SPACEWALK: A Remote Participation Study of ALK Resistance Leveraging Plasma Cell-Free DNA Genotyping

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ABSTRACT

Introduction: Remote consent and enrollment offer a unique opportunity to provide rare cancer populations with access to clinical research. The genomic analysis of plasma cell-free DNA (cfDNA) permits remote characterization of the cancer genome. We hypothesized we could leverage these approaches to remotely study drug resistance in patients with metastatic ALK-positive NSCLC.

Methods: The SPACEWALK study (Study of Plasma Next-Generation Sequencing for Remote Assessment, Characterization, Evaluation of Patients With ALK Drug Resistance) enrolled patients with ALK-positive NSCLC and progression on a next-generation ALK inhibitor who could participate remotely. Plasma was collected for next-generation sequencing (NGS) of cfDNA before initiating subsequent therapy, with results returned and subsequent therapy studied.

Results: Of the 62 patients enrolled, an ALK fusion was detected in 27 (44%) with a median allelic fraction of 2.6%. Among these 27 patients, a potential resistance mechanism was identified in 17 patients (63%): eight cases (30%) had secondary ALK kinase domain resistance mutations, three cases (11%) had bypass track resistance, and six cases (22%) had both ALK resistance mutations and bypass resistance. The most frequently detected mechanism of bypass resistance was MET amplification. Repeat plasma NGS was performed in 14 patients after subsequent treatment was initiated, with seven (50%) patients exhibiting greater than 50% reductions in ALK fusion allelic fraction.

Conclusions: Through the leveraging of remote participation, plasma NGS offers an optimal mechanism for characterizing resistance to emerging targeted therapies in rare cancer populations, though sensitivity depends on adequate tumor DNA samples. Repeat cfDNA analysis on therapy may offer an objective monitoring approach to remotely study treatment response.

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Introduction

NSCLCs harboring ALK rearrangements can gain dramatic benefits from treatment with a growing number of potent next-generation ALK tyrosine kinase inhibitors (TKIs), which are available in the first-line setting. Despite initial durable responses to ALK TKIs, the emergence of drug resistance is inevitable. As with efforts underway in other oncogene-addicted NSCLC, investigators are studying targeted approaches to overcome drug resistance and prolong the benefit from targeted therapy, delaying the eventual need for chemotherapy. With the average expected median survival now extending several years for patients with metastatic ALK-positive NSCLC, it is expected that most patients will receive several lines of targeted therapies.

It has been challenging to characterize mechanisms of TKI resistance in ALK-positive NSCLC. ALK fusions are found in only approximately 4% of patients with lung adenocarcinoma, such that the study of large real-world cohorts is difficult. Furthermore, the spectrum of resistance mechanisms to potent next-generation ALK TKIs like alectinib, brigatinib, and lorlatinib clearly differs compared with the first-generation agent, crizotinib, which is now used as a MET TKI. Finally, although the numbers are small, data suggest that different next-generation ALK TKIs can induce different resistance mutations, some of which can be overcome by using specific alternate ALK-targeted therapies. More importantly, such molecular-guided resistance therapy is now a standard approach in EGFR-mutant NSCLC, in which osimertinib is used to overcome TKI resistance mediated by the resistant mutation EGFR T790M.

To better characterize the spectrum of resistance mechanisms arising in patients with ALK-positive NSCLC, we designed this study to use the genotyping of plasma cell-free DNA (cfDNA). We have recently reported that some plasma next-generation sequencing (NGS) approaches are particularly effective at detecting ALK fusions in cfDNA. Furthermore, blood collection is feasible remotely, increasing the potential enrollment pool for such a study. We have found success previously in studying rare NSCLC populations using remote consent and enrollment, and remote phlebotomy might be a more attractive option for patients compared with in-person clinic visits during the coronavirus disease 2019 pandemic, which has resulted in a steep decline in outpatient oncology visits. We, therefore, hypothesized that we could conduct a remote participation study using plasma NGS to characterize resistance mechanisms arising after progression on next-generation ALK TKIs in advanced NSCLC.

