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CORRESPONDENCE

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CSF3R T618I mutant chronic myelomonocytic leukemia (CMML) defines a proliferative CMML subtype enriched in *ASXL1* mutations with adverse outcomes

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Dear Editor,

Chronic myelomonocytic leukemia (CMML) is a clonal myeloid disorder characterized by peripheral blood (PB) monocytosis (absolute monocyte count (AMC) $\geq 1 \times 10^9/L$ and $\geq 10\%$ of the total white blood cell count (WBC)) and overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms (MPN)¹. Sustained PB monocytosis is a hallmark of CMML, with a mutational signature consisting of biallelic *TET2*, or *TET2* and *SRSF2* co-mutations, biasing hematopoiesis toward monocytosis². Chronic neutrophilic leukemia (CNL) is a rare MPN characterized by sustained mature neutrophilia (WBC $\geq 25 \times 10^9/L$, with segmented neutrophils and band forms $\geq 80\%$ of the WBC), with an AMC $< 1 \times 10^9/L$ ³. CNL commonly occurs due to oncogenic driver mutations involving the colony-stimulating factor receptor, *CSF3R* (90–100%)^{4,5}. Among *CSF3R* mutations described in CNL, the T618I membrane proximal point mutation activating Janus-activated kinase (JAK)/signal transducer and activator of transcription factor signaling is the most common (74%)^{4,6}. These mutations potentially render CNL responsive to therapy with JAK inhibitors, such as ruxolitinib⁷. On the other hand, *CSF3R* mutations, especially *CSF3R* T618I, are very infrequent in CMML ($< 5\%$)^{8,9}. We carried out this study to assess the prevalence,

phenotypic features, and outcomes of patients with CMML who harbor the *CSF3R* T618I mutation.

Eight hundred and forty-six patients with CMML, defined per the World Health Organization (WHO) 2016 criteria, from Mayo Clinic, Minnesota and the Groupe Francais des Myelodysplasies were included in this study (August 1994 through July 2019). All patients underwent targeted next-generation sequencing for myeloid-relevant genes obtained at diagnosis or at first referral using previously described methods^{2,10}. Categorical variables were compared by Fisher's exact or Pearson's chi square. Continuous variables were compared by Wilcoxon test. Overall survival (OS) was defined as the time from diagnosis to death. Acute myeloid leukemia-free survival (AML-FS) was defined as the time from diagnosis to transformation to AML or death. Patients who underwent hematopoietic cell transplantation prior to AML transformation were censored for AML-FS estimates. Both OS and AML-FS were estimated by the Kaplan–Meier method and compared by log-rank test.

We identified 6 (1%) patients who met the 2016 WHO criteria for CMML and who harbored *CSF3R* mutations, all of whom had the *CSF3R* T618I missense alteration; 3 (50%) were males, median age 63 years, with a median AMC of $6 \times 10^9/L$ (range 2–23). Five (100%) of five evaluable patients had bone marrow (BM) dysplasia, a finding not seen in CNL. As expected, all six *CSF3R* T618I mutant patients had a proliferative CMML phenotype, with marked neutrophilia in addition to the monocytosis. Four (100%) of the 4 evaluable patients also had circulating immature myeloid cells (myelocytes and metamyelocytes).

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Table 1 Individual patient's characteristics and outcomes.

