Treatment Outcomes in Patients with Atypical *EGFR*-positive Non-small Cell Lung Cancer in Nagano Prefecture, Japan

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Background : This study was performed to evaluate clinical practices in patients with atypical epidermal growth factor receptor (*EGFR*)-positive inoperable non-small cell lung cancer (NSCLC) in Nagano Prefecture, Japan.

Patients and methods : Patients with newly diagnosed atypical *EGFR*-positive inoperable NSCLC in 14 hospitals in Nagano, Japan, between May 2016 and March 2019 were enrolled in this study. Atypical *EGFR* mutations included G719X, S768I, L861Q, compound mutations, and coexistence of de novo T790N in this study. After registering baseline clinical characteristics and initial treatment, serial data were recorded every 4 months in each patient. Initial and serial therapies were at the discretion of the attending physician.

Results : The study population consisted of 24 patients with atypical *EGFR*-positive NSCLC (12 men and 12 women ; median age : 78.5 years ; range : 49-89 years). Fourteen patients had single G719X, S768I, or L861Q mutation and 10 had compound *EGFR* mutations. Performance statuses 0/1/2/3/4 were seen in 11/7/3/2/1 cases and clinical stage I/II/III/IV/ recurrence occurred in 1/0/0/15/8 cases, respectively. One patient with clinical stage IA was treated with radiotherapy. Other patients were treated with EGFR-tyrosine kinase inhibitors (TKIs) as first ($n = 21$) or second ($n = 2$)-line therapy, and the response rate to TKIs was 56.5 %. Median overall survival was 23.9 months (95 % confidence interval [CI] : 10.2 months to NA) in atypical *EGFR*-positive cases.

Conclusion : The present results reveal that clinical outcomes in patients with atypical *EGFR*- positive NSCLCs in Nagano prefecture were comparable with those in other clinical trials and studies. *Shinshu Med J 70 : 397—405, 2022*

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Key words : EGFR-TKI, non-small cell lung cancer, compound mutation, uncommon mutation, T790M

I Introduction

Lung cancer is the most common type of cancer and the leading cause of cancer mortality worldwide[1], including Japan[2)3)]. Non-small cell lung cancer (NSCLC) is the most frequent histological type, and non-squamous NSCLC is the predominant histological subtype[3]. Molecular targeted agents, such as epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) have markedly improved overall survival in populations harboring these targetable genetic

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alterations[4)-7)]. Indeed, gefitinib and erlotinib (first-generation EGFR-TKI), afatinib (second-generation EGFR-TKI), and osimertinib (third-generation EGFR-TKI) have been widely used in clinical practice.

L858R mutations and exon 19 deletions represent the most common classical *EGFR* mutations in patients with NSCLC, accounting for 80 %-90 % of *EGFR* mutations[8)9)], and numerous clinical studies have demonstrated the usefulness of EGFR-TKIs in these patients[4)-7)]. Other *EGFR* mutations are designated as uncommon mutations, and account for 10 %-20 % of all *EGFR* mutations[9)-13)]. The sensitivity of uncommon *EGFR* mutations to EGFR-TKIs is highly heterogeneous. Patients harboring one group of uncommon, recurrent *EGFR* mutations (G719X, S768I, L861Q) respond to EGFR-TKIs, referred to as sensitive uncommon *EGFR* mutations[9)-13)]. However, it has been shown that the efficacy of EGFR-TKIs in patients with sensitive uncommon *EGFR* mutations is low compared with classical common *EGFR* mutations[9)-13)], Furthermore, uncommon *EGFR* mutations were observed as single and compound *EGFR* mutations[14)-16)]. Compound *EGFR* mutations have also been observed even in cases of common L858R mutations and exon 19 deletions[15)16)]. In particular, the combination of T790M mutations, acquired resistance to first- or second-generation EGFR-TKIs[17)], accounts for 0.5 % of TKI-naïve NSCLC patients, and survival data for such cases are lacking[18)]. Thus, information about the clinical efficacy and/or practice data in these atypical *EGFR* mutations are still insufficient, and therapeutic strategies are still challenging for this population.

