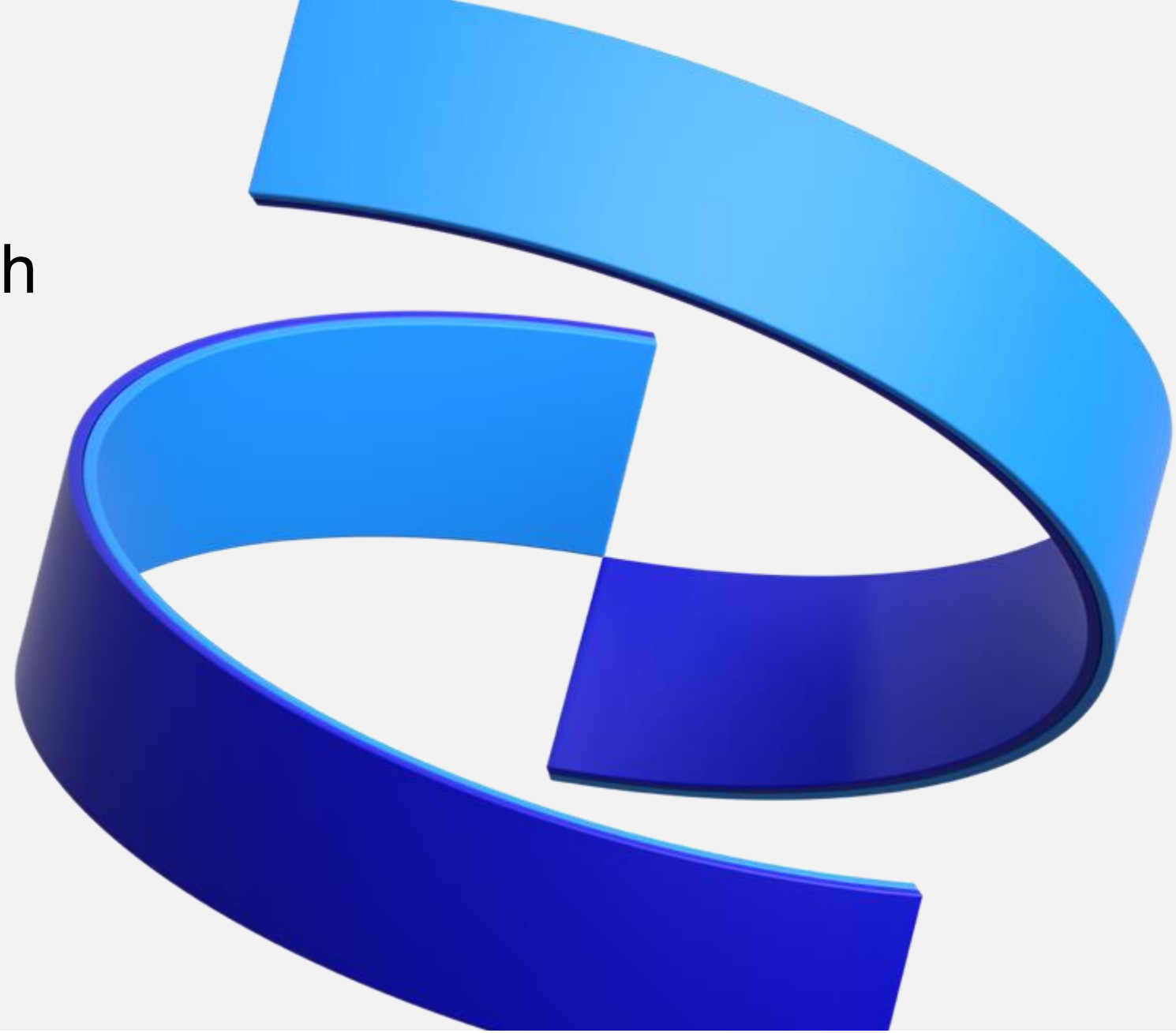
Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase 3 CROWN Study



April 2025

EM-DEU-lor-0117

Pfizer

Indication

- Lorlatinib as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor
- Lorlatinib as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after:
  - Alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
  - Crizotinib and at least one other ALK TKI

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Lorviqua® Summary of Product Characteristics; Pfizer, 2024.

CROWN: Study Overview

CROWN: Background

- ALK rearrangements occur in a subset of NSCLCs resulting in sensitivity to small-molecule ALK TKIs[1,2]
- Resistance to ALK TKIs commonly develops and often includes CNS progression[3–5]
- Lorlatinib is a highly potent, brain-penetrant, third-generation ALK TKI[6,7] with overall and intracranial activity in advanced ALK-positive NSCLC[3,7–9]
- The CROWN study is a randomized phase 3 study comparing lorlatinib versus crizotinib as first-line treatment in ALK-positive NSCLC[10,11]
  - 296 patients (104 study sites; 23 countries) were randomized from May 2017 to February 2019
  - Imaging assessments included chest, abdomen, and pelvis CT or MRI scans and brain MRI every 8 weeks

ALK, anaplastic lymphoma kinase; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Soda M, et al. *Nature*. 2007;448:561–566; 2. Kwak EL, et al. *N Engl J Med*. 2010;363:1693–1703; 3. Dagogo-Jack I, et al. *J Clin Oncol*. 2020;38:9595; 4. Gainor JF, et al. *Cancer Discov*. 2016;6:1118–1133; 5. Ali A, et al. *Curr Oncol*. 2013;20:e300–e306; 6. Johnson TW, et al. *J Med Chem*. 2014;57:4720–4744; 7. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590–1599; 8. Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654–1667; 9. Bauer TM, et al. *Target Oncol*. 2020;15:55–65; 10. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029; 11. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.12. Lorviqua® Summary of Product Characteristics; Pfizer, 2024. Lorbrena® [US Prescribing Information]. New York, NY: Pfizer Inc; 2023.

CROWN: Background – Cont'd

- Results presented here are from the:
  - Planned interim analysis (data cutoff: March 20, 2020)[1]
  - Unplanned, updated 5-year analysis (data cutoff: October 31, 2023)[2]
- The primary endpoint of PFS by BICR was met in the CROWN trial primary analysis (median follow-up for PFS: 18.3 months for patients receiving lorlatinib and 14.8 months for patients receiving crizotinib); median PFS was not estimable for the lorlatinib arm and was 9.3 months (95% CI: 7.6–11.1 months) with crizotinib (HR: 0.28; 95% CI: 0.19–0.41; *P*<0.0001)[1,3]
- Confirmed objective response by BICR was higher with lorlatinib (76%) than with crizotinib (58%); in patients with measurable baseline brain metastases, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)[1]
- The unplanned, updated 5-year analysis was performed at a median follow-up of 60.2 months for patients on lorlatinib (55.1 months for patients on crizotinib)[2]
  - **Limitations: no formal hypothesis testing was performed, given the PFS endpoint was previously met in the CROWN trial primary analysis; results are presented descriptively since the Type I error was spent at the primary analysis**

BICR, blinded independent central review; HR, hazard ratio; IC, intracranial response; PFS, progression-free survival.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029; 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 3. Lorviqua® Summary of Product Characteristics; Pfizer, 2024. Lorbrena® [US Prescribing Information]. New York, NY: Pfizer Inc; 2023.

