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Comparative Effectiveness of Alectinib versus Crizotinib as First-Line Therapy in ALK-Positive Non-Small Cell Lung Cancer: A Real-World Quasi-Experimental Analysis

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BACKGROUND

- Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) is a rare subtype primarily affecting non-smokers[1]
- National Comprehensive Cancer Network (NCCN) guidelines designate four anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs): alectinib, brigatinib, lorlatinib, and ensartinib, as category 1 preferred options for first-line therapy in advanced ALK+ NSCLC[2-5]
- Lack of head-to-head comparisons and scarce real-world evidence (RWE) create significant treatment outcome uncertainty[6,7]
- Robust evidence to guide medical decision-making is therefore essential

OBJECTIVE

To evaluate the real-world comparative effectiveness of alectinib versus crizotinib as first-line (1L) treatment for advanced ALK+ NSCLC in the United States.

METHODS

Study Design: Retrospective observational cohort study

Data Source: Optum Clinformatics® Data Mart (2016-2021), a large administrative claims database including commercially insured and Medicare Advantage patients in the U.S.

Study Population: Advanced ALK-positive NSCLC patients initiating first-line treatment with an ALK tyrosine kinase inhibitor (TKI)

Inclusion Criteria (must satisfy both):

1) Lung cancer diagnosis, based on International Classification of Diseases, Tenth Revision [ICD-10] code: C34x
2) Receipt of any of the following ALK TKIs: alectinib, crizotinib

Exclusion Criteria:

1) Age < 18 years at index date (first ALK TKI fill)
2) <6 months of continuous enrollment on health plan prior to index date

Outcomes:

- Overall survival (OS)
- Time-to-treatment discontinuation (TTD)

Statistical Analysis:

Unadjusted Survival Analysis

- Kaplan-Meier method to establish median OS and TTD

Propensity Score Estimation

- Logistic regression including baseline covariates: age, sex, race, region, insurance type, index year, months of continuous enrollment before ALK TKI initiation, Charlson Comorbidity Index (CCI), and presence of brain metastases

Comparative Effectiveness

Cox proportional hazards models estimated hazard ratios (HRs) for OS and TTD via:

- **Overlap weighting (OW)** based on propensity scores (PS): primary specification
- **Inverse probability of treatment weighting (IPTW)** based on PS: robustness check
- **Two-Stage Residual Inclusion (2SRI)** using index year as an instrument for treatment selection (first stage), with residuals included in a Cox model for OS and TTD (second stage): exploratory analysis

Additional Information:

- Analyses were conducted using SAS software, version 9.4 and STATA software, version 18.0

RESULTS

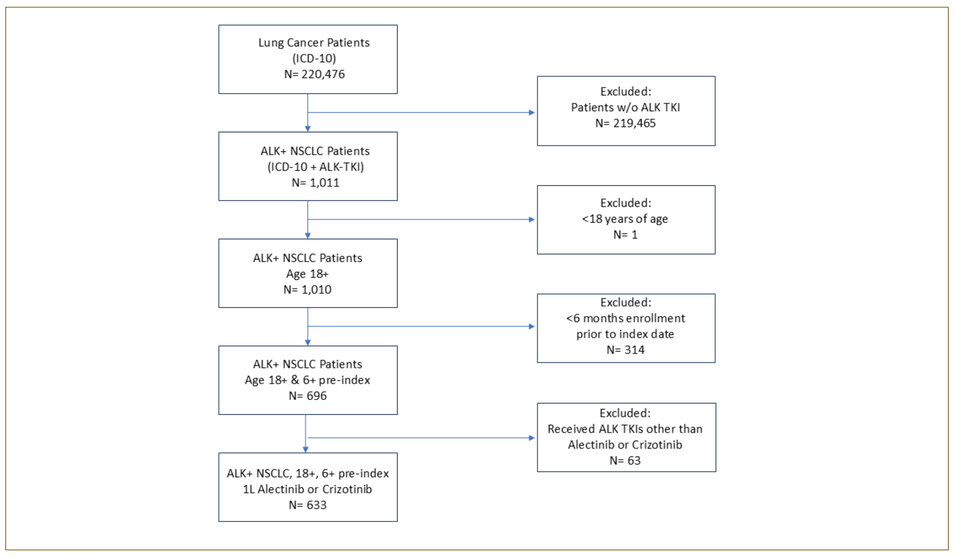

Figure 1. Study population selection.

Table 1. Patient Characteristics (All ALK TKIs)

Variable	n = 696
Age, years	
Mean (SD)	64.2 (13.7)
Sex, n (%)	
Male	317 (45.6)
Female	379 (54.4)
Race, n (%)	
White	438 (68.5)
Black	82 (12.8)
Hispanic	64 (10.0)
Asian	55 (8.6)
Insurance Type, n (%)	
Commercial	352 (50.6)
Medicare	344 (49.4)
Charlson Comorbidity Index (CCI) Score	
Mean (SD)	5.0 (2.2)
1st-line ALK TKI Type, n (%)	
Alectinib	267 (38.4)
Brigatinib	22 (3.2)
Ceritinib	25 (3.6)
Crizotinib	366 (52.6)
Lorlatinib	16 (2.3)

