Comprehensive Summary (Abstract) as Published in the Thesis

Title of Thesis: Molecular Genetic Analysis in B-cell Lymphomas: A Focus on the p53 Pathway and *p16^{INK4a}*

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The presence of *TP53* mutations has been associated with inferior outcome in diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). In DLBCL, the impact of the *TP53* codon 72 polymorphism and *MDM2* SNP309 has not been clearly elucidated, whereas *MDM2* SNP309 was suggested as a poor-prognostic marker in CLL. In addition, *p16^{INK4a}* promoter hypermethylation has been implicated as a negative prognostic factor in DLBCL. The aim of this thesis was to further evaluate these molecular markers in well-characterised materials of DLBCL and CLL.

In paper I, we investigated the prognostic role of *TP53* mutation, codon 72 polymorphism and *MDM2* SNP309 in DLBCL (n=102). The presence of *TP53* mutations (12.7%) correlated with a poor lymphoma-specific and progression-free survival, and a particularly pronounced effect was observed in the germinal center subtype. Neither the *MDM2* SNP309 nor the *TP53* codon 72 polymorphism had an impact on age of onset or survival. In paper II, we applied pyrosequencing to measure the level of *p16^{INK4a}* methylation in DLBCL (n=113). Thirty-seven percent of cases displayed *p16^{INK4a}* methylation; however, no clear association could be observed between degree of methylation and clinical characteristics or lymphoma-specific survival.

In papers III–IV, we investigated the prognostic role of *MDM2* SNP309 (n=418) and *TP53* mutation (n=268) in CLL. No correlation was observed between any particular *MDM2* SNP309 genotype and time to treatment and overall survival. Furthermore, no association was found between the different *MDM2* SNP309 genotypes and established CLL prognostic markers. *TP53* mutations were detected in 3.7% of CLL patients; where the majority showed a concomitant 17p-deletion and only three carried *TP53* mutations without 17p-deletion. We confirmed a significantly shorter overall survival and time to treatment in patients with both *TP53* mutation and 17p-deletion.

Altogether, our studies could confirm the negative prognostic impact of *TP53* mutations in DLBCL, whereas *MDM2* SNP309 and *TP53* codon 72 polymorphisms appear to lack clinical relevance. We also question the role of *p16^{INKa}* methylation as a poor-prognostic factor in DLBCL. Finally, the presence of *TP53* mutation in CLL appears to be rare at disease onset and instead arise during disease progression.

Keywords: diffuse large B-cell lymphoma, chronic lymphocytic leukemia, *TP53* mutation, *MDM2* SNP309, codon 72 polymorphism, *p16^{INK4a}* methylation