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## **TP53 mutations in myelodysplastic syndromes with deletion of 5q**

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av

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## ABSTRACT

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of malignant bone marrow disorders characterized by peripheral cytopenia(s) and increased risk of progression to acute myeloid leukemia (AML). International Prognostic Scoring system (IPSS) Low- or Intermediate (INT)-1 risk MDS with a deletion of 5q (del5q) were considered to have an indolent course and a low risk for progression to AML as compared to other MDS subtypes. However, more recent studies have shown that overall survival (OS) and risk for AML progression vary greatly in del(5q) MDS patients indicating that factors beyond established risk scoring systems impact patient outcome. Molecular abnormalities have emerged as putative prognostic markers.

We performed molecular studies in a patient with classical 5q- syndrome who unexpectedly evolved to high-risk MDS with complex karyotype (*Paper I*). Immunohistochemistry (IHC) of pre-treatment marrow biopsies revealed a small fraction of progenitors with strong p53 expression and sequencing confirmed a *TP53* mutation. *TP53* mutated subclones had not been described in MDS with isolated del(5q) and indicated a previously unknown heterogeneity. In a subsequent study of 55 patients with lower-risk del(5q) MDS, 18% of the patients were found to have *TP53* mutated subclones at diagnosis which rendered them at higher risk for progression (*Paper II*). Interestingly, the association with outcome was even stronger for p53 IHC indicating a high sensitivity of this method for early identification of patients with adverse outcome. As a next step, we assessed p53 protein expression in a cohort of 85 lower-risk del(5q) MDS patients treated with lenalidomide within a clinical trial (*Paper IV*). P53 IHC positive patients showed significantly shorter overall survival, higher risk for leukemic transformation, and lower cytogenetic response rate to lenalidomide, hence validating the results from Paper II. Importantly, pyrosequencing analysis of microdissected IHC stained cells confirmed that cells with strong staining carried *TP53* mutations, while moderate staining reflected wild-type *TP53*.

Due to the apparently exquisite sensitivity of the del(5q) clone to len, we hypothesized that higher doses of lenalidomide may induce cytogenetic and clinical responses also in patients with high-risk MDS/AML with chromosome 5 abnormalities who were refractory or ineligible for standard treatment (*Paper III*). In this study, we demonstrated that treatment was able to inhibit the del(5q) tumor clone in a cohort of patients with extremely advanced disease, which suggests that the selective inhibitory effect of len *in vitro* may be translated into a therapeutic response *in vivo*. Importantly, *TP53* mutations were common (62%) in this cohort, and uniformly associated with treatment failure. Altogether, our findings suggest an important role of the p53 pathway in both low- and high-risk del(5q) MDS, and in relation to treatment with lenalidomide. These findings will have major implications for risk stratification and the choice of therapy.