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CSF3R-mutated chronic neutrophilic leukemia: a two-center study of 44 consecutive patients

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Running head: *CSF3R*-mutated chronic neutrophilic leukemia

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performed analyses and wrote the manuscript. AA, AP, AT, MAE, MS, NG, TB, and WJH participated in

patient care. CM, KKH, and RH provided hematopathology and molecular laboratory expertise. All authors

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Key points:

- In patients with *CSF3R*-mutated chronic neutrophilic leukemia(CNL), white blood cell response (≥50% reduction from baseline count) was not significantly different between those who received ruxolitinib-based combination therapy and those treated with hydroxyurea.
- *ASXL1* and/or *SETBP1* mutations were observed in 78% of patients and were associated with early blast transformation (BT) and inferior overall survival (OS).
- Allogeneic stem cell transplantation significantly improved OS in patients with *CSF3R*-mutated CNL.

TO THE EDITOR:

CSF3R mutations (*CSF3R*^{MUT}), most commonly T618I, represent the defining genomic alteration in chronic neutrophilic leukemia (CNL) and is present in ~80% of cases.[1-4] Although relatively few studies have explored disease characteristics, both the largest population-based study utilizing SEER and NCBI databases and Mayo Clinic study of 19 consecutive *CSF3R*-mutated CNL (*CSF3R*^{MUT}-CNL) patients have played a major role in describing the clinical manifestations and outcomes. These studies highlighted prognostic indices such as age, baseline white blood cell (WBC) count >60 × 10^9/L, platelet < 160×10^9/L and the presence of *ASXL1* mutations.[2,5]

Despite these reports, data on treatment outcomes and prognostic factors remain limited due to the rarity of CNL. In this two-center retrospective study, we examined clinical and molecular predictors of treatment response, overall survival (OS), and blast transformation (BT) in *CSF3R*^{MUT}-CNL patients diagnosed at Mayo Clinic (USA) and the University of Montreal (Canada) using the International Consensus Classification criteria.[6] We also assessed outcomes following allogeneic stem cell transplantation (ASCT).

The study was approved by the institutional review boards of both institutions. Electronic medical records were reviewed to identify patients and extract relevant data. Categorical and continuous variables were summarized using frequencies (%) and medians (range). Kaplan-Meier estimates (with log-rank tests) and cox regression models were utilized to identify predictors of OS and BT. Statistical analyses were performed using JMP Pro 17.0.0 software (SAS Institute, Cary, NC, USA).

Forty-four patients diagnosed between October 1995 and April 2025 were included. The median age at diagnosis was 68 years (range:26-93) and 30 (68%) were male. *CSF3R*^{MUT}/variants included

39 (89%) with T618I, 2 (5%) with M696T, and 1 (2%) each with I598I, Q739*, and T640N. Seven of the 39 patients with *CSF3R*-T618I had additional $CSF3R^{MUT}$. Frequent co-mutations involved *ASXL1* in 25 (60%) patients, *SETBP1* in 14 (36%), and *SRSF2* in 8 (31%), with overlapping occurrence. Of the 26 patients who had data available for all three co-mutations, 10 (38%) had ≥2. Further details of baseline characteristics are shown in **Table 1** and **Figure 1.**

Ten patients (median WBC 29 $\times 10^9$/L [range: 19-58]) were initially observed without treatment for a median of 8.6 months; two remained on observation alone at 46 and 77 months. Hydroxyurea monotherapy was the most common first-line therapy, used in 26 (65%) patients. Other first-line regimens included ruxolitinib or ruxolitinib-based combinations (Ruxo/Ruxoc), as well as other agents such as tyrosine kinase inhibitors (imatinib and dasatinib), immunomodulatory drugs, interferon, and azacitidine, as detailed in **Supplemental Table 1**. Second-line therapies comprised Ruxo/Ruxoc in 12 (42.8%) patients and hydroxyurea alone or in combination with other agents excluding ruxolitinib (HU/HUc) in 8 (28.6%) patients. A white blood cell (WBC) response, defined as a ≥50% reduction from baseline, was achieved in 21 (78%) patients treated with HU/HUc versus 9 (60%) treated with Ruxo/Ruxoc (p=0.2); further details of treatment response are provided in **Supplemental Table 1**. WBC response to HU/HUc was lower with abnormal karyotype (2[40%] vs. 17[94%]; p=0.02). Among those who had Ruxo/Ruxoc, WBC response was lower in patients with $SETBP1^{MUT}$ (0% vs. 9[72%]; p=0.05) and males (4[40%] vs. 5[100%]; p=0.04).

