ORIGINAL ARTICLE

Real-World Treatment and Outcomes in ALK-Rearranged NSCLC: Results From a Large U.S.-Based Database

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ABSTRACT

Introduction: *ALK*–rearranged advanced NSCLC (aNSCLC) represents 4% of all NSCLCs, and multiple ALK-targeted therapies (ALK-inhibitors) are now available for use. Little is known about changes in treatment patterns, or how prognostic factors and sequence of therapy may impact overall survival in the real-world setting. We aim to describe initial and subsequent treatments used, survival outcomes, prognostic factors, and the impact of treatment on overall survival in the largest (N = 739) real-world cohort of patients with ALK+ aNSCLC reported in the literature.

Methods: Retrospective observational cohort study with data drawn from a U.S.-based electronic health record–derived, deidentified database. Eligible patients were diagnosed with ALK+ aNSCLC between 2011-2020 and were treated in multiple different cancer clinics and across multiple geographic regions throughout the United States.

Results: From a cohort of 63,667 patients with aNSCLC, 739 patients with ALK+ NSCLC were eligible for analysis, median age was 63 years, 54% patients were female, and 85% were managed in community setting. More than 168 different treatment sequences were observed, and treatment utilization changed over time. Cohort median overall survival was 37 months (95% confidence interval: 33–45). Positive prognostic factors were as follows: never-smoking history, younger age, treatment in an academic setting, and initial early stage at diagnosis. Initial treatment with a second-generation ALK-inhibitor was associated with improved survival compared with chemotherapy.

Conclusions: For people with ALK+ aNSCLC, this study has identified several important clinical prognostic factors and is practice affirming; first-line treatment with a second-generation ALK-inhibitor improves survival compared with chemotherapy.

Keywords: ALK+ lung cancer; Prognostic factors; Treatment sequence; Real-world

Introduction

ALK-rearrangements were first discovered as an oncogenic driver in a subset of lung cancers in 2007 and

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are found in approximately 4% of patients with NSCLC.[1] With a multitude of ALK-targeted tyrosine kinase inhibitors (ALK-inhibitors) now available, overall survival (OS) seems to be improving over time, and many patients receive multiple lines of therapy. Despite this, ALK+ aNSCLC remains an incurable condition. Little is known about what clinical factors or sequence of therapy (beyond first line) are associated with optimal survival outcomes.

The progression-free survival (PFS) for patients with ALK+ NSCLC has improved over time as newer generation ALK-inhibitors have become available. PROFILE 1014 was the earliest randomized controlled trial (RCT) investigating an ALK-inhibitor in the first-line setting and revealed a PFS of 10.9 months for those receiving crizotinib versus 7.0 months for those receiving chemotherapy (0.45, 95% confidence interval [CI]: 0.35–0.60, $p < 0.001$).[2] Subsequently, in the ALEX study, those receiving alectinib had a PFS of 34.8 months, and in the CROWN study, those receiving lorlatinib (third-generation ALK-inhibitor) had a PFS of beyond 36 months (PFS not yet reached).[3,4]

OS for patients with ALK+ NSCLC also seems to be improving over time. In PROFILE 1014 (first-line crizotinib versus chemotherapy), the median OS (mOS) was 47.5 months for those receiving chemotherapy (95% CI: 32.2 months–NR), and in the more recent ALEX study, mOS for those receiving crizotinib was 57.4 months (95% CI: 34.6-NR) and not yet reached for those receiving alectinib.[3,5] Real-world studies have shown mOS ranging from 31 months up to 86 months, depending on the cohort studied.[6–9] Despite this, RCTs have not yet revealed statistically significant improvements in OS using ALK-inhibitors. This is likely secondary to crossover in some trials and effective poststudy treatment.

Identifying clinical prognostic factors in patients with ALK+ aNSCLC is important because it may help to select patients requiring intensified treatment and to guide discussions around prognosis and advance care planning. Sex, age, and smoking status have all been explored as potential prognostic factors, and data from the real-world are conflicting.[7–9] Other clinical factors including sites of metastatic disease (e.g., brain, liver) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) are usually recorded in clinical trial data but may be incompletely recorded in observational cohort data.

Although several phase 3 studies demonstrating superiority of next-generation ALK-inhibitors over crizotinib have established these agents as standard of care in the first-line setting, the lack of head-to-head trials comparing these agents contributes to a wide variety of treatment patterns in the first line.[2,10–17] Furthermore, when patients progress on first-line treatments, there are no RCTs to guide subsequent treatment. Limited small real-world studies have reported treatment patterns, and fewer still attempt to address the question of which sequence confers the best survival benefit for patients.[6,18–21] U.S. Food and Drug Administration–approved agents include the first-in-class ALK-inhibitor, crizotinib (first-generation ALK-inhibitor); second-generation ALK-inhibitors alectinib, ceritinib, and brigatinib; and third-generation ALK-inhibitor lorlatinib. In addition, chemotherapy/immunotherapy combinations are often used despite a paucity of data showing efficacy of immunotherapy for these patients.[22]

The primary aims of this study are to describe drug treatment sequences and OS in the largest reported real-world cohort of patients with ALK+ aNSCLC over 10-year window. Secondary aims are to determine clinical prognostic factors of survival and to determine if a particular treatment sequence is associated with improved survival.

Materials and Methods

Study Design and Database

This is a retrospective observational cohort study that uses the nationwide (U.S.-based) Flatiron-Health electronic health record–derived deidentified database; a longitudinal database, comprising deidentified patient-level structured and unstructured data, curated by means of technology-enabled abstraction.[23–25] Institutional review board approval of the study protocol was obtained before study conduct and included a waiver of informed consent.

Patient Eligibility/Exclusions

During the study period, deidentified data originated from approximately 280 cancer clinics (approximately 800 sites of care). Eligible patients were diagnosed with aNSCLC between January 1, 2011, and February 29, 2020, including those with advanced disease at time of initial diagnosis (defined as American Joint Committee on Cancer, Eighth Edition stage IIIB, IIIC, IVA, IVB, and IVC) or progressed to advanced disease after initial early stage diagnosis (defined as occult, stage 0, I, IA, IA1, IA2, IA3, IB, II, IIA, IIB, and IIIA disease), had a positive test for the presence of *ALK*-rearrangement at any point during their care (including fluorescence in situ hybridization, immunohistochemistry, or genomic testing), had a follow-up period of at least 90 days, and were 18 years of age or older at diagnosis. Patients were excluded if they had no structured activity within 90 days of aNSCLC diagnosis, had no first-line treatment captured, if first-line treatment started more than 90 days after aNSCLC diagnosis, if first-line end date was on

or before start day, or if they also had a positive test result for EGFR or ROS1.

