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AML typical mutations (*CEBPA*, *FLT3*, *NPM1*) identify a high-risk chronic myelomonocytic leukemia independent of CPSS molecular

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Key Points

- Infrequent in CMML, AML-like mutations (CEBPA, FLT3, or NPM1) detect poor-prognosis CMML.

Mutations commonly associated with acute myeloid leukemia (AML), such as *CEBPA*, *FLT3*, *IDH1/2*, and *NPM1*, are rarely found in chronic myelomonocytic leukemia (CMML), and their prognostic significance in CMML has not been clearly identified. In 127 patients with CMML, we have retrospectively analyzed next-generation sequencing and polymerase chain reaction data from bone marrow samples collected at the time of CMML diagnosis. Seven patients harbored *CEBPA* mutations, 8 *FLT3* mutations, 12 *IDH1* mutations, 26 *IDH2* mutations, and 11 *NPM1* mutations. Patients with CMML harboring *CEBPA*, *FLT3*, and/or *NPM1* mutations (mutCFN) more frequently had the myeloproliferative subtype, a high prevalence of severe cytopenia, and elevated blast counts. Regardless of their CMML Prognostic Scoring System molecular classification, mutCFN patients with CMML had a poor prognosis, and the multivariate analysis identified mutCFN as an independent marker of overall survival. The genetic profile of these mutCFN patients with CMML closely resembled that of patients with AML, with higher-risk clinical characteristics. Our findings lead us to suggest including the assessment of these mutations in CMML prognostic models and treating these patients with AML-type therapies,

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In accordance with privacy and ethical guidelines, data supporting the findings of this study are available upon reasonable request from the corresponding author, Marina Díaz-Beyá (diazbeya@clinic.cat).

The full-text version of this article contains a data supplement.

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including intensive chemotherapy and allogeneic stem cell transplantation, whenever feasible. Furthermore, certain targeted therapies approved for use in AML should be considered.

Introduction

Approximately 90% of individuals diagnosed with chronic myelomonocytic leukemia (CMML) harbor at least 1 somatic mutation affecting various pathways. Mutations in *TET2* (~60%), *SRSF2* (~50%), *ASXL1* (~40%), and the oncogenic *RAS* pathway (~30%) are the most frequent,[1-3] and *ASXL1, NRAS, RUNX1*, and *SETBP1* mutations are associated with poor prognosis.[4,5] The *TP53* mutation is infrequent in CMML but has also been associated with adverse prognosis.[5]

Patients with CMML may also harbor (albeit infrequently) mutations commonly found in acute myeloid leukemia (AML), such as *CEBPA*, *FLT3*, *IDH1/2*, and *NPM1*. These mutations are well-known in the context of AML, both for their prognostic implications and, in some cases, as therapeutic targets. However, data on the clinical significance of these AML-associated mutations and their potential impact on patient with CMML management are scarce,[6-8] likely due in part to their relatively rare occurrence. *CEBPA* and *FLT3* mutations have been reported in only 4% to 8%[9,10] and <5%,[9,11,12] respectively, of patients with CMML. *IDH* mutations have been described in <5%[13-16] of patients with CMML and are frequently considered mutually exclusive with *TET2* mutations.[13] *NPM1* mutations have been detected in ~3% to 5% of patients with CMML.[6,7,17-23] Although current knowledge of the frequency and prognostic impact of *NPM1* mutations in CMML is limited to findings from small series and case reports,[23] they are generally associated with a rapidly evolving clinical course and indicate the need for intensive AML treatment protocols when feasible, including allogeneic hematopoietic stem cell transplantation (alloHSCT).[8,24-32] The status of these AML-associated mutations is not currently included in CMML prognostic models (CMML Prognostic Scoring System molecular [CPSS-Mol], the Groupe Français des Myélodysplasies, and the Mayo Molecular Model[4,33,34]), although they may have prognostic implications, in that they can identify higher-risk patients. In addition, they may have therapeutic implications, particularly regarding *IDH1/2*[34,35] and *FLT3* inhibitors.[11,36-39]

To elucidate the clinical and biological characteristics and prognostic impact of *CEBPA*, *FLT3*, *IDH1/2*, and *NPM1* mutations in CMML, we have retrospectively analyzed data on the, to our knowledge, largest cohort to date including patients with these mutations, with the aim of suggesting personalized treatment of these patients based on the mutational status of these AML-associated genes.

Patients and methods

This was a retrospective analysis of 127 patients with CMML. A total of 83 patients had been diagnosed with CMML at our hospital from 2015 to 2022 and an additional 44 patients had been diagnosed at other institutions affiliated with the Spanish Group of Myelodysplastic Syndromes. The patients from our center were included if they had available targeted next-generation sequencing (NGS) data regardless of their mutational status, whereas the patients selected from other institutions were known to harbor mutations in at least 1 AML-associated gene. Thus, the present cohort was enriched with patients with CMML harboring AML-like mutations. Patient diagnoses were made on the basis of the 2022 criteria established by the World Health Organization and the International Consensus Classification in 2022.[40-42] Bone marrow samples were collected both at the time of CMML diagnosis and, whenever feasible, at progression to AML. Cytogenetic analysis involved the examination of G-banded metaphase cells.

Genetic analyses were performed on all patients at the time of CMML diagnosis. Targeted NGS was performed using the Ion AmpliSeq AML Research Panel (Thermo Fisher Scientific), Oncomine Myeloid Research Assay panel (Thermo Fisher Scientific), or the Sophia DDM Myeloid Solution panel (Sophia Genetics), as previously described.[43-45] *FLT3*-internal tandem duplication (ITD), *FLT3*-tyrosine kinase domain (TKD) (835/836 variants), *IDH1*, *IDH2*, and *NPM1* mutations were also assessed with conventional polymerase chain reaction–based techniques, as previously described.[46,47] The *FLT3*-ITD allelic ratio was assessed using polymerase chain reaction DNA fragment analysis (3500xL Genetic Analyzer; Applied Biosystems, Thermo Fisher Scientific), as previously described.[46,47] We acknowledge the limited capacity of NGS techniques to detect some *CEBPA* variants.

Categorical variables were expressed as numbers and percentages, whereas continuous variables were presented as median (range). Group differences were assessed with the Fisher exact test, χ^2test, Mann-Whitney *U* test, or Student *t* test, as appropriate. Overall survival (OS) was defined as the duration from CMML diagnosis to death from any cause or the last follow-up. OS was computed using the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis was performed using Cox proportional hazards regression analysis. The median follow-up was determined using the Kaplan-Meier estimate of potential follow-up.[48] The cumulative incidence of progression (CIP) to AML was estimated with a competing risk approach, wherein death from any cause without disease progression served as a competing event. The cumulative incidence of relapse (CIR) was estimated with a competing risk approach, wherein death without relapse served as a competing event. The impact of quantitative covariates was assessed using the Fine-Gray regression model.[49] Patients with no events were censored at the time of the last follow-up. All statistical analyses were performed with IBM SPSS Statistics, Version 23.0 (IBM Corp, Armonk, NY) or R, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Significance was set at $P < .05$.

The prognosis of patients was assessed using the CPSS and CPPS-Mol.[4,50] Treatment response to hypomethylating agents was categorized into 5 groups based on the criteria established by Savona et al[51]: no response, complete response, hematologic response, partial response, and clinical benefit.

We used a validation series from different centers affiliated with the Spanish Group of Myelodysplastic Syndromes. The validation series consists of 168 patients with CMML with available NGS data (supplemental Tables 1 and 2).

