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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Venetoclax and Azacitidine for Molecular Relapse during First Line Intensive Chemotherapy in Patients with *NPM1* Mutated or Core Binding Factor (CBF) AML. a Study from the Dataml Registry

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Introduction: Molecular follow-up (FU) for AML patients (pts) with *NPM1* mutation, *RUNX1::RUNX1T1* or *CBFB::MYH11* fusion transcripts has been established over the last ten years. Real-time quantitative PCR (qPCR) is the gold standard for the evaluation of measurable residual disease (MRD) in pts undergoing intensive chemotherapy (IC). Failure to achieve a deep molecular response is a strong predictive factor of relapse and survival and may guide post remission therapy (Ivey A, NEJM 2016). Moreover, the ELN MRD working party recommended a schedule for molecular FU and recently established a definition of molecular relapse (Heuser M, Blood 2021). However, there is no therapeutic consensus for pts with molecular relapse before overt clinical relapse. Frontline allogeneic hematopoietic cell transplantation (alloHCT), salvage IC or even waiting for morphological relapse in order to screen molecular characteristics of the relapsing disease or propose a clinical trial, may be discussed with pts. Venetoclax with azacitidine (VEN/AZA) was recently approved in unfit AML pts and demonstrated a particular efficacy in *NPM1*-mutated AML. In this study, we thought to describe the safety and efficacy of VEN/AZA in pts with *NPM1* mutated or CBF AML in molecular relapse after first line IC.
Methods: Pts of the DATAML registry with the following criteria were included in this study : AML with *NPM1* mutation, *RUNX1::RUNX1T1* or *CBFB::MYH11* transcripts, first line IC, morphological complete remission (CR), no alloHCT in first line, regular monitoring of MRD by qPCR in bone marrow (BM) and/or blood, molecular relapse defined according to ELN2021 guidelines on two successive samples, at least one cycle of VEN/AZA. Pts with molecular relapse followed by morphological relapse before VEN/AZA or those who relapsed after alloHCT were not included.
Treatment: First line IC was cytarabine 200 mg/m² d1-7 with idarubicin 9mg/m²/d1-5 or daunorubicin 90mg/m²/d1-3 in pts 18-60y or cytarabine 100 mg/m² d1-7 with idarubicin 8mg/m²/d1-5 and lomustine 200 mg/m²/d1 in pts > 60y. Post remission therapy was intermediate or high dose cytarabine or mini-consolidations according to age and performance status. Midostaurin was added in FLT3-mutated pts. At time of molecular relapse, pts received off label venetoclax 400 mg/d (d1-14, d1-21 or

d1-28 according to centers) with no ramp-up and azacitidine 75 mg/m²/d subcutaneously (d1-5, d8-9). Antifungal/antibiotic prophylaxis and G-CSF use were not systematically recommended.

Results: Twenty-two pts treated with VEN/AZAfrom 21/09/2020 to30/03/2023 were included. Their characteristics at diagnosis were: female (n= 14), median age 55y (range 27-71), de novo AML (n=21), median WBC (68 giga/L, range 2.32-339.7), *NPM1* mutation (n=20), *CBFB::MYH11* (n=2), *FLT3* mutation (n=13). All pts achieved first CR after one cycle of induction chemotherapy. Pts received a median of three consolidation cycles. All but three pts had negative MRD or low level MRD (LL-MRD) in blood and/or BM at the end of consolidation. The median time between CR1 and molecular relapse was 9.5 months (range, 1-50). The median time between molecular relapse and first VEN/AZA cycle was 51 days. During first cycle of VEN/AZA, 12, 5 and 5 pts received 14, 21 or 28 days venetoclax, respectively; 19 were treated as out-pts, 4 received posaconazole and GCSF was used in 11 pts. 12 and 3 pts had grade 3-4 neutropenia or febrile neutropenia (FN), respectively. Only 3 pts (14%) were hospitalized for FN. The median number of VEN/AZA cycles was 2 (range 1-12). After C1+/-C2, 10 (45%) and 11 pts (55%) had undetectable or LL MRD in blood, respectively (Fig1). 20 pts were bridged to alloHCT in morphological CR after a median of 2 cycles (range, 1-4). Only one pt had a molecular progression before transplantation after 2 cycles. Two pts died, one had a molecular relapse after 7 cycles and progress rapidly to frank relapse, the other one died of post-transplant complication while in CR with undetectable MRD. All other pts remained in CR at date of last news. With a median FU from D1C1 of 13.5 months, median OS wat not reached and 1y-OS was 86% (Fig2).

