Association of anticoagulant use with clinical outcomes from crizotinib in ALK- and ROS1-rearranged advanced non-small cell lung cancers: A retrospective analysis of PROFILE 1001

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Abstract

Background: ROS1- and ALK-rearranged advanced NSCLCs are associated with increased thromboembolic risk. We hypothesized that a prothrombotic phenotype offers an evolutionary advantage to subsets of these cancers. The impact of this phenotype could alter outcomes from targeted therapy.

Methods: In a retrospective analysis of ROS1- and ALK-rearranged NSCLCs treated with crizotinib in a phase 1 trial, we compared progression-free survival (PFS) and objective response rate (ORR) based on the history of anticoagulation use (a possible surrogate of thromboembolism) at baseline (within 90 days before study enrollment) or within 90 days of study treatment.

Results: Twelve out of 53 (22.6%) ROS1- and 39 out of 153 (25.5%) ALK-rearranged NSCLCs received anticoagulation before or during the trial. Most ROS1 and ALK patients on anticoagulation received low-molecular-weight heparin (75% and 64.1%, respectively). In the ROS1-rearranged group, the median PFS (95% CI) values were 5.1 (4.4–14.4) and 29.0 (16.5–48.8) months, and the ORR values were 41.7% (95% CI: 15.2 to 72.3) and 80.5% (95% CI: 65.1 to 91.2) among those with and without anticoagulation treatment, respectively. In the ALK-rearranged group, the median PFS (95% CI) was 7.1 (5.4–7.7) and 12.0 (9.4–18.3) months, and the ORR was 41% (95% CI: 25.6 to 57.9) and 74.3% (95% CI: 65.3 to 82.1) among those with and without anticoagulation treatment, respectively.

Conclusions: Anticoagulation (as a potential surrogate of a prothrombotic subset) in ROS1- and ALK-rearranged NSCLCs may be associated with a lower PFS and ORR to crizotinib.

ClinicalTrial.gov: NCT00585195.
1. INTRODUCTION

Although any active cancer has long been associated with an increased risk of thrombosis, multiple studies have reported that the risk of thrombosis in advanced non-small cell lung cancer (NSCLC) is likely influenced by the specific driver oncogene present in cancer. One study previously reported that patients with ROS1-rearranged NSCLC have significantly elevated rates of arterial or venous thromboses within plus or minus 90 days of the diagnosis of advanced disease compared to EGFR- or KRAS-mutant cases (34.7% versus 13.7% and 18.4%, respectively).1 Most of the events occurred within the 90-day perdiagnostic window, with only a few thromboembolic events captured outside this window. While the rate of thromboembolic events with ROS1-rearranged NSCLC was also numerically higher than with ALK-rearranged NSCLC (22.3%), it was not significantly higher ($p = 0.229$). Similar findings have also been reported in other ROS1 and ALK lung cancer cohorts, further supporting the notion that ROS1-rearranged and ALK-rearranged NSCLCs are specifically associated with an elevated risk of thromboembolic events.2-7 The elevated rates of thrombosis seen among NSCLC with ROS1 and ALK fusions raise the possibility of a direct oncogene-related mechanism driving the pro-thrombotic risk. There is precedence for oncogenes being associated with elevated thrombotic risk. Specifically, JAK2 V617F in myeloproliferative disorders8,9 and PML-RARA fusions in acute promyelocytic leukemia (APL)10,11 are well-described genetic alterations associated with marked thrombotic risk.

These novel observations associating different driver oncogenes with different clot risk raise multiple additional questions for exploration. Firstly, the mechanistic basis of how different driver oncogenes influence the rate of clotting likely occurs through complex interactions between cancer cells, the endothelial system, and the coagulation cascade, but these remain unclear.12-19 Secondly, we hypothesize that these prothrombotic effects in certain oncogene subtypes are not an incidental consequence of cancer, but rather, they represent a selection advantage that cancer cells exploit for growth and survival. This implies that the presence of a thromboembolic event could be associated with different anti-cancer outcomes including overall survival. Thirdly, if the above hypothesis is true, it also raises the question of whether this prothrombotic phenotype and treatment with anticoagulation could affect more proximal outcomes from targeted therapy such as the objective response rate or progression-free survival.