Patient	Age, years	Gender	CBC				BM			Karyotype	CSF3R VAF %	Co-mutations (VAF %)	Treatment	Outcomes		
			FAB WHO subtype	Hb, g/dL	Plts, $\times 10^9/L$	WBC, $\times 10^9/L$	ANC, $\times 10^9/L$	AMC, $\times 10^9/L$	PB blasts (%)						Blasts (%)	Dysplasia
1	62	F	P 2	13	50	40	21 (53)	6 (15)	12	16	+	46, X, i(Xq13) [14]/46, XX [6]	10	SRSF2 (49)	HU/ induction	AML transformation in 1 month and death 9 months later
2	39	F	P 2	6	50	134	114 (85)	19 (14)	6	15	+	46, X, i(Xq13) [7]/ 46, XX [4]	63	ASXL1 (35)/ STEBP1 (51)	HU	No follow-up
3	48	M	P 0	7	168	180	151 (84)	23 (13)	0	1	+	46, XY [20]	58	ASXL1 (25)	HMA	Refractory disease and died in 20 months
4	66	M	P 0	8	60	31	25 (81)	4 (13)	0	1	+	46, XY [20]	51	ASXL1 (45)	HU	Alive at 6 months
5	69	F	P 1	8	173	35	23 (66)	5 (14)	2	0	+	46, X, del(X) [12]/ 46, XX [8]	12	ASXL1 (46)	HU	No follow-up
6	64	M	P 0	11	302	21	18 (86)	2 (11)	0	3	UK	46, XY [UK]	UK	ASXL1 (49)/ UAZF1 (44)	HU	Died in 17 months

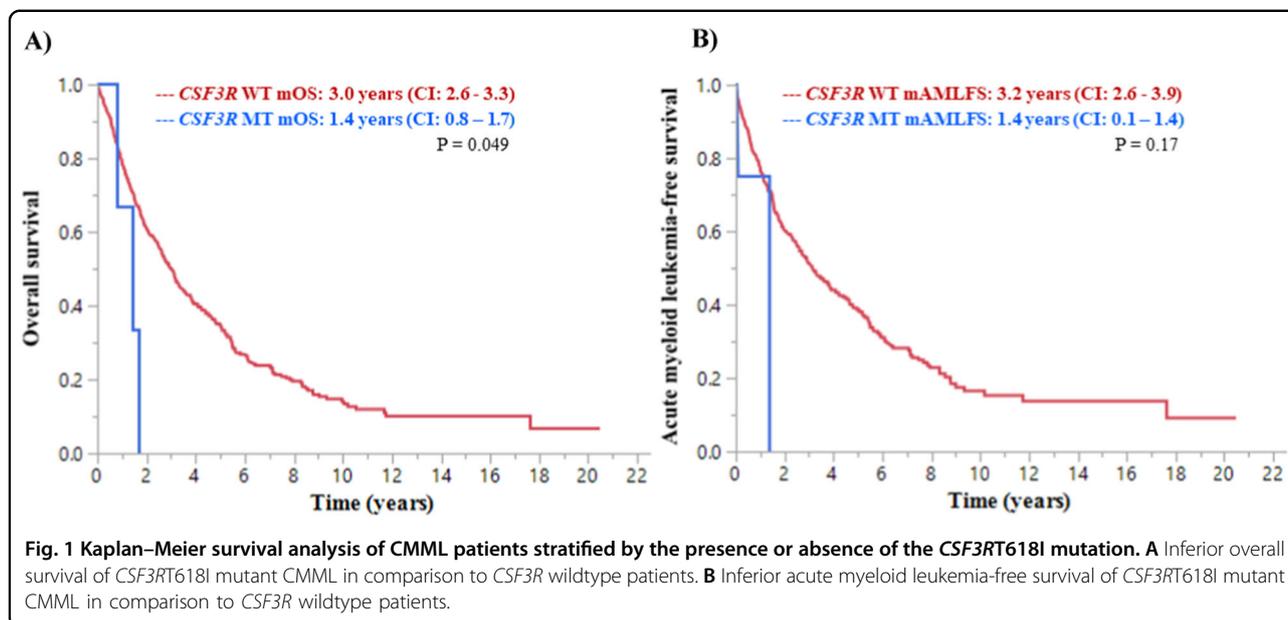
Individual characteristics and outcomes of CMML patients with CSF3R T6181 mutation. Characteristics are based on diagnosis or first referral. M male, F female, WHO World Health Organization, FAB French-American-British, CBC complete blood count, Hb hemoglobin, WBC white blood count, AMC absolute monocyte count, Plt platelets, PB peripheral blood, BM bone marrow, VAF variant allele frequency, HU hydroxyurea, induction cytarabine-based intense chemotherapy regimens, RBC red blood cells, AML acute myeloid leukemia, UK unknown.