Conclusion: In the setting of molecular relapse, VEN/AZA is safe, prevent overt relapse, and induce a high rate of molecular response before alloHCT. Molecular relapse becomes a major therapeutic challenge. Clinical trial endpoints should include the treatment of molecular relapse as an event for RFS and EFS estimation.

Disclosures Dumas: *Novartis:* Honoraria, Other: Research support for institution; *Servier:* Honoraria, Other: Research support for institution; *BMS:* Honoraria, Other: Research support for institution; *Abbvie:* Honoraria; *Astellas:* Honoraria, Other: Research support for institution; *Daiichi-Sankyo:* Honoraria, Other: Research support for institution; *Jazz pharmaceutical:* Honoraria; *Janssen:* Honoraria; *Roche:* Other: Research support for institution. **Forcade:** *Alexion:* Other: Travel support, Speakers Bureau; *Novartis:* Consultancy, Other: Travel support, Speakers Bureau; *Astellas:* Speakers Bureau; *Gilead Sciences:* Other: Travel support, Speakers Bureau; *GSK:* Speakers Bureau; *Sanofi:* Speakers Bureau; *MSD:* Other: Travel support. **Bertoli:** *Astellas:* Honoraria; *BMS-Celgene:* Honoraria; *Abbvie:* Honoraria, Other: Travel; *Servier:* Honoraria; *Novartis:* Honoraria; *Jazz Pharmaceuticals:* Honoraria, Other: Travel. **Pigneux:** *Jazz Pharmaceuticals:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Gilead:* Honoraria; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings; *Servier:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Support for attending meetings, Research Funding; *Roche:* Research Funding; *BMS:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Astellas:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Honoraria; *Pfizer:* Membership on an entity's Board of Directors or advisory committees. **Recher:** *Jazz Pharmaceuticals:* Other: Personal fees, Research Funding; *Novartis:* Other: Personal fees; *Astellas:* Other: Personal fees; *BMS:* Other: Personal fees, Research Funding; *Amgen:* Research Funding; *Abbvie:* Honoraria; *Servier:* Other: Personal fees; *MaatPharma:* Research Funding; *IQVIA:* Research Funding; *Takeda:* Other: Personal fees.

OffLabel Disclosure: Venetoclax is not allowed for AML molecular relapse

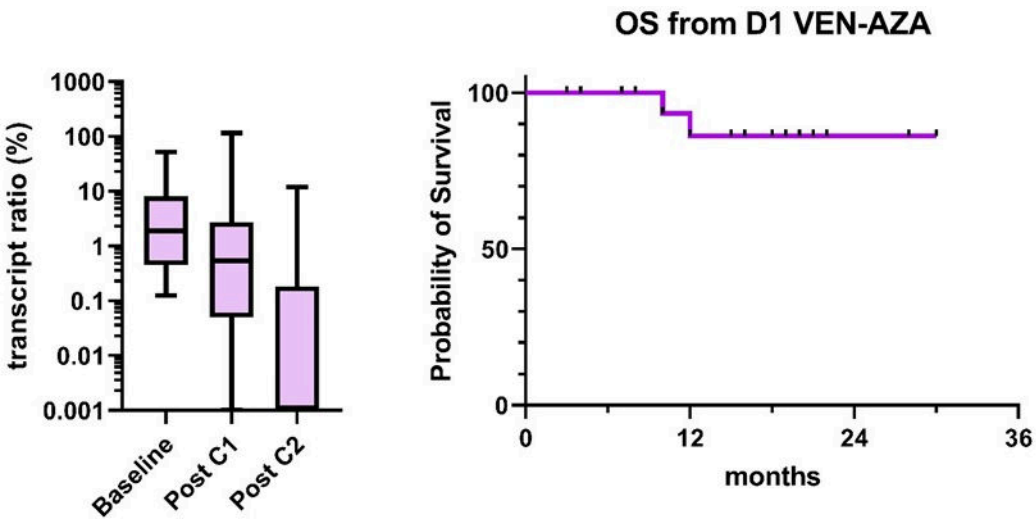

Figure 1

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