We performed a prospective and multicenter observational study to determine the treatment patterns and outcomes of treatment-naïve patients with newly diagnosed inoperable *EGFR*-positive NSCLC in Nagano prefecture, Japan[14)]. Here, we selected and summarized daily practice data on clinical and treatment outcomes of patients with sensitive uncommon and/or combined *EGFR*-positive NSCLCs in Nagano prefecture, Japan.

Ⅱ Materials and Methods

A Patients and data collection

Registration of eligible patients for this prospective study was conducted centrally at the Shinshu Cancer Center, Shinshu University Hospital. Patients with histologically or cytologically proven *EGFR*-positive and inoperable NSCLC newly diagnosed between May 6, 2016, and March 31, 2019, with no history of prior therapy or recurrence after thoracic surgery were eligible for inclusion in the study. To avoid selection bias at the time of enrollment, patients who were eligible for this study were enrolled in a consecutive and sequential manner in each participating hospital. Patients were anonymized before registration in participating hospitals, and their anonymous data were collected from serial case report forms. Data were collected on baseline demographic and clinical characteristics, including age, sex, smoking history, performance status (PS), histology, and clinical stage. Fourteen hospitals in Nagano prefecture participated in the present study **(Table 1)**. The study protocol was approved by the institutional review board of Shinshu University (Approval No. 3407, 10/May/2016, UMIN000003645) and the ethics committee of each participating hospital. The histological diagnosis and stage of NSCLC were based on the World Health Organization (WHO) classification (version 7 until 2016 and version 8 from 2017). PS was estimated according to the Eastern Cooperative Oncology Group (ECOG) classification.

EGFR mutations were analyzed by polymerase chain reaction (PCR) or direct sequencing methods in each hospital or laboratory center. Patients with any type of *EGFR* mutation were registered and a flow diagram for selection of patients for enrollment in the study is shown in **Fig. 1**. Patients with G719X, S768I, and L861Q single mutations and combined with common exon 19 deletion and exon 21 L858R were selected for inclusion in the present study. In addition, those with combined *EGFR* mutation and T790M in exon 20 and other rare types were also enrolled into the present study. These *EGFR* mutations were classified as atypical in this study. Treatment and

choice of TKI were determined at the discretion of the attending physician. The types of drugs given as initial treatment were also registered at baseline. The response, toxicities, subsequent therapy, and clinical outcomes were recorded every 4 months. Patient privacy was protected when using individual information.

B Analysis and statistics

The analysis of survival was locked on May 31, 2022. Overall survival (OS) was defined as the interval from the initial date of induction therapy to the date of death or the last follow-up visit. Kaplan-Meier plots were used for OS analyses and the median and 95 % confidence interval (CI) were determined. Statistical analysis was performed using NZR Statistics.

Ⅲ Results

A Clinical characteristics

There were 281 *EGFR*$^{+}$ NSCLC patients in Nagano

Table 1 Participating hospitals

Hospital	Department
Nagano Municipal Hospital	Department of Pulmonary Medicine
Nagano Red Cross Hospital	Department of Pulmonary Medicine
Nagano Prefectural Shinshu Medical Center	Department of Thoracic Surgery
Nagano Matsushiro General Hospital	Department of Pulmonary Medicine
Minami Nagano Iryou Center, Shinonoi Hospital	Department of Pulmonary Medicine
Shinshu Ueda Medical Center	Department of Pulmonary Medicine
Saku Central Hospital Advanced Care Center	Department of Pulmonary Medicine
Aizawa Hospital	Department of Pulmonary Medicine
Shinshu University Hospital	First Department of Internal Medicine, Medical Oncology
Suwa Red Cross Hospital	Department of Pulmonary Medicine
Ina Central Hospital	Department of Pulmonary Medicine, Department of Thoracic Surgery
Showa Inan General Hospital	Department of Thoracic Surgery
Iida Municipal Hospital	Department of Pulmonary Medicine
Iida Hospital	Department of Thoracic Surgery