At a median follow-up of 44 months for living patients, disease transformation occurred in 10 patients, including 7 with BT (six with T618I and one with T640N) and 3 with chronic myelomonocytic leukemia (two with M696T and one with T618I). BT rate at 2, 3, and 5 years was 15%, 31%, and 43%, respectively. Univariate analysis (UVA) identified male sex (p<0.01), >5%

immature WBCs (p=0.045), platelets <160×10⁹/L (p=0.04), and presence of *ASXL1* or *SETBP1* mutation (*ASXL1*^{MUT}/*SETBP1*^{MUT}) (p<0.01) as risk factors for BT, **Supplemental Table 2**. On multivariable analysis (MVA), only *ASXL1*^{MUT}/*SETBP1*^{MUT} remained significant.

Median OS was 26 months (95% CI: 21-43) for the entire cohort; 24 months for patients with T618I *CSF3R*^{MUT} vs. 53 months for those with other *CSF3R*^{MUT}, p=0.1. In UVA, age >60 years (Hazard ratio [HR] 5.1; p<0.01), WBC >50×10⁹/L (HR 2.6; p=0.02), platelets <160×10⁹/L (HR 3.6; p<0.01) and *ASXL1*^{MUT}/*SETBP1*^{MUT} (HR 4.2; p=0.03) were associated with shorter OS, **Supplemental Table 2**. In MVA, age >60 years (HR 6; p=0.03), WBC >50×10⁹/L (HR 12; p<0.01), and *ASXL1*^{MUT}/*SETBP1*^{MUT} (HR 9.5; p=0.01) remained significant.

Based on the HR on MVA, one adverse point was allocated for age >60 years, and two adverse points each for WBC >50×10⁹/L and *ASXL1*^{MUT}/*SETBP1*^{MUT}. Patients were accordingly stratified into low (0-2 points), intermediate (3) and high (4-5) risk groups, with corresponding median OS of "not reached", 29 months, and 16 months (p<0.01), **Figure 2**. Causes of death included disease progression (82%), infection/bleeding (9%), and ASCT complications (9%).

Seven patients underwent ASCT, including 2 after BT. Four (57%) of the 7 remain alive, including 2 without evidence of disease (both 45 months post-ASCT; one harbored *ASXL1*^{MUT}) and the other 2 with active disease (both harbored *ASXL1*^{MUT}). Three patients died, one each from veno-occlusive disease (Day+34), CNS relapse with AML (105 months post-ASCT), and unrelated causes (44 months post-ASCT).

These outcomes are consistent with findings in prior studies, suggesting that ASCT offers long-term survival in an otherwise aggressive disease with limited treatment options.[5,7-9] In one study, although none of the five patients responded to pre-transplant treatments, four achieved complete

remission after transplantation and two remained in remission at 362 and 441 days post-ASCT.[7] Similarly, the population-based study by Ruan *et al.* reported good outcomes in two patients who had ASCT, both remaining alive after 5 years.[5] In our cohort, transplanted patients had significantly superior median OS compared to non-transplanted patients (115 vs 23 months; p=0.03), further strengthening the argument for early transplant referral, particularly in patients with high risk features.[10]

Although WBC response to ruxolitinib, a JAK inhibitor (JAKi), was observed in 60% of *CSF3R*^{MUT}-CNL patients, this was not superior to hydroxyurea. In a phase II trial that applied more stringent response criteria, 13 (76%) of the 17 patients with *CSF3R*^{MUT}-CNL had partial or complete response to ruxolitinib.[11] Similarly, a phase II study of fedratinib, another JAKi, showed preliminary efficacy in the trial participants, reporting symptom improvement in 3 of 5 evaluable patients and associated splenic response in one.[12]. It is worth mentioning that the study included patients with MDS/MPN (n=19) and those with CNL(n=5); however, outcomes for the CNL subgroup were not reported separately. The study also reported enriched response in patients with *CSF3R*^{MUT}. In our cohort, one patient received fedratinib combined with hydroxyurea, achieving partial WBC reduction without splenic response, treatment was discontinued after 10 months due to cytopenia. This patient harbored *ASXL1*, *SETBP1*, and *SRSF2* mutations and did not respond to prior ruxolitinib therapy. Further characterization of the CNL subgroup in the fedratinib study and comparative evaluation of JAK inhibitors would be valuable.

