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Venetoclax and azacitidine for molecular relapse after intensive chemotherapy in NPM1 or CBF AML: a FILO study

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Dear Editor,

In acute myeloid leukemia (AML), molecular response assessment and sequential follow-up by real-time quantitative PCR (RT-qPCR) during remission are routinely used in patients with *NPM1* mutations (*NPM1*^{mut}), *RUNX1::RUNX1T1*, or *CBFB::MYH11* transcripts [1, 2]. Even though patients who achieve complete molecular response have a better prognostic and can be cured without transplantation, they should be closely monitored according to ELN MRD guidelines since up to 30% of them may present MRD relapse (MRD_{Rel}) [3]. Recent retrospective studies showed that *NPM1*^{mut} or CBF-AML patients who received preemptive therapy at time of MRD_{Rel} had a better overall survival (OS) than those treated for morphologic relapse [4, 5]. However, there is no consensus on the best treatment approach in this situation. Preliminary studies have shown promising results with venetoclax–based low intensity therapies for both molecular failure and MRD_{Rel} in *NPM1*^{mut} and *CBFB::MYH11* AML [6–8].

Patients with *NPM1*^{mut} or CBF-AML who received VEN-AZA for MRD_{Rel} between February 2020 and October 2024 were retrospectively identified from 10 French Innovative Leukemia Organization (FILO) centers. MRD monitoring by RT-qPCR in blood (PB) or bone marrow (BM) samples (*RUNX1::RUNXT1*, *CBFB::MYH1* or *NPM1* mutations) during first-line chemotherapy and follow-up is standard-of-care since the CBF-2006 and BIG-1 trials [9, 10]. All MRD_{Rel} were confirmed on a second sample (day of first sample was used to define the date of MRD_{Rel}). Inclusion criteria were: age ≥18 years, first morphologic CR with negative MRD or MRD-LL (<2%) during first line chemotherapy, no previous allo-HSCT, MRD_{Rel} according to ELN criteria [2, 11], at least 1 cycle of VEN-AZA for MRD_{Rel}. Patients received off-label venetoclax 400 mg/d (d1-7, d1-14, d1-21 or d1-28 according to centers) without ramp-up and azacitidine 75 mg/m^2/d subcutaneously (d1-7 or d1-5, d8-9).

Assessment of MRD responses was performed locally and response definitions followed those published by Jimenez-Chillon et al. : MRD negativity, MRD reduction for reduction ≥1log_{10} from pre-treatment value, MRD progression for increase ≥1log_{10} from pre-treatment value, and stable MRD for patients not meeting any of these previous criteria [7].

Morphologic relapse was defined according to ELN criteria. OS was measured from the date of MRD_{Rel} to the date of death from any cause. Relapse-free Survival (RFS) was measured from the date of MRD_{Rel}, to the date of morphologic relapse or death of any cause. RFS_{MRD} was measured from the date of MRD_{Rel} to the date of morphologic relapse, second MRD_{Rel} (for patients achieving MRD negativity or MRD reduction after VEN-AZA) or death from any cause. In accordance with the Declaration of Helsinki, the study was approved by the research ethics committee at Toulouse University Hospital. Because of the retrospective nature of our study, informed consent was waived according to national regulations.

Seventy patients were included (Supplementary Table 1). Most patients had *NPM1* mutations and only four patients had CBF-AML. All patients achieved best molecular response of CR_{MRD-} ($n = 44$) or CR_{MRD-LL} ($n = 26$) during first-line treatment according to the ELN criteria [11]. The median time between diagnosis and MRD_{Rel} was 10 months (IQR 8-15; min-max 2-51).

The median time between MRD_{Rel} and first VEN-AZA cycle was 48 days (IQR 32-71; min-max 6-526). Most patients (77%) received the first cycle as outpatient (Supplementary Table 2). Fifteen patients (21%) received posaconazole prophylaxis and 28 (42%) patients received G-CSF. Patients received a median of 2 cycles (IQR 2-3.8; min-max 1-28). During cycle 1, the duration of VEN treatment was 7, 14, 21, and 28 days in 2 (3%), 30 (43%), 15 (21.5%) and 22 (31.5%) patients, respectively. Six (9%) and seven (10%) patients had red blood cell or platelet transfusions. Grade 3-4 neutropenia was observed in 36 patients (52%) but only 11 patients (16%) presented febrile neutropenia. Neutropenia was not associated with duration of VEN treatment (Supplementary Table 2). There was no early death at day-60.

