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Real-world therapeutic effectiveness of lorlatinib after alectinib in Japanese patients with *ALK*-positive non-small-cell lung cancer

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Abstract

Alectinib, an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), is the recommended first-line treatment for *ALK*-positive non-small-cell lung cancer (NSCLC) in Japan. Lorlatinib was approved as a subsequent therapeutic option after progression while receiving ALK TKI treatment. However, data on the use of lorlatinib in the second- or third-line setting after alectinib failure are limited in Japanese patients. This retrospective real-world observational study investigated the clinical effectiveness of lorlatinib in second- or later-line settings after alectinib failure in Japanese patients. Clinical and demographic data collected in the Japan Medical Data Vision (MDV) database between December 2015 and March 2021 were used. Patients diagnosed with lung cancer who received lorlatinib following alectinib failure after the November 2018 marketing approval of lorlatinib in Japan were included. Of 1954 patients treated with alectinib, 221 were identified from the MDV database as receiving lorlatinib after November 2018. The median age of these patients was 62 years. Second-line lorlatinib treatment was reported for 154 patients (70%); third- or later-line lorlatinib treatment was reported for 67 patients (30%). The median duration of treatment (DOT) for all lorlatinib-treated patients was 161 days (95% confidence interval [CI], 126–248), and 83 patients (37.6%) continued treatment after data cut-off (March 31, 2021). Median DOTs of 147 days (95% CI, 113–242) and 244 days (95% CI, 109 to not reached) were reported with second-line and third- or later-line treatment, respectively. Consistent with clinical trial data, this real-world observational study supports data suggesting the effectiveness of lorlatinib after alectinib failure in Japanese patients.

KEYWORDS
anaplastic lymphoma kinase, carcinoma, Japan, lorlatinib, non-small-cell lung cancer, real-world clinical trials

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; DOT, duration of treatment; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; mDOT, median duration of treatment; MDV, Medical Data Vision; NSCLC, non-small-cell lung cancer; PEM, pemetrexed; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor.

1 | INTRODUCTION

Lung cancer is the leading cause of cancer death both worldwide[1] and among men in Japan.[2] Non-small-cell lung cancer accounts for approximately 80% of all lung cancers in Japan.[3] Approximately 4% of NSCLCs have rearrangements of the *ALK* gene; these rearrangements are considered to be oncogenic drivers and a therapeutic target for small-molecule TKIs.[4–6] The frequency of *ALK* gene rearrangements has been reported to be similar among Western and Asian populations.[5] Patients with *ALK*-positive NSCLC tend to be younger, tend to have more adenocarcinomatous histology, and are more likely to be nonsmokers compared with their *ALK*-negative counterparts.[5] Several ALK TKIs have been developed for use in *ALK*-positive NSCLC. At the time the present study was conducted, four ALK TKIs were approved as first-line treatment for *ALK*-positive NSCLC in clinical practice in Japan (crizotinib, alectinib, ceritinib, and lorlatinib).[7,8] Alectinib is widely recommended as first-line treatment for *ALK*-positive NSCLC based on the results of the J-ALEX study[7,9,10] and as such, is the most commonly used treatment in Japan.[7,11]

Lorlatinib is a highly potent, brain-penetrant, third-generation ALK TKI that, compared with other ALK inhibitors, has demonstrated broad activity against *ALK*-resistance mutations that develop following treatment with first-generation (crizotinib) or second-generation ALK inhibitors (alectinib, ceritinib).[12,13] Lorlatinib demonstrated potent antitumor activity after the failure of previous ALK inhibitor therapy in a global phase I/II study (NCT01970865), including in patients who had previously received either first-generation or second-generation ALK TKIs, or both.[14,15] The median PFS in patients who were previously treated with one second-generation ALK TKI was 5.5 months (95% CI, 2.7–9.0 months) with 7-month follow-up, and the updated follow-up period demonstrated to provide the longer mDOT after the second-generation ALK TKI.[15,16] Lorlatinib was approved in 2018 in Japan for second-, third-, or later-line treatment. Current clinical practice guidelines for lung cancer in Japan recommend lorlatinib as a subsequent therapeutic option for patients with *ALK*-positive NSCLC that has progressed after any ALK TKI treatment, including alectinib.[7] Other treatment options include other ALK TKIs not used in first-line treatment, and chemotherapy, which is often used in Japan after progression on an ALK TKI.[17]

