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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Novel Gene Mutations Associated with Disease-Free Survival in Elderly Patients with Acute Myeloid Leukemia Receiving First-Line Induction-Consolidation with or without Azacitidine Post-Remission Treatment

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Background: The achievement of complete remission (CR) is an important milestone for patients with acute myeloid leukemia (AML) undergoing curative-intent therapy. However, patients who achieve CR with induction therapy for AML will relapse within months. Therefore, research is focused on prolonging leukemia-free survival (DFS). We have recently reported on the randomized phase III study to compare the efficacy and safety of azacitidine (AZA) versus best supportive care (BSC) for treatment of AML in elderly patients who achieved first CR after a homogeneous intensive induction and consolidation phase (QoLESS AZA-AMLE, Oliva et al. Cancers 2023). At 2 and 5 years, DFS was 6.0 (95% CI:0.2-11.7) months in the BSC arm vs. 10.8 (95% CI:1.9-19.6 p=0.23) months in the AZA arm. We report on the ancillary translational study (QOL-ONE Trans-2) to evaluate biological changes in bone marrow samples through Next Generation Sequencing (NGS).
Objective: In patients enrolled in the trial who reached CR and were randomized to receive AZA or BSC, the endpoint of the present study was to evaluate the effect modification by gene mutations at AML diagnosis on the relationship between treatment allocation and relapse (disease-free survival, DFS).

Methods: The study was performed on available biological samples collected at baseline, randomization, and 6-month post remission. DNA was subjected to high throughput NGS using genes commonly mutated in myeloid malignancies and prepared with a home-set of 350 genes for Illumina (University of Kyoto, Japan) for all subjects with available vials. Only variants with high-quality reads, were considered. A Variant Allele Frequency (VAF) $\geq$ 4% was considered an appropriate threshold for minimal burden of clonality to be reported.

Results: Samples were available for 24 patients, 12 males, of median age 71 (65-74) years, 11 allocated in AZA arm and 13 in BSC arm. At diagnosis, mutations were detected in all patients with a range of 5 to 17 (median 10) simultaneous mutations, the most frequent being DNMT3A (42%), NPM1 (33%) and TET2 (33%). The most frequently mutated genes at diagnosis are represented in the figure. Only FANCA gene, mutated in 4 patients was associated with a hazard risk (HR) 4.96 (95% CI 1.34 - 18.35; p=0.02) of relapse and, interestingly, HLA-A, which was mutated in 7 patients, was associated with a HR 0.277 (95% CI 0.08 - 0.95; p=0.049). Patients with HLA-A mutation had a significantly longer survival (Figure 2). Three HLA-A mutated patients were allocated in 5-Aza arm and 4 in BSC arm. In a multivariate COX model, the effect of baseline HLA-A mutation on DFS is independent of the allocation arm (P=0.041). HLA Class I and Class II alleles were assessed based on the Luminex xMAP technology: for all cases, the HLA-SNPs are located on chromosome 6 in exon 2, 3 and 4 within protein-codifying sequences.

Conclusions: HLA gene mutations are not usually investigated for diagnostic or prognostic purposes in AML. The extensive 350-gene panel used in this study included HLA genes and has revealed a possible favorable role of HLA-A polimorphisms for the prognosis of elderly patients with AML undergoing intensive chemotherapy. Further specific HLA NGS analyses are undergoing to determine whether this concerns genuine somatic mutations. The present finding is worthy of further investigation to confirm its value in prognosis and its therapeutic implications.

Disclosures Oliva: *Daiichi:* Consultancy, Honoraria; *Novartis:* Honoraria, Speakers Bureau; *Alexion:* Consultancy, Honoraria, Speakers Bureau; *Janssen:* Consultancy, Honoraria; *Ryvu:* Consultancy, Honoraria; *Grande Ospedale Metropolitano BMM:* Current Employment; *Bristol Myers Squibb:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Honoraria, Speakers Bureau; *Sobi:* Honoraria, Speakers Bureau; *Servier:* Patents & Royalties. **Candoni:** *Servier, Astellas, Janssen, Incyte:* Membership on an entity's Board of Directors or advisory committees; *Pfizer, Astellas, Servier, Abbvie, Incyte, Bristol, Janssen:* Honoraria; *Bristol:* Honoraria; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Palumbo:** *BMS:* Consultancy, Honoraria, Speakers Bureau; *ASTRA ZENECA:* Consultancy, Honoraria; *GSK:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Speakers Bureau; *MorphoSys:* Consultancy, Honoraria; *ABBVIE:* Consultancy, Honoraria, Speakers Bureau. **Reda:** *BeiGene:* Consultancy; *Astrazeneca:* Consultancy, Current Employment; *AbbVie:* Consultancy; *Jannsen:* Consultancy. **Tripepi:** *ABBVIE:* Consultancy; *ABIOGEN:* Consultancy; *Janssen-Cilag:* Consultancy; *ALEXION:* Consultancy. **Alati:** *AbbVie:* Honoraria; *Jazz:* Honoraria. **Musto:** *BeiGene:* Research Funding; *Sanofi:* Research Funding; *Roche:* Research Funding; *Novartis:* Research Funding; *Abbvie:* Research Funding; *Takeda:* Research Funding; *BMS:* Research Funding; *Janssen:* Research Funding; *Amgen:* Research Funding. **Nannya:** *Otsuka Pharamaceuticals:* Consultancy; *Daiichi Sankyo Novare:* Research Funding; *Takeda:* Speakers Bureau; *Pfizer:* Speakers Bureau; *Chugai Pharmaceutical:* Speakers Bureau; *Dainippon Sumitomo pharma:* Speakers Bureau; *Astra Zeneca:* Speakers Bureau; *Novartis:* Speakers Bureau; *Fuji Pharma:* Speakers Bureau; *Kyowa Kirin:* Speakers Bureau; *Nippon Shinyaku:* Speakers Bureau; *Janssen Pharma:* Speakers Bureau; *Bristol Meyers Squibb:* Speakers Bureau; *MSD:* Speakers Bureau; *AbbVie:* Speakers Bureau.