Among the 64 patients evaluated in PB after one or two VEN-AZA cycles, 27 (42%), 16 (25%) and 14 (22%) achieved MRD negativity, MRD reduction or stable MRD respectively. Of the 44 patients evaluated in BM after one or two VEN-AZA cycles, 12 (27%), 20 (46%), and 5 (11%) achieved MRD negativity, MRD reduction or stable MRD respectively (Table 1). Response rates were consistent between *NPM1*^{mut} patients with ($n = 31$) or without ($n = 35$) *FLT3*-ITD or *N/KRAS* mutations (Table 1). At last news, 58 patients (83%) were still in morphologic CR including 52 patients (74%) with negative MRD. With a median follow-up from MRD_{Rel} of 22.5 months (IQR 14.25-28), median OS was not reached with 1y- and 2y-OS of 95% and 83%, respectively (Fig. 1A). Median RFS and RFS_{MRD} were not reached, with 1y- and 2y-RFS of 82% and 71%, and 1y- and 2y-RFS_{MRD} of 73% and 62% (Supplementary Figure 1).

Morphologic relapse was documented in 14 patients (20%) including 2 pre-transplant, 3 post-transplant, and 9 in non-transplanted patients. The two patients with pre-transplant relapses were salvaged with etoposide-amsacrin or gilteritinib, then transplanted and achieved negative MRD. Targeted NGS analysis on available paired samples at diagnosis and morphologic relapse identified one patient with *NPM1*^{mut} loss and two patients with emergence of *BAX* mutations. We also observed two patients with *FLT3*-ITD loss or acquisition, and three patients with *FTL3*-TKD loss (Supplementary Table 3).

Fifty-four patients (77%) proceeded to allo-HSCT after a median of two VEN-AZA cycles (IQR 1-3). The median time between MRD_{Rel} or first VEN-AZA cycle and allo-HSCT was 138.5 days (IQR 112.3-189.5) and 94 days (IQR 66-109.8), respectively. Of the 48 evaluated patients, 34 (71%) achieved response in PB before transplantation, including 27 (56%) and 7 (15%) with MRD

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Table 1. MRD response after C1 +/− C2.

	All patients ($n = 70$)		*NPM1*^{mut} with *FLT3*-ITD and/or *N/KRAS*^{mut} ($n = 31$)		*NPM1*^{mut} without *FLT3*-ITD and *N/KRAS*^{mut} ($n = 35$)		VEN ≤14j ($n = 29$)		VEN>14j ($n = 31$)	
	Blood	BM	Blood	BM	Blood	BM	Blood	BM	Blood	BM
MRD negativity, *n* (%)	27 (42)	12 (27)	13 (48)	7 (35)	14 (43)	5 (24)	12 (44)	2 (12)	14 (50)	9 (38)
MRD reduction, *n* (%)	16 (25)	20 (46)	9 (33)	12 (60)	4 (12)	7 (33)	8 (30)	11 (69)	5 (18)	7 (29)
Stable MRD, *n* (%)	14 (22)	9 (20)	4 (15)	0 (0)	10 (30)	7 (33)	4 (15)	2 (13)	6 (21)	6 (25)
MRD progression, *n* (%)	7 (11)	3 (7)	1 (4)	1 (5)	5 (15)	2 (10)	3 (11)	1 (6)	3 (11)	2 (8)
Not evaluated, *n*	6	26	4	11	2	14	2	13	3	7

Evaluation is given as the most recent available among the 55 patients who completed C1 + C2 and the 15 patients who completed C1 only. Patients with dose modification between C1 and C2 ($n = 10$) were not considered for comparison according to the dose.