CROWN: Study Design

KEY ELIGIBILITY CRITERIA

- Stage IIIB/IV ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx
- No prior systemic treatment for metastatic disease
- ECOG PS 0–2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required
- Patients with severe acute or chronic psychiatric conditions were excluded[a]

N=296

1:1 RANDOMIZATION

Lorlatinib 100 mg QD (n=149)

Crizotinib 250 mg BID (n=147)

Stratification factors

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

Treatment continued until disease progression or unacceptable toxicity

PRIMARY ENDPOINT

- PFS[b] by BICR

SECONDARY ENDPOINTS

- PFS (investigator assessed), ORR by BICR and investigator, ic-ORR, DOR and ic-DOR by BICR, ic-TTP by BICR, OS
- Safety: adverse reactions & lab abnormalities
- QoL

No crossover between treatment arms was permitted

[a]Including recent (within the past year) or active suicidal ideation or behavior.
[b]Defined as the time from randomization to RECIST-defined progression or death due to any cause.
ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Groups performance status; ic-DOR, intracranial duration of response; ic-ORR, intracranial objective response rate; ic-TTP, intracranial time to tumor progression; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, each day; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number: NCT03052608 (Study B7461006); 1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029.

CROWN: Study Participants

296 Patients Were Randomized

149 patients were assigned to receive lorlatinib	
149 received assigned treatment	
Patient status at data cutoff:	
74 continued to receive lorlatinib	
75 discontinued treatment	
36 had progressive disease	
15 had adverse event	
12 died	
9 withdrew consent	
2 had global deterioration of health	
1 had other reasons	
Analysis set	**n**
Intention-to-treat	149
Safety	149

147 patients were assigned to receive crizotinib	
142 received assigned treatment	
5 did not receive assigned treatment	
Patient status at data cutoff:	
7 continued to receive crizotinib	
135 discontinued treatment	
104 had progressive disease	
14 had adverse event	
9 withdrew consent	
4 died	
3 had global deterioration of health	
1 had other reasons	
Analysis set	**n**
Intention-to-treat	147
Safety	142

Data cutoff: October 31, 2023.

Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Baseline Patient Characteristics[1]

Footnote

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Age, years		
Mean (standard deviation)	59.1 (13.1)	55.6 (13.5)
Median (IQR)	61 (51–69)	56 (45–66)
Sex		
Female	84 (56)	91 (62)
Male	65 (44)	56 (38)
Race		
White	72 (48)	72 (49)
Asian	65 (44)	65 (44)
Black or African American	0 (0)	1 (1)
Missing	12 (8)	9 (6)
ECOG PS		
0	67 (45)	57 (39)
1	79 (53)	81 (55)
2	3 (2)	9 (6)
Smoking status		
Never smoked	81 (54)	94 (64)
Previous smoker	55 (37)	43 (29)
Current smoker	13 (9)	9 (6)
Current stage of disease		
Stage IIIA	1 (1)	0 (0)
Stage IIIB	12 (8)	8 (5)
Stage IV	135 (91)	139 (95)
Other[a]	1 (1)	0 (0)
Histology		
Adenocarcinoma	140 (94)	140 (95)
Adenosquamous carcinoma	6 (4)	5 (3)
Large cell carcinoma	0 (0)	1 (1)
Squamous cell carcinoma	3 (2)	1 (1)
Prior anticancer drug therapy[b]	12 (8)	9 (6)
Prior brain radiotherapy	9 (6)	10 (7)
Brain metastases at baseline[c]	38 (26)	40 (27)

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029; 2. Solomon BJ, et al. *J Clin Oncol*. 2022;40(21):3593–3602.

CROWN: Baseline Patient Characteristics Footnote

Data are presented as no. of patients (%) unless otherwise specified.

[a]The disease stage in one patient who had locally advanced disease at trial entry was defined according to the American Joint Committee on Cancer (AJCC), version 8.0, instead of AJCC, version 7.0, as required by the protocol. This stage was therefore classified as "other."

[b]According to the protocol, previous adjuvant or neoadjuvant anticancer therapy was allowed if it had been completed >12 months before randomization. One patient with metastatic disease who had received previous chemotherapy was reported as having a protocol violation.

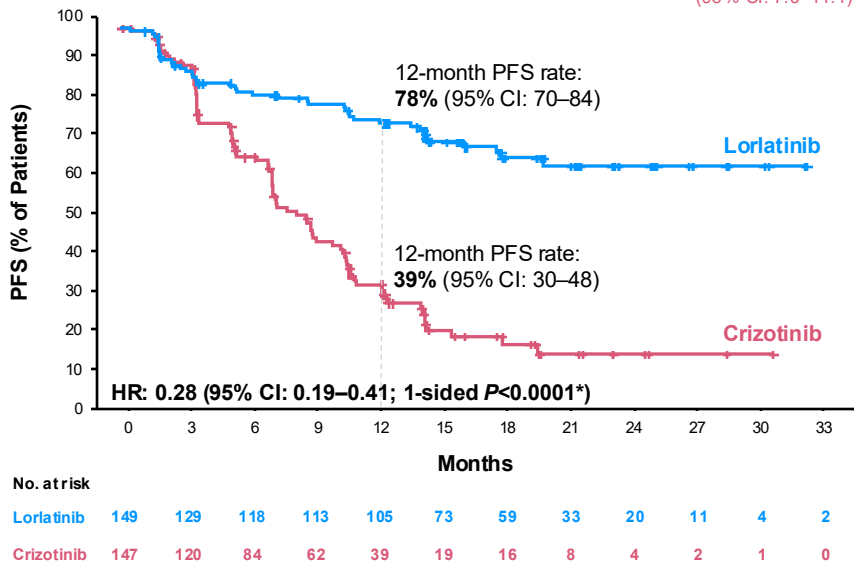
[c]21% of the patients with brain metastases had received prior brain radiotherapy on the lorlatinib arm and 25% on the crizotinib arm.

CROWN: Planned Interim Analysis Efficacy

CROWN: PFS (Planned Interim Analysis, ITT population)

PFS by BICR[1,2]

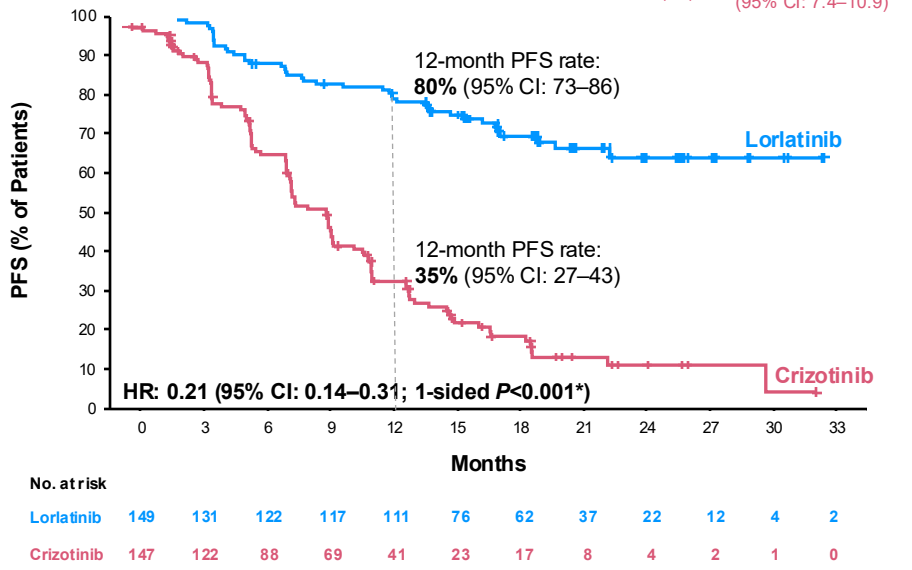
	Patients, n	Events, n %	mPFS, months
Lorlatinib	149	41 (28)	NR (95% CI: NR–NR)
Crizotinib	147	86 (59)	9.3 (95% CI: 7.6–11.1)



This analysis was a **primary endpoint** for the CROWN study

PFS by Investigator Assessment[3,4]

	Patients, n	Events, n %	mPFS, months
Lorlatinib	149	40 (27)	NR (95% CI: NR–NR)
Crizotinib	147	104 (71)	9.1 (95% CI: 7.4–10.9)



