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Received: August 3, 2026.

Accepted: October 13, 2026.

Citation: Emma Barthelemy, Clementine Chauvel, Pierre Lemaire, Nicolas Boissel, Laureen Chat, Emmanuelle Clappier, Victoire De Marcellus, Nathalie Dhedin, Alessandro Di Lucia, Matthieu Duchmann, Matthieu Jestin, Stephanie Mathis, Florence Rabian, Loic Vasseur, Nicolas Duployez and Florian Chevillon. Menin inhibition with revumenib clears measurable residual disease in acute myeloid leukemia with UBTF tandem duplication after allogeneic stem cell transplantation. *Haematologica*. 2026 Oct 22. doi: 10.3324/haematol.2026.301758 [Epub ahead of print]

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Menin inhibition with revumenib clears measurable residual disease in acute myeloid leukemia with *UBTF* tandem duplication after allogeneic stem cell transplantation

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Short title: Menin inhibition clears MRD after allogeneic transplantation.

Acknowledgments: the authors thank the patient for providing consent for publication.

Declaration of Artificial Intelligence Use: [ChatGPT](#) was used solely for linguistic improvement of the manuscript, word count reduction and minor figure formatting improvements. No scientific content, analysis, or interpretation was generated by the tool.

Disclosure: The authors declare that they have no conflicts of interest related to this article.

Funding Statement: No funding was received for this work.

Authors' contributions: FC, NB, VDM, ND, ADL, MJ, FR, LV managed the patient, EB and FC collected and interpreted the clinical data; CC, PL, LC, EC, MD, SM, ND performed and interpreted laboratory analyses; CC and PL collected the images; EB and FC wrote the manuscript; all authors read and approved the final manuscript.

Data sharing statement: Data are available from the corresponding author upon request.

To the Editor,

Acute myeloid leukemia (AML) with tandem duplication of exon 13 of the upstream binding transcription factor (*UBTF*-TD) represents a recently recognized molecular entity characterized by a distinct transcriptional profile and adverse outcomes.

UBTF encodes a nucleolar protein involved in ribosomal DNA transcription and chromatin organization. The tandem duplication of exon 13 results in an altered protein with aberrant chromatin-binding properties, promoting ectopic recruitment to genomic loci and co-localization with the *KMT2A* menin transcriptional complex. This interaction dysregulates *HOX* gene expression, a hallmark of leukemogenic transcriptional programs.¹ *HOX* genes regulate hematopoietic stem cell self-renewal, lineage commitment, and myeloid differentiation. Their sustained overexpression promotes leukemic transformation by maintaining an undifferentiated, proliferative state. Similar transcriptional dependencies occur in AML with *KMT2A* rearrangements, *NPM1* mutations, or *NUP98* fusions, supporting a shared *HOX*-driven oncogenic program.^{1–4}

AML with *UBTF* tandem duplication (*UBTF*-TD) accounts for approximately 4% of pediatric AML, while representing approximately 3% of adult AML.^{5,6} This subtype is associated with high-risk features, including chemoresistance, persistence of measurable residual disease (MRD), and a high incidence of relapse. In pediatric cohorts, *UBTF*-TD AML has been associated with inferior outcomes, with a reported 5-year overall survival of approximately 44% compared with 64% in non-*UBTF*-TD AML.⁵ In adults, outcomes are similarly unfavorable. In a cohort reported by Duployez et al., 25% of patients were refractory to standard induction therapy, and although some achieved remission after salvage therapy, relapse occurred in approximately two-thirds of cases.⁶ Notably, even after allogeneic

hematopoietic stem cell transplantation (allo-HSCT), relapse rates remain substantial, highlighting the persistence of resistant leukemic clones.

Given this poor prognosis, the development of targeted therapies addressing the underlying transcriptional dependencies of *UBTF*-TD AML is of major interest. Menin inhibitors have emerged as promising agents in AML subtypes characterized by *HOX* gene dysregulation. By disrupting the interaction between menin and *KMT2A*, these agents suppress *HOX*-driven transcriptional programs, leading to decreased proliferation and induction of myeloid differentiation. Clinical activity of menin inhibitors has been demonstrated in *KMT2A*-rearranged and *NPM1*-mutated AML.^{7–10} Preclinical studies suggest that *UBTF*-TD AML may similarly depend on the menin-*KMT2A* axis. In vitro and in vivo models have demonstrated that menin inhibition reduces leukemic proliferation and promotes differentiation in *UBTF*-TD AML.¹ However, clinical evidence supporting this therapeutic approach in *UBTF*-TD AML remains limited with only one case reported showing a transient response after relapse¹¹.

