

Prolonged treatment-free remission after venetoclax in combination with a hypomethylating agent in acute myeloid leukemia with inv(16)

Morgan L. Shannon

Stanford Health Care

Jared Wallace

Stanford Health Care

Amy Kuo

Stanford Health Care

Gabriel N. Mannis

gmannis@stanford.edu

Stanford Health Care

Case Report

Keywords: core binding factor acute myeloid leukemia (CBF-AML), treatment-free remission, hypomethylating agent, venetoclax

Posted Date: July 8th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10134070/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: Competing interest reported. M.L.S, J.W., and A.K. have no competing interests to declare. G.N.M. reports consultancy with Abbvie (ongoing) and Menarini-Stemline (ongoing), prior Scientific Advisory Committee roles with Abbvie, Astellas, Cullinan Therapeutics, Daiichi Sankyo, Genentech, Johnson & Johnson, Menarini-Stemline, Mitsubishi Pharma, Rigel, Servier, Syndax, Taiho (all ended), and receives research funding from Aptose, Blossom Hill, Crossbow Therapeutics, Daiichi Sankyo, Immune Onc (ended), Menarini-Stemline, Sumitomo, Syndax (all ongoing except as indicated).

Version of Record: A version of this preprint was published at Annals of Hematology on August 10th, 2026. See the published version at <https://doi.org/10.1007/s00277-026-07237-0>.

Abstract

Core binding factor acute myeloid leukemia (CBF-AML)—defined by t(8;21) or inv(16) chromosomal rearrangements—is classified as favorable-risk disease per the European LeukemiaNet 2022 risk model and is typically treated with intensive chemotherapy. Patients unsuitable for intensive therapy increasingly receive hypomethylating agents plus venetoclax (HMA/ven), though CBF-AML was excluded from pivotal trials of this regimen. Furthermore, HMA/ven is typically administered as indefinite therapy in AML; however, there is increasing interest in exploring the feasibility of therapy cessation given persistent treatment-free remissions with this regimen. Here, we report the first case of sustained treatment-free remission following HMA/ven in CBF-AML. Features in this case that suggest a higher likelihood of achieving a durable treatment-free remission include inv(16) disease and rapid measurable residual disease (MRD) clearance. We summarize the current retrospective data comparing response rates of inv(16) vs t(8;21) AML to HMA/ven: inv(16) AML consistently exhibits higher response rates compared with t(8;21) disease, although an overall survival benefit is not well established. Emerging data also suggest achieving MRD-negative complete remission after induction may predict more durable outcomes. This case provides proof-of-concept that carefully selected CBF-AML patients achieving sustained MRD-negative remission with HMA/ven can successfully discontinue therapy. Future prospective trials should include CBF-AML patients to define optimal treatment duration and identify candidates for therapy discontinuation.

Introduction

Core binding factor acute myeloid leukemia (CBF-AML) is defined by the presence of either t(8;21) (q22;q22) or inv(16) (p13q22)/t(16;16), giving rise to the fusion genes RUNX1::RUNX1T1 and CBFB::MYH11, respectively. CBF-AML is categorized as favorable risk per the European LeukemiaNet (ELN)-2022 genetic risk model. Accordingly, for functionally fit, newly diagnosed patients, intensive induction chemotherapy with anthracycline and cytarabine-based regimens is given with curative intent[1]. However, due to age, functional status, co-morbidities, and/or patient preference, not all patients are candidates for intensive induction. While the standard of care for patients “unfit” for intensive induction chemotherapy consists of a hypomethylating agent (HMA) or low dose cytarabine in combination with the BCL2 inhibitor venetoclax, patients with CBF-AML have been excluded from all major studies demonstrating efficacy of these regimens[2–5]. Although the incidence of CBF-AML decreases with increasing age, as high as 8% of patients older than 60 years of age may have CBF rearrangements[6]. As the field has increasingly shifted away from intensive chemotherapy in younger patients, the question of whether patients with CBF-AML can achieve sustained treatment-free remissions—and potentially even be cured—with HMA plus venetoclax (HMA/ven) remains an unanswered question.

