# The Cumulative Incidence of Brain Metastases in US Medicare Patients with ALK+ mNSCLC Treated with Second-Generation ALK TKIs

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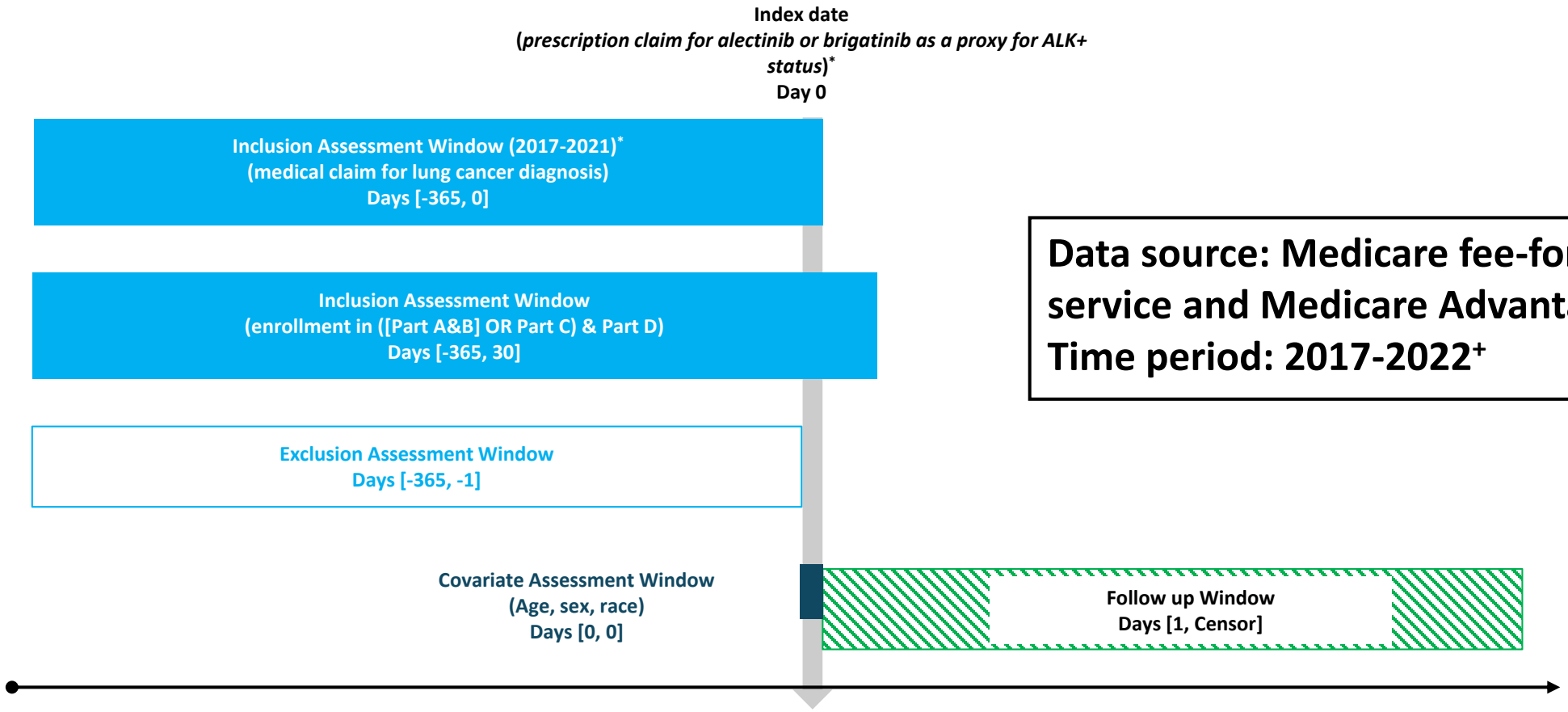
# Background: Brain Metastases in Patients with ALK+ mNSCLC

- Anaplastic lymphoma kinase (ALK) gene rearrangements occur in approximately 3–5% of patients with non-small-cell lung cancer (NSCLC)[1]
- Brain metastases (BM) are common in patients with ALK-positive metastatic non-small-cell lung cancer (mNSCLC), and may occur at diagnosis or during disease progression[2]
- In the pivotal randomized controlled trials (RCTs)[3-5] of the next-generation ALK tyrosine kinase inhibitors (TKIs), baseline BM were present in:
  - Second-generation ALK TKIs: alectinib (ALEX): 40.3% and brigatinib (ALTA-1L): 29%
  - Third-generation ALK TKI: lorlatinib (CROWN): 26.4%
- Limited contemporary real-world evidence (RWE) exists on the impact of BM in these patients and their association with mortality
- The objective was to estimate the cumulative incidence of BM in patients with ALK-positive mNSCLC treated with a second-generation ALK TKI in the first-line setting; and to assess the association between incident BM and mortality

