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Effectiveness and Treatment Patterns in Patients With First-Line 2G ALK TKI Across the ESME French Real-World Cohort

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Introduction

- Anaplastic lymphoma kinase–positive (*ALK*+) non-small cell lung cancer (NSCLC) is a rare lung cancer subtype, occurring in 3% to 7% of patients with NSCLC[1]
- The European Society for Medical Oncology guidelines recommend the second-generation (2G) ALK tyrosine kinase inhibitors (TKIs) alectinib and brigatinib and the third-generation (3G) ALK TKI lorlatinib as preferred first-line (1L) treatments for *ALK*+ advanced NSCLC (aNSCLC)[2]
- Brain metastases (BM) are common at the time of diagnosis, occurring in 26% to 42% of patients with *ALK*+ aNSCLC,[3-5] and the cumulative incidence of new BM is 20% after 5 years[6]
  - Patients with incident BM have an increased risk of mortality compared with patients without BM[6]
- Despite clinical advances, real-world evidence on treatment patterns and outcomes with 1L 2G ALK TKIs remains limited due to the rarity of *ALK*+ aNSCLC
- This retrospective study aims to describe treatment patterns and real-world outcomes in patients initiated on a 1L 2G ALK TKI for *ALK*+ aNSCLC in France

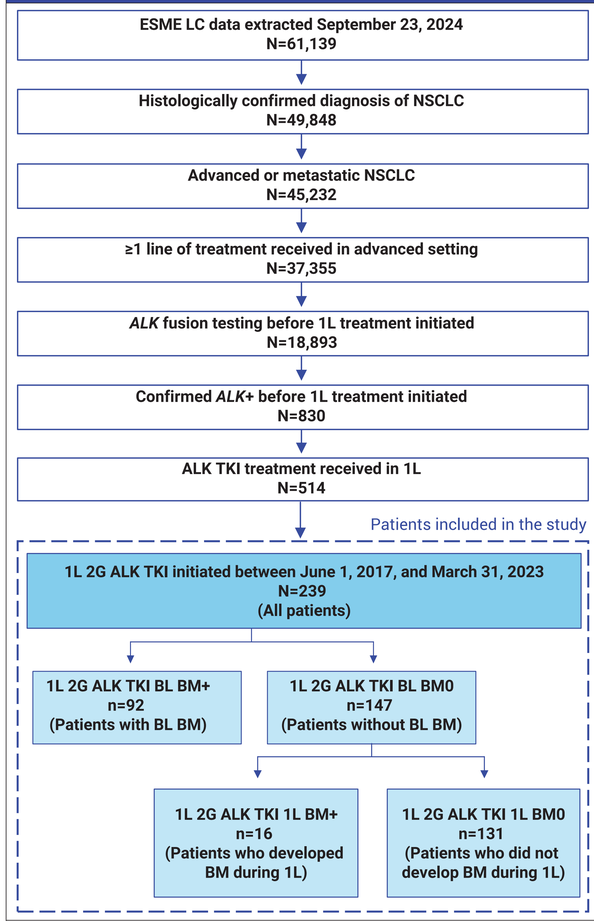
Methods

- This retrospective observational study used electronic medical records and chart review data from the Epidemiological Strategy and Medical Economics Lung Cancer (ESME LC) database
- The ESME LC database (NCT03848052) is a centralized de-identified structured database that derives electronic health records of consecutive patients treated for lung cancer at 1 of 38 participating French hospitals, including 20 private nonprofit comprehensive cancer centers and 18 public hospitals
  - All the centers participating in the ESME LC database are academic centers
- Adult patients aged ≥18 years with a histologically confirmed diagnosis of *ALK*+ aNSCLC treated with 2G ALK TKIs (alectinib and brigatinib) in 1L between June 2017 and March 2023 were selected. Patients were followed up until September 2024
- The primary outcomes of the study were treatment patterns and effectiveness of treatment by BM status

