Impact of *EML4-ALK* fusion variant and co-occurring *TP53* mutation on treatment duration of first-line next-generation ALK TKIs in *ALK* fusion+ NSCLC

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Introduction

- Tyrosine kinase inhibitors (TKIs) targeting anaplastic lymphoma kinase (ALK) are standard of care for first-line (1L) treatment of advanced *ALK*+ non–small cell lung cancer (NSCLC)[1]
- Next-generation ALK TKIs (alectinib, brigatinib, ceritinib, and lorlatinib) have improved long-term outcomes for patients with *ALK*+ NSCLC; however, many patients still develop progressive disease during treatment[2]
- Identification of molecular biomarkers associated with poor outcomes on 1L ALK TKI treatment may help guide treatment selection
- Liquid-biopsy detection of biomarkers such as *EML4-ALK* fusion variant (v) 3 and the *TP53* mutation in circulating tumor DNA (ctDNA) has been correlated with earlier disease progression in clinical trials in patients with *ALK*+ NSCLC[3-7]

Objective

- We evaluated the effect of *EML4-ALK* fusion variants and *TP53* mutation status on time-to-treatment discontinuation (TTD) of 1L treatment with a next-generation ALK TKI in patients with *ALK*+ NSCLC in the real-world setting

Methods

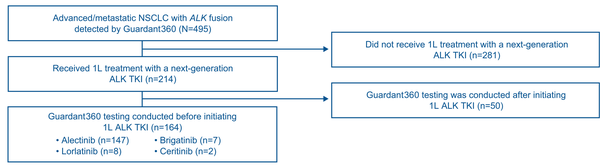
- **Data source:** Guardant INFORM (Redwood City, CA, USA) real-world clinical-genomics database
- **Patient population:**
  - Advanced/metastatic NSCLC
  - *ALK* fusion detected in ctDNA by Guardant360 liquid biopsy test between January 1, 2018, and December 31, 2021
  - Received 1L monotherapy with a next-generation ALK TKI (alectinib, brigatinib, ceritinib, or lorlatinib)
- **Outcomes:**
  - Median TTD of 1L ALK TKI treatment was determined by Kaplan-Meier (KM) methods
  - Impact of *EML4-ALK* fusion variant and *TP53* mutation status on TTD was evaluated
- **Statistical analysis:**
  - The effect of *TP53* mutation status and *EML4-ALK* fusion variant on TTD was analyzed using a Cox proportional hazard model that adjusted for age, sex, and presence of baseline brain metastases

Results

Patients

- Of 495 patients with *ALK* fusion+ advanced/metastatic NSCLC identified in the Guardant360 database,164 patients met inclusion criteria for this analysis **(Figure 1)**

Figure 1: Patient flow diagram



- Among all 164 patients, 66 (40%) had a *TP53* mutation
- Of 130 patients with *EML4-ALK* fusion variant type detected, 63 (48%) had v1, 54 (42%) had v3, 8 (6%) had v2, 4 (3%) had v5, and 1 (1%) had v8
- *EML4-ALK* v3 and a *TP53* mutation co-occurred in 21 (18%) of 117 patients who had *TP53* data and *EML4-ALK* fusion v1 or v3
- Baseline characteristics and demographics are presented by *EML4-ALK* fusion variant and *TP53* mutation status in **Table 1**

Table 1: Demographics and baseline characteristics

	Total (n=164)	*TP53* WT (n=98)	*TP53* mutation (n=66)	*EML4-ALK* v1 or v3 (n=117)	*EML4-ALK* v1 (n=63)	*EML4-ALK* v3 (n=54)
Median age, years (range)	58.6 (20.4–84.2)	57.8 (20.4–84.2)	59.8 (25.6–83.3)	58.0 (25.6–84.2)	56.8 (29.1–82.9)	59.3 (25.6–84.2)
Sex, female, n (%)	87 (53)	53 (54)	34 (52)	57 (49)	27 (43)	30 (56)
Brain metastases at baseline, n (%)	48 (29)	25 (26)	23 (35)	35 (30)	20 (32)	15 (28)
Time from diagnosis of advanced disease to start of 1L treatment, months	(n=150)	(n=90)	(n=60)	(n=107)	(n=59)	(n=48)
Mean (SD)	4.7 (11.1)	4.6 (9.9)	4.9 (12.8)	4.0 (8.4)	4.6 (9.5)	3.3 (6.8)
Median (range)	0.8 (0.0–86.6)	0.8 (0.0–45.2)	0.9 (0.0–86.6)	0.8 (0.0–43.8)	0.9 (0.0–43.8)	0.8 (0.0–38.2)
Duration of follow-up from start of 1L treatment, months						
Mean (SD)	16.7 (11.1)	17.4 (11.8)	15.6 (10.1)	17.1 (10.7)	18.5 (11.1)	15.3 (10.1)
Median (range)	14.8 (0.8–45.3)	15.7 (0.8–45.3)	13.4 (1.4–38.7)	17.2 (1.4–45.3)	18.9 (1.4–45.3)	11.7 (1.7–44.5)

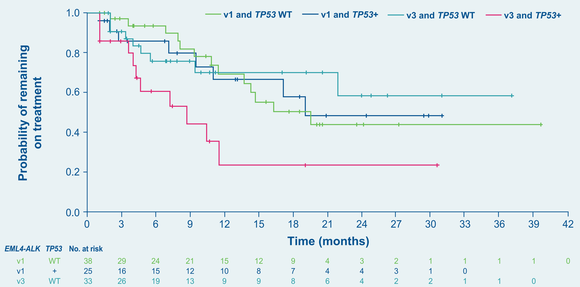
Question

What is the effect of baseline *EML4-ALK* fusion variant and *TP53* mutation status on TTD of 1L treatment with next-generation ALK TKIs in patients with *ALK*+ NSCLC in the real-world setting?

