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DOES LONGER TREATMENT PERSISTENCE IN THE REAL WORLD TRANSLATE TO IMPROVED CLINICAL OUTCOMES? A CASE STUDY OF ANAPLASTIC LYMPHOMA KINASE–POSITIVE NON–SMALL CELL LUNG CANCER

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INTRODUCTION

There is growing interest in the use of real-world endpoints, especially in regulatory and postmarketing analyses. Real-world surrogate endpoints in oncology, such as treatment duration (TD), can be useful when data on clinical outcomes, including progression-free survival (PFS) or overall survival (OS), may be unavailable. In cases where administrative claims data may be the only available data, real-world endpoints may be valuable in postmarketing use cases, such as value-based contracting or assessing how benefit design impacts clinical outcomes.

Thus far, there has been limited assessment of the correlation between TD and either PFS or OS. An exploratory analysis found real-world time-to treatment discontinuation was correlated with OS in advanced non–small cell lung cancer (NSCLC) patients treated with immunotherapy.[1] There are few data on the correlation between oral tyrosine kinase inhibitors and clinical outcomes in NSCLC patients.

OBJECTIVE

This retrospective study of electronic health record (EHR) data aimed to determine how real-world anaplastic lymphoma kinase (ALK) inhibitor (ALKi) TD correlates with PFS and OS.

METHODS

Study Design

Data from the Flatiron Health EHR–derived database was used to measure ALKi TD and outcomes for patients who received a diagnosis of ALK positive (ALK+) advanced NSCLC within the identification period (1/1/2011–10/31/2018). The date of each study subject's initial ALKi prescription within the identification period was the subject's index date. The full study period included dates of service from 1/1/2011 through 1/31/2019.

Database

The Flatiron Health database includes nationwide, longitudinal, deidentified data from over 280 cancer clinics (approximately 800 sites of care). This demographically and geographically diverse database represents more than 2.2 million US cancer patients available for analysis.

Eligible Study Subjects

Eligible study subjects met all of the following criteria:

- Had at least 1 visit with an advanced NSCLC diagnosis within the identification period;
- Had an ALK+ test result within the identification period;
- Used an ALKi within 90 days of their ALK+ test result and before 11/1/2018.

Statistical Methods

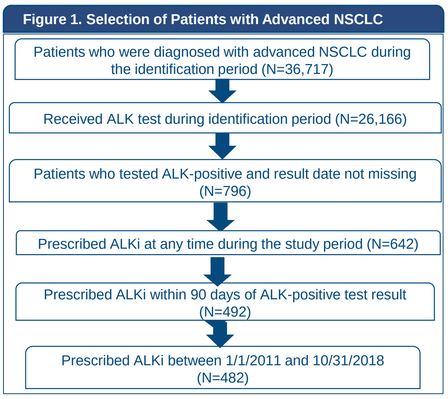
- Proportions were calculated to describe the cohort and descriptive estimates.
- TD was plotted versus PFS and OS, with correlation estimated via Pearson's correlation.
- PFS and OS were described by TD categories (0-3 months, 4-6 months, 7-12 months, >12 months) using Kaplan-Meier estimates.
- The association of TD with PFS and OS within 12 months was estimated via Cox proportional hazards model (95% CI). Treatment was included as a time-varying covariate to account for potential immortal time biases. Cox models were adjusted for the following baseline characteristics:
  - Age, gender, race, region, payer type, smoking status, practice type, year of advanced diagnosis, metastasis at baseline (CNS, bone, or adrenal).
- Predicted PFS at 3 and 6 months was estimated by holding covariates fixed at the following values:
  - Age = 55-64, gender = female, race = White, region = South, payer type = commercial, smoking status = no history of smoking, practice type = community, year of advanced NSCLC diagnosis = 2016-2019, baseline metastasis = no baseline CNS, bone, or adrenal metastases.

RESULTS

Study Population

A total of 482 patients were identified as having ALK+ advanced NSCLC during the identification period. **Figure 1** presents the study subject selection process.

Figure 1. Selection of Patients with Advanced NSCLC



ALK, anaplastic lymphoma kinase; ALKi, anaplastic lymphoma kinase inhibitor; NSCLC, non–small cell lung cancer.