Materials and Methods

The study entitled “Study of Plasma Next-Generation Sequencing for Remote Assessment, Characterization, Evaluation of Patients With ALK Drug Resistance” (SPACEWALK) (NCT03833934) is a remote participation study open across the United States to patients with advanced ALK-positive NSCLC progressing on a next-generation ALK TKI (Fig. 1). Plasma NGS is provided on-study to understand resistance mechanisms, with results returned to the patient and their provider. Patients are then followed up to characterize the outcome of subsequent treatments. The study is coordinated by the Addario Lung Cancer Medical Institute (ALCMI), a nonprofit research consortium.

Eligibility

Eligibility is limited to patients over 18 years of age with advanced ALK-positive NSCLC. In addition, patients must have systemic progression (excluding central nervous system only) within the past 30 days, having previously been treated with a next-generation ALK TKI and having not started a new line of therapy before signing the informed consent form. Because of remote consent, the study was limited to those able to read, write, and communicate in English.

Recruitment and Enrollment

Participants were referred by means of their treating physician or social media to a study website (https://alcmi.net/research/spacewalk-study/). On this website, they completed a contact form indicating their interest in participating in the study and answered a prescreening questionnaire regarding potential eligibility. If the patients indicated they have ALK-positive NSCLC and are progressing on an ALK TKI, they were contacted by the study staff who then released access to an online consent form to the patient. A study coordinator calls the patient and was available if any questions arise during the consent process. To determine the eligibility before enrollment, source documentation was obtained either from the patient (to facilitate timely screening) or through a medical record request from their local oncology office (Fig. 1A).

Keywords: ALK; Drug resistance; Plasma NGS; Remote participation
After enrollment, a specimen collection kit was immediately shipped to each participant. Phlebotomy was performed either at a local laboratory or by means of a mobile phlebotomist sent to the patient’s home. Four 10-cm³ Streck tubes were filled and sent to Resolution Bioscience for testing. Plasma NGS results were expected within 14 days and returned to patients and their providers with drug sensitivity annotated for any potential resistance mutations detected. Patients were then
followed up for 2 years with the option for repeat blood collection after starting a new treatment or at progression (Fig. 1B).

**Plasma NGS**

The analysis of plasma cfDNA was performed by Resolution Bioscience using Resolution ctDx Lung, an assay that has exhibited strong performance previously for detecting targetable fusions. The Resolution platform could detect point mutations, insertions and deletions, copy number variation, and fusions. Fusions were detected by analysis of abnormal reads pulled down by sets of tiled, 40-nucleotide, directional probes. Copy number variation was detected by taking probe read count data from the sample of interest and comparing it with probe read count data from a set of wildtype reference samples. Normalized probe read count data was then used to detect and measure shifts in gene coverage. For calling gene amplifications, a significant ($p < 1e-10$) shift between the probes in a gene and a background set of probes was required, with a change in raw (plasma) copy number of at least 0.1 copies. The clinical turnaround time was calculated from the date of specimen draw to the date of result reporting.

**Results**

Between January 2019 and March 2020, a total of 172 individuals expressed interest in study participation through the contact form or study hotline (Fig. 1C). A total of 82 patients passed initial prescreening requirements and were invited to sign consent. A total of 72 patients signed consent, and 63 patients met all eligibility requirements and were enrolled. One enrolled patient was excluded from analysis owing to a diagnosis of ALK-positive cancer of another primary lesion (not lung). Patient characteristics can be seen in Table 1.

