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Real world treatment and outcomes in *EGFR* mutation-positive non-small cell lung cancer: Long-term follow-up of a large patient cohort

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ABSTRACT

Objectives: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been shown to be effective for the treatment of *EGFR* mutation-positive non-small cell lung cancer (NSCLC) in clinical trials. However, there is a lack of data from routine clinical practice. This study determined treatment and outcomes in patients with *EGFR* mutation-positive NSCLC treated in a real world setting.

Materials and methods: Clinical characteristics, information about NSCLC treatment regimens and survival outcomes data were obtained retrospectively from 17 medical centers across Japan. In addition to overall survival (OS), subgroup analyses were conducted based on first- and second-line treatments and combinations, and for patients who had survived > 5 years from initiation of first-line treatment.

Results: The full analysis set comprised 1656 patients (mean 67 years, 80.6% with performance status 0 or 1). Median follow-up was 29.5 months and median OS was 29.7 months; 3- and 5-year survival rates were 41.2% and 21.5%, respectively. Significant predictors of OS were younger age, no smoking history, histological diagnosis of adenocarcinoma, less advanced clinical stage, good performance status and major *EGFR*-activating mutation. Despite some imbalances in baseline characteristics, patients who received first-line chemotherapy had numerically higher 5-year survival rates than those who received first-line EGFR-TKIs.

Conclusions: This large, long-term analysis of *EGFR* mutation-positive NSCLC patients provides useful information about treatment outcomes in clinical practice. Updated analyses are required to determine real world outcomes for NSCLC patients treated with the latest available agents, including immunotherapies.

1. Introduction

Previous clinical studies, including several phase III trials, have shown that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are superior to chemotherapy in terms of progression-free survival and objective response rate [1–8]. Based on these data, EGFR-TKIs are now recommended as first-line treatment for *EGFR* mutation-positive NSCLC by major international and Japanese clinical guidelines [9–11]. However, there are many patient groups encountered in clinical practice that do not meet the stringent inclusion criteria required for participation in clinical trials. Therefore, the effectiveness of EGFR-TKIs in patients treated in the real world setting remains unclear. Furthermore, although some *EGFR* mutation-positive NSCLC patients survive over the long term, most clinical trials do not

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor

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include detailed data on long-term survivors because of relatively short follow-up periods.

There is no doubt that EGFR-TKIs are important therapeutic agents for the treatment of *EGFR* mutation-positive NSCLC patients. However, there is uncertainty around how chemotherapies are used and for how long. In addition, the contribution of different chemotherapies to overall survival is not clearly understood. To address these important clinical questions, this study determined treatment and outcomes in a large group of patients with *EGFR* mutation-positive NSCLC managed in a real world clinical setting.

2. Materials and methods

This retrospective study was conducted at 17 medical centers across Japan (clinical trial registration: NCT02475720). The study was approved by the institutional review boards or ethics review boards at each site and conducted in accordance with the Declaration of Helsinki. This research was defined as a study without human samples by the Japanese guidelines presented by the Ministry of Health, Labour and Welfare: 'Ethical guidelines for epidemiologic research, dated 17 June 2002', 'Ethical guidelines for clinical research, dated 30 July 2003' and 'Ethical guidelines for medical research involving human subjects, dated 22 December 2014'. Therefore, written informed consent was not required.

2.1. Patients

All patients had *EGFR* gene mutation-positive NSCLC diagnosed by histology or cytology samples and started first-line treatment between January 2008 and December 2012. Those treated with agents that were not approved in Japan as of 31 December 2014 were excluded from the current analysis.

2.2. Data collection

Clinical data were collected from the medical records of each patient. This included patient characteristics (date of NSCLC diagnosis, sex, age at the time of diagnosis, histological diagnosis, clinical staging at initial diagnosis, distant metastasis organ, Eastern Cooperative Oncology Group [ECOG] performance status [PS], smoking history, type of *EGFR* mutation); survival data (status as at the end of December 2015, date of death or date of last follow-up); and information about NSCLC treatments (regimens, date of first dose, date of last dose, PS at the start of each treatment regimen, best response for each treatment regimen, reason for treatment discontinuation or change of treatment regimen, presence or absence of radiotherapy and target region for radiotherapy, presence or absence of brain metastasis, date of progressive disease [PD]). PD was defined according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 or clinical PD.