Baseline characteristics of study population

As summarized in Table 1, the average patient age at the time of initial advanced NSCLC diagnosis during the study period was 61.0 years old (28.4% aged 18 to 54, 30.1% aged 55 to 65, 25.7% aged 65 to 74, and 15.8% aged 75 or older). Average TD of first ALKi prescribed was 10.6 months (28.4% of subjects had TD of ≤3 months, 15.6% had TD of 4 to 6 months, 27.2% had TD of 7 to 12 months, 28.8% had TD of >12 months).

Table 1. Baseline characteristics of study population (N = 482)

	No. (%)
First ALKi prescribed during study period	
Alectinib	88 (18.3)
Ceritinib	4 (0.8)
Crizotinib	390 (80.9)
TD of first ALKi drug prescribed (mo)	
0-3	137 (28.4)
4-6	75 (15.6)
7-12	131 (27.2)
>12	139 (28.8)
Average TD of ALKi use in months (SD)	10.6 (11.9)
Age as of initial advanced NSCLC diagnosis	
18-54	137 (28.4)
55-64	145 (30.1)
65-74	124 (25.7)
≥75	76 (15.8)
Average age of initial advanced NSCLC patient (SD)	61.0 (12.8)
Male	227 (47.1)
Region	
Midwest	73 (15.2)
Northeast	93 (19.3)
South	153 (31.7)
Unknown	63 (13.1)
West	100 (20.8)
Payer	
Commercial	225 (46.7)
Medicare	64 (13.3)
Medicaid	5 (1.04)
Other/Unknown	188 (39.0)
History of Smoking	213 (44.2)
Practice Type	
Academic	61 (12.7)
Community	421 (87.3)
Histology: Non-squamous cell carcinoma	482 (100)
Year of advanced NSCLC diagnosis	
2011-2013	146 (30.3)
2014-2015	151 (31.3)
2016-2019	185 (38.4)
Metastasis at baseline (CNS)	47 (9.8)
Metastasis at baseline (bone)	83 (17.2)
Metastasis at baseline (adrenal)	7 (1.5)

ALKi, anaplastic lymphoma kinase inhibitor; CNS, central nervous system; mo, month; NSCLC, non–small cell lung cancer; SD, standard deviation; TD, treatment duration.

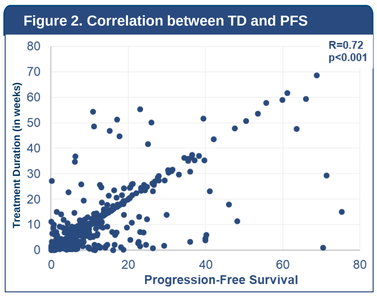
Timing of disease progression following discontinuation of ALKi treatment

53.7% of patients experienced progression or death within 4 weeks of discontinuing ALKi treatment, while 41.7% experienced disease progression or death within 2 weeks of discontinuing ALKi treatment. However, no consistent association was found between TD and disease progression following discontinuation of ALKi treatment. Disease progression or death within 2 weeks of discontinuing ALKi treatment varied inconsistently by TD category (31.4% of subjects with ≤3 months ALKi TD, 54.7% with 4 to 6 months TD, 45.8% with 7 to 12 months TD, 41.0% with TD >12 months). Disease progression or death within 4 weeks of discontinuing ALKi treatment also showed no clear pattern by TD category (52.6% for those with TD ≤3 months, 60.0% for 3-6 months TD, 54.2% for 7-12 months TD, 51.1% for TD >12 months.

Correlation between TD and outcomes (PFS, OS)

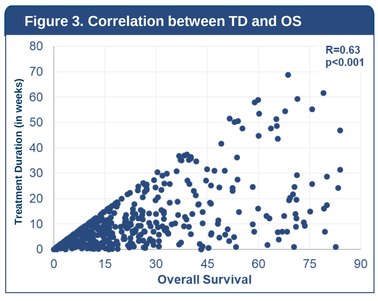
A strong correlation was observed between TD and PFS (R=0.72, p<0.001), as shown in Figure 2. A moderate correlation was observed between TD and OS (R =0.63, p<0.001), as shown in Figure 3.

Figure 2. Correlation between TD and PFS



PFS, progression-free survival; TD, treatment duration.