Statistical Analysis

Descriptive statistics were used to summarize patients' characteristics and treatment utilization, with Sankey diagrams and Sunburst plots to visualize treatment sequences. Systemic cancer treatments were categorized as ALK-inhibitor (first/second/third generation), chemotherapy (platinum or nonplatinum), immunotherapy, chemotherapy + immunotherapy, chemotherapy + ALK-inhibitor, "other" treatment, and "other combination" (Supplementary Material 1). A line of treatment was defined as a drug or combination of drugs given concurrently (or within 28 d) that is known to be used for the treatment of ALK+ aNSCLC. Treatments known to be used for other cancer types, such as hormone therapies for breast or prostate cancer, were not counted as lines of therapy, but use did not result in patient exclusion (aNSCLC likely to remain life-limiting condition). A treatment "sequence" was defined as two or more lines of treatment. Treatment "pattern" was defined as any treatment given, including one treatment line only. Where patients were commenced on first-line chemotherapy with or without immunotherapy but switched to ALK-inhibitor within 30 days of receiving a only one cycle, this was categorized as "ALK-inhibitor" rather than "combination." OS was calculated from the date of commencing first-line treatment for advanced disease to the date of death or censorship. Patients were censored on the last confirmed activity date, defined as the date on which there was a record of confirmed structured activity including patient vital signs, medication administration, or reported laboratory tests/results or treatment activity abstracted from patient records. Kaplan-Meier was used to visualize survival outcomes for the overall cohort and according to clinical prognostic factors, with p values generated using the log-rank test.

OS was assessed according to treatment sequence. This analysis was limited to (1) OS according to first line only and (2) OS according to first line to second-line treatment sequence. For the analysis of first line only, the following three different categories were compared: (1) chemotherapy as baseline reference, (2) first-generation ALK-inhibitor, and (3) second-generation ALK-inhibitor.

For the survival analysis according to first- and second-line treatment sequence, analysis was limited to seven categories: (1) chemotherapy to first-generation ALK-inhibitor (baseline reference), (2) chemotherapy to chemotherapy (change of chemotherapy regimen or rechallenge with same after ≥120 d), (3) chemotherapy to immunotherapy, (4) first-generation ALK-inhibitor to second-generation ALK-inhibitor, (5) first-generation ALK-inhibitor to chemotherapy, (6) second-generation ALK-inhibitor to second-generation ALK-inhibitor (either different second-generation ALK-inhibitor or rechallenge with same after ≥120 d), and (7) second-generation ALK-inhibitor to third-generation ALK-inhibitor.

These categories were chosen for clinical relevance or largest patient numbers. Multivariable regression analysis was conducted using Cox-proportional hazards, controlling for the following covariates: age, sex, stage at initial diagnosis (early versus advanced), smoking history, year of diagnosis (2011–2014 versus 2015–2020), geographic region, and practice setting (community versus academic).

Results

Patient Characteristics

Of a total of 63,667 patients with aNSCLC in this real-world database, 739 ALK+ patients were eligible (Fig. 1). Median age at diagnosis was 63.0 years (interquartile range [IQR] 53.0–71.0 y), 54% were female, and 47% were current or former smokers (Table 1). Sixty-one percent of patients had an ECOG of 0 to 1, 13.3% had an ECOG of 2 to 4, and 26% had an undocumented ECOG. Eighty-five percent of patients were treated in community settings, and 39.6% had private/commercial health plans (Table 1). Smaller numbers of patients were diagnosed during the earliest years (11% in 2011–2012) and in the latest years (15% in 2019–2020) of the study period (Table 1).

OS and Prognostic Factors

The mOS for the entire cohort was 37.0 months (95% CI: 31.4–44.5 mo) (Fig. 2), and mOS follow-up time was 25.8 months (13.1–46.1 mo) (Table 1).

On univariate analysis, smoking history, age, and year of diagnosis were prognostic, whereas sex was not. The mOS for never-smokers versus ever-smokers was 45.9 months (95% CI: 38.9–55.2) versus 28.2 months (95% CI: 24.0–34.0), $p < 0.0001$ (Fig. 2). Those who were younger than the median age (<63.0 years) had a longer mOS compared with those who were ≥63 years ($p = 0.0013$): mOS 46.5 months (95% CI: 36.2–58.8) versus 31.1 months (95% CI: 27.2–39.5 months) (Fig. 2). There was no statistically significant difference in survival according to sex ($p = 0.18$); mOS for females versus males was 37.6 months (95% CI: 29.8–45.9) versus 35.6 months (95% CI: 28.9–46.5) (Fig. 2).

Multivariable analysis of potential prognostic factors was conducted for the subgroup of patients included in the survival analysis according to first-line treatment (n = 646). Covariates associated with improved