2.3. Grouping of treatment regimens

For analysis of treatments, regimens were categorized into the following three groups: 1) EGFR-TKIs (EGFR-TKI as monotherapy or in combination with other agents), 2) chemotherapy (platinum- or non-platinum-based combination chemotherapy [excluding combinations including EGFR-TKIs]) and 3) other (any treatment that did not fall into the other two groups, e.g., bevacizumab monotherapy).

2.4. Statistical analysis

Overall survival (OS) was defined as the interval from the date of first dose of first-line treatment until the date of death. Patients lost to follow-up were censored at the date they were last known to be alive. Time-to-event data were calculated as median values with 95% confidence intervals (CI). Survival analysis was performed using the Kaplan–Meier method.

The influence of patient characteristics on OS was assessed using univariate and multivariate Cox regression analysis. For the multivariate full model, which included all items as explanatory variables, variants were selected by the backward elimination method. Analyzed factors were year of diagnosis, year first-line treatment was started, sex, age, histological diagnosis, *EGFR* mutation type, clinical stage, PS, smoking history and type of first-line treatment. In addition, a post-hoc analysis was conducted in the 799 patients who started first-line treatment before 31 December 2010 (i.e., prior to > 5 years before the data cut off)—multiple logistic regression analysis was used to compare 5-year survivors in this group with other patients.

Average cumulative periods of three treatment options (EGFR-TKIs, chemotherapy and no treatment [drug holidays]) were calculated and differences for each period between patients who received first-line EGFR-TKIs compared with first-line chemotherapy were assessed using the Wilcoxon test.

Median survival time and 5-year survival rate by first- and second-line treatment sequences were calculated in patients for whom sufficient clinical data on first- and second-line treatment were available. In an exploratory analysis, the inverse probability of treatment weighting using the propensity score calculated from data before, during and after first-line treatment was determined and OS rates for patients in each group were estimated.

3. Results

3.1. Patient characteristics and EGFR-TKI treatment

A total of 1660 *EGFR* mutation-positive advanced NSCLC patients were enrolled in the study. After excluding four ineligible patients, 1656 patients were included in the full analysis set (FAS) (Fig. 1). Baseline demographics and clinical characteristics of included patients are summarized in Table 1. The number of patients who received second-line, third-line, and fourth-line therapy were 1192 (72.0%), 800 (48.3%), and 490 (29.6%), respectively. Of the 1656 patients, 1608 (97.1%) received at least one EGFR-TKI in any treatment line. The first administered EGFR-TKI was gefitinib in 1347 (81.3%) patients, erlotinib in 245 (14.8%) patients, and afatinib in 16 (1.0%) patients.

3.2. Overall survival

Median follow-up was 29.5 months, and median OS was 29.7 months (95% CI 28.1–31.4). From the start of first-line treatment, 3- and 5-year survival rates were 41.2% (95% CI 38.7–43.7) and 21.5% (95% CI 19.1–23.9), respectively (Supplementary Fig. S1). In patients with stage IV disease (n = 1104), median OS was 25.2 months (95% CI 23.8–26.4), and 3- and 5-year survival rates from the start of first-line treatment were 32.0% (95% CI 29.1–35.0) and 13.8% (95% CI 11.4–16.5), respectively. On multivariate final model Cox regression analysis, younger age (< 75 years), no smoking history, histological diagnosis of adenocarcinoma, less advanced clinical stage, good PS and major *EGFR*-activating mutation were identified as significant predictors of OS (Table 2). The mean survival times of patients with exon 19 deletion (n = 814) and the L858R mutation (n = 666) were 31.87 and 28.27 months, respectively (data not shown).

