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Venetoclax and gilteritinib combination for *FLT3*-mutated relapsed/refractory acute myeloid leukemia: a real-world single-center experience

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Author contributions

Conceptualization, patient management, writing - original draft preparation, FM; methodology, patient management, case reporting, and writing FC, GC, LF, EQ, AP, JC; case reporting GM, RS; methodology, patient management MP, BS, GG; writing—review and editing, PG, AMV. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest Disclosures

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Data sharing

The data that support the findings of this study are available on request from the corresponding author.

To the editor

FLT3 inhibition is an important therapeutic option for *FLT3*-mutated (*FLT3*^{mut}) acute myeloid leukemia (AML). Gilteritinib is a highly selective FLT3 inhibitor with activity against both *FLT3* mutation subtypes (ITD and TKD)[1]. The multi-center, randomized ADMIRAL trial showed the superiority of gilteritinib over conventional chemotherapy in patients with relapsed/refractory (R/R) *FLT3*^{mut} AML[2]. In the pivotal trial, gilteritinib induced a higher composite complete remission (CCR, 54.3% vs 21.8%) and a longer overall survival (OS, 9.3 vs 5.6 months, HR=0.64) than conventional therapy[2], a figure confirmed at a longer follow-up[4] and in a large real-world dataset[5]. Remarkably, a higher percentage of patients were bridged to allogeneic stem cell transplant (HSCT) with gilteritinib (25.5% vs. 15.3%).

However, there are shortcomings of gilteritinib therapy to take into an account. First, the relatively long time to response, which was in median 2.3 months in the ADMIRAL trial[2], may be of concern particularly in the R/R *FLT3*^{mut} subset. Also, few patients achieved deep molecular responses[7], that in a post hoc analysis of the Chrysalis study accounted for 25% of the patients[8]. The selective mechanism of action could represent a further flaw in patients with a predictable lower addiction to FLT3-related pathways, as are those with unfavorable cytogenetic abnormalities[2,5] and/or low *FLT3*-ITD allelic ratios[4,9]. In this scenario, combining gilteritinib with other drugs might offer the chance to increase responses while maintaining acceptable toxicity. At this regard, based on preclinical data reporting synergy of venetoclax with FLT3 inhibitors[10], Daver *et al* reported high response rates in a phase Ib, multicenter study in R/R *FLT3*^{mut} AML using combination of gilteritinib and venetoclax (VenGilt)[11]. A recent observational study reported on 17 consecutive patients with R/R *FLT3*^{mut} AML treated with VenGilt approach, with findings supportive of additive effects with respect to gilteritinib monotherapy[12].

In this study, we report our experience on treating R/R *FLT3*^{mut} AML patients not qualifying for enrollment in clinical trials with VenGilt as off-label use. Of note, due to administrative issues in our country, all but one patient received previous gilteritinib monotherapy showing poor response and later added-on venetoclax. This sequential schedule is the main novelty of our experience and differs from the study by Daver *et al*, in which no patients have previously received gilteritinib and the two agents were started together[11]. Therefore, the addition of venetoclax in patients poorly responding to gilteritinib configures a strategy which might improve the management of R/R patients in a real-world setting. The study was approved by the local institutional review board (IRB: project MYNERVA, approval 14560). Written informed consent was obtained from study patients in accordance with the Declaration of Helsinki.

From November 2023 to December 2025, 12 R/R *FLT3*^{mut} patients received VenGilt. Individual patient characteristics are reported in Table S1, and the outcomes are depicted in Figure 1. The median age was 59 (range 18–78) years. ELN 2022 risk stratification at diagnosis was favourable in 3 (25.0%), intermediate in 6 (50.0%), and adverse in 3 (25.0%) patients. *NPM1* co-mutation was detected in 7 (58.3%) patients. All but one patient carried a *FLT3* mutation at disease onset, including one patient with *FLT3*-TKD. Patient # 11 was initially diagnosed with *NPM1*^{mut} / *FLT3*^{wt} AML and then experienced a relapse which resulted *FLT3*-ITD mutation positive five months after completing consolidation therapy. The median number of therapy lines before VenGilt was 3 (range 1-3). All patients had previously received gilteritinib monotherapy for a median of 42 days (range 28–616). Additionally, 7 (58.3%) patients had already been exposed to an FLT3 inhibitor, having received midostaurin in induction and consolidation therapy. Venetoclax was administered during the first cycle with a conventional 3-day dose ramp-up and was given for 28 (n=2), 21 (n=8) and 15 (n=2) days per cycle, based on clinical conditions and PB counts during treatment. Overall, venetoclax was administered for a median of 21 days per cycle (range 14–28) for a median of 1.5 cycles (range 1-8). Gilteritinib was administered continuously.