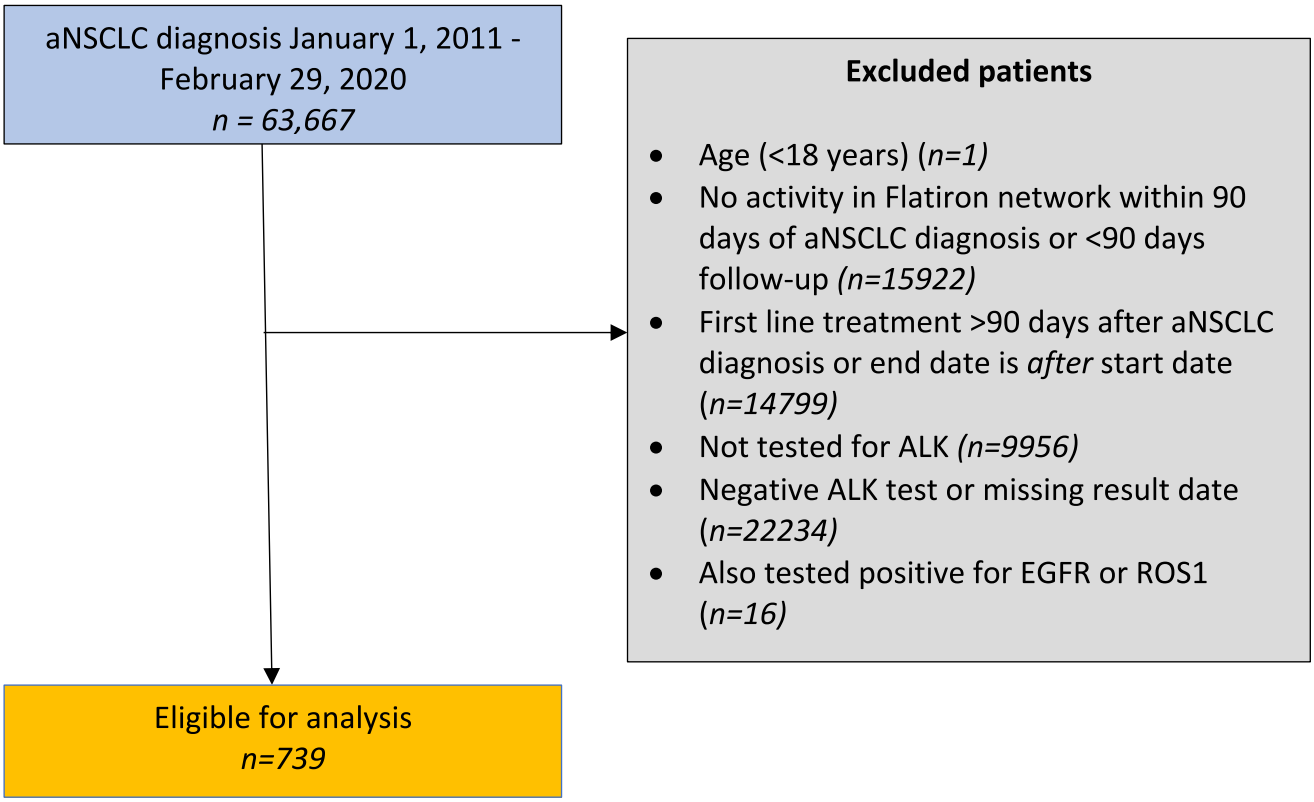

Figure 1. Study attrition. ALK, anaplastic lymphoma kinase; aNSCLC, advanced NSCLC.

prognosis were never-smoking history (hazard ratio [HR] = 0.70, 95% CI: 0.57–0.87) and early stage at diagnosis (HR = 0.56, 95% CI: 0.41–0.76). Treatment in a community center was associated with poorer prognosis compared with treatment within an academic center (HR = 2.48, 95% CI: 1.34–4.60). Sex, year of advanced diagnosis (2011–2014 versus 2015–2020), and region (Midwest, Northeast, South, West, Other) were not found to be prognostic (Supplementary Material 2).

Treatment Patterns

One-hundred sixty-eight unique treatment sequences were observed within the first five lines of treatment (Fig. 3). Patients received up to 11 lines of treatment (n = 1; 0.13%), with 37.9% receiving at least three lines (Fig. 4). Eighty-nine percent of patients received an ALK-inhibitor during their treatment course, 65.4% of all patients in the first line. Specifically, 57.4% received a first-generation, 65.6% received a second-generation, and 10.7% received a third-generation ALK-inhibitor. Fifty-six percent of patients received chemotherapy; most often in the first line (35.4% of all patients) (Supplementary Material 3). Twenty percent of patients received immunotherapy; most often in the first line (7.6% of all patients). The most common first-line treatment was crizotinib (41.1%) (Fig. 4). Of those who had greater than three lines of treatment, the most common sequence was chemotherapy to crizotinib to second-generation ALK-inhibitor (4.6%). Of those receiving first-line crizotinib, 69.0% went on to receive subsequent therapy, and of those receiving first-line second-generation ALK-inhibitor, 41.1% went on to receive subsequent treatment.

Treatment patterns changed over the study period (Fig. 5). Forty-eight percent of those diagnosed in 2011–2012 received first-line chemotherapy, reducing to 14.5% of those diagnosed in 2019–2020 (Fig. 5). First-line crizotinib use increased from 44.4% in 2011–2012 to 58.2% in 2015–2016 and then reduced no use in 2019–2020, as use of first-line second-generation ALK-inhibitor increased from no use in those diagnosed during or before 2014, to 69.1% of those diagnosed in 2019–2020 (Fig. 5).

OS According to Treatment Sequence

First Line Only. Survival time was compared among 646 patients receiving first-line treatment with either chemotherapy (reference), first-generation ALK-inhibitor or second-generation ALK-inhibitor. Multivariate analysis was conducted, adjusting for age at first-line treatment start date, sex, stage at initial NSCLC

Table 1. Baseline Characteristics of 739 Patients With ALK-Positive Advanced NSCLC From Flatiron-Health Database, Diagnosed 2011–2019

Characteristics	All Cohort (N = 739)
Age at advanced diagnosis (y)	
Median (IQR)	63.0 (53.0-71.0)
Sex	
Male	339 (46)
Female	400 (54)
Smoking status	
Ever-smoked	349 (47)
Never-smoked	388 (52)
Not reported	2 (0.3)
Race/ethnicity	
White	478 (65)
Black or African American	51 (7)
Other	152 (21)
Not reported	58 (8)
ECOG[a]	
0-1	449 (61)
2-4	98 (13)
Not reported	192 (26)
Stage at initial NSCLC diagnosis[b]	
Early stage	124 (17)
Advanced stage	607 (82)
Not reported	8 (1)
Practice type	
Community center	627 (85)
Academic center	112 (15)
Insurance type at advanced diagnosis	
Private/commercial health plan	239 (39)
Public/government	224 (30)
Other	89 (12)
Not reported	133 (18)
Geographic region[c]	
Midwest	100 (13.5)
Northeast	119 (16.1)
South	251 (34.0)
West	141 (19.1)
Other/not reported	128 (17.3)
Year of diagnosis	
2011/2012	81 (11)
2013/2014	167 (23)
2015/2016	194 (26)
2017/2018	187 (25)
2019/2020	110 (15)
Overall survival follow-up time, median (IQR), mo	25.8 (13.1-46.1)

