Intra-individual tumor heterogeneity of NSCLC: Longitudinal in vivo analysis of clonal evolution and selection of chemo-resistant clones

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Background/State of the art. Non-small cell lung cancer (NSCLC) is among the tumors with the largest number of acquired mutations per tumor (Alexandrov et al. 2013). In accordance, not only inter-individual tumor heterogeneity of these tumors poses a major challenge for treatment concepts, but also the intra-individual heterogeneity, which contributes to the development of resistance and treatment failure (Vogelstein et al. 2013). Thus, a better understanding of the intra-individual tumor heterogeneity is a prerequisite for new therapeutic approaches that might be able to delay or even prevent the development of chemo-resistance via a “precise” combination therapy.

Preliminary work. The supervisors have a longstanding track record in studying tumor heterogeneity by applying novel state of the art molecular genetic techniques. For example, L. Bullinger’s group was among the first to use next-generation sequencing to decipher the genomic heterogeneity of several tumor entities such as e.g. acute myeloid leukemia (AML) (Dolnik et al. 2012), acute lymphoblastic leukemia (ALL) (Mar et al. 2014), and multiple myeloma (Kortüm et al. 2014). Similarly, R. Marienfeld has been involved in the genomic characterization of hairy cell leukemia (Lennerz et al. 2012) and primary mediastinal B cell lymphoma (Nagel et al. 2014). Furthermore, there is also a tremendous expertise to link genomic information with clinical data in order to come up with clinically relevant implications (Gaidzik et al. 2013). With regard to the intended study of lung cancer, L. Bullinger has significantly contributed to build up the LuCa bioregistry, which already contains samples from over 300 clinically well annotated lung cancer cases (including follow-up samples from individual cases, which will enable “minimal residual disease” detection and/or monitoring of the occurrence of resistant clones). In parallel, in close collaboration L. Bullinger and R. Marienfeld have established a targeted resequencing panel for the “routine”-analysis of solid tumor samples, including protocols that work with little DNA that can be obtained from FFPE conserved tumor biopsies. In addition, in-house data analysis pipelines for both targeted resequencing and whole exome sequencing have been established and are running well. Finally, functional analyses based on CRISPR/Cas9 technology have been set up successfully in leukemia and solid tumor derived cell line models and can be applied to lung cancer cell line models as well as primary lung cancer derived cell models (in vitro culture of primary cells and/or xenograft models).

Overall hypothesis. We will study the intra-individual heterogeneity within selected patients with adenocarcinoma using next generation sequencing (NGS) technology.