

Real-World Comparative Effectiveness of Next-Generation Anaplastic Lymphoma Kinase-Positive (ALK+) Tyrosine Kinase Inhibitors (TKIs) in First-Line ALK-Positive Advanced Non-Small Cell Lung Cancer

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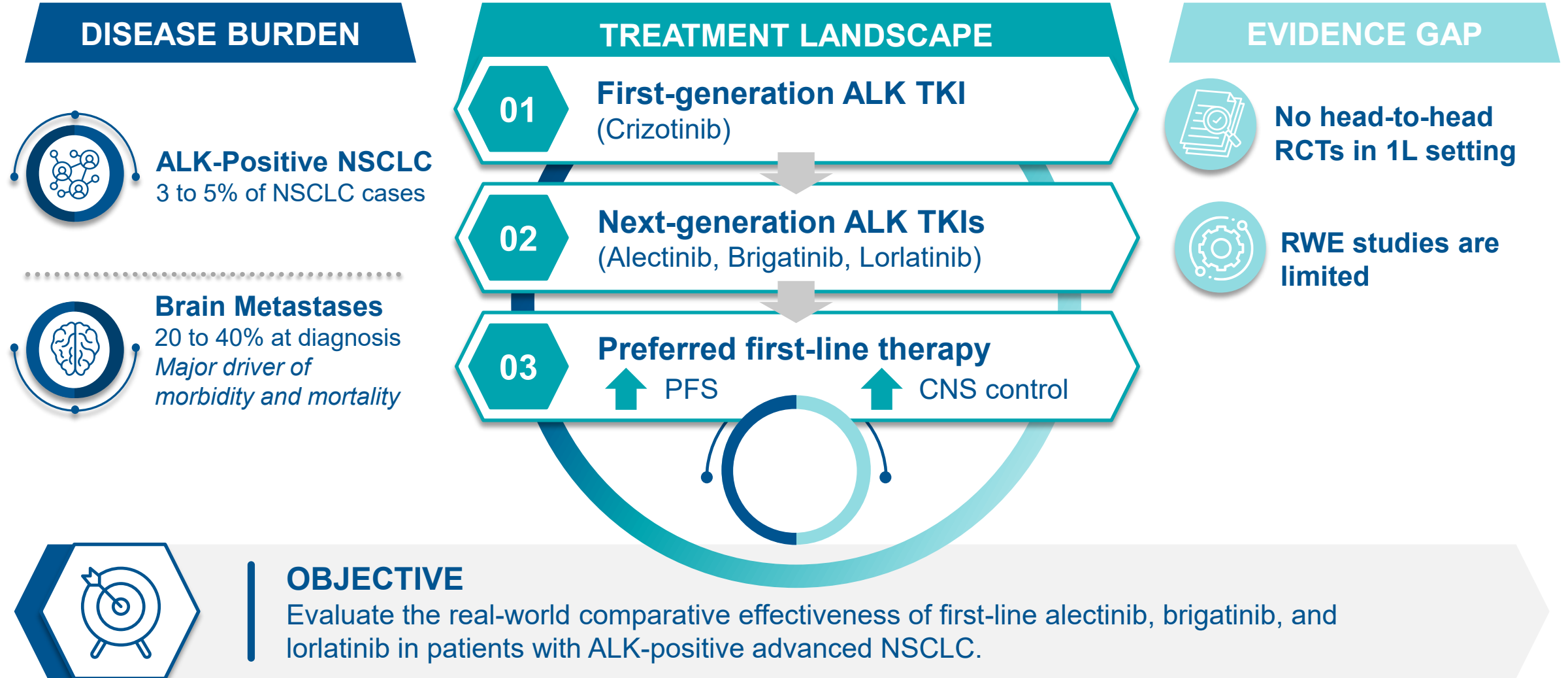
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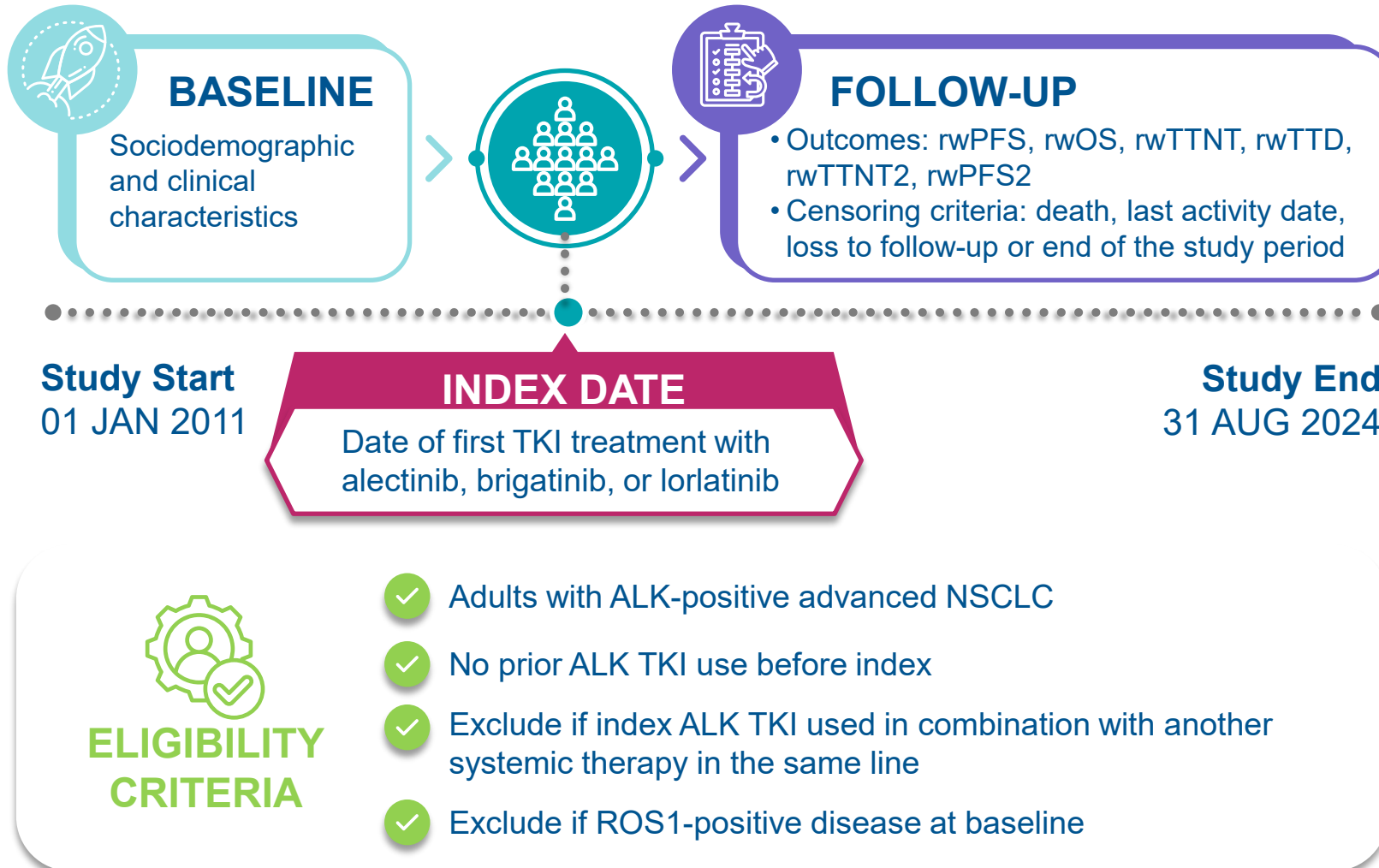
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Background and Rationale