In order to investigate these hypotheses further, we explored the clinical outcomes of the ALK- and ROS1-rearranged NSCLC populations treated with crizotinib (the first licensed ALK and ROS1 inhibitor) within the industry-sponsored phase I trial, PROFILE 1001, according to the presence or absence of anticoagulant use as a surrogate for a thromboembolic phenotype.

2. METHODS

PROFILE 1001 is an open-label, multicenter, phase 1 trial of crizotinib evaluating the safety and efficacy in an expanded cohort of patients with lung cancers who have ALK and ROS1 rearrangements. Crizotinib 250 mg twice daily was established as the recommended phase 2 dose.

Detailed study eligibility criteria for the original trial have been published previously.20,21 Key study exclusion criteria which may have impacted the inclusion of those with elevated thromboembolic risk included a history of central nervous system metastases, significant cardiovascular disease, or cerebrovascular accident including transient ischemic attack within 12 months or pulmonary embolus within 6 months before starting study treatment.

Analyses of the ROS1 and ALK cohorts were conducted separately according to whether patients had or had not received anticoagulation treatment at any time within 90 days before study enrollment or within 90 days of starting study treatment. Progression-free survival (PFS) and objective response rate on crizotinib were determined in each subgroup. Age, sex, race, weight, height, ECOG performance status, smoking history, and anticoagulation treatment history (timing of anticoagulation and type of anticoagulant drug) in each subgroup were reported descriptively using appropriate summary statistics. All patients who received at least one dose of crizotinib were included in the analyses of PFS. Response-evaluable patients were defined as all treated patients who had an adequate baseline disease assessment and a minimum of one post-baseline disease assessment at least 6 weeks from the first dose or who withdrew from the study or had disease progression or death at any time during the study. Overall survival was not available for assessment in the dataset.

Confidence intervals (CIs) for the ORR were estimated using the exact binomial method based on the F-distribution. Time-to-event data were analyzed using the Kaplan–Meier method to estimate median event times, with two-sided 95% CIs generated using the Brookmeyer–Crowley

KEYWORDS
ALK, crizotinib, lung cancer, ROS1, thromboembolism
method. All analyses were performed with SAS statistical software, v9.2 or later (SAS Institute, Inc.).

3. RESULTS

Within PROFILE 1001, 53 patients with advanced ROS1-rearranged NSCLC and 153 patients with advanced ALK-rearranged NSCLC were treated. Of these, 12 and 39 patients, respectively, received anticoagulant therapy prior to or during the trial.

The demographics of ROSI- and ALK-rearranged NSCLC patients in the study based on anticoagulant use are reported in Table 1. There were no apparent imbalances in clinical or demographic features based on anticoagulant use in both the ROSI- and ALK-rearranged subgroups.

In the ROSI-rearranged group, anticoagulation treatments included low-molecular-weight heparin (LMWH), heparin, warfarin, fondaparinux, or a direct oral anticoagulant (DOAC) (Table S1). Of the 12 patients on anticoagulation, nine patients were already on anticoagulation at baseline, two patients started anticoagulation during study treatment, and one discontinued all anticoagulation before starting crizotinib (i.e., they were on anticoagulation at screening but had discontinued by the start of crizotinib therapy).

In the ALK-rearranged group, anticoagulation treatments included LMWH, heparin, warfarin, and fondaparinux (Table S1). Of the 39 patients on anticoagulation, 25 patients were already on anticoagulation at baseline, 12 patients started anticoagulation during study treatment, and two discontinued all anticoagulants before starting crizotinib.

This was a retrospective analysis on available datasets. The data cutoff date for patients with ROSI-rearranged NSCLC was June 30, 2018 and for patients with ALK-rearranged NSCLC was April 13, 2012, with some patients still on treatment.

