



## Early View

### Research letter

## **Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced *ALK*-rearranged non-small-cell lung cancer**

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## **Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced *ALK*-rearranged non-small-cell lung cancer**

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Thromboembolic disease is fairly common in patients with lung cancer(1-3). This incidence seems to be higher in patients with lung adenocarcinomas(4), with approximately 15 % of those with advanced-stage disease developing venous thromboembolisms (VTE) during the whole course of their disease(5-7). Pulmonary adenocarcinomas are a heterogeneous group of diseases, that can be stratified according to the presence major oncogenic driver alterations. Anaplastic lymphoma kinase (*ALK*) rearrangements are detected in approximately 4 % of these cases(8). Isolated reports have suggested that patients bearing *ALK*-rearranged tumors might have a higher than expected incidence of thromboembolisms(9,10). In the present study, we have analyzed the incidence, predictors and prognostic significance of thromboembolic events in a large, multi-institutional and homogeneous cohort of advanced-stage patients with *ALK*-rearranged lung cancers from Spain and Portugal. Our primary objective was to estimate the incidence of thromboembolic events and their association with overall survival (OS) in these patients.

A centralized Institutional Ethics Committee approval at the 12 de Octubre University Hospital valid for all Spanish centers, and an Institutional Ethics Committee approval at Portuguese Institute of Oncology of Porto, were obtained before the study was initiated. We retrospectively selected all consecutive patients diagnosed with advanced-stage (stages III and IV) *ALK* fusion positive non-small-cell lung cancers (NSCLCs) between January 2012 and December 2016. Data were contributed by 29 Medical Centers from Spain and one from Portugal. *ALK* positivity was determined according to local standard protocols in each institution. We excluded patients with neuroendocrine tumors and patients on therapeutic doses of anticoagulants prior to advanced-stage cancer diagnosis. We defined a thromboembolic event as any venous or arterial thromboembolism, documented by imaging studies, that occurred at the time or after advanced-stage cancer diagnosis. In addition to thromboembolic events, collected during the whole patients' follow up period, we collected baseline information (within one-month of advanced-stage cancer diagnosis) of several clinical and analytical variables of interest.

We included 241 *ALK*-rearranged NSCLCs in this study. The median age was 56 years (range 17-84). Half of the patients were never smokers (52 %), and most had stage IV pulmonary adenocarcinomas (n = 204, 85 %). Baseline brain and liver metastasis were

detected in 22 % and 25 % of the patients respectively. Seventeen patients (7 %) and 185 patients (77 %) had high and intermediate Khorana Risk Scores (KRS)(11) respectively. The median follow-up of our study population was 19 months (range 0-59 months), and 127 (53 %) of the patients died. The median follow-up of alive patients was 30 months (range 4-49 months). The estimated median OS was 26 months for the entire series, and 31 months for those patients that received ALK tyrosine kinase inhibitors (TKIs) (n = 207, 86 %).

Seventy-three patients (30 %) experienced thromboembolic complications. Seventy-one out of 73 patients (97 %) had VTE, with pulmonary embolism as the most frequent location (n = 30; 41 %). Four patients (5 %) developed arterial thromboembolisms, 2 of them with concurrent VTE. Thromboembolic events occurred within the first 6 months from cancer diagnosis in 54 patients (74 %), of whom 24 (33 %) were detected within the first month from diagnosis. Twenty-two patients (30 %) were deemed to have incidental (asymptomatic or clinically unsuspected) thromboembolisms. Twelve patients (16 %) developed recurrent thrombosis (7 while receiving appropriate therapeutic anticoagulation). The mortality directly attributed to thromboembolic disease in this series was 2 % (n = 5).

To study the association between baseline characteristics and thromboembolic disease, we first conducted a univariate competing risk regression analysis(12) including gender, age, body mass index, performance status, smoking history, histology, tumor stage, central nervous system metastasis, liver metastasis, number of metastatic sites, hemoglobin, leucocyte, platelet and albumin counts, INR range and KRS. In this analysis, *the* presence of baseline liver metastases, leucocyte counts > 11000 cells/mm<sup>3</sup>, three or more metastatic organ involvement and a high KRS (HR 2.82, CI 95 % 1.48-5.37; p = 0.002) were significantly associated with increased risk of thromboembolic disease. In the multivariate model (in which we did not include KRS because it already incorporates leucocyte counts), only liver metastases and leukocytosis remained as independent predictors of thromboembolic disease, with corresponding HR of 1.85 (CI 95 % 1.09-3.15; p = 0.021) and HR of 2.34 (CI 95 % 1.43-3.82; p = 0.001) respectively. Patients that experienced thromboembolic events at any time point had shorter median OS (20 months) than patients without thrombosis (36 months) (p = 0.035) (**figure 1a**). Patients with thromboembolic events at baseline (n = 24) had a median OS of 15 months (**figure 1b**). Patients that experienced recurrent thromboembolisms (n = 12) had a median OS of 10 months, without statistically significant differences when compared

with those without recurrent thromboembolism ( $n = 61$ ; 21 months) ( $p = 0.369$ ). Considering the development of thrombotic events as a time-dependent covariate, thromboembolic disease was significantly associated with an increased risk of death (HR 2.22, CI 95 % 1.53-3.21;  $p = 0.000$ ). We conducted a multivariate Cox regression analysis including smoking history, comorbidities, leukocytosis, liver metastasis, performance status and ALK TKI treatment as fixed covariates, and thromboembolic disease as a time-varying covariate. In this analysis, thromboembolic disease remained as an independent predictor of OS with a HR of 1.70 (CI 95 % 1.10-2.62;  $p = 0.016$ ) (**figure 1c**). The presence of thromboembolic disease at baseline ( $n = 24$ ) was associated with a numerically non-significant increased risk of death (HR 1.67, CI 95 % 0.96-2.91;  $p = 0.068$ ).