Following the initial approval of lorlatinib in Japan, real-world data on the optimal ALK TKI sequence and the use of lorlatinib as second- or third-line treatment after failure of alectinib in clinical practice in Japan are limited, as alectinib has demonstrated high efficacy together with good tolerability over long-term use,[18] and *ALK*-positive NSCLC is relatively rare (approximately 4% of NSCLC).[5] For investigation of the benefits of lorlatinib, it is important to understand its postmarketing use and treatment patterns after alectinib failure in Japanese patients with *ALK*-positive NSCLC in real-world clinical practice. The Japan MDV database was established in 2003 and collects anonymized hospital-based data about inpatient and outpatient services provided in hospitals that use the diagnosis procedure combination/per-diem payment system as secondary data. The Japan MDV is able to reach a large patient population and collects over 1 million health claims per month; therefore, the large body of evidence in the Japan MDV can reflect the real-world landscape of diseases and treatments. The real-world data can be extracted and analyzed retrospectively by organizations, such as pharmaceutical companies and research institutions. Such analysis can provide insights into patient outcomes and drive advancement in research.[19] The objective of this study was to investigate the real-world clinical effectiveness of lorlatinib in second- or later-line settings after failure of alectinib, as well as understanding subsequent treatment patterns following lorlatinib, in Japanese patients with *ALK*-positive NSCLC.

2 | MATERIALS AND METHODS

2.1 | Study design

The Japan MDV is a hospital-based data source that describes demographics, diagnoses, inpatient and outpatient encounters, medical practices, medications, and laboratory tests. The Japan MDV was the data source for this descriptive analysis of the demographic and clinical characteristics of ALK TKI use in Japanese patients with *ALK*-positive NSCLC and of the patterns and sequences of treatment in these patients. As of September 2021, the Japan MDV database contained information for more than 37.4 million patients from 451 medical facilities that used the Japanese diagnosis procedure combination/per-diem payment system. The Japan MDV database does not include protected health information.

2.2 | Patients

Patients were included in this study if they visited a health-care facility included in the Japan MDV between December 2015 and March 2021, had a diagnosis of lung cancer according to ICD-10-CM (malignant neoplasm of bronchus and lung; diagnosis code C34), and had a prescription order for alectinib followed by lorlatinib after the November 2018 marketing approval of lorlatinib in Japan. There were no exclusion criteria.

2.3 | Data collection and analysis

Baseline demographic and clinical characteristics collected for patients included age at the index date, sex, pre-index date medical conditions (defined using ICD-10-CM codes), and smoking status at index date. There was no minimum follow-up period, and patients were followed up through the last contact date available within the dataset. No imputation for missing data was made.

2.4 | Statistical analysis

As this was a descriptive study, there was no formal analysis to determine sample size; all patients who met the inclusion criteria

during the study period were included. Baseline characteristics were summarized descriptively. Patients were stratified according to the position of lorlatinib in their treatment sequence (second vs. third or later line). The second-line setting was defined as any case without a prescription of another drug (ALK TKI or chemotherapy and/or immune checkpoint inhibitor) prior to alectinib. The third- or later-line setting was defined as any case with a confirmed prescription of another drug prior to alectinib. Duration of treatment was calculated from the date of the start of the first prescription until the date of the last prescription; mDOT and 95% CIs for any line, second-line, and the third- or later-line setting were estimated using the Kaplan–Meier method. For the analyses, treatment was considered to continue if no other antineoplastic treatment was started and the date of last lorlatinib prescription was on or after the data cut-off date (March 31, 2021). Cessation was defined as having started no other antineoplastic treatment and having a date of last lorlatinib prescription less than 5 weeks prior to the data cut-off date. If the treatment end date (the last day of prescription period on the last prescription order date) was after data cut-off, it was defined as censored. A patient was classified as being with posttreatment if another antineoplastic treatment was started after lorlatinib therapy commenced. A swimmer plot was generated to visualize the DOT of lorlatinib and postlorlatinib therapy stratified by subsequent therapy.