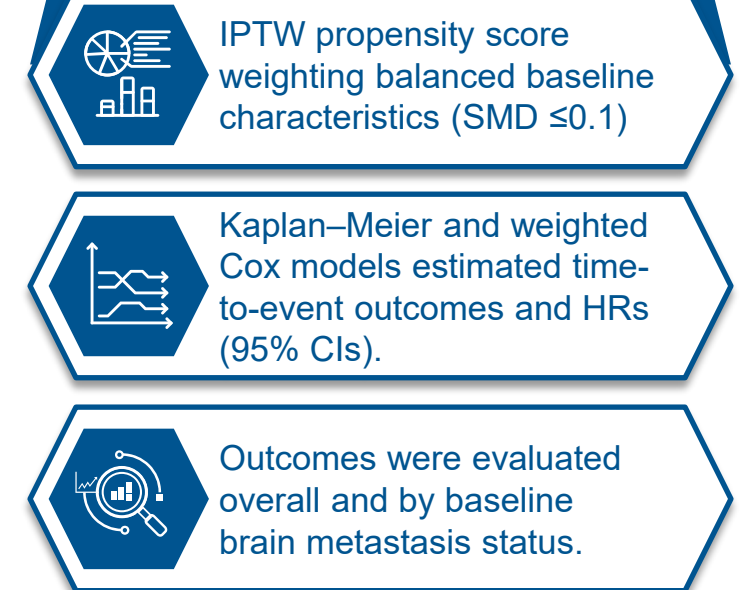


Methods



 **flatiron.**
Flatiron Health Spotlight database

Statistical Analysis



Note: Since substantially more eligible patients received alectinib than brigatinib or lorlatinib, a random sample of eligible alectinib-treated patients was selected to obtain more comparable cohort sizes across treatment groups.