We report a case of rapid and sustained MRD clearance following treatment with the menin inhibitor revumenib after allo-HSCT in a patient with *UBTF*-TD AML. The patient provided written informed consent for publication.

A 24-year-old patient was diagnosed in December 2020 with FAB-M4 AML with hyperleukocytosis, white blood cell count at $216 \times 10^9/\text{L}$. The karyotype was normal (46XY). Next generation sequencing (NGS) identified a *FLT3* internal tandem duplication (*FLT3*-ITD) with an allelic ratio of 0.5, and a *WT1* mutation. *UBTF*-TD was retrospectively identified by NGS in 2024, after *UBTF* was added to the panel.

Frontline induction therapy with daunorubicin and cytarabine in combination with the *FLT3*-inhibitor gilteritinib failed to achieve remission. Salvage therapy consisting of high-dose cytarabine (18g/m^2) combined with gilteritinib induced cytologic remission. However, MRD, assessed by multiparametric flow cytometry (MFC) using the Leukemia-Associated ImmunoPhenotype (LAIP), Different-from-Normal (DfN) and Leukemic Stem Cell (LSC) approaches according to AML French Flow Intergroup recommendations¹², remained detectable in the LAIP/DfN « CD34+/CD38low-neg/CD117+ » and « CD34-/CD38low-neg/CD117+ » targets. MRD levels were 5.1% and 2.0%, respectively, after the first treatment cycle, decreasing to 0.9% and 0.4% after the second cycle. In addition, LSC remained detectable but not quantifiable at the 10^{-4} sensitivity threshold following the first cycle of high-dose cytarabine.

In April 2021, the patient underwent allo-HSCT from an HLA-matched unrelated donor (MUD) following myeloablative conditioning with fludarabine and busulfan (FB4). Graft-versus-host disease (GVHD) prophylaxis included anti-thymocyte globulin, cyclosporine and methotrexate. The post-transplant course was complicated by stage 2 cutaneous and stage 1 gastrointestinal acute GVHD, which responded favorably to corticosteroid therapy.

In June 2021, bone marrow aspirate confirmed persistent remission. MRD assessment by MFC remained detectable but not quantifiable within the « CD34+/CD38low-neg/CD117+ » leukemic clone at a sensitivity threshold of 10^{-3} . In contrast, LAIP/DfN-MRD assessed in the second leukemic clone (« CD34-/CD38low-neg/CD117+ »), as well as LSC-MRD, were undetectable, with sensitivities of 10^{-3} and 10^{-4} , respectively. Given *FLT3*-ITD at diagnosis and the evidence available at that time, post-transplant sorafenib maintenance was administered from July 2021 to July 2023.

A cytologic relapse occurred in November 2024, 42 months after allo-HSCT. Molecular characterization showed persistence of *UBTF*-TD, *FLT3*-ITD, and *WT1* mutations and acquisition of trisomy 8. The patient received four cycles of azacitidine in combination with gilteritinib achieving morphological remission after one cycle. However, LAIP/DfN-MRD persisted after the final cycle at 1.5% within a newly identified leukemic clone (« CD34+/CD38+/CD117-/HLA-DR-/CD33+/CD13- ») detected at relapse. In contrast, LSC-MRD was undetectable at a sensitivity threshold of 10^{-4} . A second allo-HSCT from another MUD was performed in March 2025 using a reduced-intensity conditioning regimen (FB2), with graft-versus-host disease (GVHD) prophylaxis by anti-thymocyte globulin, cyclosporine and mycophenolate mofetil. The post-transplant course was complicated by steroid-refractory stage 3 cutaneous GVHD, which was successfully managed with ruxolitinib and phototherapy.