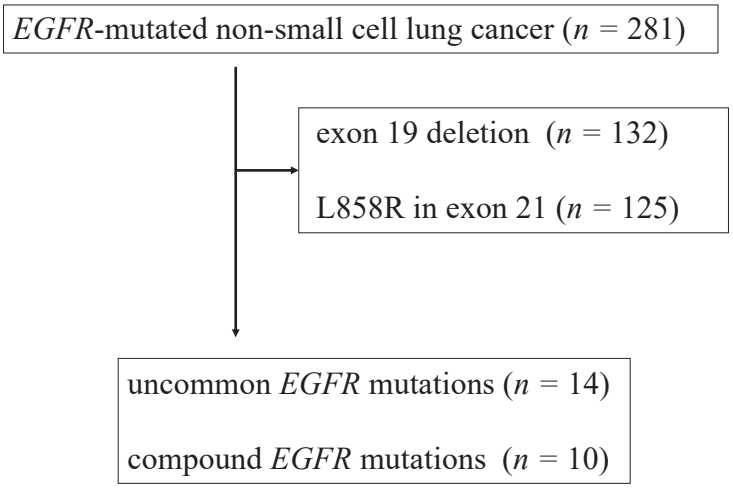

Fig. 1 Flow diagram in the present study

Table 2 Characteristics of patients with atypical epidermal growth factor receptor (*EGFR*)-positive inoperable non-small cell lung cancer (NSCLC) in the present study

Patients (N = 24)			
Median age	78.5 years (49 – 89)	Type of Atypical *EGFR* mutations	
Sex		G719X	8
Male	12	L861Q	4
Female	12	S768I	2
Performance Status		L858R + S768I	2
0/1/2/3/4	11/7/3/2/1	L858R + T790M	3
Smoking status		Del19 + G719X	1
Never smoked	14	Del19 + T790M	2
Ex-smoker	9 BI 962 (400-1720)	Del19 + E746-A750del(2236-2250)	1
Current smoker	1 BI 210	Exon19-duplication (K739-1744duplication)	1
Histology		Site of metastasis	
Adenocarcinoma	22	Bone	8
Adenosquamous cell cacinoma	2	Pleura	8
		Lung	4
		Brain	3
		Adrenal gland	2
		Liver	2
		Muscle	1
		Pancreas	1
		Skin	1

prefecture between May 6, 2016, and March 31, 2019. Among them, 24 patients with atypical *EGFR*-positive NSCLC (12 men and 12 women ; median age : 78.5 years ; range : 49-89 years) were analyzed in this study **(Fig. 1)**. Fourteen patients had single G719X, S768I, or L861Q mutation and 10 had combined *EGFR* mutations. The clinical characteristics are summarized in **Table 2**. Eleven patients were classified as PS 0, 7 as PS 1, 3 as PS 2, 2 as PS 3, and 1 as PS 4. Histological type was adenocarcinoma in most cases (22 cases), and two cases had adenosquamous carcinoma. The clinical stages were metastatic stage (stage IV : 15 cases, 62.5 %), recurrence after surgery (8 cases, 24.9 %), and stage 1 (stage 1A, one case). Metastatic sites included bone ($n = 8$), pleura ($n = 8$), intrapulmonary ($n = 4$), and brain ($n = 3$), etc.

B First-line treatment choice and serial treatments

The first-line therapy in atypical *EGFR*-positive NSCLCs is summarized in **Table 3**. In first-line therapy, EGFR-TKI was used in 21 cases. Gefitinib and afatinib were used in 8 cases, respectively and followed by osimertinib in 4, and erlotinib in 1. One patient with stage I disease was treated with radiotherapy. Two patients with compound *EGFR* mutation were initially treated with platinum-based chemotherapy followed by EGFR-TKI as second-line therapy. Twenty-three patients, with the exclusion of one patient with stage I disease, received EGFR-TKIs. Complete response was achieved in two cases and partial response was obtained in 11 cases, resulting in an overall response rate (ORR) of 56.5 %. Gefitinib and afatinib were used in two cases each after cisplat-

Table 3 Initial therapy in patients with atypical epidermal growth factor receptor (*EGFR*)-positive inoperable non-small cell lung cancer (NSCLC) in the present study

Single mutation ($n=14$)		
Gefitinib	3	
Erlotinib	1	
Afatinib	7	
Osimertinib	2	
Radiation	1	
Compound mutation ($n=10$)		with T790M ($n=5$)
Gefitinib	5	2
Afatinib	1	1
Osimertinib	2	1
Cytotoxic chemotherapy	2	1

in-based chemotherapy, but the response was stable disease in both cases.