Patient Characteristics at a Glance



Alectinib cohort

N=117

Median follow-up: 677 days



Brigatinib cohort

N=70

Median follow-up: 566 days



Lorlatinib cohort

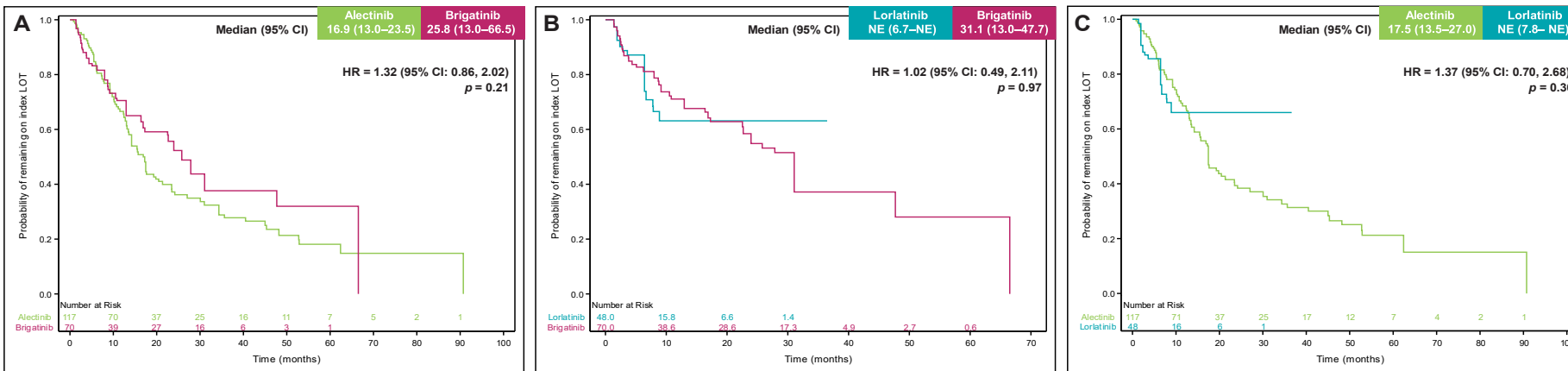
N=48

Median follow-up: 281 days

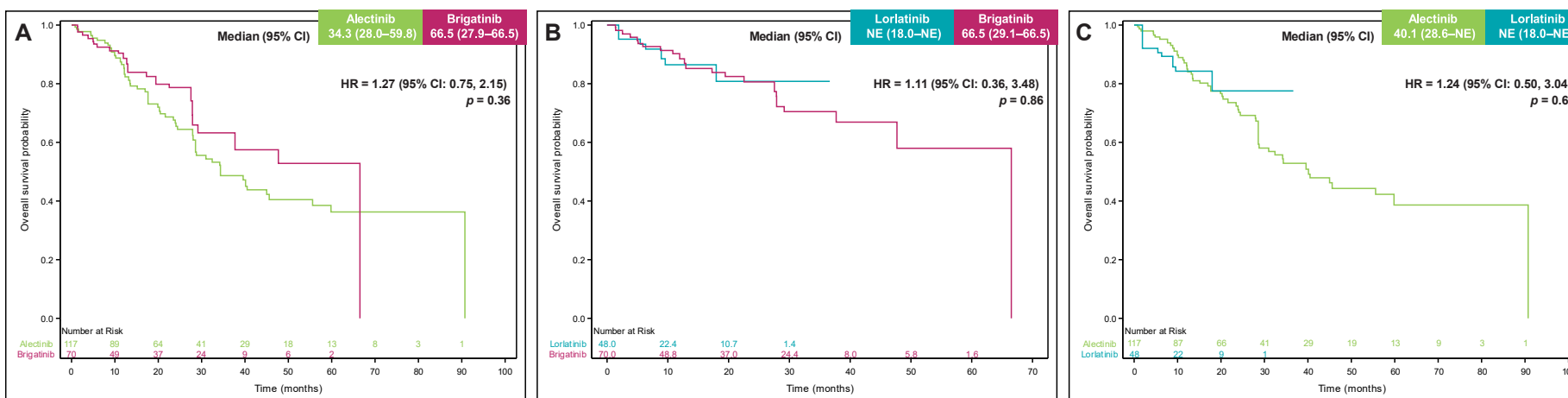
Select Characteristics		Range across cohorts
	Mean age, years	60.0–62.4
	Female sex	48.5%–56.1%
	Race	
	White	55.4%–64.0%
	Black or African American	4.0%–10.8%
	Other/Missing	25.8%–40.6%
	Brain metastases	31.4%–36.9%
	ECOG PS ≥ 2	10.6%–15.6%

Results – Real-world time to next treatment (rwTTNT) & real-world overall survival (rwOS)

Real-World Time to Next Treatment (rwTTNT)



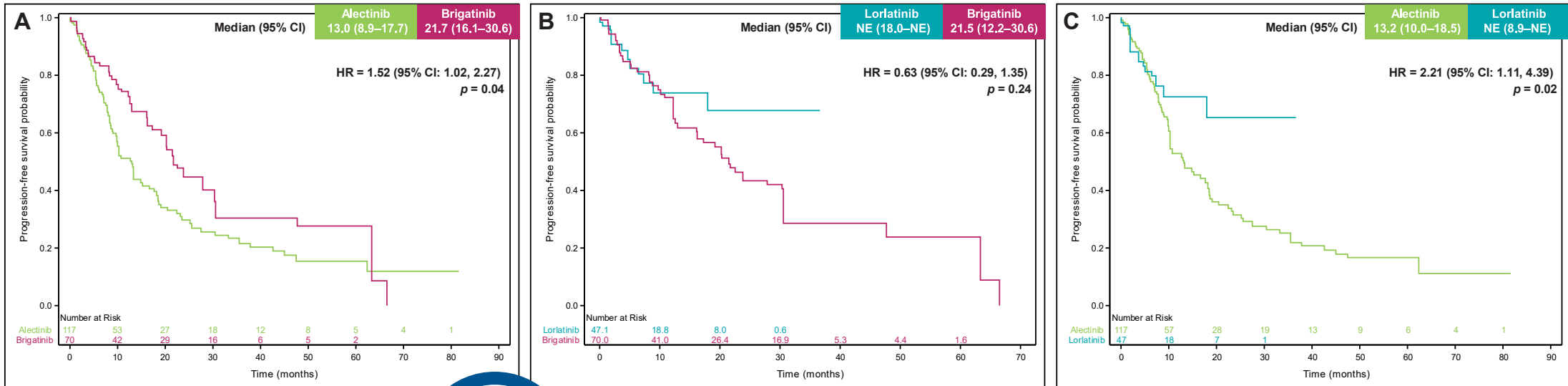
Real-World Overall Survival (rwOS)



No statistically significant differences in TTNT or OS across the three TKI groups

Results – Real-World Progression-Free Survival (rwPFS)

Real-World Progression-free Survival (rwPFS)



Median rwPFS was shorter with alectinib than with brigatinib or lorlatinib, while no difference was observed between brigatinib and lorlatinib.

