

## **Non-invasive molecular profiling for therapy monitoring of ALK+ lung cancer [Abstract]**

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## Non-Invasive Molecular Profiling for Therapy Monitoring of ALK+ Lung Cancer

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**Purpose:** Non-small cell lung cancer (NSCLC) patients with *ALK* rearrangements are routinely treated with tyrosine kinase inhibitors (TKIs), leading to improved survival. However, clinical courses vary widely as the tumors inevitably develop resistance. Thus, early detection and molecular characterization of treatment failure is important for patient outcome.

**Methods:** To identify indicators of therapy response and progression, we performed an analysis of circulating tumor DNA (ctDNA) from serial plasma samples (n=278) of 73 NSCLC patients with *ALK* rearrangements. Using targeted sequencing and shallow whole genome sequencing (sWGS), we achieved mean unique coverages of >4000x and 0.5x, respectively.

**Results:** Variable mutation levels were marked in all patients and correlated with clinical features. For example, mutant ctDNA levels were low in cases of stable disease, but increased at the time of TKI failure. Targeted sequencing identified known and novel mutations indicating TKI resistance. We also found mutated *TP53* at the time of progression in patients with initially *TP53* wildtype tumors. The progression-free survival of patients with acquired *TP53* mutations was comparable to that of primarily *TP53* mutated and shorter than that of persistently *TP53* wildtype cases. sWGS of ctDNA identified copy number variations, some of which might contribute to tumor progression. We also measured miRNA abundances in corresponding serum samples and noted fluctuating miRNA levels during therapy that correlated with the clinical course in several cases.

**Conclusions:** Our data suggest that liquid biopsies can improve ALK+ NSCLC patient care through early detection of progression and tailored treatment of resistant tumors. ctDNA and miRNA can indicate the need to switch treatment and provide information to guide the next-line therapy. Detection of acquired *TP53* mutations in liquid rebiopsies at the time of disease progression identifies additional high-risk cases and suggests potential clinical utility of ctDNA monitoring for this disease beyond profiling of *ALK* resistance mutations.

### Conflicts of Interest:

SD reports speaker's honoraria from Roche;

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