

Patterns of progression and efficacy of subsequent therapy in patients with advanced *ALK*+ NSCLC in the phase 3 CROWN study

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Conclusions

- Consistent with the durable progression-free survival (PFS) benefit at 7 years,¹ lorlatinib substantially delayed disease progression, with median time to progression (TTP) not reached and a pronounced treatment effect when assessed specifically on progression events (HR, 0.15)
- Clinical benefit extended beyond first progression, as reflected by higher response rates to first subsequent therapy and a substantial improvement in time from randomization to disease progression with first subsequent systemic anticancer therapy or death (PFS2) with a HR of 0.43
- Overall, lorlatinib delivered durable long-term disease control, with clinical benefit extending to subsequent treatments



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Funding: The study was sponsored by Pfizer.

Acknowledgments: The authors thank the participating patients and their families, investigators, sub-investigators, research nurses, study coordinators, and operations staff. Editorial assistance was provided by Caitlin Cash, PhD, of Nucleus Global, and was funded by Pfizer.

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Presented at the IASLC 2026 World Conference on Lung Cancer
September 12-15, 2026 | Seoul, Republic of Korea

Background

- Lorlatinib, a potent, brain-penetrant anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), is indicated for the treatment of patients with advanced or metastatic *ALK*-positive non-small cell lung cancer (NSCLC)^{2,3}
- After 7 years of follow-up in the phase 3 CROWN study (NCT03052608), median PFS was not reached (NR; 95% CI, 68.5 months-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9) with crizotinib¹
 - Since the 5-year analysis,⁴ 7 new PFS events were reported with lorlatinib; 4 were disease progression events and 3 were deaths considered not treatment related
- In this analysis, we evaluated PFS2, patterns of progression, and subsequent anticancer therapies in the CROWN study after 7 years of follow-up
- As a complementary endpoint to PFS, a post hoc analysis evaluated TTP to assess the effect of treatment on disease progression independent of deaths occurring before progression

Results

- At 7 years, the probability of patients to remain free from disease progression was 63% with lorlatinib compared with 3% with crizotinib (**Figure 1**)
- Median TTP was NR (95% CI, 88.4 months-NR) with lorlatinib and 9.2 months (95% CI, 7.6-11.1) with crizotinib. The HR for disease progression was 0.15 (95% CI, 0.10-0.22)
- The median follow-up for PFS2 was 84.9 months (95% CI, 83.0-87.2) and 86.0 months (95% CI, 83.9-87.2) with lorlatinib and crizotinib, respectively; the median PFS2 was NR (95% CI, 80.0 months-NR) and 34.7 months (95% CI, 24.9-44.4), respectively (**Figure 2**)
 - HR was 0.43 (95% CI, 0.31-0.59)
 - 7-year PFS2 probability was 57% with lorlatinib and 27% with crizotinib
- In total, 83 of 149 (56%) and 138 of 142 (97%) patients had discontinued treatment with lorlatinib and crizotinib, respectively
- At the time of this analysis, 42 patients in the lorlatinib group and 116 in the crizotinib group received ≥1 subsequent systemic anticancer therapy (**Table 1**)
 - The first subsequent treatment was an ALK TKI in 24 (57%) and 107 (92%) patients and chemotherapy (chemo) in 17 (40%) and 5 (4%), respectively
- Median duration of the first subsequent treatment was 10.5 months (IQR, 2.6-24.1) in the lorlatinib group and 15.8 months (IQR, 5.5-53.5) in the crizotinib group
- Objective response rates with the first subsequent systemic anticancer therapy were numerically higher in patients previously treated with lorlatinib (26.2%) vs crizotinib (19.8%) (**Table 2**)
 - Higher response rates were observed regardless of whether they received an ALK TKI or non-ALK TKI as the first subsequent treatment

