haematologica
Journal of the Ferrata Storti Foundation

Real-life outcome after failure to venetoclax and hypomethylating-based therapy for acute myeloid leukemia

by Carlos Jiménez-Vicente, Iago Arribas, Helena Pomares, Guillermo Ramil, Sandra Castaño-Diez, Amanda Isabel Pérez-Valencia, Antonella Luciana Sturla, Mònica López-Guerra, Alexandra Martinez-Roca, Inés Zugasti, Francesca Guijarro, Albert Cortés-Bullich, Beatriz Merchán, Ana Triguero, Inés Monge, Albert Tuca, Guadalupe Oñate, Ana Garrido, Jorge Sierra, Montserrat Arnan, Jordi Esteve, and Marina Díaz-Beyá and Spanish CETLAM Group.
Collaborative Groups: Spanish CETLAM Group.

Received: September 7, 2024.
Accepted: January 14, 2025.

Citation: Carlos Jiménez-Vicente, Iago Arribas, Helena Pomares, Guillermo Ramil, Sandra Castaño-Diez, Amanda Isabel Pérez-Valencia, Antonella Luciana Sturla, Mònica López-Guerra, Alexandra Martinez-Roca, Inés Zugasti, Francesca Guijarro, Albert Cortés-Bullich, Beatriz Merchán, Ana Triguero, Inés Monge, Albert Tuca, Guadalupe Oñate, Ana Garrido, Jorge Sierra, Montserrat Arnan, Jordi Esteve, and Marina Díaz-Beyá and Spanish CETLAM Group.
Collaborative Groups: Spanish CETLAM Group.
Real-life outcome after failure to venetoclax and hypomethylating-based therapy for acute myeloid leukemia.
Haematologica. 2025 Jan 23. doi: 10.3324/haematol.2024.286589 [Epub ahead of print]

Real-life outcome after failure to venetoclax and hypomethylating-based therapy for acute myeloid leukemia

Carlos Jiménez-Vicente[1,2,3], Iago Arribas[4], Helena Pomares[4], Guillermo Ramil[5], Sandra Castaño-Diez[1,2], Amanda Isabel Pérez-Valencia[1,2], Antonella Luciana Sturla[4], Mònica López-Guerra[2,6,7], Alexandra Martinez-Roca[1,2], Inés Zugasti[1,2,3], Francesca Guijarro[2,6], Albert Cortés-Bullich[1,2], Beatriz Merchán[1], Ana Triguero[1,2], Inés Monge[8], Albert Tuca[9], Guadalupe Oñate[5], Ana Garrido[5], Jorge Sierra[5], Montserrat Arnan[4], Jordi Esteve[1,2,3,10*] and Marina Díaz-Beyá[1,2,3,10*]

[1] Hematology Department. Hospital Clínic de Barcelona, Barcelona, Spain.

[2] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[3] University of Barcelona, Barcelona, Spain

[4] Hematology Department, Institut Català d'Oncologia - Hospital Duran I Reynals; Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain

[5] Department of Hematology. Hospital de la Santa Creu i Sant Pau. Universitat Autònoma de Barcelona and IIB Sant Pau

[6] Hemopathology Unit, Pathology Department. Hospital Clinic de Barcelona, Barcelona, Spain.

[7] Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain.

[8] Pharmacy Department, Hospital Clínic de Barcelona, Barcelona

[9] Medical Oncology Department, Hospital Clinic de Barcelona, Barcelona

[10] Josep Carreras Leukemia Research Institute, Barcelona, Spain.

MDB and JE contributed equally in the senior authorship of this study. Collaborative Groups: Spanish CETLAM Group.

Corresponding author: Marina Diaz-Beyá. Hematology Department, Hospital Clínic of Barcelona. Villarroel 170, 08036 Barcelona, Spain. Tel: 34 93 227 54 28; Fax: 34 93 227 54 84; e-mail: diazbeya@clinic.cat

1. Data Availability Statement: Due to privacy and ethical considerations, the data underlying the findings of this study can be obtained by contacting the corresponding author.

