Real-World Treatment Patterns and Effectiveness in Patients With *ALK*+ Advanced NSCLC Treated With 1L ALK TKIs

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Background

- Anaplastic lymphoma kinase-positive (*ALK*+) non-small cell lung cancer (NSCLC) accounts for approximately 4–5% of all NSCLC cases.[1,2]
- Approved targeted therapies for *ALK*+ NSCLC include the first-generation ALK tyrosine kinase inhibitor (TKI), crizotinib, and next-generation ALK TKIs, such as brigatinib, alectinib, and lorlatinib.[3-8]
  - For first-line (1L) treatment of advanced *ALK*+ NSCLC, crizotinib, brigatinib, alectinib, and lorlatinib received Food and Drug Administration (FDA) approvals in January 2013, May 2020, November 2017, and March 2021, respectively.[4]
- In their respective phase III clinical trials, brigatinib, alectinib, and lorlatinib exhibited superior clinical efficacy compared with crizotinib for the 1L treatment of patients with *ALK*+ NSCLC.[9-11]
- There is a lack of real-world data on treatment patterns and clinical outcomes in the 1L setting for patients with *ALK*+ advanced NSCLC.

Objective

- To describe real-world treatment patterns and effectiveness in patients with *ALK*+ advanced NSCLC treated with 1L ALK TKIs.

Methods

Study design and patients

- This retrospective cohort study used data extracted from the US Flatiron electronic medical record-derived database (Jan 2011–Sept 2023) (**Figure 1**).
- Patients were included if they:
  - Had a diagnosis of *ALK*+ advanced NSCLC;
  - Received alectinib, brigatinib, crizotinib, or lorlatinib monotherapy as their first ALK TKI treatment after initial advanced NSCLC diagnosis; and
  - Were aged ≥18 years at the time of initiating 1L alectinib, brigatinib, crizotinib, or lorlatinib monotherapy.
- Patients with a positive ROS1 test result anytime were excluded.
- Index date was defined as the date of initiation of 1L ALK TKI.

Study outcomes and statistical analyses

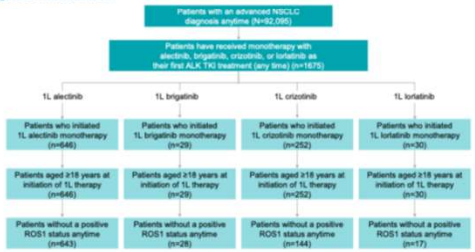
- Study outcomes included first subsequent treatment (second-line [2L]) after 1L ALK TKI; real-world time to treatment discontinuation (rwTTD); and real-world time to next treatment (rwTTNT) of 1L ALK TKI.
- Kaplan-Meier survival analyses were used to estimate the median rwTTD and rwTTNT for each study cohort.
- A multivariate Cox proportional hazard model was performed to compare rwTTD and rwTTNT for 1L brigatinib or 1L alectinib vs. 1L crizotinib, adjusting for relevant covariates (age, sex, race, Eastern Cooperative Oncology Group performance score [ECOG PS], smoking, baseline brain metastasis, and time from advanced diagnosis to index date).
- To further compare the real-world effectiveness of 1L brigatinib vs. 1L alectinib or 1L crizotinib, propensity score matching using an inverse probability of treatment weighting (IPTW) method was applied; adjusted covariates used for propensity matching included age, sex, smoking status, ECOG PS, baseline brain metastasis, and time from advanced diagnosis to index date.
- A sensitivity analysis was conducted to minimize bias resulting from different FDA approval dates of the ALK TKIs, which included patients treated with alectinib, brigatinib, or crizotinib on or after May 22, 2020 (the FDA approval date for brigatinib).
- Formal assessments on the outcomes (TTD/TTNT) of 1L lorlatinib were not conducted due to the small sample size and immature data.

Results

Patients

- The study included 832 patients, of which 643 patients received 1L alectinib, 28 received 1L brigatinib, 144 received 1L crizotinib, and 17 received 1L lorlatinib (**Figures 1** and **2**).
- Mean (standard deviation [SD]) age of patients in the 1L alectinib, 1L brigatinib, 1L crizotinib, and 1L lorlatinib cohorts were 61.6 (13.2), 61.1 (14.1), 70.0 (11.5), and 60.6 (11.3) years, and 44.0%, 57.1%, 45.1%, and 35.3% of patients were male, respectively (**Table 1**).