Figure 1. Time to progression

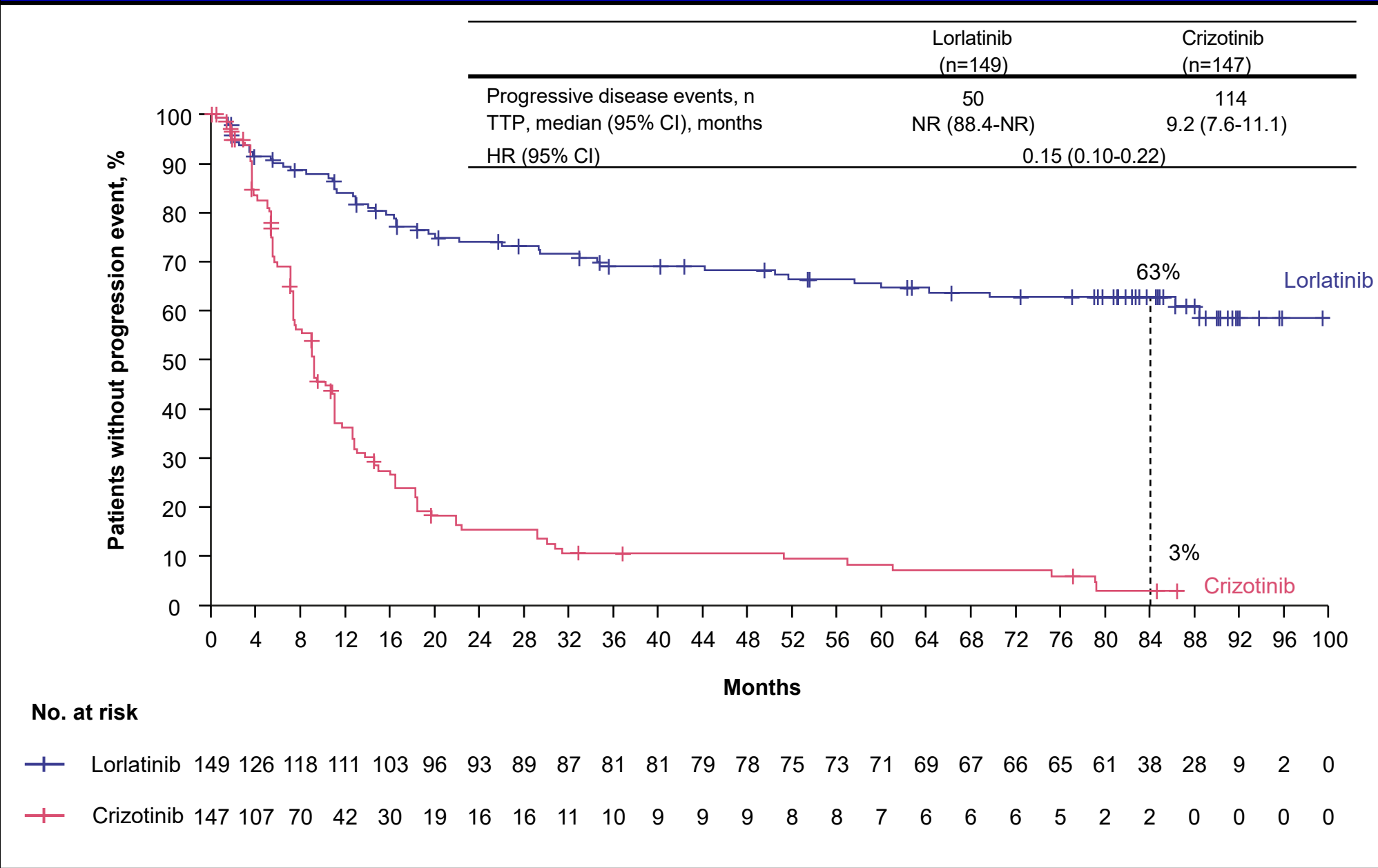