Abbreviations: 1L, first-line; anaplastic lymphoma kinase; BM, brain metastases; mNSCLC, metastatic non-small-cell lung cancer; RCT, randomized controlled trial; RWE, real-world evidence; TKI, tyrosine kinase inhibitor

[1]Lockney NA, et al. *Journal of Thoracic Disease* 2017;9:E152-E4.; [2] Rangachari D, et al. *Lung Cancer* 2015;88:108-111.; [3] Peters S, et al. *N Engl J Med*. 2017;377:829-838.; [4] Camidge DR, et al. *N Engl J Med*. 2018;379:2027–2039.; [5] Shaw AT, et al. *N Engl J Med.* 2020;383:2018–29.

# Design: Retrospective cohort RWE study in Medicare




**Data source: Medicare fee-for-service and Medicare Advantage**
**Time period: 2017-2022+**

Abbreviations: ALK, anaplastic lymphoma kinase; RWE, real-world evidence

*Alectinib and brigatinib were the most common ALK TKIs used to treat ALK+ mNSCLC during the study period
+For patient enrolled in Medicare fee-for-service, for patients enrolled in Medicare Advantage, the study period was 2021

# Methods: Brain Metastases in Patients with ALK+ mNSCLC

- BM occurring during the 12-month baseline period were defined as **baseline BM**
- The cohort at-risk for incident BM included all patients without baseline BM, and the presence of a BM during the follow-up period was defined as **incident BM**
- Mortality was defined using the Medicare Master Beneficiary Summary, 99% of death dates have been validated[1]
- Baseline patient characteristics were summarized using descriptive statistics, and stratified by the presence or absence of baseline BM
- Cumulative incidence functions of BM (accounting for the competing risk of death), death, and a composite of BM/death in the cohort of patients at-risk for incident BM were estimated[2]
- Cox proportional hazards models were used to compare the incidence of mortality between those patients with an incident BM and those patients without an incident BM during follow-up

Abbreviations: 1L, first-line; anaplastic lymphoma kinase; BM, brain metastases; mNSCLC, metastatic non-small-cell lung cancer; RCT, randomized controlled trial; RWE, real-world evidence; TKI, tyrosine kinase inhibitor

[1]https://resdac.org/articles/death-information-research-identifiable-medicare-data. [2] Austin PC, et al. *Circulation* 2016;133:601-609.

# Results: Large contemporary cohort of ALK+ mNSCLC patients

≥ 1 prescription claim for alectinib or brigatinib from January 1, 2017 through December 31, 2021 (for fee-for-service beneficiaries) or December 31, 2020 (for Medicare Advantage beneficiaries) – index date = first prescription
**N = 2518**

≥ 1 medical claim for lung cancer the 12 months preceding and including the index date
**N = 2382**

Continuous enrollment in Medicare for the 12 months prior to the month of the index date and the month of the index date (13 months total), while ≥ 65 years old
**N = 1560**

NO pharmacy claim for an ALK TKI* in the 12 months preceding the index date
**N = 1057**

NO pharmacy claim for an EGFR TKI+ in the 12 months preceding the index date
**N = 1040**

| ≥ 1 medical claim for brain metastasis in the 12 months preceding and including the index date | NO medical claim for brain metastasis in the 12 months preceding and including the index date |
|---|---|
| **N = 289 [Baseline Brain Metastasis Cohort]** | **N = 751 [At-risk for Incident Brain Metastasis Cohort]** |

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small-cell lung cancer; TKI, tyrosine kinase inhibitor