Figure 3. Correlation between TD and OS

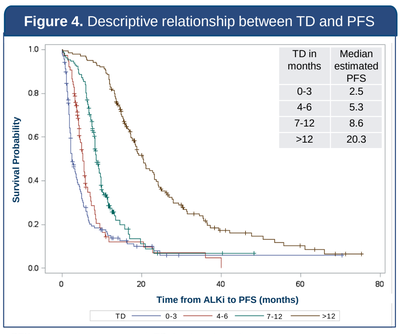


OS, overall survival; TD, treatment duration.

Descriptive relationship between TD and PFS, OS

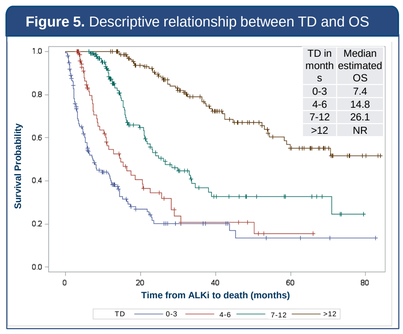
Longer ALKi TD category (≤3 months, 4 to 6 months, 7 to 12 months, >12 months) corresponded with higher median estimated PFS (2.5, 5.3, 8.6, 20.3), as shown in Figure 4. Longer ALKi TD category (≤3 months, 4 to 6 months, 7 to 12 months) also corresponded with higher median estimated OS (7.4, 14.8, 26.1, respectively), as shown in Figure 5. No median was reached for subjects with TD category >12 months.

Figure 4. Descriptive relationship between TD and PFS



PFS, progression-free survival; TD, treatment duration.

Figure 5. Descriptive relationship between TD and OS



OS, overall survival; TD, treatment duration; NR, not reached.

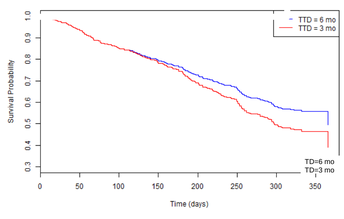
TD and risk of progression or death within 12 months

Each additional month of time on treatment up to 12 months was associated with a 13% lower risk of progression or death and a 32% lower risk of death, as shown in Table 2. Figure 6 summarizes differences in predicted PFS for 3-month TD versus 6-month TD.

Table 2. Cox model adjusting for immortal time bias (PFS, OS)

	Hazard Ratio	95% Hazard Ratio Confidence Limits
Progression or death within 12 months (PFS)	0.87	(0.82, 0.93)
Death within 12 months (OS)	0.68	(0.62, 0.75)

Figure 6. Predicted PFS for 3- and 6-month TD



DISCUSSION

This study examined how persistence with ALKi treatment affected disease progression, specifically PFS and OS. The percentage of disease progression events (including death) within 4 weeks of ALKi treatment discontinuation was similar for patients across all TD groups (50-60%). This could indicate that physicians discontinue ALKi treatment once evidence of disease progression is clear. However, persistence with ALKi (TD) did correlate highly with PFS and moderately with OS. Results from this study suggest an indirect link between clinical and non-clinical factors are associated with treatment persistence and clinical outcomes. Possible clinical factors that could shorten persistence with ALKi treatment may include treatment toxicity. Alternatively, non-clinical factors, such as copay assistance, might support treatment persistence, thereby leading to improved clinical outcomes in patients with NSCLC.

LIMITATIONS

Like many studies using secondary-source data, this study had limitations, including:

- The capture of treatment data for oral medications was limited to information gathered from the EHR, which may not be a precise estimate of treatment persistence;
- This study does not allow one to delineate the impact of an individual event contributing to TD (progression or toxicity or death), nor how many patients discontinued ALKi treatment due to toxicity versus disease progression; and
- Treatment adherence could not be determined.

These limitations may be addressed by linking claims data to the Flatiron Health EHR.

REFERENCE

1. Stewart M, et al. An exploratory analysis of real-world end points for assessing outcomes among immunotherapy-treated patients with advanced non–small-cell lung cancer. JCO Clin Cancer Inform. 2019;3:1-15. doi:10.1200/CCI.18.00155.

ACKNOWLEDGMENTS

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