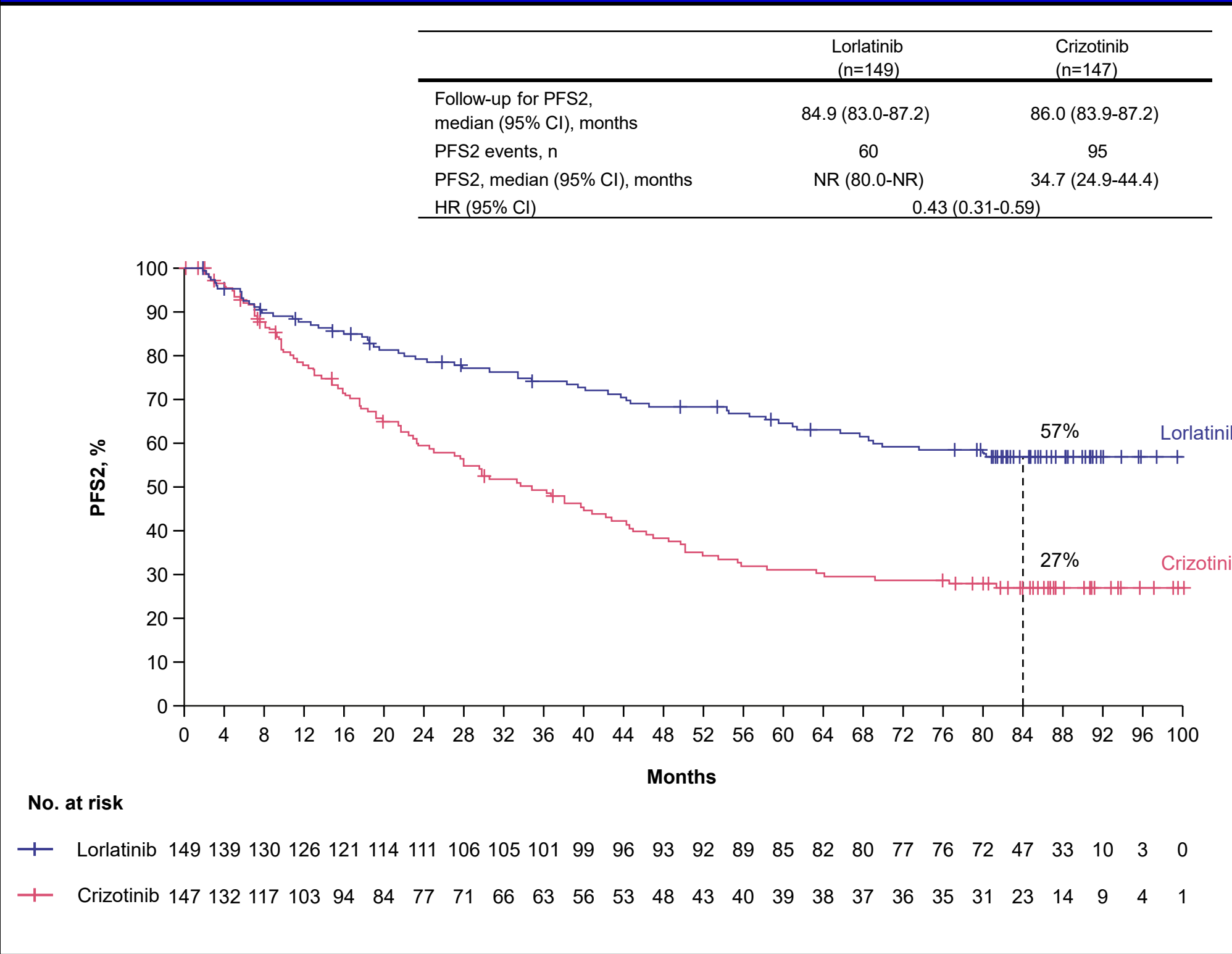


