Continuation of Lorlatinib in ALK-Positive NSCLC Beyond Progressive Disease

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ABSTRACT

Introduction: Lorlatinib, a potent, selective third-generation ALK tyrosine kinase inhibitor (TKI), exhibited overall and intracranial antitumor activity in patients with ALK-positive NSCLC.

Methods: Retrospective analyses in the ongoing phase 2 trial (NCT01970865) investigated the clinical benefit of continuing lorlatinib beyond progressive disease (LBPD). Patients with previous crizotinib treatment as the only ALK TKI were group A (n = 28); those with at least one previous second-generation ALK TKIs were group B (n = 74). LBPD was defined as greater than 3 weeks of lorlatinib treatment after investigator-assessed progressive disease. Only patients with the best overall response of complete or partial response or stable disease were included.

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**Results:** There were no major differences in baseline characteristics between groups. The median duration of treatment for patients who continued LBPD was 32.4 months (group A) and 16.4 months (group B) versus 12.5 months (group A) and 7.7 months (group B) for patients who did not continue LBPD. The median overall survival in group A was not reached (NR) in patients who continued LBPD versus 24.4 months (95% confidence interval [CI]: 12.1–NR); group B’s median was 26.5 months (95% CI: 18.7–35.5) in patients who continued LBPD versus 14.7 months (95% CI: 9.3–38.5) in patients who did not continue LBPD. The median overall survival postprogression for groups A and B was NR (95% CI: 21.4–NR) and 14.6 months (95% CI: 11.2–19.2) in patients who continued LBPD and 8.0 months (95% CI: 1.5–NR) versus 5.3 months (95% CI: 2.8–14.3) in patients who did not continue LBPD.

**Conclusions:** Continuing LBPD is a viable treatment strategy for select patients with ALK-positive NSCLC who progressed on lorlatinib.

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**Keywords:** ALK+ NSCLC; Lorlatinib; Lorlatinib beyond progressive disease; Postprogression treatment; RECIST 1.1; Treatment beyond progression

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**Introduction**

Lorlatinib is a third-generation ALK tyrosine kinase inhibitor (TKI) with the widest inhibition spectrum of acquired-resistance mutations to crizotinib, including the solvent-front mutation ALK G1202R. On the basis of the results of a global phase 2, multicohort, single-arm study (NCT01970865), lorlatinib was approved in Japan for the treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed after one ALK TKI. In the United States, lorlatinib has been approved as first-line treatment of patients with ALK-positive metastatic NSCLC, and in the European Union, lorlatinib is approved for use after alectinib or ceritinib as the first ALK TKI or crizotinib and at least one other ALK TKI.

Almost all clinical trials in medical oncology treatment define progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Not considering new lesions and nontarget lesions, PD in target lesions is defined as >20% increase from the lowest aggregate denominator achieved with minimum 5 mm increase over the nadir measurement. In the era of targeted therapy for thoracic malignancies, in which measurable responses can be deep and durable, any subsequent progression that reaches greater than 20% (calculated from the lowest aggregate baseline measurement achieved, which satisfied PD definition by RECIST) could potentially still be far smaller than the original aggregate tumor measurable at the beginning of treatment. Thus, RECIST has limitations in the assessment of ongoing clinical benefits in the setting of highly effective therapy. Hence, the continuation of lorlatinib after RECIST-defined PD was allowed in the lorlatinib phase 2 study for patients still deriving clinical benefit from lorlatinib treatment on the basis of the investigator’s judgment. Here, we evaluated the clinicopathologic characteristics, previous response to lorlatinib, survival, and patient-reported outcomes in patients who experienced initial RECIST progression on lorlatinib and continued lorlatinib beyond PD (LBPD) versus those who did not in the phase 2 part of the pivotal study, to assess how patients may potentially benefit from continuing LBPD in the treatment of ALK-positive NSCLC.

**Materials and Methods**

The study design of this pivotal single-arm, multicohort, phase 2 lorlatinib trial has been previously described. For these analyses, we analyzed patients with ALK-positive NSCLC enrolled into cohorts 2 to 5. Briefly, expansion cohort 2 (EXP2) enrolled patients with disease progression after crizotinib only, EXP3A enrolled patients who had received crizotinib and chemotherapy, and EXP3B enrolled patients who had received a second-generation ALK TKI (such as ceritinib, alectinib, brigatinib, or entrectinib) with or without chemotherapy. EXP4 enrolled patients with two previous lines of ALK TKIs with or without previous chemotherapy, whereas EXP5 enrolled patients with three previous lines of ALK TKI treatment with or without previous chemotherapy. For the treatment beyond progression analyses, patients were categorized into two groups: those who previously received crizotinib only (group A: EXP2 and EXP3A) and those who previously received at least one second-generation ALK TKI (group B: EXP3B, EXP4, and EXP5) (Supplementary Fig. 1).

