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Received: July 6, 2026.

Accepted: September 21, 2026.

Citation: Laura Polmann, Christoph Schliemann, Lisa M. Sgonina, Britta Heptner, Christine Eisfeld, Julia Marx, Jan-Henrik Mikesch, Christian Reicherts, Annalen Bleckmann, Georg Lenz, Matthias Stelljes and Klaus Wethmar. Measurable residual disease-negative remission of BRAF-V600E-mutated acute myeloid leukemia with dabrafenib and trametinib.

Haematologica. 2026 Oct 1. doi: 10.3324/haematol.2026.301553 [Epub ahead of print]

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Measurable residual disease-negative remission of *BRAF*-V600E-mutated acute myeloid leukemia with dabrafenib and trametinib

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Dabrafenib and trametinib for *BRAF*-V600E-mutated AML

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Data sharing statement

Additional clinical data are available upon reasonable request to the corresponding author.

Author contributions

LP, CS, and KW conceptualized the report, prepared the figure and wrote the original manuscript. LP, CS, LMS, BH, CE, JM, JHM, CR, AB, GL, MS, and KW were closely involved in clinical management, collected clinical data, and revised the manuscript. All authors had full access to the data and approved the final submission.

Author disclosures

CS:

Honoraria/advisory boards: AbbVie, Astellas, AstraZeneca, BMS, Daiichi Sankyo, Laboratories Delbert, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, Roche

Research support (institutional): Jazz Pharmaceuticals

Congress/travel grants: AbbVie, BMS, Daiichi Sankyo, Jazz Pharmaceuticals, Pfizer

KW:

Honoraria/advisory boards: Takeda, Amgen, Incyte, Pfizer, AstraZeneca, RG, MSD, BMS

Congress/travel grants: Merck, Pierre-Fabre, Servier, BeiGene, AstraZeneca

Research support (institutional): AstraZeneca

AB:

Honoraria/advisory boards/travel grants: Bayer, BMS, Takeda, MSD, Boehringer, AstraZeneca, Sanofi, Pfizer, Lilly, Amgen, RG GmbH, Roche, Novartis, Janssen, Daiichi

Research support (institutional): BeiGene, BMS, AstraZeneca, MSD, Daiichi, Janssen, Eli Lilly
Cork Limited, Servier, Immatics

Case Report

For relapsed or refractory acute myeloid leukemia (AML), common salvage strategies comprise re-exposure to intensive chemotherapy, hypomethylating agents plus venetoclax, allogeneic hematopoietic stem cell transplantation (HCT), and a limited number of targeted therapies. These include gilteritinib for *FLT3*-mutated AML, ivosidenib and enasidenib for *IDH1*- and *IDH2*-mutated AML, and menin inhibitors for *NPM1*-mutated or *KMT2A*-rearranged AML.¹ Here, we report a case of relapsed and refractory *BRAF*-V600E-mutated AML that achieved measurable residual disease-negative complete remission upon salvage therapy with dabrafenib and trametinib. The case report was prepared in accordance with applicable ethical standards in Germany, and written informed consent was obtained from the patient.

Activating mutations of the *BRAF* gene are highly prevalent in several solid tumors and hematologic malignancies², including melanoma, thyroid cancer and hairy cell leukemia, but are found in only ~1% of AML cases^{3,4}. The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib is approved by the FDA for tumor-agnostic treatment of advanced solid tumors with a *BRAF*-V600E mutation⁵ and demonstrated efficacy in hematologic malignancies like hairy cell leukemia, multiple myeloma⁶ and histiocytic disorders⁷. Class I *BRAF* mutations at codon V600 induce RAS-independent monomeric kinase activity and are most responsive to combined BRAF and MEK inhibition. Class II mutations (non-V600-mutations) signal less strongly as RAS-independent dimers, whereas class III mutations promote enhanced downstream signaling in a RAS-dependent manner despite reduced or absent BRAF kinase activity.⁸

A 54-year-old man with a 4-year history of untreated myelodysplastic syndrome with multilineage dysplasia (MDS-MLD) according to WHO 2016 classification presented to the emergency department with general malaise, recurring fever, and cough. Initial blood samples showed a white blood cell count of 12.6/nL, hemoglobin 12.8 g/dL, platelets 47/nL, and 5% blasts. Bone marrow assessment revealed 60% of infiltration by myelomonocytic leukemia with AML-associated immunophenotype (cyMPO+CD34-CD33+HLA-DR-/++CD117-CD13-CD7-

CD56+CD15+CD14+/-CD4-TdT-CD123-). Karyotyping and fluorescence in situ hybridization (FISH) demonstrated trisomy 8 and trisomy 3 involving the 3q26 region, without evidence of chromosomal rearrangements (Table 1). Further molecular workup identified a *BRAF*-V600E mutation and additional variants in *ASXL1*, *SRSF2*, and *TET2*. Based on these findings, the patient was diagnosed with AML, myelodysplasia-related.

