NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT ABSTRACT

Title: Real-World Incidence and Prevalence of Brain Metastasis and Its Impact on Clinical Outcomes among Anaplastic Lymphoma Kinase (ALK) Positive Metastatic Non-small Cell Lung Cancer (mNSCLC) Patients Receiving ALK Tyrosine Kinase Inhibitors (TKIs) as First-Line (1L) Treatment in the United States (US)

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Keywords: ALK tyrosine kinase inhibitors; Brain metastasis; Metastatic non-small cell lung cancer; Real-world evidence; Clinical outcomes

Rationale and background: ALK+ NSCLC accounts for roughly 5% of lung cancer cases, with successive generations of ALK TKIs showing increased clinical benefit compared to crizotinib, a first-generation (1G) ALK TKI. However, brain metastases (BM) remain a significant challenge among ALK+ metastatic NSCLC (mNSCLC) patients. Limited data exists on the impact of both existing (prevalent) and newly developed (incident) BM on clinical outcomes. This study used [redacted] electronic health record (EHR) database to assess the incidence and prevalence of BM and its impact on overall survival (OS), real-world progression-free survival (rwPFS), and time to treatment discontinuation (TTD).

Research question and objectives:

Primary Objectives

1. To describe the demographics and clinical characteristics of patients with ALK+ mNSCLC receiving first-line (1L) treatment with either 1G or second-generation (2G) ALK TKIs, both overall and stratified by baseline BM status
2. To assess the real-world incidence and prevalence of BM among patients with ALK+ mNSCLC receiving 1L treatment with either 1G or 2G ALK TKIs
3. To assess the impact of baseline BM and incident BM on OS (mortality) among ALK+ mNSCLC patients receiving 1L treatment with either 1G or 2G ALK TKIs
4. To assess the impact of baseline BM and incident BM on rwPFS among ALK+ mNSCLC patients receiving 1L treatment with either 1G or 2G ALK TKIs
5. To assess the impact of baseline BM and incident BM on TTD among ALK+ mNSCLC patients receiving 1L treatment with either 1G or 2G ALK TKIs

Secondary Objective

1. To stratify the above analyses by generation of ALK TKI (1G: crizotinib; 2G: ceritinib, alectinib, brigatinib)

Study design: This was a retrospective, observational study using data from the [redacted] EHR database. The index date was defined as the initiation date of either 1G or 2G ALK TKI as 1L treatment within the study period (January 1, 2016-November 30, 2022). The baseline period was defined as either 6 months prior to the index date or the period between mNSCLC diagnosis and the index date, whichever was longer. The follow-up period was defined as the time from the index date to earliest of death, the last confirmed activity date or the data cutoff date (i.e., November 30, 2023). The index treatment period was defined as the time from the index date to earliest of index treatment discontinuation or end of follow-up.

Setting: The study population included ALK+ mNSCLC patients, who received 1L treatment with either 1G or 2G ALK TKIs in the [redacted] database between January 1, 2016 and November 30, 2022.

Subjects and study size, including dropouts: Patients were eligible for inclusion if they had confirmed ALK+ mNSCLC, initiated 1G or 2G ALK TKI as 1L treatment, and were at least 18 years old on the index date. Exclusion criteria included prior ALK TKI use, evidence of another primary cancer, or initiation of 1L ALK TKI in a clinical trial or in combination with other treatments. A total of 475 patients were included based on these inclusion and exclusion criteria: 382 received 2G ALK TKIs (alectinib: n=362, brigatinib: n=15, ceritinib: n=5), and 93 received 1G ALK TKI crizotinib. As no priori hypotheses were specified, sample size calculations were not applicable for this study.

Variables and data sources: The study used [redacted] EHR database, with a data cutoff of November 30, 2023. Baseline covariates included but not limiting to age at index, gender, race, ethnicity, region, site of care, index year, histology, tumor stage at initial diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS) at index, site of metastases, and comorbidities. Baseline BM, incident BM and cumulative prevalence of BM were assessed as outcomes. Clinical outcome variables included OS, rwPFS, and TTD. Cumulative incidence and prevalence of BM were estimated using cumulative incidence function (CIF) accounting for the competing risk of death. Time-to-event clinical outcomes were analyzed using Kaplan-Meier (KM) method, and the impact of incident and baseline BM on clinical outcomes was assessed using multivariate time-varying Cox regression models.