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Figure 1. Mutated genes at diagnosis

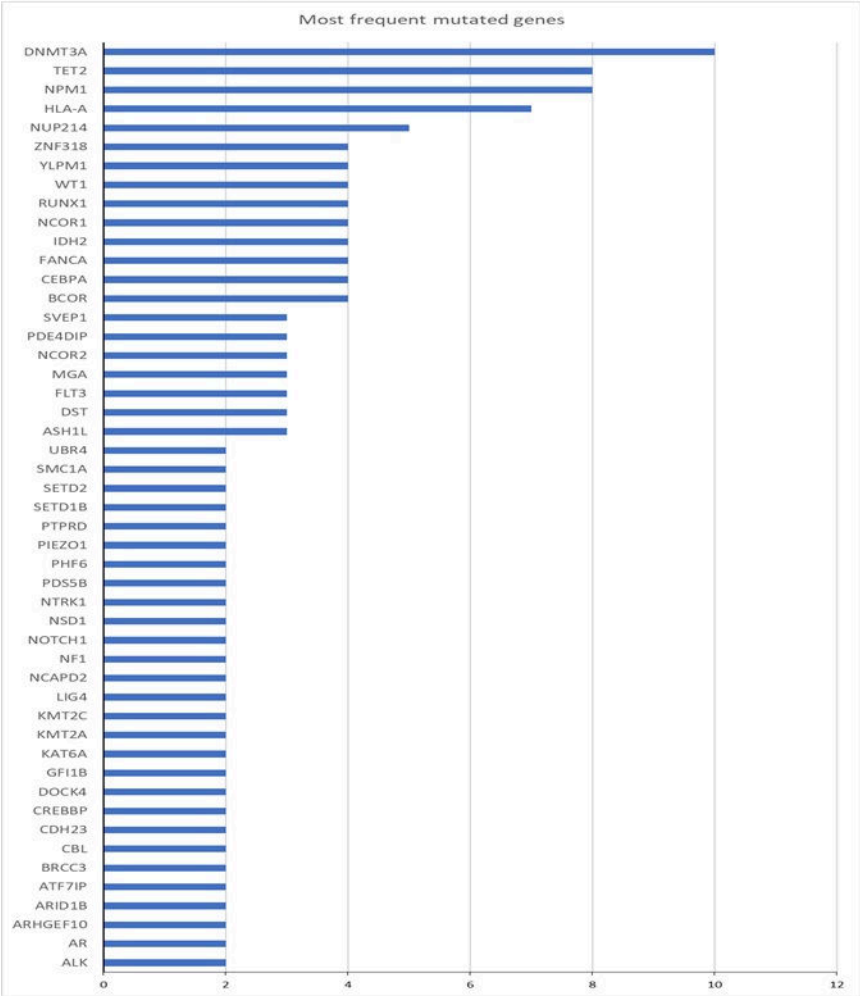

Figure 2. Kaplan-Meier analysis of DFS according to HLA-A mutation status at diagnosis

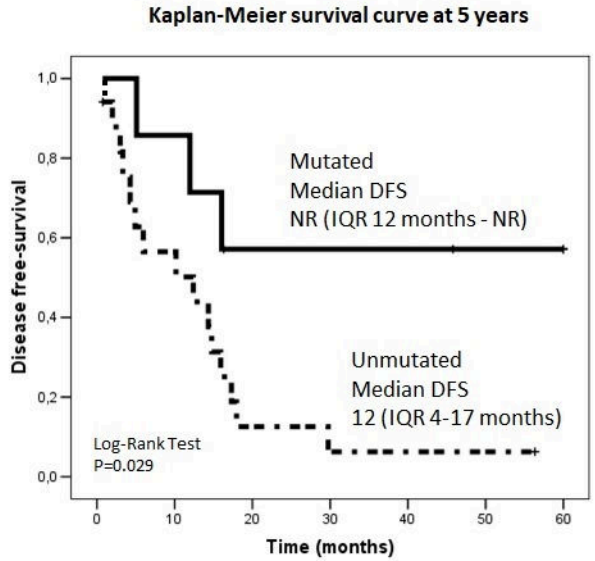

Figure 1