In the present study, we show that thromboembolic disease is a frequent complication in patients with advanced-stage *ALK*-positive NSCLCs (30 %), particularly in the presence of baseline liver metastasis or leukocytosis ( $\approx 50$  %), and it is associated with a lower OS in this particular subtype of lung cancer. This study was not designed to compare the incidence of thromboembolic events between different molecular subtypes of lung cancers. However, the high incidence observed here is consistent with what has been reported in smaller *ALK*-positive cohorts(9,10), and exceeds the observed in other subtypes of lung cancers(2,3,5-7). We found that thromboembolic disease was an independent prognostic factor in advanced *ALK*-positive NSCLCs. Although the mortality rate of thromboembolic complications might had been underestimated in this study(13), the differences in survival do not seem to be directly related with the fatality of thromboembolic events themselves (2 % of mortality attributed to thromboembolic disease in this cohort). In the present study, both leukocytosis and liver metastasis significantly predicted both the occurrence of thrombotic complications and reduced OS (**figure 1c**). A relatively low proportion of patients had progressive disease at the time of thromboembolic complications (22 %), but we cannot definitely exclude that the association of thromboembolic disease with lower OS was confounded by subsequent development of liver metastasis and/or leukocytosis in some patients, as we only had baseline information for these variables.

Our findings have relevant implications for clinical practice. First, physicians should actively interrogate for the presence of signs or symptoms of thrombosis at diagnosis and during follow-up of these patients, and accordingly rule out the existence of thromboembolic disease with appropriate imaging studies. Additional surveillance

strategies in high risk patients, including those with leukocytosis or liver metastasis, would need to be eventually considered. Second, these results justify to investigate, in the context of a randomized trial, the clinical benefit, in terms of thromboembolisms risk reduction, and potentially in OS improvement, of adding prophylactic doses of anticoagulants to standard anticancer treatments in these patients. And ultimately, with median OS estimates exceeding 4 to 5 years with the incorporation of novel-generation ALK TKIs into the clinic(14,15), thromboembolic disease will be one of the main cancer-related complication during the whole course of the disease in these patients.



**Authors contributions**

JZ, AM, LPA, SPA and AJM conceived and designed the study. All authors were involved in data collection. DL, together with JZ and AM, did the statistical analysis. JZ, AM, DL and LPA contributed to data interpretation. JZ and AM, together with LPA, wrote the original draft of the manuscript. All authors participated in manuscript writing and editing, and approved the final version of the article.

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**Conflicts of interest**

The authors declare no conflicts of interest related to this study.

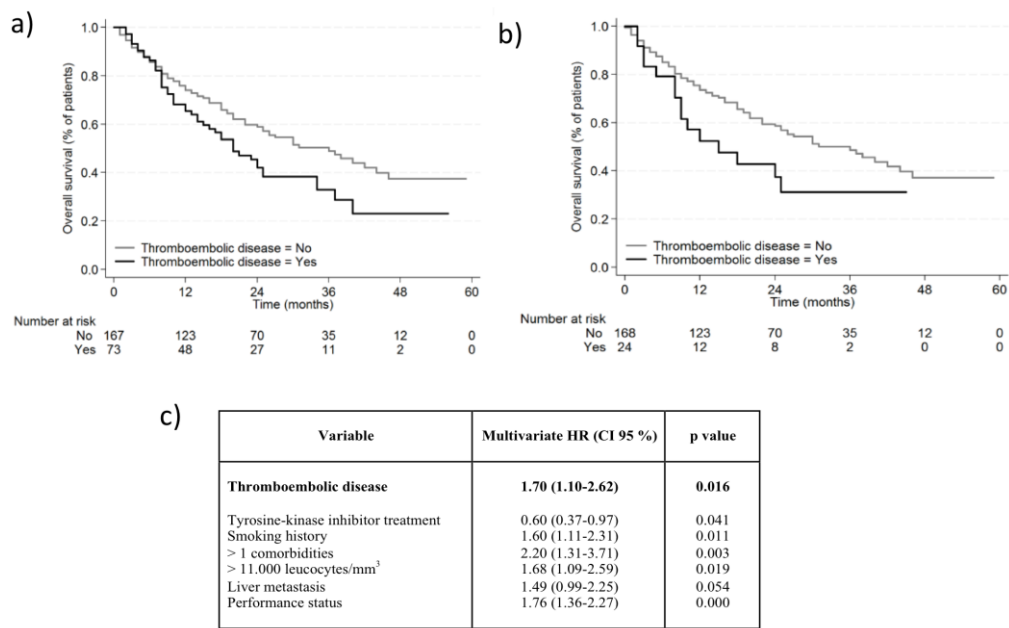
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**Figure 1. Prognostic significance of thromboembolic disease in advance *ALK*-positive NSCLC patients:** a) Kaplan-Meier curve for overall survival for patients with and without thromboembolic disease, b) Kaplan-Meier curve for overall survival for patients with baseline thromboembolic disease, c) Multivariate analysis showing the association of thromboembolic disease and overall survival