In the ROSI-rearranged group, among those without anticoagulation, 26 (63.4%) of 41 subjects had experienced a PFS event, two of which were recorded as death without objective progression (Table S2). Among those with anticoagulation, 10 (83.3%) of 12 subjects had experienced a PFS event, one of which was recorded as death without objective progression. The median PFS (95% CI) among those with and without anticoagulation was 5.1 (4.4–14.4) and 29 (16.5–48.8) months, respectively (Figure 1).

In the ALK-rearranged group, among those without anticoagulation, 77 (67.5%) of 114 subjects had experienced a PFS event, five of which were recorded as death without objective progression (Table S2). Among those with anticoagulation, 34 (87.2%) of 39 subjects had experienced a PFS event, 10 of which were recorded as death without objective progression. The median PFS (95% CI) among those with and without anticoagulation was 7.1 (5.4–7.7) and 12 (9.4–18.3) months, respectively (Figure 1).

The objective response rate in the ROSI-rearranged group among those with and without anticoagulation was 41.7% (95% CI: 15.2–72.3), with 5 out of 12 (41.7%) achieving a partial response, and 80.5% (95% CI: 65.1–91.2), with 6 out of 41 (14.6%) achieving a complete response and 27/41 (65.8%) achieving a partial response, respectively (Table 2).

The objective response rate in the ALK-rearranged group among those with and without anticoagulation was 41% (95% CI: 25.6–57.9), with 1 out of 39 (2.6%) achieving a complete response and 15 out of 39 (38.5%) achieving a partial response, and 74.3% (95% CI: 65.3–82.1), with 4 out of 113 (3.5%) achieving a complete response and 80 out of 113 (70.8%) achieving a partial response, respectively (Table 2).

DISCUSSION

The interaction between cancer and the hemostatic system is bidirectional. Tumors promote a procoagulant state, but components of the hemostatic system may also play a role in tumor growth, angiogenesis, invasion, and metastases.22 Evidence supporting this hypothesis comes from the interplay between protease-activated receptors (PARs) and the coagulation system. PAR-1 is expressed on cancer cells and activated by thrombin.23 Activated PAR-1 appears to play a crucial role in prometastatic activities through β1-integrin and matrix metalloprotease24,25 and proangiogenic programs.23,26,27 Consequently, thrombin generation (through TF-VIIa) could create a positive feedback loop for cancer growth, invasion, and vascularization. With the recognition of the differing risk of thromboembolic events among oncogenic driver subgroups in advanced NSCLC, the concept that a prothrombotic phenotype may directly impact cancer outcomes, assuming this phenotype reflects some evolutionarily advantageous strategies of cancer, must also be considered. Therefore, we sought to determine whether there is an association between therapeutic anticoagulation (as a surrogate of thrombosis) and clinical outcomes within the initial trial of crizotinib in advanced ROSI- and ALK-rearranged NSCLCs.

Considering the rate of anticoagulation as a surrogate for the rate of thromboembolic events, 22.6% with ROSI- and 25.5% with ALK-rearranged NSCLCs in this study had documented anticoagulant use within 90 days before or after the study enrollment. In the ALK-rearranged NSCLC cohort, the percentage of anticoagulation was similar to
our previously reported thromboembolic rate (22.3%). Although the percentage of anticoagulation in the ROSI cohort was lower than the thromboembolic rate in our previous report (34.7%), it is still consistent with a higher frequency of thromboembolic events compared to other molecular subtypes of lung cancer.1 Furthermore, the difference between the ROSI cohorts could be explained by a larger margin of error associated with a smaller sample size in the PROFILE 1001 study (/n = 53).

In this study, PFS outcomes in the subgroup that used anticoagulation were consistently worse relative to the overall trial population and the subgroup without anticoagulation history. In the overall trial population, crizotinib in ROSI-rearranged NSCLC (/n = 53) led to a median PFS of 19.3 months (95% CI: 15.2–39.1).31 In comparison, the ROSI subgroups with and without anticoagulation had a median PFS of 5.1 months (95% CI: 4.4–14.4) and 29 months (95% CI: 16.5–48.8), respectively. Similarly, in the previously published ALK cohort (/n = 143), the median PFS was 9.7 months (95% CI: 7.7–12.8).20 In our analyses, which included an additional 10 patients, the median PFS (95% CI) in the subgroups with and without anticoagulation use was 7.1 months (5.4–7.7) and 12 months (9.4–18.3), respectively.