Table 2. Unweighted Kaplan-Meier Results

Outcome	Treatment	Median (Months, 95% CI)
OS	Alectinib	46.5 (39.0–NR)
OS	Crizotinib	21.4 (18.3–26.5)
TTD	Alectinib	33.5 (24.6–46.3)
TTD	Crizotinib	12.2 (10.6–14.5)

**OS* Overall Survival; *TTD* time to treatment discontinuation or death; *NR* not reached

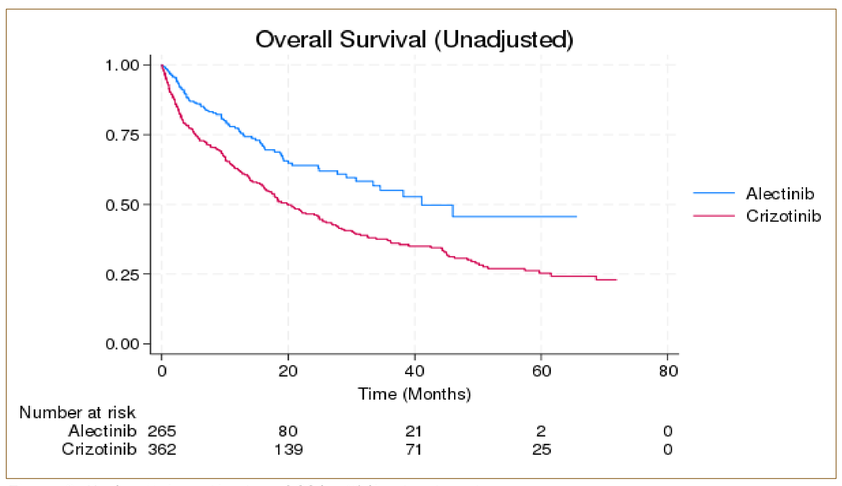

Figure 2. Kaplan-Meier estimates of OS by 1st-line treatment.

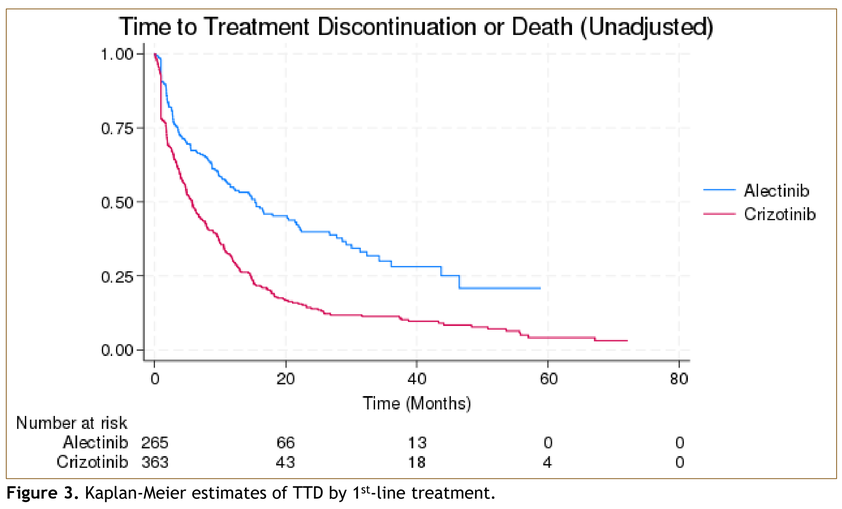

Figure 3. Kaplan-Meier estimates of TTD by 1st-line treatment.

Table 3. Comparative Effectiveness (Alectinib vs. Crizotinib)

Outcome	Overlap-Weighted HR (95% CI)	IPTW HR (95% CI)	2SRI HR (95% CI)
OS	0.60 (0.45–0.79)	0.65 (0.48–0.87)	0.62 (0.34–1.13)
TTD	0.48 (0.38–0.61)	0.54 (0.43–0.67)	0.77 (0.48–1.22)

**HR* hazard ratio; *IPTW* inverse probability of treatment weighting

RESULTS

- Among 633 patients analyzed (subset of 696 total ALK TKI recipients), 267 received alectinib, and 366 received crizotinib
- In overlap-weighted Cox models, alectinib was associated with significantly improved OS (HR: 0.60; 95% CI: 0.45-0.79) and TTD (HR: 0.48; 95% CI: 0.38-0.61)
- IPTW specification yielded consistent results for OS (HR: 0.65; 95% CI: 0.48-0.87) and TTD (HR: 0.54; 95% CI: 0.43-0.67)
- In 2SRI models using index year as an instrument, the estimated OS benefit for alectinib (HR: 0.62; 95% CI: 0.34-1.13) remained directionally consistent, but with greater uncertainty

LIMITATIONS

Data Limitations:

- Patients could be misclassified as 1st-line users if prior ALK TKI prescriptions are unrecorded

Nonrandomized Design:

- Potential selection bias exists due to unobserved factors (e.g., tumor growth rate, TKI resistance), limiting causal inference regarding treatment effectiveness
- Index year as instrument is unlikely to adequately address selection bias

CONCLUSION

To our knowledge, this is the largest real-world comparative effectiveness analysis of first-line targeted therapies for ALK-positive NSCLC and the first to explicitly address unobserved confounding.

Our findings reaffirm alectinib's improved effectiveness over crizotinib in real-world practice.

As crizotinib approaches generic availability and newer agents such as alectinib remain costly, these results provide timely, policy-relevant evidence to inform value-based treatment decisions for payers and clinicians.

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