Results

- A total of 239 patients who received 1L 2G ALK TKIs were included in the study; 92 (38%) had baseline BM (**Figure 1**)
- In all patients, the median age was 63 years (IQR, 52–73), 130 (54%) were female, and of the 154 with a recorded Eastern Cooperative Oncology Group performance status (ECOG PS), 126 (82%) had an ECOG PS of 0-1 (**Table 1**)
- With a median follow-up of 40.8 months (95% CI, 35.3–45.6), 141 (59%) patients progressed during 1L treatment (**Figure 2**)
- 198 patients (83%) received alectinib in 1L, while 29 (12%) received brigatinib
- 128 (54%) patients discontinued 1L treatment. Of these, 94 (73%) discontinued due to progression and 9 died after discontinuation
- 112 (47%) patients received a second-line (2L) treatment. Of these, 94 (73%) discontinued due to progression and 9 died after discontinuation
- 29 (12%) patients died during 1L treatment, and 23 (21%) died during 2L treatment

Figure 1: Selection of study population from ESME LC database



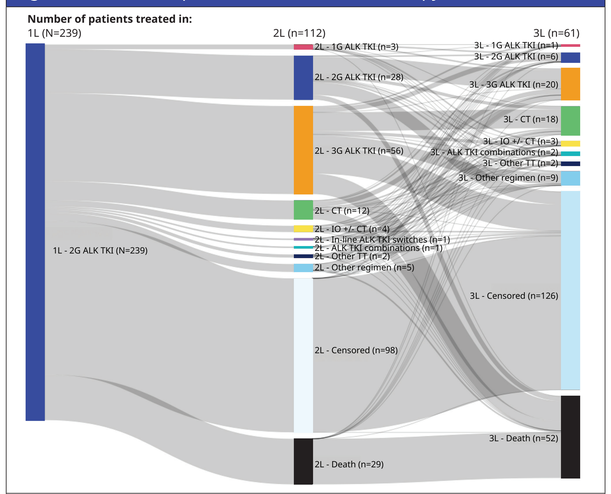
BL, baseline.

Table 1: Patient and disease characteristics

	All patients (N=239)	Patients without baseline BM (n=147)[a]	Patients with baseline BM (n=92)[a,b]
Age at aNSCLC diagnosis, median (IQR), years	63.0 (52–73)	64.0 (52–73)	62.5 (52–72)
Female, n (%)	130 (54)	68 (46)	62 (67)
ECOG PS at baseline, n/N (%)[c]			
0-1	126/154 (82)	81/92 (88)	45/62 (73)
≥2	28/154 (18)	11/92 (12)	17/62 (27)
Smoking status, n/N (%)			
Never smoked	131/230 (57)	85/144 (59)	46/86 (53)
Ever smoked	99/230 (43)	59/144 (41)	40/86 (47)
aNSCLC adenocarcinoma histology, n (%)	220 (92)	134 (91)	86 (93)
Bone metastases at aNSCLC diagnosis, n (%)	109 (49)	67 (52)	42 (46)
Brain metastases at aNSCLC diagnosis, n (%)	86 (39)	0	86 (93)
Liver metastases at aNSCLC diagnosis, n (%)	60 (27)	40 (31)	20 (22)
History of surgery prior to aNSCLC diagnosis, n (%)	28 (12)	17 (12)	11 (12)

RT, radiotherapy.
[a]Baseline is defined as the 1L 2G ALK TKI treatment start date.
[b]Of the 92 patients with baseline BM, 16 (17%) received brain RT before 1L therapy, and 11 (12%) received brain RT during 1L therapy.
[c]Baseline is defined as 30 days before through 15 days after the 1L 2G ALK TKI treatment start date.

Figure 2: Treatment patterns across lines of therapy[a,b]



1G, first generation; CT, chemotherapy; IO, immunotherapy; 3L, third line; TT, targeted therapy.
[a]Sankey diagram of treatments received across lines of therapy. Possible reasons for not receiving 2L treatment include death, still receiving 1L treatment, clinical factors, and patient preference.
[b]Patients were censored in 2L or 3L due to the absence of a documented end date for 1L or 2L therapy, respectively, and were considered either still on 1L or 2L therapy or lost to follow-up.