Our study highlights the prognostic weight of having either *ASXL1* or *SETBP1* mutations, which not only predicted worse OS but was also independently associated with BT, **Figure 1** and **Supplemental Table 2**. One or both of these mutations were present in 75% of patients in this study, supporting previous reports and further revealing the central role of these mutations in

disease biology.[2,3] *ASXL1*, an epigenetic modulator, has been shown in vivo to synergistically drive myeloid proliferation when co-occurring with *CSF3R*^{MUT}.[13] Similarly, *SETBP1* induces a Myc-driven transcriptional program that promotes leukemogenesis in the setting of *CSF3R*^{MUT}.[14] Together, these biological insights reinforce their emerging clinical relevance and these will be more precisely defined as larger patient cohorts are studied.

We reported new clonal abnormalities observed at CNL progression/transformation in **Supplementary Table 3**. Notably, new trisomy 21 was observed in 3 of the 11 patients with available data on clonal evolution, one at BT and two at CNL progression. This finding aligns with a recent report suggesting chromosome 21 amplification, potentially occurring here from copy number gain, may drive BT in myeloproliferative neoplasm through overexpression of *DYRK1A*.[15]

In summary, this study provides a comprehensive description of *CSF3R*^{MUT}-CNL patients, highlighting survival benefits of ASCT in eligible patients and the prognostic impact of *ASXL1*^{MUT}/*SETBP1*^{MUT}, providing a framework for better risk stratification and individualized management.

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Table 1. Baseline characteristic of patients with Chronic Neutrophilic Leukemia					
Variable	All n(%)	*CSF3R*-T618I *n=39* n(%)	Others n=5 n(%)	P	OR (95%CI)
Gender(M)	30 (68.2)	28 (71.8)	2 (40.0)	0.3	0.27 (0.02–2.70)
Median Age at diagnosis (years)*	68 (26–93)	68(33–93)	59(26–72)	0.1	0.95 (0.90–1.01)
Median Variant Allele frequency*	43 (5–51.4)	43(5–51.4)	21	0.2	0.9(0.8–1.1)
Presence of symptoms at diagnosis	16 (44.4)	16 (48.5)	0	0.23	NA
Prior leukocytosis before diagnosis*	21 (50)	19 (51.4)	2 (40.0)	1	0.64 (0.05–6.27)
Prior cytotoxic therapy	6 (13.6)	5 (12.8)	1 (20.0)	0.5	1.7 (0.03–22.6)
Family history of hematological neoplasm	18 (52.9)	15 (48.4)	3 (100.0)	0.22	NA (0.38–NA)
History of thrombosis	6 (14.6)	6 (16.7)	1 (20.0)	1	NA
History of hemorrhage	8 (18.6)	8 (21.1)	0 (0.0)	0.56	NA
Sweet syndrome	3 (7.0)	3 (7.9)	0 (0.0)	1	NA
Splenomegaly	28 (66.7)	26 (70.3)	2 (40.0)	0.31	0.3 (0.02–2.9)
Hepatomegaly	7 (17.1)	5 (13.9)	2 (40.0)	0.2	3.9 (0.3–44.9)
Lymphadenopathy	4 (9.8)	4 (11.1)	0 (0.0)	1	NA
Hemoglobin (g/dl)*	11.2(6.4–16.1)	10.8 (6.4–16.1)	12.7(11.4–16)	0.1	1.5(0.94–2.5)
Platelet (x10^9/L)*	190 (25–476)	168(25–476)	250(243 – 362)	0.14	1.01(1–1.02)
Leukocyte count (x10^9/L)*	52.4(17.4-391)	52 (17.4–391)	71.4(34–176)	0.64	1(0.99–1.01)
Percentage immature WBC†	20 (46.5)	17 (44.7)	3 (60)	0.65	1.9 (0.3 – 12.3)
Monocyte*	2 (0.0–11.0)	2 (0.00–10.0)	4 (1.0–11.0)	0.28	1.2 (0.9–1.6)
Myeloid :Erythroid ratio*	9.4 (3.0–92.0)	9.35 (3.0–92.0)	8.5 (3.0–10)	0.4	0.9 (0.7–1.03)
Bone Marrow Blast	40 (93.0)	3(7.7)	0	1	NA
Abnormal Karyotype	7 (18.4)	7 (20.6)	0 (0.0)	1	NA
Abnormal FISH	2 (5.3)	2 (5.9)	0 (0.0)	1	NA
***ASXL1* mutations**	25 (60.0)	22 (56.4)	3 (60.0)	1	1(0.1–13.4)
***SETBP1* mutations**	14 (35.9)	13 (38.2)	1 (20.0)	0.64	0.4(0.01–4.8)
***SRSF2* mutations**	8 (30.8)	8 (33.3)	0 (0.0)	1	NA
Uric acid*	7.9 (2.3–14.4)	7.9 (2.3–14.4)	8 (6.7–9.2)	0.97	0.99 (0.6–1.7)
LDH*	261 (133–1814)	261 (133–1814)	266 (185–397)	0.61	1 (0.99–1)
Ferritin ng/ml*	414(61–12706)	467(108–12706)	273(61–285)	0.29	1(0.98–1)
*FISH – fluorescence in situ hybridization; OR – odds ratio; NA- could not be estimated; * – Presented as median (range); † – peripheral blood.*					

