

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

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 (internal tandem duplication [ITD] and tyrosine kinase domain [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; hazard ratio [HR]=0.64) than conventional therapy,² a figure confirmed at a longer follow-up⁴ 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 a deep molecular response,⁷ which 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 response while maintaining acceptable toxicity. Hence, 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 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 (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 *Online Supplementary Table S1*, and the outcomes are depicted in Figure 1. The median age was 59 (range, 18–78) years. European LeukemiaNet (ELN) 2022 risk stratification at diagnosis was favorable in three (25.0%), intermediate in six (50.0%), and adverse in three (25.0%) patients. *NPM1* co-mutation was detected in seven (58.3%) patients. All but one patient carried an *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 5 months after completing consolidation therapy. The median number of therapy lines before VenGilt was three (range, 1–3). All patients had previously received gilteritinib monotherapy for a median of 42 days (range, 28–616). Additionally, seven (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 peripheral blood 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.

Regarding response rates, a CCR was achieved in eight patients (66.7%), including five CR and three 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 three responding patients (37.5%). Moreover, among patients eligible for HSCT (N=9), seven (77.8%) proceeded to transplantation, of whom five 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% confidence interval [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

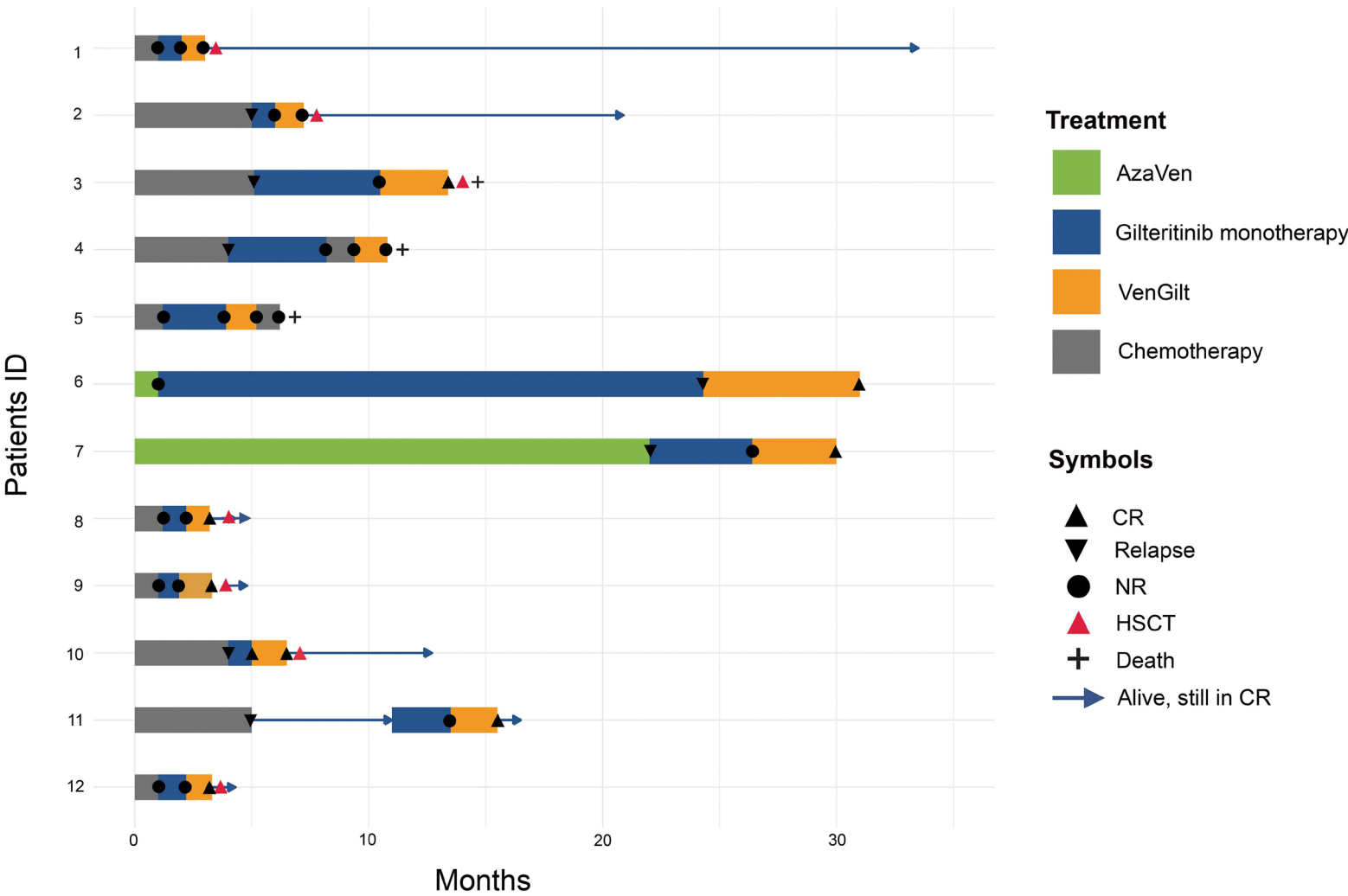


Figure 1. Swimmer plot illustrating treatment duration of gilteritinib monotherapy (blue) and combination venetoclax-gilteritinib (orange), response status, and follow-up for individual patients over time. Aza: azacitidine; CR: complete remission; Gil: gilteritinib; HSCT: hematopoietic stem cell transplant; NR: not reached; Ven: venetoclax.

patients achieving a response, the median time to neutrophil and platelet recovery (absolute neutrophil count $>1.0 \times 10^9/L$ and platelet count $>50 \times 10^9/L$) 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 alanine transferase 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 (*Online Supplementary 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 computed tomography scan (*Online Supplementary Figure S1B*), and further a more profound molecular response (*Online Supplementary 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 Ib 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. 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 cannot 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 paper⁴ and in the 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 an outpatient setting with a 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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Contributions

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

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Data-sharing statement

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

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