Figure 2. Patient attrition



1L alectinib patients initiated monotherapy on or after Nov 7, 2017; 1L brigatinib patients initiated monotherapy on or after May 22, 2020; 1L crizotinib patients initiated monotherapy on or after Jan 1, 2018; 1L lorlatinib patients initiated monotherapy on or after March 3, 2021.
1L, first-line; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Question

What are the real-world treatment patterns and effectiveness in patients with *ALK*+ advanced NSCLC treated with 1L ALK TKIs?

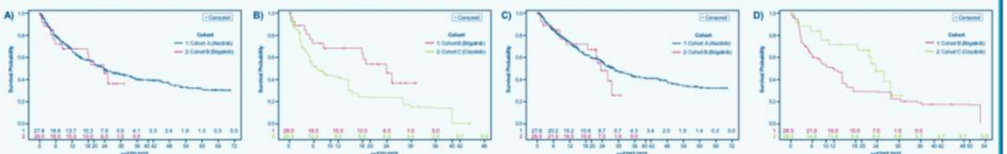
Study Design

Figure 1. Study design

1L, first-line; ALK, anaplastic lymphoma kinase; RWD, real-world data; rwTTD, real-world time to treatment discontinuation; rwTTNT, time to next treatment; TKI, tyrosine kinase inhibitor; US, United States.

Results

Figure 3. Kaplan-Meier curves for adjusted rwTTD for (A) 1L alectinib vs. 1L brigatinib, and (B) 1L brigatinib vs. 1L crizotinib, and adjusted rwTTNT for (C) 1L alectinib vs. 1L brigatinib, and (D) 1L brigatinib vs. 1L crizotinib



1L, first-line; DOT, duration of treatment; rwTTD, real-world time to treatment discontinuation; rwTTNT, time to next treatment.

Key Takeaways

- **This real-world study showed that treatment with 1L alectinib and 1L brigatinib had similar rwTTD and rwTTNT.**
- **The real-world findings from this study mirror and support the phase III ALTA-1L trial data demonstrating the efficacy of 1L brigatinib vs. crizotinib in patients with *ALK*+ advanced NSCLC.**

Table 1. Baseline characteristics

Baseline characteristics	1L alectinib n=643	1L brigatinib n=28	1L crizotinib n=144	1L lorlatinib n=17
Age at index date, years, mean (SD)	61.6 (13.2)	61.1 (14.1)	70.0 (11.5)	60.6 (11.3)
Male, n (%)	283 (44.0)	16 (57.1)	65 (45.1)	6 (35.3)
Race, n (%)				
Asian	48 (7.5)	2 (7.1)	8 (5.6)	0
Black or African American	47 (7.3)	1 (3.6)	14 (9.7)	4 (23.5)
Hispanic or Latino	1 (0.2)	0	0	0
Other/Unknown	143 (22.2)	14 (50.0)	25 (17.4)	5 (29.4)
White	404 (62.8)	11 (39.3)	97 (67.4)	8 (47.1)
History of smoking, n (%)	273 (42.5)	8 (28.6)	100 (69.4)	4 (23.5)
Patients with brain metastasis at baseline, n (%)	97 (15.1)	5 (17.9)	29 (20.1)	6 (35.3)
ECOG PS at index date, n (%)				
0	215 (33.4)	8 (28.6)	28 (19.4)	11 (64.7)
1	228 (35.5)	6 (21.4)	59 (41.0)	
2	60 (9.3)	1 (3.6)	21 (14.6)	
3	13 (2.0)	0	8 (5.6)	1 (5.9)
4	2 (0.3)	1 (3.6)	1 (0.7)	
Unknown	125 (19.4)	12 (42.9)	27 (18.8)	5 (29.4)
Time from initial advanced diagnosis to 1L ALK TKI, months, median (IQR)	1.5 (0.9, 4.4)	2.5 (1.2, 44.6)	7.5 (2.4, 18.7)	4.0 (1.6, 35.6)
Prior non-ALK TKI treatments after initial advanced diagnosis, n (%)				
Chemo	33 (5.1)	1 (3.6)	5 (3.5)	1 (5.9)
Chemo+others	5 (0.8)	0	5 (3.5)	0
IO	8 (1.2)	0	8 (5.6)	0
IO+chemo/other agents	79 (12.3)	3 (10.7)	52 (36.1)	0
Others	9 (1.4)	0	11 (7.6)	2 (11.8)
No prior non-ALK TKI therapy, n (%)	509 (79.2)	24 (85.7)	63 (43.8)	14 (82.4)
Number of prior lines of therapy,[a] n (%)				
1	94 (14.6)	2 (7.1)	40 (27.8)	3 (17.6)
2	27 (4.2)	1 (3.6)	20 (13.9)	0
≥3	17 (2.6)	1 (3.6)	22 (15.3)	0
Follow-up duration from start of 1L ALK TKI treatment until death or last activity date, months				
Mean (SD)	24.4 (19.3)	17.1 (10.8)	14.1 (15.2)	13.7 (8.1)