The patient was initially deemed unfit for intensive chemotherapy due to pre-existing dilated cardiomyopathy following myocarditis. Treatment with azacitidine and venetoclax resulted in complete remission with incomplete count recovery after the first treatment cycle, which was also maintained after the second cycle (**Figure 1**). After induction therapy the initial *BRAF* mutation was neither detectable by next generation sequencing (not shown) nor allele-specific quantitative real time PCR and the karyotype was normal with residual detection of the *MECOM* gain [1/200] by FISH (**Table 1**). All other mutations identified at baseline persisted, with only minor decreases in variant allele fractions. The patient proceeded to HCT from a matched unrelated donor after conditioning therapy with fludarabine and treosulfan without relevant complications. Despite receiving immunosuppressive prophylaxis (anti-thymocyte globulin, tacrolimus, and mycophenolate), the patient developed severe (stage 4, grade IV) steroid-refractory graft-versus-host disease (GvHD) of the upper and lower gastrointestinal tract during the second month after transplantation (**Figure 1**). Therapy with ruxolitinib resulted in complete resolution of GvHD.

About four and a half months after transplantation the patient presented with AML relapse. Bone marrow aspiration showed 80-90% infiltration by myelomonocytic leukemia with an immunophenotype similar to the one at initial diagnosis. The cytogenetic and molecular workup revealed all previously identified alterations except for the trisomy 8 (**Table 1**). The patient was re-exposed to azacitidine and venetoclax. The treatment course was complicated by persistent grade IV pancytopenia, severe HSV-1 stomatitis with viremia, persistent anorexia requiring parenteral nutrition, and recurrent fever necessitating multiple empiric antibiotic regimens.

Following a bone marrow aspiration on day 14 that demonstrated the persistence of 80-90% AML infiltration, the molecular tumor board recommended salvage therapy with dabrafenib and trametinib, based on a previous case report in AML⁹ and the efficacy of BRAF/MEK inhibition in other *BRAF*-V600E-mutated malignancies^{10, 11, 6}. Trametinib was initiated at 2 mg together with a reduced dose of dabrafenib (75-0-150 mg per day), due to interaction with posaconazole. Bone marrow sampling on day 14 demonstrated a morphologically leukemia-free state and a significant reduction of the *BRAF* ratio from 18.7% to 2.1% (**Table 1**). Treatment with granulocyte-colony stimulating factor was applied from day 21 until recovery of leukocyte counts on day 31. Two days later platelets recovered to >100/nL. Possible drug-related adverse reactions were first suspected on day 25 of treatment, when the patient developed a generalized, fine, non-pruritic maculopapular rash. After ruling out viral causes, the rash was kept under supervision. On day 33 the patient was diagnosed with a perforated gallbladder which was managed by laparoscopic cholecystectomy, escalated antibiotic treatment, CT-guided drainage of postoperative bilioma and stenting of the common bile and main pancreatic duct. Another bone marrow aspiration on day 42 showed measurable residual disease-negative complete remission, with the *BRAF* variant below the assay-specific cutoff for positivity of 0.076%¹². On day 49 after initiation of dabrafenib and trametinib the patient was discharged with resolved infections.

On day 62, skin changes, oral ulcerations, elevated liver enzymes and diarrhea were judged as GvHD-related. Initiation of methylprednisolone led to resolution of the rash, and the subsequent addition of tacrolimus resulted in improvement of the other signs of GvHD. This supported the hypothesis that these symptoms were primarily caused by GvHD rather than representing specific adverse effects of dabrafenib/trametinib. On day 89, a chimerism analysis showed ≥ 98% cells of donor origin in all subpopulations (CD3, CD14, CD19, CD34) and molecular remission was confirmed (**Table 1**). On day 124, the patient was hospitalized due to an *Escherichia coli* and *Enterococcus faecium* blood stream infection. Dabrafenib and trametinib were paused due to suspected drug-related thrombocytopenia (21/nL). Thirty days after treatment interruption another bone marrow analysis on day 154 demonstrated ongoing

molecular remission and complete donor-derived hematopoiesis. BRAF/MEK inhibition was re-started after recovery of platelets without evidence of persisting or relapsing AML on day 197. On day 244 the patient remained in cytological and molecular remission.

In AML, *BRAF* mutations have been associated with poor outcomes. In a recently published retrospective analysis of 50 patients with *BRAF*-mutated AML, median survival was 5.7 months in the overall cohort and approximately 14 months in newly diagnosed patients.⁴ The dismal prognosis was independent of treatment intensity and the use of venetoclax, highlighting the need for effective targeted therapeutic approaches. In another cohort of patients with relapsed or refractory RAS-mutated AML or high-risk myelodysplastic syndrome, trametinib induced responses in 20-27% of patients, but did not improve survival.¹³ However, the *BRAF* mutational status was not reported in that study, while our patient remained negative for *RAS* mutations throughout the clinical course. *Ex vivo* drug sensitivity data from the BEAT AML cohort showed that five *BRAF*-mutated AML samples were significantly more sensitive to trametinib and vemurafenib (another *BRAF* inhibitor) than *BRAF* wild-type samples.⁴

Here, we report successful treatment of a case of *BRAF*-V600E-mutated AML that had relapsed after HCT and had been refractory to re-exposure to azacitidine/venetoclax. Treatment with dabrafenib and trametinib induced a rapid response, resulting in complete molecular remission by day 42. Notably, molecular remission was maintained despite an interruption of treatment due to suspected hematologic toxicity between days 124 and 197. However, given the patient's severe chronic GvHD and recurrent systemic infections, the thrombocytopenia was likely multifactorial in origin.

