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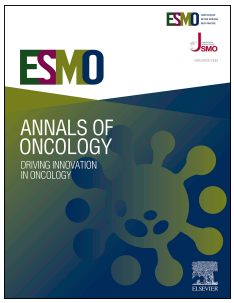

Lorlatinib versus crizotinib as first-line treatment for advanced *ALK*-positive non-small cell lung cancer: 7-year update from the phase 3 CROWN study

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Background & Methods

Lorlatinib is a preferred standard-of-care first-line therapy for patients with advanced *ALK*-positive NSCLC

At 5 years of follow-up, median PFS by investigator was not reached with **lorlatinib** vs 9.1 months with **crizotinib**

We report long-term outcomes from the phase 3 CROWN study after 7 years of follow-up

CROWN (NCT03052608): A Randomized, Global, Phase 3 Study

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG performance status 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1

- **Lorlatinib 100 mg once daily**
- **Crizotinib 250 mg twice daily**

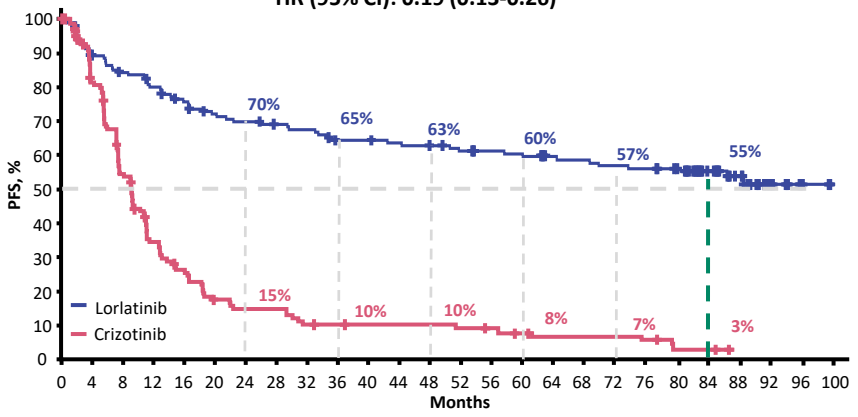
Stratified by:
- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

No crossover between treatment arms was permitted

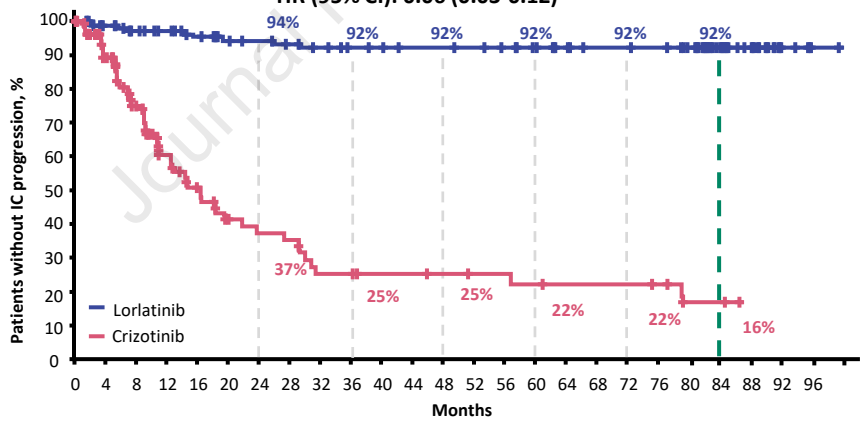
Primary endpoint: PFS by BICR
Secondary endpoints: overall survival (key secondary endpoint), PFS by investigator, objective response, IC objective response, IC time to progression, DOR, IC DOR, safety, and biomarker analyses

Results

Median PFS was still not reached with **lorlatinib** and 9.1 months with **crizotinib** after ~7 years of follow-up
HR (95% CI): 0.19 (0.13-0.26)



Time to IC progression was still not reached with **lorlatinib** and 16.4 months with **crizotinib**; no new IC progression events occurred after the first 30 months
HR (95% CI): 0.06 (0.03-0.12)



In the **lorlatinib** arm, no emerging new ALK resistance mutations were detected in the ctDNA samples at end of treatment

The safety profile of **lorlatinib** was similar to that reported in the primary analysis of the CROWN study and in subsequent follow-up analyses

- The most common any-grade all-causality AEs were hypercholesterolemia (73%), hypertriglyceridemia (71%), and edema (58%)
- There was no increase in the frequency of patients with maximum grade 3 or 4 AEs since the 5-year analysis (77%)
- No new treatment-related AEs led to treatment discontinuation after the first 26 months

AE, adverse event; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

Results from this 7-year analysis show that **lorlatinib** as a single agent is able to **persistently control the disease,** over the entire duration of treatment and **has the potential to transform advanced *ALK*-positive NSCLC into a chronic disease** for a substantial proportion of patients

Original Article

Lorlatinib versus crizotinib as first-line treatment for advanced *ALK*-positive non-small cell lung cancer: 7-year update from the phase 3 CROWN study

Short title: 7-year update from the phase 3 CROWN study

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Original Article	**Journal specifications**	**Current counts***
Abstract	300	301
Text	4500 (10% over limit is acceptable)	4089 + 750 = 4839
Figures/tables	6 (counted as 150 words each)	4 figures/1 table (750 words)
Supplement	Allowed	7 figures/10 tables
* Word counts per Microsoft Word, version 2512		

ABSTRACT

Background: Due to the unprecedented PFS benefit with lorlatinib after 5 years of follow-up in the phase 3 CROWN study, we aimed to quantify long-term outcomes at 7 years.

Patients and methods: 296 treatment-naive patients with advanced *ALK*-positive NSCLC were randomized 1:1 to receive lorlatinib 100 mg OD (*n*=149) or crizotinib 250 mg BID (*n*=147). This post hoc analysis presents investigator-assessed efficacy outcomes, safety, and biomarker analyses.