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Table 1. Mutations in *CEBPA*, *FLT3*, *IDH1*, *IDH2*, or *NPM1* detected at diagnosis

Number of patients	cDNA	Protein	VAF*	Comutations (VAF, %)
***CEBPA* (n = 7)**				
1	c.998G>C	p.(Arg333Pro)†	5.4	*DNMT3A* (38.5), *FLT3* (7.7), *NPM1* (38.2), *IDH1* (18.5)
1	c.971T>A	p.(Leu324Gln)†	33.05	*EZH2* (55.07), *ETV6* (50.09), *PTPN11* (12.54), *SRSF2 (34.94)*
1	c.890G>T	p.(Arg297Leu)†	7.38	*TET2* (42.44), *EZH2* (84.39), *ASXL1* (43), *RUNX1* (24.3, 6.76, 23.17), *ZRSR2* (87.65), *STAG2* (13.31, 11.47)
1	c.48_49insGGCTAA	p.(Ser16.Ser17insGlyTer)	4	*SRSF2* (46.1), *ASXL1* (46.8), *CBL* (1), *TET2* (47.4, 45.3)
	c.700_710dup	p.(Pro239fs)	31.2	
1	c.988C>T	p.(Gln330Ter)‡	42.94	None
	c.325_326insGCGGGCGTAAAAAACTACC	p.(Pro109fs)	41.4	
1	c.767T>A	p.(Leu256Gln)	27.72	*CSF3R* (20.63), *EZH2* (86.22), *NF1* (25.68), *ZRSR2* (84.85), *RUNX1* (40.98, 4.17)
1	c.950T>A	p.(Leu317Gln)†	27.93	*ASXL1* (48), *RUNX1* (31.51, 9.16)
***FLT3*§ (n = 8)**				
6	TKD			
1	c.2503G>T	p.(Asp835Tyr)‖	30.36	*DNMT3* (46.48), *NPM1* (37.04)
1	c.2516A>G	p.(Asp839Gly)‖	7.7	*CEBPA* (5.4), *DNMT3A* (38.5), *NPM1* (38.20), *IDH1* (18.5)
1	c.1879G>A	p.(Ala627Thr)¶	51.41	*TET2* (46.92), *NPM1* (40.58), *FLT3*-ITD (11.64, 21 bp)
1	c.A1993C	p.(Met665Leu)¶	13.87	*DNMT3A* (50.42), *MTOR* (9.21), *KRAS* (25.81), *NPM1* (38.71)
	c.G1992A	p.(Met664Ile)¶	13.55	
1	c.T1771G	p.(Tyr591Asp)¶	25.71	*NRAS* (2.83), *CUX1* (47.03), *KMT2D* (45.91), *SRSF2* (43.08), *ASXL1* (43.32), *BCORL1* (95.18)
	c.A1715G	p.(Tyr572Cys)¶	28.9	
1	c.1852T>C	p.(Ser618Pro)¶	50.22	*JAK2* (3.68), *TET2* (88.37), *ASXL1* (49.81)
3	ITD		11.6 (5.5-30)	Patient 1: *DNMT3A* (36.69), *U2AF1* (41.7), *SF3B1* (39.75) Patient 2: *NPM1* (37.28), *DNMT3A* (34.15), *SF3B1* (41.6), *PDGFRB* (40.14) Patient 3: *TET2* (46.92), *NPM1* (40.58), FLT3-TKD (51.41)
***IDH1* (n = 12)**				
5	c.395G>A	p.(Arg132His)	25 (16-45)	Patient 1: *CEBPA* (5.4), *DNMT3A* (38.5), *FLT3*-TKD (7.7), *NPM1* (38.20) Patient 2: *SRSF2* (37.87), *RUNX1* (34.8%) Patient 3: *DNMT3A* (39.8), *TET2* (38.3) Patient 4: *ASXL1* (33.60), *SRSF2* (15.94), *TET2* (27.13) Patient 5: *ASXL1* (10, 23), *SRSF2* (43)
3	c.394C>T	p.(Arg132Cys)	13 (5-21)	Patient 1: *NRAS* (3.71), *TET2* (50.87, 44.59, 47.77), *EZH2* (92.79), *RUNX1* (20.48), *STAG2* (6.52) Patient 2: *RUNX1* (16.38), *STAG1* (16.98) Patient 3: *RUNX1* (2.15), *SRSF2* (44), *TET2* (45.3, 18.5, 4.4)
1	c.298C>T	p.(Arg100Ter)	51.75	*ASXL1* (32.8), *RUNX1* (32.8), *SRSF2* (50.5), *STAG2* (10.3)
1	c.122+2T>G	Splice site	18.2	*SRSF2* (11.2, 21.8), *TET2* (45.4, 43.3)
2			Not available	

cDNA, complementary DNA; NA, not available; VAF, variant allele frequency.
*For mutations present in >1 patient, we show VAF median and range. For mutations present in only 1 patient, we show %VAF.
†*CEBPA* in-frame point mutations in the bZIP region (n = 4).
‡*CEBPA* mutations in the bZIP region (n = 5).
§One patient had both *FLT3*-ITD and *FLT3*-TKD.
‖*FLT3-TKD2* variants (n = 2).
¶*FLT3*-TKD1 variants (n = 6).

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee/institutional review board of Hospital Clinic Barcelona (2021-1230; on 20 July 2022). This study was approved by all the participating centers. All participants provided informed consent for inclusion in the study.

Results

CEBPA, *FLT3*, *IDH1/2*, and *NPM1* mutations

CEBPA mutations were detected in 7 patients, with 5 occurring in the basic leucine zipper (bZIP) region. Among these, 4 were bZIP

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Table 1 (continued)

Number of patients	cDNA	Protein	VAF*	Comutations (VAF, %)
***IDH2* (n = 26)**				
26	c.419G>A	p.(Arg140Gln)	41 (1.9-50)	Patient 1: *ASXL1* (27.5), *U2AF1* (44.5) Patient 2: *ASXL1* (36.9), *KRAS* (43.3), *SRSF2* (46.8) Patient 3: *ASXL1* (40), *SRSF2* (44), *STAG2* (45) Patient 4: *JAK2* (35.1) Patient 5: *SRSF2* (47), *TET2* (21) Patient 6: *ASXL1* (40.2), *SRSF2* (50), *TET2* (42.2) Patient 7: *DNMT3A* (1.98), *SF3B1* (7.3) Patient 8: *ASXL1* (22), *JAK2* (3.6), *SH2B3* (48.5, 22.6), *SRSF2* (44.4) Patient 9: *SRSF2* (42) Patient 10: *SRSF2* (47.2), *JAK2* (47.6), *CBL* (94.6) Patient 11: *ASXL1* (24), *TET2* (4.6), *U2AF1* (48) Patient 12: *SRSF2* (34.32), *EZH2* (8.66), *ETNK1* (32.17) Patient 13: *JAK2* (4.12), *ASXL1* (46.92), *CBL* (24.1), *SRSF2* (58.84, 44.12, 43.11) Patient 14: *U2AF1* (43), *MPL* (25), *ZRSR2* (38) Patient 15: *ASXL1* (29), *U2AF1* (46.44), *ZRSR2* (44) Patient 16: *DNMT3A* (40), *NPM1* (34.45), *NF1* (50), *SETBP1* (45.36) Patient 17: *DNMT3A* (36.09), *NPM1* (33.13) Patient 18: *CSF3R* (16.26), *CDH23* (45.45), *SH2B3* (50.54), *SETBP1* (20), *STAG2* (29.6, 12.31) Patient 19: *DNMT3A* (51.9) Patient 20: *JAK2* (88.4), *SRSF2* (53.2) Patient 21: *ZRSR2* (84.6), *TET2* (48.2), *MPL* (48.5) Patient 22: *ZRSR2* (86.62) Patient 23: *ASXL1* (38.82), *SRSF2* (47.93) Patient 24: *KRAS* (23.81) Patient 25: *CBL* (4.45), *KRAS* (3.98, 8.58), *SRSF2* (50.07) Patient 26: *ASXL1* (36.27, 11.36), *U2AF1* (46.82), *ZRSR2* (35.95)
***NPM1* (n = 11)**				
6	c.863_864insTCTG	p.(Trp288CysfsTer12)	41 (37-47)	Patient 1: *DNMT3* (41.5, 46.48), *FLT3*-TKD (30.36) Patient 2: *CEBPA* (5.4), *DNMT3A* (38.5), *FLT3*-TKD (7.7), *IDH1* (18.5) Patient 3: *TET2* (46.92), *FLT3*-TKD (51.41), *FLT3*-ITD (11.64) Patient 4: *DNMT3A* (44.42, 48.80) Patient 5: *SF3B1* (49) Patient 6: *DNMT3A* (NA), *NRAS* (NA)
4	c.772_773insTCTG	p.(Leu258fs)	5.6 (33-39)	Patient 1: *DNMT3A* (50.4), *MTOR* (9.21), *KRAS* (25.81), *FLT3*-TKD (13.87, 13.55) Patient 2: *FLT3*-ITD (5.45), *DNMT3A* (34.15), *SF3B1* (41.6), *PDGFRB* (40.14) Patient 3: *DNMT3A* (40), *IDH2* (38.04), *NF1* (50), *SETBP1* (45.36) Patient 4: *DNMT3A* (36.09), *IDH2* (37.96%)
1	c.861_862insTGCA	p.(Leu287fs)	30.77	*PTPN11* (23.37), *WT1* (18.43)

cDNA, complementary DNA; NA, not available; VAF, variant allele frequency.
*For mutations present in >1 patient, we show VAF median and range. For mutations present in only 1 patient, we show %VAF.
†*CEBPA* in-frame point mutations in the bZIP region (n = 4).
‡*CEBPA* mutations in the bZIP region (n = 5).
§One patient had both *FLT3*-ITD and *FLT3*-TKD.
‖ *FLT3-TKD2* variants (n = 2).
¶*FLT3*-TKD1 variants (n = 6).

