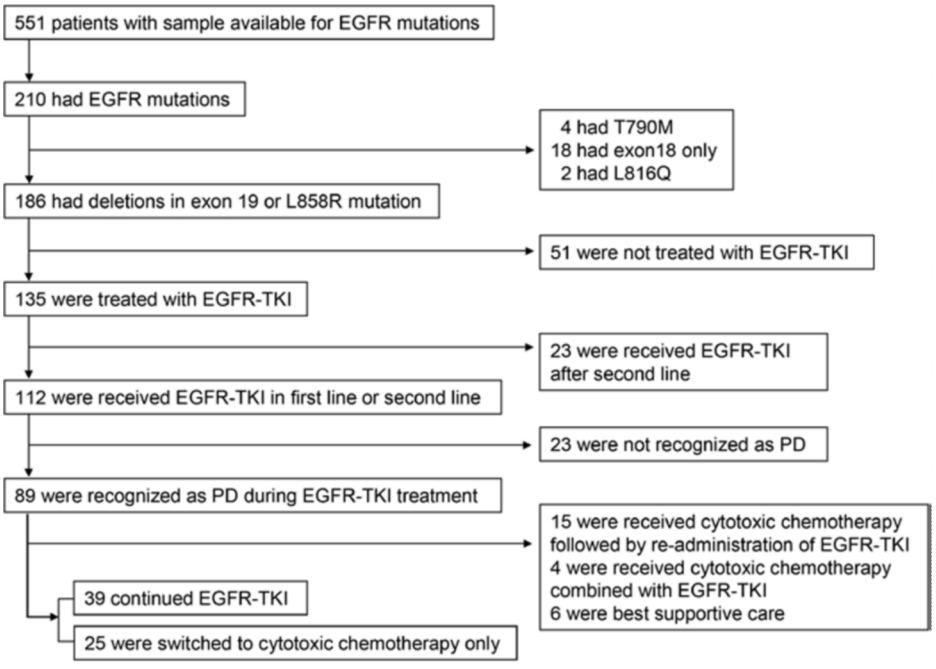

FIGURE 1. Flowchart of patient selection. EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; PD, progressive disease.

112 patients who received EGFR-TKI in first line or second line, 89 were recognized as having PD during EGFR-TKI treatment, whereas 23 were not recognized as PD. Among 89 patients, 64 patients were selected for analysis and 25 patients were excluded for a variety of reasons; 15 patients received cytotoxic chemotherapy followed by readministration of EGFR-TKI, four patients received cytotoxic chemotherapy combined with EGFR-TKI, and six patients received just best supportive care after the failure. Demographics of the 64 patients are listed in Table 1. No differences were observed between the two groups, except that the patients in the continuous group were significantly older than those in the group switching to chemotherapy (p = 0.008). Median duration of follow-up period for survival was 25.7 months (range, 5.7–75.1). There were 13 men and 51 women with activating *EGFR* mutations, and median age was 65.5 years (range, 42–86). A total of 31 patients had deletions in exon 19, and 33 had a point mutation resulting in L858R, and none of them had double mutations. Thirty-nine patients were continuing EGFR-TKI after PD. Twenty-five patients switched EGFR-TKI to cytotoxic chemotherapy regimens: carboplatin/paclitaxel (2 patients), carboplatin/gemcitabine (2 patients), docetaxel (6 patients), pemetrexed (9 patients), and S-1 (6 patients) The objective response (complete response + partial response) to initial EGFR-TKI was seen in the 22 patients (65%) in the continuous group among the 34 patients evaluable for the response, and in 14 patients (64%) in the switching group among 22 patients. There was no significant difference between the two groups ($p = 0.935$). As for the relapse site after *EGFR*-TKI treatment, 29 patients (74.3%) were confirmed at primary region, six (15.4%) at brain site, three (7.7%) at bone site, and one (2.6%) at liver in the continuous group; 21 patients (84.0%) were confirmed as PD at primary region, three (12.0%) at brain site, and one (4.0%) at liver, in the switching group. There was also no significant difference between the two groups ($p = 0.360$). Grade 3 or 4 hematologic toxicity after PD was observed in one patient (2.9%) continuing in the EGFR-TKI group, whereas nine patients (36.0%) were observed in the switching to chemotherapy group. No elevated serum value of progastrin-releasing peptide, a selective tumor marker for small-cell lung cancer (SCLC), was observed at the time of PD, suggesting that they had no conversion to SCLC.