3.3. Overall survival by treatment sequences

A total of 1055 patients were included in the analysis of OS by the sequence of first- and second-line treatment (see Fig. 1 for details of exclusions). In patients treated with first-line EGFR-TKIs and second-line chemotherapy, 87.8% (295/336) changed treatment because of disease progression, and 74.1% (249/336) received platinum-based combination chemotherapy as second-line treatment. In the group

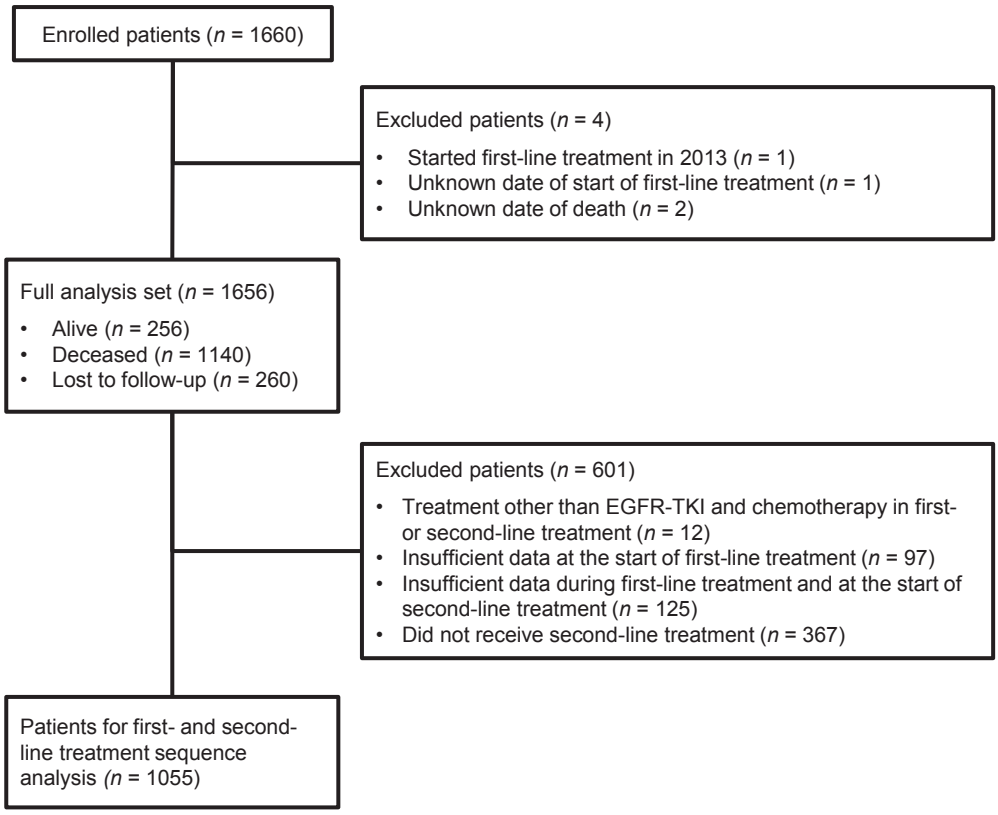

Fig. 1. Study flow diagram.

Table 1
Patient characteristics.

Characteristics		All (N = 1656, 100.0%)
Age (at start of first treatment: years)	Median (range)	67.0 (27–97)
Sex	Male	583 (35.2%)
	Female	1073 (64.8%)
Smoking history	Smoker	645 (38.9%)
	Non-smoker	981 (59.2%)
	Unknown	30 (1.8%)
Histology	Adenocarcinoma	1576 (95.2%)
	Others	80 (4.8%)
Clinical stage	IV	1104 (66.7%)
	IIIB	125 (7.5%)
	Post-operative recurrence	427 (25.8%)
PS	0	654 (39.5%)
	1	680 (41.1%)
	2	117 (7.1%)
	3	81 (4.9%)
	4	12 (0.7%)
	Unknown	112 (6.8%)
EGFR mutation type	Del19	814 (49.2%)
	L858R	666 (40.2%)
	Del19 + L858R	7 (0.4%)
	Others	169 (10.2%)
Presence of brain metastasis	Yes	489 (29.5%)
	No/Unknown	1167 (70.5%)
Number of metastatic organs	0	288 (17.4%)
	1	726 (43.8%)
	2	353 (21.3%)
	More than 3	289 (17.5%)