The sequences of serial treatment in each case are shown in **Fig. 2**. Ten patients received only first-line EGFR-TKI and six of these patients died. First-line EGFR-TKI treatment has been continued in four cases, both of whom remain alive without recurrence. Second-line therapy after front line EGFR-TKIs was performed in 10 cases, with a switch to another EGFR-TKI in 5 cases, platinum-doublet cytotoxic chemotherapy in 3 cases, monotherapy in 1 case, and immune checkpoint inhibitor in 1 case **(Fig. 2)**.

Five patients were treated with third- and fourth-line therapy, respectively. One patient was treated until eighth-line therapy.

C Survival

The median observation time was 23.9 months (range : 6.0-62.3 months). Survival curves in all cases of atypical *EGFR*-positive NSCLC are shown in **Fig. 3**. Median OS in all subjects was 23.9 months (95 % CI : 10.2 to NA months) and there was no significant difference between uncommon and compound *EGFR* +NSCLC (27.9 months [95 %CI ; 7.4 to NA months] vs. 20.7 months [95 % CI, 8.7 to NA months] ; $P=0.54$, log-rank test).

Ⅳ Discussion

This study examined clinical practice in patients with atypical *EGFR*-positive NSCLCs in Nagano prefecture, Japan. A total of 281 patients with *EGFR*-positive NSCLCs were treated between May 2016 and March 2019. In the present study, we selected 14 sensitive uncommon and 10 compound *EGFR* mutations, including those combined with de novo T790M, and reviewed their clinical outcomes. The population (24/281 cases, 8.5 %) and median OS were similar to previous studies[10)-13)].

Wu et al.[11)] reported that objective responses to gefitinib or erlotinib (first-generation EGFR-TKIs) were observed in 57.1 % of patients with Gly719 or Leu861 mutations, with an OS of 16.4 months. Yang et al.[12)] reported post hoc analysis of afatinib data from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trial populations. The ORR of afatinib was 71 % and the median progression free survival (PFS) and OS were 11 months and 19.4 months, respectively. Furthermore, a phase II study in Korea[13)] showed an ORR of osimertinib for uncommon *EGFR*-positive NSCLC of 50 % (18 of 36 patients) and median PFS of 8.2 months, although the study included four *EGFR*-positive mutations in addition to G719X, S768I, and L861Q. Thus, the higher response rate and prolonged survival with afatinib was validated in a larger number of patients using real-world data. However, the optimal TKI for uncommon *EGFR*-positive NSCLC was still unclear because of the small sample sizes

