CLINICAL RELEVANCE OF ALK/ROS1 RESISTANCE MUTATIONS AND OTHER ACQUIRED MUTATIONS DETECTED BY LIQUID BIOPSY IN ADVANCED NSCLC PATIENTS

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INTRODUCTION

- Liquid biopsies for circulating tumor DNA (ctDNA) can be a tool for somatic mutation detection, such as EGFR, BRAF or KRAS mutations.
- In ALK and ROS1 populations, ctDNA can be used for detecting and monitoring ALK/ROS1 fusions or resistance mechanisms, as well as other acquired mutations.
- However, the applicability and clinical relevance of ALK/ROS1 alterations and other acquired mutations detected by liquid biopsy, is poorly described in TKI-treated patients.

OBJECTIVE

- We evaluated the feasibility and clinical relevance of ALK/ROS1 resistance mechanisms and other acquired mutations detected by ctDNA in a large cohort of ALK/ROS1+ NSCLC patients.

METHODS

- Advanced ALK/ROS1+ NSCLC patients were prospectively enrolled from October 2015 to April 2018 across 9 French institutions.
- ctDNA molecular analysis was performed using amplicon-based NGS (InVision® liquid biopsy platform, InVisionFirst™-SLC34A2, SDC4 and EZR) for ALK (EML4 variant r1, v2, v3), ROS1 (CD74, SLC34A2, SDC4 and EZR) fusions, and other somatic mutations.
- 2mlm blood were collected in Streck RICT or EDTA tubes and processed for DNA extraction.

RESULTS

- 128 patients were included: 101 ALK, 27 ROS1.
- Blood samples (n=275) were collected at different timepoints: tyrosine kinase inhibitors (TKI)-naive (n=206) or at progression (n=69).
- 42 samples were collected post-crizotinib: 25 post 2nd gen-TKI and 25 post next gen-TKI.
- Higher incidence of ALK resistance mutation following treatment with 2nd and next gen-TKI vs. crizotinib: 7% vs. 12% (p=0.05) vs 36% (P=0.00641).
- Other concurrent mutations detected in 78% of patients with ALK resistance and concurrent non-ALK mutations according to prior TKI therapy.

ALK RESISTANCE MECHANISMS

- 95 samples were collected at PD to TKI; 92 were available for analysis.
- 128 patients were included: 101 ALK, 27 ROS1.
- Blood samples (n=275) were collected at different timepoints: tyrosine kinase inhibitors (TKI)-naive (n=206) or at progression (n=69).
- 4 ROS1 G203R2 mutations were detected (30%): 2 post-crizotinib from the same patient, and 2 post-totalkins.

CONCLUSIONS

- Routine liquid biopsies can assess the heterogeneity of the TKI resistance, detecting ALK resistance and other acquired mutations in pretreated advanced ALK & ROS1 NSCLC patients.
- Feasibility of using liquid biopsy with InVision platform in routine clinical practice was demonstrated in this study, across a breadth of ALK and non-ALK resistance mutations.
- In our cohort, next generation TKIs lead to increase ALK resistance mutations than crizotinib.
- Patients who develop TKI-ALK resistance mutations show trend to having poorer outcomes, suggesting that routine ctDNA monitoring could benefit patients in supporting treatment decisions.
- This study is currently ongoing to further evaluate ctDNA dynamics for correlation to clinical response, patient outcomes and clinical characteristics.

REFERENCES


Additional data of this study is presented by A. Swalousz, L. Mezquita et al (MA16.09) mini oral communication: 25/09/2018, 14:30h, Room 203 BD