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Efficacy of Ruxolitinib in Patients With Chronic Neutrophilic Leukemia and Atypical Chronic Myeloid Leukemia

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abstract

PURPOSE Colony-stimulating factor-3 receptor (*CSF3R*)-T618I is a recurrent activating mutation in chronic neutrophilic leukemia (CNL) and to a lesser extent in atypical chronic myeloid leukemia (aCML) resulting in constitutive JAK-STAT signaling. We sought to evaluate safety and efficacy of the JAK1/2 inhibitor ruxolitinib in patients with CNL and aCML, irrespective of *CSF3R* mutation status.

METHODS We conducted a phase II study of ruxolitinib in 44 patients (21 CNL and 23 aCML). The primary end point was overall hematologic response rate (ORR) by the end of 6 continuous 28-day cycles for the first 25 patients enrolled. We considered a response as either partial (PR) or complete response (CR). We expanded accrual to 44 patients to increase our ability to evaluate secondary end points, including grade ≥ 3 adverse events, spleen volume, symptom assessment, genetic correlates of response, and 2-year survival.

RESULTS ORR was 32% for the first 25 enrolled patients (8 PR [7 CNL and 1 aCML]). In the larger cohort of 44 patients, 35% had a response (11 PR [9 CNL and 2 aCML] and 4 CR [CNL]), and 50% had oncogenic *CSF3R* mutations. The mean absolute allele burden reduction of *CSF3R*-T618I after 6 cycles was greatest in the CR group, compared with the PR and no response groups. The most common cause of death is due to disease progression. Grade ≥ 3 anemia and thrombocytopenia were observed in 34% and 14% of patients, respectively. No serious adverse events attributed to ruxolitinib were observed.

CONCLUSION Ruxolitinib was well tolerated and demonstrated an estimated response rate of 32%. Patients with a diagnosis of CNL and/or harboring *CSF3R*-T618I were most likely to respond.

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INTRODUCTION

Chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML) are rare *BCR-ABL1*–negative myeloid neoplasms. The 2016 WHO diagnostic criteria for CNL and aCML incorporate recurrent genetic markers,[1,2] which provide diagnostic clarity for these diseases.[1,2] In particular, *CSF3R* (colony stimulating factor-3 receptor) mutations are present in the vast majority of patients with CNL,[3,4] whereas RAS pathway–centric mutations are common in aCML and other myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap neoplasms.[5] *CSF3R*-T618I and -T615A are in the extracellular domain (known as membrane-proximal mutations), whereas the -T640N is in the transmembrane domain. These mutations result in ligand-independent dimerization and activation of CSF3R, leading to constitutive JAK/STAT signaling.[6]

There is no standard of care or approved therapy for CNL and aCML. The median survival for both diseases is approximately 2 years, with hemorrhage, marrow failure, and blastic transformation as common causes of death.[7,8] Allogeneic hematopoietic stem-cell transplantation is recommended for eligible patients with donor options.[9-11] Experience with nontransplant therapies is limited. In mouse models driven by oncogenic *CSF3R*, leukocytosis, splenomegaly, and deaths are significantly alleviated by JAK1/2 inhibition.[12,13] On the basis of these preclinical data,[3,12,13] we sought to determine safety and efficacy of single-agent ruxolitinib in patients with CNL or aCML.

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Baseline Clinical Characteristics and Overall Study Outcomes