Radiologic assessment of disease, including brain metastases regardless of presence or absence of baseline brain metastases at study entry, was conducted every 6 weeks, and response confirmation was required. In these analyses, PD was on the basis of overall investigator assessment of tumor data and according to RECIST. For patients who continued LBPD, the same schedule of activities as that used before PD was followed for the collection of data. A period of 3 weeks of treatment after the first documentation of PD was chosen as the cutoff for defining continuing or not continuing LBPD (>3 versus ≤3 weeks, respectively) because it was within one treatment cycle for most patients—the time frame within which
investigators generally decided whether or not to continue LBPD.

Only patients who achieved a best overall response (BOR) to lorlatinib of complete response, partial response, or stable disease lasting at least 6 weeks and progressed on lorlatinib per RECIST were eligible for the analyses. Patients whose BOR to lorlatinib treatment was PD or indeterminate were excluded from the analyses because the inclusion of these patients could confound the assessment of post-PD survival in patients who did or did not continue LBPD. These patients are highly unlikely to benefit from the continuation of LBPD and are more likely to fall into the group that did not continue LBPD, thereby making the analyses biased.

Patient clinical characteristics at baseline and at progression, efficacy outcomes during lorlatinib treatment, modality of progression, duration of treatment (DoT) from the first dose and from the time of PD, and overall survival (OS) from the first dose and from the time of PD were assessed in patients who continued LBPD and who did not continue LBPD. Time to deterioration in the European Organization for Research and Treatment of Cancer Quality of Life (QoL) Questionnaire-C30 score (defined as the time from the date of progression to deterioration—that is, the first occurrence of a decrease of greater than or equal to 10 points in the QoL scale) was assessed for both groups in patients who continued LBPD. The Kaplan-Meier method was used to estimate the time to tumor progression, OS, and OS postprogression end points. Two-sided 95% confidence intervals (CIs) were determined using the Brookmeyer-Crowley method. The data cutoff date for these analyses was May 14, 2019.

The study was conducted in compliance with Good Clinical Practice, guidelines of the International Conference on Harmonization, and the Declaration of Helsinki. All participants provided written, informed consent before study participation.

Results

At the time of data cutoff, 124 patients with ALK-positive NSCLC progressed on previous treatment with ALK TKIs in the phase 2 lorlatinib trial. Of those, a total of 102 patients achieved a BOR of complete response, partial response, or stable disease to lorlatinib and were included in the analyses: 28 from group A and 74 from group B. Among the 28 patients in group A, 21 continued LBPD and seven did not continue LBPD. Among the 74 patients in group B, 56 patients continued LBPD and 18 patients did not continue (Supplementary Fig. 1). The median follow-up time for all patients who continued LBPD in group A and group B was 35.2 and 34.2 months, respectively. The number of patients still on treatment was 13 in group A and nine in group B. The low number of patients who did not continue LBPD (n = 7) in group A does not allow definitive conclusions to be drawn in that group; nevertheless, results are provided for completeness.

Patient Characteristics

Overall, the baseline characteristics of the patients who continued LBPD and who did not continue LBPD were similar. There were lower proportions of patients of Asian race among patients who continued LBPD than patients who did not continue LBPD (19% versus 85.7% in group A; 26.8% versus 77.8% in group B) (Table 1).

As detailed in Table 1, more patients who continued LBPD had brain metastases at the time of lorlatinib study entry (group A: 76.2% versus 42.9%; group B: 67.9% versus 44.4%) and at the time of progression (group A: 76.2% versus 42.9%; group B: 73.2% versus 50.0%) than patients who did not continue LBPD.

Response to Initial Lorlatinib Treatment

In group A, there was no difference in the initial response to lorlatinib among the patients who continued LBPD (overall response rate [ORR]: 71.4%) and the patients who did not continue LBPD (ORR: 71.4%) (Fig. 1 and Supplementary Table 1). Among group B patients, the initial response to lorlatinib was higher among patients who continued LBPD than patients who did not continue LBPD (46.4% versus 22.2%) (Fig. 1 and Supplementary Table 1).