Case Presentation

Here we describe the case of a patient with inv(16) AML who, after initial treatment with HMA/ven, has remained in remission for more than 6 years since diagnosis and has sustained a treatment-free remission for nearly 3 years (Fig. 1). This patient presented with pancytopenia and was initially diagnosed with AML at age 70. Cytogenetic evaluation of his leukemia was notable for the presence of inv(16); in addition to inv(16), 6 metaphases harbored trisomy 8 and 6 metaphases harbored deletion 7q. Molecular studies were negative for *NPM1*, *FLT3*, and *TP53* mutations at diagnosis. Given his preserved functional status, both traditional high-intensity induction chemotherapy and HMA/ven were offered. The patient opted for HMA/ven, citing concerns regarding toxicity and the impact on quality of life with intensive chemotherapy. He achieved a complete remission (CR) with no measurable residual disease (MRD) by flow cytometry after one cycle. The patient was offered an allogeneic stem cell transplant in first remission but declined in favor of ongoing maintenance therapy with HMA/ven. He continued HMA/ven for a total of 39 cycles, with progressive dose-reductions and longer intervals between cycles over time due to neutropenia and patient preference. After 39 cycles, the patient opted to stop therapy in favor of active surveillance. Bone marrow biopsy performed at time of discontinuation of therapy showed no evidence of AML and was again MRD negative by both flow cytometry and *CBFB-MYH11* PCR, with a sensitivity of 0.0001 normalized copy number (ARUP Laboratories, Salt Lake City, UT). Since therapy discontinuation, he has been monitored with *CBFB-MYH11* PCR MRD testing from peripheral blood approximately every three to six months, which has remained consistently undetectable. To our knowledge, this is the first description of up-front therapy with HMA/ven followed by a sustained treatment-free remission in a patient with CBF-AML.

Discussion

Several features of this case may have increased the likelihood of achieving a durable remission. First, despite all CBF-AML considered to be genetically favorable risk, numerous studies have shown differences in clinical outcomes between t(8;21) and inv(16) AML, so much so that some clinicians suggest the two should be treated as entirely separate clinical entities. Using an intensive chemotherapy backbone, long-term outcomes—particularly overall survival (OS) and relapse free survival (RFS)—are worse in t(8;21) AML compared to inv(16) [7]. Inv(16) and t(8;21) AML are typically associated with different co-mutational profiles, such as the increased prevalence of mutations in epigenetic regulators and cohesion complex genes in t(8;21) AML, which are likely drivers of worse outcomes[8–10]. Few studies have specifically evaluated outcomes in CBF-AML patients treated with HMA/ven as first line therapy. At present, data specific to differences in treatment outcomes between inv(16) and/or t(8;21) in patients treated with HMA/ven are retrospective and limited to small studies or subgroup analyses within larger studies. The currently published or presented literature regarding patients with CBF-AML treated with HMA/ven is summarized in Table 1[11–18]. Two studies specifically compared outcomes between inv(16) and t(8;21) AML patients treated with HMA/ven at diagnosis. Zhang *et al.* performed the first larger retrospective analysis of outcomes in 30 total CBF-AML patients treated with HMA/ven[12]. They showed improved responses after induction in inv(16) compared to t(8;21) AML (100% CR versus 31% CR) as well as a trend toward improved two-year overall survival (100% versus 81.5%). Notably,

while all patients in their cohort received HMA/ven induction, patients were subsequently consolidated with cytarabine-based therapy. Shen *et al.* retrospectively analyzed a cohort of 72 patients with CBF-AML and further demonstrated inferior response rates in patients with t(8;21) AML, specifically those with concurrent mutations in the tyrosine kinase pathway[11]. After one cycle of induction with HMA/ven, 42.9% of patients with t(8;21) AML with tyrosine kinase pathway mutations achieved a CR compared to 96.6%, 90.0%, and 66.7% CR rates in AML patients with inv(16) with tyrosine kinase pathway mutations, inv(16) without tyrosine kinase pathway mutations, and t(8;21) without tyrosine kinase pathway mutations, respectively. Overall, these and other studies have consistently demonstrated high complete remission (CR) rates for AML patients with inv(16) treated with HMA/ven, with inferior responses in patients with t(8;21) disease. Interestingly, several studies show no difference in OS or RFS in t(8;21) AML patients treated with HMA/ven compared to intensive induction despite lower CR rates. However, interpretation of the efficacy of HMA/ven in these studies is limited due to the vast majority of patients receiving cytarabine-based consolidation after initial induction.