Note: All values are n (%) unless otherwise specified.
[a]ECOG scores range from 0 to 5, with higher scores indicating greater disability. ECOG refers to that documented at time of starting first-line of treatment.
[b]Early stage includes occult, 0, I, IA, IA1, IA2, IA3, IB, II, IIA, IIB, and IIIA. Advanced stage includes IIIB, IIIC, IV, IVA, IVB, and IVC. Not reported includes missing and stage III (A/B/C not specified).
[c]Geographic locations, per United States census regions: Midwest = IL, IN, MI, OH, WI, IA, KS, MN, MO, NE, ND, SD; Northeast = CT, ME, MA, NH, RI, VT, NJ, NY, PA; South = DE, DC, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX; West = AZ, MT, CO, ID, NV, NM, UT, WY, AK, CA, HI, OR, WA; Other includes Puerto Rico.
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

diagnosis, smoking status, year of advanced diagnosis (2011–2014 versus 2015–2020), geographic region, and practice setting. With chemotherapy as reference, the HR for first-generation ALK-inhibitor was 1.19 (95% CI: 0.93–1.49), and for second-generation ALK-inhibitor was 0.62 (95% CI: 0.44–0.88) (Supplementary Material 4).

First Line and Second Line. OS was then compared among 361 patients according to first- to second-line treatment. The reference treatment sequence was first-line chemotherapy followed by second-line first-generation ALK-inhibitor. Six treatment sequences were compared with this reference (see Methods section). Treatment with first-generation ALK-inhibitor followed by second-generation ALK-inhibitor was associated with improved survival (HR = 0.69, 95% CI: 0.49–0.99) (Supplementary Material 5). Treatment with first-generation ALK-inhibitor followed by chemotherapy was associated with an increased hazard (HR = 1.91, 95% CI: 1.13–3.21). No other sequences studied were associated with a statistically significant difference in survival.

Discussion

To our knowledge, this real-world cohort of 739 patients with ALK-rearranged aNSCLC is the largest ALK+ cohort reported in the literature. This cohort had different clinical and demographic features from those included in relevant RCTs; patients were older (median age 63.0 y), many were current/former smokers (48%), and the majority were treated in the community setting (85%). Key findings were as follows: (1) median survival of 37.0 months, less than that reported in contemporary clinical trials but consistent with some retrospective real-world studies; (2) patients were treated with a wide variety of treatment sequences and treatment patterns changed across the study period, and many did not receive contemporary standard of care first-line treatment; (3) positive clinical prognostic factors included younger age, never-smoking status, initial early stage at diagnosis, and treatment in an academic setting, and sex was not prognostic; (4) first-line treatment with a second-generation ALK-inhibitor was associated with improved survival compared with chemotherapy, and when considering the impact of first- and second-line treatment together, treatment with a first-generation ALK-inhibitor followed by a second-generation ALK-inhibitor was associated with an improvement in survival.

The demographic profile of this ALK+ patient cohort differs from that in clinical trials investigating the licensed ALK-inhibitors for ALK+ aNSCLC.[12,14–17] Patients involved in the relevant clinical trials were

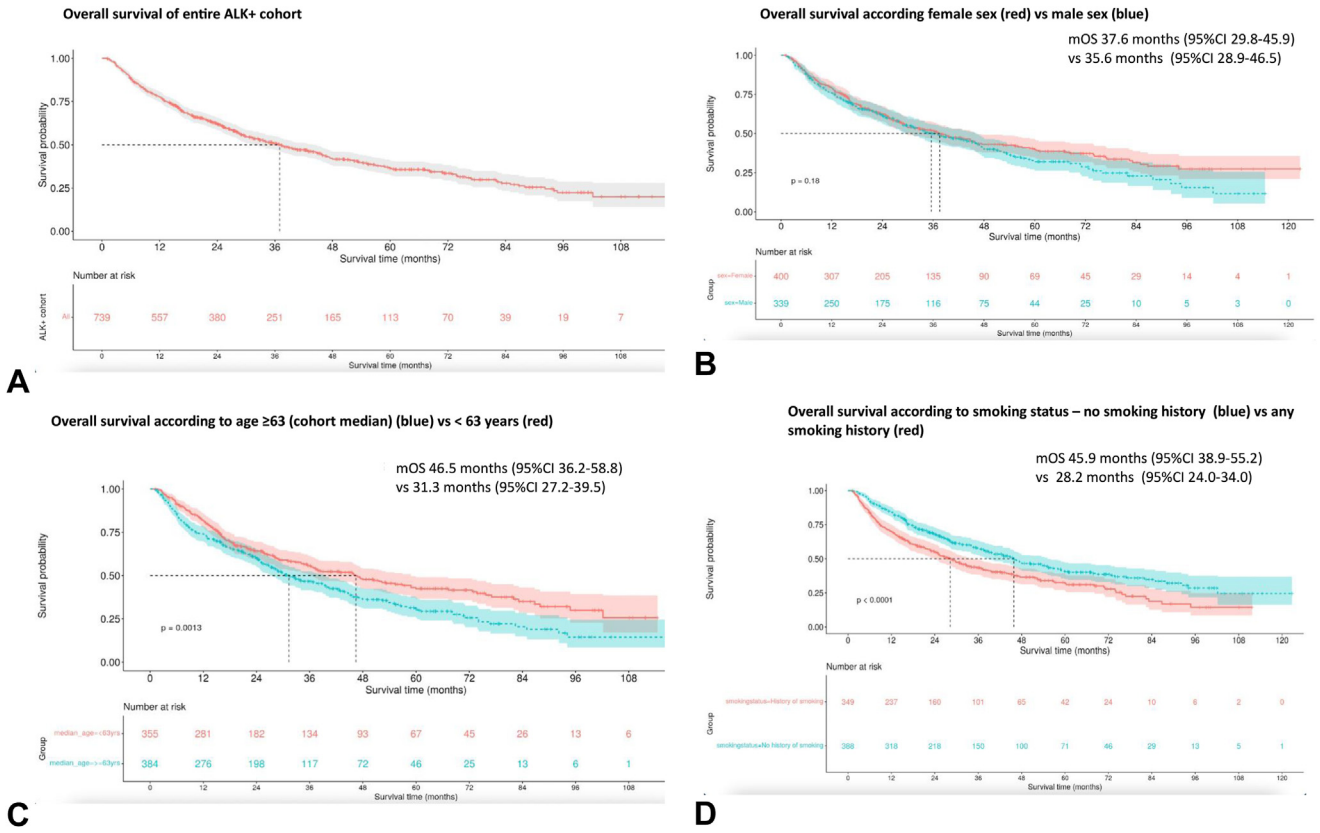

Figure 2. Kaplan-Meier showing overall survival of 739 patients with ALK-positive aNSCLC from Flatiron-Health database. (*A)* Overall survival for entire cohort, *(B)* overall survival by sex, *(C)* overall survival by median age at the time of diagnosis, and *(D)* overall survival by smoking status (never/ever). aNSCLC, advanced NSCLC; CI, confidence interval; mOS, median overall survival.