The intracranial ORR was greater in patients who did not continue LBPD than patients who continued LBPD (66.7% versus 37.5%) in group A (Supplementary Fig. 2A and Supplementary Table 1). Conversely, in group B, the intracranial ORR was higher in patients who continued LBPD than in patients who did not continue LBPD (39.5% versus 25.0%) (Supplementary Fig. 2A and Supplementary Table 1). In group A, the extracranial ORR was the same in patients who continued LBPD and patients who did not continue LBPD (ORR: 71.4% for both) (Supplementary Fig. 2B and Supplementary Table 1). In group B, the extracranial ORR was higher among patients who continued LBPD versus patients who did not continue LBPD (ORR: 46.4% versus 22.2%) (Supplementary Fig. 2B and Supplementary Table 1). The median times to treatment progression were similar among patients who continued LBPD and who did not continue LBPD in both groups A and B (Supplementary Table 1).

Mode of Progression on Initial Lorlatinib

Patients who continued LBPD had less extracranial progression than patients who did not continue LBPD.
In addition, among group A patients, more patients who continued LBPD had target lesion progression than patients who did not continue LBPD (76.2% versus 42.9%) and fewer new lesions (28.6% versus 57.1%). Among the group B patients, both patients who continued LBPD and who did not continue LBPD had widespread progression, many with target lesion progression (41.1% versus 61.1%) and new lesions (42.9% versus 44.4%).

**Postprogression Treatments**

Approximately one-quarter of patients who did not continue LBPD did not receive any subsequent treatment. Of those who did receive additional therapy, many received treatment with a different ALK TKI (71.4% in group A, 55.6% in group B). Radiotherapy was received by 9.5% of patients who continued LBPD in group A and 8.9% of patients who continued LBPD in group B.

**Overall and Postprogression Treatment Duration and OS**

Median total DoT (pre- and post-RECIST progression) in group A patients who continued LBPD was 32.4 months (range: 4.6–41.9) compared with 12.5 months for patients who did not continue LBPD (range: 0.4–38.8) (Table 2). The median DoT post-PD in patients who continued LBPD in group A was 11.8 months (range: 0.8–36.8).

In group B, the median total DoT for patients who continued LBPD was 16.4 months (range: 3.7–43.2)

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<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics and Clinical Characteristics at Progression on Lorlatinib, Including Mode of Progression at Initial Progression on Lorlatinib, and Postprogression Treatment</th>
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<tbody>
<tr>
<td>Clinical Characteristics</td>
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</tr>
<tr>
<td>LBPD (n = 21)</td>
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<tr>
<td>Median age, y (range)</td>
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<tr>
<td>Sex, female, n (%)</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
<td>White</td>
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<td>Black</td>
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<tr>
<td>Asian</td>
</tr>
<tr>
<td>Other</td>
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<tr>
<td>Unspecified</td>
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<tr>
<td>ECOG PS at baseline, n (%)</td>
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<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>Brain lesions at baseline (before lorlatinib), n (%)</td>
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<tr>
<td>Median time from diagnosis to start of initial lorlatinib, y (range)</td>
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<tr>
<td>ECOG PS at progression, n (%)</td>
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<tr>
<td>0</td>
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<td>1</td>
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<td>2–4</td>
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<tr>
<td>Presence of brain metastases at progression, n (%)</td>
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<tr>
<td>Intracranial PD, n (%)</td>
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<td>Extracranial PD, n (%)</td>
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<td>Target lesion, n (%)</td>
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<td>Nontarget lesion, n (%)</td>
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<tr>
<td>New lesion, n (%)</td>
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<tr>
<td>Subsequent treatments, n (%)</td>
</tr>
<tr>
<td>Non-ALK TKI</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>No subsequent treatment</td>
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</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; LBPD, lorlatinib beyond progressive disease; PD, progressive disease; TKI, tyrosine kinase inhibitor.
compared with 7.7 months for patients who did not continue LBPD (range: 2.8–38.2). The median DoT post-PD was 5.7 months (range: 0.8–32.7) in patients who continued LBPD (Table 2). An overview of DoT and DoT beyond progression by patient is presented in Figure 2.

In group A, the median OS was not reached (NR) for patients who continued LBPD and was 24.4 months (95% CI: 12.1–NR) for patients who did not continue LBPD. In group B, the median OS was 26.5 months (95% CI: 18.7–35.5) and 14.7 months (95% CI: 9.3–38.5) in

Figure 1. Response to initial lorlatinib treatment on the basis of investigator assessment by the individual patient. The best percentage change from baseline was calculated from the start of study treatment up to the first visit with disease progression. Unconfirmed CR/PR were downgraded to SD; SD at day less than 42 was rated as indeterminate. Patients with at least one on-study target lesion assessment were included. If any procedure was different and not interchangeable from the procedure at screening, the percentage change from baseline could not be calculated and is not displayed. CR, complete response; LBPD, lorlatinib beyond progressive disease; PR, partial response; SD, stable disease.
patients who continued LBPD and who did not continue LBPD, respectively (Fig. 3 and Table 2). The median OS post-PD in group A was NR (95% CI: 21.4 mo–NR) in patients who continued LBPD and 8.0 months (95% CI: 1.5–NR) in patients who did not continue LBPD; in group B, it was 14.6 months (95% CI: 11.2–19.2) and 5.3 months (95% CI: 2.8–14.3) in patients who continued LBPD and who did not continue LBPD, respectively (Supplementary Fig. 3).