Study Design

Results

KM estimates of TTD by *TP53* mutation status and *EML4-ALK* fusion v1 versus v3



EML4-ALK fusion	*TP53* mutation	n[a]	Median TTD (95% CI), months	HR (95% CI)	*P* value
v1	WT	38	19.5 (11.4–NE)	Reference	
v1	+	25	19.0 (9.5–NE)	1.01 (0.42–2.44)	0.9849
v3	WT	33	NE (9.4–NE)	0.89 (0.38–2.09)	0.7873
v3	+	21	8.7 (3.9–NE)	2.59 (1.15–5.84)	0.0219

[a]117 patients had data for both *TP53* and *EML4-ALK* v1 or v3
NE, not estimable

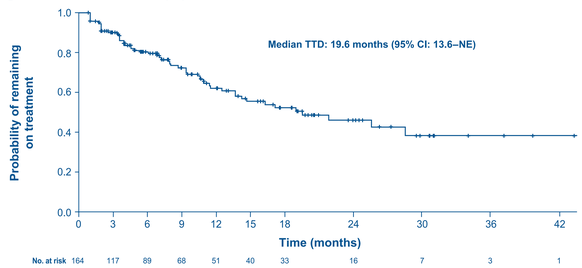
Key Takeaway

Co-occurrence of *EML4-ALK* v3 and *TP53* mutation was associated with the shortest TTD of all subgroups evaluated

TTD of 1L ALK TKI treatment

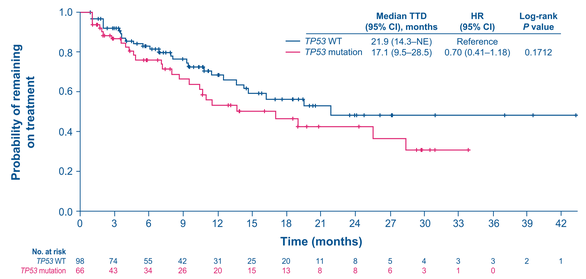
- Median TTD of 1L treatment was 19.6 months in the overall population **(Figure 2)**
- The upper limit of the 95% CI was not reached, likely due to the relatively short follow-up (median of 14.8 months); median TTD may change with additional follow-up

Figure 2: TTD in the overall population



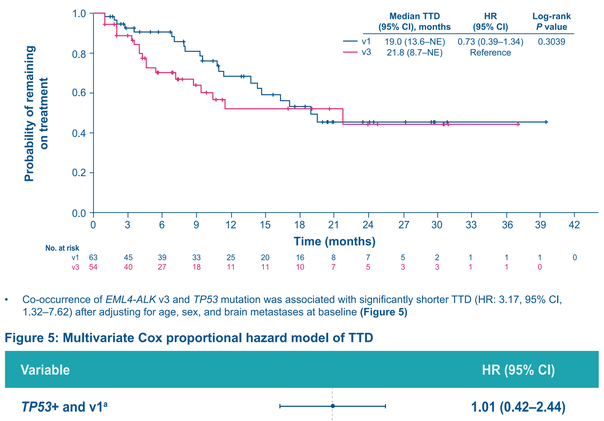
- In patients with *TP53* mutation versus WT at baseline, median TTD was 17.1 versus 21.9 months **(Figure 3)**

Figure 3: TTD by baseline *TP53* status



- For patients with *EML4-ALK* fusion v1 versus v3, the KM plot showed numerically longer TTD in patients with v1 during the first 18 months; however, the lines crossed at the tail end, resulting in numerically shorter median TTD in patients with v1 versus v3 **(Figure 4)**
- The upper limits of the 95% CIs were not reached in either cohort; median TTD may change with additional follow-up

Figure 4: TTD by baseline *EML4-ALK* fusion v1 versus v3



- Co-occurrence of *EML4-ALK* v3 and *TP53* mutation was associated with significantly shorter TTD (HR: 3.17, 95% CI, 1.32–7.62) after adjusting for age, sex, and brain metastases at baseline **(Figure 5)**

Figure 5: Multivariate Cox proportional hazard model of TTD

[a]Reference: *TP53* WT and *EML4-ALK* v1; [b]Reference: age <65 y; [c]Reference: male sex; [d]Reference: no baseline brain metastases

Limitations

- The line-of-therapy data were from an open claims database that may have missing data for treatments and procedures. As a result, the line of therapy may have been mislabeled for some patients in this analysis
- The patient population evaluated in this study is expected to have a worse prognosis than the general *ALK*+ NSCLC population due to the requirement for detection of *ALK* fusion by liquid biopsy at baseline[8,9]

Summary

- In this analysis of real-world data, co-occurrence of *EML4-ALK* fusion v3 and *TP53* mutations in ctDNA was associated with a high risk of early discontinuation of 1L treatment with next-generation ALK TKIs, most likely due to disease progression
- These findings align with previous reports that co-occurrence of *EML4-ALK* v3 and a *TP53* mutation is associated with increased metastatic spread and shorter progression-free survival and overall survival compared with occurrence of each gene alteration independently[6,10]
- Additional novel or combination therapies, such as ALK TKI/chemotherapy combinations, are required to improve outcomes in patients with co-occurring *EML4-ALK* v3 and a *TP53* mutation

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Acknowledgments

Medical writing support for the development of this poster, under the direction of the authors, was provided by Lela Creutz, PhD, and Lauren Gallagher, RPh, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, and funded by Takeda Development Center Americas, Inc., Lexington, MA, and complied with the Good Publication Practice (GPP3) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–1304). The study was sponsored by Takeda Development Center Americas, Inc.

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