Comparative Effectiveness of First-Line (1L) Tyrosine Kinase Inhibitors (TKIs) in ALK+ Metastatic NSCLC (mNSCLC) by Presence of Brain Metastases (BM)

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Background

- Patients with ALK+ NSCLC have a more aggressive histologic grade, are younger, and are more likely to have metastatic disease at time of diagnosis[1,2]
- ~25% have BM at diagnosis; this rate increases post diagnosis[1,3]
- The toxicity profiles of currently approved 1L ALK-TKIs vary, and treatment-related side effects may result in dose modifications[4]
- There is limited real-world evidence on treatment patterns, comparative effectiveness, and dose modifications for 1L ALK TKIs in the US setting

Objectives

- Describe characteristics, treatment patterns, and outcomes of ALK+ mNSCLC patients treated with 1L crizotinib, brigatinib, alectinib, or lorlatinib monotherapy
- Compare outcomes among patients with vs without BM
- Describe patterns of optimal dose achievement and dose reduction among patients treated with 1L brigatinib, alectinib, or lorlatinib monotherapy

Methods

- Retrospective cohort study using data from Komodo Healthcare Map, a nationally representative US database of de-identified claims from >330 million insured people

Study population

- Patients with ALK+ mNSCLC were identified using *ICD-10-CM* diagnosis codes for lung cancer and metastatic disease
- Patients with ≥1 paid claim for 1L monotherapy with crizotinib, brigatinib, alectinib, or lorlatinib after initial metastatic lung cancer diagnosis were included
- Patients who received any ALK-TKI prior to the index date, any anti-cancer treatments between metastatic diagnosis date and index date, any other anti-cancer drugs in combination with index 1L ALK-TKI, or ROS1-specific drugs (entrectinib or repotrectinib) at any point during the study period were excluded

Outcomes and analysis

- The study sample was stratified based on presence of BM (yes/no) at baseline
- Patient characteristics were presented using descriptive statistics
- Treatment patterns were presented as the frequency and percentage of patients receiving each type of regimen by treatment line
- The Kaplan-Meier (KM) method was used to describe time to treatment discontinuation (TTD), time to next treatment (TTNT), overall survival (OS), and time to dose reduction (TTDR) for each 1L ALK-TKI cohort
- Multivariable and propensity score (PS)-weighted Cox proportional hazard models compared TTD, TTNT, and OS across 1L ALK-TKI cohorts (alectinib, brigatinib, lorlatinib vs crizotinib; brigatinib vs alectinib; brigatinib vs lorlatinib)
- Dose reduction and dose intensity (the percentage of the optimal dose that a patient achieved over the course of treatment) were reported descriptively
  - Optimal dose/day: alectinib, 1200 mg; brigatinib, 180 mg; lorlatinib, 100 mg

Question

What are the real-world comparative effectiveness and dosing patterns of 1L ALK-TKI monotherapy in US patients with ALK+ metastatic NSCLC?

Study design

Key take aways

- **1L brigatinib, alectinib, and lorlatinib demonstrated real-world effectiveness vs crizotinib**
- **Comparable effectiveness was observed for brigatinib vs alectinib and lorlatinib**
- **1L brigatinib, alectinib, and lorlatinib were effective in patients with and without BM**
- **Fewer optimal dose achievements and earlier dose reductions were observed for 1L lorlatinib vs alectinib and brigatinib in the real world**

Table 1. Multivariable Cox proportional hazard regression model results (reference: crizotinib)[a]

Outcome	1L Cohort	Hazard Ratio (95% CI) Overall	With BM	Without BM
Time to treatment discontinuation	Alectinib	**0.42 (0.36-0.49)**	**0.32 (0.24-0.42)**	**0.47 (0.39-0.56)**
	Brigatinib	**0.41 (0.27-0.61)**	**0.32 (0.16-0.64)**	**0.44 (0.26-0.75)**
	Lorlatinib	**0.38 (0.25-0.58)**	**0.25 (0.12-0.50)**	**0.47 (0.28-0.81)**
Time to next treatment	Alectinib	**0.41 (0.35-0.48)**	**0.30 (0.22-0.40)**	**0.47 (0.39-0.57)**
	Brigatinib	**0.46 (0.29-0.71)**	**0.33 (0.16-0.68)**	**0.53 (0.30-0.91)**
	Lorlatinib	**0.35 (0.22-0.56)**	**0.21 (0.11-0.43)**	**0.47 (0.25-0.85)**
Overall survival	Alectinib	**0.49 (0.40-0.61)**	**0.38 (0.26-0.56)**	**0.52 (0.40-0.68)**
	Brigatinib	**0.51 (0.26-1.00)**	0.43 (0.16-1.15)	0.49 (0.19-1.30)
	Lorlatinib	**0.42 (0.23-0.77)**	**0.22 (0.08-0.64)**	0.58 (0.27-1.25)

Bold formatting indicates statistical significance. [a] Using backwards selection criteria, adjusted for age, sex, race, region, payer type, Charlson comorbidity index score, number of metastatic sites, selected sites of metastasis (brain, liver, bone), and time from metastasis to 1L treatment initiation.