**Patient-Reported Outcomes**

In the lorlatinib phase 2 study, the patients were requested to complete the European Organization for Research and Treatment of Cancer QoL Questionnaire-C30 module questionnaires until the last day of treatment regardless of whether there had been disease progression. The mean change from baseline in global QoL score for those patients who continued LBPD (pooled group A and group B) is presented by cycle in Figure 4. The improvement from baseline was maintained over time even after PD.

**Discussion**

In these retrospective analyses of a single-arm, multicohort, pivotal phase 2 study of lorlatinib in patients with previously treated ALK-positive NSCLC, most patients who experienced investigator-assessed progression continued lorlatinib treatment post-RECIST progression. We observed that patients who were able to continue LBPD had a longer median OS than patients who did not continue LBPD. This difference in median OS was about 1 year among patients who previously received at least one second-generation ALK TKI (group B) and was not calculable in those who previously received only crizotinib (group A) because few of the 21 patients died during the study period. In addition, the estimated postprogression OS Kaplan-Meier curves were consistently higher in patients who continued LBPD than in patients who did not continue LBPD (Supplementary Fig. 3). In addition to prolonging survival outcomes, the QoL assessments for patients who continued LBPD were also preserved; thus, patients were not sacrificing QoL for prolonged survival outcomes.

Previously, we analyzed the characteristics of patients who continued crizotinib beyond PD (CBPD) before the next-generation ALK TKIs were widely available even in clinical trials. We found that a higher percentage of patients who continued CBPD had better Eastern Cooperative Oncology Group performance status at the time of disease progression, numerically higher ORRs, greater depth of response, and longer median time to tumor progression than patients who did not continue CBPD. In addition, patients who continued CBPD achieved significantly longer OS from the first dose of crizotinib (HR = 0.28, 95% CI: 0.18–0.44, p < 0.0001) and postprogression median OS (HR = 0.27, 95% CI: 0.17–0.45, p < 0.0001) than patients who did not continue CBPD, similar to the observations in this study.

In this study, more patients who continued LBPD had brain metastases before lorlatinib treatment and at the time of progression. From the same phase 1-2 lorlatinib study, lorlatinib has been found to continue to suppress brain metastases in patients who progressed on crizotinib, with a cumulative incidence rate of 22% at 1 year for those who had brain metastases at baseline and 9% for those without brain metastases at baseline. For patients who progressed after at least one second-generation ALK TKI, the cumulative incidence rate was 23% for patients with brain metastases at baseline versus 12% for patients without brain metastases at baseline.

The median DoTs post-initial progression on lorlatinib were longer for group A than group B. This is consistent with the overall results of the phase 2 study. In addition, a retrospective real-world study revealed that the median progression-free survival (PFS) of lorlatinib decreased after a second-generation ALK TKI and decreased with more lines of ALK TKI therapies. Sequential use of next-generation ALK TKIs often led to the rapid emergence of on-target double-acquired ALK resistance mutations leading to inactivation of all current ALK TKIs including lorlatinib. Translational analysis of the same lorlatinib phase 2 trial revealed that in those patients who previously received crizotinib as the only ALK TKI, lorlatinib achieved similar clinical efficacy with either on-target (acquired ALK resistance mutations) or off-target (no