The CSF3R T618I variant allele frequency (VAF) burdens were >40% in 3 (60%) of 5 evaluable cases (range 10–63%). While the CSF3R mutational VAF in three patients was in the heterozygous range, all three had adult-onset leukocytosis/monocytosis, making the likelihood that these variants were germline, quite low¹¹. We, however, acknowledge that we did not have germline tissue for further confirmation. Three patients had a normal karyotype, while the remaining three had X chromosome abnormalities (Table 1).

In comparison to CSF3R wild-type (WT) CMML patients, those with the CSF3R T618I mutation were younger (median 63 vs. 72 years; $p = 0.0055$), had lower hemoglobin values (Hb, median 8 vs. 11 g/dl; $p = 0.0186$), higher WBC (median 38 vs. $13 \times 10^9/L$; $p = 0.0013$), higher percentage of neutrophils (median 83 vs. 52%; $p = 0.001$), higher AMC (median 6 vs. $2 \times 10^9/L$; $p = 0.024$), lower percentage of monocytes (median 13 vs. 23%; $p = 0.0069$), higher percentage of PB blasts (median 1 vs. 0%; $p = 0.0472$), and were more likely to be classified as proliferative CMML (100 vs. 48%; $p = 0.012$). There were no TET2 mutations in the CSF3R T618I mutant CMML group, vs. 59% in the WT group ($p = 0.005$), while ASXL1 mutations were more frequent in the CSF3R T618I mutant group (83 vs. 41%; $p = 0.045$) in comparison to the WT group (Supplementary Table 1). While not statistically significant, 5 of the 6 (83%) CSF3R T618I mutant CMML patients did not have concomitant SRSF2 mutations, with 4 of the 6 (66%) not having any splicing mutation at all.

At last follow-up, 3 (50%) and 400 (48%) deaths and 1 (17%) and 122 (15%) leukemic transformations were documented in the CSF3R T618I mutant and WT CMML groups, respectively. The median OS was significantly shorter in CMML patients with the CSF3R T618I mutation (median 1.4 vs. 3.0 years; $p = 0.049$), in comparison to the WT patients, with no difference in the AML-FS (1.4 vs. 3.2 years; $p = 0.17$) (Fig. 1). None of our patients received ruxolitinib or underwent allogeneic stem cell transplantation. Five of the six patients were treated with hydroxyurea and one patient was treated with hypomethylating agent therapy, with no response.

Given the higher prevalence of ASXL1 mutations in the CSF3R T618I mutated cohort, and the known detrimental prognostic impact of ASXL1 mutations in CMML, we performed a subgroup analysis comparing CSF3R T618I mutant CMML with ASXL1 mutant CMML patients (Supplementary Table 1)¹⁰. In this comparison, once again, CSF3R mutant CMML patients were more likely to be younger in age ($p = 0.009$), have lower Hb levels ($p = 0.005$), have higher WBC ($p = 0.009$), have lower AMC ($p = 0.012$), and were less likely to have TET2 mutations ($p = 0.029$). There was no OS difference between the two groups (Supplementary Fig. 1).