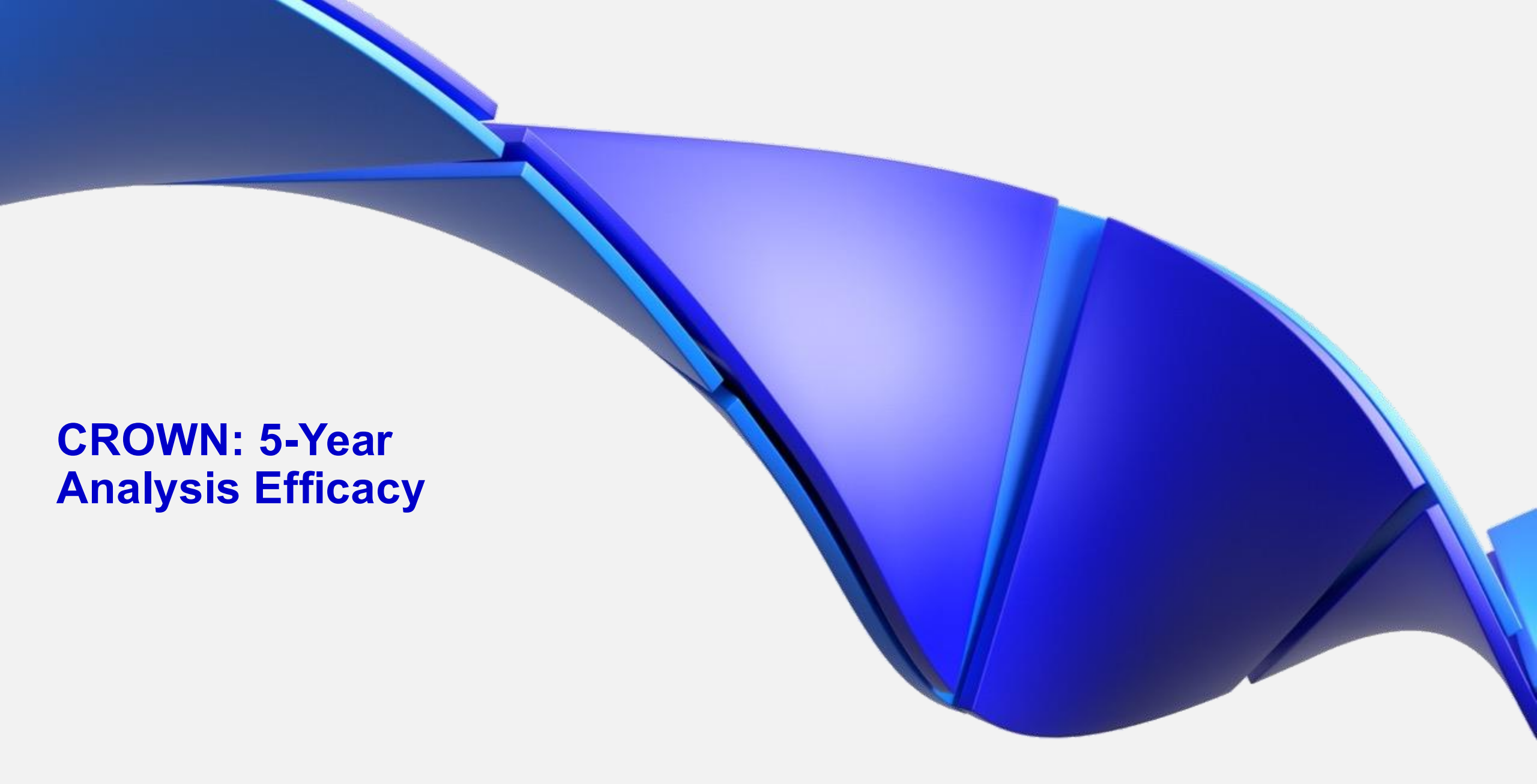
This analysis was a **secondary endpoint** for the CROWN study

The primary endpoint of PFS by BICR was met in the CROWN trial primary analysis and was supported by the secondary endpoint of PFS by investigator assessment[2,4]

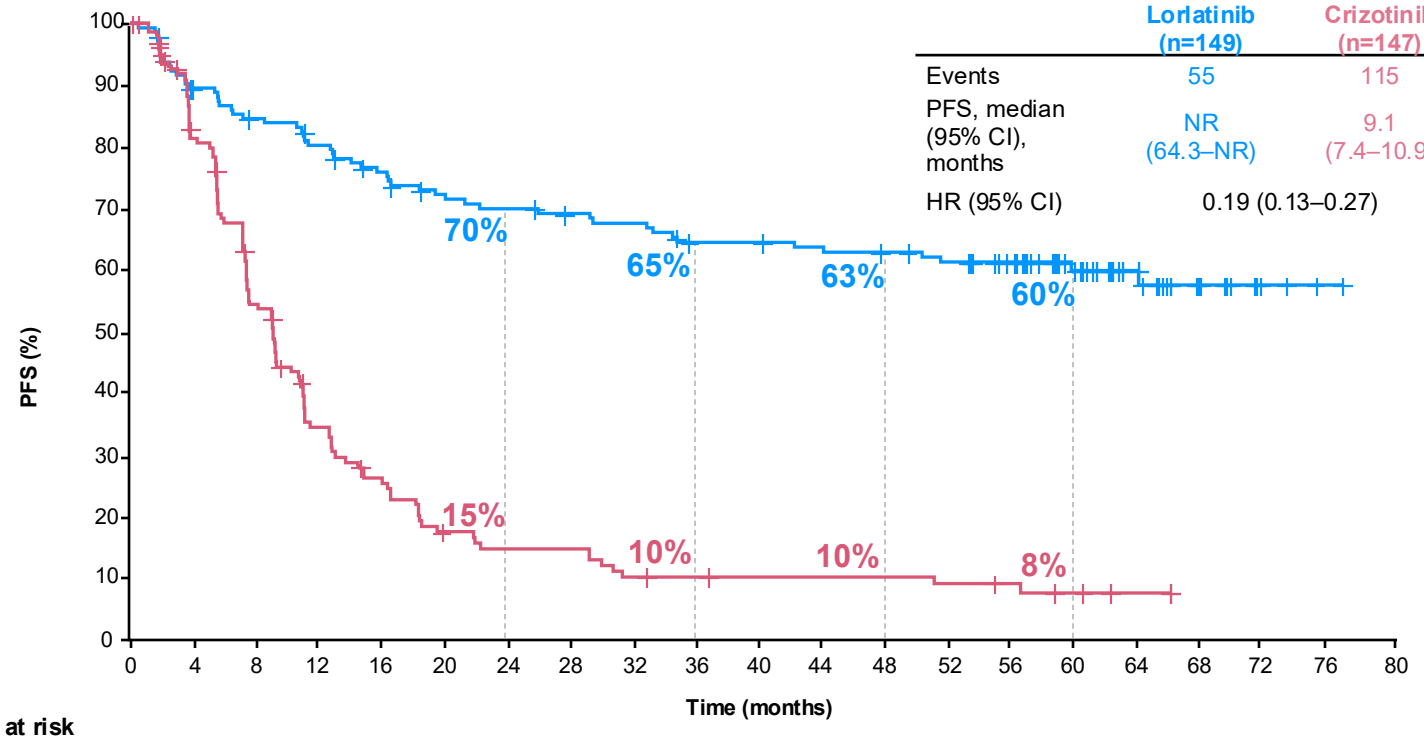
*By stratified log-rank test.
Data cutoff: March 20, 2020.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

1. Lorviqua® Summary of Product Characteristics; Pfizer, 2024. Lorbrena® [US Prescribing Information]. New York, NY: Pfizer Inc; 2023; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029; 3. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 4. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–2029; Supplementary Appendix.