Results: With median follow-up of 83.0 and 77.2 months, median PFS (95% CI) was not reached (NR; 68.5-NR) with lorlatinib and 9.1 months (7.4-10.9) with crizotinib (HR, 0.19; 95% CI, 0.13-0.26); 7-year PFS was 55% and 3% respectively. With lorlatinib, patients without a PFS event at the end of 24 months had a 79% probability of survival without progression at year 7. No new intracranial progression events occurred after the first 30 months on lorlatinib. Median time to intracranial progression (95% CI) was NR (NR-NR) with lorlatinib and 16.4 months (12.7-21.9) with crizotinib (HR, 0.06; 95% CI, 0.03-0.12). Overall survival follow-up is ongoing; the number of events for a protocol-specified analysis has not been met. The safety profile was consistent with the 5-year results. With lorlatinib, treatment-related AEs did not lead to discontinuations after the first 26 months. More genetic alterations were detected in ctDNA samples from early progressors than in long-term responders on lorlatinib; new potential resistance mechanisms were identified.

Conclusions: With median PFS yet to be reached after 7 years of follow-up in CROWN, lorlatinib continues to show unprecedented long-term benefit in patients with advanced *ALK*-positive NSCLC. Patients without progression within 24 months on lorlatinib have a low risk of progression or death at year 7 and may continue long-term treatment. Findings suggest that sustained long-term disease control with first-line lorlatinib may enable advanced *ALK*-positive NSCLC to evolve toward a chronic condition.

ClinicalTrials.gov identifier: NCT03052608

Keywords: CROWN, lorlatinib, crizotinib, non-small cell lung cancer, progression-free survival

Highlights *(3-5; 125 characters, including spaces, per highlight)*

- After 7 years of follow-up in the CROWN study, median PFS was not reached with lorlatinib and 9.1 months with crizotinib
- No new intracranial progression events occurred after the first 30 months on lorlatinib
- The safety profile at 7-year was consistent with the 5-year results
- With lorlatinib, treatment-related adverse events did not lead to discontinuations after the first 26 months
- Lorlatinib continues to show unprecedented long-term benefit in patients with advanced *ALK*-positive NSCLC

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 77% of all lung cancers and remains the leading cause of cancer-related mortality worldwide.[1, 2] Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are found in approximately 4% of NSCLC and confer sensitivity to treatment with ALK tyrosine-kinase inhibitors (TKIs).[3] Lorlatinib is a highly potent third-generation macrocyclic ALK TKI, specifically developed to penetrate the blood-brain barrier and have broad activity against most known *ALK* resistance mutations. Lorlatinib is a preferred standard-of-care first-line therapy for patients with advanced *ALK*-positive NSCLC.[4-9]

In the phase 3 CROWN study, lorlatinib showed superior efficacy over crizotinib in patients with treatment-naive advanced *ALK*-positive NSCLC, with marked progression-free survival (PFS) benefit and intracranial efficacy.[9-11] After 5 years of follow-up, median PFS by investigator assessment was not reached (NR; 95% CI, 64.3 months-NR) with lorlatinib, corresponding to the longest PFS reported with any single-agent targeted therapy in advanced NSCLC.[11] Median intracranial time to progression (TTP) was also NR (95% CI, NR-NR) with lorlatinib.

Circulating tumor DNA (ctDNA) analysis from CROWN suggested that lorlatinib effectively suppressed the emergence of new *ALK* kinase domain mutations.[11] Instead, aberrations in bypass signaling pathways appeared to be the predominant mechanism driving resistance to lorlatinib. The remarkably durable responses associated with first-line use of lorlatinib may be due to its potential ability to prevent or delay the emergence of on-target resistance.

Given the outstanding overall and intracranial efficacy and absence of new safety signals after 5 years of follow-up with lorlatinib, this post hoc analysis aimed to further quantify long-term outcomes from CROWN after approximately 7 years of follow-up.

PATIENTS AND METHODS

Study Design and Endpoints

CROWN(ClinicalTrials.gov identifier: NCT03052608) is an ongoing, international, open-label, randomized phase 3 trial comparing lorlatinib versus crizotinib in patients with previously untreated, advanced *ALK*-positive NSCLC. Full study details were previously published.[9, 10] Patients were randomly assigned 1:1 to receive lorlatinib 100 mg once daily or crizotinib 250 mg twice daily in 28-day cycles. Brain MRI was required at baseline and at each tumor assessment, regardless of baseline CNS status, with intracranial response assessed using a modified version of RECIST 1.1. To reduce patient burden and cumulative radiation exposure, the protocol was amended after the 5-year follow up to extend the interval between tumor assessments from every 8 to 16 weeks.

Primary endpoint was PFS by blinded independent central review (BICR) per RECIST 1.1, which was met at the planned interim analysis[9] after 18.3 months of follow-up in lorlatinib group; no further formal comparative analysis of PFS planned. Key secondary endpoint is overall survival (OS), which will be assessed at the protocol-specified second interim analysis after 139 deaths have occurred (70% information fraction). Other secondary endpoints included investigator-assessed PFS, objective response, intracranial objective response, intracranial TTP, duration of response (DOR), intracranial DOR, safety, and biomarker analyses. Per protocol, endpoint evaluation by BICR stopped after 3-year analysis.

Protocol and amendments were approved by institutional review boards or independent ethics committees at each site and complied with International Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and local laws. All patients provided written informed consent.

This post hoc analysis conducted after approximately 7 years of follow-up presents efficacy by investigator assessment, safety, and blood-based ctDNA biomarker analyses.

Statistical Analyses

PFS was estimated using the Kaplan-Meier method. Conditional PFS was calculated to assess long-term outcomes among patients who remained progression free at 24 months by using the ratio of the Kaplan-Meier PFS estimates at 7 and 2 years.

To assess whether dose level had an impact on PFS or intracranial TTP, Cox proportional hazards model with time-dependent covariates was used. Dose level was treated as a time-varying exposure, allowing patients to transition from full to reduced dose levels at the time reduction occurred. Follow-up time for each patient was partitioned into consecutive intervals defined by timing of dose reductions, The model was fitted using a counting process (start-stop) formulation. Dose-reduction indicators were updated at each interval to reflect current dose level. Landmark analysis on PFS and intracranial TTP was also implemented so only patients who had survived without progression up to 26 weeks were analyzed, ensuring that the dose-reduction group was formed fairly based on information available.