In summary, we present a cohort of patients who met 2016 WHO criteria for CMML and who harbored an oncogenic driver mutation in *CSF3R* T618I. While this mutation is fairly specific to CNL, infrequent occurrences in other myeloid neoplasms have been documented^{8,9}. In our opinion, in the context of accurate histopathological analyses, the true frequency of these mutations in CMML is <1%. In addition, the *CSF3R* T618I mutation when present defines a unique proliferative CMML subtype characterized by pronounced leukocytosis/neutrophilia/monocytosis, with a unique molecular signature (*ASXL1*mt/*TET2*wt), with infrequent splicing mutations. The high frequency of X chromosome abnormalities remains to be defined. We have in the past demonstrated the negative prognostic impact of the *ASXL1*mt/*TET2*wt genotype in CMML, a finding once again validated by the poor OS of this group in the current study (median OS 1.4 years)^{2,12}. In fact, the molecular landscape of *CSF3R* T618I mutant CMML is more akin to *BCR-ABL1*-negative atypical chronic myeloid leukemia (CML), where *ASXL1* mutations are frequent (80%) and splicing mutations are less common (30%)¹³. However, atypical CML is not associated with monocytosis, and given the fact that in CMML biallelic *TET2* or *TET2/SRSF2* co-mutations skew hematopoiesis toward monocytosis, the etiology of monocytosis in these patients remains to be elucidated. While the presence of BM dysplasia along with concomitant monocytosis/neutrophilia morphologically distinguishes *CSF3R* T618I mutant CMML from CNL, further work is needed to see whether *CSF3R* T618I mutant CMML is truly a CMML subtype, or if akin to *PDGFRA/B* and *FGFR1* rearranged myeloid neoplasms, it deserves its own classification schema as a *CSF3R* T618I mutant myeloid neoplasm with monocytosis.

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Author contributions

E.D.B. collected and interpreted the data, performed statistical analysis, and wrote the manuscript; T.L.L. interpreted the data and reviewed the manuscript; C.M.F. collected the data; A.N.S., M.A.E., A.D.P., N.G., A.A.M., R.P.K., A.T., and E.S. reviewed the manuscript; and M.M.P. conceived the study, interpreted the data, and revised the manuscript.

Conflict of interest

The authors declare no competing interests.

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References

- Arber, D. A. et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. **127**, 2391–2405 (2016).
- Coltro, G. et al. Clinical, molecular, and prognostic correlates of number, type, and functional localization of *TET2* mutations in chronic myelomonocytic leukemia (CMML)-a study of 1084 patients. *Leukemia* **34**, 1407–1421 (2020).
- Zuber, N., Elliott, M. & Tefferi, A. Chronic neutrophilic leukemia: 2020 update on diagnosis, molecular genetics, prognosis, and management. *Am. J. Hematol.* **95**, 212–224 (2020).
- Maxson, J. E. et al. Oncogenic *CSF3R* mutations in chronic neutrophilic leukemia and atypical CML. *N. Engl. J. Med.* **368**, 1781–1790 (2013).

5. Pardanani, A. et al. CSF3R T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. *Leukemia* **27**, 1870–1873 (2013).
6. Szuber, N. et al. CSF3R-mutated chronic neutrophilic leukemia: long-term outcome in 19 consecutive patients and risk model for survival. *Blood Cancer J.* **8**, 21 (2018).
7. Dao, K. T. et al. Efficacy of ruxolitinib in patients with chronic neutrophilic leukemia and atypical chronic myeloid leukemia. *J. Clin. Oncol.* **38**, 1006–1018 (2020).
8. Kosmider, O. et al. Mutation of the colony-stimulating factor-3 receptor gene is a rare event with poor prognosis in chronic myelomonocytic leukemia. *Leukemia* **27**, 1946–1949 (2013).
9. Ouyang, Y., Qiao, C., Chen, Y. & Zhang, S. J. Clinical significance of CSF3R, SRSF2 and SETBP1 mutations in chronic neutrophilic leukemia and chronic myelomonocytic leukemia. *Oncotarget* **8**, 20834–20841 (2017).
10. Itzykson, R. et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. *J. Clin. Oncol.* **31**, 2428–2436 (2013).
11. Plo, I. et al. An activating mutation in the CSF3R gene induces a hereditary chronic neutrophilia. *J. Exp. Med.* **206**, 1701–1707 (2009).
12. Patnaik, M. M. et al. Prognostic interaction between ASXL1 and TET2 mutations in chronic myelomonocytic leukemia. *Blood Cancer J.* **6**, e385 (2016).
13. Palomo, L. et al. Molecular landscape and clonal architecture of adult myelodysplastic/myeloproliferative neoplasms. *Blood* **136**, 1851–1862 (2020).