Results

Study population

- 1623 patients received 1L crizotinib (n=384), alectinib (n=1100), brigatinib (n=58), or lorlatinib (n=81)
- Overall, the mean patient age was 59.6 years and 37.0% had BM
  - Alectinib: 58.6 years, 38.2% BM
  - Brigatinib: 58.8 years, 43.1% BM
  - Crizotinib: 62.3 years, 28.9% BM
  - Lorlatinib: 61.4 years, 48.1% BM

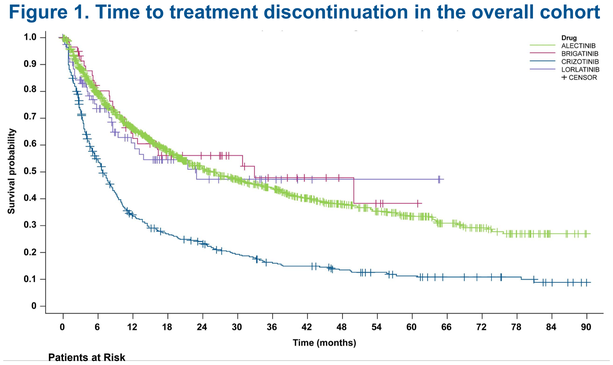
Treatment patterns

- Median (IQR) follow-up was 24.6 (9.9-48.3) months
- In 2L (n=643), lorlatinib was the most common ALK-TKI monotherapy received (n=220, 34.2%; n=94 with BM, n=126 without BM)

TTD, TTNT, and OS

- Patients with vs without BM had higher 24-month KM estimates for TTD and TTNT (brigatinib and lorlatinib cohorts) and OS (alectinib and lorlatinib cohorts)
- Brigatinib, alectinib and lorlatinib vs crizotinib had significant hazard ratios (HRs) for TTD (**Figure 1**) and TTNT, overall and within BM subgroups (**Table 1**); OS results were numerically consistent

Figure 1. Time to treatment discontinuation in the overall cohort



- There was no statistically significant difference in PS-weighted HRs (95% CIs) for:
  - 1L brigatinib vs alectinib: TTD, 0.85 (0.56-1.28); TTNT, 0.94 (0.60-1.48); OS, 0.86 (0.44-1.70)
  - 1l brigatinib vs lorlatinib: TTD, 0.93 (0.49-1.76); TTNT, 1.46 (0.64-3.32); OS, 1.41 (0.41-4.84)
- PS-weighted comparisons by BM were not conducted due to small sample size

Dose modifications

- Optimal dose was achieved by 97% of alectinib patients, 89% of brigatinib patients, and 70% of lorlatinib patients at any point during treatment (**Table 2**)
- For patients who achieved optimal dose, a subsequent dose reduction occurred for 21% of alectinib patients, 23% of brigatinib patients, and 30% of lorlatinib patients (**Table 2**)
- Dose reductions occurred earlier for lorlatinib compared to alectinib (**Table 2**)
- Dose intensity was lower for lorlatinib patients (86%) compared to alectinib (91%) and brigatinib (89%) patients, although the differences were not statistically significant (**Table 2**)

Table 2. Dose modification outcomes (unadjusted)

Characteristic	Alectinib (N = 1,030)	Brigatinib (N = 54)	Lorlatinib (N = 76)	P value
Optimal dose achieved				
Yes, n (%)	999 (97.0)	48 (88.9)	53 (69.7)	**<0.001**
Dose reduction following achievement of optimal dose[a]				
Yes, n (%)	205 (20.5)	11 (22.9)	16 (30.2)	0.231
Time to dose reduction from the date of optimal dose, months				
HR (95% CI)	Ref	1.25 (0.68-2.29)	2.11 (1.27-3.51)	**0.012**
Patients still on optimal dose at time point[a]				
3 months	92.6%	88.6%	81.7%	**0.011**
6 months	86.6%	82.5%	72.5%	
9 months	82.8%	82.5%	68.9%	
12 months	79.0%	78.2%	64.6%	
Dose intensity				
Mean (SD)	91% (22%)	89% (28%)	86% (28%)	0.415

Bold formatting indicates statistical significance. [a] Percentages are out of the number of patients who achieved optimal dose. HR, hazard ratio; NE, not estimable.

Limitations

- Claims data are subject to miscoding, errors, underreporting, or missing values
- Results may not be generalizable to uninsured US or ex-US populations
- There may be residual bias from unobserved confounding factors
- Sample size was limited for the brigatinib and lorlatinib cohorts

Conclusions

- 1L brigatinib, alectinib and lorlatinib demonstrated real-world effectiveness vs crizotinib. Comparable effectiveness was observed for 1L brigatinib vs alectinib and lorlatinib
- The observed effectiveness of brigatinib, alectinib, and lorlatinib in patients with and without BM highlights the importance of individualized patient-centered care when considering therapies
- More patients on 1L alectinib or brigatinib achieved optimal dose and stayed on the optimal dose for longer over the course of treatment as compared to 1L lorlatinib

References

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Acknowledgments

Writing and editorial assistance was provided by Catherine Mirvis of OPEN Health and was funded by Takeda Development Center Americas, Inc.

Disclosures

SG: honoraria and consulting or advisory role for AstraZeneca, Chugai, Merck Sharp & Dohme, Pfizer, Roche, and Takeda. DC, AA, CD: Employees of Takeda. KR, TL, VC, KML: Employees of OPEN Health, which received funding from Takeda to conduct this study. YC, CK: Nothing to disclose.

Presented at ESMO Congress, 17–21 October 2025, Berlin, Germany. For questions or comments, please contact Dr Sharmistha Ghosh: Sharmistha.Ghosh@gstt.nhs.uk