Editorial

EML4-ALK V3, treatment resistance, and survival: refining the diagnosis of ALK$^+$ NSCLC

Petros Christopoulos[1,2], Martina Kirchner[2,3], Volker Endris[2,3], Albrecht Stenzinger[2,3#], Michael Thomas[1,2#]

[1]Department of Thoracic Oncology, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany; [2]Translational Lung Research Center Heidelberg (TLRC-H), Heidelberg, Germany; [3]Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany

[#]These authors contributed equally to this work.

Correspondence to: Petros Christopoulos, MD. Department of Thoracic Oncology, Thoraxklinik at the Heidelberg University Hospital, Röntgenstr. 1, 69126 Heidelberg, Germany. Email: petros.christopoulos@med.uni-heidelberg.de.

Submitted Apr 13, 2018. Accepted for publication May 04, 2018.
doi: 10.21037/jtd.2018.05.61
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.61

Anaplastic lymphoma kinase (*ALK*) gene fusions drive approximately 5% of non-small cell lung cancers (NSCLC) (1). Fluorescence *in situ* hybridization (FISH) and immunohistochemistry are widely used to identify them based on *ALK* translocation and ALK overexpression, which are common in all cases and equally predict response to tyrosine kinase inhibitors (TKI) (2). On the other hand, the *ALK* fusion itself varies among patients. It can be typed by reverse-transcription polymerase chain reaction (RT-PCR) or next-generation sequencing (NGS) (3), but this is not currently required as part of the diagnostic workup (2,4). Even though different variants of the *ALK* fusion were first recognized over ten years ago (1) and have been extensively characterized *in vitro* (5,6), until very recently their clinical significance remained unclear. Major obstacles have been the complex management of ALK$^+$ NSCLC patients, including highly variable sequences of TKI and local ablative treatments, as well as their long survival, currently exceeding 5 years in median after two ALK inhibitors (7), which have confounded and limited early studies. During the past months, however, several reports combining detailed clinical annotation with state-of-the-art molecular profiling in larger cohorts, have revealed a major impact of the specific *ALK* alteration on tumor biology and patient outcome. Echinoderm microtubule-associated protein-like 4 (*EML4*)-*ALK* fusion variant 3 (V3) in particular emerges as marker suitable for the selection of higher-risk cases under several therapeutic circumstances and calls for reconsideration of basic concepts and management strategies (8-11).

In the first line, *EML4-ALK* V3 appears to be associated with increased disease aggressiveness independent of treatment: Noh *et al.* have observed a higher frequency of metastatic disease among newly diagnosed ALK$^+$ NSCLC cases harboring V3 *vs.* other variants (8), and own data have demonstrated an increased number of metastatic sites at initial diagnosis for stage IV ALK$^+$ V3 NSCLC patients (9). In both studies, *EML4-ALK* V3 was associated with enhanced metastatic spread already before the start of treatment indicating higher clinical risk, which is present at baseline and not related to a specific therapy regimen (*Figure 1*). In addition, *EML4-ALK* V3 is associated with shorter progression-free survival (PFS) after non-TKI treatments, namely chemotherapy and cerebral radiotherapy (*Figure 1*) (9), while its polypeptide product shows a longer half-life and stronger oncogenic signaling *in vitro* (5,6,10). Collectively, these data suggest important and clinically relevant biological differences between tumors harboring V3 *vs*. other *EML4-ALK* variants regardless of TKI exposure.

Moreover, there is accumulating evidence that *EML4-ALK* V3 is associated with a shorter PFS of patients receiving first- and second-generation ALK TKI in the first and second treatment lines (9,10), and even with a significantly worse overall survival (OS) compared to the other two common *EML4-ALK* variants V1 and V2 (*Figure 1*) (9). Interestingly, these observations are nicely explained by the increased propensity of V3- *vs.* V1-driven tumors to develop *ALK* resistance mutations as reported by Lin *et al.* (11), since sequential TKI administration is an

