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POSTER ABSTRACTS

503.CLONAL HEMATOPOIESIS, AGING AND INFLAMMATION

Mutational Profile and Dynamics of *PPM1D*-Mutant Clones in the Spectrum of Myeloid Disorders

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Introduction

Mutations in *PPM1D* a regulator of DNA damage response, are enriched in patients with clonal hematopoiesis (CH) exposed to cytotoxic treatment or with therapy-related myeloid neoplasm. However, their role in leukemic transformation is unclear. Here, we describe a large cohort of patients with *PPM1D* mutations from CH to acute myeloid leukemia (AML) to understand the molecular landscape of mutant *PPM1D* related disease and the longitudinal dynamics of CH under treatment.

Methods

We included, in a non-sequential cohort, 96 *PPM1D* mutated patients treated at Gustave Roussy with CH, clonal cytopenia of unknown significance (CCUS), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN) or AML. A 77 gene panel NGS analysis was performed. An additional 16 *PPM1D* mutated AML patients from ALFA trials (1200, 0701,0702) were included. 10 patients with ovarian cancer from this cohort had sequential blood samples (OvBIOMark trial) available prior to hematologic evaluation, from the diagnosis or first relapse of their cancer through the course of therapy. Those samples were analyzed with a UMI based 18 gene panel (HaloplexHS, Agilent). Overall survival (OS) analyses were performed with the Kaplan-Meier method from the time of diagnosis until death from any cause.

Results

Among the 112 patients with *PPM1D* mutations, 23 (21%) had CH, 36 (32%) CCUS, 19 (17%) MDS, 25 (22%) AML (including 4 relapses), and 9 (8%) MPN. Median age was 65 [range, 21-88] years with 67% of females. Only 18% of the patients had no previous cancer history. Most frequent primary cancers were gynecological cancer (27%), lymphoid malignancies (22%), and breast cancer (17%). Median time between primary cancer diagnosis and hematologic assessment was 5.3 [range, 1.2-8.5] years.

Eighty six percent of patients had one *PPM1D* mutation, 9% had 2, and 5% had 3 or more (restricted to CH and CCUS). Median variant allele frequency (VAF) was 3% [0.2-38], 3% [1-31], 2.4% [1-41], 23% [1-50], and 4% [1-42] in CH, CCUS, MDS, AML and MPN, respectively. Among CH/CCUS patients, *PPM1D* was the sole detected somatic mutation in 39% (23/59), compared to 9% (5/53) in MDS/AML/MPN patients (odds ratio=6, p=0.0004); 3/5 of the latter had complex karyotype. The most frequently co-mutated genes were *DNMT3A* (29%) and *TP53* (25%), uniformly across all conditions (**Fig 1A**). MDS-related gene mutations, *RUNX1 (7%)*, *ASXL1* (4%), *SF3B1 (4%)*, *SRSF2 (4%)*, *U2AF1 (4%)*, were specific to AML/MDS/MPN. Among 28 patients with both *PPM1D* and *TP53* mutations, *PPM1D* mutations were dominant or co-dominant in 64% (18/28), and secondary in 36% (10/28). IPSS-M risk of evaluable MDS was high/very high in 54% (7/13) of patients. ELN 2022 classification of AML was adverse in 68% (17/25) of patients. AML treatment options included best supportive care for 8% of patients (2), 5-Azacytidine for 32% (8), intensive chemotherapy for 60% (15).

With a median follow up of 2.4 years, the median OS was 4.6 (CI95%; 4.1-NA), 1.31 (CI95%; 0.53-NA), 1.27 (0.43-NA), 0.66 (CI95%; 0.42-1.26) and 20.4 (CI95%; 20.4-NA) years for CH, CCUS, MDS, AML and MPN, respectively. *TP53* mutation status did not stratify OS. Four ovarian cancer patients with CH/CCUS transformed to MDS/AML with a median of 5.3 [1-12] years. At transformation, 3/4 had a stable *PPM1D* mutation, 1/4 an increase in *PPM1D* VAF (2 to 28%), and 3/4 had *TP53* mutations before and at transformation.

We analyzed 67 timepoints from 10 ovarian cancer patients during therapy (median 7 per patient). 10/10 received alkylating agents and 5/10 PARPi. The median number of mutations per patient was 4 and 6 at baseline and last follow-up, respectively. *PPM1D*-mutated clone size increased from 0.4% [0.1-3] at baseline to 7% [2-30] at last follow-up. Beyond clonal expansion, *PPM1D* VAF dynamics showed non-linear changes related to alkylating agents exposure: 2/10 patients had a continuous expansion, 2/10 had expansion then contraction (GR-1/3, **Fig 1B**), and 6/10 had expansion then stabilization (GR-2, **Fig 1B**).

Conclusion

We described a large cohort of *PPM1D* mutated patients from CH to AML. Their prognosis was poor independently of *TP53* mutation at AML/MDS stage. *PPM1D* mutations were frequently part of the dominant clone. To confirm the clonal architecture, single cell sequencing analysis in 8 AML/MDS patients are ongoing. Trajectory of *PPM1D* mutations in ovarian cancer patients revealed a non-linear alkylating agent dependency which warrants further investigation.