Results: A total of 475 patients were included in the overall sample. The median (Q1, Q3) age was 62.0 (51.0, 71.0) years and the majority of patients were treated in community settings (73.1%, n = 347), had baseline ECOG PS of 0 or 1 (82.9% among patients with available ECOG PS, n = 281), and stage IV at initial NSCLC diagnosis (82.1%, n = 390). 80.4% patients received 2G ALK TKIs (n = 382) with 95% using alectinib (n = 362), while 19.6% received 1G ALK TKI crizotinib (n = 93). Crizotinib was mainly initiated in 2017 or before, with limited use afterwards.

Baseline BMs were present in one-third of the patients (overall sample: 31.6% [n = 150]; 2G subgroup: 32.2% [n = 123]; 1G subgroup: 29.0% [n = 27]). Among those without baseline BM, the cumulative incidence of BM while on index treatment was 17% after year 3 in the overall sample, with rates of 14% for those on 2G ALK TKI and 52% for those on 1G ALK

TKI. Estimates beyond year 3 were not available for the 1G ALK TKI subgroup due to no patients remaining at risk for the outcome.

Patients in the 2G ALK TKI subgroup had a median OS, rwPFS and TTD of 56.5, 23.4, and 24.3 months, respectively. Patients in the 1G ALK TKI subgroup had a median OS of 32.3 months, median rwPFS of 6.3 months and median TTD of 6.1 months.

In the overall sample, incident BM was associated with a significantly higher hazard of death (hazard ratio [HR], 95% confidence interval [CI]: 2.38 [1.48, 3.83]), significantly higher hazard of progression or death (3.66 [1.79, 7.48]), and significantly higher hazard of treatment discontinuation (3.62 [2.09, 6.26]). Among the 2G ALK TKI subgroup, similar results were observed. Incident BM were associated with a significantly higher hazard of death (HR [95% CI]: 2.97 [1.59, 5.53]), significantly higher hazard of progression or death (7.40 [3.46, 15.82]), and significantly higher hazard of treatment discontinuation (4.89 [2.59, 9.27]). For the 1G ALK TKI subgroup, there was no statistically significant association between incident BM and the three outcomes. Baseline BM had no significant impact on the three clinical outcomes, after adjusting for incident BM and other factors.

Discussion: The study found the majority of patients (80%) received 2G ALK TKIs after 2017. This trend reflects the preference for 2G ALK TKIs due to their superior efficacy and CNS penetration compared to 1G ALK TKI – an advantage also observed in the current study.

A substantial BM burden was observed in this population, with 32% of patients presenting with BM at baseline, and 17% of those without baseline BM developing incident BM within three years. The median survival in this population was 4.2 years. Incident BM was strongly associated with worse clinical outcomes in the overall sample, including more than double the risk of death, and a threefold increase in the risk of disease progression or death, and treatment discontinuation. In contrast, after adjusting for incident BM and other factors, baseline BM did not have a significant impact on these clinical outcomes. These findings highlight the continued need for more effective treatments to delay CNS progression. Future research is needed to assess the real-world effect of lorlatinib, a third-generation ALK TKI, on BM incidence and its subsequent impact on clinical outcomes.

This study has several limitations. The [redacted] database primarily captures community practice in the US, potentially limiting generalizability to the broader ALK+ mNSCLC population. [redacted] relies on abstraction, so information bias from erroneously captured data is a possibility if errors in data entry were made at the time of entry into the patient chart or EHR. Additionally, the lack of radiation treatment data and baseline BM progression details may introduce potential biases due to unobserved confounders influencing outcomes.

In conclusion, this study expands the limited real-world evidence on the epidemiology of BM and their impact on clinical outcomes in patients with ALK+ mNSCLC. The findings highlight that BM remains a significant burden in this population, with incident BM significantly associated with poorer survival and treatment outcomes. While 2G ALK TKIs have improved survival and disease control compared with 1G ALK TKIs in clinical trials, BM development continues to pose a major challenge in patients being treated with 1L 2G ALK TKIs. These

results underscore the urgent need for using effective BM prevention and management strategies in patients with ALK+ mNSCLC.

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