Molecular Profiling

Details of molecular profiling were previously published.[11, 12] In the prior analysis, distribution of *ALK* variants was based on a 74-gene Guardant 360 ctDNA platform. For the current analysis, ctDNA from plasma was analyzed with a validated, commercially available Guardant Infinity ctDNA NGS assay (Guardant Health, Palo Alto, CA) which covers fusions, single nucleotide variants (SNVs), insertions/deletions (indels), and copy number changes from 755 genes and broad methylation-based quantification of tumor fraction. Microsatellite instability and blood-based tumor mutation burden are also reported. Resistance mechanisms in the lorlatinib-treated patients with end of treatment (EOT) samples (n=23) were explored by assessing newly emerged mutated genes identified ≥2 EOT samples. Genetic alterations were explored in patients who progressed early versus those who had long-term response. Early progressors

were defined as patients with PFS events (progressive disease or death) within 12 months of the study start, and long-term responders were defined as patients who were progression free at 84 months. Current analyses also explored outcomes by *TP53* status and *EML4::ALK* variants.

OncoPrints included SNVs, indels, gene fusions, and focal amplifications. Copy number deletions were excluded to ensure consistent comparison between baseline and EOT samples. This exclusion was motivated by the higher tumor fraction (TF≥20%) requirements for reliable copy number deletion calling, which do not apply to other variants. Excluding these calls prevents misinterpretation of technical detection limits as biological changes.

RESULTS

Patients

296 patients were randomly assigned to the lorlatinib group (*n*=149) or the crizotinib group (*n*=147; **Fig 1**). Five patients in the crizotinib group did not receive treatment but were included in the intention-to-treat population. At data cutoff (October 31, 2025), treatment was ongoing in 66 of 149 patients (44%) in the lorlatinib group and 4 of 142 (3%) in the crizotinib group. Overall, 154 of 296 patients (52%) discontinued the study, including 123 of 296 (42%) due to death; 142 of 296 (48%) were still on study, either on treatment or in follow-up for survival. Baseline characteristics have been previously published.[9, 10]

Efficacy

Median duration of follow-up (95% CI) for PFS was 83.0 months (81.2-86.3) in the lorlatinib group and 77.2 months (36.8 to not evaluable [NE]) in the crizotinib group. The HR for disease progression or death with lorlatinib versus crizotinib was 0.19 (95% CI, 0.13-0.26). Median PFS (95% CI) was NR (68.5 months-NR) with lorlatinib and 9.1 months (7.4-10.9) with crizotinib (**Fig 2A**). 7-year PFS (95% CI) was 55% (46-63) with lorlatinib and 3% (1-8) with crizotinib. Since the

5-year analysis, 7 new PFS events were reported with lorlatinib—4 were disease-progression events, all meeting the definition of oligoprogressions (≤5 progressive lesions)[13] and 3 were deaths without progression that were considered not treatment related (**Supplementary Table S1**). Most PFS events (68%) occurred within the first 24 months. Among patients who were progression free at the end of 24 months, their probability of being alive and progression free at year 7 was 79% (**Supplementary Figure S1**). Probability of disease progression or death was 30% within the first 2 years; the estimated proportion of patients experiencing a PFS event during each subsequent yearly interval decreased and plateaued at approximately 3% over the next 5 years. PFS benefit was consistently observed across all prespecified subgroups, including patients with and without baseline brain metastases, Asian and non-Asian patients, and patients <65 and ≥65 years of age (**Supplementary Figure S2**).

Among patients with baseline brain metastases (measurable and/or nonmeasurable), the HR for disease progression or death with lorlatinib versus crizotinib was 0.08 (95% CI, 0.04-0.19); median PFS (95% CI) was 86.3 months (32.9-NR) with lorlatinib and 6.0 months (3.7-7.6) with crizotinib. 7-year PFS (95% CI) was 53% (35-68) with lorlatinib and NE with crizotinib because all patients progressed or died or were censored within 24 months (**Fig 2B**). In patients without baseline brain metastases, HR for disease progression or death with lorlatinib versus crizotinib was 0.23 (95% CI, 0.16-0.34); median PFS (95% CI) was NR (69.7-NR) with lorlatinib and 10.8 months (9.0-12.8) with crizotinib. The 7-year PFS (95% CI) was 56% (46-65) with lorlatinib and 4% (1-11) with crizotinib (**Fig 2C**).

In the intention-to-treat population, the intracranial TTP by investigator assessment was longer with lorlatinib than with crizotinib, with an HR of 0.06 (95% CI, 0.03-0.12; **Fig 3**). Median intracranial TTP (95% CI) was NR (NR-NR) with lorlatinib and 16.4 months (12.7-21.9) with crizotinib. The probability of being free of intracranial progression (95% CI) was 92% (85-96) with lorlatinib and 16% (6-30) with crizotinib at 7 years. No new intracranial progression events occurred after the first 30 months in the lorlatinib group of the intention-to-treat population.

Among patients with baseline brain metastases, the HR for intracranial TTP favored lorlatinib over crizotinib, with an HR of 0.03 (95% CI, 0.01-0.13; **Supplementary Figure S3**). At 7 years, the probability of being free of intracranial progression (95% CI) was 83% (64-93) with lorlatinib and NE with crizotinib because all patients progressed in the brain or were censored within 24 months. In patients without baseline brain metastases, the HR for intracranial TTP was 0.04 (95% CI, 0.02-0.12), favoring lorlatinib over crizotinib. At 7 years, the probability of preventing development of brain metastases (95% CI) was 96% (89-98) with lorlatinib versus 22% (8-39) with crizotinib. No new intracranial progression events occurred after the first 16 months in patients without baseline brain metastases in the lorlatinib group.

The cumulative incidence of progression of brain metastases as the first event, with adjustment for the competing risks of progression other than brain metastases and death, remained consistent with the 5-year results (**Supplementary Figure S4**). At 6 years, the cumulative incidence of progression of brain metastases was 8% with lorlatinib and 75% with crizotinib in the intention-to-treat population (cumulative incidence could not be calculated at 7 years since last intracranial event occurred earlier, at 79 months, in the crizotinib group).