Figure 2. PFS2



Methods

- The CROWN study is an ongoing, international, open-label, randomized, phase 3 trial comparing lorlatinib vs crizotinib in patients with previously untreated advanced *ALK*-positive NSCLC
 - Patients were randomized 1:1 to receive oral lorlatinib 100 mg once daily or crizotinib 250 mg twice daily
- The primary endpoint was PFS by blinded independent central review; secondary endpoints included investigator-assessed PFS, PFS2, and outcomes of subsequent anticancer therapies
- TTP (post hoc endpoint) was calculated from randomization until disease progression
- Data cutoff for this analysis was October 31, 2025



Figure 3. Subsequent treatments in patients who had an ALK TKI or chemo as the first subsequent treatment after lorlatinib

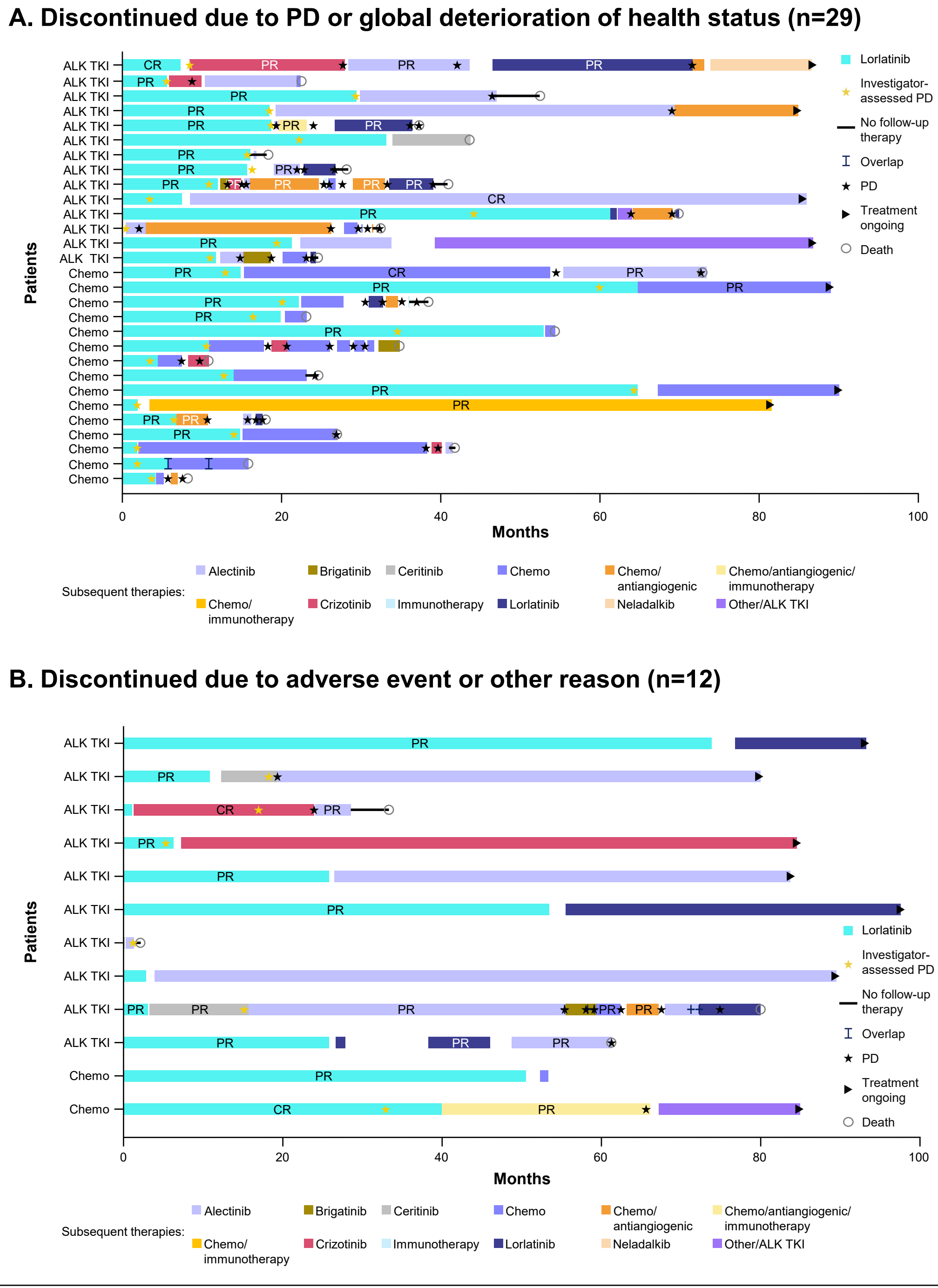
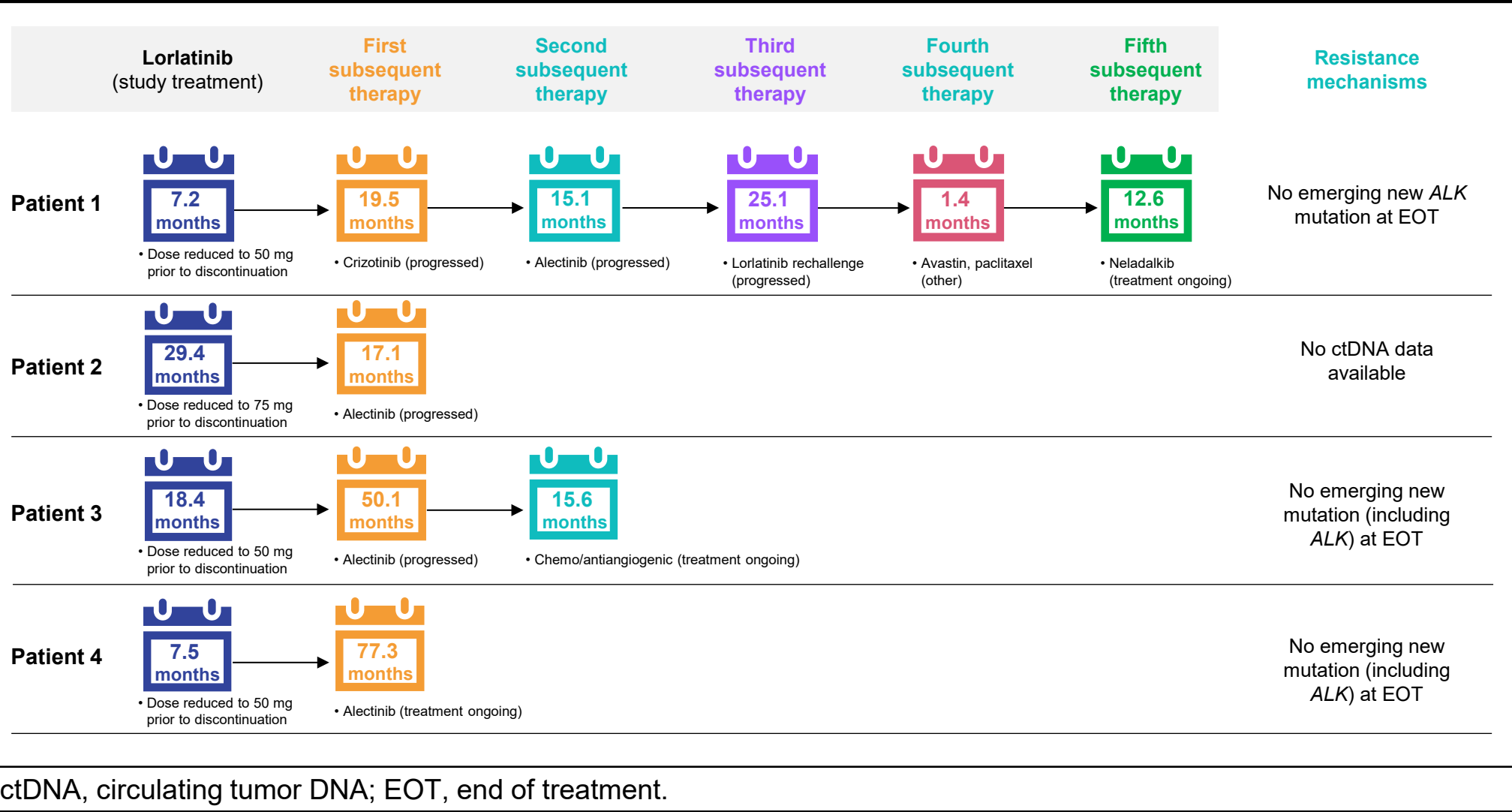