CROWN: 5-Year Analysis Efficacy



CROWN: PFS by Investigator Assessment (ITT Population)



After 5 years of follow-up, the median progression-free survival with lorlatinib treatment has not been reached, with an investigator-assessed PFS rate of 60%, with only 6 additional PFS events occurring between Year 3 and Year 5.
This PFS benefit, which exceeds 5 years, is the longest reported PFS in advanced NSCLC to date.

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by investigator assessment: lorlatinib, 60.2 months; crizotinib, 55.1 months.
CI, confidence interval; HR, hazard ratio; NR, not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival.
Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

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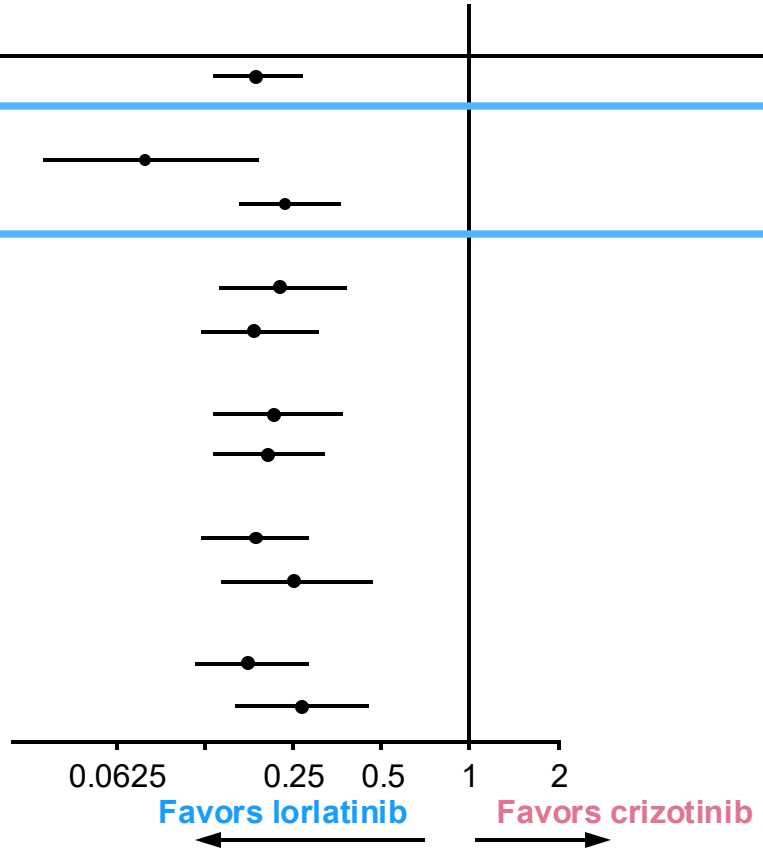
PFS by Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



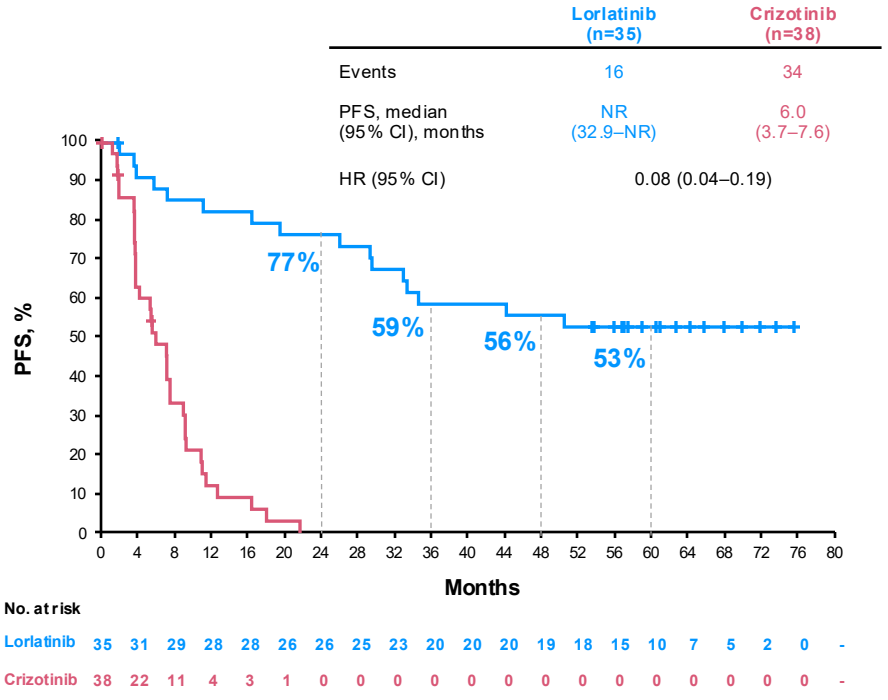
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.

PFS, progression-free survival.

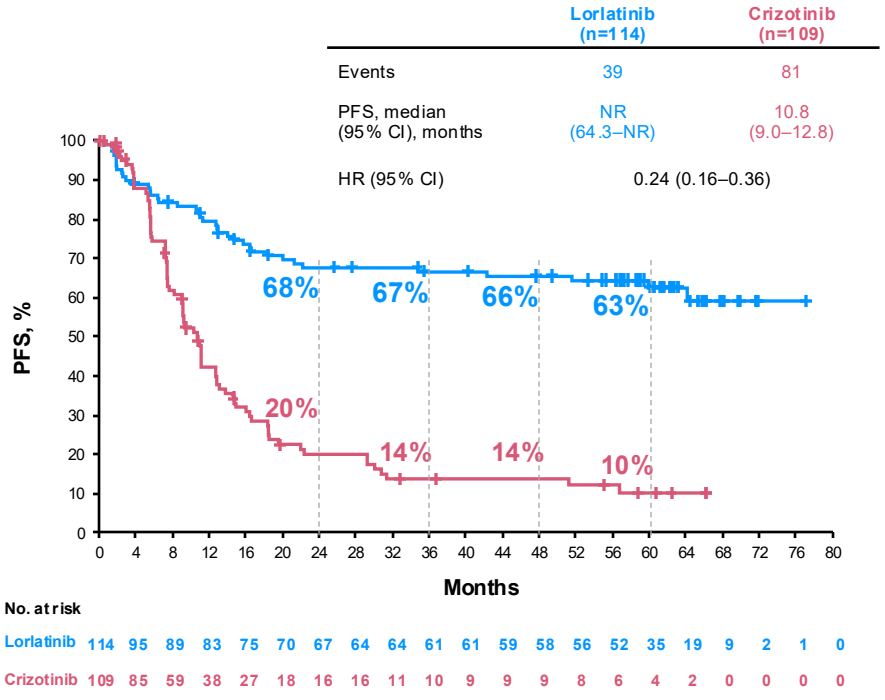
Solomon BJ, et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL.

CROWN: PFS by Investigator Assessment in Patients With and Without Brain Metastases at Baseline[a,1]

Patients With Baseline Brain Metastases



Patients Without Baseline Brain Metastases



In patients both with and without baseline brain metastases, lorlatinib improved PFS with median PFS not reached in either group[2]

[a]Randomization was stratified according to the presence of brain metastases (yes or no).[3]
Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by investigator assessment: lorlatinib, 60.2 months; crizotinib, 55.1 months.
CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 3. Shaw AT, et al. N Engl J Med. 2020;383(21):2018–2029.