At 2 months post-transplant, LAIP/DfN-MRD within the new clone remained detectable à 0.21%. LSC - MRD was undetectable at the 10^{-4} threshold. Moreover, MRD assessment using detection of *FLT3* by ultrahigh-sensitivity (UHS)-NGS¹³, showed a variant allele frequency (VAF) of 0.23%. In this context, gilteritinib was reintroduced preemptively; however, MRD remained stable one month after treatment resumption. Consequently, treatment with the oral menin inhibitor revumenib was initiated on June 18, 2025, at a dose of 160 mg twice daily in combination with posaconazole. The level of immunosuppression was not reduced during this period, given the presence of GVHD.

One month after treatment initiation, bone marrow evaluation demonstrated complete remission, with morphologic evidence of leukemic differentiation characterized by progressive myeloid maturation with promyeloblasts, promyelocytes, myelocytes, metamyelocytes, mature neutrophils, and monocytes (Figure 1C). Interestingly, LAIP/DfN-

MRD within the new clone became undetectable at the 10^{-3} threshold. In parallel, detection of *FLT3*-ITD by UHS-NGS prior to revumenib initiation showed a variant allele frequency (VAF) of 0.23% which decreased to 0.02% after one month of treatment and became undetectable after 3 months of treatment by October 2025. Figure 2 and 3 illustrate the follow-up of MRD assessments throughout the patient's treatment course. One-year after revumenib initiation, the patient remains in complete remission, with an excellent tolerability.

This case highlights key features of *UBTF*-TD AML and provides clinically relevant insights into its management. First, it underscores the aggressive nature of this subtype, characterized by resistance to conventional chemotherapy, MRD persistence, and relapse, sometimes occurring late, despite intensive therapeutic strategies including allo-HSCT, with the co-occurring *FLT3*-ITD and *WT1* mutations in our patient potentially contributing to this adverse phenotype⁶. Indeed, AML cells persisted despite intensive chemotherapy, hypomethylating agents, *FLT3* inhibitors and allo-HSCT with GVHD.

Second, this case provides clinical evidence supporting the therapeutic potential of menin inhibition in *UBTF*-TD AML. The rapid conversion from MRD positivity to undetectable by both MFC and molecular assays within three months of revumenib initiation suggests a strong biological dependency of this leukemia on the menin-*KMT2A* transcriptional axis. Mechanistically, menin inhibition disrupts the maintenance of *HOX* gene overexpression, thereby promoting differentiation of leukemic blasts, as observed on bone marrow assessment after one month of treatment in our patient, and reducing proliferative capacity. This mode of action is distinct from conventional cytotoxic chemotherapy and may explain its efficacy in chemoresistant disease. Moreover, the early observation of differentiation

observed in our patient supports a direct antileukemic effect of revumenib although a contribution from graft-versus-leukemia activity or residual gilteritinib cannot be excluded. While menin inhibitors have demonstrated clinical efficacy in AML subtypes with *KMT2A* rearrangements and *NPM1* mutations, their role in *UBTF*-TD AML remains largely unexplored in the clinical setting, with only a single case report published to date¹¹. Our observation extends preclinical findings and further supports the hypothesis that *UBTF*-TD AML may represent an additional menin-dependent subtype.^{1,6-8}

Third, the use of a menin inhibitor as a post-transplant preemptive strategy is of particular interest. MRD persistence after allo-HSCT is a well-established predictor of relapse and poor survival. Preemptive strategies in this context remain limited. Revumenib-induced MRD clearance, together with its favorable tolerability and the potential enhancement of graft-versus-leukemia effects by menin inhibition, supports further investigation in the post-transplant setting.¹⁴

In conclusion, this report describes the first case of sustained MRD clearance following treatment with the menin inhibitor revumenib in a patient with high-risk *UBTF*-TD AML after allo-HSCT. These findings provide clinical support for targeting the menin-KMT2A axis in this molecular subtype and highlight the potential of precision medicine approaches in AML. Prospective clinical studies are warranted to evaluate the efficacy of menin inhibitors in *UBTF*-TD AML, both as monotherapy and in combination with other agents, and to define their role in post-transplant strategies aimed at preventing relapse. Importantly, patients with *UBTF*-TD AML should systematically be included in clinical trials evaluating menin inhibitors, as this high-risk molecular subgroup is not consistently represented in current studies.

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Figure 1. Cytologic findings at diagnosis, relapse and 30 days after initiation of revumenib.
(A) At diagnosis, December 2020. Blasts: mixture of myeloblasts (a), promonocytes (b) and monoblasts (c).