Figure 4. Patients who discontinued due to PD on lorlatinib and received an ALK TKI as first subsequent treatment for ≥12 months



- Separately, among patients who had disease progression on study treatment, 28 of 50 (56%) in the lorlatinib group and 42 of 114 (37%) in the crizotinib group continued treatment beyond progression according to the protocol, based on investigator-assessed clinical benefit
 - Median duration of treatment beyond progression was 19.0 weeks (IQR, 7.1-78.6) and 12.1 weeks (IQR, 5.9-20.9), respectively
- 8 of 28 patients who continued lorlatinib beyond progression received concomitant anticancer therapy, including concomitant radiation therapy in 7 patients and surgical resection of lung lesion in 1 patient

Table 1. Summary of subsequent treatments

	Lorlatinib (n=42)	Crizotinib (n=116)
No. of subsequent systemic anticancer therapies, n (%)		
1	20 (48)	58 (50)
2	9 (21)	26 (22)
3	3 (7)	12 (10)
≥4	10 (24)	20 (17)
First subsequent systemic anticancer therapy, n (%)		
ALK TKI	24 (57)	107 (92)
Alectinib	12 (50)	72 (67)
Crizotinib	4 (17)	5 (5)
Lorlatinib	4 (17)	5 (5)
Ceritinib	3 (13)	4 (4)
Brigatinib	1 (4)	21 (20)
Neladalkib	0	1 (1)
Chemo-based regimen ^a	17 (40)	5 (4)
Other ^b	1 (2)	4 (3)
Duration of treatment on first subsequent therapy, median (IQR), months		
Overall	10.5 (2.6-24.1)	15.8 (5.5-53.5)
ALK TKI as first subsequent therapy ^c	11.9 (2.4-32.4)	19.1 (7.8-59.8)
Non-ALK TKI as first subsequent therapy ^d	7.9 (2.6-24.1)	1.0 (0.8-1.8)

^aIncludes chemo alone or in combination with antiangiogenic and/or immunotherapy.
^bIncludes investigational drugs, cabozantinib, and osimertinib.
^cNumber of patients is 24 in the lorlatinib group and 107 in the crizotinib group.
^dNumber of patients is 18 in the lorlatinib group and 9 in the crizotinib group.

Table 2. Outcomes with first subsequent treatment

Study treatment	Lorlatinib			Crizotinib		
	Overall (n=42)	Any ALK TKI (n=24) ^a	Any non-ALK TKI (n=18) ^b	Overall (n=116)	Any ALK TKI (n=107) ^a	Any non-ALK TKI (n=9) ^b
Objective response rate, % (95% CI) ^c	26.2 (13.9-42.0)	25.0 (9.8-46.7)	27.8 (9.7-53.5)	19.8 (13.0-28.3)	19.6 (12.6-28.4)	22.2 (2.8-60.0)
Best overall response, n (%)						
Complete response	3 (7)	2 (8)	1 (6)	2 (2)	1 (1)	1 (11)
Partial response	8 (19)	4 (17)	4 (22)	21 (18)	20 (19)	1 (11)
Stable disease	8 (19)	3 (12)	5 (28)	34 (29)	34 (32)	0
Progressive disease	7 (17)	5 (21)	2 (11)	11 (9)	8 (7)	3 (33)
Unknown	11 (26)	5 (21)	6 (33)	13 (11)	9 (8)	4 (44)
Not reported, therapy ongoing	5 (12)	5 (21)	0	35 (30)	35 (33)	0

^aIncludes alectinib, brigatinib, ceritinib, crizotinib, lorlatinib, and neladalkib.
^bIncludes chemo ± antiangiogenic, chemo/immunotherapy, chemo/immunotherapy/antiangiogenic, or other (investigational drugs, cabozantinib, osimertinib).
^cClopper-Pearson method used.

- Sequencing of treatments in patients who received an ALK TKI (n=24) or chemo (n=17) as the first subsequent treatment after lorlatinib was discontinued is shown in **Figure 3**, based on the reason for discontinuation
 - Patients discontinued lorlatinib due to progressive disease (PD) or global deterioration of health status (n=29) or adverse event or another reason (n=12)
- Of the 24 lorlatinib patients whose first subsequent treatment was an ALK TKI, 11 (46%) received it for ≥12 months
 - Of these 11 patients, 6 discontinued lorlatinib due to adverse events, 4 due to disease progression, and 1 due to other reasons
- Treatment sequencing of the 4 patients who discontinued due to disease progression on lorlatinib and received an ALK TKI as first subsequent treatment for ≥12 months is shown in **Figure 4**