CROWN: Tumor Response by Investigator Assessment[1] (ITT Population)

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Confirmed ORR (%)	81	63
(95% CI)	(73–87)	(54–70)
Odds ratio[a]	2.43 (1.43–4.43)	
CR, n (%)	15 (10)	3 (2)
PR, n (%)	105 (70)	89 (61)
SD, n (%)	16 (11)	38 (26)
PD, n (%)	8 (5)	7 (5)
NE, n (%)	5 (3)	10 (7)
Median DOR, months (95% CI)	NR (NR–NR)	9.2 (7.5–11.1)

Objective response rates by investigator assessment were in line with those reported by BICR in the previous analyses[1-3]

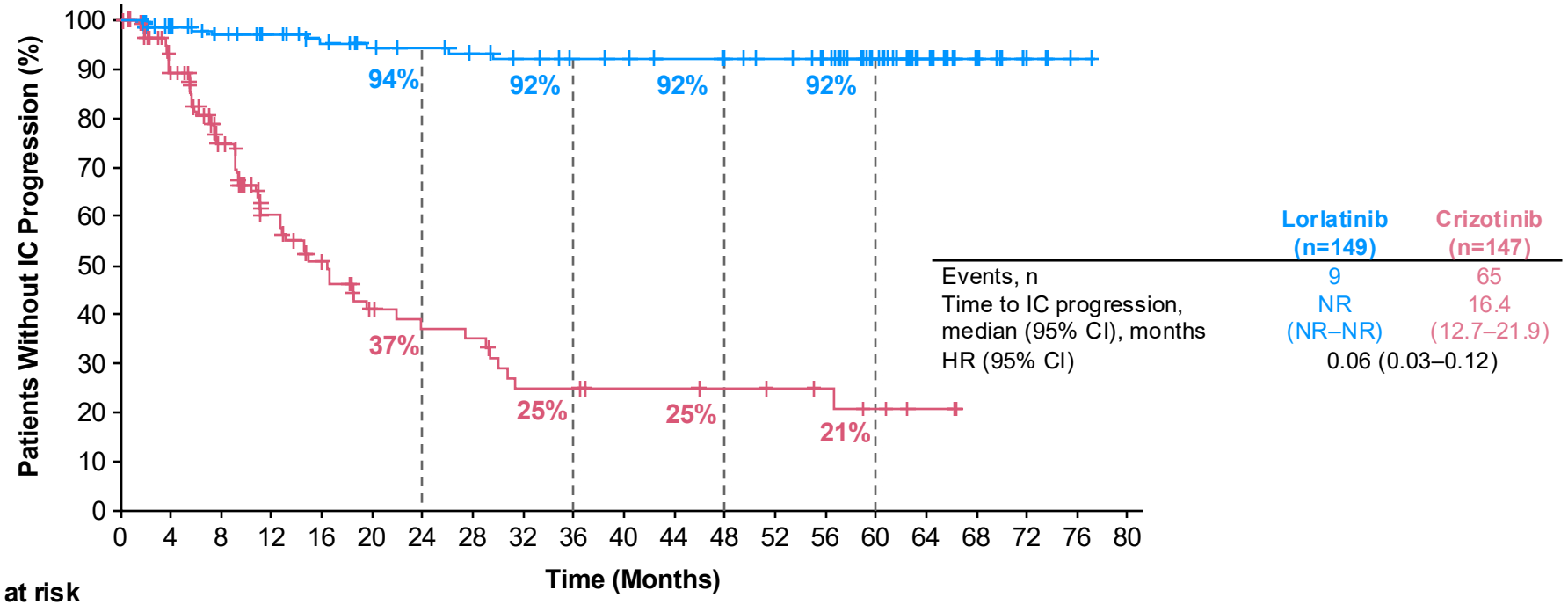
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.

[a]Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018–2029; 3. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366.

CROWN: Time to IC Progression[a] by Investigator Assessment[1] (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR–NR)	16.4 (12.7–21.9)
HR (95% CI)	0.06 (0.03–0.12)	

Lorlatinib delayed intracranial progression versus crizotinib, with no new IC events occurring between between Year 3 and Year 5.

A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.

[a]Time to CNS progression was defined as the time from randomization to the first objective progression of CNS disease (either new brain metastases or progression of existing brain metastases). Tumour assessments, including brain magnetic resonance imaging, have been performed every 8 weeks in all patients throughout the study. The secondary endpoint of intracranial time to progression was not part of the statistical testing hierarchy.[1,2]

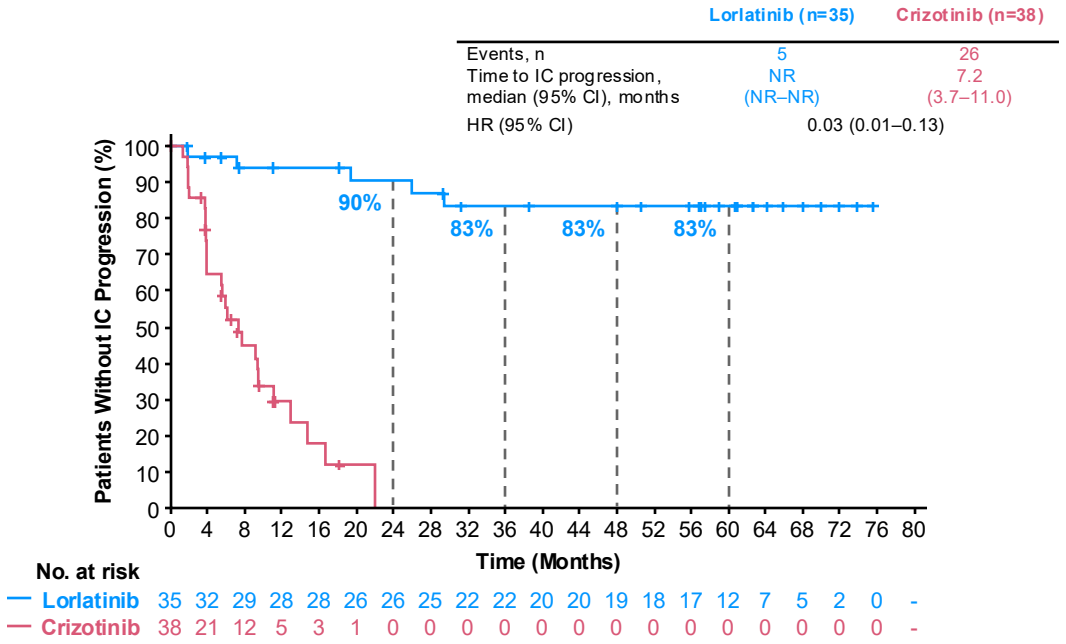
Data cutoff: October 31, 2023. Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.

CI, confidence interval; HR, hazard ratio; IC, intracranial; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.

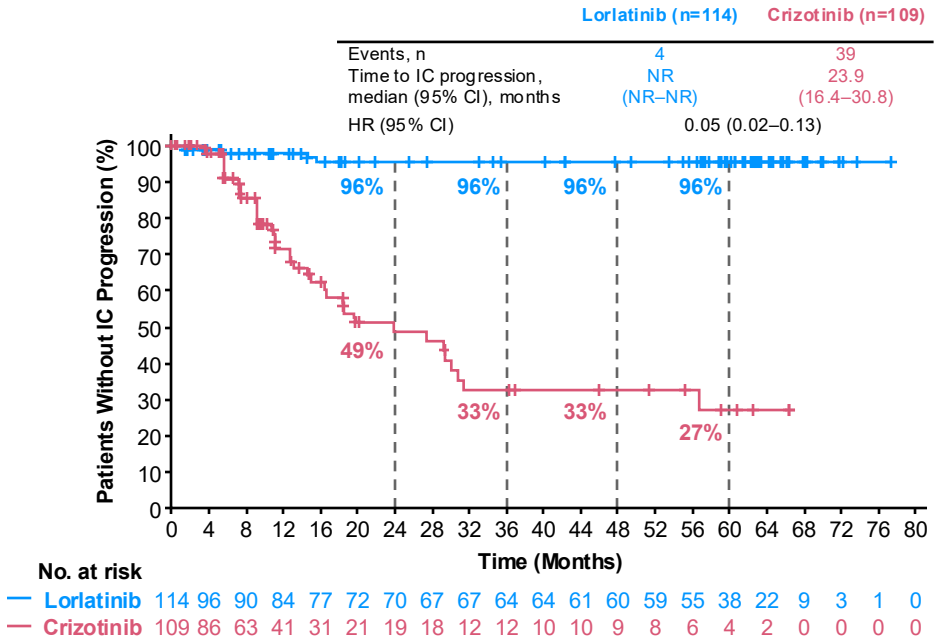
1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018–2029.