in-frame mutations, all of which were point mutations, with no bZIP in-frame insertions or deletions observed. *FLT3* mutations were detected in 8 patients: 2 had *FLT3*-ITD; 5 had *FLT3*-TKD, 2 of whom harbored 2 different variants; and 1 had both *FLT3*-ITD and *FLT3*-TKD. A total of 6 *FLT3*-TKD1 variants and 2 *FLT3*-TKD2 variants were detected. All these variants were distinct from typical D835/I836 mutations except for one. *IDH1* mutations were detected in 12 patients and *IDH2* in 26. All the *IDH2* mutations were the c.419G>A p.(Arg140Gln) variant. *NPM1* mutations were observed in 11 patients (Table 1; Figure 1; supplemental Figure 1).

Patient characteristics and outcomes according to CEBPA, FLT3 ITD/TKD, IDH1/2, and NPM1 mutational status

Patients harboring *CEBPA*, *FLT3*, or *NPM1* mutations had unfavorable characteristics and a poorer prognosis than those without these mutations (Table 2). Specifically, in comparison with *CEBPA* wild-type patients, those with *CEBPA* mutations had a higher bone marrow blast count ($P = .002$); were more frequently categorized as CMML-2 according to the 2022 International Consensus Classification/World Health Organization classification ($P = .001$);

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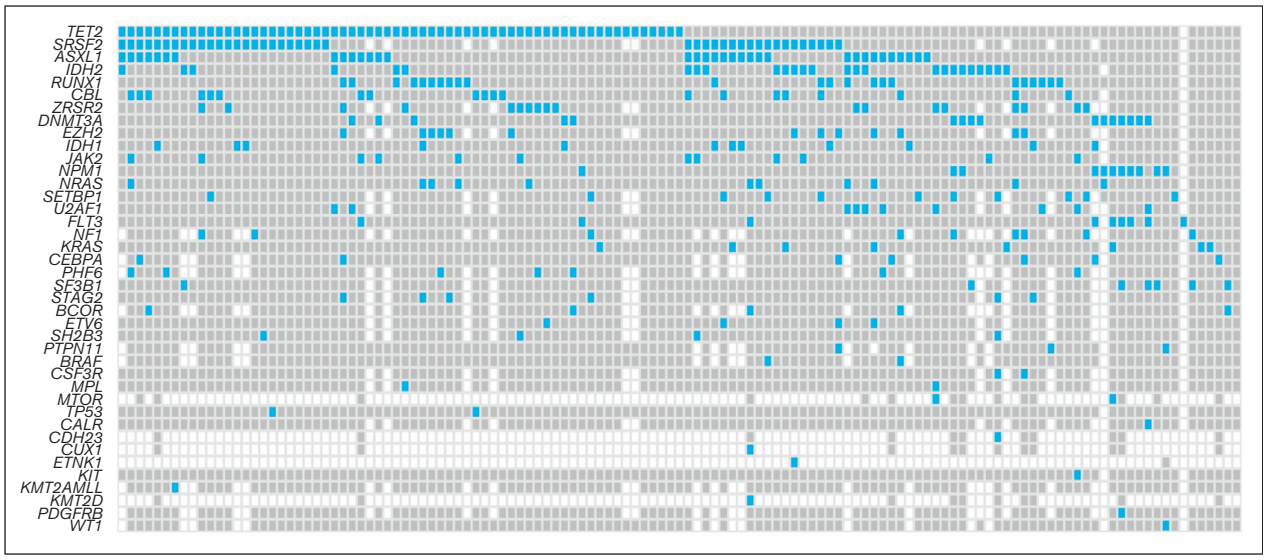

Figure 1. Mutations detected at diagnosis in the entire cohort. Each column corresponds to 1 patient. Each row corresponds to 1 gene. Gray squares indicate wild-type genes. White squares indicate unanalyzed genes. Blue squares represent mutated genes.

had elevated risk according to CPSS-Mol ($P = .06$); more frequently received modifying treatments ($P = .04$), such as chemotherapy ($P = .01$) and alloHSCT ($P = .003$); and had a shorter OS when censored at the time of alloHSCT ($P = .002$) (Table 2). When we examined the OS of 4 patients with bZIP in-frame *CEBPA* mutations vs the 3 patients without bZIP in-frame *CEBPA* mutations, we found no significant differences (21.8 months [95% confidence interval (CI), 8.2 to not achieved(NA)] vs 22.2 months [95% CI, 10 to NA]; $P = .446$; supplemental Figure 2).

In comparison with *FLT3* wild-type patients, those with *FLT3* mutations were younger ($P = .04$); had higher leukocyte ($P = .004$), monocyte ($P = .01$), and bone marrow blast counts ($P = .003$) and lower hemoglobin levels ($P = .002$); more commonly had the myeloproliferative (MP) CMML subtype ($P = .006$); were more frequently categorized as CMML-2 ($P = .002$); had elevated risk according to CPSS ($P = .009$) and CPSS-Mol ($P = .013$); had greater transfusion dependence ($P < .001$); more frequently received modifying treatments ($P = .04$), such as chemotherapy ($P < .001$) and alloHSCT ($P = .002$); had a shorter OS when censored at the time of alloHSCT ($P < .001$); and had a higher 2-year CIP to AML ($P < .001$; Table 2). We did not detect significant differences in clinical and biological characteristics or outcomes between patients with *FLT3*-ITD and *FLT3*-TKD (data not shown). However, the small sample size of patients with CMML with *FLT3* mutations precluded a robust analysis.

In comparison with *NPM1* wild-type patients, those with *NPM1* mutations had higher leukocyte ($P = .002$), monocyte ($P = .002$), and bone marrow blast counts ($P < .001$) and lower hemoglobin levels indicating anemia ($P < .001$); more frequently had the MP-CMML subtype ($P = .008$); were more frequently categorized as CMML-2 ($P < .001$); had elevated risk according to CPSS ($P < .001$); had greater transfusion dependence ($P < .001$); more frequently received modifying treatments ($P = .008$), such as chemotherapy ($P < .001$) and alloHSCT ($P = .005$); had a shorter time to treatment (0.8 vs 3 months; $P = .01$); had a shorter OS when censored at the time of alloHSCT (9 vs 35.2 months; $P < .001$); and had a higher 2-year CIP to AML (36.4% vs 15%; $P = .01$; Table 2). Patients with *NPM1* mutations who received intensive 7+3–type chemotherapy had longer OS than those who did not receive it (28.7 vs 5.6 months; $P < .001$; supplemental Figure 3).

There were no significant differences in patient characteristics and outcomes between patients with mutations in *IDH1* or *IDH2* and those with wild-type *IDH* (Table 3).