As regards response rates, a CCR was achieved in 8 patients (66.7%), including 5 CR and 3 CR with incomplete hematopoietic recovery (CRi). Measurable residual disease (MRD) negativity, assessed by molecular evaluation of *NPM1* and/or *FLT3*-ITD or by multiparameter flow cytometry, was achieved in 3 responding patients (37.5%). Moreover, among patients eligible for HSCT (n = 9), 7 (77.8%) proceeded to transplantation, of whom 5 were in CR. Three patients resumed gilteritinib after HSCT and remain alive in continuous CR. Median OS was not reached, with a median follow-up of 19.2 months (95% CI, 8.8–36.4).

At 30 and 60 days from VenGilt start, mortality rates were 8.3% and 16.7%, respectively, due to disease progression (n=2) and transplant-related mortality (n=1); notably, no deaths were attributed to treatment-related toxicities. In patients achieving a response, the median time to neutrophil and platelet recovery (ANC > 1,000/μL and platelets > 50,000/μL) was 16 days (range 0–68) and 22 days (range 0–67), respectively. No QTc prolongation was observed. No grade ≥3 adverse events were reported; two patients experienced grade 2 ALT elevation, seen in both gilteritinib monotherapy and VenGilt combination phase.

Notably, one patient (#3) experienced differentiation syndrome (DS) while on gilteritinib monotherapy, characterized by fever, weight gain, bilateral pleural and pericardial effusion and multiple lung consolidations (Figure S1A). Of note, the initiation of venetoclax on top of gilteritinib led to significant clinical improvement with complete resolution of chest findings by chest CT scan (Figure S1B), and further a more profound molecular response (Figure S1C).

No study has directly compared gilteritinib and VenGilt. Although no head-to-head comparison is available, some considerations on the putative advantages of VenGilt can be indirectly inferred by the selection criteria of the phase 1b study by Daver et al, certainly less stringent than in ADMIRAL trial[2,11]. Daver et al posed no limits to previous lines of therapy (almost 40% received 3 prior treatments), whereas ADMIRAL included patients only after first relapse/primary refractory disease. Furthermore, a higher proportion of patients had previously received FLT3 inhibitors (59%) with respect to ADMIRAL (13%)[2,11].

A potential pitfall of the combination is represented by a higher hematological toxicity compared to monotherapy, which might be modestly impacting in the context of a bridge-to-HSCT strategy. In this perspective, maximizing the anti-leukemic effect with VenGilt before transplant and reserving gilteritinib monotherapy for post-transplant maintenance might represent a rational approach, also considering its immunomodulatory action and good efficacy on prevention of relapse in MRD-positive patients, as demonstrated by results of the MORPHO trial[13].

With the limits of a small series, our data are consistent with previously published reports[11,12] and provide evidence that the addition of venetoclax enables profound responses even when applied in patients who had received gilteritinib single-agent for variable time exposures. In two of our cases, the addition of venetoclax to gilteritinib allowed the achievement of CR after previous exposure to azacitidine-venetoclax combination and gilteritinib monotherapy; although clear clinical implications can't be drawn, such findings are hypothesis-generating and deserve confirmation on larger series.

In terms of safety profile, a pattern of response with terminal differentiation of blasts was described with gilteritinib use[14], potentially leading to DS[15], three cases of which were reported in the long term follow up paper[4] and in Chrysalis study[14]. An additional challenge in DS recognition with respect to the classical DS observed in acute promyelocytic leukemia is that patients on gilteritinib are often managed in outpatient setting with possible diagnostic delay. As we observed in case #3, clinical manifestations were subtle, and only a-posteriori ascribed to a DS. Interestingly, the concomitant use of venetoclax appeared to taper the manifestation of DS, an effect potentially ascribed to more rapid pro-apoptotic activity of the combination, suggesting that the addition of venetoclax may offer additional clinical benefits.