The proportion of patients with a confirmed objective response by investigator assessment remained consistent with that shown in the 5-year results; 1 patient converted from partial to complete response with lorlatinib in the 7-year analysis (**Supplementary Table S2**). Responses were durable with lorlatinib. Median DOR was NR, with 53% of patients remaining in response (range for observed DOR, 2-98 months). In patients with measurable and/or nonmeasurable baseline brain metastases, intracranial objective response was 66% with lorlatinib, with 2 additional complete responses between the 5- and 7-year analyses. Median intracranial DOR was also NR with lorlatinib, with 65% of patients remaining in response (range for observed DOR, 4-90 months).

At the time of this analysis, OS remains immature because the required number of events for the protocol-specified second interim analysis has not been reached. OS follow-up is ongoing.

Safety

Median duration of treatment was 62.6 months (IQR, 13.9-87.2) with lorlatinib and 9.6 months (IQR, 4.7-17.1) with crizotinib. All-causality any-grade adverse events (AEs) occurred in all 149 patients (100%) in the lorlatinib group and 140 of 142 patients (99%) in the crizotinib group; grade 3 or 4 AEs occurred in 77% and 57% of patients, respectively (**Table 1**). There was no increase in the frequency of patients with maximum grade 3 or 4 AEs since the 5-year analysis. The higher incidence of all-causality grade 3 or 4 AEs in patients in the lorlatinib group versus crizotinib group was largely due to hypertriglyceridemia (26% versus 0%), weight increase (24% versus 2%), and hypercholesterolemia (22% versus 0%) (**Supplementary Table S3**). With lorlatinib, hypercholesterolemia and hypertriglyceridemia occurred in 109 (73%) and 106 (71%) patients, respectively. Edema occurred in 87 (58%) and peripheral neuropathy in 68 (46%) patients, with most events being grade 1 or 2 (91% and 97%, respectively). Weight gain occurred in 67 patients (45%), comprising 11 (7%) grade 1, 20 (13%) grade 2, and 36 (24%) grade 3.

At 7 years, all-causality central nervous system (CNS) AEs occurred in 64 patients (43%) in the lorlatinib group, the majority of which (86%) were of grade 1 or 2 severity (**Supplementary Table S4**). CNS AEs led to dose reduction in 8 (5%), dose interruption in 20 (13%), and treatment discontinuation in 3 patients (2%). All-causality any-grade cardiovascular AEs occurred in 44 of 149 patients (30%) in the lorlatinib group and 41 of 142 (29%) in the crizotinib group (**Supplementary Table S5**); treatment-related cardiovascular AEs occurred in 19 (13%) and 25 patients (18%), respectively. Among patients with hyperlipidemia that was either present at baseline or developed during the study, 39 of 135 patients (29%) in the lorlatinib group and

16 of 32 (50%) in the crizotinib group had cardiovascular AEs (**Supplementary Table S6**); treatment-related cardiovascular AEs occurred in 19 (14%) and 9 (28%) of patients, respectively.

With lorlatinib, all-causality AEs led to dose reduction in 23% of patients, dose interruption in 64%, and treatment discontinuation in 12% (**Table 1**); 2 additional patients discontinued lorlatinib between year 5 and 7 due to cellulitis (grade 3) and dyspnoea (grade 3), which were not treatment related. Treatment-related AEs led to dose reduction in 21%, dose interruption in 42%, and treatment discontinuation in 5% of patients in the lorlatinib group; no new treatment-related AEs led to discontinuation after the first 26 months (**Supplementary Figure S5**). Dose reductions based on investigator recommendation were reported in 34% of patients in the lorlatinib group—17% had 1 dose reduction and 17% had 2 dose reductions. Two new dose reductions were recorded between years 5 and 7. One due to grade 3 lipase increase and one following a grade 3 chronic obstructive pulmonary disease (which resolved upon dose interruption). Median time to dose reduction was 25 weeks (range, 2-313) with lorlatinib.

In a post hoc analysis at 7 years, lorlatinib dose reduction within the first 26 weeks (landmark timepoint) did not seem to impact PFS or intracranial TTP compared with not having dose reduction in the same time frame (**Figure 4**). A multivariable Cox proportional hazards model was also fitted to evaluate the association between PFS or intracranial TTP and the received lorlatinib doses (100 mg, 75 mg, or 50 mg). Using this approach, no evidence of a difference in PFS or intracranial TTP was observed across the 3 dose levels, further supporting the landmark analysis (**Supplementary Table S7**).

Biomarker analyses

Baseline plasma samples were available from 120 patients in the lorlatinib group and 111 in the crizotinib group. Paired baseline and EOT ctDNA samples were available for 23 patients in the lorlatinib group and 61 patients in the crizotinib group. No emerging new *ALK* resistance

mutations were detected in the ctDNA samples collected at the end of lorlatinib treatment. Analysis of paired baseline and EOT ctDNA samples focusing on newly acquired mutations from at least 2 patients showed that resistance to lorlatinib may be driven by bypass mechanisms, with no dominant resistance pathway identified. Potential key lorlatinib resistance pathways involved alterations in RTK/RAS/MAPK signaling, tumor suppressor genes, DNA damage repair mechanisms, gene amplifications (in MYC, MET and NOTCH2), angiogenesis-related pathways (FLT/VEGFR1) and epigenetic regulation (**Supplementary Figure S6**). Putative lorlatinib resistance pathways and newly acquired gene alterations in EOT ctDNA samples are shown in **Supplementary Table S8**. Baseline ctDNA analyses indicated that more genetic alterations were detected in samples from the early progressors (PFS events within 12 months) than in the long-term responders (patients alive with no progression at 84 months) to lorlatinib. Early progressors had a higher median number of altered genes (10 vs 6) and a higher median blood-based tumor mutational burden (7.7 vs 5.1) compared with long-term responders. In addition, *TP53* mutations were observed in 50% of samples from early progressors compared with 17% in long-term responders (**Supplementary Figure S7**). This analysis could not be conducted in the crizotinib group because of the small number of long-term responders at 7 years (n=4). Efficacy by baseline *TP53* status and *EML4::ALK* variant showed results consistent with those reported at 5 years. With lorlatinib, the median PFS (95% CI) was 51.6 months (16.4-NR) in the *TP53* mutation–positive subgroup and NR (NR-NR) in the *TP53* mutation–negative subgroup; with crizotinib, the median PFS (95% CI) was 7.2 months (5.6-9.3) and 10.9 months (9.0-12.8), respectively (**Supplementary Table S9**). The median PFS (95% CI) was 80.3 months (20.1-NR) in patients with *EML4::ALK* variant 1, NR (34.6-NR) in patients with *EML4::ALK* variant 2, and 60.0 months (33.3-NR) in those with *EML4::ALK* variant 3 in the lorlatinib group; in the crizotinib group, the median PFS (95% CI) was 7.4 months (3.7-9.3), 17.2 months (1.9-NR), and 7.2 months (5.4-9.3), respectively (**Supplementary Table S10**).