2. Conflict of interest disclosure: CJV serves as educational speaker for AbbVie and received travel grants from AbbVie, Jazz Pharmaceuticals and Pfizer. FG serves as educational speaker for AbbVie. AMR serves as a consultant or in an advisory role, for Bristol Myers Squibb (BMS), AbbVie, and Kite Gilead; received travel grants from Kite Gilead, Roche, Takeda, Janssen, and AbbVie; and serves as a speaker for AbbVie and Gilead. MDB serves as a consultant for, in an advisory role for, received travel grants from, or served as speaker for BMS, AbbVie, Astellas, JazzPharma, Takeda, and Novartis. JE declares consultancy honoraria from AbbVie, Novartis, Astellas, Jazz Pharmaceuticals, BMS-Celgene, Pfizer, and Daichii-Sankyo, and received research grants from Novartis, Jazz Pharmaceuticals, and Pfizer. The remaining authors declare no competing financial interests. The founders had no role in the design of the study; in the collection, analyses or interpretation of the data; in the writing of the manuscript; or in the decision to publish the results.

3. Author contributions: CJV and MDB designed the study, performed the statistical analysis and wrote the manuscript; JE and MDB supervised the study; HP, IA, GR, SCD, AIPV, ASL, MLG, AMR, IZ, FG, ACB, BM, AT, IM, GO and AG collected data. All authors contributed valuable revisions and approved the final version of the manuscript.

Venetoclax and azacitidine became the gold standard frontline treatment for patients diagnosed with acute myeloid leukemia (AML) ineligible for intensive chemotherapy (unfit) since the publication of the phase III Viale-A trial in 2020[1] with a better composite response rate and an increased median overall survival (OS) compared to azacitidine .

Though the treatment changed the paradigm in AML unfit patients, the results of the long-term follow-up of the Viale-A[2] and the real-life series[3] have shown that eventually most patients will relapse. After failure, outcome has not been broadly studied. Only selected patients, especially those with actionable targets (e.g., *NPM1, IDH1/2 or FLT3* mutation,*or KMT2A* rearrangement) may benefit from salvage treatment if available at this moment, including clinical trial enrollment.

Here, we analyze the outcomes of AML patients after failure to venetoclax in combination with hypomethylating agents (VenHMA), with an emphasis on salvage feasibility after relapse.

We performed a retrospective study with patients treated with VenHMA at three academic centers in the metropolitan area of Barcelona (Hospital Clínic de Barcelona, Hospital de la Santa Creu i Sant Pau, and Hospital Duran i Reynals) between September 2019 and December 2023. All patients received VenHMA as frontline therapy, with an initial dose of venetoclax 400mg daily during 21 or 28 days and hypomethylating agents at standard dose in 4-week cycles. Patients who subsequently underwent allogeneic hematopoietic cell transplantation were excluded from the study. Dose decrease was decided based on myelotoxicity during treatment at the discretion of the physicians. The study was approved by the Ethics Committee of the Hospital Clínic de Barcelona and conducted following standards set forth by the Declaration of Helsinki. Our primary endpoint was to analyze the overall survival after treatment failure to VenHMA, defined as treatment inefficacy to obtain any morphological response according to the ELN 2022 response criteria. Secondary objectives included studying salvage treatments offered in patients who relapsed, including their overall response rate (ORR) and palliative care policy applied.

AML was classified according to the ICC 2022 and WHO 5th classification of myeloid neoplasms[4,5]. AML disease risk stratification and response criteria during treatment were assessed locally at each center, in all cases according to the 2022 European LeukemiaNet risk criteria[6] (ELN 2022). Cytogenetics were assessed on G-banded metaphase cells and next generation sequencing (NGS) at diagnosis were performed with the Ion AmpliSeq™ AML Research Panel, Oncomine™ Myeloid Research Assay

and the Healthincode Haematology OncoKitDx™. Performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) score[7].

Median and range were used for continuous variables and frequency and percentage for categorical variables. OS was defined as survival from confirmed morphological relapse or treatment refractoriness onwards, being estimated using the Kaplan-Meier method. Univariate analyses for survival were done using the log-rank test. Time-dependent variates for survival were analyzed using the Mantel-Byar method. All p values were two-sided with statistical significance evaluated at the 0.05 alpha level. All statistical analyses were performed with R statistics version 4.0.3 (R core Team, R Foundation for Statistical Computing, Vienna, Austria).

Sixty-seven patients were included, 42 of them relapsing after an initial response (62.7%) and 25 after treatment refractoriness (27.3%). Baseline characteristics are displayed in Table 1. Median age was 75 years (range 33-91) in both subgroups, with males comprising 61.6% of the participants.