Figure Legends

Figure 1: Co-mutations and their prognostic impact in *CSF3R*-mutated chronic neutrophilic leukemia

(A) Heatmap showing co-occurrence of myeloid mutations. *ASXL1*, *SETBP1*, and *SRSF2* were the most frequent co-mutated genes. The intensity of shading represents the percentage of co-occurrence between gene pairs.

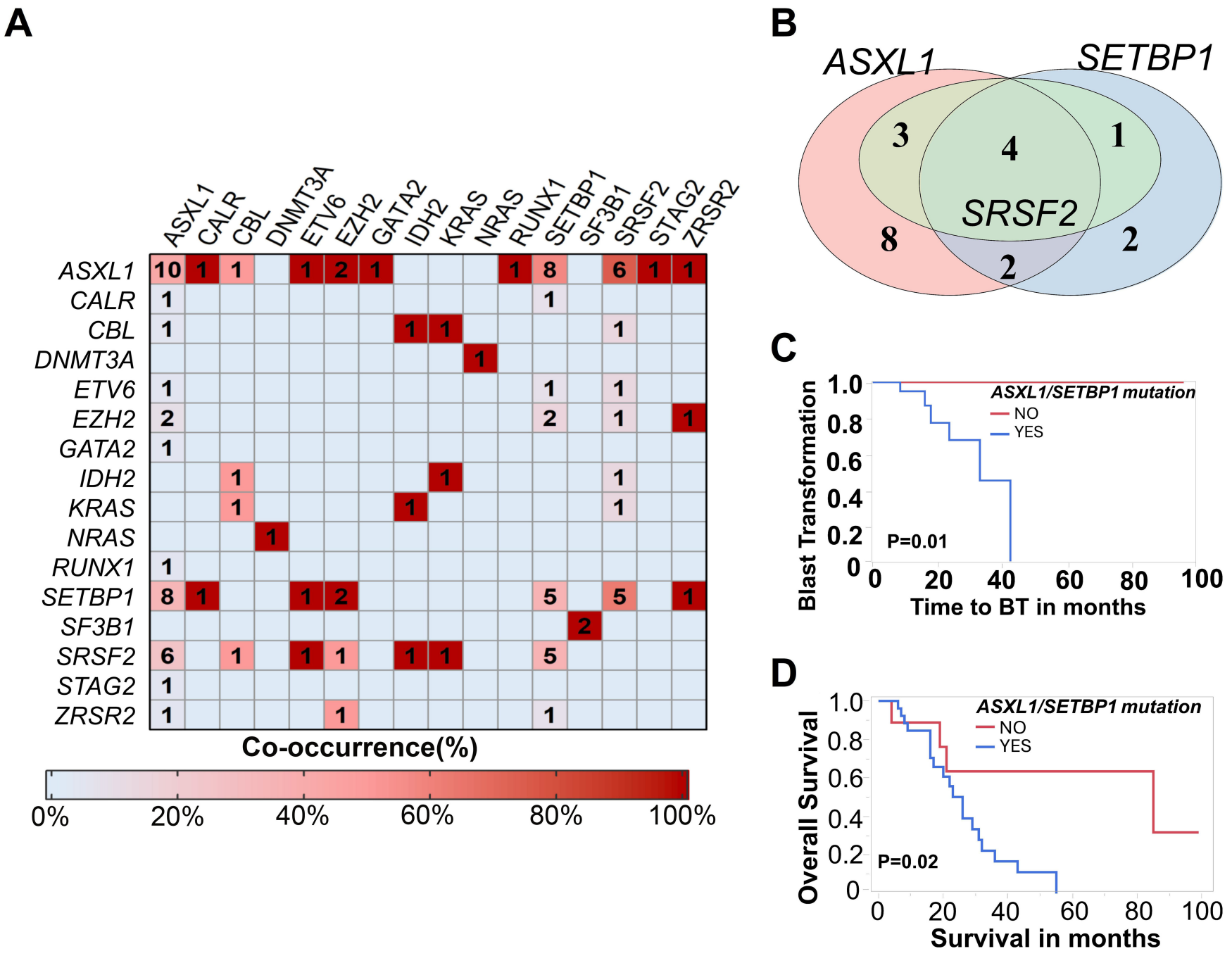
(B) Venn diagram illustrating overlap between *ASXL1*, *SETBP1*, and *SRSF2* mutations.