Table 1

Summary of available data evaluating outcomes of patients with inv(16) versus t(8;21) AML treated with HMA/ven. CR = complete remission; CRi = complete remission with incomplete count recovery; PR = partial remission; NR = no response; HSCT = hematopoietic stem cell transplant; MRD = measurable residual disease; OS = overall survival; RFS = relapse free survival; R/R = relapsed/refractory; EFS = event free survival

Article	Total number of CBF-AML patients receiving HMA/ven	Mutation breakdown	Response after induction	OS	RFS	Notes
Shen <i>et al</i> , <i>Blood Cancer Journal</i> , 2025	72	inv(16) = 39	94.9% CR 5.1% PR 0.0% NR	w/ HSCT = 16.4 months w/o HSCT = 8.7 months	w/ HSCT = 11.6 months w/o HSCT = 7.8 months	Most nonresponders to HMA/ven switched over to other regimens after a single cycle of HMA/ven, limiting overall evaluation.
		t(8;21) = 33	51.5% CR 27.3% PR 12.5% NR	w/ HSCT = 20.3 months w/o HSCT = 7.1 months	w/ HSCT = 11.1 months w/o HSCT = 5.9 months	
Zhang <i>et al</i> , <i>Blood Cancer Journal</i> , 2023	30	inv(16) = 17	100% CR/CRi 0% PR 0% NR	100% at 2 years	n/a	All patients received cytarabine-based regimens for consolidation.
		t(8;21) = 13	31% CR/CRi 31% PR 38% NR	81.5% at 2 years	n/a	All patients were "unfit" for high intensity induction.
Feng <i>et al</i> , <i>Haematologica</i> , 2024	37	inv(16) = 37 (all patients in study)	94.6% CR 5.4% CRi	97.2% at 2 years	71.3%	Follow up study to Zhang <i>et al</i> , 2023. 36 of 37 patients switched to cytarabine-based consolidation regimens. Of 5 patients who relapsed, all had

Article	Total number of CBF-AML patients receiving HMA/ven	Mutation breakdown	Response after induction	OS	RFS	Notes
						persistent molecular MRD throughout consolidation.
Wang <i>et al</i> , <i>Blood Cancer Journal</i> , 2023	18	t(8;21) = 18 (all patients in study)	33.3% CR/CRi 5.5% PR 61.1% NR	78.2% at 2 years	58.5% at 2 years	Many non-responders to HMA/ven switched to other regimens after 1 cycle.
Lu <i>et al</i> , <i>Blood</i> , 2025	20	inv(16) = 11	100% CR/CRi	n/a	n/a	While inv(16) and t(8;21) OS and RFS were not reported individually, OS in favorable risk disease was significantly worse in patients treated with HMA/ven compared to intensive induction.
		t(8;21) = 9	44% CR/CRi	n/a	n/a	
Ruhnke <i>et al</i> , ASH Poster, 2025	53	inv(16) = 27	67% CR/CRi	14 months	n/a	European study with primarily Caucasian cohort. Prior studies included primarily patients with Chinese ancestry. Median follow up only 14 months, perhaps limiting comparison of OS.
		t(8;21) = 26	72% CR/CRi	12 months	n/a	
Arslan <i>et al</i> , <i>Am J Hematology</i> , 2020	10	Unknown	80% CR/CRi	n/a	n/a	44% of the total cohort was R/R, and a portion of those had previously received HMA. 10 patients had CBF-AML; 6 of 10 were R/R.