Results – Other Effectiveness Outcomes

Weighted Hazard Ratio and 95% CI of the association between ALK-targeted TKI and other key clinical outcomes among patients with ALK+ advanced NSCLC

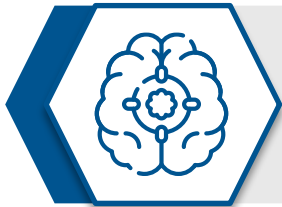
First TKI	TTD		PFS2		TTNT2	
	Hazard Ratio (95% CI)	<i>P</i> value	Hazard Ratio (95% CI)	<i>P</i> value	Hazard Ratio (95% CI)	<i>P</i> value
Alectinib vs. Brigatinib	1.31 (0.85, 2.02)	0.213	1.59 (0.95, 2.68)	0.077	1.69 (1.02, 2.81)	0.041
Lorlatinib vs. Brigatinib	0.88 (0.42, 1.82)	0.727	1.08 (0.35, 3.35)	0.898	2.19 (0.87, 5.50)	0.094
Alectinib vs. Lorlatinib	1.59 (0.81, 3.10)	0.176	1.90 (0.78, 4.59)	0.156	0.95 (0.46, 1.98)	0.889

Note: HRs are reported as the first treatment relative to the second (reference) treatment. HR <1 indicates a lower hazard of the respective event for the first treatment; HR >1 indicates a higher hazard.

Results – rwPFS by Baseline Brain Metastasis Status

Kaplan-Meier Estimates of Real-World Progression Free Survival (rwPFS) among ALK+ aNSCLC Patients by Use of First TKI and Presence of Brain Metastasis

PFS	Overall N=235		Brain Metastasis N=80			No Brain Metastasis N=155		
	Brain Metastasis	No Brain Metastasis	Alectinib	Brigatinib	Lorlatinib	Alectinib	Brigatinib	Lorlatinib
Median (95% CI), in months	10.8 (8.6–18.5)	20.2 (15.2–23.8)	10.7 (8.3– 25.6)	10.8 (8.2– 20.3)	18.0 (1.9–NE)	14.8 (9.7–19.1)	22.5 (17.3– NE)	NE (NE–NE)



Baseline brain metastases remained an adverse prognostic factor, and were associated with a shorter median rwPFS (10.8 vs. 20.2 months), while clinical outcomes among patients with baseline brain metastases were generally comparable across treatment groups

Strengths and Limitations

STRENGTHS



Population-based

Broader spectrum of patients and clinical practice patterns.



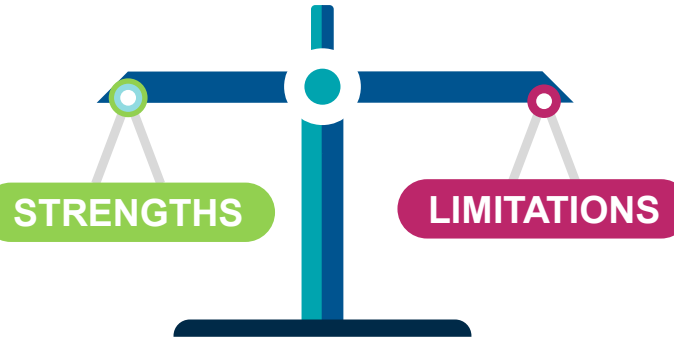
Structured data

Provides a detailed picture of healthcare encounters.



NLP and machine learning

Efficient and systematic identification of ALK status and relevant clinical information.



LIMITATIONS



Potential residual confounding

despite IPTW adjustment.



Clinician-documented

rwPFS $\neq$ standardized radiographic assessment.



Random sampling of alectinib patients

- More eligible patients received alectinib than brigatinib or lorlatinib.
- Alectinib-treated patients were randomly sampled, which may introduce sampling variability.

Key Findings



Comparable real-world effectiveness across next-generation ALK TKIs.



Although rwPFS differences were observed, they were not consistently reflected across other real-world effectiveness endpoints (rwOS, rwTTNT, rwTTD, rwTTNT2, and rwPFS2).



Presence of brain metastases at baseline was associated with shorter rwPFS.

Given the broadly comparable real-world effectiveness observed in this study, selection among next-generation ALK TKIs may be individualized based on tolerability, dosing considerations, patient comorbidities, and CNS disease burden, rather than being driven solely by presumed differences in effectiveness.