2.5 | Institutional review board approval and patient consent

The Japan MDV database holds anonymized information about diagnoses, patient characteristics, drug prescriptions, medical procedures, features of medical facilities, and reimbursement costs. All patient data are encrypted before entry. Therefore, institutional review board approval and patient consent were not required for this study, because the analysis used secondary data that were devoid of any patient-identifying information based on the Japanese ethical guideline.[20]

3 | RESULTS

3.1 | Analysis cohort

Between December 2015 and March 2021, 1954 patients were treated with alectinib. Of them, 371 received an ALK TKI or chemotherapy after alectinib (Figure 1). After the initial marketing approval of lorlatinib in Japan in November 2018, 221 patients received lorlatinib, 38 received ceritinib, and 9 received chemotherapy, all after treatment with alectinib (Figure 1). Of the patients who were treated with lorlatinib following alectinib (any line), 58.4% were female, and the mean age was 62 years. Background characteristics were similar between patients who received second-line or third- or later-line lorlatinib (Table 1).

3.2 | Duration of lorlatinib treatment

The follow-up periods for any-line, second-line, and third- or later-line treatment were 248, 238, and 329 days, respectively. Of the 221 patients who received any-line lorlatinib, the mDOT was 161 days (95% CI, 126–248 days) (Figure 2). Overall, 138 patients (62.4%) discontinued treatment during the follow-up period. For patients receiving second- and third- or later-line lorlatinib, the mDOTs were 147 days (95% CI, 113–242 days) (Figure 3) and 244 days (95% CI,