In conclusion, the results from this real-world series highlight some of the challenges that may impact the use of treatment strategies with gilteritinib in R/R AML patients. Reported cases herein illustrate how the use of venetoclax on top of gilteritinib might offer the opportunity of achieving more profound responses, making it a potentially valuable bridging approach in HSCT eligible patients. The mitigation of differentiation syndrome by venetoclax that we observed in one patient is clinically plausible and hypothesis-generating, although no conclusions can be stated on a single case.

In our opinion, the combination approach may be particularly suitable in the pre-transplant setting, by optimizing disease control without adding substantial toxicity and with manageable hematologic toxicity. Further studies are warranted to substantiate efficacy and safety profile of this promising treatment combination.

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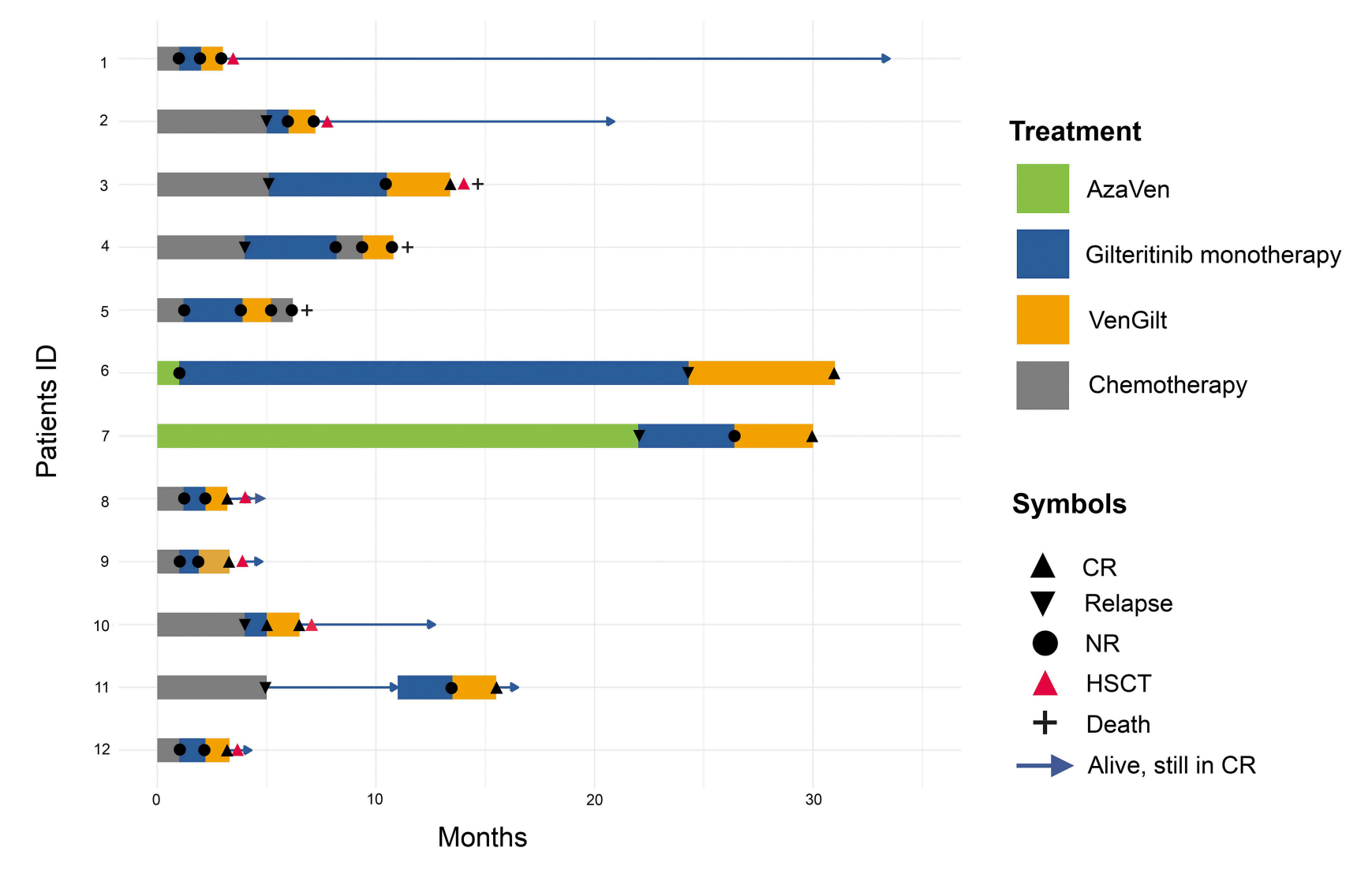
Figure legends