| TABLE 1 | Demographics of patients with ROSI- and ALK-rearranged NSCLCs based on anticoagulant use |
|---------|------------------------------------------------------------------------------------------------|
| **ROS1+ (n = 53)** | **Without anticoagulant (n = 41)** | **ALK+ (n = 153)** | **Without anticoagulant (n = 114)** |
| **With anticoagulant (n = 12)** | **Without anticoagulant (n = 39)** | | |
| **Age, median (range)** | 53.0 (35–66) | 55.0 (25–81) | 54.0 (22–79) | 51.0 (25–86) |
| **Age category (years)** | | | | |
| <65 | 10 (83.3) | 28 (68.3) | 31 (79.5) | 100 (87.7) |
| ≥65 | 2 (16.7) | 13 (31.7) | 8 (20.5) | 14 (12.3) |
| **Sex (%)** | | | | |
| Male | 8 (66.7) | 15 (36.6) | 20 (51.3) | 54 (47.4) |
| Female | 4 (33.3) | 26 (63.4) | 19 (48.7) | 60 (52.6) |
| **Race** | | | | |
| White | 7 (58.3) | 23 (56.1) | 29 (74.4) | 68 (59.6) |
| Black | 0 | 2 (4.9) | 2 (5.1) | 3 (2.6) |
| Asian | 5 (41.7) | 16 (39.0) | 5 (12.8) | 38 (33.3) |
| Japanese | 0 | 0 | 0 | 15 (13.2) |
| Korean | 2 (16.7) | 11 (26.8) | 3 (7.7) | 20 (17.5) |
| Chinese | 2 (16.7) | 2 (4.9) | 0 | 2 (1.8) |
| Other | 1 (8.3) | 3 (7.3) | 2 (5.1) | 1 (0.9) |
| Other | 0 | 0 | 3 (7.7) | 5 (4.4) |
| **Mean weight, kg (SD)** | 80.2 (19.03) | 69.4 (14.32) | 73.7 (17.58) | 69.4 (14.97) |
| **Mean height, kg (SD)** | 174.5 (8.54) | 165.1 (9.55) | 167.0 (9.12) | 168.4 (10.43) |
| **Smoking history** | | | | |
| Never smoked | 10 (83.3) | 30 (73.2) | 26 (66.7) | 83 (72.8) |
| Ex-smoker | 2 (16.7) | 11 (26.8) | 12 (30.8) | 31 (27.2) |
| Smoker | 0 | 0 | 1 (2.6) | 0 |
| **ECOG status** | | | | |
| 0 | 3 (25.0) | 20 (48.8) | 12 (30.8) | 45 (39.5) |
| 1 | 9 (75.0) | 20 (48.8) | 22 (56.4) | 55 (48.2) |
| 2 | 0 | 1 (2.4) | 5 (12.8) | 13 (11.4) |
| 3 | 0 | 0 | 0 | 1 (0.9) |
Whether the differential PFS outcomes seen in association with anticoagulation reflect an impact on death related to thromboses or other non-cancer-related etiologies as opposed to an effect on the progression of cancer per se, has to be considered. The proportion of PFS events attributable to death in the absence of documented radiographic progression was numerically higher among those on anticoagulation than among those not on anticoagulation in the ALK-rearranged group (10/34 [29%] versus 5/77 [6%], respectively), suggesting that a worse PFS might partly be attributed to non-cancer-related deaths. However, the same trend was not apparent in the ROSI-rearranged group; the proportion of PFS events attributable to death in the absence of documented radiographic progression was 1 out of 10 (10%) among those on anticoagulation versus 2/26 (8%) among those not on anticoagulation.

Worsened PFS outcomes in the anticoagulation subgroup may also simply reflect thrombosis as a surrogate for a greater disease burden and likelihood for a shorter disease control period as well as worse general health status.