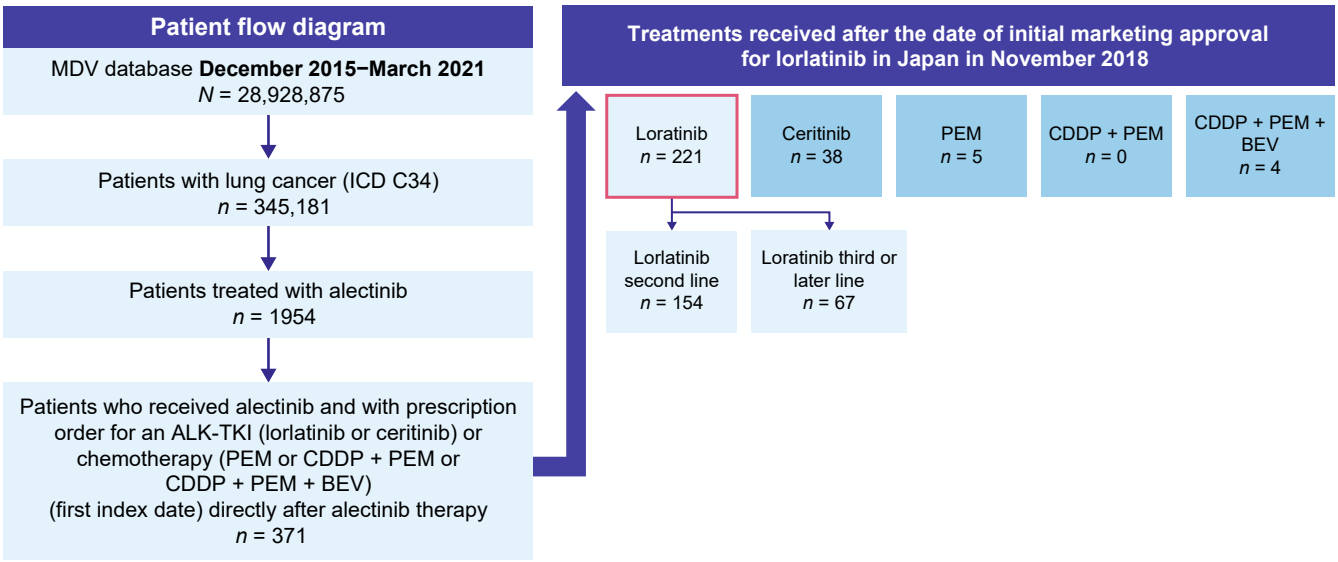


FIGURE 1 Patient flow diagram. ALK, anaplastic lymphoma kinase; BEV, bevacizumab; CDDP, cisplatin; ICD, International Classification of Diseases; MDV, Medical Data Vision; PEM, pemetrexed; TKI, tyrosine kinase inhibitor. Alectinib was recommended in Japan as a first-line treatment option for *ALK*-positive non-small-cell lung cancer in November 2015.

109 days to not reached) (Figure 4), respectively. Overall, 103 patients (66.9%) discontinued second-line lorlatinib during the follow-up period, and 51 (33.1%) were still receiving treatment at the data cut-off. For those receiving lorlatinib as third- or later-line treatment, 35 (52.2%) discontinued lorlatinib during the follow-up period, and 32 (47.8%) were still receiving treatment at the data cut-off.

Patients who received any-line lorlatinib had a 1-year DOT rate of 33.4%; patients who received lorlatinib as either second- or third- or later-line treatment had respective 1-year DOT rates of 27.7% and 44.7%. The 2-year DOT rates were 18.0%, 8.7%, and 36.1% for any line, second line, and third or later line, respectively.

Of the patients prescribed lorlatinib (any line, $N = 221$), 83 (37.6%) continued treatment, 51 (23.1%) ceased treatment, and 87 (39.4%) were categorized as being with posttreatment (Figure 5). Of those patients who received posttreatment, 28 (40.0%) were prescribed a different ALK TKI, 28 (40.0%) were prescribed chemotherapy alone, and 7 were prescribed chemotherapy plus an immune checkpoint inhibitor, an immune checkpoint inhibitor alone ($n = 5$), or another treatment option ($n = 2$) immediately following lorlatinib. The longest postlorlatinib DOT was for chemotherapy plus an immune checkpoint inhibitor (median [range], 100 [1–253] days) followed by chemotherapy alone (99 [1–652] days), immune checkpoint inhibitor alone (43 [1–274] days), and another ALK TKI (37 [1–757] days) (Table S1). The DOT of lorlatinib and postlorlatinib therapy for each individual patient according to posttreatment type is shown in Figure S1.

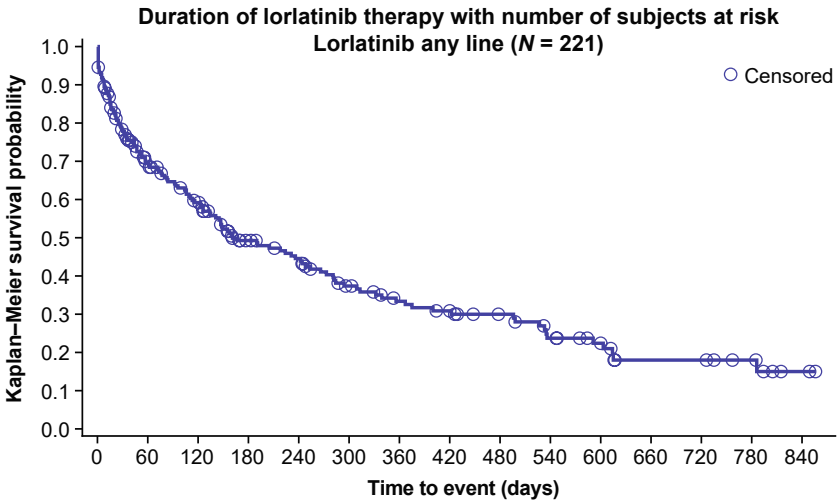
TABLE 1 Baseline patient characteristics for patients receiving lorlatinib following alectinib.