Figure 1. Swimmer plot illustrating treatment duration of gilteritinib monotherapy (blue) and combination venetoclax-gilteritinib (orange), response status, and follow-up for individual patients over time.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VenGilt
Chemotherapy
Symbols
CR
Relapse
NR
HSCT
Death
Alive, still in CR

Supplemental data

Figure S1.

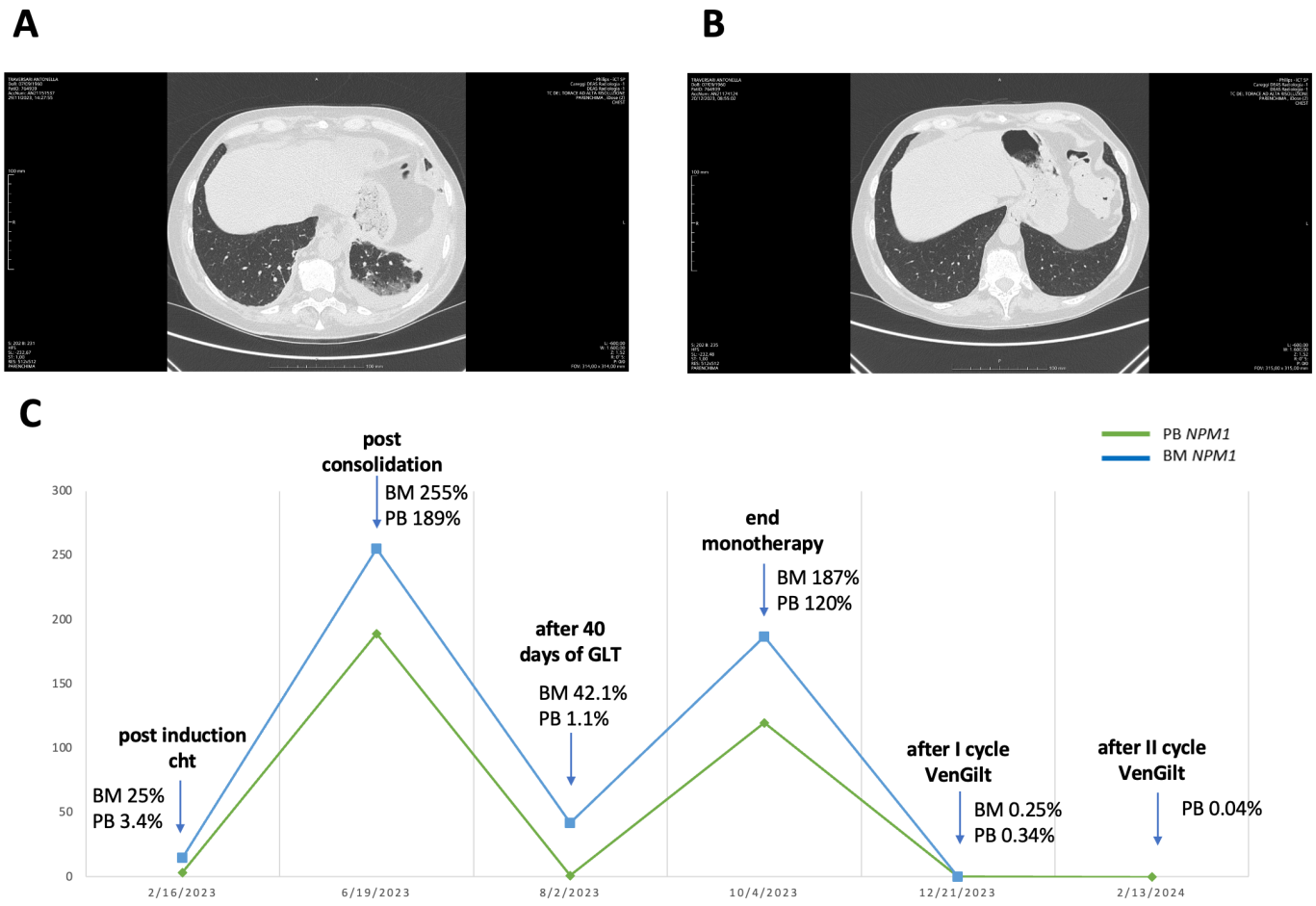

Figure S1. Visual summary of relevant clinical issues in patient # 3. (A) CT chest scans along with gilteritinib monotherapy (A), showing differentiation syndrome-related features (pulmonary infiltrates, pleural effusion), and (B) after the introduction of venetoclax, with resolution of imaging findings. (C) Trends of NPM1 transcript during treatment course. Cht, chemotherapy; Glt, gilteritinib monotherapy; VenGilt, venetoclax and gilteritinib combination; PB, peripheral blood; BM, bone marrow.

Table S1. Characteristics and outcome of patients.

Case n°	Gender	Age	Disease characteristics	Previous treatments	Response	Status
1	M	65 y	sAML Normal karyotype NGS: *ASXL1, PTPN11, SRSF2, STAG2* and *FLT3*-TKD (VAF 34%) mutations	1st line: CPX-351 2nd line: gilteritinib (1 cycle) 3rd line: gilteritinib + venetoclax (1 cycle) Bridged to HSCT with active disease	1st line: NR 2nd line: NR 3rd line: NR CR MFC-MRD negative after HSCT	Alive, still in CR