generally younger, had a better performance status, and had a higher proportion of never-smokers.[2,15,17,26,27] ECOG was incompletely recorded in our cohort, but at least 13% had an ECOG of 2 to 4. In addition, most of this real-world cohort was treated in community settings (85%) compared with the academic setting of most patients on clinical trials. These differences underscore the importance of considering the generalizability of clinical trial findings to routine oncology care and may contribute to survival disparities between cohorts.

Treatment sequences varied widely in this study, reflecting the rapidly evolving drug availability and lack of consensus regarding optimal treatment sequence. The most common sequence observed for those who had at least three lines of therapy was chemotherapy to second-line crizotinib to third-line second-generation ALK-inhibitor; this likely reflects the limited availability of treatment options earlier during the study period and may also reflect a group of patients where chemotherapy was started before ALK results becoming available and continued owing to a treatment response or variations in clinical practice. This was not explicitly investigated in this study. Chemotherapy or immunotherapy were prescribed mostly in the first-line setting, again possibly due to starting treatment while awaiting ALK results or owing to variation in clinical practice. When first-generation ALK-inhibitor (crizotinib) was used as first-line treatment, 68% went on to receive second-line treatment; when second-generation ALK-inhibitor was used as first-line treatment, only 41% went on to receive second-line treatment. This is likely explained by the longer duration of treatment with first-line second-generation ALK-inhibitors (18.7 months, IQR: 8.5–29.5) compared with first-line crizotinib (7.1 months, IQR: 3.0–16.9), lack of options beyond second-generation ALK-inhibitor for most study period (lorlatinib received U.S. Food and Drug Administration approval for second and subsequent lines in 2018) and also the more recent commencement of second-generation ALK-inhibitors and thus less opportunity to receive next line therapy during the study period.

The mOS for this real-world cohort of patients was 37 months, compared with beyond 57 months in clinical trials.[3] Reported OS from some of the larger real-world studies are more consistent with our findings, such as the mOS of 31 months reported in a French retrospective cohort study by Duruisseaux et al.[7] including 318 ALK+ patients diagnosed between 2012 and 2013. However,

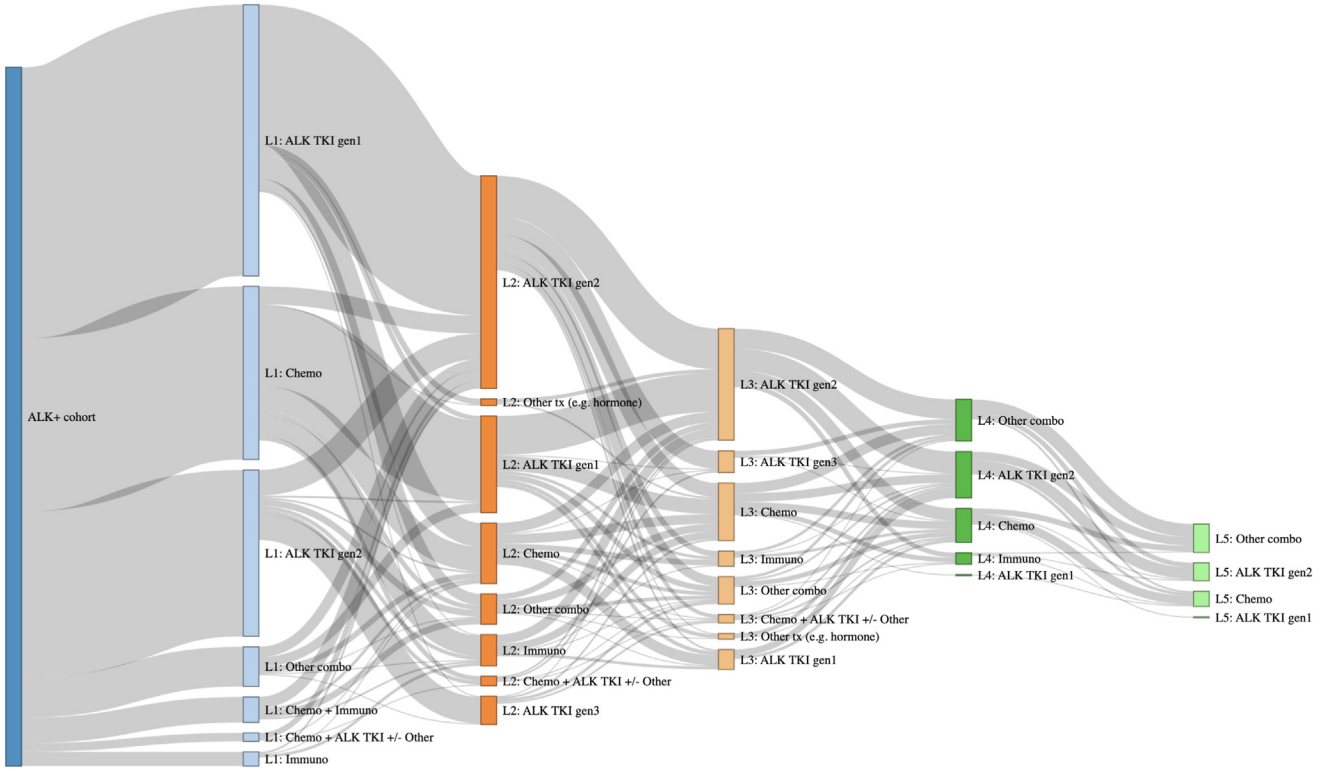

Figure 3. Sankey diagram showing treatment sequences for 739 patients with ALK-positive aNSCLC from Flatiron-Health database. From left to right shows flow of people from first-line of treatment (L1), second-line (L2), third-line (L3), fourth-line (L4), and fifth line (L5). ALK, anaplastic lymphoma kinase; ALK TKI gen 1, first-generation ALK-inhibitor (crizotinib); ALK TKI gen 2, second-generation ALK-inhibitor (alectinib, brigatinib, or ceritinib); ALK TKI gen 3, third-generation ALK-inhibitor (lorlatinib); aNSCLC, advanced NSCLC; Chemo, chemotherapy; Combo, combination; Immuno, immunotherapy; TKI, tyrosine kinase inhibitor.