Characteristics and outcomes of patients with *CEBPA, FLT3*, and/or *NPM1* mutations

A total of 21 patients had mutations in *CEBPA*, *FLT3*, and/or *NPM1* (mutCFN), whereas the remaining 93 patients had the wild-type form of all 3 genes (wtCFN). More than 1 of these mutations was harbored by 17 patients. Of the 83 patients from our institution, 7 (8%) had mutCFN, whereas 14 patients from the other institutions had mutCFN. mutCFN patients had more unfavorable characteristics and poorer prognosis than wtCFN patients (Table 4). In comparison with wtCFN patients, mutCFN patients were younger (63 vs 71 years; $P = .03$); had higher leukocyte (19.6×10^9/L vs 7.6×10^9/L; $P = .003$), monocyte (2.9×10^9/L vs 1.7×10^9/L; $P = .006$), and bone marrow blast count (12% vs 4%; $P < .001$); and had lower hemoglobin levels (8.6 vs 11.4 g/dL; $P < .001$) and platelet count (98×10^9/L vs 117×10^9/L; $P = .04$). They were also more frequently associated with the MP-CMML subtype (61.9% vs 29%; $P = .01$); were more frequently categorized as CMML-2 (81% vs 14.1%; $P < .001$); and had elevated risk according to CPSS (75% vs 29.8%; $P < .001$) and CPSS-Mol (88.2% vs 44%; $P = .001$).

mutCFN patients had greater transfusion dependence (66.7% vs 21.5%; $P < .001$) and more frequently received modifying treatment (81% vs 36.6%; $P < .001$), including hypomethylating agents (61.9% vs 31.2%; $P = .01$), chemotherapy (57.1% vs 6.5%; $P < .001$), and alloHSCT (57.1% vs 11.8%; $P < .001$). They also had a shorter time to treatment (0.9 vs 4.5 months; $P = .002$), shorter OS (22.2 vs 46.8 months; $P = .01$), and a higher 2-year CIP to AML (39.8% vs 13.7%; $P < .001$) (Table 4; Figure 2). mutCFN patients who received chemotherapy (n = 12) showed a trend toward longer OS than those

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Table 2. Patient characteristics and outcomes according to *CEBPA*, *FLT3*, and *NPM1* mutational status

Characteristics	mut*CEBPA* (n = 7), n (%)	wt*CEBPA* (n = 105), n (%)	*P* value	mut*FLT3* (n = 9), n (%)	wt*FLT3* (n = 117), n (%)	*P* value	mut*NPM1* (n = 11), n (%)	wt*NPM1* (n = 115), n (%)	*P* value
Age, y, median (range)	64 (50-76)	71 (28-95)	.08	63 (55-75)	71 (28-95)	.04	60 (47-86)	71 (28-95)	.1
Sex (men/women)	7/0 (100/0)	79/26 (75.2/24.8)	NS	7/2 (77.8/22.2)	88/29 (75.2/24.8)	NS	8/3 (72.7/27.3)	87/28 (75.7/24.3)	NS
Leukocytes, $\times 10^9$/L, median (range)	8.9 (4-78)	8.3 (2-94)	NS	22 (6-56)	7.7 (2-94)	.004	20.4 (10-31)	7.6 (2-94)	.002
Neutrophils, median (range)	2.6 (0.4-41)	4 (0.4-40.3)	NS	7.2 (2-20)	3.5 (0.4-41)	.1	5.2 (2.2-20)	3.5 (0.4-41)	.05
Monocytes, median (range)	1.4 (1.1-29)	1.8 (0.5-33.7)	NS	3 (1.5-24)	1.6 (0.5-34)	.01	5 (1.5-12.2)	1.6 (0.5-33.7)	.002
% monocytes, median (range)	22.5 (15-36)	21.5 (10-62)	NS	25.3 (10-42)	21.9 (10-62)	NS	28 (10-62)	21 (10-61)	NS
Platelets, $\times 10^9$/L, median (range)	107.5 (39-207)	111.5 (6-982)	NS	70 (6-149)	127 (7-982)	.09	86 (13-167)	125 (6-982)	NS
Hemoglobin, g/dL, median (range)	10.6 (6-13)	11 (5-8.5)	NS	8.6 (5-12)	11.3 (6-8.5)	.002	8.3 (5-11)	11.4 (6-8.5)	<.001
Blasts BM, % median (range)	12 (6-19)	4 (0-19)	.002	15 (2-19)	4 (0-19)	.003	14 (1-19)	4 (0-19)	<.001
Cytogenetic alterations	2 (28.6)	20 (21.1)	NS	2 (22.2)	21 (19.6)	NS	1 (10)	22 (20.8)	NS
Cytogenetic risk			NS			NS			NS
Low	5 (83.3)	77 (81)		7 (77.8)	88 (83)		9 (90)	86 (81.9)	
Intermediate	1 (16.7)	8 (8.5)		2 (22.2)	7 (6.6)		1 (10)	8 (7.6)	
High	0	10 (10.5)		0	11 (10.4)		0	11 (10.5)	
Therapy-related	0	4 (4)	NS	0	5 (4.6)	NS	0	5 (4.7)	NS
ICC/WHO 2022 classification			NS			.006			.008
MD-CMML	4 (57.1)	69 (65.7)		2 (22.2)	82 (70.1)		3 (27.3)	80 (69.6)	
MP-CMML	3 (42.9)	36 (34.3)		7 (77.8)	35 (29.9)		8 (72.7)	35 (30.4)	
ICC/WHO 2022 classifications			.001			.002			<.001
CMML-1	1 (14.3)	81 (77.9)		2 (22.2)	89 (76.7)		1 (9.1)	89 (78.1)	
CMML-2	6 (85.7)	23 (22.1)		7 (77.8)	27 (23.3)		10 (90.9)	25 (21.9)	
CPSS			NS			.03			<.001
Low	1 (14.3)	33 (34.7)		0	41 (38.3)		0	41 (38.7)	
Intermediate-1	1 (14.3)	28 (29.5)		2 (22.2)	32 (29.9)		1 (10)	32 (30.2)	
Intermediate-2	4 (57.1)	28 (29.5)		6 (66.7)	27 (25.3)		9 (90)	25 (23.6)	
High	1 (14.3)	6 (6.3)		1 (11.1)	7 (6.5)		0	8 (7.5)	
Dichotomized CPSS			.1			.009			<.001
Low + intermediate-1	2 (28.6)	61 (64.2)		2 (22.2)	73 (68.2)		1 (10)	73 (68.9)	
Intermediate-2 + high	5 (71.4)	34 (35.8)		7 (77.8)	34 (31.8)		9 (90)	33 (31.1)	
CPSS-Mol			.06			.01			.003
Low	0	20 (23.3)		0	23 (23.5)		0	23 (23.7)	
Intermediate-1	1 (16.7)	23 (26.7)		0	27 (27.6)		1 (12.5)	26 (26.8)	
Intermediate-2	1 (16.7)	26 (30.2)		6 (85.7)	26 (26.5)		7 (87.5)	25 (25.8)	
High	4 (66.6)	17 (19.8)		1 (14.3)	22 (22.4)		0	23 (23.7)	

HMA, hypomethylating agents; ICC, International Consensus Classification; MD, myelodysplastic; BM, bone marrow; mut, mutated; NS, Not Significant; WHO, World Health Organization; wt, wild-type.
*Patients who received alloSCT were censored at the time of alloHSCT.

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Table 2 (continued)