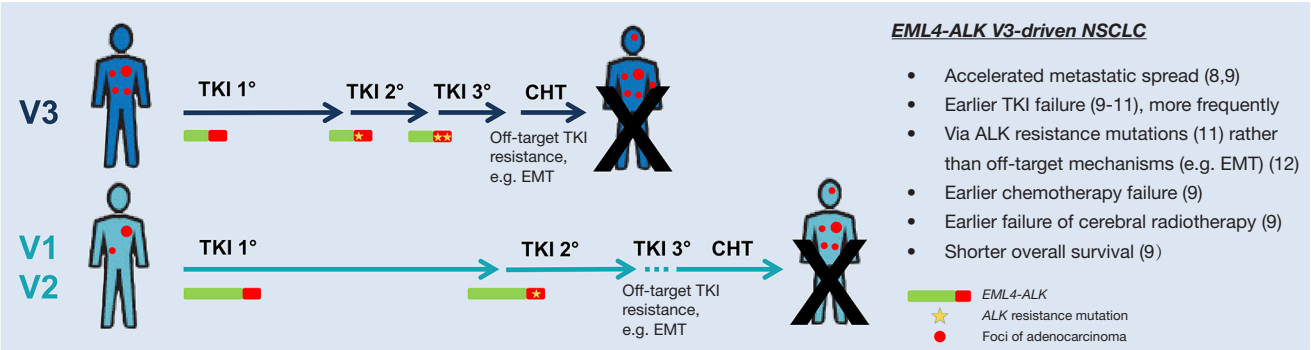

Figure 1 Clinical impact of *EML4-ALK* fusion variant V3. Differences in clinical course and patient outcome with various therapeutic modalities of lung adenocarcinoma driven by *EML4-ALK* V3 *vs.* V1/V2. The collective insight from several recent publications (8-12) is visualized, with arrow lengths roughly proportional to the corresponding progression-free and overall survival intervals as estimated by considering the different published series together. However, there is substantial heterogeneity, which probably reflects additional effects from further important biological factors that remain to be determined. Numbers in parentheses indicate references of the article; EML4, echinoderm microtubule-associated protein-like 4; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; EMT, epithelial-mesenchymal transition.

important determinant of longer OS in ALK$^+$ NSCLC (7).

Integrating these findings, it appears that V3-positive patients progress faster through TKI treatment lines (i.e., have a shorter PFS after first- and second-line TKI treatment, *Figure 1*), predominantly through development of TKI resistance mutations (11) and possibly facilitated by incomplete tumor cell suppression due to the higher IC50 of "wild-type" V3 (10). In contrast, V1 patients need longer to acquire resistance, but at the same time presumably progress rather due to more complex resistance mechanisms, which are not amenable to further TKI treatment (12). Thus, TKI-refractory V3 and V1 patients are expected to also differ in terms of several other important biological factors besides the frequency of *ALK* resistance mutations. These additional differences, which remain to be explored, will likely affect response to further ALK inhibitor treatment and probably account for the paradox of *EML4-ALK* V3 being unfavorable in all statistical analyses meticulously performed by several investigators (9-11)—except for patients receiving lorlatinib beyond the second treatment line in one study, where the V3 variant appears to confer longer PFS than V1 (11).

In daily clinical practice, this enhanced benefit from lorlatinib in later treatment lines will largely depend on whether an *ALK* mutation has emerged as the cause of TKI failure (i.e., on *ALK* sequencing results of a repeat biopsy at that time) rather than on the gene fusion variant as such, which does not change during therapy. However, detection of the unfavorable *EML4-ALK* variant V3 could be used to select patients for more aggressive surveillance and treatment strategies earlier in the course of their disease, which carries features of higher risk already at baseline (8,9). The recent approval of alectinib for first-line treatment of ALK$^+$ NSCLC is probably not going to have a major impact in this regard, because *in vitro* data show a similar resistance of V3 expressing cells to alectinib, crizotinib and ceritinib with IC50 values >500 nM (10). Whether upfront administration of a third-generation ALK inhibitor with broader activity against *ALK* resistance mutations, such as lorlatinib (12), could to some extent negate the V3-associated risk, is unclear at present. Other strategies to consider currently are a closer monitoring of V3 ALK$^+$ patients with radiologic studies and ctDNA assays as well as a more aggressive approach regarding local ablative treatments. We anticipate the development of novel management strategies and drugs against the higher-risk, V3-driven disease to become a main research objective in ALK$^+$ NSCLC. While typing of the *ALK* fusion variant and *ALK* resistance mutation testing are not recommended by the current CAP/IASLC/AMP guidelines (2), data by several researchers illustrate the great potential of a more fine granular ALK analysis in clinical trials and eventually also in routine patient care (5,6,9-11).

Acknowledgements

None.

Footnote

Conflicts of Interest: V Endris reports advisory board honoraria and lecture fees from AstraZeneca and ThermoFisher. A Stenzinger reports advisory board honoraria from Novartis, AstraZeneca, ThermoFisher, BMS, lecture fees from Illumina, AstraZeneca, Novartis, ThermoFisher and travel grants from Illumina, AstraZeneca, ThermoFisher. M Thomas reports advisory board honoraria from Novartis, Lilly, BMS, MSD, Roche, Celgene, Takeda, AbbVie, Boehringer, lecture fees from Lilly, MSD, Takeda, research funding from AstraZeneca, BMS, Celgene, Novartis, Roche and travel grants from BMS, MSD, Novartis, Boehringer. P Christopoulos and M Kirchner have no conflicts of interest to declare.

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Cite this article as: Christopoulos P, Kirchner M, Endris V, Stenzinger A, Thomas M. *EML4-ALK* V3, treatment resistance, and survival: refining the diagnosis of ALK$^+$ NSCLC. J Thorac Dis 2018;10(Suppl 17):S1989-S1991. doi: 10.21037/jtd.2018.05.61