2	M	18 y	AML with *CEBPA* mutation Normal karyotype, NGS: *CEBPA*, *FLT3-ITD* (ratio 0.5) and *WT1* mutations	1st line: Induction (3+7), I consolidation (unknown), II consolidation (Ida-HDAraC) 2nd line: azacitidine + venetoclax (1 cycle) 3rd line: gilteritinib (1 cycle) 4th line: gilteritinib + venetoclax (2 cycles) Bridged to HSCT with active disease	1st line: CR, MFC-MRD positive Relapse during II consolidation 2nd line: NR 3rd line: NR 4th line: NR CR MFC-MRD negative after HSCT	Alive, still in CR
3	F	61 y	AML with *NPM1* mutation Normal karyotype NGS: *FLT3*-ITD (ratio 0.63), *TET2* and *DNMT3A* mutations	1st line: According to GIMEMA AML1919 protocol: Induction chemotherapy: 3+7+midostaurin Two consolidation cycles: HDAC + midostaurin 2nd line: gilteritinib (7 cycles) 3rd line: gilteritinib + venetoclax (3 cycles) Bridged to HSCT with MRD pos	1st line: CR, Mol-MRD positive Relapse during II consolidation 2nd line: NR 3rd line: CRi, MRD positive (*NPM1* 0.04% in BM)	Death due to septic shock and MOF after HSCT
4	F	49 y	AML with *NPM1* mutation Normal karyotype NGS: *FLT3*-ITD ITD (ratio 1), *DNMT3A, TET2* mutations	1st line: Induction (Ida-HDAraC), consolidation cycle (HDAC + midostaurin) 2nd line: gilteritinib (4 cycles) 3rd line: salvage chemotherapy (HAM) 4th line: gilteritinib + venetoclax (1 cycle)	1st line: CR, Mol-MRD positive Relapse during I consolidation 2nd line: NR 3rd line: NR 4th line: NR	Death due to septic shock