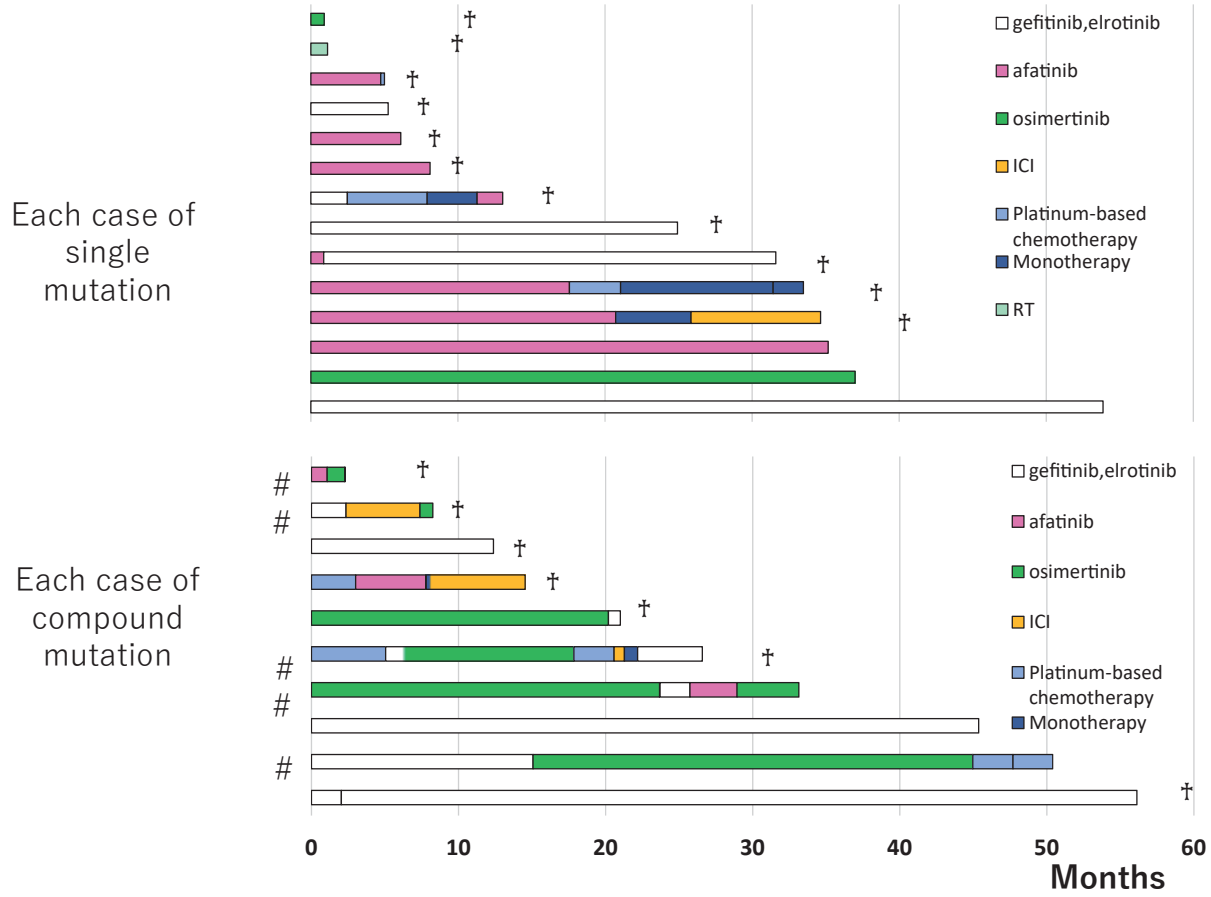

Fig. 2 Serial treatment and outcomes in each case. Each colored bar indicates the treatment intervals of various therapies in each case.
+ ; time of death. # ; case of compound epidermal growth factor receptor (*EGFR*) mutation with T790M. ICI ; immune-check point inhibitors, RT ; radiotherapy.

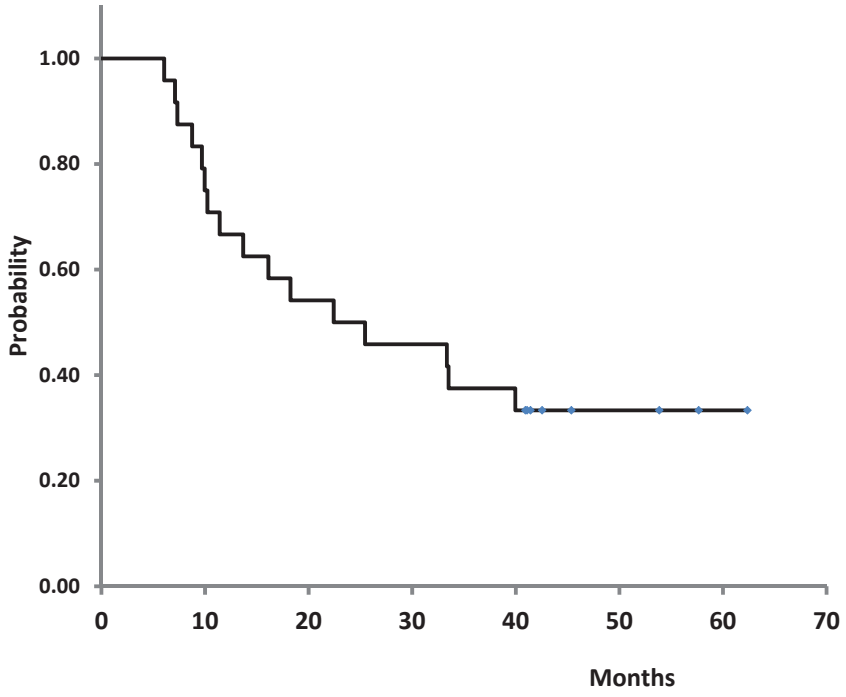

Fig. 3 Kaplan-Meier plot of overall survival after initial therapy in patients with atypical epidermal growth factor receptor mutated non-small cell lung cancer.