Our observation of marked clinical activity of combined *BRAF* and MEK inhibition in *BRAF*-V600E-mutated AML is supported by another report, where treatment with dabrafenib and trametinib resulted in the rapid clearance of peripheral blast, reduced bone marrow infiltration, and a decrease in *BRAF* mutational burden within two weeks of treatment initiation. However, the response was short-lived. Disease progression occurred after five weeks and was likely driven by the emergence of subclonal *KRAS* mutations that conferred resistance to

the therapy.⁹ Therefore, further consolidation by HCT may be considered depending on the individual condition of each patient. In our patient, a second HCT was not pursued because of limited overall patient fitness.

We hypothesize that the *BRAF*-V600E mutation detected in our patient was restricted to the leukemic clone. At the time of initial diagnosis, all non-*BRAF* molecular alterations were present at higher VAFs than the *BRAF*-V600E mutation. Unlike the *BRAF* mutation, these alterations persisted before HCT, suggesting their origin in the underlying dysplastic hematopoiesis. Following transplantation, however, these alterations became undetectable. At relapse, *BRAF*-V600E and the remaining variants were detected at comparable VAFs, consistent with recurrence of the leukemic clone, which was subsequently suppressed by treatment with dabrafenib and trametinib. Given the persistent immunologic activity of the graft, reflected by recurrent chronic GvHD, a graft-versus-leukemia effect probably contributed to maintain the durable remission.

Together, our findings and the limited published evidence suggest that combined BRAF/MEK inhibition with dabrafenib and trametinib may represent an effective therapeutic option for patients with *BRAF*-V600E-mutated AML. Given the rarity of *BRAF*-V600 mutations in AML, randomized clinical trials are unlikely to be feasible. Therefore, the efficacy and durability of BRAF/MEK inhibition should be further evaluated through prospective documentation of individual cases and collaborative AML registry efforts.

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Table 1

	Initial diagnosis	Prior to HCT	Relapse	Dabrafenib & trametinib treatment				
Day	-246	-178	-30	14	42	89	154	244
	Allele-specific qPCR, target gene / control gene (%)							
<i>BRAF</i> p.Val600Glu	12.9	neg.	18.7	2.1	neg.	neg.	neg.	neg.
	NGS, variant allele fraction (%)							
<i>ASXL1</i> p.Val515Glyfs*13	38	29	11	-	-	0	0	-
<i>SRSF2</i> p.Pro95His	37	11	13	-	-	0	0	-
<i>TET2</i> p.Asn901Ilefs*20	37	20	12	-	-	0	0	-
<i>TET2</i> p.Tyr1255*	39	21	12	-	-	0	0	-
<i>MED12</i> p.Gly44Cys [#]	-	-	53	-	-	-	-	-
<i>DPYD</i> p.Cys29Arg [#]	-	-	27	-	-	-	-	-
	Karyotype							
	47,XY, der(3)(3qter ->3q25::3p25->3qter), +8[14]/46,XY[11]	46,XY	46,XY,der(3)(3qter->3q25::3p25->3qter)[11]/46,XY[14]	-	-	-	-	-
	FISH, aberrant / normal							
nuc ish(<i>MECOM</i> x3)	9/100	1/200	87/200	-	-	-	0/100	-
nuc ish(<i>RUNX1T1</i> x3, <i>RUNX1</i> x2)	7/100	-	-	-	-	-	0/100	-

Legends

Table 1. Molecular disease characteristics during the course of treatment.

HCT, allogeneic hematopoietic cell transplantation; qPCR, quantitative real-time PCR; neg., measurable residual disease negative, with the BRAF variant below the assay-specific cutoff for positivity of 0.076%¹²; NGS, next generation sequencing; -, not determined; FISH, fluorescence in situ hybridization; Days are counted relative to treatment initiation with dabrafenib and trametinib. #, these variants were detected only once in a larger NGS panel performed as part of the molecular tumor board evaluation.

Figure 1. Course of treatment. The figure displays the timeline of the patient's course of treatment, with numbers indicating days before (-) and after (+) start of treatment with dabrafenib and trametinib. The fishplot indicates variant allele fractions of indicated genes. aza, azacitidine; CRi, complete remission with incomplete count recovery; CRM RD-, complete remission without measurable residual disease; CTCAE, common terminology criteria for adverse events; dabra, dabrafenib; Dx, initial diagnosis; GvHD, graft-versus-host disease; HCT, hematopoietic stem cell transplantation; MLFS, morphologically leukemia-free state; tram, trametinib; ven, venetoclax.