**Table 2. Duration of Treatment, OS, and Overall and Postprogression DoT**

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Median DoT, mo (range)</td>
<td>LBPD (n = 21)</td>
<td>LBPD (n = 56)</td>
</tr>
<tr>
<td></td>
<td>32.4 (4.6–41.9)</td>
<td>16.4 (3.7–43.2)</td>
</tr>
<tr>
<td>Median DoT post-PD, mo (range)</td>
<td>11.8 (0.8–36.8)</td>
<td>5.7 (0.8–32.7)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (NR–NR)</td>
<td>26.5 (18.7–35.5)</td>
</tr>
<tr>
<td>Median OS post-PD, mo (95% CI)</td>
<td>NR (21.4–NR)</td>
<td>26.5 (18.7–35.5)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DoT, duration of treatment; LBPD, lorlatinib beyond progressive disease; NR, not reached; OS, overall survival; PD, progressive disease.
Figure 2. Time to progression and duration of treatment beyond progression. Patients were ordered by the duration of LBPD. The duration of treatment beyond progression was estimated using the following equation: total number of months = (last dose date - first progression date on the basis of investigator assessment + 1)/30.44. *Lorlatinib treatment was discontinued the day after the cutoff date (May 14, 2019). LBPD, lorlatinib beyond progressive disease; PR, partial response.
Figure 3. Kaplan-Meier plots of OS by lorlatinib treatment beyond progression status in group A (patients previously treated with crizotinib with or without chemotherapy) and group B (patients treated with one or more second-generation ALK TKI inhibitor with or without chemotherapy). LBPD, lorlatinib beyond progressive disease; OS, overall survival; TKI, tyrosine kinase inhibitor.
acquired-resistance ALK mutations), but in those who had failed one or more second-generation ALK TKIs, the ORR with lorlatinib was higher in those with ALK mutations. A second single retrospective analysis study found that MET amplification was found in almost a quarter of biopsies from patients who progressed on subsequent lines of lorlatinib. Thus, with more lines of ALK TKI therapy, lorlatinib monotherapy is potentially less effective against both on-target and off-target resistance mechanisms.

Although this study provides new data for the outcomes of patients who continued lorlatinib treatment post-RECIST progression, it is subject to the limitations of a retrospective analysis and the results may be affected by selection bias. For example, patients treated beyond progression could be expected to represent a subgroup with inherently favorable prognostic factors. However, in our cohort, the proportion of patients with brain metastases at baseline and progression was higher in the LBPD group than in the non-LBPD group. The presence of brain metastases in patients with NSCLC is a well-known negative prognostic factor associated with poorer survival compared with patients without brain metastases and those with metastases to other sites in the body. Despite the higher proportion of patients with brain metastases in the LBPD group in our analysis, the median OS was higher in this group than in the non-LBPD group. The CROWN phase 3 study comparing lorlatinib to crizotinib for the first-line treatment of ALK-positive NSCLC revealed significantly improved PFS, with a hazard ratio of 0.28 (95% CI: 0.19–0.41; *p* < 0.001) overall, 0.20 (95% CI: 0.10–0.43) for patients with baseline brain metastases, and 0.32 (95% CI: 0.20–0.49) for patients without baseline brain metastases. On the basis of outcomes from the phase 3 CROWN trial, lorlatinib recently received U.S. Food and Drug Administration registration for the treatment of adult patients with metastatic ALK-positive NSCLC as detected by an approved test by the U.S. Food and Drug Administration. It will be important to investigate the clinicopathologic characteristics of patients in the lorlatinib arm of CROWN who continued LBPD and the subsequent survival outcome such as the median PFS while on LBPD compared with those patients who did not continue LBPD, because although a clinical benefit with LBPD was observed in these analyses in which lorlatinib was used in a second-line or beyond setting, the survival benefit diminished with more previous lines of therapy, including the sequential use of ALK TKIs.

Figure 4. Change from baseline for EORTC QLQ-C30 Global QoL (pooled group A and group B)—PRO-assessable population—in patients who continued LBPD. Baseline was defined as the last PRO assessment before the first dose, which could be day 7 or cycle 1, day 1. The number of patients at risk was the number of patients who completed the scale at baseline and the respective cycle. Mean change (± SE) was truncated to be in (−100, 100). The figure was drawn on a scale of (−40, 40) to reveal trends. Baseline cycles up to 50 and EOT are included. The visit label and visit windows were applied for the analysis of the PRO end points. In the case of multiple records for a patient within a particular visit window, the assessment that was closest to the target day was used. In the unlikely event that both (or all) the records were equidistant from the target day, the patient’s last assessment within that visit window was used. BL, baseline; EORTC QLQ, European Organization for Research and Treatment of Cancer quality of life questionnaire; EOT, end of treatment; QoL, LBPD, lorlatinib beyond progressive disease; quality of life; PRO, patient-reported outcome.
CRediT Authorship Contribution Statement
Sai-Hong I. Ou, Benjamin J. Solomon, Alice T. Shaw, Shirish M. Gadgeel, Benjamin Besse, Ross A. Soo, Antonello Abbattista, Francesca Toffalorio, Robin Wiltshire, Alessandra Bearz: Conceptualization of the manuscript, Critically reviewed the manuscript, Approved the final version for submission.
Antonello Abbattista, Francesca Toffalorio: Data curation.
Antonello Abbattista: Formal analysis.

Data-Sharing Statement
On 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.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.12.011.

References