[a]All prior therapies were non-ALK TKI drugs.
1L, first-line; ALK, anaplastic lymphoma kinase; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; IO, immuno-oncology; IQR, interquartile range; SD, standard deviation; TKI, tyrosine kinase inhibitor.

- Among the 1L alectinib, 1L brigatinib, 1L crizotinib, and 1L lorlatinib cohorts, 68.9%, 50.0%, 60.4%, and 64.7% of patients had ECOG PS scores of 0–1 at index date, respectively (**Table 1**).
  - Among these cohorts, 19.4%, 42.9%, 18.8%, and 29.4% had unknown ECOG PS scores, respectively.
- Mean (SD) follow-up duration from the start of 1L ALK TKI treatment was 24.4 (19.3) months for 1L alectinib, 17.1 (10.8) months for 1L brigatinib, 14.1 (15.2) months for 1L crizotinib, and 13.7 (8.1) months for 1L lorlatinib (**Table 1**).

Real-world treatment patterns

- In the 1L alectinib cohort, 2L lorlatinib was the most common ALK TKI (17.4%) followed by brigatinib monotherapy (5.6%) (**Table 2**).
- In the 1L brigatinib cohort, 2L lorlatinib was the most common ALK TKI (17.9%).
- In the 1L crizotinib cohort, 2L alectinib was the most common ALK TKI (4.2%).
- In the 1L lorlatinib cohort (N=17), one patient received brigatinib in the 2L setting (5.9%), and one patient received a 2L combination therapy of ALK TKI plus chemotherapy (5.9%).

rwTTD

- Unadjusted median (95% confidence interval [CI]) rwTTD for 1L alectinib, 1L brigatinib, and 1L crizotinib was 23.2 (18.2–29.2), 23.9 (8.4–not reached [NR]), and 4.1 (3.0–5.0) months, respectively.
- Post-IPTW analysis showed that adjusted median (95% CI) rwTTD for 1L alectinib, 1L brigatinib, and 1L crizotinib was 23.5 (18.6–34.2), 23.9 (8.4–NR), and 6.7 (3.0–15.7) months, respectively (**Figures 3A** and **3B**).
- Adjusted hazard ratio (HRs) for rwTTD comparing 1L alectinib vs. 1L crizotinib was 0.304 (95% CI 0.241–0.384; *P*<0.0001), and for 1L brigatinib vs. 1L crizotinib was 0.357 (95% CI 0.199–0.641; *P*=0.0006) (**Table 3**).
- In the sensitivity analysis with index date on or after May 22, 2020 (date of FDA approval for brigatinib), median (95% CI) rwTTD for 1L alectinib, 1L brigatinib, and 1L crizotinib was 23.5 (19.3–NR), 23.9 (8.4–NR), and 6.1 (2.8–10.8), respectively (**Figure 4A**).