Characteristic	Lorlatinib, any line ($N = 221$)	Lorlatinib, second line ($n = 154$)	Lorlatinib, third or later line ($n = 67$)
Age, years			
Median	62.0	62.0	62.0
Mean	61.85	61.81	61.93
Age range, *n* (%)			
18–49 years	41 (18.6)	30 (19.5)	11 (16.4)
50–64 years	79 (35.8)	54 (35.1)	25 (37.3)
65–74 years	62 (28.1)	42 (27.3)	20 (29.9)
≥75 years	39 (17.7)	28 (18.2)	11 (16.4)
Sex, *n* (%)			
Female	129 (58.4)	93 (60.4)	36 (53.7)
Male	92 (41.6)	61 (39.6)	31 (46.3)
Smoking status, *n* (%)			
Never smoked	125 (56.6)	86 (55.8)	39 (58.2)
Current smoker	63 (28.5)	41 (26.6)	22 (32.8)
Unknown/missing	33 (14.9)	27 (17.5)	6 (9.0)
Median BMI, kg/m^2	22.5	22.8	21.7

Abbreviation: BMI, body mass index.

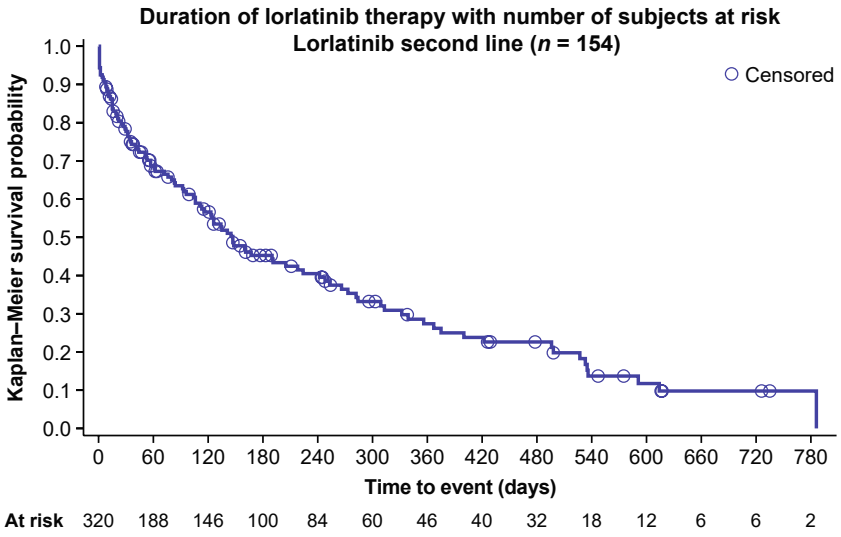
4 | DISCUSSION

This retrospective, real-world observational study, which reviewed lorlatinib prescribing practices in Japanese patients with *ALK*-positive NSCLC for a period of more than 5 years, found that following the initial marketing approval of lorlatinib in Japan (November 2018), lorlatinib was the most frequently prescribed treatment following alectinib therapy. More than two-thirds of patients prescribed