treated with EGFR-TKIs for first- and second-line therapy, 63.7% (142/223) switched treatment because of disease progression. The most common EGFR-TKI switch was from gefitinib to erlotinib (78.9%, 176/223). No patients received a third-generation EGFR-TKI because none were authorized during the study period. Among patients treated with chemotherapy in both first- and second-line, 69.5% (41/59) went on to receive EGFR-TKIs as third-line treatment. Median survival times were similar for the different patient groups based on first- and second-line treatment sequences (Fig. 2). Five-year survival rates were higher in patients who received first-line chemotherapy than those who received first-line EGFR-TKIs (Fig. 2), although there were several imbalances in characteristics among patient groups (Supplementary Table S1).

In the post-hoc analysis comparing patients with > 5 years' follow-up, first-line treatment with chemotherapy, female sex, less advanced clinical stage and good PS were significantly associated with survival for more than 5 years (Table 3).

3.4. Treatment periods analysis

Additionally, the treatment period was analyzed by categorizing patients into two groups based on the type of first-line therapy. The average cumulative period of EGFR-TKIs, chemotherapy and no treatment (drug holidays) were calculated and compared between patients who received first-line EGFR-TKIs versus first-line chemotherapy. The average EGFR-TKI treatment period was significantly longer, and average chemotherapy and "no treatment" periods significantly shorter in patients who received first-line EGFR-TKIs compared with first-line chemotherapy (Table 4).

4. Discussion

To the best of our knowledge, this is the largest real world survival analysis of *EGFR* mutation-positive NSCLC patients (1140 deaths confirmed in 1656 patients). In addition, long-term follow-up data were available (median 25.5 months, maximum 96 months) Furthermore,

Table 2
Cox regression analysis of prognostic factors for overall survival.

Item	Category	*N*	Number of Deaths (%)	Univariate Model			Multivariate Full Model, Backward Elimination $P < 0.05$		
				Hazard Ratio		[Item *p* Value]	Hazard Ratio		[Item *p* Value]
				Point Estimation	95% CI	Category *p* Value	Point Estimation	95% CI	Category *p* Value
Age (years)	< 75	1180	819 (69.4%)	Reference	–	[0.009]	Reference	–	[< 0.001]
	≥75	472	319 (67.6%)	1.222	(1.074, 1.391)	0.002	1.318	(1.155, 1.505)	< 0.001
	Unknown	4	2 (50.0%)	0.837	(0.209, 3.353)	0.802	1.278	(0.316, 5.160)	0.731
Smoking history	Non-smoker	981	651 (66.4%)	Reference	–	[0.074]	Reference	–	[0.004]
	Smoker	645	469 (72.7%)	1.147	(1.019, 1.292)	0.023	1.223	(1.084, 1.380)	0.001
	Unknown	30	20 (66.7%)	0.999	(0.640, 1.560)	0.997	0.920	(0.584, 1.450)	0.719
Histology	Adenocarcinoma	1576	1079 (68.5%)	Reference	–	–	Reference	–	–
	Others	80	61 (76.3%)	1.722	(1.330, 2.230)	< 0.001	1.955	(1.503, 2.543)	< 0.001
Clinical stage	IV	1104	830 (75.2%)	Reference	–	[< 0.001]	Reference	–	[< 0.001]
	IIIB	125	81 (64.8%)	0.569	(0.452, 0.715)	< 0.001	0.532	(0.422, 0.671)	< 0.001
	Post-operative recurrence	427	229 (53.6%)	0.463	(0.400, 0.537)	< 0.001	0.500	(0.429, 0.583)	< 0.001
PS	0	654	406 (62.1%)	Reference	–	[< 0.001]	Reference	–	[< 0.001]
	1	680	505 (74.3%)	1.612	(1.414, 1.838)	< 0.001	1.478	(1.294, 1.687)	< 0.001
	2, 3, 4	210	164 (78.1%)	3.764	(3.126, 4.533)	< 0.001	3.264	(2.700, 3.945)	< 0.001
	Unknown	112	65 (58.0%)	0.956	(0.736, 1.242)	0.735	0.971	(0.744, 1.266)	0.826
EGFR mutation type	Del19	814	543 (66.7%)	Reference	–	[0.004]	Reference	–	[0.014]
	L858R	666	464 (69.7%)	1.147	(1.013, 1.298)	0.030	1.111	(0.981, 1.260)	0.098
	Del19 + L858R	7	5 (71.4%)	2.029	(0.841, 4.896)	0.115	2.563	(1.038, 6.327)	0.041
	Others	169	128 (75.7%)	1.353	(1.116, 1.641)	0.002	1.279	(1.053, 1.553)	0.013