Of the 62 patients analyzed, 52 consented and enrolled remotely, whereas 10 were enrolled at Dana-Farber Cancer Institute. Patients were enrolled from 25 U.S. states (Fig. 2). Of the 52 patients enrolled remotely, three patients were ineligible at the time of initial consent, therefore the timing of enrollment (e.g., duration of screening) was studied in the remaining 49 patients. A total of 36 patients were able to provide their own medical records and were enrolled a median of 1 day (range: 0–9 d) after consent (Supplementary Fig. 1). A total of 13 patients were unable to provide medical records and the study staff requested records instead from their local hospital; these patients were enrolled in a median of 5 days (range: 1–11 d) after consent. Of the 52 patients enrolled remotely, 18 patients used mobile phlebotomy services, and their blood draw on enrollment has been completed in a median of 4 days (range: 1–13 d) after enrollment (Supplementary Fig. 1). A total of 34 patients had their blood drawn at a local hospital or phlebotomy facility; they completed the blood draw at a median of 6 days (range: 1–69 d) after enrollment.

| Table 1. Patient Characteristics |
|---------------------------------|
| Characteristic                  | ctDNA Detected (N=27) | ctDNA not Detected (N=35) | Total (N=62) |
|---------------------------------|------------------------|---------------------------|--------------|
| Age - yr                         | 53                     | 58                        | 55           |
| Range                           | 35-69                  | 26-81                     | 26-81        |
| Sex - no. (%)                   | 11(40.7)               | 11(31.4)                  | 22(35.5)     |
| Male                            | 16(59.3)               | 24(68.6)                  | 40(64.5)     |
| ALK TKI at enrollment- no. (%)  |                        |                          |              |
| Alectinib                       | 18(66.7)               | 27(77.1)                  | 45(72.6)     |
| Lorlatinib                      | 9(33.3)                | 4(11.4)                   | 13(21.0)     |
| Brigatinib                      | 0                      | 2(5.7)                    | 2(3.2)       |
| Ceritinib                       | 0                      | 2(5.7)                    | 2(3.2)       |
| Prior ALK TKIs- no. (%)         |                        |                          |              |
| Alectinib                       | 27(100)                | 34(97.1)                  | 61(98.4)     |
| Brigatinib                      | 1(3.7)                 | 5(14.3)                   | 6(9.7)       |
| Ceritinib                       | 3(11.1)                | 5(14.3)                   | 8(12.9)      |
| Crizotinib                      | 10(37.0)               | 16(45.7)                  | 26(41.9)     |
| Lorlatinib                      | 9(33.3)                | 4(11.4)                   | 13(21.0)     |
| Number of prior ALK TKIs- no. (%)|                        |                          |              |
| 1                               | 13(48.1)               | 14(40.0)                  | 27(43.5)     |
| 2                               | 7(25.9)                | 16(45.7)                  | 23(37.1)     |
| 3                               | 5(18.5)                | 3(8.6)                    | 8(12.9)      |
| 4                               | 2(7.4)                 | 1(2.9)                    | 3(4.8)       |
| 5                               | 0                      | 1(2.9)                    | 1(2.6)       |
The median turnaround time of testing was 12 days across the 62 patients studied with an interquartile range of 10 to 16 days. The timing of result return and presence of detectable tumor DNA was further studied in 59 patients with at least 3 months of adequate follow-up data (Fig. 3A). In 17 patients, a change of treatment was initiated before receiving plasma NGS results—10 (59%) of these patients had an ALK fusion detected. Another 32 patients initiated a new treatment after receiving their plasma NGS results, with an ALK fusion detected in 15 (47%) of these. Finally, there were 10 patients who did not change treatment for their progressive cancer in the 3 months after plasma NGS, and only one (10%) had an ALK fusion detected.  

As compared with the date of blood draw, in the 26 patients with an ALK fusion detected, a new treatment has initiated a median of 16.5 days after the blood draw; whereas in the 33 patients in which an ALK fusion was not detected, a new treatment was initiated a median of 41 days after blood draw (Fig. 3B), including 10 patients who had not yet changed therapy after 3 months of follow-up.