Disclosures Heiblig: *Jazz Pharmaceuticals:* Honoraria; *Pfizer Inc.:* Honoraria; *AbbVie:* Honoraria; *Astellas:* Honoraria; *Servier:* Honoraria. **Meunier:** *Pfizer, Novartis, Alexion:* Honoraria. **Pautas:** *AbbVie:* Honoraria; *Bristol Meyers Squibb:* Honoraria. **Dumas:** *Jazz pharmaceutical:* Honoraria; *Astellas:* Honoraria, Other: Research support for institution; *Abbvie:* Honoraria; *BMS:* Honoraria, Other: Research support for institution; *Servier:* Honoraria, Other: Research support for institution; *Novartis:* Honoraria, Other: Research support for institution; *Daiichi-Sankyo:* Honoraria, Other: Research support for institution; *Janssen:* Honoraria; *Roche:* Other: Research support for institution. **Itzykson:** *Servier:* Honoraria; *Jazz Pharma:* Honoraria, Research Funding; *Novartis:* Honoraria; *Abbvie:* Honoraria, Research Funding; *Gilead:* Honoraria, Research Funding. **Dombret:** *Astellas:* Research Funding; *Celegene:* Research Funding; *Servier:* Other: Advisory board, Research Funding; *Pfizer:* Research Funding; *Jazz Pharmaceuticals:* Other: Advisory board, Research Funding; *Incyte:* Honoraria, Other: Support for attending meetings and/or travel, Advisory board. **Bernard:** *PFIZER:* Speakers Bureau. **Micol:** *Servier:* Honoraria; *JazzPharmaceuticals:* Honoraria; *Abbvie:* Honoraria; *Gilead:* Honoraria.

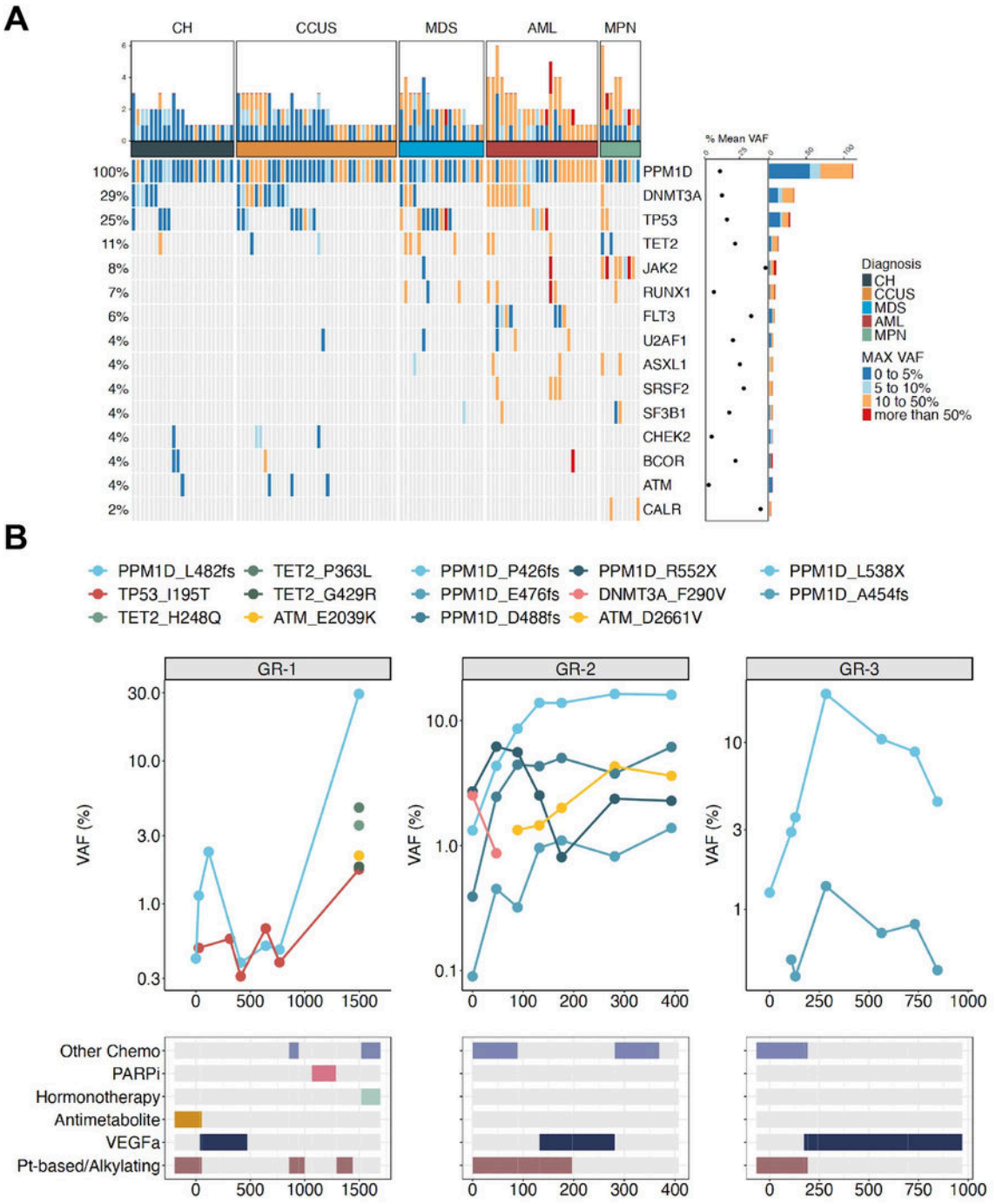

Figure 1. A. Oncoplot of the 112 included patients grouped by diagnostic category **B.** Panel of 3 patients with sequential UMI-sequencing showing evolution of mutations of which VAF surpasses 1% in at least one time point. Duration of treatment with different pharmacological categories is shown below revealing a treatment dependency of PPM1D-mutant clonal expansion. PARPi: PARP inhibitor. Pt: Platinum.

Figure 1

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