and different patient backgrounds in each study. Indeed, afatinib was used in the present study in first-line and subsequent therapy. The response rate of 56.5 % in the present study was similar to previous studies[10)-13)]. Although six cases were treated with only first-line therapy, subsequent therapies were continued in 14 cases. Clinical practice analysis revealed that OS in the present study was 23.9 months, which was longer than in previous studies, suggesting that patients with atypical *EGFR* positive NSCLCs in Nagano prefecture were appropriately treated in terms of clinical practice.

Several clinical studies indicated that patients harboring compound mutations or double uncommon mutations showed better clinical outcomes than those with a single uncommon mutation. Si et al.[10)] summarized the treatment outcomes in 132 cases of uncommon *EGFR*-positive NSCLC and reported that patients with compound mutations and double uncommon *EGFR* mutations had longer OS than those with a single uncommon *EGFR* mutation, although the difference was not significant. Chiu et al.[19)] analyzed 19 patients with double uncommon *EGFR* mutations and found significant differences in PFS between those with double uncommon *EGFR* mutations and those with a single uncommon mutation (11.9 vs. 6.5 months, respectively ; $P=0.010$). There was no significant difference in OS between duplicated and single mutation in the present study. Recently, next-generation sequencing (NGS)-based molecular tests have become available in clinical practice, and their sensitivity may facilitate the application of single companion diagnostics (CDx) methods[19)20)]. Several case reports and studies indicated the presence of compound *EGFR* mutation by NGS-based profiling that were negative by single CDx, suggesting the limitation of single CDx for detecting compound mutations[20)-22)]. We would like to emphasize the submission of NGS-based molecular tests in cases without known biomarkers in NSCLC using companion tests.

There were five cases with primary *EGFR* T790M mutation in the present study. As osimertinib was developed to overcome the acquired T790M mutated NDCLCs[5)], it may be considered the first choice for treatment in patients with de novo T790M mutation. However, this agent became available in Japan for first-line therapy in 2018. Therefore, various therapies were selected in our case series with de novo T790M-positive NSCLC. Initial therapy was as follows : gefitinib in two cases, afatinib in one case, osimertinib in one case, and cytotoxic chemotherapy including cisplatin, pemetrexed, and bevacizumab in one case each. Osimertinib was used as second-line ($n=2$) and third-line ($n=2$) line therapy. In addition, re-challenge with osimertinib was performed in two cases. Five patients showed survival of 7.3 months (dead), 10.0 months (dead), 33.3 months (dead), 40.9 months (currently alive), and 57.7 months (currently alive). A recent study showed that patients who received sequential treatment with first- and second-generation EGFR-TKIs followed by osimertinib had longer median OS (37.3 months) than patients without subsequent osimertinib treatment (23.0 months) or those treated with osimertinib alone (8.2 months)[23)]. Further clinical experience is needed to verify the best sequence of TKIs for treatment of de novo T790M-positive NSCLC.

This study had several limitations. First, there were no detailed data regarding molecular biomarker testing rates in participating hospitals and *EGFR* testing methods differed between participating hospitals. The detection rates of de novo T790M and uncommon *EGFR* mutation depend on the sensitively of methods used for *EGFR* testing. Therefore, our results do not reflect actual clinical practice with atypical *EGFR*-positive NSCLC, including molecular profile testing rate. Second, we did not have data on dose reduction and/or suspension of each TKI. Therefore, physician treatment bias may have affected our clinical outcomes. Nevertheless, the present results provide references for clinical practice in treatment of patients with atypical *EGFR*-positive NSCLC.

In conclusion, the results presented here reveal the clinical outcome data in patients with atypical *EGFR*-positive NSCLC in Nagano prefecture, Japan. Although these clinical results were based on observational analyses, our clinical practice for atypical

EGFR-positive NSCLC in Nagano prefecture was comparable to those in other clinical studies.

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Disclosure of Potential Conflicts of Interest

The authors have no conflicts of interest to disclose.

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