Overall, the driver ALK fusion was detected in 27 of the 62 analyzed results (44%) with a median allelic frequency (AF) of 2.6% (range: 0.1%–37%). Of the 27 results with an ALK fusion detected, 17 (63%) detected an additional potential resistance mechanism (Fig. 4). In 14 cases, one or more ALK resistance mutations were detected; no somatic ALK mutations were seen in the absence of a detected fusion. In nine cases, a potential off-target resistance mechanism was detected, which was seen in addition to an ALK resistance mutation in six cases. The most frequent off-target resistance mechanism was MET amplification, which was seen in six cases (median of eight estimated copies, range: 3–22). In one patient, a KRAS G12V mutation was seen at 10% AF along with an intra-ALK rearrangement at 7.8% AF and an ALK L1196Q point mutation. Previous tissue testing for this patient at diagnosis has found an ALK fusion by fluorescence in situ hybridization and no KRAS mutation on plasma NGS or on tissue NGS, confirming an acquired KRAS mutation.

To better understand the relatively low detection rate of ALK fusions, we studied a subset of 21 patients who had both plasma NGS results on-study (using Resolution ctDx Lung) and results from another liquid biopsy assay (Supplementary Table 1). In 13 of these cases, the alternate assay was performed within 3 months of the on-study plasma NGS (median time between assays of 2 wk), whereas eight were tested more than 3 months before the on-study plasma NGS assay (median of 60 wk...
ALK resistance mutations and bypass resistance. In the 62 analyzed results, the known ALK fusion was found in 27 (44%). Of the 27 results with an ALK fusion detected, 17 (63%) detected a resistance mechanism. Eight cases (30%) had one or more secondary ALK kinase domain resistance mutations, three cases (11%) had bypass track resistance, and six (22%) cases had both ALK resistance mutations and bypass resistance. MET amp was the only off-target resistance mutation seen in the absence of an ALK resistance mutation. amp, amplification.

between assays). The ALK fusion was detected by both assays in five cases and was not detected by either assay in eight cases, although they were discordant in eight cases. There was one case in which on-study plasma NGS was negative but an alternate assay (Guardant360 CDx, Guardant) drawn 5 days later detected an ALK fusion (0.07% AF). In contrast, there were seven cases in which an ALK fusion was detected by Resolution Bioscience but missed by an alternate assay (median 1.2% AF). The fact that alternate assays were unlikely to detect the driver ALK fusion in cases missed on-study supports the possibility that the relatively low detection rate for ALK fusions was owing to low tumor DNA shed in this cohort of patients with resistance to targeted therapy.

A total of 14 patients underwent an additional optional blood draw after starting a new treatment. A median of 5 weeks passed between the initial blood draw and response blood draw. Three patients (21%) had no circulating tumor DNA detected on both initial and on-treatment blood draws. Of the remaining 11 patients, seven had greater than 50% reductions in ALK fusion AF on therapy (Fig. 5A). In two patients, an increase in ALK fusion AF was seen—interestingly, both had a clearance of their ALK G1202R resistance mutation on treatment, although overall tumor content increased (Fig. 5B). One patient had no change in ALK fusion AF on crizotinib—this patient had previously progressed on lorlatinib and developed MET amplification (seven copies), which was cleared using crizotinib while an ALK G1269A mutation emerged (Fig. 5C). Finally, one patient enrolled after progression on alectinib and subsequent crizotinib, and plasma NGS revealed EMLA-ALK (2.9% AF) and a high MET amplification at 22 copies. On the basis of these results, combination therapy with alectinib plus crizotinib was initiated and scans revealed evidence of response; however, this was short-lived. Repeat plasma NGS on treatment revealed a 75% decrease in ALK fusion AF with a clearance of the MET amplification and with the emergence of low-level EGFR amplification (Supplementary Fig. 2). These findings highlight the challenge of subclonal resistance mechanisms, which may be effectively targeted without resulting in an overall response for a patient owing to coexistent resistant clones.