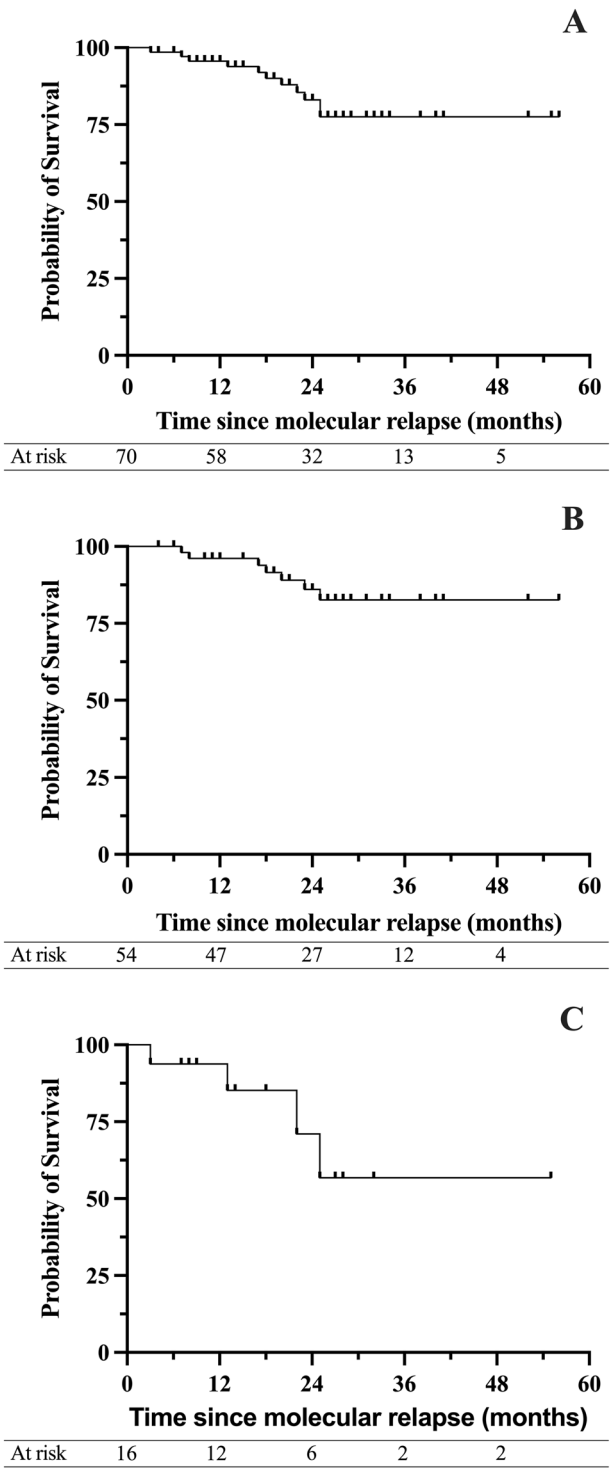

Fig. 1 Survival outcomes. Overall survival since molecular relapse in the whole cohort (**A**), in transplanted (**B**) and non-transplanted patients (**C**).

negativity or MRD reduction respectively. Most patients ($n = 36$, 67%) received reduced-intensity conditioning regimen mainly from unrelated donors (Supplementary Table 4). At last news, 47 were alive, including 46 (98%) with morphologic CR and 41 (87%) with negative MRD whereas 7 patients died including 4 deaths while in CR because of infection and/or graft versus host disease, and 3 after morphologic relapse. With a median follow up of 23.5 months (IQR 18-31.5), median OS was not reached with 1-y

and 2y-OS of 96% and 86%, respectively (Fig. 1B). The median RFS and RFS_{MRD} were not reached. 1-y and 2y-RFS was 88% and 81%, and 1-y and 2y-RFS_{MRD} was 83% and 74% respectively (Supplementary Figure 1).

The 16 patients who did not proceed to allo-HSCT received a median of 9 VEN-AZA cycles (IQR 7-14). The reasons for not proceeding to allo-HSCT were comorbidities or age ($n = 11$), donor availability ($n = 2$), refusal ($n = 1$), or disease progression ($n = 2$). During follow-up, 9/16 patients relapsed, and 7/16 were still in morphologic remission, including 6 (44%) with negative MRD. Two patients discontinued VEN-AZA after 8 and 14 cycles and maintained negative MRD with treatment-free survival of 29 and 9 months, respectively. With a median follow up of 13.5 months (IQR 8.8-25.5), median OS was not reached with 1-y and 2y-OS of 93% and 71%, respectively (Fig. 1C). The median RFS was 14 months with 1-y and 2y-RFS was 61% and 38%, respectively. The median RFS_{MRD} was 12 months with 1-y and 2 y RFS_{MRD} was 41% and 27% respectively (Supplementary Figure 1).