Characteristic or Outcome	All Patients (N = 44)	CNL (n = 21)	aCML (n = 23)	P[a]
Characteristic				
Age, years	72.9 (43.1-92.3)	73.9 (43.4-92.3)	67.1 (43.1-86.0)	**.026**
Sex				
Female	18 (40.9)	11 (52.4)	7 (30.4)	.241
Male	26 (59.1)	10 (47.6)	16 (69.6)	
CSF3R				
Wild type	22 (50.0)	5 (23.8)	17 (73.9)	**.002**
T618I/T640N/T615A	22 (50.0)	16 (76.2)	6 (26.1)	
Diagnosis				
CNL	21	N/A	N/A	N/A
aCML	23	N/A	N/A	
Splenomegaly[b]				
No	8 (18.2)	7 (33.3)	1 (4.3)	**.036**
Yes	36 (81.8)	14 (66.7)	22 (95.7)	
Spleen volume by US, cm^3	596.5 (96.2-3,042.4)	513.0 (96.2-2,091.9)	711.1 (289.1-3,042.4)	**.029**
Palpable spleen length at LMC, cm	6.0 (0.0-26.0)	5.5 (0.0-15.0)	7.5 (0.0-26.0)	.853
WBC, $\times 10^9$/L[c]	53.5 (8.5-256.9)	63.5 (13.6-209.0)	48.1 (8.5-256.9)	.366
ANC, $\times 10^9$/L	42.9 (6.9-200.6)	59.1 (10.9-200.6)	35.4 (6.9-105.3)	.155
Hemoglobin, g/dL	10.9 (6.7-14.5)	10.9 (6.7-13.8)	10.6 (7.0-14.5)	.751
Platelets, $\times 10^9$/L	129.5 (25.0-488.0)	138.0 (41.0-488.0)	112.0 (25.0-487.0)	.589
Prior therapy				
No	17 (38.6)	7 (33.3)	10 (43.5)	.704
Yes	27 (61.4)	14 (66.7)	13 (56.5)	
Type of prior therapy				
Hydroxyurea	22 (81.5)	12 (85.7)	10 (76.9)	.789
Hypomethylating agent	2 (7.4)	1 (7.1)	1 (7.7)	
Other[d]	3 (11.1)	1 (7.1)	2 (15.4)	
IPSS total score[e]	2.0 (1.0-5.0)	2.0 (1.0-5.0)	3.0 (1.0-5.0)	.742
MPN-SAF TSS[f]	25.0 (0.0-72.0)	25.5 (1.0-72.0)	23.0 (0.0-55.0)	.865
Prestudy disease duration, months	7.0 (0.7-68.5)	7.4 (0.7-68.5)	6.6 (0.8-66.3)	.378
Overall study outcomes for 44 patients				
On study, 4-week cycles				
≤ 6 cycles	15 (34.1)	3 (14.3)	12 (52.2)	**.011**
> 6 cycles	29 (65.9)	18 (85.7)	11 (47.8)	
On study time, months	8.8 (0.2-41.4)	15.3 (2.0-41.4)	5.5 (0.2-27.8)	**.003**
Starting ruxolitinib, daily dose,[g] mg	20.0 (10.0-40.0)	20.0 (10.0-40. 0)	30.0 (10.0-40.0)	.526
Mean ruxolitinib, daily dose,[g] mg	30.8 (10.0-48.5)	30.0 (10.0-43.2)	31.7 (10.0-48.5)	.306
Protocol-defined response[h]				
Nonresponder	28 (65.1)	7 (35.0)	21 (91.3)	**< .001**
Responder (PR + CR)	15 (34.9)	13 (65.0)	2 (8.7)	
IWG-defined response[h]				
Nonresponder	39 (90.7)	16 (80.0)	23 (100.0)	**.039**
Responder (PR + CR)	4 (9.3)	4 (20.0)	0 (0.0)	

(continued on following page)

TABLE 1. Baseline Clinical Characteristics and Overall Study Outcomes (continued)

Characteristic or Outcome	All Patients (N = 44)	CNL (n = 21)	aCML (n = 23)	P[a]
Response for first 25 enrolled patients				
Protocol-defined response				
Nonresponder	17 (68.0)	5 (41.7)	12 (92.3)	**.011**
Responder (PR + CR)	8 (32.0)	7 (58.3)	1 (7.7)	
IWG-defined response				
Nonresponder	24 (96.0)	11 (91.7)	13 (100.0)	.480
Responder (PR + CR)	1 (4.0)	1 (8.3)	Not estimable	

NOTE. Data presented as median (range) or No. (%).