DISCUSSION

After 7 years of follow-up in CROWN, median PFS was still NR with lorlatinib. The PFS benefit, which exceeds 7 years, corresponds to the longest PFS reported to date with any molecularly targeted therapy in advanced NSCLC and across metastatic solid tumors.[11] The sustained long-term efficacy of lorlatinib is clearly reflected in the PFS curve over 7 years. The probability of disease progression or death was 30% in the first 24 months, then the estimated proportion of patients experiencing a PFS event declined and stabilized at approximately 3% per year thereafter. Most PFS events (68%) occurred within the first 24 months. Patients without a PFS event at 24 months had a 79% probability of being alive without progression at year 7, underscoring the importance of achieving and maintaining disease control during the first 2 years of lorlatinib treatment to improve long-term outcomes. This unprecedented PFS benefit was consistent across all prespecified subgroups, including patients with and without baseline brain metastases. Although head-to-head comparisons with other first- line ALK TKIs are not available, long-term efficacy of lorlatinib in the CROWN study surpassed that of other approved ALK TKIs, with a 7-year PFS of 55% and median PFS being NR. In other first-line ALK TKI trials, median PFS ranged from ~26 to 35 months, with 4-year PFS rates of 36–44% across alectinib, brigatinib, and ensartinib[14,15,16]

With longer follow-up, lorlatinib continued to show remarkable and durable intracranial activity in patients with advanced *ALK*-positive NSCLC. No new intracranial progression event occurred after the first 30 months on lorlatinib, resulting in a sustained plateau in intracranial TTP and indicating a prolonged protective effect against the development of new brain metastases and a sustained control of the existing ones. With up to 7 years of follow-up, lorlatinib remains the only ALK TKI to demonstrate such long-term intracranial efficacy in the first line setting. While these findings likely reflect the potency and strong CNS penetration of lorlatinib, the potential contribution of its Tropomyosin Receptor Kinase (TRK)-inhibitory activity warrants further clinical and translational investigation. Emerging preclinical and clinical data[17, 18]

suggest that inhibition of wild-type Trk B may limit early brain metastatic seeding, consistent with the distinctive “flat line” of intracranial TTP observed with lorlatinib especially in patients without baseline brain metastases – a pattern also reported with other TRK-inhibitory agents such as the ROS1/TRK inhibitors entrectinib and repotrectinib but not seen so far with drugs lacking anti-TRK activity.[17-19]

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis was not met in CROWN, and OS follow-up is ongoing. In the ALEX study (median follow-up,53.5 months), median OS was 81.1 months (95% CI, 62.3 months-not estimable) and the 7-year OS was 48.6% with alectinib.[20] In the ALTA-1L study (median follow-up,40.4 months), median OS was NR, with a 4-year OS probability of 66% with brigatinib.[15] Lorlatinib 7-year PFS (55%) is trending higher than previously reported OS with second-generation ALK TKIs. Consistent with CROWN results, in the pivotal phase 2 study of lorlatinib in patients with treatment-naive *ALK*-positive advanced NSCLC (*n*=30), with a median follow-up for OS of 72.7 months, median OS was NR (95% CI, NR-NR) and the 5-year OS rate was 76% (95% CI, 57-88).[11, 21] In first-line treatment, PFS seems to be a significant contributor to OS in lung cancer. The notably prolonged PFS observed with lorlatinib in first-line will likely translate into a meaningful OS benefit with lorlatinib. Previously reported pivotal ALK TKI studies have failed to demonstrate significant OS benefit versus crizotinib.[15, 20, 22, 23] In these studies, OS may have been confounded due to crossover and higher rate of subsequent anticancer therapy in the crizotinib group. CROWN is currently ongoing and powered to show a difference in OS with active follow-up.

The safety profile of lorlatinib was similar to that reported in the primary analysis of CROWN and in subsequent follow-up analyses, with no new safety signals detected—suggesting no cumulative toxicity—with additional follow-up.[9, 10] There was no increase in the frequency of patients with maximum grade 3 or 4 AEs since the 5-year analysis. Grade 3 or 4

AEs with lorlatinib were mostly due to an increase in lipid values. Despite a higher incidence of hyperlipidemia with lorlatinib, the incidence of cardiovascular AEs was lower with lorlatinib than crizotinib after 7 years of follow-up in patients with hyperlipidemia that was either present at baseline or developed during the study. Similarly, CNS AEs did not increase in frequency or severity with longer follow-up, and most of the cases were controlled by simple dose modification. Only a limited increase in the frequency of weight gain was observed between years 5 and 7 with two additional patients reporting weight gain. Despite the higher incidence of grade 3 or 4 AEs with lorlatinib than with crizotinib, treatment-related discontinuations were similar between the two treatment groups, and majority occurred within the first 2 years of lorlatinib treatment. Dose reductions of lorlatinib did not compromise either systemic or intracranial efficacy. Moreover, prior exposure-response analyses (March 20, 2020, data cutoff; data on file) did not identify a significant relationship between lorlatinib plasma exposure and PFS, overall response rate, or intracranial response rate.