Article	Total number of CBF-AML patients receiving HMA/ven	Mutation breakdown	Response after induction	OS	RFS	Notes
						Did not distinguish between inv(16) and t(8;21).
Chang <i>et al</i> , <i>Leukemia Research</i> , 2026	9	t(8;21) = 9 (No inv(16) patients in study)	22% CR/CRi	n/a	n/a	Across all therapies, presence of CBF rearrangements (inv(16) and t(8;21) grouped together) was associated with improved OS and EFS. No Comparison of OS and EFS in CBF-AML patients treated with HMA/ven vs CAG.

In addition to harboring inv(16) rather than t(8;21), our patient's rapid achievement of an MRD-negative remission after one cycle of HMA/ven potentially suggested a remission that was more likely to be durable and eventually afford him a prolonged treatment-free remission. Recently, emerging data has suggested improved RFS in patients with AML who achieve MRD-negative remission after induction, though studies have focused mostly on patients undergoing intensive induction[19]. HMA/ven has traditionally been administered as indefinite maintenance therapy in AML, without significant prospect for cure. Given the increasing utilization of HMA/ven in AML at large, both in the older and less "fit" population[2] as well as more recently in the young and "fit" population[4], there is growing interest from clinicians and patients alike regarding the possibility of treatment-free remission following HMA/ven therapy. To date, the existing literature consists of a limited number of small, retrospective studies examining select cohorts of patients opting for treatment-free intervals after HMA/ven induction and maintenance therapy. Chua *et al*. evaluated 29 patients who achieved remission for at least 12 months with venetoclax-based therapy, 45% of whom electively discontinued therapy. There was no difference in OS or RFS between patients who continued versus stopped therapy after over five years of follow up[20]. Garciaz *et al*. analyzed 62 patients treated with HMA/ven at diagnosis who subsequently discontinued therapy due to poor tolerance, comparing subsequent treatment-free interval to continuation of HMA monotherapy. No difference was observed in OS or RFS between the two groups at a median of 23 months follow up[21]. Notably, neither Chua *et al*. nor Garciaz *et al*. reported any patients with CBF-AML in their cohorts.

Conclusion

In conclusion, our clinical experience has been consistent with the currently available literature suggesting that, despite a dearth of prospective data, HMA/ven is a very effective initial therapy in patients with CBF-AML who are “unfit” for intensive chemotherapy, specifically those with inv(16) chromosomal rearrangements. For the first time, we report the possibility of a prolonged treatment-free remission in a patient with AML with inv(16) treated with HMA/ven. Whether this holds true for AML with t(8;21) is unknown. We posit that those patients who respond rapidly (i.e. achieve MRD-negative remission after 1 cycle of HMA/ven) and maintain this MRD negativity for an extended period of time are more likely to be candidates for consideration of therapy discontinuation. As future studies of HMA/ven-based therapy are designed for patients newly diagnosed with AML, patients with CBF-AML should not be excluded. Prospective data from these studies will help elucidate the cytogenetic and molecular features that predict response to HMA/ven in CBF-AML patients and will potentially help identify patients who are candidates for treatment cessation.

Declarations

Contributions:

M.L.S. conceived and drafted the correspondence and integrated the supporting literature. G.N.M. contributed to the conceptual framing and provided intellectual input during manuscript refinement. J.W. and A.K. contributed to the conceptual development of the correspondence and provided expert review and critical feedback on the final version. All authors approved the manuscript before submission.

Funding:

No funding was received for conducting this study

Competing Interests:

M.L.S, J.W., and A.K. have no competing interests to declare. G.N.M. reports consultancy with Abbvie (ongoing) and Menarini-Stemline (ongoing), prior Scientific Advisory Committee roles with Abbvie, Astellas, Cullinan Therapeutics, Daiichi Sankyo, Genentech, Johnson & Johnson, Menarini-Stemline, Mitsubishi Pharma, Rigel, Servier, Syndax, Taiho (all ended), and receives research funding from Aptose, Blossom Hill, Crossbow Therapeutics, Daiichi Sankyo, Immune Onc (ended), Menarini-Stemline, Sumitomo, Syndax (all ongoing except as indicated).

Ethics Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board (IRB) of Stanford University (Protocol #54286, Date of approval: 1/27/2020).

Consent to Publish:

The participant has verbally consented to the submission of the case report to the journal.