Survival Analysis for Continuous *EGFR*-TKI Versus Switching to Chemotherapy

Univariate analysis showed that the median OS was 32.2 months in the patients continuing EGFR-TKI, and 23.0 months in those switching to cytotoxic chemotherapy. As shown in the survival curves in Figure 2, there was a significant difference between the two groups ($p = 0.005$).

In the patients receiving first-line EGFR-TKI treatment, PFS was 14.4 months in the continuous group ($n = 18$) and 12.4 months in the switching group ($n = 9$). Although the continuous group had longer PFS numerically, there was no significant difference ($p = 0.176$). Multivariate analysis in a Cox model showed that better PS (hazards ratio [HR] 3.16, 95% confidence interval [CI]: 1.50–6.68, $p = 0.026$) and continuous EGFR-TKI treatment after PD (HR 0.42, 95%CI: 0.21–0.83, $p = 0.013$) were associated with longer survival

TABLE 1. Patient Characteristics ($n = 64$)

Parameter	Total ($n = 64$)	Continuous EGFR-TKI ($n = 39$)	Switching to Chemotherapy ($n = 25$)	*P*
Age (yrs)				
Median (range)	65.5(42–86)	69(45–86)	58(42–82)	0.008
Sex				
Male/Female	13/51	6/33	7/18	0.221
Smoking history				
Current smoker/former smoker/never smoker	8/9/47	4/6/29	4/3/18	0.838
ECOG performance status				
0–1/2–4	52/12	32/7	20/5	0.838
Tumor type				
Adenocarcinoma/ non–small-cell carcinoma	60/4	37/2	23/2	0.640
Tumor stage				
IIIA/ IIIB/ IV/postoperative recurrence	2/11/34/17	1/5/22/11	1/6/12/6	0.654
Brain metastasis				
No/yes	48/16	29/10	19/6	0.882
Site of progressive disease				
Primary region /brain/bone/abdomen	50/9/3/2	29/6/3/1	21/3/0/1	0.538
EGFR mutation				
Deletions in exon 19/L858R	31/33	19/20	12/13	0.955
Initiation of EGFR-TKI				
1st line/2nd line	27/37	18/21	9/16	0.422

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; ECOG, Eastern Cooperative Oncology Group.