rwTTNT

- Unadjusted median (95% CI) rwTTNT for 1L alectinib, 1L brigatinib, and 1L crizotinib was 25.5 (20.5–31.6), 23.9 (10.8–NR), and 5.3 (4.1–7.4) months, respectively.
- Post-IPTW analysis showed that adjusted median (95% CI) rwTTNT for 1L alectinib, 1L brigatinib, and 1L crizotinib was 28.9 (22.8–36.9), 23.9 (10.8–NR), and 12.5 (NR–NR) months, respectively (**Figures 3C** and **3D**).
- Adjusted HR for rwTTNT comparing 1L alectinib vs. 1L crizotinib was 0.321 (95% CI 0.254–0.405; *P*<0.0001), and for 1L brigatinib vs. 1L crizotinib was 0.377 (95% CI 0.210–0.675; *P*=0.001) (**Table 3**).
- In the sensitivity analysis with index date on or after May 22, 2020 (date of FDA approval for brigatinib), median (95% CI) rwTTNT for 1L alectinib, 1L brigatinib, and 1L crizotinib was 26.2 (19.8–NR), 23.9 (10.8–NR), and 6.3 (3.6–13.4), respectively (**Figure 4B**).

Table 2. Distribution of first subsequent treatment following 1L treatments

n (%) patients with subsequent treatment	1L alectinib n=643	1L brigatinib n=28	1L crizotinib n=144	1L lorlatinib n=17
None	410 (63.8)	21 (75.0)	82 (56.9)	14 (82.4)
Chemo	10 (1.6)	0	16 (11.1)	0
Chemo+IO	8 (1.2)	0	6 (4.2)	0
IO	8 (1.2)	0	8 (5.6)	0
TKI	186 (28.9)	6 (21.4)	13 (9.0)	2 (11.8)
ALK TKI-based regimen[a]	32 (5.0)	0	5 (3.5)	1 (5.9)
Alectinib monotherapy	8 (1.2)	1 (3.6)	6 (4.2)	0
Brigatinib monotherapy	36 (5.6)	0	1 (0.7)	1 (5.9)
Ceritinib monotherapy	4 (0.6)	0	0	0
Crizotinib monotherapy	2 (0.3)	0	2 (1.4)	0
Lorlatinib monotherapy	112 (17.4)	5 (17.9)	0	0
Others	13 (2.0)	1 (3.6)	18 (12.5)	1 (5.9)

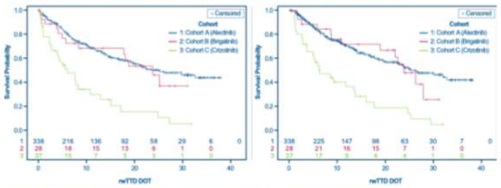
[a]Refers to ALK TKI in combination with other agents such as chemo and IO.
1L, first-line; ALK, anaplastic lymphoma kinase; chemo, chemotherapy; IO, immuno-oncology; TKI, tyrosine kinase inhibitor.

Table 3. Unadjusted and adjusted rwTTD and rwTTNT

1L ALK TKI[a]	N	Unadjusted median[b] months (95% CI)	Adjusted median[c] months (95% CI)	Adjusted HR[d] (95% CI)	*P* value
rwTTD					
1L alectinib	643	23.2 (18.2–29.2)	23.5 (18.6–34.2)	0.304 (0.241–0.384)	<0.0001
1L brigatinib	28	23.9 (8.4–NR)	23.9 (8.4–NR)	0.357 (0.199–0.641)	0.0006
1L crizotinib	144	4.1 (3.0–5.0)	6.7 (3.0–15.7)	–	
rwTTNT					
1L alectinib	643	25.5 (20.5–31.6)	28.9 (22.8–36.9)	0.321 (0.254–0.405)	<0.0001
1L brigatinib	28	23.9 (10.8–NR)	23.9 (10.8–NR)	0.377 (0.210–0.675)	0.001
1L crizotinib	144	5.3 (4.1–7.4)	12.5 (NR–NR)	–	

[a]1L lorlatinib was not assessed due to small sample size. [b]Estimated using Kaplan-Meier survival analysis. [c]Post-IPTW (conducted separately for brigatinib vs. alectinib and brigatinib vs. crizotinib. [d]Cox proportional hazard model with crizotinib as control.
1L, first-line; ALK, anaplastic lymphoma kinase; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NR, not reached; rwTTD, real-world time to treatment discontinuation; rwTTNT, time to next treatment; TKI, tyrosine kinase inhibitor.