Consistent with earlier analysis, EOT ctDNA samples ─ although limited by a small sample size ─ indicated that lorlatinib was able to suppress emergence of new *ALK* mutations.; instead, gain of a few mutated genes, including FLT1/VEGFR1 and HDAC6 not reported before, were observed and may be associated with resistance mechanisms in some patients who developed disease progression on lorlatinib. Overall, more genetic alterations, including *TP53* mutations, and higher blood-based tumor mutation burden were detected in the early progressors compared to the long-term responders, suggesting the possibility that increased genomic complexity and tumor heterogeneity at baseline may modulate dependency on ALK. However, similar to results from the earlier analysis, PFS was still improved with lorlatinib versus crizotinib regardless of *TP53* mutation status or *EML4::ALK* variants.

Despite the unprecedented results observed at 7-years of follow-up in CROWN, these analyses have some limitations. Per protocol, BICR assessments ended after 3 years. Although investigator-assessed PFS may introduce bias in an open-label trial, there was concordance at

the 3-year analysis between BICR (median PFS: NR vs 9.3 months; HR, 0.27) and investigator assessment (median PFS: NR vs 9.1 months; HR, 0.19)[10] Biomarker analyses from EOT ctDNA arehypothesis generating and warrants confirmation in a larger cohort.

CROWN 7-year findings underscore that the therapeutic benefits of lorlatinib substantially outweigh the potential risks associated with the treatment-related AEs, reinforcing its value as a preferred first-line option. To optimize outcomes, proactive therapy management strategies should be implemented with particular emphasis during the initial phase of treatment.[23] Future directions should focus on 1) identifying mechanisms of resistance to first-line lorlatinib and developing rational combination strategies to overcome or prevent resistance, 2) using ctDNA to identify patients at highest and lowest risk of recurrence, and 3) improving disease control by eradicating residual disease through local consolidation approaches such as radiotherapy or by eliminating limited sites of progression, particularly in light of new progressions on lorlatinib occurring as oligoprogressions. In the phase 1 BRIGHTSTAR study, local consolidation therapy with brigatinib showed promising PFS benefit in patients with *ALK*-rearranged metastatic NSCLC. These approaches could guide tailored interventions, including treatment intensification or consolidation strategies, to further extend disease control and improve long-term outcomes as was explored with other TKIs in several studies.[24, 25]

In summary, results from this 7-year analysis continue to show unprecedented outcomes with lorlatinib in patients with newly diagnosed, advanced, *ALK*-positive NSCLC. Results from the CROWN study suggest that patients who do not progress within 24 months of lorlatinib treatment have a low risk of progression and can continue treatment for a very long time. Lorlatinib as a single agent is able to persistently control the disease, both systemically and intracranially, over the entire duration of treatment and may help shift advanced *ALK*-positive NSCLC toward a more chronic disease trajectory for a substantial fraction of patients.

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Data Sharing 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.

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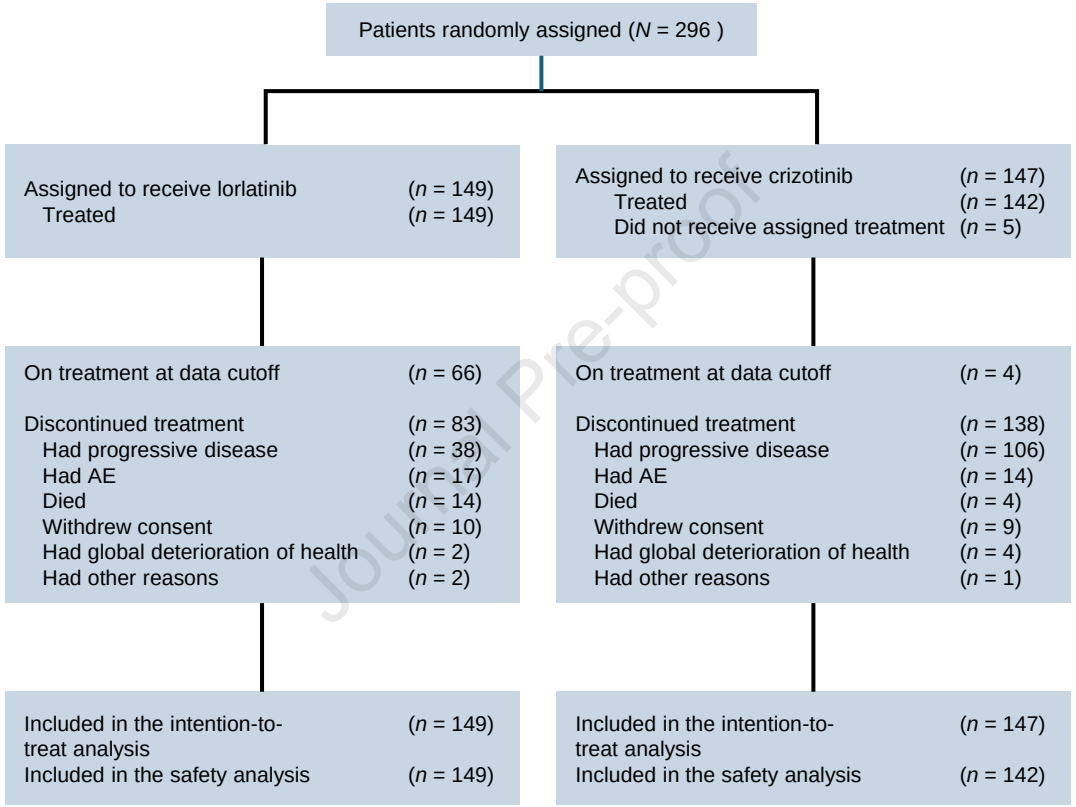
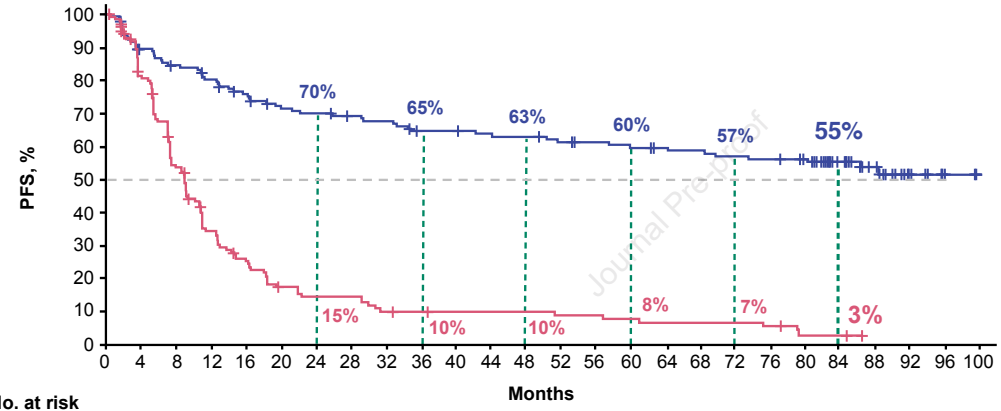
TABLE 1. Summary of AEs