AML with myelodysplasia-related (MR) gene mutations was the most frequent diagnosis (29/67 of all patients, 38.2%). According to the ELN 2022 risk classification, 4 patients had a favorable risk (6%), 16 (23.9%) had an intermediate risk and 47 an adverse risk (70.1%). Most frequent mutations were observed in *TET2* (29.8%), *ASXL1* (26.3%) and *RUNX1* (24.6%) (Figure 1S). Seventeen patients (33%) harbored an actionable mutation, including *FLT3* (n=7), *IDH1/2* (n=15) and/or *NPM1*/*KMT2A*r (n=10). Eight of these patients (10.5%) had previously received azacytidine during MDS phase.

Response characteristics to VenHMA can be seen in Table 1S. Out of the 67 patients, 25 patients (37%) were initially refractory while 42 (63%) relapsed. Complete response (CR) without hematologic recovery (66.6%, 28/42) was the most frequent response while CR + CRi rate was 92.3%. Median cycles to response were 1 (range 1-3) and median cycles received were 6 (range 2-16).

OS was 2.3 months (95% CI: 1.8-4.6, Figure 2S) with no difference between patients who achieved any response and refractory patients (2.8 vs. 1.2 months, p = 0.28, Figure 1A). There were no differences in OS by the mutational landscape of the patients (2.5 vs. 1 month, p = 0.27). After relapse, a molecular reassessment was performed in 18 patients, with emergent mutations in 11 of them (61.1%). Emergent mutations in *FLT3-TKD, NRAS*, *TP53* (n = 2 each) and *KRAS and FLT3-ITD* (n = 1 each) were the most relevant mutations.

Only 13 patients (30.9%) could undergo salvage treatment, including 6 patients enrolled in different clinical trials. Three patients underwent standard chemotherapy after VenHMA with no response to treatment, Five patients were treated with targeted therapies: 2 with *FLT3* inhibitor gilteritinib, 2 enrolled in clinical trials with *IDH1/2* inhibitors and one in a clinical trial with a menin inhibitor. Salvage ORR rate was 3/13 patients (23.3%) (one CR and one CRi with in *IDH1/2* inhibitors within clinical trials, and one CR to gilteritinib).

Reasons to rule out salvage treatment included lack of suitable treatment at physician's discretion in 20 patients (54.9%), comorbidities (13.7%), lack of available clinical trial (CT) or targeted therapy in 2 patients and CT screening failure in one patient. We could not observe differences in OS by receiving a salvage treatment (2.2 vs 4 months, p = 0.22, Figure 1B) (Table 2S). OS if achieving a CR after salvage was 11.6 months vs. 2.53 in refractory patients (p = 0.17, Figure 1C)

Finally, a hospice care team was enabled in 19 patients after relapse (45.2%), while the rest of patients could not have access to any special care system at home that could enhance comfort and quality of life during their last days of life. Within these palliative measures, 9 of these patients died at home (21.4%) while the rest of the patients required a last admission before death.

This study highlights the poor outcome of unfit patients diagnosed with AML after frontline therapy failure with VenHMA. The low percentage of patients that are able to undergo salvage treatment in our setting (30%) and its lack of efficacy would explain the dismal survival after VenHMA discontinuation (2.3 months). To our knowledge, this study represents the first approach to survival after progressive disease to VenHMA in AML in a European real-world data cohort.

In this context, of the main struggles to offer adequate salvage treatments relies on the accessibility. Previous to this report, only series of patients treated mostly within the United States of America have been published, and in two cases, patients had been enrolled in the Viale A study[2,8,9]. Interestingly, the percentage of patients that underwent salvage treatment (24/41 (58.5%), 11/71 (15%) and 59/171 (34.5%)) and its ORR differ a lot between the studies, remarking also the variability of therapeutical options between centers in this context and the feasibility to receive therapy after failure. The recent long-term follow-up of the Viale A shows a longer survival after treatment failure (6 months), probably based on a relatively high percentage of patients treated afterwards and the CT selection bias.