CROWN: Time to IC Progression[a] by Investigator Assessment in Patients With and Without Brain Metastases at Baseline[b,1]

Patients With Baseline Brain Metastases



Patients Without Baseline Brain Metastases



Lorlatinib delayed the onset of CNS disease versus crizotinib in patients with and without baseline brain metastases. Of 114 lorlatinib-treated patients without baseline brain metastases, only 4 patients developed intracranial lesions while on lorlatinib treatment, suggesting lorlatinib may cause a delay in the development of brain metastases.

[a]Time to CNS progression was defined as the time from randomization to the first objective progression of CNS disease (either new brain metastases or progression of existing brain metastases). The secondary endpoint of intracranial time to progression was not part of the statistical testing hierarchy.[2] These results are presented for descriptive purposes only and should be interpreted within this context. [b]Randomization was stratified according to the presence of brain metastases (yes or no).[2] Data cutoff: October 31, 2023. Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; IC, intracranial; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018–2029.

CROWN: Overall and IC Efficacy by Investigator Assessment

	Lorlatinib	Crizotinib
ITT population, n	**149**	**147**
Confirmed ORR by investigator assessment (95% CI), %	81 (73–87)	63 (54–70)
Complete response, n (%)	15 (10)	3 (2)
DOR, median (95% CI), months	NR (NR–NR)	9.2 (7.5–11.1)
Patients with measurable and/or non-measurable baseline brain metastases	**35**	**38**
Confirmed IC ORR by investigator assessment (95% CI), %	60 (42–76)	11 (3–25)
Complete IC response, n (%)	17 (49)	2 (5)
IC DOR, median (95% CI), months	NR (NR–NR)	12.8 (7.5–NR)
Patients with measurable baseline brain metastases, n	**12**	**6**
Confirmed IC ORR by investigator assessment (95% CI), %	92 (62–100)	33 (4–78)
Complete IC response, n (%)	7 (58)	0
IC DOR, median (95% CI), months	NR (NR–NR)	10.2 (7.5–NR)

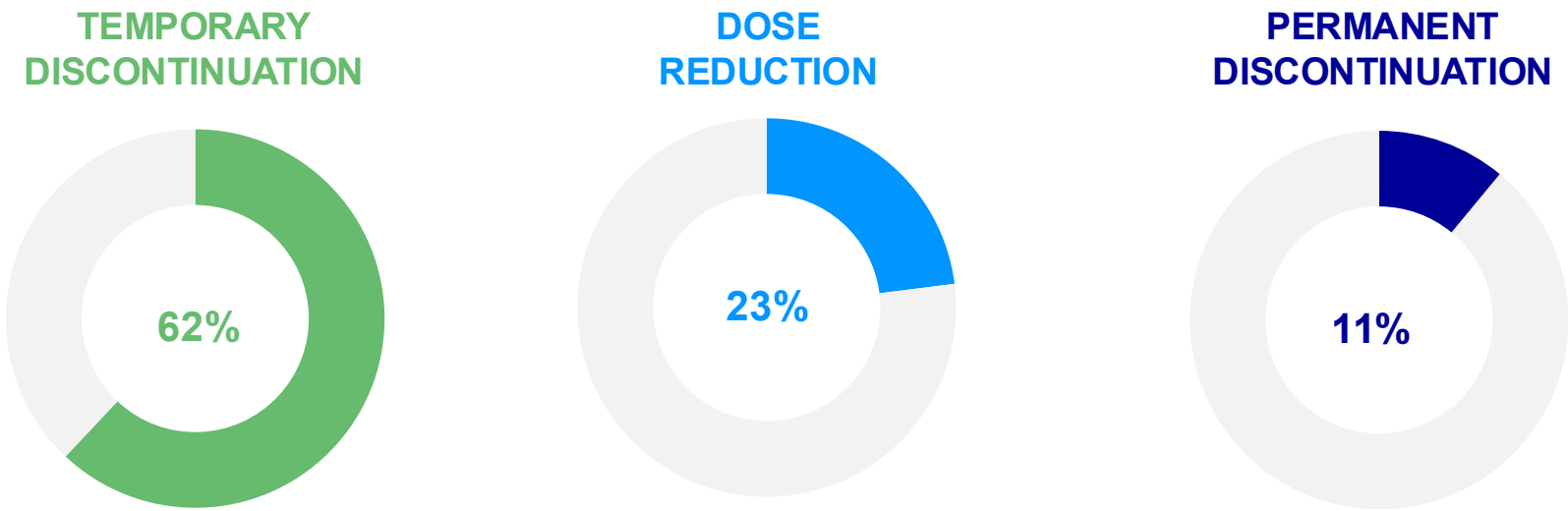
In patients with baseline brain metastases, lorlatinib resulted in high intracranial response, the majority of which were complete and durable responses

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
Median duration of treatment: lorlatinib, 57.0 months; crizotinib, 9.6 months.
CI, confidence interval; DOR, duration of response; IC, intracranial; ITT, intent to treat; NR, not reached; ORR, objective response rate.
Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: 5-Year Analysis Efficacy by First Lorlatinib Dose Reduction Within 16 Weeks

Dose Modifications in CROWN[1] (Safety Population)

AEs leading to… (lorlatinib-treated patients, N=149)