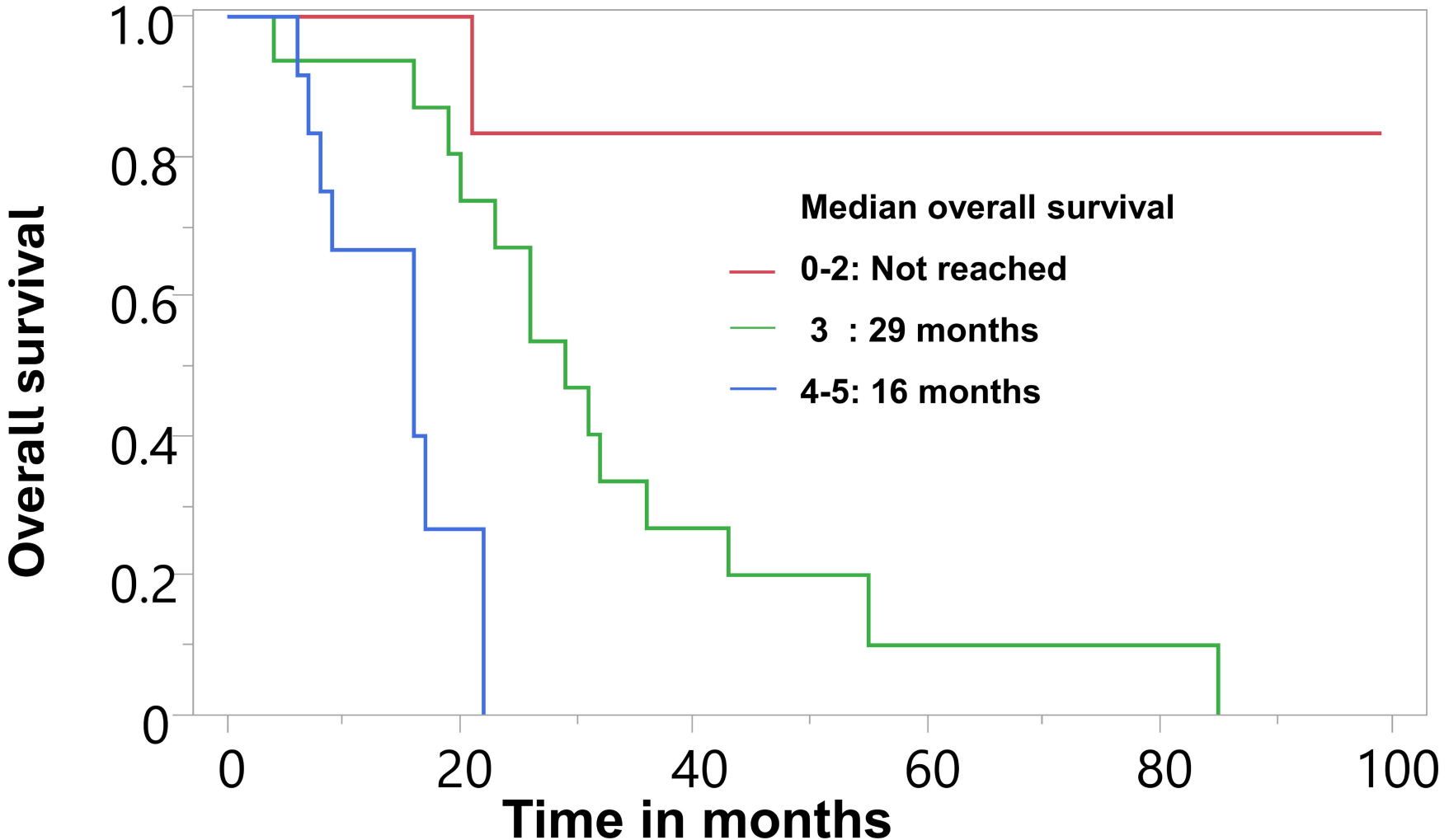
(C) Kaplan–Meier analysis of time to blast transformation (BT). Patients with *ASXL1* or *SETBP1* mutations (blue) had significantly shorter time to transformation (median 35 months, 95% CI 19–45) compared to those without these mutations, in whom no transformation was observed within the follow up period (P = 0.01).

