374

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

Steffen Dietz[1,2]; Petros Christopoulos[2,3]; Lisa Gu[1,2]; Volker Endris[4]; Zhao Yuan[5]; Simon J. Ogrodnik[1]; Tomasz Zemojtel[6]; Marc A. Schneider[2,7]; Anna-Lena Volkmar[4]; Michael Meister[2,7]; Thomas Muley[2,7]; Martin Reck[8]; Matthias Schlesner[2,5]; Michael Thomas[2,3]; Albrecht Stenzinger[2,4,9]; Holger Sültmann[1,2]

[1]Division of Cancer Genome Research, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), and National Center for Tumor Diseases (NCT), Heidelberg, Deutschland
[2]German Center for Lung Research (DZL), TLRC Heidelberg, Heidelberg, Deutschland
[3]Department of Oncology, Thoraxklinik at University Hospital Heidelberg, Heidelberg, Deutschland
[4]Institute of Pathology at University Hospital Heidelberg, Heidelberg, Deutschland
[5]Bioinformatics and Omics Data Analytics, German Cancer Research Center (DKFZ), Heidelberg, Deutschland
[6]Berlin Institute of Health (BIH) Genomics Core Facility, Charité University Medical Center, Berlin, Deutschland
[7]Translational Research Unit, Thoraxklinik at University Hospital Heidelberg, Heidelberg, Deutschland
[8]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research (DZL), Großhansdorf, Deutschland
[9]German Cancer Consortium (DKTK), Heidelberg, Deutschland

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;
PC reports research funding from Novartis, Roche, AstraZeneca and Takeda as

well as advisory board and/or lecture fees from Boehringer, Pfizer and Chugai;
AV reports speaker's honoraria from Astra Zeneca;
VE reports advisory board and lecture fees from AstraZeneca and ThermoFisher;
MT reports advisory board honoraria from Novartis, Lilly, BMS, MSD, Roche, Celgene, Takeda, AbbVie, Boehringer, speaker's honoraria from Lilly, MSD, Takeda, research funding from AstraZeneca, BMS, Celgene, Novartis, Roche and travel grants from BMS, MSD, Novartis, Boehringer;
AS reports advisory board honoraria from BMS, Bayer, AstraZeneca, ThermoFisher, Novartis, Seattle Genomics speaker's honoraria from BMS, Bayer, Illumina, AstraZeneca, Novartis, ThermoFisher, MSD, Roche, as well as research funding from Chugai, Bayer and BMS;
HS reports advisory board and speaker's honoraria from Roche.