Some targeted therapies have recently shown promising activity this refractory/relapsed to VenHMA setting, such as revumenib[10] in *KMT2A* rearranged and *NPM1* AML, or recently, myeloid kinase inhibitor tuspetinib[11], but only gilteritinib[12] in monotherapy for R/R AML with *FLT3* mutation is approved in Europe while enasidenib[13] and ivosidenib have FDA approval in this R/R

Treatment after VenHMA failure is a current unmet need in unfit AML patients, clearly observed in our series, the salvage treatment rate was only 25%, although a 33% of the patients presented an actionable target, and all responses after VenHMA were achieved using therapies against them. Therefore, in this setting, where the main objective is to offer salvage treatment to all eligible patients, targeted therapies become essential nowadays. There is, though, relevant differences in the drug access between the European and American setting that hinder its prescription and that should probably more noticed in the standard treatment guidelines.

If there are not any available options, clinical trial enrollment is needed to add new options to the therapeutical arsenal, since it is the best likely option in all patients without any actionable targets after VenHMA.

Finally, we remark the palliative care relevance in this setting, whose rates had not been published yet. Although the activation of hospice care is improving through years, less than 50% of the patients benefited from it in our study. We consider it really low, though similar to what has been shown in other studies related to the disease[15]. Since survival is still short after failure, its activation velocity should improve so more patients can benefit from hospice care in the future.

Limitations of this study include its retrospective nature and the limited size of the cohort and patients receiving salvage treatments which underpowers the likely differences observed. Further knowledge is needed in studies with more patients included.

BIBLIOGRAPHY

1. DiNardo CD, Pratz KW, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.
2. Pratz KW, DiNardo CD, Thirman MJ, et al. Long-term follow-up of VIALE-A: venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(6):615-624.
3. Matthews AH, Perl AE, Luger SM, et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. Blood Adv. 2022;6(13):3997-4005.
4. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
5. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
6. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.
8. Maiti A, Qiao W, Sasaki K, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. Haematologica. 2021;106(3):894-898.
9. Gangat N, Morsia E, Al-Kali A, et al. Outcome of patients with acute myeloid leukemia following failure of frontline venetoclax plus hypomethylating agent therapy. Haematologica. 2023;108(12):3170-3174.
10. Issa GC, DiNardo CD, Schuh AC, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukemia. Nature. 2023;615(7954):920-924.
11. Daver N, Trotman J, Knapper S, et al. Tuspetinib myeloid kinase inhibitor safety and efficacy as monotherapy and combined with venetoclax in phase 1/2 trial of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML). Blood. 2023;142(Supplement 1):162.

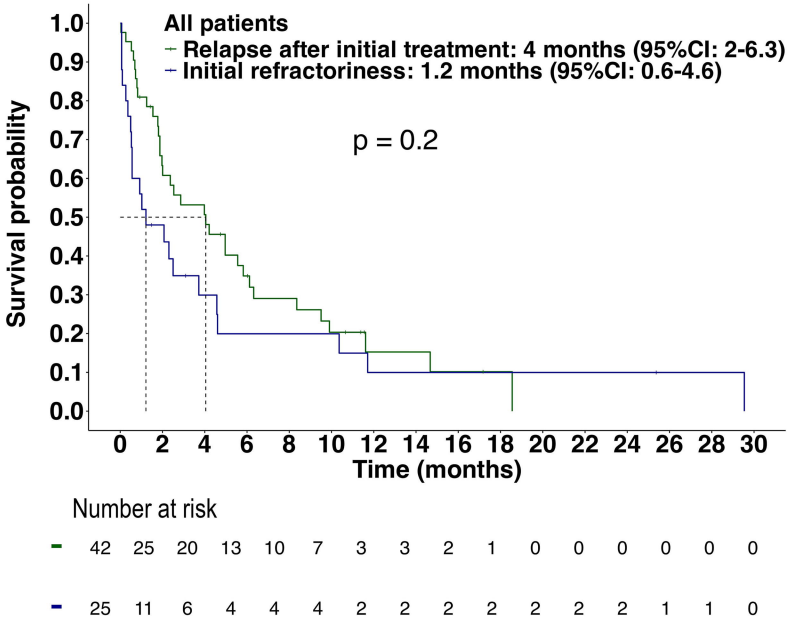
12. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728-1740.
13. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722-731.
14. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386-2398.
15. Wang R, Zeidan AM, Halene S, et al. Health care use by older adults with acute myeloid leukemia at the end of life. J Clin Oncol. 2017;35(30):3417-3424.