Figure 4. Kaplan-Meier curves for sensitivity analyses[a] (A) rwTTD and (B) rwTTNT



[a]Included patients treated with alectinib, brigatinib, or crizotinib on or after May 22, 2020 (the FDA approval date for brigatinib).
DOT, duration of therapy; FDA, Food and Drug Administration; rwTTD, real-world time to treatment discontinuation; rwTTNT, time to next treatment.

Limitations

- The sample size for the 1L brigatinib cohort is small; larger sample size and longer follow-up are warranted for future studies.
- Data generated from real-world clinical practice are subject to miscoding, errors, underreporting, or missing values.
  - ECOG data were missing across the treatment cohorts, with a high percentage of missing data for the 1L brigatinib cohort.
  - Information on interventions that happened outside of the Flatiron network were not captured.
  - The majority of the clinics or institutions within the Flatiron network are community-based practices; therefore, the results may not be generalizable to academic institutions.

Discussion

- In patients with *ALK*+ advanced NSCLC, treatment with 1L alectinib and 1L brigatinib was found to have similar rwTTD and rwTTNT.
- 1L alectinib and 1L brigatinib were associated with improved rwTTD and rwTTNT vs. 1L crizotinib.
- IPTW analysis showed similar effectiveness for 1L alectinib and 1L brigatinib and improved effectiveness for 1L brigatinib and 1L alectinib vs. 1L crizotinib.

REFERENCES

1. Barlesi F, et al. *Lancet*. 2016;387(10026):1415-1426.
2. Solomon B, et al. *J Thorac Oncol*. 2009;4(12):1450-1454.
3. Spagnuolo A, et al. *Expert Opin Emerg Drugs*. 2016;23(3):231-241.
4. Peng L, et al. *Front Oncol*. 2022;12:863461.
5. XALKORI® (crizotinib) [prescribing information]. Pfizer, New York, NY. 2023.
6. ALUNBRIG® (brigatinib) [prescribing information]. Takeda Pharmaceuticals America, Inc., Lexington, MA. 2022.
7. ALECENSA® (alectinib) [prescribing information]. Genentech USA, Inc., South San Francisco, CA. 2024.
8. LORBRENA® (lorlatinib) [prescribing information]. Pfizer, New York, NY. 2023.
9. Camidge DR, et al. *J Thorac Oncol*. 2021;16(12):2081-2106.
10. Peters S, et al. *N Engl J Med*. 2017;377(9):829-838.
11. Solomon BJ, et al. *J Clin Oncol*. 2024;JCO2400561.

DISCLOSURES

Yuanbin Chen reports honoraria from AstraZeneca, Amgen, Takeda, Guardant Health, Bristol Myers Squibb/Pfizer, and Jazz; consulting/advisory roles for Bristol Myers Squibb and AstraZeneca; speakers' bureau from AstraZeneca, Bristol Myers Squibb, Takeda, Guardant Health, Amgen, and Jazz; research funding from AstraZeneca, Bristol Myers Squibb, Amgen, Genentech, Merck, and Daiichi Sankyo/Astra Zeneca; expert testimony given for AstraZeneca and Takeda.
Huamao Mark Lin, Yin Wan, Yu Yin, Yanyu Wu, Luis Hernandez, Christopher Danes, and Eric Churchill report employment with Takeda.
Anastasios Dimou reports consulting/advisory roles for TP Therapeutics, Guardant Health, Archeart Therapeutics, and ChromaCode; travel/accommodations/expenses from Guardant Health; honoraria from Roche/Genentech, and Intellisphere; research funding from Merck, Guardant Health, Bystrix Biosystems, Novartis, Sorrento Therapeutics, and Archeart Therapeutics; and other relationship with institution: Rising Tide Foundation.

ACKNOWLEDGMENTS

This study was funded by Takeda Development Center Americas, Inc. (TDCA). Medical writing and editorial support was provided by SNELL Medical Communication, Inc., and funded by TDCA.