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ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

TP53 Gene allelic State in Myelodysplastic Syndromes (MDS) with Isolated 5q Deletion

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Background & aim: The mutational status of *TP53* gene is a significant prognostic factor in MDS, with two-thirds of patients harboring *TP53* multihit alterations which are associated with poor outcomes. Approximately 20% of patients with MDS with isolated 5q deletion (MDS-del5q) exhibit *TP53* aberrations, though their characteristics and prognostic impact have not been fully elucidated. In this study, we aimed to analyze the characteristics and impact of *TP53* allelic state in patients with MDS-del5q.

Methods: We conducted an international multicenter study in *de novo* MDS-del5q patients according to WHO 2017 classification. Clinical and biological characteristics, including the genetic profile were collected at diagnosis. Genetic profiling included conventional G-banding, *TP53* deletion by FISH and/or SNP-arrays (for *TP53* deletion and copy number neutral loss of heterozygosity). Also, the presence of mutations in myeloid-related genes was assessed by NGS or Sanger. Variant filtering and categorization were performed according to the Spanish Guidelines. Patients were classified as TP53 wild-type (TP53-wt), TP53-monoallelic, and TP53-multihit as proposed by Bernard *et al*. 2020. Clinical and molecular variables were evaluated for associations with acute myeloid leukemia (AML) evolution and overall survival (OS). In addition, a prognostic model to predict risk of AML evolution was developed using variables selected by the LASSO-cox method with minimum lambda. To calculate the points for each variable, a multivariate competitive risk model (Fine-Gray model) was fitted. Evolution to AML was used as the event and death as the competitive event. Statistical analysis was performed by R (4.2.2).

Results: We included 682 patients with MDS-del5q (Table 1). Median follow-up was 66.8 months (CI95% 61.6-75.2). *TP53* mutations were evaluated by NGS in 92.2% (n=629) and by Sanger in 7.8% (n=53) of patients. Overall, 18.7% (n=128) of MDS-del5q presented *TP53* mutations. After integrating mutational data (FISH and SNP-arrays), 72.7% (n=93) of *TP53*-mutated patients were classified as *TP53*-monoallelic, whereas 27.3% (n=31) as *TP53*-multihit (4.5% of the whole cohort). Other recurrent mutations were *SF3B1* (21%), *DNMT3A* (18%), *TP53* (18%), *TET2* (14%), *ASXL1* (10%), *CSNK1A1* (6%) and *JAK2* (6%). Only bone marrow blasts differ between the *TP53*-wt and *TP53*-mutated groups (p=0.031). Furthermore, only gender and VAF were different between *TP53*-monoallelic and *TP53*-multihit, being the number and type of co-occurring mutations similar among all subgroups (Table 1).

Median OS of the whole cohort was 73.8 months (CI95% 63.7-83.4), and 77.3 months (CI95% 66.5-85.3) for MDS-del5q *TP53*-wt and 104 months (CI95% 56.9-89.4) for MDS-del5q *TP53*-mutated (p=0.3). Similarly, there was no significant differences in the risk to AML evolution between *TP53*-wt and *TP53*-mutated patients (AML evolution at 60 months of 19.9% and 29.7%, respectively; p=0.307). Of note, however, the *TP53*-multihit group presented worse prognosis compared to *TP53*-monoallelic and *TP53*-wt patients (median OS of 55.2, 73.2 and 77.3 months, and AML evolution at 60 months of 40.4%, 25.5% and 19.9% in *TP53*-multihit, *TP53*-monoallelic and *TP53*-wt MDS-del5q) [Figure 1]. Interestingly, *TP53*-monoallelic MDS with a *TP53* VAF >20% showed similar prognosis to *TP53*-multihit patients (median OS of 43.7 and 55.2 months, and AML evolution at 60 months of 36.7% and 40.4%, respectively).

Finally, a risk score (MDS-del5q score) for AML evolution was developed with five variables, each assigned a different weight based on the regression coefficients: additional chromosomal abnormality, 2 points; *TP53*-multihit, 2 points; BM blast >2%, 2 points; platelets $\leq 100 \times 10^9$/L, 3 points, and *SF3B1*-mutation, 1 point. Three risk-groups were defined: Low, intermediate, and high-risk for $\leq$1, 2, or $\geq$3 points, respectively, with an AML evolution at 60 months of 11.5%, 23.3% and 43.7%, respectively; p <0.05)

Conclusions: In contrast to previous findings in MDS without del5q, our series of MDS-del5q, the longest described to date, reveals that multihit *TP53* status is uncommon in MDS-del5q. However, multihit alterations have prognostic significance in this subgroup. Finally, the MDS-del5q score allows to stratify patients into three distinct risk groups for AML evolution. These findings could hold considerable implications for guiding treatment decisions.

Disclosures Haferlach: *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Meggendorfer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Jerez:** *GILEAD:* Research Funding; *Novartis:* Consultancy; *Astrazeneca:* Research Funding; *BMS:* Consultancy. **Santini:** *CTI:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Otsuka:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Syros:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Other: Travel support; *Gilead:* Membership on an entity's Board of Directors or advisory committees; *Geron:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Platzbecker:** *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *Merck:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *AbbVie:* Consultancy; *Novartis:* Consultancy, Honoraria, Research Funding; *Geron:* Consultancy, Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Curis:* Consultancy, Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *Amgen:* Consultancy, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Celgene:* Honoraria; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Fibrogen:* Research Funding; *Roche:* Research Funding; *BeiGene:* Research Funding; *BMS:* Research Funding. **Diez-Campelo:** *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors

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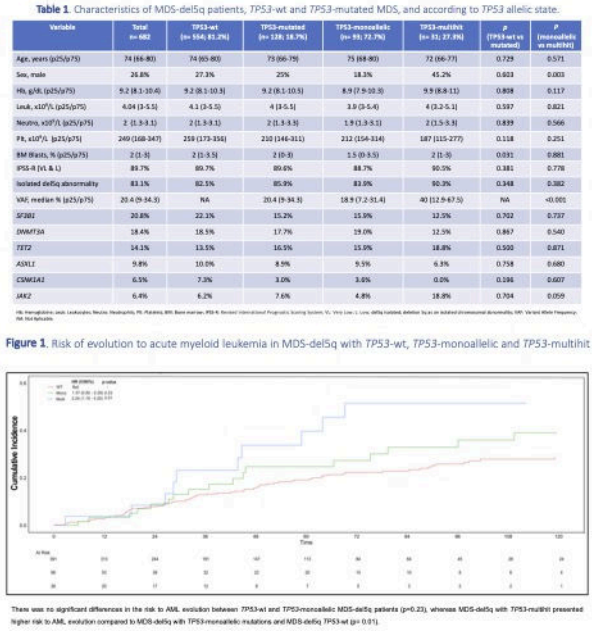

Figure 1

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