Factors included in the model were year of diagnosis, the year first-line treatment was started, sex, age, histological diagnosis, epidermal growth factor receptor (EGFR) mutation type, clinical stage, performance status, smoking history, and type of first-line treatment.

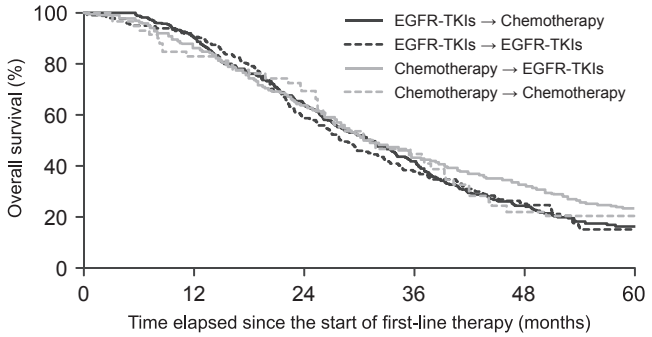

Fig. 2. Kaplan-Meier Curve, median survival time and 5-year survival rate in patient subgroups based on first- and second-line treatment sequences.

this analysis included a large proportion of frail patients who would likely have been excluded from clinical trials (e.g., those with poor PS). The inclusion of patients from a large number of centers means that the results are applicable across a range of clinical practice settings.

Although the current standard first-line treatment for *EGFR* mutation-positive patients is EGFR-TKI monotherapy, approximately one-third of patients included in our study actually received chemotherapy as first-line treatment. Of these, approximately 60% had started first-line treatment by the end of 2010. The results of the majority of the randomized controlled phase III trials showing the superiority of EGFR-TKIs versus chemotherapy with respect to progression-free survival in *EGFR* mutation-positive NSCLC patients were reported later than 2010, and first-line EGFR-TKI treatment only became standard after that. This is likely to be the reason so many patients in our study received first-line chemotherapy.

Our data showed that 5-year survival rates for patients treated with first-line chemotherapy were numerically higher than those treated with first-line EGFR-TKIs. Even after adjustment for imbalances of baseline patient characteristics by multivariate analysis, first-line treatment of chemotherapy was associated with > 5-year survival (Table 3). This could be for several potential reasons. First, transition rates from first-line to second-line were different between patients who received initial therapy with EGFR-TKIs compared with chemotherapy: 93% of those who received first-line chemotherapy went on to receive second-line treatment, but < 60% of those initially treated with EGFR-TKIs received second-line treatment. Furthermore, over half of first-line EGFR-TKI-treated patients did not receive chemotherapy at any time throughout their treatment. As a result, the duration of chemotherapy treatment was significantly shorter in patients who received first-line EGFR-TKIs compared with those who had first-line chemotherapy. This

Table 4
Average treatment duration for patient subgroups based on therapy type.