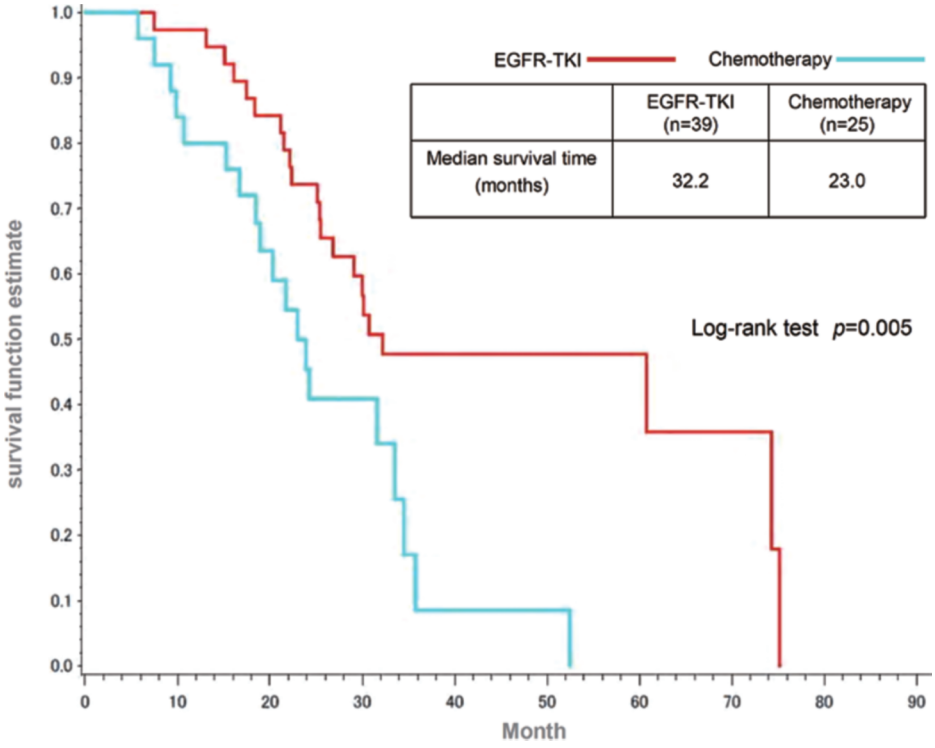

FIGURE 2. Overall survival curves on the basis of the time from the initiation of first-line chemotherapy. Kaplan–Meier estimates of continuous EGFR-TKI and switching to chemotherapy. EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors.

TABLE 2. Cox Regression Analysis of Overall Survival (n = 64)

	Overall Survival		
Variables	**HR**	**95%CI**	***p***
Age	0.98	0.95–1.02	0.261
Sex		0.34–1.63	0.460
Male	1.00		
Female	0.75		
ECOG performance status		1.50–6.68	0.026
0–1	1.00		
2–4	3.16		
Brain metastasis		0.44–1.99	0.849
Yes	1.00		
No	0.93		
EGFR mutation		0.62–2.39	0.562
Deletions in exon 19	1.00		
L858R	1.22		
Continuous EGFR-TKI after the failure		0.21–0.83	0.013
No	1.00		
Yes	0.42		
Initiation of EGFR-TKI		0.33–1.37	0.272
1st line	1.00		
2nd line	0.67		

HR, hazards ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; ECOG, Eastern Cooperative Oncology Group.

(Table 2). Continuous treatment of EGFR-TKI was a significant and independent prognostic factor in patients with activating *EGFR* mutations. Any other variables such as age, sex, brain metastasis, type of *EGFR* mutations, and initiation of EGFR-TKI were not associated with OS.

DISCUSSION

In this retrospective study, we have shown that NSCLC patients with *EGFR* mutations, who continued EGFR-TKI treatment after PD had significantly longer survival compared with those who switched to cytotoxic chemotherapy. This study suggests that continuing EGFR-TKI treatment after disease progression might be a reasonable option for improving patient survival.

There are a few other studies investigating the treatment of EGFR-TKI after PD, but we believe this is the first report suggesting a survival benefit of continuing EGFR-TKI treatment for patients with *EGFR* mutations beyond disease progression.

In previous studies, Maruyama et al.[18] retrospectively analyzed 60 patients who had treatment failure after achieving disease control with gefitinib. These patients were treated with or without continuing gefitinib. Continuing the drug was associated with a better survival based on multivariate analyses (HR 0.51, 95%CI: 0.26–0.98, p = 0.042).[18] Faehling et al.[19] also reported retrospectively that NSCLC patients treated with erlotinib, whose disease progressed after long-term erlotinib, responded and showed treatment with TKI after disease

progression, leading to prolonged OS. However, both the studies did not analyze patients based on *EGFR* mutation status.

The concept of *beyond PD* has been established and accepted in the treatment of several malignant tumors. Bevacizumab beyond initial PD could play an important role in improving the OS in patients with metastatic colorectal cancer.[20] Also, trastuzumab beyond PD offers a survival benefit to breast cancer with human *EGFR* type 2.[21] In addition, continuing imatinib over disease progression is considered to be an option for relapsed or progressed advanced gastrointestinal stromal tumor patients.[22] These studies indicate that continuing the treatment that blocks the cascade of oncogenes may still have a clinical benefit when tumor depends on only one oncogene. On the basis of these results and our data, the concept can be applied to advanced NSCLC. Gregory et al.[16] reported that stopping EGFR-TKI use results in symptomatic progression, and an increase in standardized uptake value of positron emission tomography and an increase in tumor size in patients with NSCLC who develop acquired resistance. Our study enhanced this observation and could show an extension of the OS.