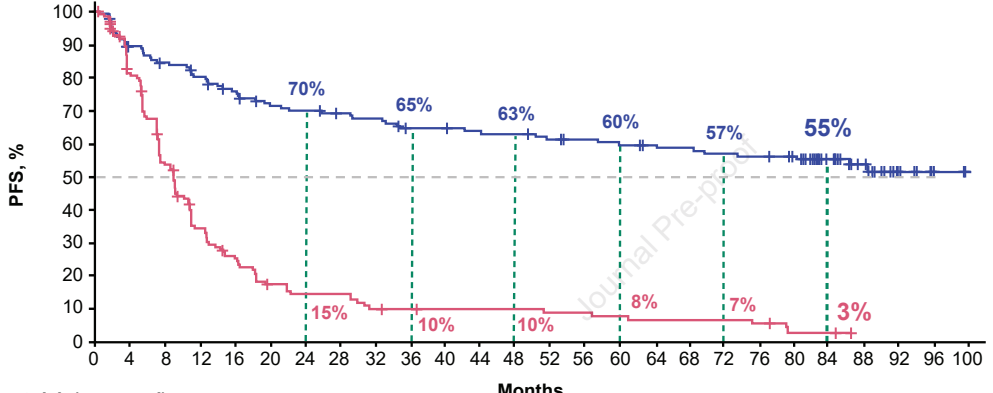
***n* (%)**	**Lorlatinib (*n*=149)**	**Crizotinib (*n*=142)**
All-causality any-grade AE	149 (100)	140 (99)
Treatment-related	145 (97)	133 (94)
All-causality grade 3/4 AE	115 (77)	81 (57)
Treatment-related	100 (67)	55 (39)
All-causality grade 5 AE	18 (12)	7 (5)
Treatment-related	2 (1)	0
All-causality serious AE	71 (48)	45 (32)
Treatment-related	14 (9)	9 (6)
All-causality AEs leading to dose reduction	35 (23)	22 (15)
Treatment-related	32 (21)	20 (14)
All-causality AEs leading to dose interruption	96 (64)	67 (47)
Treatment-related	62 (42)	50 (35)
All-causality AEs leading to treatment discontinuation	18 (12)	15 (11)
Treatment-related	8 (5)	8 (6)

AE, adverse event.





	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, months, median (95% CI)	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	

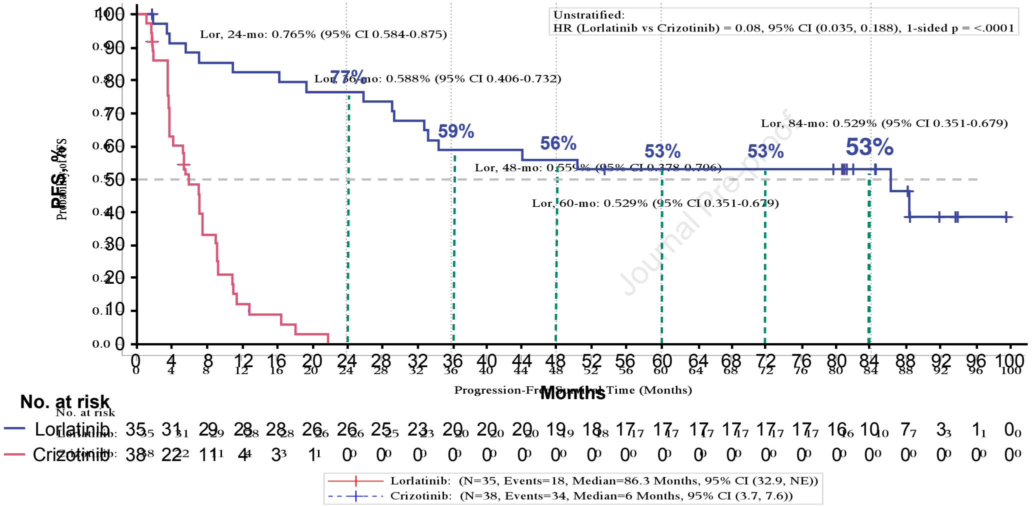


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, months, median (95% CI)	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	

No. at risk (censored)

Lorlatinib	149 (0)	126 (8)	118 (9)	111 (10)	103 (12)	96 (14)	93 (14)	89 (17)	87 (17)	81 (19)	81 (19)	79 (20)	78 (20)	75 (21)	73 (23)	71 (23)	69 (25)	68 (25)	66 (25)	65 (25)	62 (28)	38 (51)	28 (60)	9 (78)	2 (85)	0 (87)
Crizotinib	147 (0)	107 (15)	70 (17)	42 (20)	30 (22)	19 (23)	16 (23)	16 (23)	11 (23)	10 (24)	9 (25)	9 (25)	9 (25)	8 (25)	8 (25)	7 (25)	6 (25)	6 (25)	6 (25)	5 (25)	2 (26)	2 (26)	0 (28)	0	0	0

