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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Classification of Philadelphia-Negative MPN As Low Risk and High Risk MPN Based on Peripheral Blood Values and Molecular Genetics Only

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Background: Philadelphia-negative myeloproliferative neoplasms (Ph -MPN) are characterized by overproduction of differentiated hematopoietic cells mediated in the majority of cases by mutations in *JAK2*, *MPL* or *CALR* (MPN driver genes). Ph - MPN include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and MPN, unclassifiable (MPN-U) which differ in clinical presentation, prognosis, fibrosis and leukemic transformation rate as well as therapeutic options. However, WHO based classification requires experienced pathologists, in particular to diagnose prefibrotic PMF as high risk MPN, and thus remains observer dependent.
Aim: Observer independent classification of Ph - MPN solely based on molecular genetics and peripheral blood (PB) parameters.
Patients and Methods: We analyzed 267 Ph - MPN cases diagnosed as ET (n=76), PV (n=74), PMF (n=68) or MPN-U (n=49) following the WHO4R classification including only patients with an MPN driver mutation (median age: 68 years [22-91]; female: 41%; median follow-up: 5 years). All samples were analyzed by cytomorphology and whole genome sequencing (median coverage 100x). Mutation status of 20 genes associated with myeloid malignancies were analyzed in detail.
Results: Genomic landscape of the MPN cohort showed mutations in *JAK2* in 222 (83%) (n=132: single mutation; n=90: either mutation and copy neutral loss of heterozygosity or mutation and 9p gain), in *CALR* in 36 (14%), and in *MPL* in 9 (3%) patients. The median number of mutations per patient was two (range: 1-6). Within the cohort, 141 patients (53%) harbored MPN driver mutations only, while in 126 (47%) one to 5 additional mutations were found. The most frequent additional mutations were *ASXL1* (n=50), *TET2* (n=49; thereof 15 biallelic), *SRSF2* (n=26), *DNMT3A* (n=18), *U2AF1* (n=11) and *TP53* (n=9; thereof 3 biallelic). Regarding PB parameters, high WBC ($\geq 11 \times 10^9$/ L) were detected in 127 patients (48%), high PLT ($\geq 450 \times 10^9$/ L) in 116 (43%) and anemia (HB <♂12 or ♀11 g/dL) in 50 patients (19%).
We then performed Cox regression analyses for overall survival (OS) including only genetic abnormalities and PB values. In univariate analyses, biallelic *TET2* inactivation (*TET2*bi: hazard ratio/HR: 3.789), *RUNX1* (n=4; HR: 13.479), *ASXL1* (HR: 1.886), *SRSF2* (HR: 3.218) mutations as well as high PLT (HR: 0.440), high WBC (HR: 1.998) and PB blasts >1% (n=57; HR: 1.904) showed significant associations with OS (for all $p<0.02$), while no effect was observed for MPN driver mutations, *DNMT3A* and monoallelic *TET2* mutations. In addition, anemia showed a trend towards poor prognosis (HR: 1.595; $p=0.079$). Following this, we determined high and low risk MPN. In the absence of thrombocytosis, high risk MPN was defined if any of the four following risk factors were present: i) mutation in *ASXL1* or *SRSF2* or *RUNX1* or *TET2*bi, ii) PB blasts >1%, iii) high WBC or iv) anemia. In the presence of thrombocytosis, at least two of these risk factors were required (Figure 1).
Survival analysis revealed a significantly worse median OS of high risk (n=137; 51%) compared to low risk MPN (n=130; 49%) (8 years vs. not reached; $p<0.001$). This proposed novel stratification reflected prognosis better than WHO entities (median OS: MPN-U: 7 years; MF: 8 years; PV/ ET not reached; overall $p=0.001$) (Figure 1A). All 76 ET cases (100%) and 44/74 PV cases (59%) were classified as low risk MPN, while 63/68 PMF cases (93%) and 44/49 MPN-U cases (90%) were classified as high risk MPN (Figure 1B). Within low risk and high risk MPN, no significant OS differences were observed between the WHO entities ($p=0.114$ and $p=0.355$, respectively).
Conclusions: *JAK2*-pathway mutated Ph - MPN can be categorized into low and high risk MPN based on molecular genetics and PB values only. The presence of these objectively assessable risk factors in a patient with ET or PV warrants for a profound reevaluation of bone marrow histology (eventually by a reference pathologist for MPN) and clinical course before a high risk MPN (including prefibrotic PMF) can be ruled out. Whether the predictive value of low risk MPN based on molecular genetics

and PB values only could be sufficient to omit BM biopsy in selected patients, needs to be evaluated in further prospective studies.