Characteristics	mut*CEBPA* (n = 7), n (%)	wt*CEBPA* (n = 105), n (%)	*P* value	mut*FLT3* (n = 9), n (%)	wt*FLT3* (n = 117), n (%)	*P* value	mut*NPM1* (n = 11), n (%)	wt*NPM1* (n = 115), n (%)	*P* value
Dichotomized CPSS-Mol			NS			.013			.06
Low + intermediate-1	1 (16.7)	43 (50)		0	50 (51)		1 (12.5)	49 (50.5)	
Intermediate-2 + high	5 (83.3)	43 (50)		7 (100)	48 (49)		7 (87.5)	48 (49.5)	
Transfusion dependence	3 (42.9)	29 (27.6)	NS	8 (88.9)	28 (4.3)	<.001	9 (81.8)	27 (23.9)	<.001
Patients receiving modifying treatment	6 (85.7)	44 (41.9)	.04	7 (77.8)	46 (39.3)	.04	9 (81.8)	43 (37.4)	.008
Patients receiving HMA	5 (71.4)	36 (34.3)	.098	5 (55.6)	39 (33.3)	.3	5 (45.5)	38 (33)	.5
Patients receiving chemotherapy	4 (57.1)	14 (13.3)	.01	6 (66.7)	12 (10.3)	<.001	7 (63.6)	11 (9.6)	<.001
HMA response			NS			.3			NS
Complete response	3 (60)	10 (30.3)		0	13 (38.2)		2 (40)	11 (33.3)	
Marrow response	0	1 (3)		0	1 (2.9)		0	1 (3)	
Partial remission	1 (20)	3 (9.1)		0	4 (11.8)		0	4 (12.1)	
Clinical benefit	0	3 (9.1)		1 (25)	2 (5.9)		0	3 (9.2)	
No response	1 (20)	16 (48.5)		3 (75)	14 (41.2)		3 (60)	14 (42.4)	
Chemotherapy response			NS			NS			.068
Complete response	3 (75)	9 (64.3)		5 (83.3)	7 (58.3)		6 (85.7)	6 (54.5)	
Partial response	0	1 (7.1)		0	1 (8.4)		1 (14.3)	0	
No response	1 (25)	4 (28.6)		1 (16.7)	4 (33.3)		0	5 (45.5)	
Time to treatment, median (range)	1.3 (0.3-4.3)	3 (0.07-111.7)	.1	0.9 (0.3-31)	2.8 (0.07-111.7)	.1	0.8 (0.07-5.8)	3 (0.1-111.7)	.01
Allogeneic transplant	5 (71.4)	17 (16.2)	.003	6 (66.7)	18 (15.4)	.002	6 (54.5)	17 (14.8)	.005
OS, median (95% CI)*	10 (3.6-16.4)	29.8 (18.4-41.3)	.002	7.6 (5.3-9.9)	31 (18.7-43.3)	<.001	9 (6.2-11.7)	35.2 (22.4-48)	<.001
OS, median (95% CI)	22.2 (3.2-41)	36.6 (15.3-58)	.056	27.8 (13.7-41.8)	38.2 (18.7-57.7)	.2	25.1 (4.8-45.5)	36.6 (17.3-55.9)	.1
CIP to AML at 2 y, % (95% CI)	28.6 (2.5-65.4)	18.1 (11.2-26.3)	.6	50 (12.5-79.4)	14.5 (8.7-21.8)	<.001	36.4 (10.1-64)	15 (8.9-22.4)	.01

HMA, hypomethylating agents; ICC, International Consensus Classification; MD, myelodysplastic; BM, bone marrow; mut, mutated; NS, Not Significant; WHO, World Health Organization; wt, wild-type.
*Patients who received alloSCT were censored at the time of alloHSCT.

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Table 3. Patient characteristics and outcomes according to *IDH1/2* mutational status

Characteristics	mut*IDH1* (n = 12), n (%)	wt*IDH1* (n = 113), n (%)	*P* value	mut*IDH2* (n = 26), n (%)	wt*IDH2* (n = 99), n (%)	*P* value	mut*IDH* (n = 38), n (%)	wt*IDH* (n = 89), n (%)	*P* value
Age, y, median (range)	74.5 (53-92)	71 (27.8-95)	NS	72 (47-87)	71 (28-95)	NS	73 (47-92)	70 (28-95)	NS
Sex (man/woman)	9/3 (75/25)	85/28 (75.2/24.8)	NS	22/4 (84.6/15.4)	72/27 (72.7/27.3)	NS	31/7 (81.6/18.4)	65/24 (73/27)	NS
Leukocytes, $\times 10^9$/L, median (range)	4.9 (3.3-27.6)	8.3 (2.4-93.7)	NS	7.2 (3.1-54.3)	8.3 (2.4-94)	NS	7.1 (3.1-54)	9.1 (2.4-94)	NS
Neutrophils, median (range)	1.97 (0.5-14.8)	3.9 (0.4-41)	NS	3.4 (0.4-40.3)	3.9 (0.4-41)	NS	3.3 (0.4-40.3)	4.2 (0.4-41)	NS
Monocytes, median (range)	1 (0.7-8.5)	1.8 (0.5-33.7)	NS	1.6 (0.5-12.2)	1.8 (0.5-33.8)	NS	1.4 (0.5-12.2)	1.9 (0.5-33.7)	NS
% monocytes, median (range)	23.5 (10.6-60.9)	21.2 (10-62.4)	NS	20 (10-62.4)	22.8 (10-61)	NS	22 (10-62.4)	22.2 (10-60)	NS
Platelets, $\times 10^9$/L, median (range)	100 (21-323)	124 (6-982)	NS	176 (19-535)	111 (6-982)	NS	151 (19-535)	112 (6-982)	NS
Hemoglobin, g/dL, median (range)	10.6 (7.9-14.2)	11.1 (4.9-8.5)	NS	10.8 (8-16.1)	11.1 (4.9-8.5)	NS	10.8 (8-16)	11.1 (4.9-8.5)	NS
Blasts BM, % median (range)	6 (0-19)	4 (0-19)	NS	4 (0-15)	5 (0-19)	NS	5.5 (0-19)	4 (0-19)	NS
Cytogenetic alterations	3 (25)	20 (19.4)	NS	2 (8.3)	21 (23.1)	NS	5 (13.9)	18 (22.2)	NS
Cytogenetic risk			.1			NS			.1
Low	9 (75)	85 (83.4)		22 (91.7)	72 (80)		31 (86.1)	65 (81.3)	
Intermediate	0	9 (8.8)		0	9 (10)		0	9 (11.2)	
High	3 (25)	8 (7.8)		2 (8.3)	9 (10)		5 (13.9)	6 (7.5)	
Therapy-related	1 (10)	4 (3.8)	NS	2 (8)	3 (3.3)	NS	3 (8.6)	2 (2.4)	NS
ICC/WHO 2022 classification			NS			NS			NS
MD-CMML	9 (75)	74 (65.5)		19 (73.1)	64 (64.6)		28 (73.7)	56 (62.9)	
MP-CMML	3 (25)	39 (34.5)		7 (26.9)	35 (35.4)		10 (26.3)	33 (37.1)	
ICC/WHO 2022 classifications			NS			NS			NS
CMML-1	9 (75)	81 (72.3)		20 (76.9)	70 (71.4)		29 (76.3)	62 (70.5)	
CMML-2	3 (25)	31 (27.7)		6 (23.1)	28 (28.6)		9 (23.7)	26 (29.5)	
CPSS			NS			NS			NS
Low	5 (41.7)	36 (35)		12 (50)	29 (31.9)		17 (47.2)	24 (29.6)	
Intermediate-1	2 (16.7)	31 (30)		6 (25)	27 (29.7)		8 (22.2)	26 (32.1)	
Intermediate-2	4 (33.3)	29 (28.2)		5 (20.8)	28 (30.8)		9 (25)	25 (30.9)	
High	1 (8.3)	7 (6.8)		1 (4.2)	7 (7.7)		2 (5.6)	6 (7.4)	
Dichotomized CPSS			NS			NS			NS
Low + intermediate-1	7 (58.3)	67 (65)		18 (75)	56 (61.5)		25 (69.4)	50 (61.7)	
Intermediate-2 + high	5 (41.7)	36 (35)		6 (25)	35 (38.5)		11 (30.6)	31 (38.3)	
CPSS-Mol			NS			NS			NS
Low	0	23 (24.5)		6 (27.3)	17 (20.5)		6 (18.2)	17 (23.6)	
Intermediate-1	4 (36.4)	23 (24.5)		7 (31.8)	20 (24.1)		11 (33.3)	16 (22.2)	
Intermediate-2	4 (36.4)	28 (29.8)		6 (27.3)	26 (31.3)		10 (30.3)	22 (30.6)	

HMA, hypomethylating agents; ICC, International Consensus Classification; CMML, Chronic Myelomonocytic Leukemia; MD, myelodysplastic; BM, bone marrow; mut, mutated; NS, Not Significant; WHO, World Health Organization; wt, wild-type.