Discussion

In this initial report from the SPACEWALK study, we report the power of remote participation research for characterizing therapy resistance in a rare molecular subset of NSCLC. Historically, studies of acquired resistance have been performed at leading academic centers using tumor biopsies. Although such efforts are robust, it can take time to accumulate a large cohort, especially for rare cancer types. By leveraging remote consent-taking and plasma NGS, we were able to study 62 patients over a 15-month period. In an era in which telemedicine is playing an increasingly important role in patient care, we report the potential of a “teleresearch” approach that can study participants from across the United States, including those treated at smaller cancer centers that may have few research studies to offer. More importantly, this study continued to enroll briskly throughout the coronavirus disease 2019 pandemic due, in part, to its remote nature, giving patients the ability to participate from afar without requiring in-person clinic visits to participate in research.

This kind of remote participation diagnostic study, nevertheless, has its challenges, such that over the course of the study we have developed techniques to improve participation. First, we found that patients with access to their own records were able to enroll more quickly. Second, we found that the remote blood draw was feasible for all enrolled patients, though the testing was expedited through the use of a mobile phlebotomy service. Finally, we identified a need to adjust our communication strategies for remote patients—a participant getting a call from the cancer center as an anonymous caller might ignore it—so instead, a mobile
phone was requested for the study to permit more straightforward communication.

The clearest limitation of such a resistance analysis based entirely on plasma NGS was the low level of tumor DNA shed in this population. In this cohort, we detected fusions in the plasma of only 44% of patients with advanced ALK-positive NSCLC, whereas we detected fusions in 81% of patients with advanced NSCLC known to harbor ALK, ROS1, or RET fusions in a recent study using the same assay. These patients with ALK-targeted therapy resistance but without evidence of tumor DNA shed tended to change their treatment at a later stage, with several making no treatment change for a few months. This suggests our study may have unexpectedly enrolled a larger proportion of patients with more indolent disease. These risks being a recurring selection bias impacting remote participation studies of drug resistance because patients with higher tumor DNA shed may have more aggressive disease and more symptoms from their higher tumor burden, which could then make them less interested in participating in research studies.

Nevertheless, in the 27 patients with tumor DNA detected, we found a striking diversity of resistance mutations with one case harboring four secondary ALK mutations, another with an acquired KRAS G12V mutation, and several with high MET amplification. On-target second site mutations in the ALK kinase domain are a well-established mechanism of resistance; however, off-target activation of KRAS or MET is less well described and requires further investigation. Supporting the validity of our finding, another group has recently reported on the detection of targetable MET amplification in patients with ALK inhibitor resistance. Through a collection of repeat plasma NGS, we were able to gain

Figure 5. Treatment effect evaluated by serial plasma NGS. (A) A total of 14 patients underwent an additional blood draw after starting a new treatment. Three patients (21%) had no ctDNA detected on both enrollment and on-treatment blood draws and has been excluded from the graph. Of the remaining 11 patients, several had dramatic reductions in AF of the ALK fusion on therapy. (B) Two patients with an increase in AF on therapy (*) had previously progressed on alectinib and developed ALK G1202R, yet both had a clearance of their resistance mutation on treatment. A patient with no change in AF on crizotinib (#) had previously progressed on lorlatinib and developed MET amplification. The MET amplification cleared on crizotinib (C) although an ALK G1269A mutation emerged. AF, allelic frequency; ctDNA, circulating tumor DNA; N/D, not determined; NGS, next-generation sequencing.
insight into whether these resistance mutations were effectively targeted with a change in therapy and other cases in which a resistant subclone was suppressed without an overall effect on tumor burden. Remote collection of serial imaging can be cumbersome for patients because it requires obtaining and mailing scans. Serial phlebotomy for repeat plasma NGS seems to offer potential as an alternative approach to quantify treatment effect in studies like these.

With more effective targeted therapies for lung cancer and other cancer types emerging, we are hopeful that the model of remote consent for rapid plasma genotyping we report here has the potential to be emulated in other genomic settings. We have previously found through work with ALCMI that remote participation permits engagement of rare lung cancer populations with the collaboration of patient research advocacy organizations such as the GO2 Lung Cancer Foundation and ALCMI. Others have similarly found success with the model, most notably the Angiosarcoma Project of the Broad Institute. Using these techniques to enumerate and target cancer drug resistance in the real-world setting deserves further investigation.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100151.

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