some real-world studies have also reported longer survival; a cohort of 110 ALK+ patients treated at the University of Colorado between 2009 and 2017 had an mOS of 81 months.[8] All patients in this cohort received at least one ALK-inhibitor.[8] The discrepancy in survival times across different cohorts not only reflects selection bias in clinical trials and indeed in some real-world cohorts, but also results from the lengthy study period (2011–2020) necessary to accrue relatively large numbers of patients with ALK+ aNSCLC; many patients included in this analysis did not have access to contemporary standard of care treatment and the efficacy and safety of treatments received likely varied over the study period. The relatively low mOS in this cohort may also reflect different baseline characteristics (larger portion of patients with ECOG PS 2–4) and possibly unmeasured prognostic factors (such as central nervous system [CNS] metastases).

Clinical prognostic factors examined in this study included sex, smoking status, age, treatment setting (academic versus community), and initial stage at diagnosis (early versus advanced). Consistent with most previous studies, sex was not found to be prognostic.[7,8] However, it is possible that with greater patient numbers, a difference would be observed, as the tail of the curve from our study (Fig. 2) suggests more female long-term survivors. Never-smoking history was an independent positive prognostic variable. This is also consistent with multiple other retrospective ALK+ cohort studies.[7,8] Younger age (compared with cohort median) was associated with improved prognosis in this cohort. This finding is intuitive, as older patients will have a shorter life expectancy independently from a cancer diagnosis. However, observational cohort study by Duruisseaux et al.[7] with 318 French patients (majority from nationwide expanded access program for crizotinib) also analyzed the impact of age above/below median (58 y in this cohort) and found that it was not prognostic on univariate analysis. Early stage at initial diagnosis was also an independent positive prognostic variable in our cohort, possibly because those with initial early-stage disease are more likely to have surveillance imaging and thus to have relapse/advanced disease detected earlier compared with those who present with de novo advanced disease. This is consistent with a retrospective study by Pacheco et al.,[8] where number having a smaller number of sites of metastatic disease was associated with improved prognosis. Lead-time bias