5	M	58 y	AML with *NPM1* mutation Normal karyotype NGS: *FLT3*-ITD ITD (ratio 0.19), *PTPN11, IKZ11* and *CBL* mutations	1st line: Induction (3+7+midostaurin) 2nd line: gilteritinib (3 cycles) 3rd line: gilteritinib + venetoclax (1 cycle) 4th line: salvage chemotherapy (HDAC)	1st line: NR 2nd line: NR 3rd line: NR 4th line: NR	Death due to septic shock
6	M	72 y	AML with *NPM1* mutation Normal karyotype NGS: *FLT3*-ITD (ratio 7) and *DNMT3A* mutations	1st line: azacitidine + venetoclax (1 cycle) 2nd line: gilteritinib (22 cycles) 3rd line: gilteritinib + venetoclax (8 cycles)	1st line: NR 2nd line: CR, Mol-MRD negative Molecular Relapse during Gilt 3rd line: CR, Mol-MRD negative	Alive, still in CR
7	F	78 y	AML Normal karyotype NGS: *FLT3*-ITD ITD (ratio 0.03), *ASXL1, STAG2* and *EZH2* mutations	1st line: azacitidine + venetoclax (17 cycles) 2nd line: gilteritinib (5 cycles) 3rd line: gilteritinib + venetoclax (6 cycles)	1st line: CR, MFC-MRD positive Relapse during AzaVen 2nd line: NR 3rd line: CR, MFC-MRD positive	Alive, still in CR
8	F	33 y	AML del7q; t (3;11) (MECOM-r) NGS: *FLT3*-ITD (ratio 0.88) and *SF3B1* mutations	1st line: According to GIMEMA AML1919 protocol: Induction chemotherapy: 3+7+midostaurin 2nd line: gilteritinib (1 cycle) 3rd line: gilteritinib + venetoclax (1 cycle) Bridged to HSCT in CR, Mol-MRD neg	1st line: PR 2nd line: PR 3rd line: CR, Mol-MRD negative	Alive, still in CR
9	F	40 y	AML Normal karyotype NGS: *FLT3*-ITD (ratio 0.88) mutation	1st line: According to GIMEMA AML1919 protocol: Induction chemotherapy: 3+7+midostaurin 2nd line: gilteritinib (1 cycle) 3rd line: gilteritinib + venetoclax (2 cycles) Bridged to HSCT in CR, Mol-MRD neg	1st line: NR 2nd line: NR 3rd line: CR, Mol-MRD negative	Alive, still in CR
10	M	53 y	AML with *NPM1* mutation Normal karyotype NGS: *CEBPA, DNMT3A* and *FLT3*-ITD (ratio 0.92) mutations.	1st line: According to GIMEMA AML1919 protocol: Induction chemotherapy: 3+7+midostaurin Two consolidation cycles: HDAC + midostaurin 2nd line: gilteritinib (1 cycle) 3rd line: gilteritinib + venetoclax (1 cycle) Bridged to HSCT in CR, Mol-MRD pos	1st line: CR, Mol-MRD positive Molecular Relapse during II consolidation 2nd line: CR, Mol-MRD positive	Alive, still in CR

					3rd line: CR, Mol-MRD positive	
11	F	63 y	AML with *NPM1* mutation Normal karyotype NGS: *DNMT3A, NF1* and *PHF6* mutations. positive *FLT3*-ITD (ratio 0.75) retesting at relapse	1st line: Induction (3+7) and 3 consolidations cycles (HDAC) 2nd line: gilteritinib (2 cycles) 3rd line: gilteritinib + venetoclax (2 cycles)	1st line: CR, Mol-MRD negative Relapse 5 months after III consolidation 2nd line: NR 3rd line: CRi, Mol-MRD positive	Alive, ongoing
12	F	60y	AML with *NPM1* mutation Normal karyotype NGS: *TET2, DNMT3A, GATA2* and *FLT3*-ITD (ratio 11.9) mutations.	1st line: According to GIMEMA AML1919 protocol: Induction chemotherapy: 3+7+midostaurin 2nd line: gilteritinib (1 cycle) 3rd line: gilteritinib + venetoclax (1 cycle) Bridged to HSCT in CRi, Mol-MRD positive	1st line: NR 2nd line: NR 3rd line: CRi, Mol-MRD positive	Alive, ongoing

Abbreviations: sAML, secondary to MDS; NGS, next generation sequencing; HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRi, complete remission with incomplete hematopoietic recovery; NR, no response; IdaHDAraC, Idarubicin, high dose cytarabine; HDAC, high dose cytarabine; Gilt, gilteritinib; AzaVen, azacitidine + venetoclax; MRD, measurable residual disease; Mol, by molecular assessment (PCR for *NPM1*, amplicon-based NGS assay for *FLT3*-ITD); MFC, multi-parameter flow cytometry; HAM, high dose cytarabine, mitoxantrone.