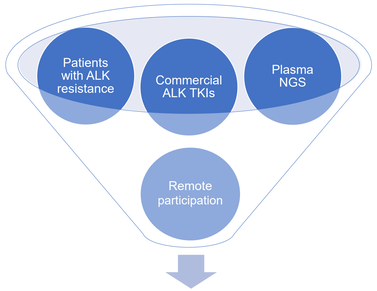
SPACEWALK: Plasma NGS for remote evaluation of ALK drug resistance in advanced NSCLC

Marissa N. Lawrence[1], Rubii M. Tamen[1], Alicia Sable-Hunt[2], Seyed Ali Hosseini[3], George R. Simon[4], Jonathan W. Riess[5], Geoffrey R. Oxnard[1]

[1]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, [2]Addario Lung Cancer Medical Institute, San Carlos, CA, [3]Resolution Bioscience, Kirkland, WA, [4]The University of Texas MD Anderson Cancer Center, Houston, TX, [5]UC Davis Comprehensive Cancer Center, Sacramento, CA

Background

- Precision therapy for cancer drug resistance requires detection of resistance mutations and treatment with appropriate targeted therapies.
- This paradigm is well established in *EGFR*-mutant NSCLC[1], yet our understanding of drug resistance in *ALK*-positive NSCLC is more limited.
- Next-generation sequencing (NGS) of plasma cell-free DNA (cfDNA) now permits noninvasive interrogation of drug resistance.
- To facilitate improved understanding of *ALK* drug resistance and the effectiveness of treatment strategies, we launched this remote participation study [NCT03833934].

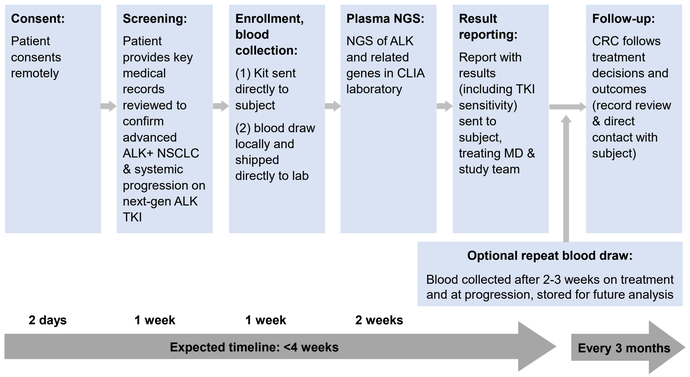


1) Study ALK resistance to next-gen ALK TKIs using plasma NGS

2) Study molecular-guided resistance therapy for ALK-positive NSCLC

Methods

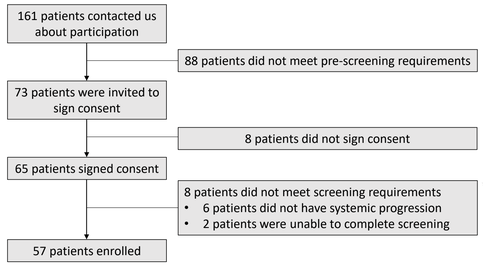
- The SPACEWALK [Study of Plasma next generation sequencing for remote Assessment, Characterization, Evaluation of patients With ALK drug resistance] study offers plasma NGS to patients with advanced NSCLC with systemic progression on a next-generation ALK TKI to assess for mechanisms of resistance.
- Patients consent, enroll and participate remotely to permitting a larger cohort of patients with *ALK* positive NSCLC to be studied.
- Remote phlebotomists can be dispatched to the patient's home when necessary to ease the burden of study participation and to ensure study compliance.
- Blood is sent to Resolution Bioscience (Kirkland, WA) for cfDNA extraction and hybrid capture NGS[2], with results returned within 14 days to the study team and the patient's physician.
- Patients are followed for 2 years and blood is collected again after starting a new treatment or at progression.

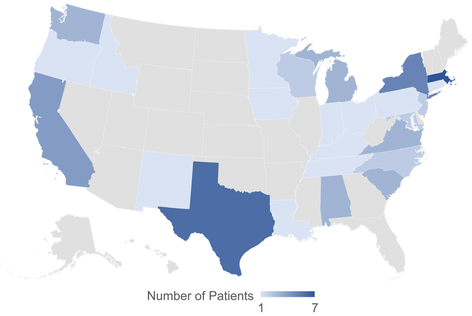


Results

A. Study Enrollment

Of 161 patients contacting us via the study website, 73 were offered consent and 65 signed consent.

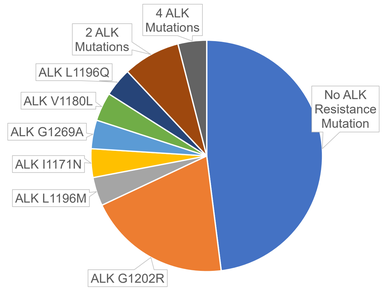




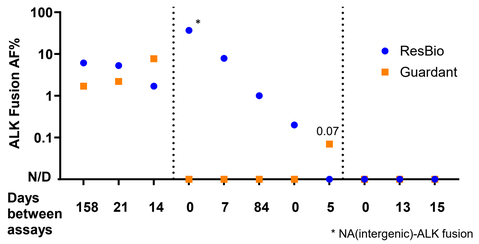
57 patients enrolled from 25 different US states and 40 different medical centers.