It seems that the patients with activating *EGFR* mutations are able to maintain quality of life (QOL) by continuing EGFR-TKI. Inoue et al.[23] reported the efficacy and feasibility of gefitinib for patients with poor PS and NSCLC harboring *EGFR* mutations. PS improvement was observed in 79% ($p < 0.00005$) and these patients maintained a good QOL.[23] In the present study, severe hematologic toxicity was more observed in the group switching to chemotherapy. Four patients who changed to cytotoxic chemotherapy died within a few months after EGFR-TKI was stopped and experienced rapid tumor growth and toxicities because of the chemotherapy. EGFR-TKI can be beneficial in reducing risks associated with side effects caused by cytotoxic chemotherapy. In NSCLC treatment, consideration for maintaining QOL and the avoidance of adverse events is considered to be of vital importance, and therefore this therapy may be reasonable after the failure of EGFR-TKI treatment, particularly to the patients showing poor PS.

The strategy regarding how to treat NSCLC after acquiring resistance to EGFR-TKI has been discussed, but there is still a challenge to overcome resistance and no practical and clinical method has been established to date. We suggest continuation of EGFR-TKI is reasonable for the suppression of EGFR-TKI sensitive clones, and adding drugs on EGFR-TKI can be a promising option to treat the patients. The treatment of cytotoxic chemotherapy has been reported in combination with EGFR-TKI as well as antibody against *c-MET* and *EGFR*.[24,25] Jänne and colleagues[26] reported the efficacy of combination therapy with erlotinib and carboplatin/paclitaxel compared with erlotinib alone. OS in the mutation-positive patients was 38.1 months in the combination group whereas it was 31.3 months in the erlotinib-alone group.[26] Our group has also conducted a prospective phase II study to evaluate the efficacy and toxicity of adding pemetrexed to EGFR-TKI after relapse in patients with active *EGFR* mutations. In the study, promising data have been obtained, and PFS was 6.2 months and disease control rate was 86.4% with mild toxicities.[27]

The mechanism to acquire resistance has been intensively studied and recent reports showed that half the relapsed patients had a secondary mutation that substitutes methionine for threonine at amino acid 790 in *EGFR*, and approximately 20% patients had *MET* amplification.[12,13] In addition, a new phenomenon of transforming from NSCLC into SCLC was demonstrated.[28] Although we did not conduct rebiopsy in our patients, there were no increasing progastrin-releasing peptides and we could not find clear evidence to confirm the transformation at least in tumor-marker levels specific for SCLC. Further molecular study of the resistant tumor taken from rebiopsy are needed.

There are some limitations in our study. The sample size is small, and the nature of progressive disease in the *EGFR*-mutated patients treated with EGFR-TKI is varying. The physicians' decision regarding continuation or switching to chemotherapy might vary as a result of retrospective analysis. Although there was no significant difference between the two groups in response to initial EGFR-TKI and relapse site during or after the treatment, the continuous group had longer PFS numerically. The physicians' decision might be influenced by the duration of EGFR-TKI use. However, the effectiveness of EGFR-TKI for the patients who received chemotherapy after having long PFS might be underestimated in this study, because those who had re-challenge of EGFR-TKI after cytotoxic chemotherapy were not counted (Fig. 1). However, the patients in the continuous EGFR-TKI group were older than the those in the group switching to chemotherapy. Older patients might tend to continue the EGFR-TKI treatment because of a concern with the toxicity of cytotoxic chemotherapy. We would need a prospective trial to examine the head-to-head comparison of continuing EGFR-TKI treatment versus switching to chemotherapy on disease progression. The median OS was 32.3 months in the continuous group and 23.0 months in the switching group. Previous studies showed that the median OS in *EGFR*-mutated patients was between 21.0 and 30.9 months.[5,7–11]

In this study, we defined a PD based on Response Evaluation Criteria in Solid Tumors, which is originally used for cytotoxic chemotherapy. It may be inappropriate to use these criteria to evaluate a PD after use of a molecular-target agent. Jackman et al.[29] proposed a clinical definition of PD for EGFR-TKI, which was limited to the status within the last 30 days while on continuous treatment with EGFR-TKI after obtaining objective clinical benefit from the treatment. According to this definition, if tumors are not growing rapidly in 30 days, continuing EGFR-TKI treatment would be a reasonable option. How to evaluate a PD after EGFR-TKI use will be critical, and we need to verify whether this definition is useful in clinical practice.

In conclusion, continuation of EGFR-TKI beyond PD is one of the choices after the failure of EGFR-TKI treatment in patients with activating *EGFR* mutations. Further evaluation of the treatment after the failure of EGFR-TKI will be needed in a prospective study in the future.

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