Granulocyte (1): pseudo-Pelger-Huet anomaly. Myelocyte (2): basophilic border, Döhle bodies, gray cytoplasm. Megaloblastic proerythroblast (3). Dysplastic orthochromatic erythroblast (4)

(B) At cytologic relapse, November 2024. Abnormal monocytic cell (a). Megaloblastic basophilic erythroblast (b).

(C) Day 30 after initiation of Revumenib, July 2025. Myeloblast (a), promyelocyte (b), myelocyte (c), metamyelocyte (d), neutrophilic granulocyte (e), and monocyte (f).

Figure 2. Monitoring of minimal residual disease (MRD) by multiparameter flow cytometry before and after revumenib introduction.

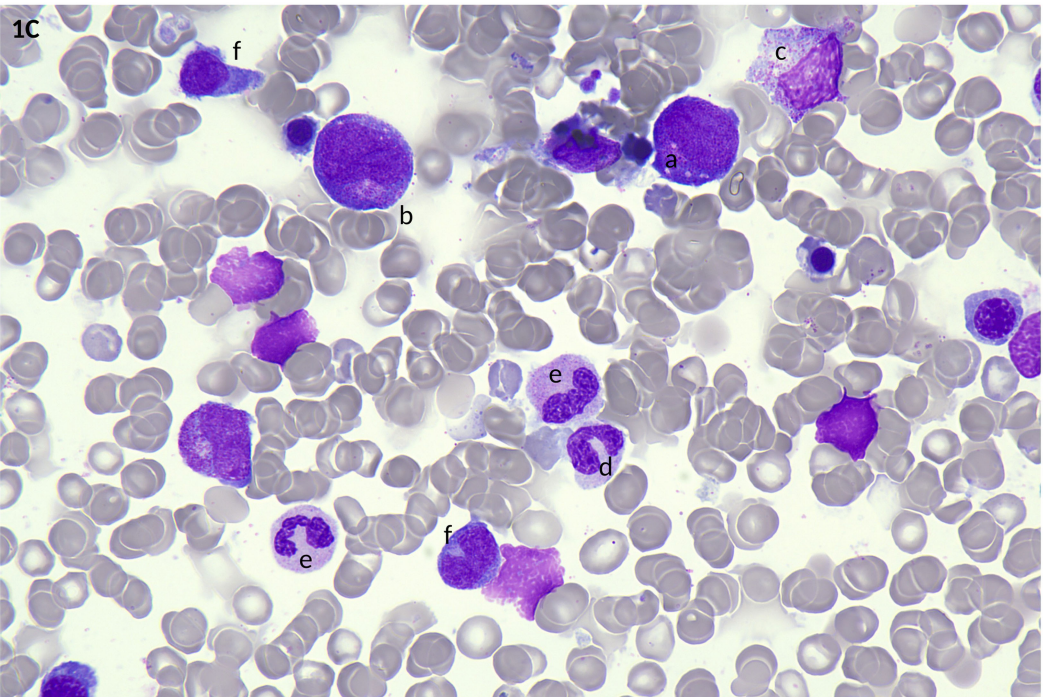
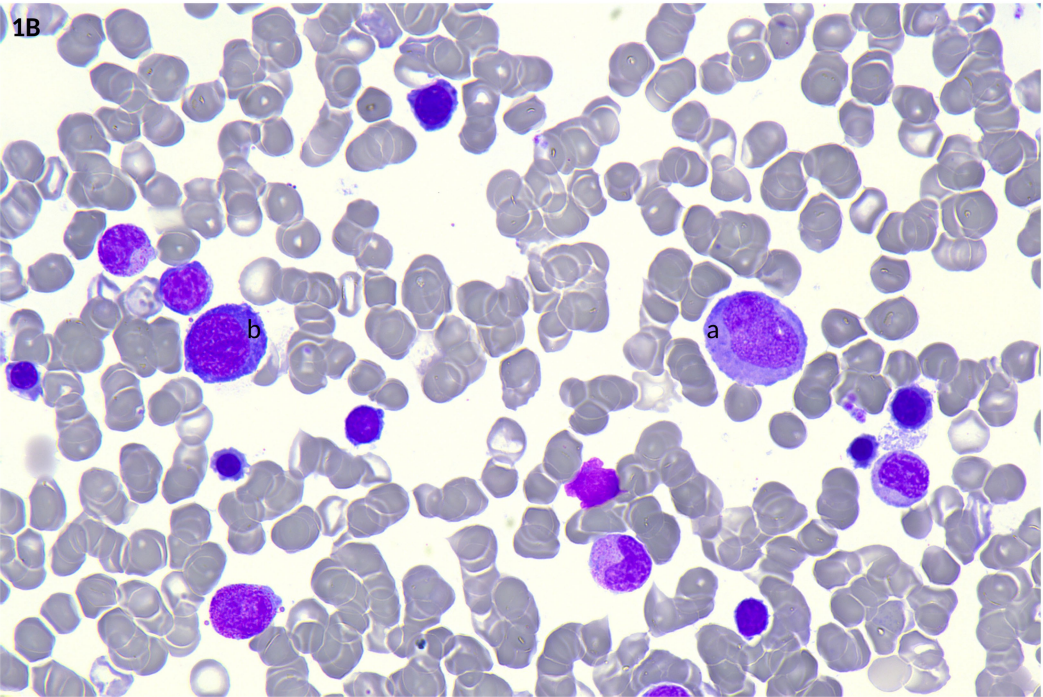
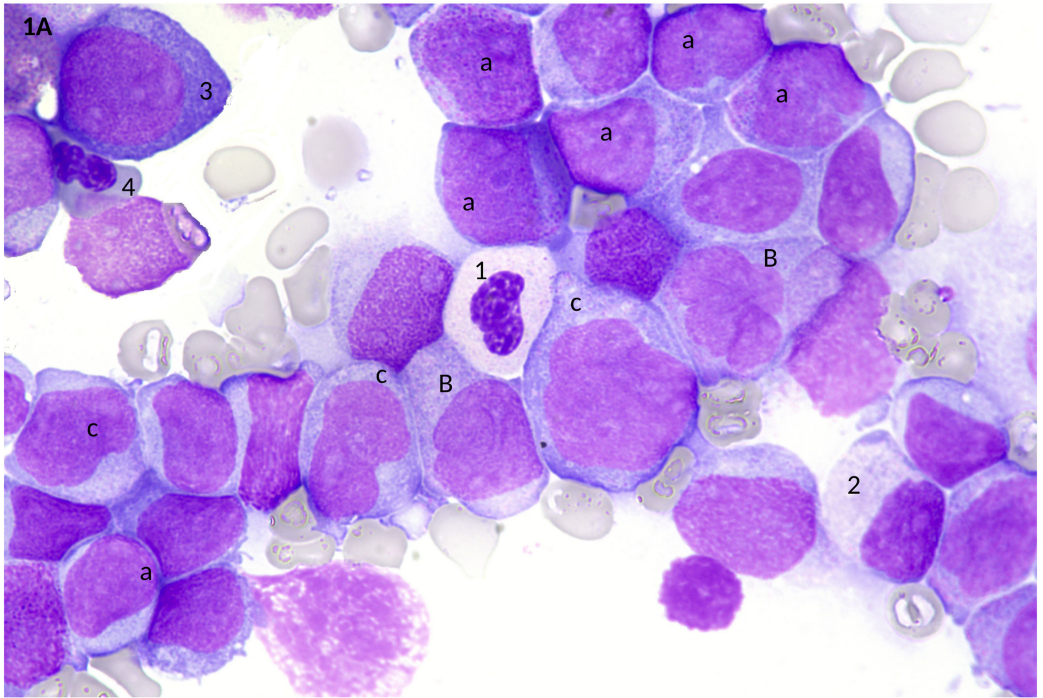
Black population: blasts monitored for MRD LAIP/DfN strategy based on the phenotypic profile CD45+dim CD34+, CD117-, CD38+, CD33+, CD13+, HLA-DR-. This phenotype represents 10% of blasts at relapse. Limit of detection (LOD) in normal bone marrow: 0.05%.