VEN-AZA treatment for molecular relapse is safe and effective in patients with *NPM1* mutations. As patients with molecular relapse have no disease-related symptoms, it was expected that general and hematological toxicity would be less pronounced than in the active phase of the disease [12]. Most patients achieved a second molecular response quickly and were therefore able to undergo transplantation in the best possible conditions (i.e., with optimal response and limited sequelae from salvage treatment toxicity).

This is the largest study evaluating VEN-AZA in the specific situation of ELN-defined molecular relapse during first line therapy in non-transplanted patients. Other recent studies have evaluated venetoclax-based combinations in oligoblastic relapses or molecular failure including molecular relapse, progression, or persistence. In the VALDAC prospective trial [12], 48 patients were enrolled including 22 oligoblastic relapse and 26 MRD_{Rel}, treated with low dose cytarabine (LDAC) and venetoclax. In the MRD relapse cohort, the rate of negative MRD was 55% in the 20 $NPM1^{mut}$ patients. In the retrospective study conducted by Jimenez-Chillon et al. [7]. 79 $NPM1^{mut}$ AML patients were treated with VEN-AZA or VEN-LDAC for molecular failure, including 34/43 patients (79%) with molecular relapse (i.e. conversion from MRD negativity to positivity confirmed on a second sample) who achieved negative MRD In these two studies, 2-year OS was 63% [12] and 67% [7] which, combined with our result (2-year OS, 82%), compares favorably with the outcome of $NPM1^{mut}$ AML patients treated with intensive chemotherapy for morphologic relapse [12, 13].

Our study has several limitations due to its retrospective, non-comparative nature, and the limited number of patients, especially CBF-AML patients. VEN was used off-label with a heterogeneous treatment duration and the timing of molecular evaluation was not pre-specified. Finally, patients who may have progressed rapidly from molecular to morphologic relapse were not included, so we were unable to assess the proportion of patients in this case. Nevertheless, our study contributes to provide benchmark data in a challenging clinical situation that needs to be prospectively studied.

In conclusion, VEN-AZA with its favorable efficacy/toxicity ratio appears to be a relevant therapeutic option for $NPM1^{mut}$ patients in first molecular relapse. Furthermore, our study illustrates a recent change in practice and supports the creation of new ELN 2022 evaluation criteria that now include molecular relapse as an event to be considered in the calculation of EFS and RFS.

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DATA AVAILABILITY

Requests for sharing deidentified data should be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

CR, JH, and CO contributed to the study conception and design. JH and CO conducted statistical analyses. JH and CR wrote the first draft of the manuscript. CO, PYD and SB helped write the manuscript. JH, CO, PYD, PP, MAH, SB, AC, MC, AC, ET, MC, ST, EF, PC, RD, GAR, and AP treated patients and participated in clinical data collection and assembly. ED, AB, AB, MJM, LV, CP, ST, PGG, SL participated in biological data assembly. All authors had full access to all the data in the study, contributed to writing the manuscript and provided final approval of the submitted version.

COMPETING INTERESTS

Sarah Bertoli declares a consulting or advisory role with Abbvie, Astellas, BMS-Celgene, Jazz Pharmaceuticals as well as Servier and received travel grants from Abbvie and Pfizer. Christian Récher declares a consulting or advisory role with Abbvie, Amgen, Astellas, BMS, Boehringer, Daiichi-Sankyo, Jazz Pharmaceuticals, Janssen and Servier, received research funding from Abbvie, Amgen, Astellas, BMS, Daiichi-Sankyo, Iqvia and Jazz Pharmaceuticals, and support for attending meetings and/or travel from Abbvie, Novartis and Servier. Arnaud Pigneux declares a consulting or advisory role with Astellas, BMS, Servier, Abbvie, Gilead, Jazz Pharmaceuticals, Novartis, Pfizer, received research funding from Astellas, BMS, Roche, Servier and support for attending meetings and/or travel from Servier, Abbvie. All other authors declare no competing interests.

ADDITIONAL INFORMATION

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