B. ALK Resistance Mutations Found with Plasma NGS

- Of the 56 returned results, the known *ALK* fusion was detected in 25 (45%) with a median *ALK* fusion AF of 2.9% (range 0.1%-37%).
- Of the 25 patients with an *ALK* fusion detected, 13 (52%) had an *ALK* resistance mutation detected. No somatic *ALK* mutations were seen in the absence of a detected fusion.
- 6 patients (24%) had a *MET* amplification detected with a median of 8 copies (range 3-22).
- 1 patient had a *KRAS* G12V mutation detected at 10% AF.



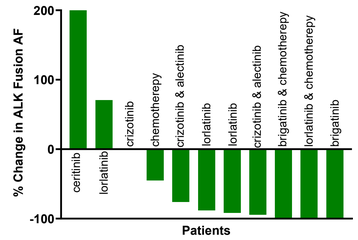
C. Resolution Bioscience vs. Guardant360



- 11 patients also underwent plasma NGS with Guardant360, with a median time between the two plasma NGS draws of 1.9 weeks (range 0-22.6).
- In 4 cases, Resolution Bioscience identified an *ALK* fusion (AF 0.2-37%) not detected on Guardant360[3].
- All fusions were EML4-ALK except for one (*).

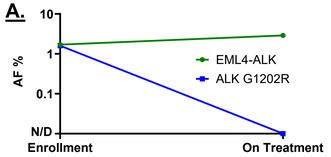
D. Treatment Response Evaluated by Plasma NGS

- 14 patients underwent an additional blood draw after starting a new treatment.
- A median of 5 weeks passed between the baseline and response blood draw.
- 3 (21%) patients had inconclusive plasma results with no tumor shed on both enrollment and on treatment blood draws.
- Of the remaining 11 patients, several had dramatic reductions in the AF of the *ALK* fusion on therapy.



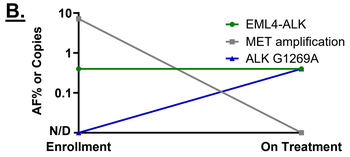
Case Studies

A.



- Two patients (one shown above) had an increase in EML4-ALK fusion AF on therapy, but had clearance of their *ALK* G1202R mutations.
- Both patients had previously progressed on alectinib and were on an alternate ALK TKI at the time of the on-treatment draw.

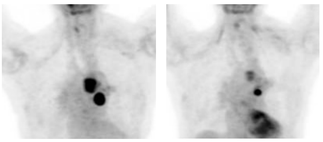
B.



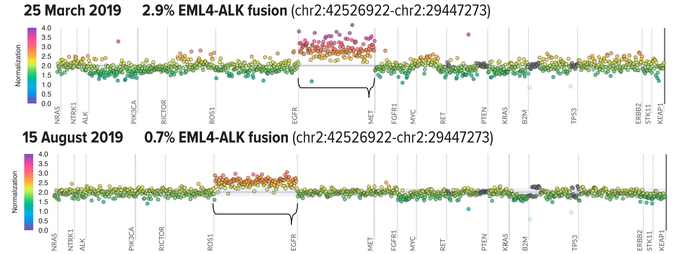
- A patient progressed on lorlatinib and at enrollment plasma NGS found EML4-ALK fusion (0.4% AF) and *MET* amplification (7.2 copies).
- Crizotinib was started and on treatment plasma NGS showed no change in the EML4-ALK fusion but *MET* amplification cleared while *ALK* G1269A emerged.
- Imaging showed progression on crizotinib.

C.

- A patient had received alectinib for 8 months and was then switched to crizotinib based on detection of *MET* amplification, with mixed response and eventual progression after 6 months.
- They enrolled on study and plasma NGS showed EML4-ALK (2.9% AF) and a high *MET* amplification at 22 copies.
- Based on these results, combination therapy with alectinib + crizotinib was initiated and scans showed evidence of response, however this was short lived.
- On treatment plasma NGS showed a 75% decrease in EML4-ALK fusion AF with clearance of the *MET* amplification and emergence of *EGFR* amplification appeared at 6.1 copies.



baseline alectinib + crizotinib



Discussion

- Remote-participation studies like SPACEWALK may offer a new mechanism for characterizing resistance to emerging targeted therapies in rare cancer populations.
- Plasma NGS permits the detection of targetable resistance mechanisms in patients with *ALK*-positive NSCLC and drug resistance.
- However, sensitivity of different plasma NGS assays for *ALK* fusions varies, and further assay optimization may be needed.
- Repeat analysis of plasma cfDNA on therapy offers a noninvasive method for capturing treatment effect.

References

1. Oxnard et al. JAMA Oncol. 2018
2. Paweletz et al. Clin Cancer Res. 2016
3. Supplee et al. Lung Cancer, 2019

Acknowledgements

Funded in part by the NCI (R21 CA234816), Takeda Pharmaceuticals, Pfizer, and the Damon Runyon Cancer Research Foundation