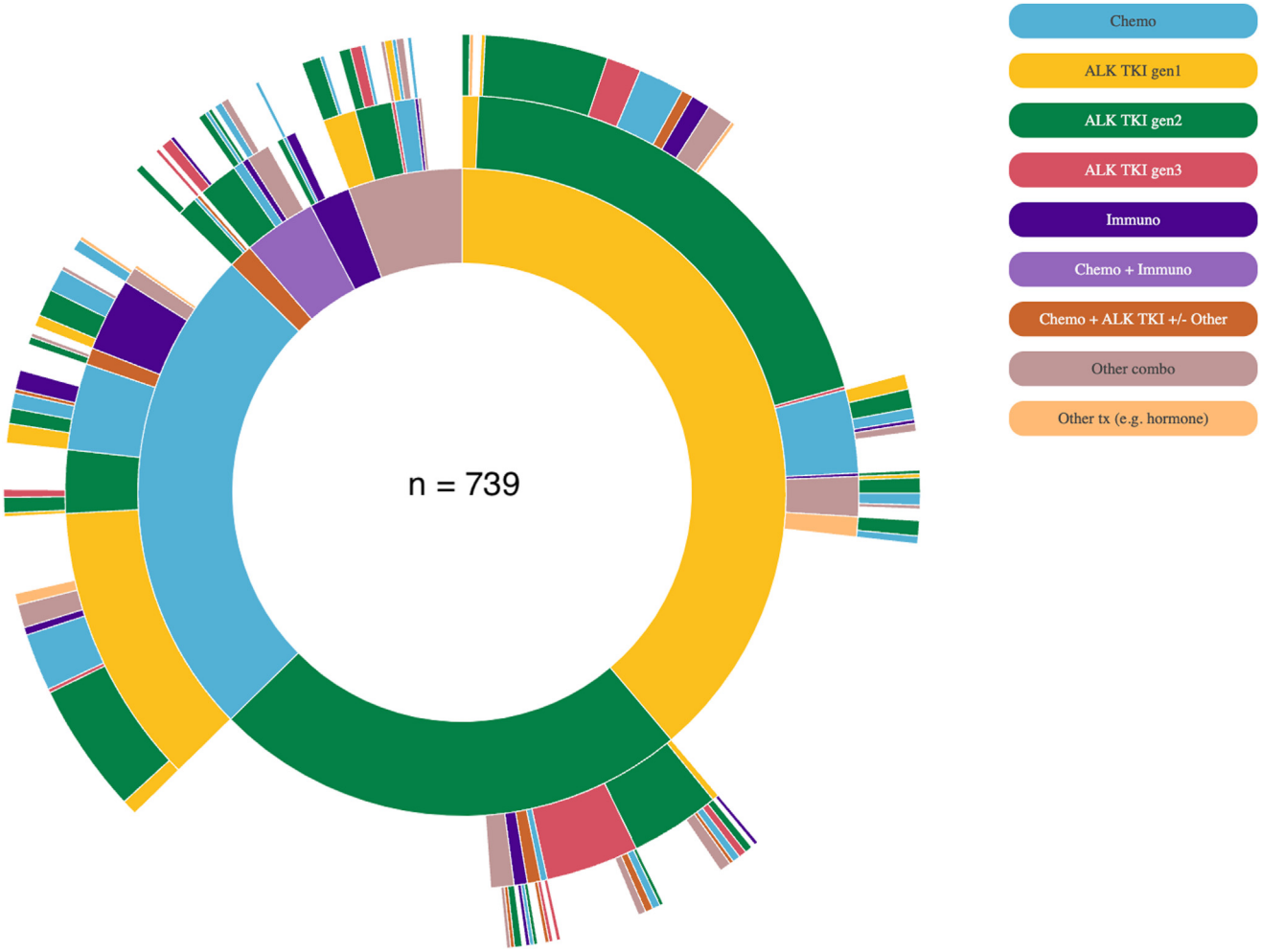

Figure 4. Sunburst plot showing treatment sequences for all 739 patients with ALK-positive aNSCLC from Flatiron-health database. Lines of treatment are represented by circles with the inner-most circle showing first-line treatment and the next circle outward showing second-line treatment, etc. ALK, anaplastic lymphoma kinase; ALK TKI gen 1, first-generation ALK-inhibitor (crizotinib); ALK TKI gen 2, second-generation ALK-inhibitor (alectinib, brigatinib, or ceritinib); ALK TKI gen 3, third-generation ALK-inhibitor (lorlatinib); aNSCLC, advanced NSCLC; Chemo, chemotherapy; Combo, combination; Immuno, immunotherapy; TKI, tyrosine kinase inhibitor; Tx, treatment.

may have also contributed to this finding. Importantly, multivariable analysis found that treatment in a community center was independently associated with a poorer prognosis compared with treatment in an academic setting. Of note, the academic setting comparator group was relatively small (n = 104 compared with n = 542 in community setting). This finding is important and suggests that there may be differences in access to treatment depending on site of care. This was not explicitly explored in this study but warrants further investigation.

One of the major aims of this study was to determine if a particular treatment sequence confers a survival benefit compared with other sequences. Because of the large number of permutations of treatment sequences, individual drugs needed to be categorized into groups and survival analysis was limited to first line (regardless of subsequent therapy) and first to second-line (regardless of subsequent therapy) to make comparisons possible. Analysis of survival according to first-line treatment choice revealed that first-line treatment with a second-generation ALK-inhibitor was associated with superior OS compared with chemotherapy (HR = 0.65, 95% CI: 0.45–0.92, $p < 0.05$). This finding is clinically relevant because, although clinical trials have revealed improvements in PFS using second-generation ALK-inhibitors (improved PFS using crizotinib compared with chemotherapy, and in turn improved PFS of second-generation ALK-inhibitors compared with crizotinib), improvements in OS have not yet been revealed statical significance.[3,5,28] Analysis of survival according to first and second-line treatment found that treatment with first-line first-generation ALK-inhibitor followed by second-line second-generation ALK-inhibitor was

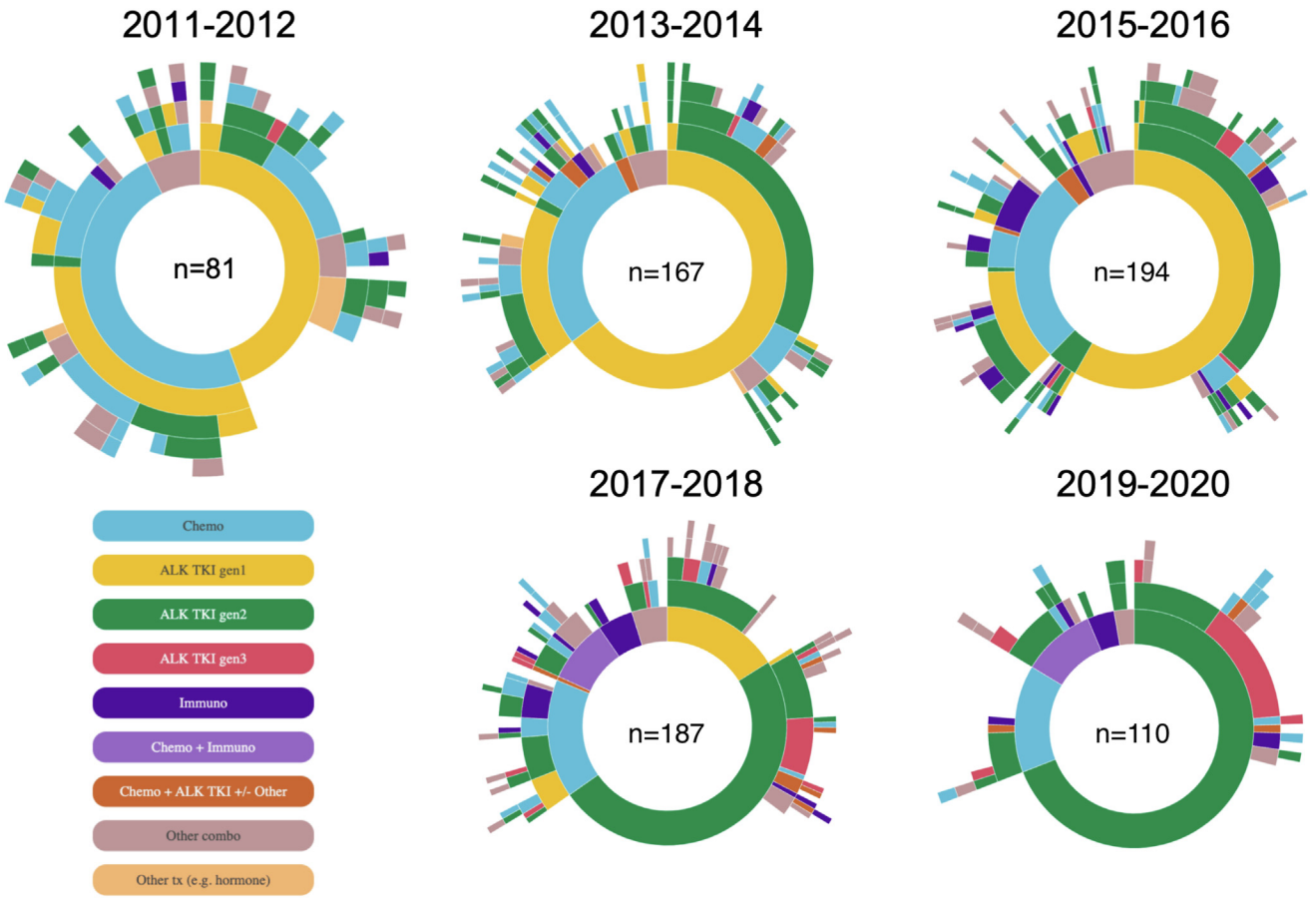

Figure 5. Sunburst plots showing treatment sequences for 739 patients with ALK-positive aNSCLC from Flatiron-Health database, by year of diagnosis. Lines of treatment are represented by circles with the inner-most circle showing first-line treatment and the next circle outward showing second-line treatment, etc. ALK, anaplastic lymphoma kinase; ALK TKI gen 1, first-generation ALK-inhibitor (crizotinib); ALK TKI gen 2, second-generation ALK-inhibitor (alectinib, brigatinib, or ceritinib); ALK TKI gen 3, third-generation ALK-inhibitor (lorlatinib); aNSCLC, advanced NSCLC; Chemo, chemotherapy; Combo, combination; Immuno, immunotherapy; TKI, tyrosine kinase inhibitor; Tx, treatment.