References

1. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H et al (2022) Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 140(12):1345–1377. 10.1182/blood.2022016867
2. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH et al (2020) Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med* 383(7):617–629. 10.1056/NEJMoa2012971
3. Pollyea DA, Winters A, McMahon C, Schwartz M, Jordan CT, Rabinovitch R et al (2022) Venetoclax and azacitidine followed by allogeneic transplant results in excellent outcomes and may improve outcomes versus maintenance therapy among newly diagnosed AML patients older than 60. *Bone Marrow Transpl* 57(2):160–166. 10.1038/s41409-021-01476-7
4. Fathi A, Perl A, Fell G, Jonas B, Ragon B, Mims A et al (2025) Results from paradigm - a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia. *Blood* 146(Supplement 1):6–6. 10.1182/blood-2025-6
5. Watts J, Madarang E, Abbott D, Hart P, Sohalski C, Zoso A et al (2026 Feb) Venetoclax and azacitidine for younger acute myeloid leukemia patients independent of fitness for intensive chemotherapy. *Haematologica* 26. 10.3324/haematol.2025.300374
6. Li JF, Cheng WY, Lin XJ, Wen LJ, Wang K, Zhu YM et al (2024) Aging and comprehensive molecular profiling in acute myeloid leukemia. *Proc Natl Acad Sci* 121(10):e2319366121. 10.1073/pnas.2319366121
7. Huang J, Huang H, Zhang Y, Xia Y, Tu Y, Xu H et al (2026) Differential Prognosis and Transplant Strategies in CBF - AML With *RUNX1:: RUNX1T1* Versus *CBFβ:: MYH11* Fusions. *Am J Hematol*. ;ajh.70237. 10.1002/ajh.70237
8. Faber ZJ, Chen X, Gedman AL, Boggs K, Cheng J, Ma J et al (2016) The genomic landscape of core-binding factor acute myeloid leukemias. *Nat Genet* 48(12):1551–1556. 10.1038/ng.3709
9. Duployez N, Marceau-Renaut A, Boissel N, Petit A, Bucci M, Geffroy S et al (2016) Comprehensive mutational profiling of core binding factor acute myeloid leukemia. *Blood* 127(20):2451–2459. 10.1182/blood-2015-12-688705
10. Yu S, Yang S, Hu L, Duan W, Zhao T, Qin Y et al (2025) Genetic abnormalities predict outcomes in patients with core binding factor acute myeloid leukemia. *Ann Hematol* 104(2):997–1006. 10.1007/s00277-024-06182-0 PubMed PMID: 39966122; PubMed Central PMCID: PMC11971224
11. Shen J, Shan M, Chu M, Cai Y, Rui J, Chen S et al (2025) Comparing the efficacy and safety of venetoclax combined with hypomethylating agents versus intensive chemotherapy as induction