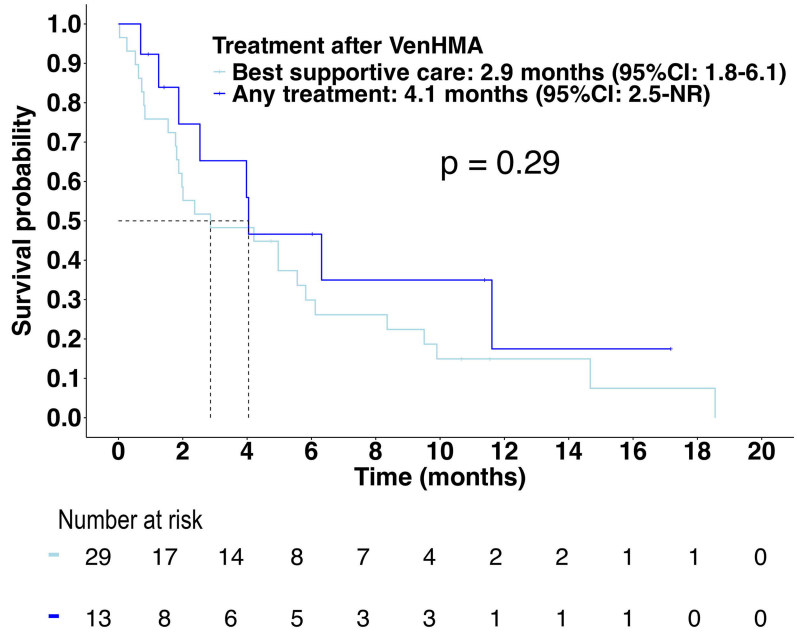
	All patients (N = 67)	Response (n = 42)	Initial refractoriness (n = 25)
Age, median (range)	75 (33-86)	75 (33-86)	75 (52-85)
Sex, n (%)			
Male	41 (61.2)	23 (54.8)	18 (72)
Female	26 (38.8)	19 (45.2)	7 (28)
Diagnosis (ICC 2022), n (%)			
AML with myelodysplasia related gene mutations	28 (41.8)	17 (40.5)	11 (44)
AML with mutated *TP53*	10 (14.9)	6 (14.3)	4 (16)
AML with myelodysplasia-related cytogenetical abnormalities	9 (13.4)	7 (16.7)	2 (8)
AML with mutated *NPM1*	8 (11.9)	6 (14.3)	2 (8)
AML, NOS	7 (10.4)	5 (11.9)	2 (8)
AML with t(9;11), *KMT2A* rearrangement	2 (3)	0 (0)	2 (8)
AML with *MECOM(EVI1)* rearrangements	2 (3)	0 (0)	2 (8)
AML with *t(8;21), RUNX1::RUNX1T1*	1 (1.)	1 (2)	0 (0)
Risk genetic scale (ELN 2022), n (%)			
Favorable	4 (6)	4 (16.7)	0 (0)

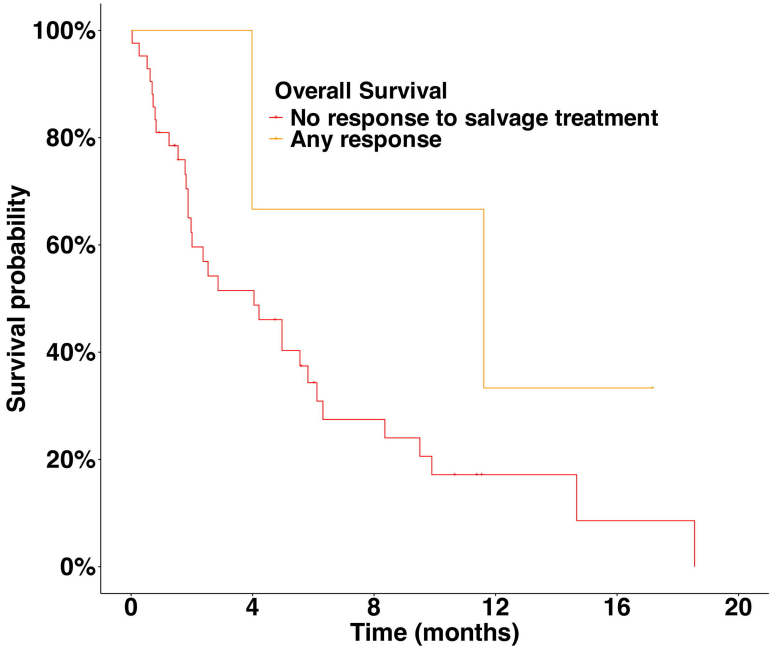
Intermediate	16 (23.9)	9 (21.4)	7 (28)
Adverse	47 (70.1)	29 (69)	18 (72)
Treatment prior to VenHMA, n (%)			
Hypomethylating agent-based regimens	8 (11.9)	4 (9.5)	4 (12)
Hypomethylating agent, n (%)			
Azacitidine	59 (88.1)	36 (85.7)	23 (92)
Decitabine	8 (11.9)	6 (14.3)	2 (8)
Hematology at PD, median (range)			
WBC ($x10^9$/L)	2.8 (0.6-56.3)	2.43 (0.6-41.9)	5.27 (0.7-56.3)
Hemoglobin (g/dL)	8.6 (6.7-12.5)	8.7 (6.7-12.5)	8.4 (7-10.7)
Platelets ($x10^9$/L)	58 (3-537)	58 (3-442)	47 (9-537)