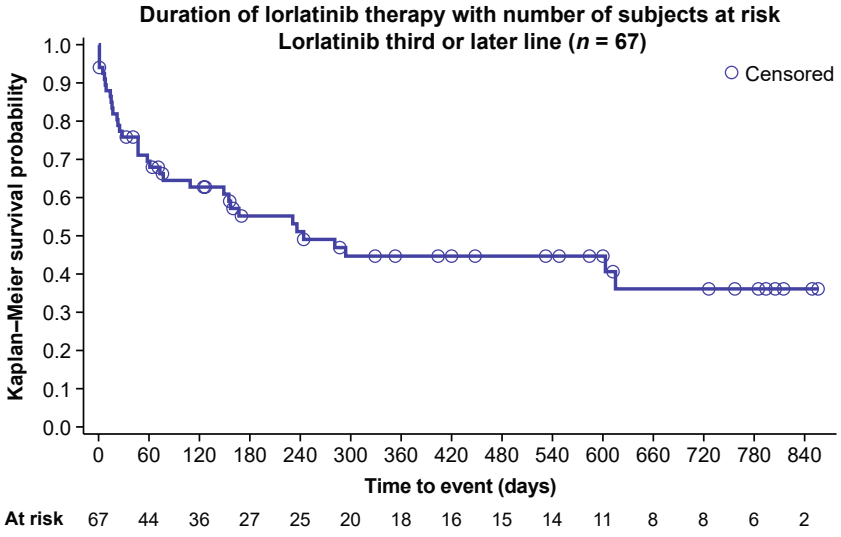
	Lorlatinib treatment status, $N = 221$	
Treatment status	Continue treatment	Treatment discontinued
Number (%) of patients	83 (37.6)	138 (62.4)

FIGURE 2 Duration of lorlatinib treatment (any line; $N = 221$). Cases were censored if the treatment end date (the last day of the prescription period on the last prescription order date) was after March 31, 2021.



	Lorlatinib treatment status, *n* = 154	
Treatment status	Continue treatment	Treatment discontinued
Number (%) of patients	51 (33.1)	103 (66.9)

FIGURE 3 Duration of lorlatinib treatment (second line). Cases were censored if the treatment end date (the last day of the prescription period on the last prescription order date) was after March 31, 2021.



	Lorlatinib treatment status, *n* = 67	
Treatment status	Continue treatment	Treatment discontinued
Number (%) of patients	32 (47.8)	35 (52.2)

FIGURE 4 Duration of lorlatinib treatment (third or later line). Cases were censored if the treatment end date (the last day of the prescription period on the last prescription order date) was after March 31, 2021.

lorlatinib received it as second-line treatment; the mDOT estimated by the Kaplan–Meier method for lorlatinib was approximately 5 months. To the authors' knowledge, these are the first data to show lorlatinib real-world prescribing practices following alectinib treatment in patients with *ALK*-positive NSCLC in clinical practice in Japan.

Prior to the approval of lorlatinib in Japan, crizotinib or ceritinib was often prescribed as second-line treatment after alectinib.[17] Our data indicate that prescribing patterns have changed, with lorlatinib being prescribed much more frequently than crizotinib or ceritinib. Our data show that only a small proportion of patients (n = 9; approximately 3%) received chemotherapy following alectinib failure, of whom the majority (n = 5) received pemetrexed. These data could indicate a decreasing trend for the use of chemotherapy as second- or later-line treatment after ALK TKI failure. Exclusion of other chemotherapy treatments, except for pemetrexed ± cisplatin, may have underestimated the proportion of patients who received chemotherapy after alectinib failure. A study of prescribing practices in Japan from 2010 through 2017 found that a much larger proportion of patients received chemotherapy following ALK TKI failure than was reported in the present study. In it, 46% of the 104 patients who discontinued ALK TKI therapy received chemotherapy, of which pemetrexed was the most commonly prescribed.[17]