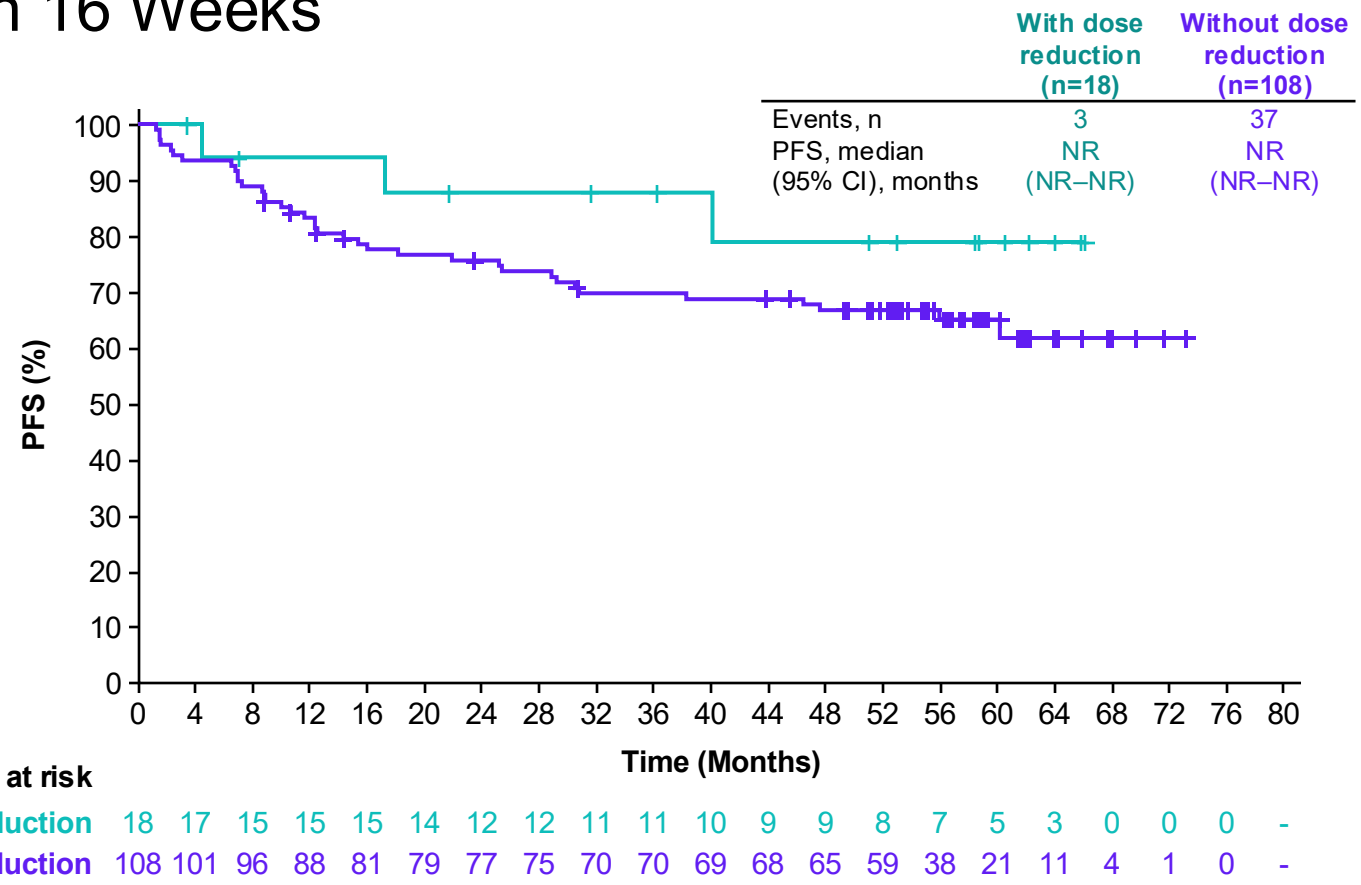


- AEs seldom resulted in permanent discontinuation and were generally manageable through dose modification and/or standard medical therapy[1,2]
- TRAEs led to permanent treatment discontinuation in 8 patients (5%), which occurred during the first 26 months[1]

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
AE, adverse event; TRAE, treatment-related adverse event.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366.

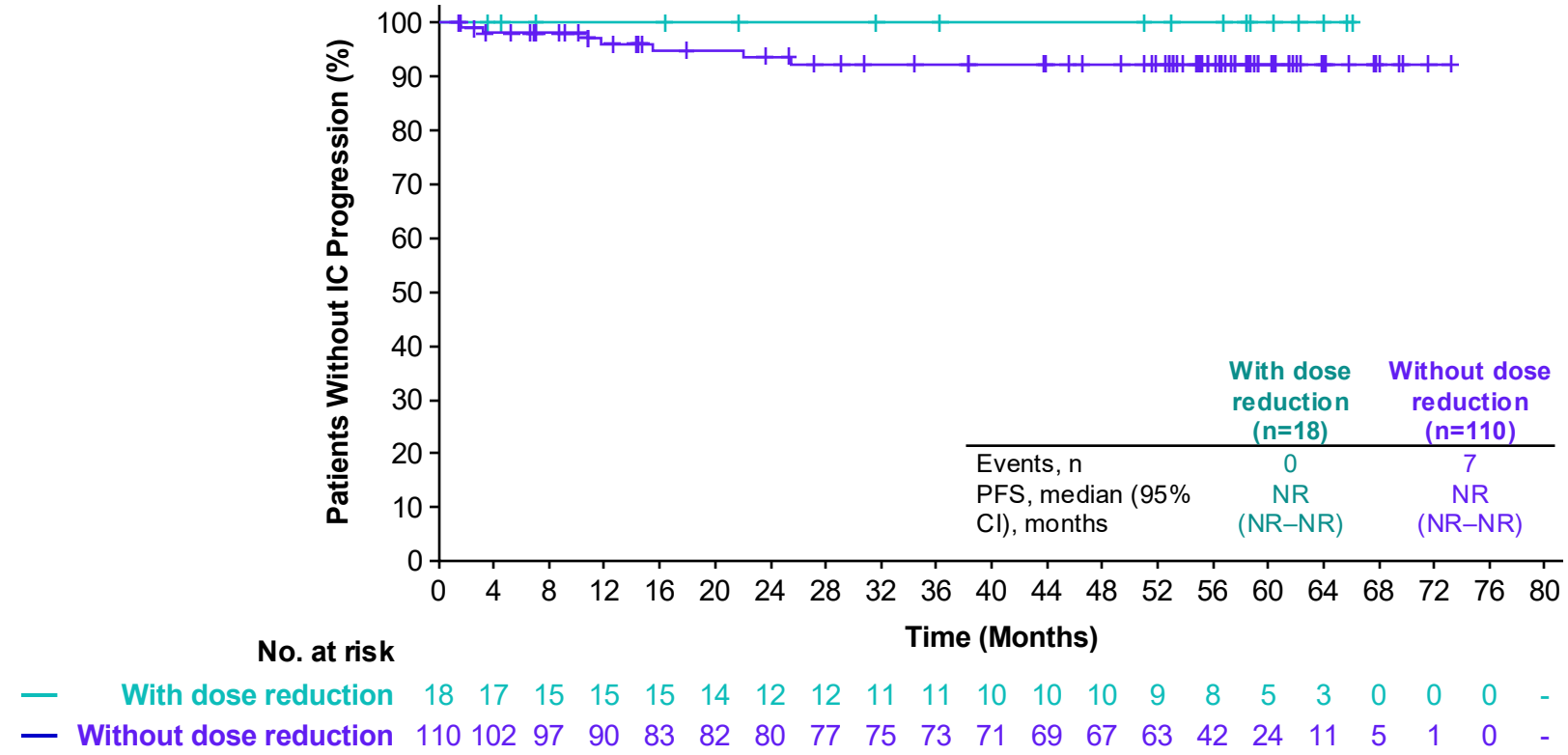
CROWN: PFS by Investigator Assessment by First Lorlatinib Dose Reduction Within 16 Weeks



Dose reduction did not appear to impact median PFS

Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
IC, intracranial; NR, not reached; PFS, progression-free survival.
Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Time to IC Progression Based on Investigator Assessment by First Lorlatinib Dose Reduction Within 16 Weeks



Dose reduction did not appear to impact time to intracranial progression

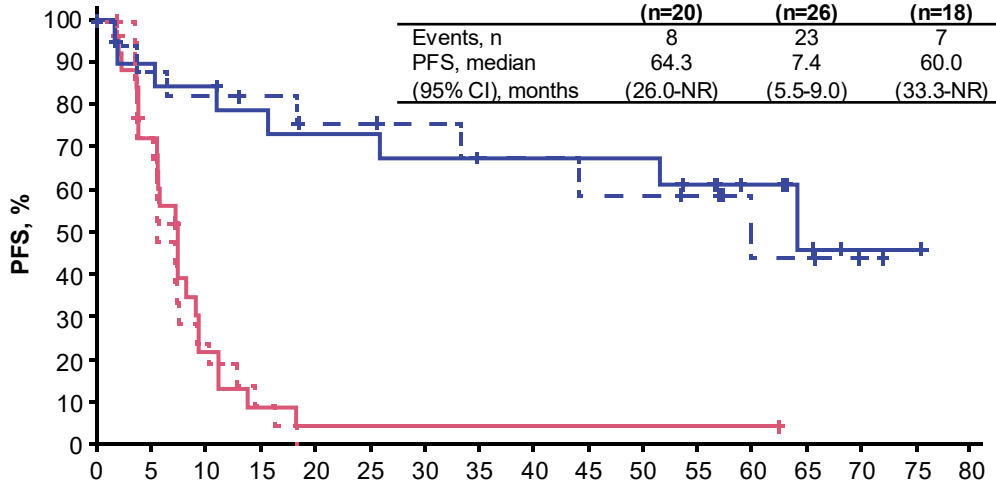
Data cutoff: October 31, 2023.
A limitation of this study is that this updated 5-year analysis, while providing substantial additional follow-up, was not prespecified. Therefore, the results provided are descriptive and exploratory in nature, and formal statistical comparisons between the treatment groups are not available.
IC, intracranial; NR, not reached; PFS, progression-free survival.
Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Genomic Analysis