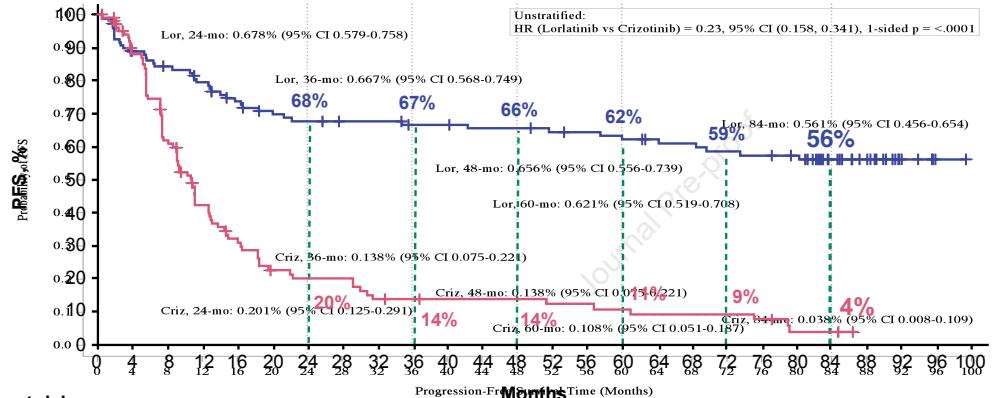
Kaplan-Meier Plot of Progression-Free Survival Based on Derived Investigator Assessment (RECIST v1.1) by Baseline Brain Metastases - Full Analysis Set
Presence of Brain Metastases = 'Y'



With baseline brain metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	18	34
PFS, months, median (95% CI)	86.3 (32.9-NR)	6.0 (3.7-7.6)
HR (95% CI)	**0.08 (0.04-0.19)**	

Kaplan-Meier Plot of Progression-Free Survival Based on Derived Investigator Assessment (RECIST v1.1) by Baseline Brain Metastases - Full Analysis Set
Presence of Brain Metastases = 'N'



No. at risk

No. at risk

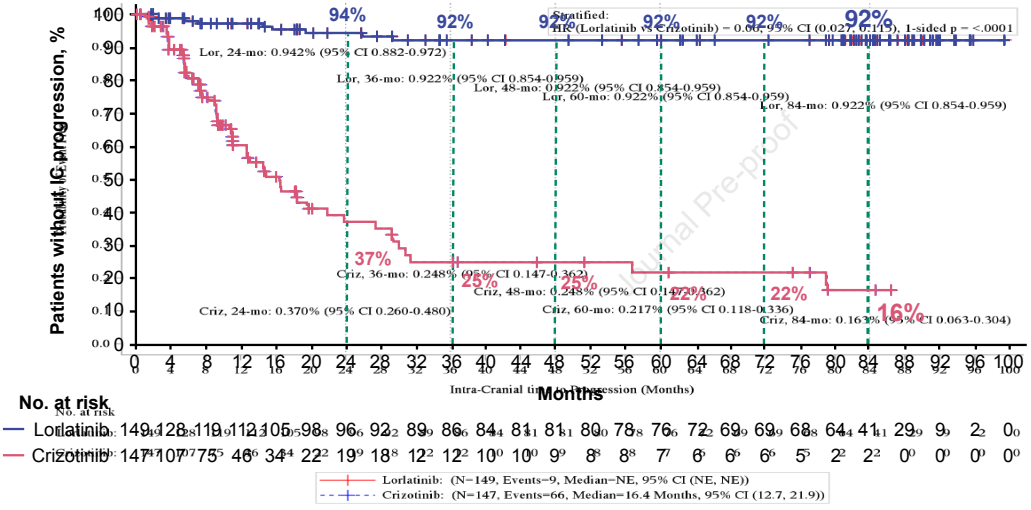
Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	59	57	56	54	52	51	49	48	46	28	21	6	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	8	7	6	6	6	5	2	2	0	0	0	0

Lorlatinib: (N=114, Events=44, Median=NE, 95% CI (69.7, NE))
Crizotinib: (N=109, Events=85, Median=10.8 Months, 95% CI (9, 12.8))

Without baseline brain metastases

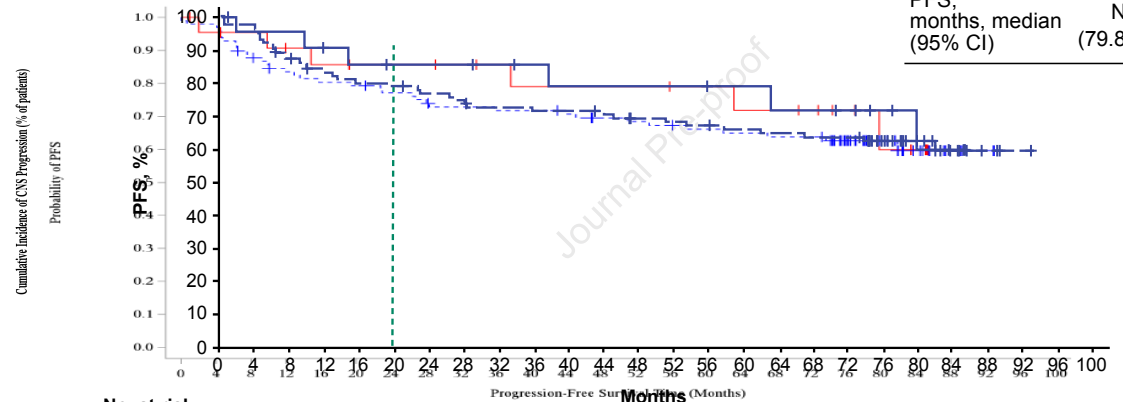
	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	44	85
PFS, months, median (95% CI)	NR (69.7-NR)	10.8 (9.0-12.8)
HR (95% CI)	**0.23 (0.16-0.34)**	

Kaplan-Meier Plot of Intra-Cranial Time to Progression Based on Derived Investigator Assessment (modified RECIST v1.1) – Full Analysis Set



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	66
Time to IC progression, months, median (95% CI)	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

	With dose reduction (n=23)	Without dose reduction (n=98)
Events, n	6	36
PFS, months, median (95% CI)	NR (79.8–NR)	NR (81.9–NR)



	With dose reduction (n=24)	Without dose reduction (n=99)
Events, n	0	6
Time to IC progression, months, median (95% CI)	NR (NR-NR)	NR (NR-NR)

Figure 14.2.1.32
PF-06463922 Protocol B7461006
Kaplan-Meier Plot of Intra-Cranial Time to Progression Based on Derived Investigator Assessment (modified RECIST v1.1) by 1st Lorlatinib Dose Reduction, landmark analysis at 26 weeks) - Full Analysis Set