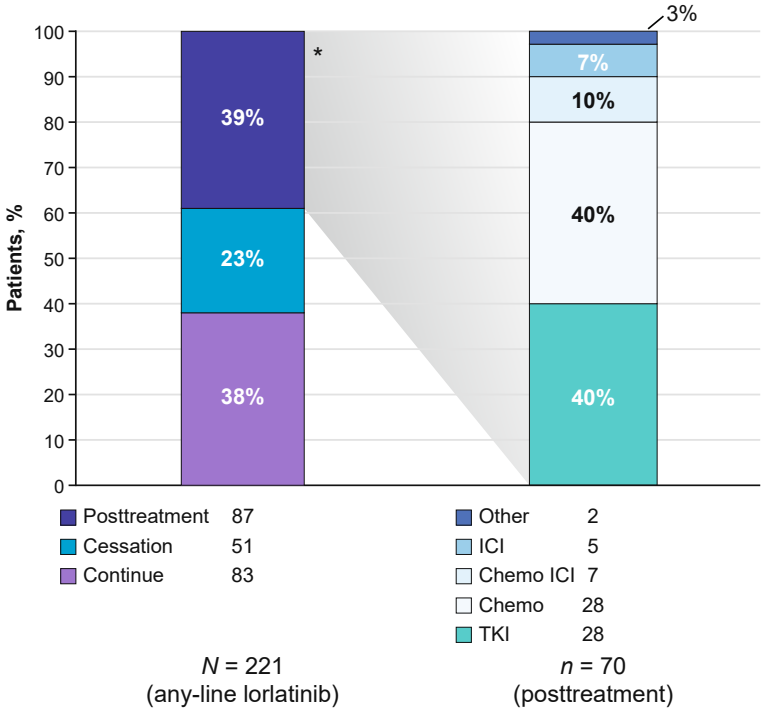


FIGURE 5 Treatment status following lorlatinib. *Of the 87 patients who switched treatment, 17 were excluded from the posttreatment breakdown graph because the prescription of the next treatment was started during the prescription period of lorlatinib. ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

A strength of this study is that prescribing practices in a real-world population across Japan were analyzed. Patients were older than those encountered in the phase II study, with a median age of 62 years in this study compared with 54 years in the phase II study.[15] These demographics are consistent with previous real-world reports of patients with NSCLC in Japan,[17,21] although it should be noted that the MDV database generally includes only patients of working age. No differences were observed in the baseline demographics or disease characteristics of patients receiving lorlatinib as second-line or third- or later-line treatment; however, it is possible that there were differences based on ECOG PS or the presence of brain metastasis. Because such data were not available in the MDV database, further studies would be required to address this question. In the present analysis, most patients received lorlatinib after alectinib (221/371; 60%), and it was most often prescribed as a second-line agent (154/221; 70%).

We report an mDOT of approximately 5 months in patients treated with lorlatinib after alectinib. No obvious differences in mDOT were observed between the overall lorlatinib population and those receiving lorlatinib as a second-line agent (161 vs. 147 days). However, patients receiving third- or later-line lorlatinib tended to have a longer mDOT (244 days). This could be due to the difference in the rate of censors between the groups (i.e., the third- or later-line group had more censors) and the difference in the general condition of the patients between groups; it may be assumed that patients who reach third- or later-line therapy are in good condition with relatively indolent tumors, given that they have survived longer-term NSCLC.[22] It is expected that the DOT obtained using the Kaplan–Meier method was underestimated due to the definition of cessation that was used in this analysis. Because patient numbers were low in this group, further analysis is warranted.

The results of our study suggest that the real-world clinical benefit of lorlatinib is consistent with that observed in clinical studies. Duration of treatment can be used as a surrogate marker to PFS when there is a lack of sufficient evidence to provide accurate assessment of disease progression.[23] In actual practice, there are some cases where treatment is continued after disease progression.[24] In general, due to the inability to factor in discontinuation due to toxicity, DOT might underestimate PFS.[25] Although it is difficult to compare the mDOT of second-line lorlatinib in this study with the median PFS reported in the phase II study, the mDOT of approximately 5 months reported in the present study is consistent with the 5.5-month PFS reported in the phase II study with same follow-up period, which showed longer mDOT (8.7 months) with updated follow-up period.[16] The 1-year DOT rate (any line) was consistent with that of the previous retrospective, multicenter, real-world analysis.[23]