FIGURE 1 Progression-free survival in ROSI-rearranged NSCLC based on anticoagulant use. Progression-free survival in ALK-rearranged NSCLC based on anticoagulant use.
due to comorbid medical conditions which may not be fully captured by ECOG performance status. However, the tumor response rate to crizotinib in the ALK-rearranged cohort was also lower in the anticoagulation subgroup than in the non-anticoagulated subgroup, and a similar trend was also observed in the cohort of ROS1-rearranged NSCLC. These observations suggest an association between anticoagulant use (a surrogate of thrombotic events) and worsened targeted therapy outcomes, and support the hypothesis that worsened PFS in the cohort with anticoagulant use reflects fundamentally different tumor biology in patients with a prothrombotic phenotype.

Potential weaknesses of our analyses include the fact that patients with a new pulmonary embolism occurring within 6 months or a cerebrovascular accident within 12 months prior to the start of the study were excluded from the study. These criteria may have excluded some patients with a prothrombotic phenotype. In addition, although the vast majority of ROS1 and ALK patients with a history of anticoagulant use (83.3% and 69.2%) were started on anticoagulation prior to starting crizotinib within the anticoagulation subgroup, patients who commenced anticoagulation within 90 days of starting crizotinib were also included. Despite this, it should be noted that crizotinib has not been significantly associated with increased thromboembolic events despite its routine use for many years. For example, the first-line PROFILE 1014 phase III trial conducted in ALK-rearranged NSCLC showed that the rate of grade 3 or 4 pulmonary embolism was 8% for the crizotinib arm and 7% for the chemotherapy arm in the second-line setting.

Multiple previous trials have evaluated the effect of anticoagulation on response rate and survival outcomes across different tumor types, most of which have suggested, if anything, an association with better outcomes. In our cohort of ALK- and ROS1-rearranged NSCLCs, as the use of anticoagulation (predominantly LMWH) was associated with worsened PFS and ORR, this supports the possibility of a unique subset of patients with a prothrombotic phenotype that is resistant to targeted therapy. One hypothesis is that any evolutionary advantage to cancer from this phenotype might manifest upstream of the site of the anticoagulant’s mechanisms of action, and therefore, the associated inferior clinical outcomes could not be reversed with anticoagulation treatment.

Although our study was a retrospective analysis, the data on clinical outcomes were generated from a prospective, multicenter trial with uniform surveillance imaging schedule and formalized tumor response measurements using RECIST 1.0. Regarding other limitations, although the reasons for anticoagulation were not available, LMWH was used in 10 out of 12 cases of anticoagulation in the ROS1 cohort and in 32 out of 39 cases in the ALK cohort. LMWH is more commonly used in the treatment of venous thromboembolic events and less commonly used in non-thrombotic indications such as stroke prevention for atrial fibrillation. Also, our study may have underestimated the total prevalence of thrombotic events due to missed asymptomatic venous thromboembolic events. The number of patients in each cohort on anticoagulation was relatively small, and the balance of other potential

|                | **ROS1+ (n = 53)** |                | **ALK+ (n = 152)*** |
|----------------|-------------------|----------------|---------------------|
|                | **With**          |                | **With**            |
|                | **anticoagulant** | **Without**    | **anticoagulant**   |
|                | *(n = 12)*        | **anticoagulant** | *(n = 39)*         |
|                | **Without**       | *(n = 41)*     |                     |
| **With**       | **Without**       | *(n = 113)*    |                     |
| **anticoagulant** | **anticoagulant** | *(n = 39)*     |                     |
| **Without**    | **anticoagulant** | *(n = 113)*    |                     |
| **anticoagulant** | **anticoagulant** | *(n = 39)*     |                     |
| **Without**    | **anticoagulant** | *(n = 113)*    |                     |

| Best Overall response | N (%) | N (%) | N (%) | N (%) |
|-----------------------|-------|-------|-------|-------|
| Complete response     | 0 (0) | 6 (14.6) | 1 (2.6) | 4 (3.5) |
| Partial response      | 5 (41.7) | 27 (65.9) | 15 (38.5) | 80 (70.8) |
| Stable disease        | 6 (50.0) | 4 (9.8) | 17 (43.6) | 21 (18.6) |
| Objective progression | 1 (8.3) | 2 (4.9) | 3 (7.7) | 4 (3.5) |
| Early deathb          | 0 (0) | 1 (2.4) | 1 (2.6) | 3 (2.7) |
| Indeterminate         | 0 (0) | 1 (2.4) | 2 (5.1) | 1 (0.9) |
| Objective response rate (CR + PR) | 5 (41.7) | 33 (80.5) | 16 (41.0) | 84 (74.3) |