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Table 3 (continued)

Characteristics	mut*IDH* (n = 12), n (%)	wt*IDH1* (n = 113), n (%)	*P* value	mut*IDH2* (n = 26), n (%)	wt*IDH2* (n = 99), n (%)	*P* value	mut*IDH* (n = 38), n (%)	wt*IDH* (n = 89), n (%)	*P* value
High	3 (27.2)	20 (21.2)		3 (13.6)	20 (24.1)		6 (18.2)	17 (23.6)	
Dichotomized CPSS-Mol			NS			NS			NS
Low + intermediate-1	4 (36.4)	46 (48.9)		13 (59.1)	37 (44.6)		17 (51.5)	33 (45.8)	
Intermediate-2 + high	7 (63.6)	48 (51.1)		9 (40.9)	46 (55.4)		16 (48.5)	39 (54.2)	
Transfusion dependence	4 (36.4)	31 (27.7)	NS	5 (20)	30 (30.6)	NS	9 (25)	28 (31.5)	NS
Patients receiving modifying treatment	4 (33.3)	48 (42.5)	NS	9 (34.6)	43 (43.4)	NS	13 (34.2)	40 (44.9)	NS
Patients treated with HMA	2 (16.7)	41 (36.3)	NS	6 (23.1)	37 (37.4)	NS	8 (21.1)	36 (40.4)	.04
Patients treated with chemotherapy	2 (16.7)	16 (14.2)	NS	3 (11.5)	15 (15.2)	NS	5 (13.2)	13 (14.6)	NS
Time to treatment, median (range)	3.1 (2.6-4)	2.1 (0.1-111.7)	NS	1.4 (0.3-57.4)	2.6 (0.1-111.7)	NS	2.8 (0.3-57.4)	2.1 (0.1-111.7)	NS
Allogeneic transplant	3 (25)	20 (17.7)	NS	4 (15.4)	19 (19.2)	NS	7 (18.4)	17 (19.1)	NS
OS, median (95% CI)	28.7 (0.1-63)	35.8 (16.8-54.7)	NS	78.2 (13.6-143)	28.7 (18-39.5)	NS	66 (7.3-123.8)	28.7 (17-40.3)	NS
CIP to AML at 2 y, % (95% CI)	17.6 (2.4-44.6)	16.6 (10.3-24.2)	NS	13.4 (3.2-30.9)	17.9 (10.9-26.3)	NS	15.3 (5.4-29.9)	17 (10-25.6)	NS

HMA, hypomethylating agents; ICC, International Consensus Classification; CMML, Chronic Myelomonocytic Leukemia; MD, myelodysplastic; BM, bone marrow; mut, mutated; NS, Not Significant; WHO, World Health Organization; wt, wild-type.

who did not (n = 9; 25 vs 9 months; $P = .067$; supplemental Figure 4). Twelve mutCFN patients received alloHSCT (supplemental Table 3) and attained longer OS than those who did not (n = 9; 28 vs 12 months; $P = .05$; Figure 3). Median OS after alloHSCT for these 12 patients was 19.6 months (95% CI, 5-72), the 2-year CIR was 50% (95% CI, 18-75) (supplemental Figure 5), and the 2-year nonrelapse mortality rate was 25% (95% CI, 5-52). The 11 wtCFN patients with CMML who underwent alloHSCT had a post-alloHSCT median OS of 91 months (95% CI, 12 to NA; supplemental Figure 6).

The multivariate analysis identified mutCFN as an adverse prognostic factor for OS independent of age and CPSS-Mol (hazard ratio, 2.452; 95% CI, 1.237-4.86; $P = .01$; Table 5).

In the validation cohort, mutCFN patients (n = 11) had a higher 2-year CIP to AML (51.1% vs 17.2%; $P < .01$; supplemental Figure 7A), a shorter median OS when censored at the time of alloHSCT (22.8 vs 44 months; $P < .01$; supplemental Figure 7B), and a trend toward shorter OS (22.8 vs 47 months; $P = .076$; supplemental Figure 7C). Given the rarity of these mutations in CMML, and to obtain more robust results, we conducted an analysis of the combined series, resulting in a total of 282 patients. mutCFN patients (n = 32) had a shorter median OS (22.8 vs 46.9 months; $P < .001$) and a higher 2-year CIP to AML (46.2% vs 15.7; $P < .001$; supplemental Figure 8). The multivariate analysis identified mutCFN as an adverse prognostic factor for OS independent of age and CPSS-Mol (hazard ratio, 1.851; $P = .017$; supplemental Table 4). Interestingly, mutCFN patients also had a mutational profile distinct from that of wtCFN patients (Figure 4). They had a higher incidence of *DNMT3A* mutations (n = 9 [45%] vs 6 [6.5%]; $P < .001$) and a lower incidence of *TET2* mutations (n = 4 [20%] vs 55 [59.1%]; $P = .002$). They also showed a trend toward a lower incidence of *SRSF2* mutations (n = 3 [15.8%] vs 30 [35.7%]; $P = .1$).

Given that most mutCFN CMML cases were classified as CMML-2 and exhibited similarities to AML, we compared mutCFN CMML cases with both CMML-2 and M4/M5 AML. We did not find statistically significant differences in the main clinical or prognostic characteristics (supplemental Results; supplemental Tables 5-8).

Five mutCFN patients with CMML had available paired samples taken at CMML diagnosis and at progression to AML. At the time of progression to AML, all of the AML-associated mutations present at CMML diagnosis were retained. In all patients with complete NGS at CMML diagnosis and transformation, new mutations emerged at the onset of AML. These mutations were observed in genes associated with signaling (*FLT3,* n = 1; *NRAS*, n = 1), transcription (*RUNX1*, n = 1), and splicing (*STAG2*, n = 1) pathways (supplemental Figure 9).

Discussion

CEBPA, *FLT3*, *IDH*1/2, and *NPM1* mutations are commonly found in AML but are rare in CMML, and their status is not included in current CMML prognostic models. In fact, there is little information available on their impact on patient prognosis or therapeutic strategy in CMML. In the present study, we have found that patients with CMML with at least 1 mutation in *CEBPA*, *FLT3*, and/or *NPM1* have a genetic profile quite similar to that of patients with AML. Moreover, these patients had a dismal prognosis

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Table 4. Patient characteristics and outcomes according to mutational status of *CEBPA*, *FLT3*, and/or *NPM1* (mutCFN vs wtCFN)

Characteristics	mut*CFN* (n = 21), n (%)	wt*CFN* (n = 93), n (%)	*P* value
Age, y, median (range)	63 (47-86)	71 (28-95)	.03
Sex (men/women)	17/4 (81/19)	71/22 (76/24)	NS
Leukocytes, $\times 10^9$/L, median (range)	19.6 (4-78)	7.6 (2-94)	.003
Neutrophils, median (range)	5 (0.4-41)	3.8 (0.4-40)	.1
Monocytes, median (range)	2.9 (1.1-29)	1.7 (0.5-33.7)	.006
% monocytes, median (range)	28 (10-62)	19 (10-61)	.2
Platelets, $\times 10^9$/L, median (range)	98 (6-207)	117 (7-982)	.04
Hemoglobin, g/dL, median (range)	8.6 (5-13)	11.4 (7-85)	<.001
Blasts BM, % median (range)	12 (1-19)	4 (0-18)	<.001
Cytogenetic risk			NS
Low	16 (84.2)	68 (81)	
Intermediate	3 (15.8)	6 (7.1)	
High	0	10 (11.9)	
ICC/WHO 2022 classification			.01
MD-CMML	8 (38.1)	66 (71)	
MP-CMML	13 (61.9)	27 (29)	
ICC/WHO 2022 classifications			<.001
CMML-1	4 (19)	19 (85.9)	
CMML-2	17 (81)	13 (14.1)	
CPSS			.001
Low	1 (5)	33 (39.2)	
Intermediate-1	4 (20)	26 (31)	
Intermediate-2	13 (65)	20 (23.8)	
High	2 (10)	5 (6)	
CPSS-Mol			.005
Low	0	20 (26.7)	
Intermediate-1	2 (11.8)	22 (29.3)	
Intermediate-2	10 (58.8)	17 (22.7)	
High	5 (29.4)	16 (21.3)	
Transfusion dependence	14 (66.7)	20 (21.5)	<.001
Patients receiving modifying treatment	17 (81)	34 (36.6)	<.001
Patients receiving HMA	13 (61.9)	29 (31.2)	.01
Patients receiving chemotherapy	12 (57.1)	6 (6.5)	<.001
Chemotherapy response			
Complete response	9 (75)	3 (50)	NS
Partial response	1 (8.3)	0	NA
No response	2 (16.7)	3 (50)	NS
Overall response rate	10 (83.3)	3 (50)	NS
Time to treatment, median (range)	0.9 (0.07-30.5)	4.5 (0.1-111.7)	.002
Allogeneic transplant	12 (57.1)	11 (11.8)	<.001
OS, median (95% CI)*	9.1 (6.3-12)	36 (20-52.4)	<.001
OS, median (95% CI)	22.2 (8.2-36.1)	46.8 (26-67.6)	.01
CIP to AML at 2 y, % (95% CI)	39.8 (18.3-60.7)	13.7 (7.5-21.8)	<.001

HMA, hypomethylating agents; ICC, International Consensus Classification; MD, myelodysplastic; BM, bone marrow; mut, mutated; NA, Not Achieved; NS, Not Significant; WHO, World Health Organization; wt, wild-type.