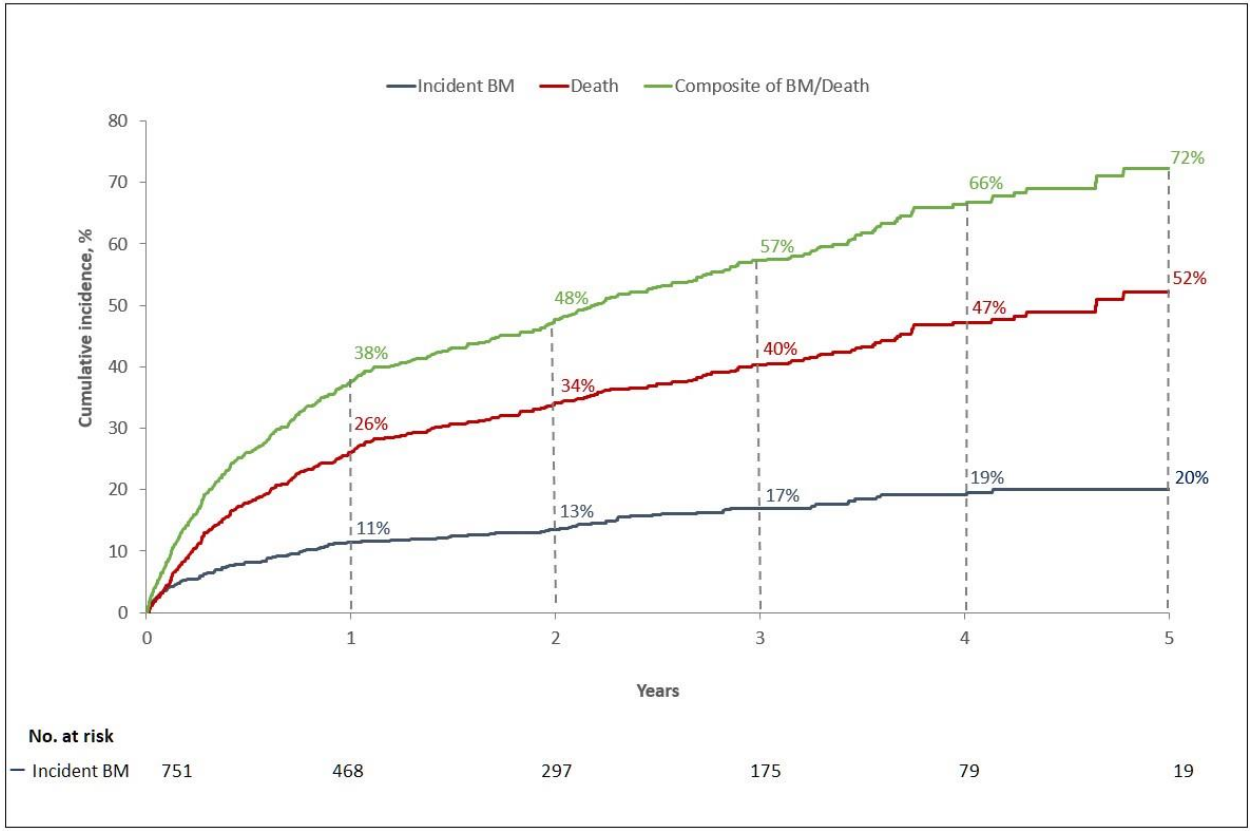
*alectinib, brigatinib, lorlatinib, ceritinib, or crizotinib; to capture 1L ALK TKI
+ afatinib, aminantamab-vmjw, dacomitinib, erlotinib, gefitinib, mobocertinib, or Osimertinib; to exclude patients with secondary ALK mutations
Median duration of follow-up = 20 months

# Results: Patients with and without baseline BM have similar characteristics

| Baseline characteristics of the cohort, stratified by presence or absence of baseline BM | | | | | |
|---|---|---|---|---|---|
| Characteristic | Baseline Brain Metastasis N = 289 | At-risk for Incident Brain Metastasis N = 751 | Characteristic | Baseline Brain Metastasis N = 289 | At-risk for Incident Brain Metastasis N = 751 |
| Age (years), median [Q1-Q3] | 72 [69-77] | 75 [70-80] | Female, n(%) | 175 (61) | 444 (59) |
| Race / ethnicity, n (%) | | | Index ALK TKI, n (%) | | |
| Non-Hispanic White | 196 (68) | 509 (68) | Alectinib | 268 (93) | 719 (96) |
| Black or African American | 22 (8) | 57 (8) | Brigatinib | 21 (7) | 32 (4) |
| Asian/Pacific Islander | 39 (13) | 91 (12) | Index Medicare coverage, n (%) | | |
| Hispanic | 18 (6) | 67 (9) | Fee-for-service | 164 (57) | 429 (57) |
| Other/Unknown | 14 (5) | 27 (4) | Medicare Advantage | 125 (43) | 322 (43) |
| Geographic region, n (%) | | | Dual Medicare-Medicaid eligibility, n (%) | 57 (20) | 200 (27) |
| Northeast | 67 (23) | 149 (20) | Charlson comorbidity index, mean (SD) | 2.5 (2.1) | 2.8 (2.1) |
| Midwest | 43 (15) | 171 (23) | Any brain radiation treatment, n (%) | 81 (28) | 21 (3) |
| South | 83 (29) | 209 (28) | Any receipt of systemic treatment, n (%) | 55 (19) | 204 (27) |
| West | 96 (33) | 218 (29) | Any inpatient hospitalization, n (%) | 150 (52) | 375 (50) |