(D) Kaplan–Meier analysis of overall survival. Patients with *ASXL1* or *SETBP1* mutations (blue) had significantly inferior survival (median 26 months, 95% CI 16–31) compared to patients without these mutations (median 85 months, 95% CI not reached; P = 0.02).

Figure 2: Overall survival according to risk categories

Overall survival stratified by adverse risk score. One adverse point was allocated for age >60 years, and two points each for white blood cell count >50×10⁹/L and the presence of *ASXL1* or *SETBP1* mutations. Patients were stratified into low-risk (0–2 points), intermediate-risk (3 points), and high-risk (4–5 points) groups, with corresponding median overall survival of not reached, 29 months, and 16 months, respectively ($p < 0.01$).


A
ASXL1
CALR
CBL
DNMT3A
ETV6
EZH2
GATA2
IDH2
KRAS
NRAS
RUNX1
SETBP1
SF3B1
SRSF2
STAG2
ZRSR2
Co-occurrence(%)
0%
20%
40%
60%
80%
100%
B
ASXL1
SETBP1
3
4
1
SRSF2
8
2
2
C
Blast Transformation
1.0
0.8
0.6
0.4
0.2
0
ASXL1/SETBP1 mutation
NO
YES
P=0.01
0
20
40
60
80
100
Time to BT in months
D
Overall Survival
1.0
0.8
0.6
0.4
0.2
0
ASXL1/SETBP1 mutation
NO
YES
P=0.02
0
20
40
60
80
100
Survival in months


Overall survival
1.0
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
Time in months
Median overall survival
0-2: Not reached
3 : 29 months
4-5: 16 months

Supplemental Table 1. Line of Therapy, Regimen Groups, and WBC Response in *CSF3R*-Mutated CNL Patients				
Line of Therapy	Regimen Group	Regimen (n)	N (%)	White blood cell Response* (%)
First-line (n=40)	Hydroxyurea	HU monotherapy	26 (65)	18 (78)
	HU + Ruxolitinib	HU + Ruxolitinib (1)	2 (5)	5 (62.5)
		HU + Peg-IFN + Ruxolitinib (1)		
	Ruxolitinib	Ruxolitinib alone	6 (15)	
	Others	TKI: imatinib (1) dasatinib (1)	6 (15)	NA
		IMiD (2)		
		IFN (1)		
		Azacitidine (1)		
Second-line (n=28)	Hydroxyurea alone	HU monotherapy	4 (14.3)	3 (75)
	HU + other (non-Ruxolitinib)	HU + Fedratinib	4(14.3)	
		HU + Peg-IFN		
		HU + Nilotinib		
		HU + Thalidomide		
	HU + Ruxolitinib	HU + Ruxolitinib (5)	6 (21.4)	3 (50)
		HU + Ruxo + Peg-IFN (1)		
	Ruxolitinib	Ruxo alone (4)	6 (21.4)	
		Ruxo + Busulfan (1)		
		Ruxo + Lenalidomide (1)		
	Others	Dasatinib (1)	8 (28.6)	NA
		Decitabine (3)		
		Ara-C (1) and Ara-C + 6-TG (1)		
		Azacitidine		
Third-line (n=12)	Hydroxyurea alone	HU alone (1)	3 (25)	NA
	HU + other (non-Ruxo)	HU + Decitabine (1)		
		HU + Lenalidomide (1)		
	Ruxo-based	Ruxo alone (3)	5(42)	4(100)
		Ruxo + Decitabine (1)		
		Ruxo + Peg-IFN (1)		
	Others	Daunorubicin + Cytarabine (1)	4 (33)	NA
		Decitabine alone (1)		
		Peg-IFN alone (1)		
		Cladribine (1)		