Disclosures Huber: *MLL Munich Leukemia Laboratory:* Current Employment. **Hoermann:** *MLL Munich Leukemia Laboratory:* Current Employment. **Meggendorfer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Hutter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Baer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Kern:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership.

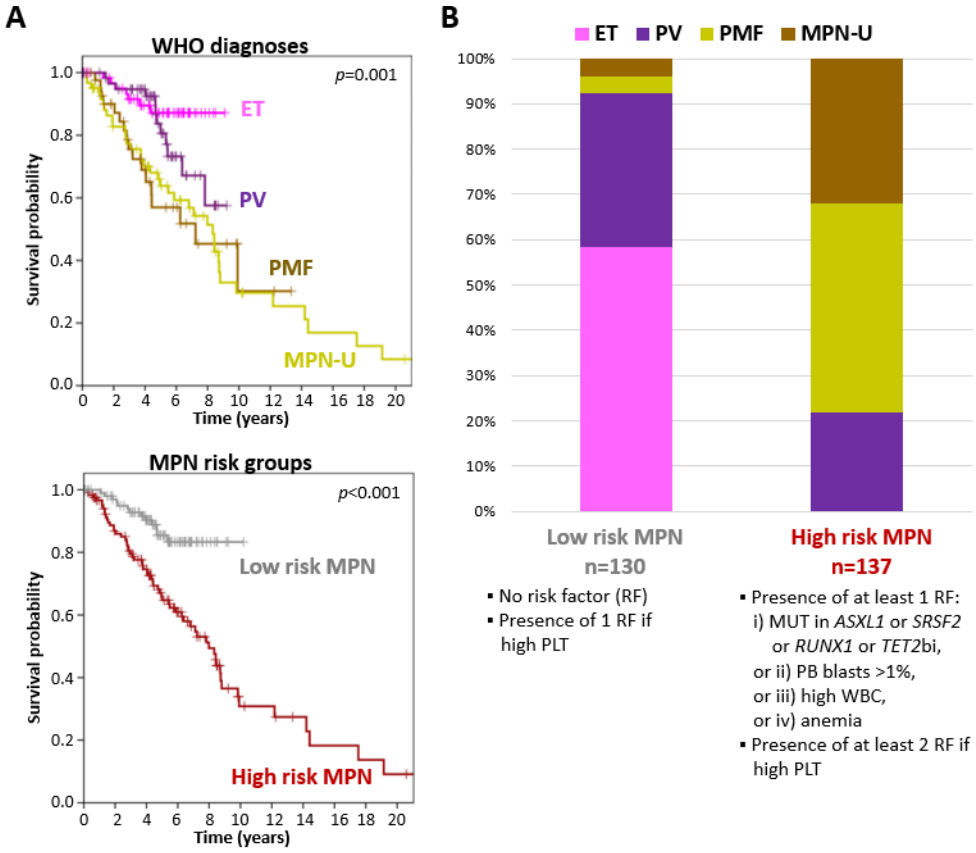

Figure 1 (A) Overall survival (OS) analyses of *JAK2*, *CALR* or *MPL* mutated Philadelphia-negative MPN stratified for WHO diagnoses and MPN risk groups. Median OS: ET (n=76)/ PV (n=74): not reached, PMF (n=68): 8 years, MPN-U (n=49): 7 years; low risk MPN (n=130): not reached; high risk MPN (n=137): 8 years. **(B)** Distribution of WHO diagnoses within low risk and high risk MPN. Inclusion criteria for the different risk groups are described below columns.

Figure 1

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