Abbreviations: ALK, anaplastic lymphoma kinase; BM, brain metastases; Q1, first quartile; Q3, third quartile; SD, standard deviation; TKI, tyrosine kinase inhibitor

# Results: 5-year cumulative incidence of BMs was 20% in ALK+ mNSCLC*




Abbreviations: 1L, first-line; ALK, anaplastic lymphoma kinase; BM, brain metastases; TKI, tyrosine kinase inhibitor

*ALK+ mNSCLC defined as 1L treatment with alectinib or brigatinib, 60% of patients were receiving the index ALK TKI when the incident BM was observed

# Results: Higher incidence of death in patients with baseline BM

| Kaplan-Meier Median Time-to-death Estimates and Cumulative Annual Incidence of Death among Patients with Baseline BM and Patients At-risk for Incident BM | | |
|---|---|---|
| | Baseline BM N = 289 | At-risk for Incident BM N = 751 |
| Death during follow-up, n (%) | 159 (55) | 377 (50) |
| Days to end of follow-up, median [Q1 – Q3] | 637 [153 – 1040] | 621 [251 – 1116] |
| Time-to-death (days) among those who died, median [Q1 – Q3] | 201 [75 – 509] | 253 [97 – 621] |
| Cumulative annual incidence of death, n (%) | | |
| Year 1 | 90 (31) | 231 (31) |
| Year 2 | 128 (46) | 299 (41) |
| Year 3 | 142 (54) | 342 (50) |
| Year 4 | 156 (65) | 370 (59) |
| Year 5 | 158 (68) | 377 (65) |

Abbreviations: BM, brain metastases; Q, quartile

- Death occurred in **55%** of those with baseline BM and **50%** of the cohort at-risk for incident BM
- Time-to-death was **shorter** for those with baseline BM compared to the cohort at-risk for incident BM
- By year 5, the cumulative incidence of death was **68%** in those with baseline BM, and **65%** in the cohort at-risk for incident BM

# Results: Patients with incident BM have 2.6 times the risk of mortality compared to patients without incident BM

| Crude and Adjusted Cox Proportional Hazards Model for the Association between Time-varying Incident BM and Death | | | |
|---|---|---|---|
| **Primary Analysis: At risk for incident BM (n=751)** | | | |
| | Number of deaths during follow-up | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
| Time-varying incident BM | 371 | 2.58 (1.98-3.36) | 2.59 (1.98-3.38) |
| **Subgroup Analysis: Dual Eligibility Status for Medicare/Medicaid (n=200)** | | | |
| Time-varying incident BM | 108 | 2.73 (1.69-4.40) | 3.06 (1.83-5.12) |

*Confounding factors: age, sex, race/ethnicity, Census region, dual Medicare-Medicaid eligibility, Charlson Comorbidity Index and time-varying lorlatinib use

Abbreviations: BM, brain metastases; CI, confidence interval; HR, hazard ratio

# Limitations

- Retrospective study using claims data
  - Data are collected for administrative purposes and not for research
  - Some patients have incomplete information for certain study characteristics or outcomes
  - Some clinical variables are not available
  - Patient information not available prior to entry into Medicare
- Biomarker data not available in claims, used alectinib/brigatinib as a proxy for ALK+ mNSCLC
- Limited generalizability to patients outside of Medicare, including those <65 years of age
- 1L lorlatinib was out of scope, given the cohort entry date range (2017-2020/2021)

Abbreviations: 1L, first-line; ALK, anaplastic lymphoma kinase; BM, brain metastases; mNSCLC, metastatic non-small-cell lung cancer

# Conclusions

- In this RWE study, 28% of patients with ALK+ mNSCLC presented with baseline BM
- At 5 years of follow-up, the cumulative incidence of BM was 20%
- Incident BM were associated with an increased risk of death (HR: 2.59, 95% CI 1.98-3.38)
- Taken together, these results highlight that while progress is being made, development of BM continues to be an important consideration for ALK+ mNSCLC patients receiving second-generation ALK TKIs
- These findings underscore the need to provide safe and efficacious approaches to the treatment and prevention of brain metastases in patients with ALK+ mNSCLC, including use of medications with improved central nervous system activity

Abbreviations: ALK, anaplastic lymphoma kinase; BM, brain metastases; CI, confidence interval; HR, hazard ratio; mNSCLC, metastatic non-small-cell lung cancer TKI, tyrosine kinase inhibitor