*HU – hydroxyurea; Ruxo – Ruxolitinib; Peg-IFN – pegylated interferon; TKI – tyrosine kinase inhibitor; IMiD – immunomodulatory agents; Ara-C – cytarabine; 6-TG – 6-thioguanine; NA – not available. *WBC response defined as ≥50% reduction from baseline; percentages reflect evaluable patients.*

Supplemental Table 2. Predictors of Blast Transformation and Overall Survival in *CSF3R*-Mutated CNL

	Blast transformation				**Overall Survival**			
Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Age at diagnosis > 60 years	0.67 (0.15–3.05)	0.47	–	–	5.13 (1.53–17.27)	0.008	6.30 (1.30–33.0)	0.03
Gender (M)	1.5×10^9 (NA)	0.004	3.9×10^8 (NA)	0.30	1.80 (0.76–4.26)	0.18	–	–
***CSF3R* mutations (non-T618I)**	1.22 (0.14–10.36)	0.85	–	–	0.41 (0.12–1.41)	0.16	–	–
>1 *CSF3R* mutation/variant	0.42 (0.05–3.59)	0.43	–	–	0.49 (0.17–1.44)	0.20	–	–
CSF3R variant allele frequency	0.96 (0.89–1.04)	0.28	–	–	1.00 (0.96–1.04)	0.91	–	–
Splenomegaly	2.06 (0.25–17.14)	0.50	–	–	0.91 (0.40–2.11)	0.83	–	–
Moderate/severe anemia	1.51 (0.33–6.91)	0.60	–	–	1.91 (0.88–4.12)	0.10	–	–
Platelet count <160 × 10^9/L	4.55 (0.94–22.03)	0.04	0.35 (0.05–2.10)	0.30	3.64 (1.60–8.27)	0.002	1.80 (0.70–5.10)	0.20
Leukocyte count >50 × 10^9/L	1.10 (0.20–5.80)	0.90	–	–	2.60 (1.20–5.60)	0.02	12.0 (2.60–55.0)	0.0013
Percentage Immature WBC (peripheral blood)	9.90 (1.10–93.0)	0.045	5.30 (0.53–52.8)	0.12	2.10 (0.90–4.90)	0.09	–	–
Abnormal karyotype	2.11 (0.41–10.97)	0.37	–	–	1.41 (0.52–3.85)	0.50	–	–
***ASXL1* or *SETBP1* mutation**	2.3×10^9 (NA)	0.002	2.2×10^9 (NA)	0.01	4.20 (1.20–15.0)	0.03	9.50 (1.70–58.0)	0.014
SRSF2 mutation	5.00 (0.50–48.6)	0.16	–	–	2.01 (0.71–5.70)	0.19	–	–

HR–Hazard ratio; CI – Confidence interval; NA – could not be estimated.

Supplemental Table 3. Clonal Evolution in Patients with Disease Progression/Transformation		
Events	**Number of Patients**	**Clonal Abnormalities**
CMML (Chronic Myelomonocytic Leukemia)	2	• 7p deletion (n=1) • 5q deletion and t(1;2) (n=1)
AML (Acute Myeloid Leukemia)	3	• Trisomy 21 (n=1) • Monosomy 7 (n=1) • New mutations: *NF1, PHF6, STAG2* (n=1)
CNL progression (without AML/CMML)	6	• Trisomy 21 (n=2) • Xq and 12q deletions (n=1) • del(17p), monosomy 7, *ASXL2* mutation (n=1) • Newly detected *ASXL1* mutation (n=1) • New *IDH2* mutation (n=1)