Table 1. Baseline characteristics of all patients. AML: Acute myeloid leukemia, MDS: Myeloidysplastic syndrome, PD: Progressive disease . ICC 2022: International Consensus Classification of myeloid neoplasms 2022. ELN 2022: European Leukemianet 2022 risk stratification

Figure 1. Overall survival in patients after treatment failure with venetoclax and hypomethylating agents. 1A: Patient subgroups by previous response to treatment. 1B: Patients who obtained a response to venetoclax and hypomethylating agents by ulterior treatment. 1C: Patients with a previous response to venetoclax and hypomethylating agents by response to salvage treatment.


All patients
Relapse after initial treatment: 4 months (95%CI: 2-6.3)
Initial refractoriness: 1.2 months (95%CI: 0.6-4.6)
p = 0.2
Survival probability
Time (months)
Number at risk
42 25 20 13 10 7 3 3 2 1 0 0 0 0 0 0
25 11 6 4 4 4 2 2 2 2 2 2 2 1 1 0


Treatment after VenHMA
Best supportive care: 2.9 months (95%CI: 1.8-6.1)
Any treatment: 4.1 months (95%CI: 2.5-NR)
p = 0.29
Survival probability
Time (months)
Number at risk
29 17 14 8 7 4 2 2 1 1 0
13 8 6 5 3 3 1 1 1 0 0


Overall Survival
No response to salvage treatment
Any response
Survival probability
Time (months)