- therapy in newly diagnosed core binding factor acute myeloid leukemia patients. *Blood Cancer J* 15(1):17. 10.1038/s41408-025-01227-7
12. Zhang K, Zhang X, Xu Y, Xue S, Qiu H, Tang X et al (2023) Efficacy of venetoclax combined with hypomethylating agents in young, and unfit patients with newly diagnosed core binding factor acute myeloid leukemia. *Blood Cancer J* 13(1):155. 10.1038/s41408-023-00928-1
 13. Feng Z, Hu X, Li W, Xu T, Xu Y, Xue S et al (2025 Feb) Venetoclax in combination with hypomethylating agents in newly diagnosed and relapsed *CBFβ::MYH11* + acute myeloid leukemia. *Haematologica* 20. 10.3324/haematol.2024.286836
 14. Wang M, Cao HY, Tan KW, Qiu QC, Huang YH, Ge S, shuai et al (2023) Venetoclax plus hypomethylating agents in newly diagnosed acute myeloid leukemia patients with *RUNX1::RUNX1T1*: a retrospective propensity score matching study. *Blood Cancer J* 13(1):173. 10.1038/s41408-023-00948-x
 15. Lu J, Xue S, li, Wang Y, He X, feng, Hu X, hui, Miao M et al (2025) Venetoclax and decitabine vs intensive chemotherapy as induction for young patients with newly diagnosed AML. *Blood* 145(22):2645–2655. 10.1182/blood.2024027217
 16. Ruhnke L, Röllig C, Kretschmer L, Middeke JM, Herold S, Poitz D et al (2025) Venetoclax in combination with hypomethylating agents in adult patients with newly diagnosed AML with *CBFB::MYH11* or *RUNX1::RUNX1T1* fusions: Real-world outcomes based on international registry data. *Blood* 146(Supplement 1):5230–5230. 10.1182/blood-2025-5230
 17. Arslan S, Zhang J, Dhakal P, Moran J, Naidoo N, Lombardi J et al (2021) Outcomes of therapy with venetoclax combined with a hypomethylating agent in favorable-risk acute myeloid leukemia. *Am J Hematol* 96(3). 10.1002/ajh.26057
 18. Chang G, Gao H, Wei Y, Fu Q, Jiang Q, Jiang H et al (2026) Venetoclax and azacitidine versus CAG for unfit patients with newly diagnosed acute myeloid leukemia: A propensity score-matched analysis. *Leuk Res* 163:108187. 10.1016/j.leukres.2026.108187
 19. Jen WY, Sasaki K, Ravandi F, Kadia TM, Wang SA, Wang W et al (2025) Impact of measurable residual disease clearance kinetics in patients with AML undergoing intensive chemotherapy. *Blood Adv* 9(4):783–792. 10.1182/bloodadvances.2024013826
 20. Chua CC, Hammond D, Kent A, Tiong IS, Konopleva MY, Pollyea DA et al (2022) Treatment-free remission after ceasing venetoclax-based therapy in patients with acute myeloid leukemia. *Blood Adv* 6(13):3879–3883. 10.1182/bloodadvances.2022007083
 21. Garciaz S, Dumas P, Bertoli S, Sallman DA, Decroocq J, Belhabri A et al (2024) Outcomes of acute myeloid leukemia patients who responded to venetoclax and azacitidine and stopped treatment. *Am J Hematol* 99(10):1870–1876. 10.1002/ajh.27417

Figures

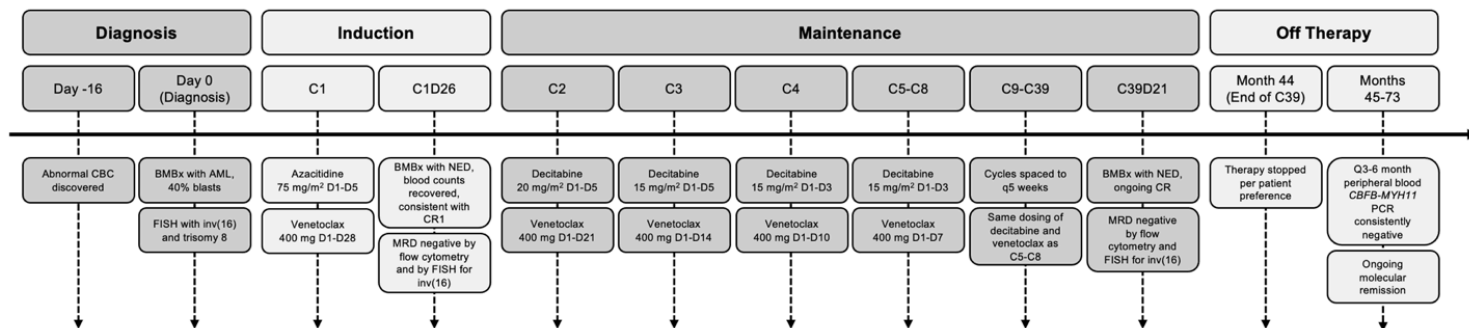


Figure 1

Treatment course and disease assessment over time of a patient with inv(16) AML treated with HMA/ven followed by a prolonged treatment-free remission. CBC = complete blood count, BMBx = bone marrow biopsy, FISH = fluorescence in situ hybridization, NED = no evidence of disease, CR = clinical remission, MRD = measurable residual disease