Currently, there are no established recommendations for effective treatment regimens after the failure of lorlatinib, nor are there any reports of clinical practice in Japan following lorlatinib failure, despite the recent evidence of a resistance mutation pattern after failure of lorlatinib. Chemotherapy and immune checkpoint inhibitor regimens were frequently observed following lorlatinib use. Analysis of the DOT in these patients after cessation of lorlatinib indicated that there is likely a treatment benefit from the use of chemotherapy. Chemotherapy combined with immune checkpoint inhibitor treatment following lorlatinib failure resulted in a DOT of approximately 3.3 months (Table S1). This is similar to the PFS of 3.2 months reported in patients for whom one or more second-generation ALK TKI treatments failed who received chemotherapy alone.[26] In the present study, some patients were re-treated with alectinib following lorlatinib failure in practice (Table S1), although

it is not referred by Japanese and European guidelines.[10,27] There have been case reports of effective dose escalation with alectinib in patients with central nervous system lesions or rechallenge in a patient with small-cell lung cancer transformation.[28,29] However, it might not be beneficial to re-treat with a drug that failed early in the treatment sequence, considering resistance mechanisms. The efficacy of this treatment strategy should be evaluated in a prospective trial.

This study had several limitations. As noted, some limitations were associated with the MDV dataset, because it does not collect information on several disease characteristics, including ECOG PS, brain metastases, *ALK* status, or induced resistance mechanism (e.g., *MET* amplification, *EGFR* activation, and secondary *ALK* mutations). In addition, the MDV dataset does not provide information on drug dosage or oral compliance, reasons for treatment discontinuations (e.g., progression, toxicity, resistance), or recurrence patterns. Resistance mechanisms and recurrent patterns are important for determining future treatment options. Due to the lack of these clinical characteristics in the MDV dataset, the assessment of efficacy could be limited due to bias from confounding by indication.[30,31] Another limitation was that a censored case was defined based on the prescription information for ALK TKIs at the patient's last hospital visit. Of the 221 patients receiving lorlatinib in any line of treatment, 83 patients (37.6%) were continuing treatment at the end of the analysis period; therefore, a longer follow-up is required for further interpretation. The follow-up was 3 months longer than the mDOT, which is considered as sufficient; however, further follow-up is desirable because of the high rate of censors, especially after the third line. It is expected that the DOT obtained using the Kaplan–Meier method was underestimated due to the definition of cessation that was used in this analysis. If the next prescription was not confirmed for more than 5 weeks from the date of the most recent prescription, it was counted as a cessation event. This likely resulted in an underestimation of efficacy because patients would not be expected to stop treatment immediately following a prescription. Finally, this study was undertaken using data from Japanese patients, potentially limiting the generalizability of these findings. This study reports the treatment patterns in Japan between December 2015 and March 2021, before the marketing approval of brigatinib as a first- and second-line therapy for patients with metastatic NSCLC in Japan in April 2021.[32] Therefore, the treatment landscape analyzed in this real-world study does not include patients treated with brigatinib.

In conclusion, this real-world study found that ALK TKIs, including lorlatinib, and chemotherapy treatment after alectinib, were observed nationwide in Japan. Most patients who were prescribed alectinib as first-line treatment for *ALK*-positive NSCLC were prescribed lorlatinib as second-line treatment. Of the 221 patients who were treated with lorlatinib after alectinib, 154 (70%) received lorlatinib as second-line treatment and 67 (30%) received lorlatinib as third- or later-line treatment. The mDOT for lorlatinib was approximately 5 months. Such results in a real-world setting support the existing clinical trial data that demonstrate the clinical benefit of lorlatinib.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. The claims database used for this study can only be obtained by purchasing from a vendor (Medical Data Vision Co., Ltd; http://www.mdv.co.jp/).

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: Approval was not required because the analysis used secondary data that were devoid of any patient-identifying information.
Informed consent: N/A.
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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