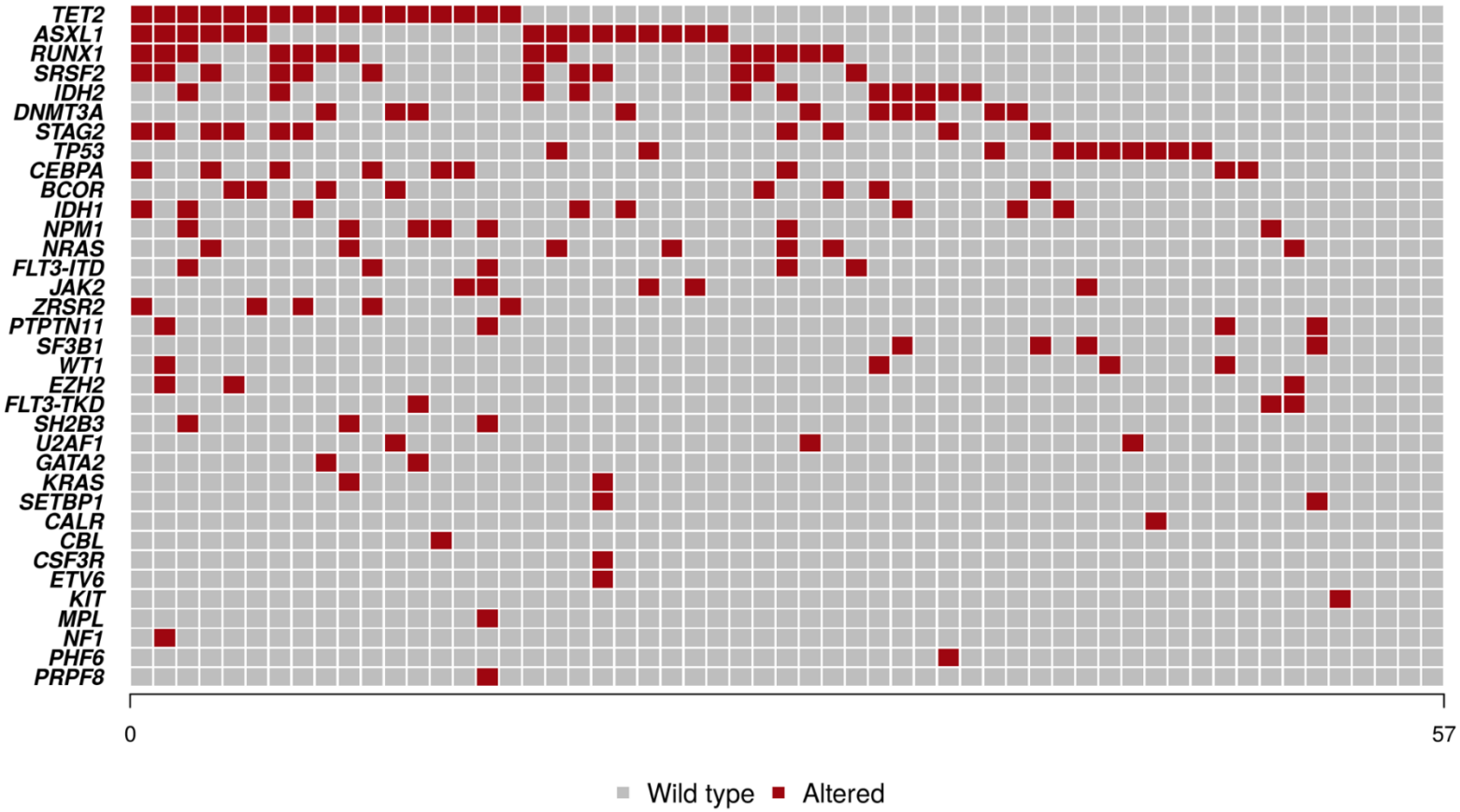


Figure 1S. Mutational landscape of the patients, both refractory and relapsed, included in the study who had undergone a next generation sequencing (NGS) assessment at diagnosis.

Overall response rate, n (%)	**Response (n = 42)**
CR + CRi	39 (92.9)
Complete response with negative MRD	7 (16.7)
Complete response with positive MRD	4 (9.5)
CRi with negative MRD	4 (9.5)
CRi with positive MRD	24 (57.1)
Partial response	3 (7.1)
Cycles to achieve any response, median (range)	1 (1-3)
Total cycles administered, median (range)	6 (2-16)
Hospice care active after PD, n (%)	19 (45.3)
Death at home after progressive disease, n (%)	9 (21.4)

Table 1S. Response characteristics to frontline treatment with VenHMA before end of treatment. CR: Complete Response, CRi: Complete Response without Hematological Recovery**.** MRD: Measurable residual disease. PD: Progressive disease

Salvage treatment after VenHMA, number (%)	**13 (30.1)**
Clinical trial enrollment	6 (14.3)
IDH inhibitors	2 (4.8)
Cereblon E3 Ligase Modulator	2 (4.8)
Myeloid kinase inhibitor	1 (2.4)
Menin inhibitor	1 (2.4)
Standard chemotherapy	3 (7.1)
Gilteritinib	2 (4.8)
Low-dose cytarabine	1 (2.4)
Magrolimab + azacitidine	1 (2.4)
ORR after salvage treatment, number (%)	3/13 (23.1)
IDH inhibitor in CT	2 (66.6)
Gilteritinib	1 (33.3)
LFS after second response, median (months, range)	8 (3-12)
Best supportive care after VenHMA	29 (69)
Lack of suitable treatment	19 (65.5)
Lack of available CT	2 (4.8)
Comorbidities	7 (16.7)
CT screening failure	1 (2.4)

Table 2S. Salvage therapeutical options in the patients included in the study. VenHMA: Venetoclax in combination with hypomethylating agents. ORR: Overall response rate. LFS: LFS:Leukemia-free survival. PD: Progressive disease. CT: Clinical trial.