Average Treatment Period, Months	First-Line Treatment		
	EGFR-TKIs	Chemotherapy	Wilcoxon Test
EGFR-TKIs	17.9	15.9	$p < 0.001$
Chemotherapy	2.9	7.3	$p < 0.001$
No treatment (including drug holidays)	4.6	8.7	$p < 0.001$

The patients whose data on treatment period were not sufficient and who received treatment other than EGFR-TKIs and chemotherapy were excluded (five patients of first-line EGFR-TKIs group, 10 patients of first-line chemotherapy group). Chemotherapy, platinum-based or non-platinum-based chemotherapy; EGFR-TKIs, monotherapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) or combination therapy including an EGFR-TKI.

suggests that many patients who received first-line EGFR-TKIs may have missed the opportunity to receive chemotherapy because they continued taking EGFR-TKIs for too long after disease progression. As documented in several studies [12–14], chemotherapy is also a potential option for *EGFR* mutation-positive NSCLC patients after first-line EGFR-TKI treatment. Therefore, chemotherapy should be considered as an option following disease progression after first-line EGFR-TKI treatment, although specific treatments targeting the different mechanisms of drug resistance that arise are desirable [15].

Although no patients received a third-generation EGFR-TKI in the present study, the third-generation EGFR-TKI osimertinib is currently considered as a first choice for patients who carry the *EGFR* T790M mutation at disease progression after first-line EGFR-TKI treatment [16]. Considering these points, chemotherapy should be recommended as third-line treatment, immediately after osimertinib, in patients who carry the *EGFR* T790M mutation at disease progression after first-line EGFR-TKI therapy.

To explore the differences in overall survival among patient groups categorized by first-line and second-line treatment sequences, it was necessary to consider the imbalances of patient background among each group shown in Supplementary Table S1. The inverse probability of treatment weighting using the propensity score calculated from data before, during, and after first-line treatment was performed and overall survival times of patients in each group were estimated. However, no differences were observed among the point estimations of OS for each group (Supplementary Table S2).

In conclusion, *EGFR* mutation-positive NSCLC patients managed in real world clinical practice had long OS durations. Our findings showed that it is important not to miss the opportunity to use chemotherapy

Table 3
Multiple logistic regression analysis comparing patient survival 5 years after the initiation of first-line treatment.

Item	Category	Univariate Model			Multivariate Full Model, Backward Elimination $p < 0.05$		
		Odds Ratio		[Item p Value]	Odds Ratio		[Item p Value]
		Point Estimation	95% CI	Category p Value	Point Estimation	95% CI	Category p Value
Sex	Male	Reference	–	–	Reference	–	–
	Female	1.284	(0.848, 1.943)	0.237	1.819	(1.149, 2.881)	0.011
Clinical stage	IV	Reference	–	[< 0.001]	Reference	–	[< 0.001]
	IIIB	2.633	(1.426, 4.862)	0.002	2.153	(1.136, 4.081)	0.019
	Post-operative recurrence	4.570	(2.966, 7.040)	< 0.001	4.459	(2.802, 7.094)	< 0.001
PS	0	Reference	–	[< 0.001]	Reference	–	[< 0.001]
	1	0.396	(0.263, 0.598)	< 0.001	0.449	(0.292, 0.689)	< 0.001
	2, 3, 4	0.028	(0.004, 0.200)	< 0.001	0.039	(0.005, 0.290)	0.001
First-line treatment	EGFR-TKIs	Reference	–	–	Reference	–	–
	Chemotherapy	1.516	(1.029, 2.235)	0.036	1.854	(1.190, 2.888)	0.006

Factors included in the model were year of diagnosis, year first-line treatment was started, sex, age, histological diagnosis, *EGFR* mutation type, clinical stage, performance status, smoking history, and type of first-line treatment. Chemotherapy, platinum-based or non-platinum-based chemotherapy.

after EGFR-TKI treatment failure in order to maximize survival time in these patients. Since this study was conducted, a number of new treatment options have become available, including third-generation EGFR-TKIs and immune checkpoint inhibitors, which have further improved outcomes in *EGFR* mutation-positive NSCLC patients. Additional real world analyses are required to more clearly define the impact of these new agents on OS in the routine clinical practice setting.

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Author contributions

NT conceived the study. All authors designed the study. IO, FI, AI, TS, NY, YO, KN, and MF collected the data. SM analyzed the data. IO, SM, FI, AI, TS, NY, YO, KN, and MF interpreted the results. IO, SM, and NT drafted the manuscript with critical revisions from FI, AI, TS, NY, YO, KN, and MF. All authors approved the final version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.01.005.

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