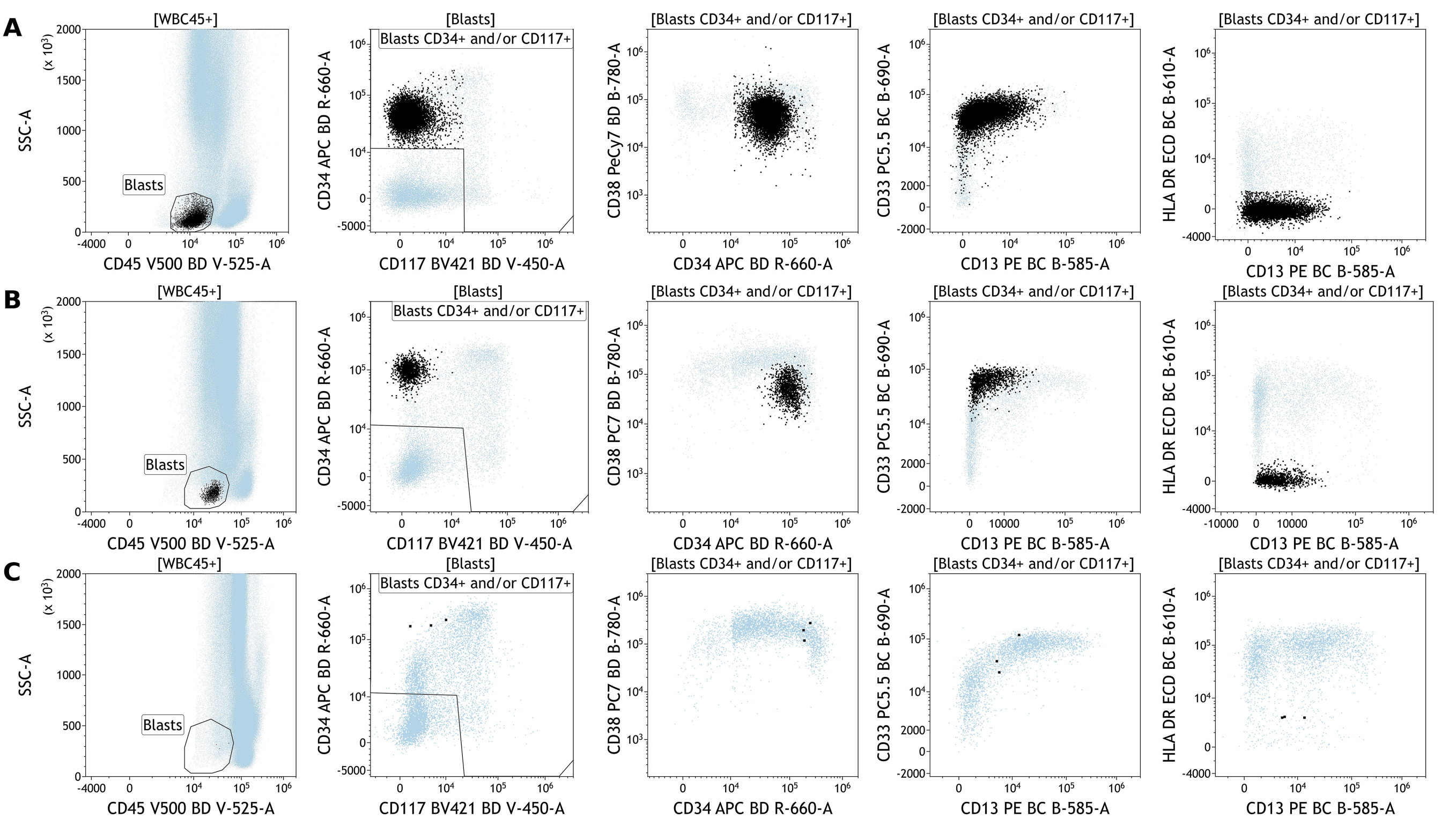
(A) Leukemic immunophenotypic profile after 4 cycles of azacytidine combined with gilteritinib (before second HSCT). (B) MRD at 2 months after second HSCT, before revumenib introduction. (C) MRD clearance 3 months after revumenib introduction.

Figure 3. Longitudinal evolution of LAIP/DfN and Flt3 NGS-MRD throughout the patient's disease course.

MRD-negative time points are plotted at 0.0001, corresponding to the limit of detection of the MRD assay, for graphical representation.

Dx: diagnosis, Post Ind: post induction, HDAC: high-dose cytarabine, HSCT: hematopoietic stem cell transplant, Aza: azacytidine, Gilte: gilteritinib, Rev: revumenib





Post-HSCT n.2 maintenance

Gilteritinib Revumenib