- Median time to treatment discontinuation (mTTD; **Figure 3**) and median time to next treatment (mTTNT; **Figure 4**) were approximately 2 years
  - mTTD was similar in patients with and without baseline BM: 21.8 and 22.5 months, respectively. The same trend was observed with mTTNT: 23.4 and 25.1 months, respectively
- With a median follow-up for overall survival of 40.8 months (95% CI, 35.3–45.6), mOS was 55.8 months in all patients (**Figure 5**) and 46.1 and 65.1 months, respectively, in patients with and without baseline BM
- Cumulative incidence of new BM in patients without baseline BM was 7% within 1 year, 14% within 2 years, 15% within 3 years, and 19% within 4 years from the 1L start date (**Figure 6**)

Figure 3: Time to treatment discontinuation

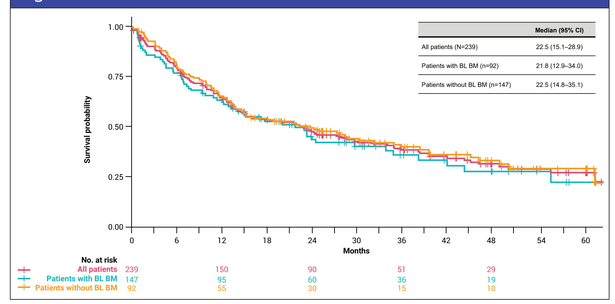


Figure 4: Time to next treatment

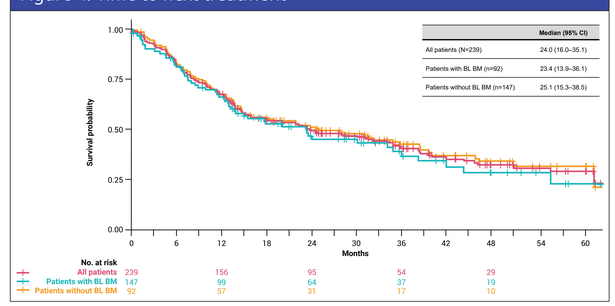
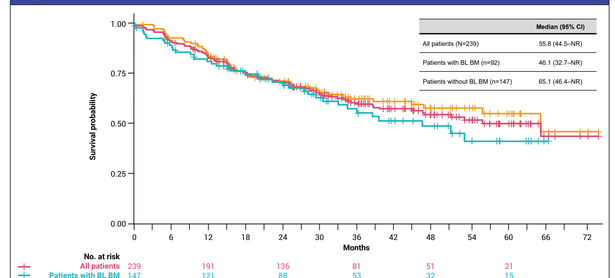
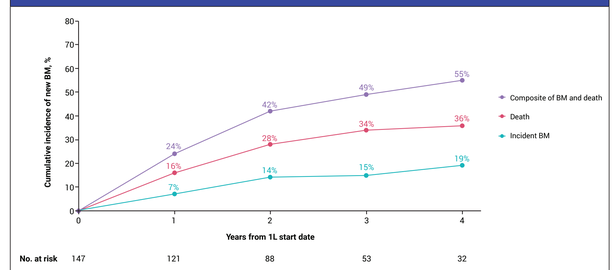


Figure 5: Overall survival[a]



[a]For context, mOS has not yet been reported in the ALEX and ALTA-1L studies.[7,8] No 2G ALK TKI has shown a statistically significant improvement in OS: Clinical trials previously reported either no OS improvement or an OS benefit as part of a descriptive analysis not powered to show statistical significance.

Figure 6: Cumulative incidence of new BM was 19% within 4 years of the 1L 2G ALK TKI start date[a,b]



[a]For context, the cumulative incidence of new BM with alectinib in patients without baseline BM in the ALEX/ALESIA studies was 4.6% at 1 year, 7.2% at 2 years, and 9.1% at 3 and 4 years.[9]
[b]Cumulative incidence of new BM is in patients without baseline BM who were alive.

Conclusions

- In this retrospective study using ESME LC data from 239 patients with *ALK*+ aNSCLC treated with 1L 2G ALK TKIs at participating academic centers, 128 (54%) patients discontinued 1L treatment and 29 (12%) died during 1L treatment
- mTTD and mTTNT were approximately 2 years, with mOS of 55.8 months after 40.8 months of follow-up
- The results of this real-world study are consistent with previous real-world studies in patients with *ALK*+ aNSCLC treated with 2G ALK TKIs,[6,10] showing an increased cumulative incidence of new BM from years 1 to 4, which reached approximately 20% after 4 years
- These results support the importance of thoughtful consideration of 1L treatment with the longest systemic and intracranial efficacy up-front to provide the greatest benefit for patients with *ALK*+ aNSCLC

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