95% confidence interval

**(15.2–72.3) (65.1–91.2) (25.6–57.9) (65.3–82.1)**

*One patient out of the total n = 153 was not evaluable.

bEarly death is death within 42 days (6 weeks) from the first dose
molecular and clinical risk factors between those with and without anticoagulation such as tumor burden or anatomic location of metastases was unknown. Finally, we were unable to generate data on any impact of the use of anticoagulation on overall survival, but this should be a focus in later studies.

Despite these caveats, based on the data generated, we propose that thromboembolic events potentially reflect a previously unidentified subset of ROSI- and ALK-rearranged NSCLC patients with a prothrombotic phenotype that confers a cancer cell survival advantage via a mechanism that is upstream of the targets of commonly used anticoagulants that therefore cannot be overcome by commonly used therapeutic anticoagulation. The observations from our study should be validated in larger studies in patients with a de novo diagnosis of metastatic ROSI- and ALK-rearranged NSCLCs to control for lead time bias and for more comprehensive tumor molecular typing. Future studies should also focus on elucidating the mechanism of how these oncogenes increase the risk of thromboembolic events in some or all patients and whether interfering with these pathways at different points in their initiation may improve treatment outcomes. The association between anticoagulant use and PFS in our study was greatest in the ROSI cohort, which is also the subtype of NSCLC with the highest known peridagnostic clot risk. Our other dataset addressed the association in ALK-rearranged NSCLC, another molecular subtype that has also been associated with a high clot risk as reported in multiple study cohorts. It would also be interesting to ask whether the association of thrombosis/anticoagulation with worse outcome is unique to ROSI- and ALK-rearranged NSCLCs by conducting similar analyses in other molecularly defined subtypes of NSCLC treated with relevant targeted therapies. Finally, our study also raises the prospect that the presence or absence of baseline thrombosis/anticoagulation should be explored as a potential stratification factor in future interventional clinical trials of targeted therapy to improve the prognostic balance between experimental and control arms.

AUTHOR CONTRIBUTIONS
T.L.N., D.C.C.T., and D.R.C. conceived the study and wrote the first draft of the manuscript. Pfizer (S.W., T.U., and K.W.) provided patient data. All authors analyzed the data, reviewed, and approved the final manuscript.

CONFLICT OF INTEREST
Dr. Ng reports grants from Takeda Oncology, personal fees from ARIAD, personal fees from Takeda Oncology, and personal fees from Boehringer Ingelheim, outside the submitted work. Dr. Tsui has nothing to disclose.

Dr. Wang reports personal fees from Pfizer, outside the submitted work. Dr. Usari reports personal fees from Pfizer, outside the submitted work. Dr. Patil reports personal fees from Roche/Genentech, personal fees from AstraZeneca, personal fees from Guidepoint Global, personal fees from FCB Health, and personal fees from Aptitude Health, outside the submitted work. Dr. Wilner reports personal fees from Pfizer Inc, outside the submitted work. Dr. Camidge reports grants from Takeda Oncology, personal fees from Takeda Oncology, personal fees from Pfizer, and personal fees from Roche, outside the submitted work.

DATA AVAILABILITY STATEMENT
Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clincal-trials/trial-data-and-results for more information.

ETHICAL APPROVAL STATEMENT
The protocol was approved by the research ethics committee at each study site, and all patients provided written informed consent before enrollment.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**How to cite this article:** Ng TL, Tsui DC, Wang S, et al. Association of anticoagulant use with clinical outcomes from crizotinib in ALK- and ROS1-rearranged advanced non-small cell lung cancers: A retrospective analysis of PROFILE 1001. *Cancer Med*. 2022;11:4422-4429. doi: 10.1002/cam4.4789