*Patients who received alloHSCT were censored at the time of alloSCT.

independently of their CPSS-Mol classification, with shorter OS and a higher CIP to AML, underscoring the unmet need for more AML-type clinical approaches and novel treatments for these patients.

Previous studies have found that *CEBPA* mutations are linked to an immature myeloid blast phenotype. The specific frequency of *CEBPA* mutations in CMML ranges from 4% to 8%.[9,10] Studies in AML have reported that high rates of complete remission and long overall and relapse-free survival were attained only by patients with bZIP in-frame insertion-deletion (inDel) *CEBPA* mutations.[52,53] We detected *CEBPA* mutations in 7 of our patients with CMML. These patients had higher-risk characteristics and poor outcome. Interestingly, 4 patients harbored bZIP in-frame mutations according to Taube et al's[52] definition, none of which were the most frequently associated with mutated *CEBPA*-AML, the bZIP in-frame InDel mutation. Recently, a study showed that the beneficial effect of *CEBPA* mutation in AML is restricted to *CEBPA* bZIP in-frame InDel mutation.[53] We did not find any of these mutations in our study. The negative impact of *CEBPA* mutations in non-AML myeloid neoplasms has been scarcely investigated, but some studies identify these mutations as indicators of poor prognosis.[21,54,55] This highlights the need for further investigation into specific implications for patient outcome and treatment response.

The *FLT3* mutation has been reported in <5%[35,56] of patients with CMML, whereas it was detected in 8 patients in our study. Although the *FLT3* mutation does not necessarily predict transformation to AML, it may help determine the optimal therapeutic strategy, which could include *FLT3* inhibitors, such as midostaurin[57] and sorafenib,[43] that have been approved for AML.[11,36-39] Interestingly, 2 of our patients with *FLT3* mutations received sorafenib following a post-alloHSCT relapse (1 molecular and 1 morphological relapse) and attained prolonged responses for 8 months and a year, respectively.[43] Previous reports have found an association between *FLT3* mutations in CMML and leukocytosis, the MP-CMML subtype, shorter OS,[56] and progression to AML.[23,58] Consistent with these findings, our patients with *FLT3* mutations had higher-risk characteristics and worse outcome. In contrast to findings in AML,[59,60] most *FLT3* mutations detected in our study were TKDs, with 6 TKD1 and 2 TKD2 variants, most of which were not p.(Asp835Tyr). This aspect remains unexplored in CMML.

IDH1 and *IDH2* mutations have been reported in <5% of patients with CMML[13-16]: *IDH1* in only 1% and *IDH2* in 5%.[15,35] All the *IDH2* mutations in our patients involved the IDH2R140 hot spot, which is consistent with a previous report.[61] The prognostic impact

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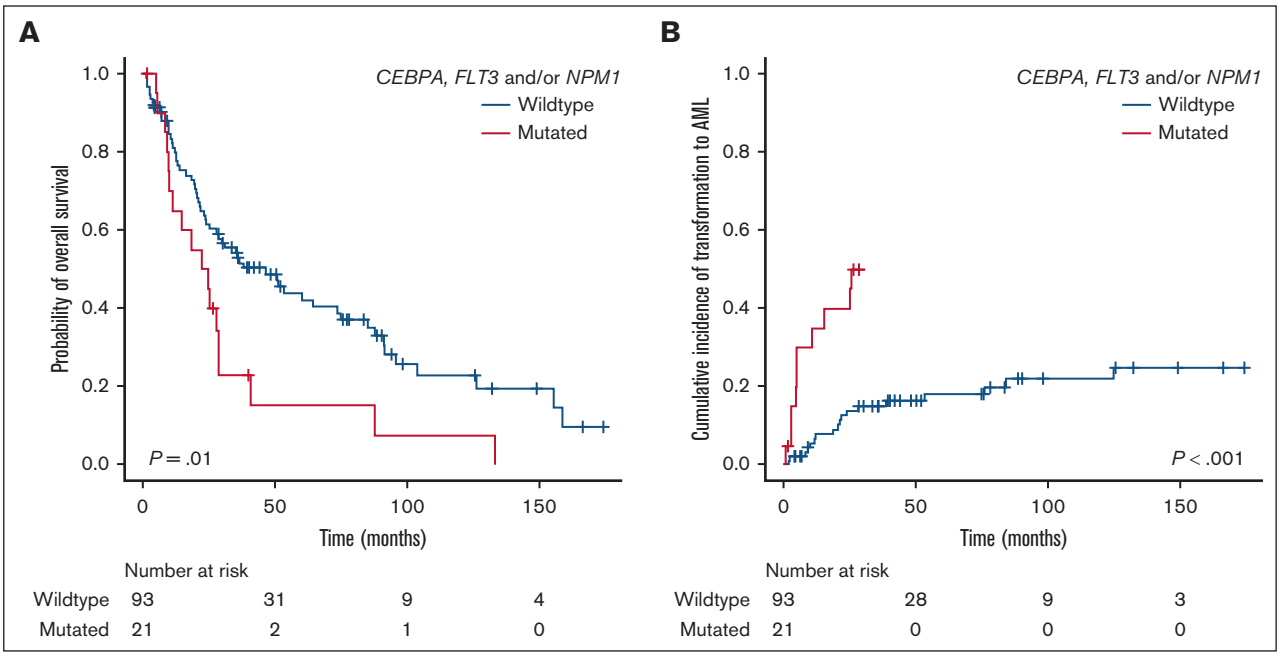

Figure 2. Survival analysis and incidence of AML transformation of patients with mutCFN vs wtCFN. OS (A) and CIP to AML (B) in mutCFN patients vs wtCFN patients.

of *IDH* mutations in CMML is not clear. One study found that OS did not differ between *IDH*-mutant and *IDH* wild-type patients,[14] whereas in another study, patients with *IDH1* mutations had a shorter OS than those with *IDH2* mutations.[15] We found no significant differences in outcomes between patients with and without *IDH1/2* mutations. Nevertheless, patients with CMML harboring *IDH* mutations may well be candidates for targeted therapy with *IDH* inhibitors, such as ivosidenib and enasidenib.[38] One of our patients received off-label treatment with the *IDH2* inhibitor enasidenib for molecular relapse after alloHSCT, and maintained a long-lasting complete response for 5 years and a half, remaining in molecular remission to this day.[43]

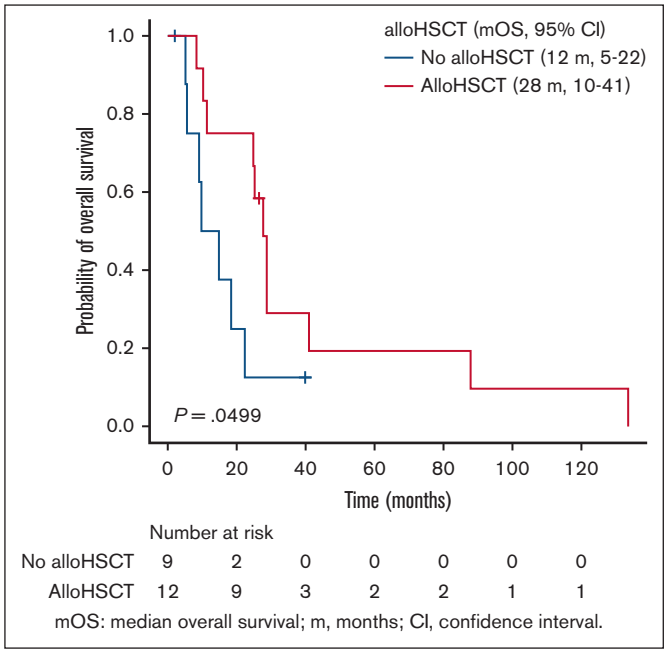

Figure 3. OS of mutCFN patients receiving (red) or not receiving (blue) alloHSCT.