associated with an improvement in OS compared with first-line chemotherapy followed by second-line first-generation ALK-inhibitor (HR = 0.69, 95% CI: 0.49–0.99, $p < 0.05$). An increased risk was observed for those receiving first-line first-generation ALK-inhibitor followed by chemotherapy (HR = 1.91, 95% CI: 1.13–3.21, $p < 0.05$). This is unexpected clinically, and small numbers in this group (n = 25) are noted. On the basis of results from RCTs, it would be expected that first-line treatment with a second-generation ALK-inhibitor followed by second-line third-generation ALK-inhibitor would improve survival compared with chemotherapy followed by first-generation ALK-inhibitor.[3,4,11,12,17] This was not observed in our study (HR = 0.75, 95% CI: 0.39–1.45). This is likely due to small patient numbers in the second-generation ALK-inhibitor followed by third-generation ALK-inhibitor group, n = 12). Obvious limitations to this analysis include that groups were not randomized, some treatment groups contained small patient numbers, the "chemotherapy" group may have included patients receiving less effective chemotherapy regimens than platinum/pemetrexed that forms the control arm in the relevant clinical trials, and "second-generation ALK-inhibitor" includes three different drugs, and thus, this finding does not provide insight into which of these drugs is driving this survival improvement or whether in fact they are equivalent. In addition, subsequent treatment (beyond first line and beyond second line) was not factored into this analysis or controlled for in the Cox model used but may have driven the survival differences observed.

This study has several important strengths. First, to our knowledge, it is the largest cohort of patients with ALK+ aNSCLC reported in the literature, facilitating statistical power compared with many other ALK+ cohorts. Patients were treated across many sites and geographic areas, and there were minimal treatment-based selection criteria (only required that systemic therapy was initiated within 90 d of diagnosis). Thus, this cohort represents a relatively unselect group of

patients with ALK+ aNSCLC. This may increase the generalizability of findings when compared with smaller and more select real-world studies. Important limitations include that molecular prognostic factors, such as ALK variant or co-mutations, were not studied (not recorded in this database), and thus unmeasured confounders may have influenced results. Comorbidities, including the presence of second malignancy or CNS metastases, were incompletely recorded, and thus not included in the analysis. The large number of permutations in treatment patterns observed necessitated categorization into larger treatment groups for statistical comparison, meaning that individual second-generation ALK-inhibitors were not compared. In addition, multivariable analysis of clinical prognostic factors was limited to a select cohort of patients who had all received first- and second-line treatment. This was done to control for these factors in an analysis of survival according to treatment sequence, but results may have differed if applied to the broader cohort. This Flatiron cohort study highlights that even with relatively large numbers in a real-world cohort, the number of patients who had access to contemporary standard-of-care therapy was small, owing to the nature of the rapidly evolving treatment landscape. This calls to light the need for collaboration between registries to facilitate larger patient numbers treated across a shorter period to address the question of how treatment sequence may affect survival. In addition, identifying a particular generic treatment sequence associated with improved survival may help to guide clinician/patient decisions but would likely only form one element in of the decision for an individual patient. This decision needs to factor in sites of disease, CNS penetrance of different drugs, side-effect profiles, access, and cost/funding barriers. Furthermore, the presence or absence of acquired resistance mechanisms (e.g., new mutations within the ALK gene or other co-mutations) after progression on one line of treatment may influence the choice of subsequent therapy.

This large retrospective observational cohort study of 739 patients with ALK+ aNSCLC treated in the United States between 2011 and 2020 has several important findings. The OS in this real-world setting was 37 months, likely reflecting baseline clinical demographics (older age, more ever-smokers, majority treated in community setting) and the lengthy study period. Clinical factors that conferred improved prognosis included younger age, never-smoking status, early-stage disease at initial diagnosis, and treatment in an academic setting; sex was not prognostic. First-line treatment with second-generation ALK-inhibitor was associated with improved OS compared with chemotherapy. First-line first-generation ALK-inhibitor followed by second-line second-generation ALK-inhibitor was associated with improved OS compared with chemotherapy followed by first-generation ALK-inhibitor. An updated analysis of this cohort may provide more insight, with larger patient numbers and inclusion of more patients who have accessed contemporary standard-of-care treatment. However, a major methodological finding from this study is that to address the question of how to "get the most" out of the multitude of available therapies, strong collaboration between ALK+ registries will be required to study large numbers of patients who have had access to relevant, contemporary standard-of-care therapies.

CRediT Authorship Contribution Statement

Grace Chazan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft, review, and editing manuscript.

Fanny Franchini: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Review and editing.

Roma Shah: Data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, review and editing.

Marliese Alexander: Conceptualization, Investigation, Methodology, Supervision, Visualization, Review and editing.

Ani John: Data curation, Formal analysis, Investigation, Methodology, Supervision, Resources, Software, Validation, Visualization, Review and editing.

Maarten IJzerman: Conceptualization, Investigation, Methodology, Supervision, Visualization, Review and editing.

Benjamin Solomon: Conceptualization, Investigation, Methodology, Supervision, Visualization, Review and editing.

Disclosure

Ms. Shah and Dr. John are employees of Roche Diagnostics. Dr. Solomon has served on advisory boards and received honoraria from Pfizer, Roche, Novartis, Takeda, Merck Sharpe Dohme, Amgen, Bristol Myers Squibb, BeiGene, and AstraZeneca. The remaining authors declare no conflict of interest.

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Submission Declaration and Verification

This work is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Collaborators

Celia Bel (Roche Diagnostics), Dr. Antony Mersiades, Dr. Malinda Itchins, Associate Professor Nick Pavlakis.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100662.

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