CROWN: Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers[1]

PFS by *EML4::ALK* Fusion Variant

	Variant 1		Variant 3a/b	
	Lorlatinib (n=20)	Crizotinib (n=26)	Lorlatinib (n=18)	Crizotinib (n=23)
Events, n	8	23	7	21
PFS, median (95% CI), months	64.3 (26.0-NR)	7.4 (5.5-9.0)	60.0 (33.3-NR)	5.6 (5.3-7.6)



***EML4::ALK* variant 1**

No. at risk

Lorlatinib	20	17	16	14	13	13	12	11	11	11	11	9	6	3	1	1	0
Crizotinib	26	18	5	2	1	1	1	1	1	1	1	1	1	0	0	0	0

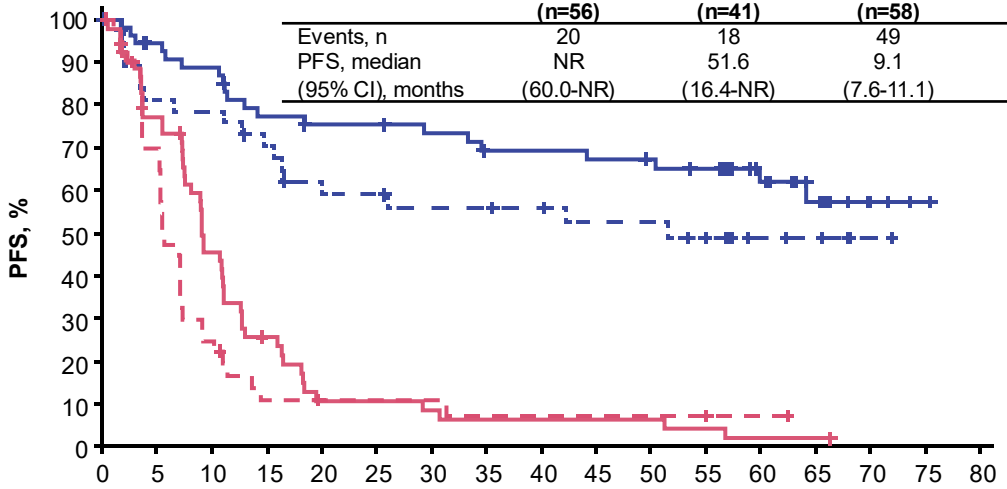
***EML4::ALK* variant 3**

No. at risk

Lorlatinib	18	15	14	13	11	11	9	8	8	7	7	6	3	3	1	0	-
Crizotinib	23	15	5	2	0	0	0	0	0	0	0	0	0	0	0	0	-

PFS by *TP53* Status

	Lorlatinib		Crizotinib	
	TP53 mut (-) (n=56)	*TP53* mut (+) (n=41)	*TP53* mut (-) (n=58)	*TP53* mut (+) (n=42)
Events, n	20	18	49	36
PFS, median (95% CI), months	NR (60.0-NR)	51.6 (16.4-NR)	9.1 (7.6-11.1)	5.7 (5.4-7.2)



Lorlatinib

No. at risk

TP53 mut (-)	56	50	47	40	38	38	36	33	33	32	31	28	20	12	4	1	0
TP53 mut (+)	41	30	29	25	21	20	18	18	17	15	15	12	6	4	1	0	0

Crizotinib

No. at risk

TP53 mut (-)	58	40	23	12	5	5	4	3	3	3	3	2	1	1	0	-	-
TP53 mut (+)	42	28	10	4	3	3	3	2	2	2	2	2	1	0	0	-	-

Lorlatinib treatment can benefit patients with poor prognostic biomarkers or difficult-to-treat alterations such as *EMLK4::ALK* variant 3 or *TP53* co-mutation relatively more than crizotinib[2]

Data cutoff: October 31, 2023.

ALK, anaplastic lymphoma kinase; CI, confidence interval; mut, mutation; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Solomon BJ, et al. Presented at: ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL; 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Emerging New ALK Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment[1]

n (%)	**Lorlatinib (n=31)**	**Crizotinib (n=89)**
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA samples at the end of lorlatinib treatment may indicate that lorlatinib can effectively suppress the emergence of new ALK kinase domain mutations[2]

Data cutoff: October 31, 2023.
ALK, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA.
1. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581; 2. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581.

CROWN: Summary

CROWN: Summary

Efficacy

- After 5 years of follow-up, median PFS has yet to be reached in the lorlatinib group, corresponding to the longest PFS ever reported with any single-agent molecular targeted treatment in advanced NSCLC and across all metastatic solid tumours[1,2]
- Lorlatinib delayed intracranial progression versus crizotinib and elicited deep and durable intracranial responses in patients with baseline brain metastases[1]
- Lorlatinib is effective in controlling pre-existing brain metastases as well as in protecting against the development of new brain metastases[1]

Safety

- With longer exposure to lorlatinib, the frequency and severity of cardiovascular and CNS AEs were in line with prior analyses[1,3,4]
- The frequency of permanent discontinuation due to AEs was numerically similar in the lorlatinib and crizotinib arms[1]
- **Long-term analysis of kinetics and management of AEs[5]**
  - With long exposure to lorlatinib, no new safety signals emerged, and treatment discontinuation remained low after 5 years of follow-up
  - Most AEs resolved with dose modifications indicating that these strategies are effective to mitigate toxicity

AE, adverse event; ALK, anaplastic lymphoma kinase; CNS, central nervous system; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. Data Supplement. doi:10.1200/JCO.24.00581.3. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354–366. Supplementary Appendix. 5. Bauer TM, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.

CROWN: Summary

Other Analyses

- PFS and time to intracranial progression were similar in patients who had lorlatinib dose reduction within the first 16 weeks and those who had no dose reductions, indicating that dose reduction may be an effective strategy to mitigate toxicity without compromising systemic or intracranial efficacy[1]
- Lorlatinib treatment can benefit patients with poor prognostic biomarkers or difficult-to-treat alterations relatively more than crizotinib and can effectively suppress the emergence of new ALK kinase domain mutations[1,2]
- PFS2 results indicated that clinical benefit was prolonged following lorlatinib vs crizotinib and was maintained with subsequent systemic anticancer therapies[3]

Conclusion

- The systemic efficacy results coupled with prolonged intracranial efficacy and the absence of new safety signals represent an unprecedented outcome for patients with advanced ALK-positive NSCLC and set a new benchmark for targeted therapies in cancer[1]

ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PFS2, time from randomization to the date of disease progression with first subsequent systemic anticancer therapy or death.

1. Solomon BJ, et al. *J Clin Oncol*. 2024. doi:10.1200/JCO.24.00581. 2. Solomon BJ, et al. *J Clin Oncol*. 2024. Supplementary Appendix. doi:10.1200/JCO.24.00581. 3. Mok. TSK, et al. Presented at: WCLC Annual Meeting; September 7-10th, 2024; San Diego, CA.