NPM1 mutations have been observed in 3% to 5% of patients with CMML,[6,7,17-23] whereas we detected them in 11 of our patients. Previous studies have shown that patients with CMML with *NPM1* mutations have a high risk of progressing to AML, leading some authors to consider them as "early-stage" AML given their shared clinical and molecular characteristics.[7,19,20] Moreover, there is currently a debate on whether AML with *NPM1* mutation should be classified as AML.[29,41,62] Patients with CMML with *NPM1* mutations were found to have lower hemoglobin levels, an elevated leukocyte count, increased percentages of bone marrow monocytes and blasts, a heightened likelihood of progression to AML, and poorer OS compared with those with wild-type *NPM1*.[6,7,18] Remarkably, patients with CMML with *NPM1* mutations who progressed to AML did not exhibit the favorable prognosis typically associated with de novo AML with *NPM1* mutations.[7,19,21,23,42] In

Table 5. Multivariate analysis of OS

Variable	HR	95% CI	*P* value
Age at diagnosis (y)	1.051	1.017-1.085	.003
CPSS-Mol			.01
Low (reference)			
Intermediate-1	1.946	0.827-4.580	.127
Intermediate-2	2.386	1.002-5.684	.049
High	4.225	1.789-9.975	.001
mutCFN	2.548	1.255-5.172	.01

HR, hazard ratio; mut, mutated.

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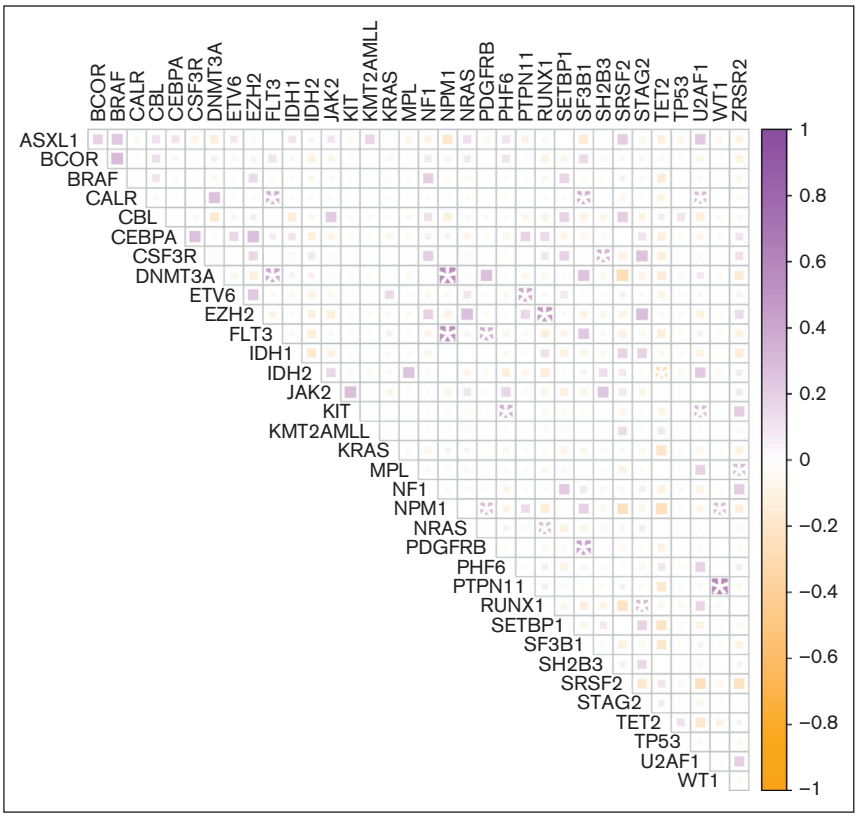

Figure 4. Co-occurrence or exclusivity of genes at diagnosis in the entire cohort. The interaction of genes repeatedly found comutated in the same patient is presented in purple. The interaction of genes observed to be mutually exclusive and those not frequently altered in the same patient is presented in orange. *$P < .05$.

line with these previous studies,[6,7] our patients with CMML with *NPM1* mutations had more adverse clinical characteristics and worse outcome than those with wild-type *NPM1*. Management of patients with CMML with these AML-associated mutations poses a challenge given the scarcity of studies with large patient cohorts.[7,8,18,23,27] Notably, some results indicate that patients with *NPM1* mutations respond well to chemotherapy,[7,8,24] implying that they might derive greater benefits from AML-type chemotherapy than from the standard CMML treatment. In fact, in the present study, OS was longer in patients with *NPM1* mutations treated with chemotherapy. However, this may reflect selection bias toward fitter patients, and the rarity of the condition makes it difficult to draw solid conclusions. Additionally, although alloHSCT is currently the only potential curative strategy for CMML, it is not clear whether patients with *NPM1*-mutated CMML should receive alloHSCT at first complete response.[7,8,18,23,27] In our patient cohort, those who received chemotherapy followed by alloHSCT had a better prognosis than those who did not, although we are aware of the treatment selection bias based on their baseline characteristics. However, we also observed a high CIR after alloHSCT, which highlights both the complexity of treating these patients and the need for further studies with larger numbers of patients.

These AML-associated mutations are not currently included in CMML prognostic scores.[4,33,34] However, our findings suggest that including *CEBPA*, *FLT3*, and/or *NPM1* mutations would help to increase prognostic accuracy despite the infrequency of these mutations in CMML. Our multivariate analysis demonstrated their independent adverse prognostic impact, suggesting that their mutational status can improve the stratification of patients with CMML.

Our study also suggests that patients with CMML with *CEBPA*, *FLT3*, and/or *NPM1* mutations exhibit a comutational pattern more typical of AML than of CMML. For example, we identified a positive correlation between *DNMT3A*, *FLT3*-ITD, and *NPM1* in these patients, which is not commonly observed in CMML but is frequently seen in AML.[7,17,63] Conversely, we observed a negative correlation with other typical CMML mutations, such as *TET2* and *ASXL1*.[7,17]

Research involving paired samples has documented clonal evolution from CMML to AML, indicating the emergence of new mutations and an increase in variant allele frequency, including *NPM1*, *FLT3*, and *SH2B3*.[23] In our study, we observed the emergence of *FLT3*, *NRAS*, *RUNX1*, and *STAG2*.

Our study has several limitations, including its retrospective nature and the relatively small numbers of patients with CMML with *CEBPA*, *FLT3*, and/or *NPM1* mutations due to the rarity of these alterations in CMML. To address this limitation and increase the number of patients with these mutations under study, our cohort was enriched with these specific mutations, which were subsequently confirmed in a validation cohort. Clearly, prospective studies involving larger cooperative cohorts are warranted. Our understanding of the pathophysiology of CMML is improving, and one of the goals is to move toward a molecular-based classification

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and risk assessment. Therefore, despite the limitations of our study, our findings provide the basis for progressing toward this goal.

In conclusion, we have found that *CEBPA*, *FLT3*, and *NPM1* mutations represent an unfavorable molecular prognostic factor in CMML not captured by existing molecularly integrated prognostic models. We therefore propose that considering these mutations in the prognostic stratification of patients with CMML will provide a useful tool for decision-making and patient management. Patients with CMML harboring these mutations exhibit a distinct genetic profile that closely resembles that of patients with AML and is linked to poorer prognosis. These patients may thus derive potential benefits from a more intensive AML-type treatment approach, including intensive chemotherapy and alloHSCT when feasible, as well as certain targeted therapies approved for AML.

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Authorship

Contributions: All authors were involved directly or indirectly in the care of patients, sample procurement, and collection of clinical data; M.D.-B. designed the study and led the research team; S.C.-D. and M.D.-B. performed the statistical analyses and wrote the manuscript; and all authors reviewed and accepted the final version of the manuscript.

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