Abbreviations: aCML, atypical chronic myeloid leukemia; ANC, absolute neutrophil count; CNL, chronic neutrophilic leukemia; CR, complete response; IPSS, International Prognostic Scoring System; IWG, International Working Group; LMC, left midcostochondral line; MPN-SAF TSS, myeloproliferative neoplasm symptom assessment form, total symptom score; N/A, not applicable; PR, partial response; US, ultrasonography.

[a]Kruskal-Wallis test for continuous variables; χ^2 or Fisher's exact test for categorical variables. Bolded *P* values indicate significant or marginally significant differences.

[b]Determined by either presence of spleen volume ≥ 250 cm^3 or palpable spleen of any length.

[c]Two patients without oncogenic *CSF3R* mutation (CNL-18 and CNL-19) who did not meet the diagnostic criterion of leukocytosis $\geq 25 \times 10^9$/L were receiving hydroxyurea at screening to control leukocytosis, but they otherwise met other CNL diagnostic criteria.

[d]Other category includes interferon, dasatinib, or multiple agents.

[e]IPSS score: 1 point each for age > 65 years, hemoglobin < 10 g/dL, leukocytosis $\geq 25 \times 10^9$/L, peripheral blasts $\geq 1\%$, or constitutional symptoms (> 10% weight loss from average adult body weight, or disease-related fevers or night sweats).

[f]MPN-SAF TSS: 10-point scale for each fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers (0 no symptoms and 10 worst possible, maximum total is 100).

[g]Total daily dose, divided as twice-daily dosing.

[h]Total of 43 evaluable cases; CNL-19 had a suboptimal bone marrow biopsy specimen at the end of cycle 6 and had a normal spleen volume at baseline so was deemed not evaluable for response assessment.

METHODS

Patient Population

Patients with a diagnosis of CNL or aCML were eligible for this study. In cases where a single WHO 2008 criterion was not met, related to an arbitrary laboratory cutoff, qualitative evaluation of dysplasia, or requirement of hepatosplenomegaly, we favored the diagnosis of CNL or aCML if the leukemia was positive for *CSF3R*-T618I, -T615A, or -T640N and the other diagnostic criteria were met.[14] The WHO 2016 criteria were not available at the time of study design. The coordinating center reviewed and confirmed eligibility on the basis of pathologic, laboratory, and genetic data.

Study Design and Treatment

This was an open-label, single-arm, phase II multicenter investigator-initiated clinical trial of ruxolitinib in patients with CNL and aCML (ClinicalTrials.gov identifier: NCT02092324). Simon's 2-stage minimax design was used for the study. The accrual goal was at least 25 evaluable patients who had completed 6 cycles (1 cycle is 28 days). In the early conduct of the study, we observed that approximately one-third of patients did not complete 6 cycles, usually because of lack of response or disease progression. Therefore, we modified the protocol to evaluate all patients enrolled and kept the original accrual goal in place for other secondary end point analyses. Patients who failed to complete 6 cycles were recorded as having no response. Inclusion and exclusion criteria are in the Data Supplement. Ruxolitinib starting dose was guided in part by prescribing guidelines based on platelet counts, but investigator discretion was allowed.

Study Oversight

Oregon Health & Science University (OHSU) Knight Cancer Institute Data and Safety Monitoring Committee was responsible for ensuring that all member and affiliate investigators conducted this clinical study in compliance with local institutional review board standards, US Food and Drug Administration regulations, and National Institutes of Health policies, and in accordance with the Data and Safety Monitoring Plan. The OHSU coordinating center audited records and provided training at 6 other participating sites.

Study Objectives

The primary end point was to determine the proportion of patients with CNL and aCML with hematologic response to ruxolitinib by the end of cycle 6 (overall response rate [ORR]), defined as either partial response (PR) or complete response (CR). Secondary end points included evaluation of: 1) frequency of grade ≥ 3 hematologic and nonhematologic adverse events (AEs), 2) median percentage reduction of spleen volume and total symptom score using a myeloproliferative neoplasm symptom assessment form [MPN-SAF], defined in Table 1 footnote,[15] 3) International Working Group (IWG)–defined criteria for clinical benefit[16]

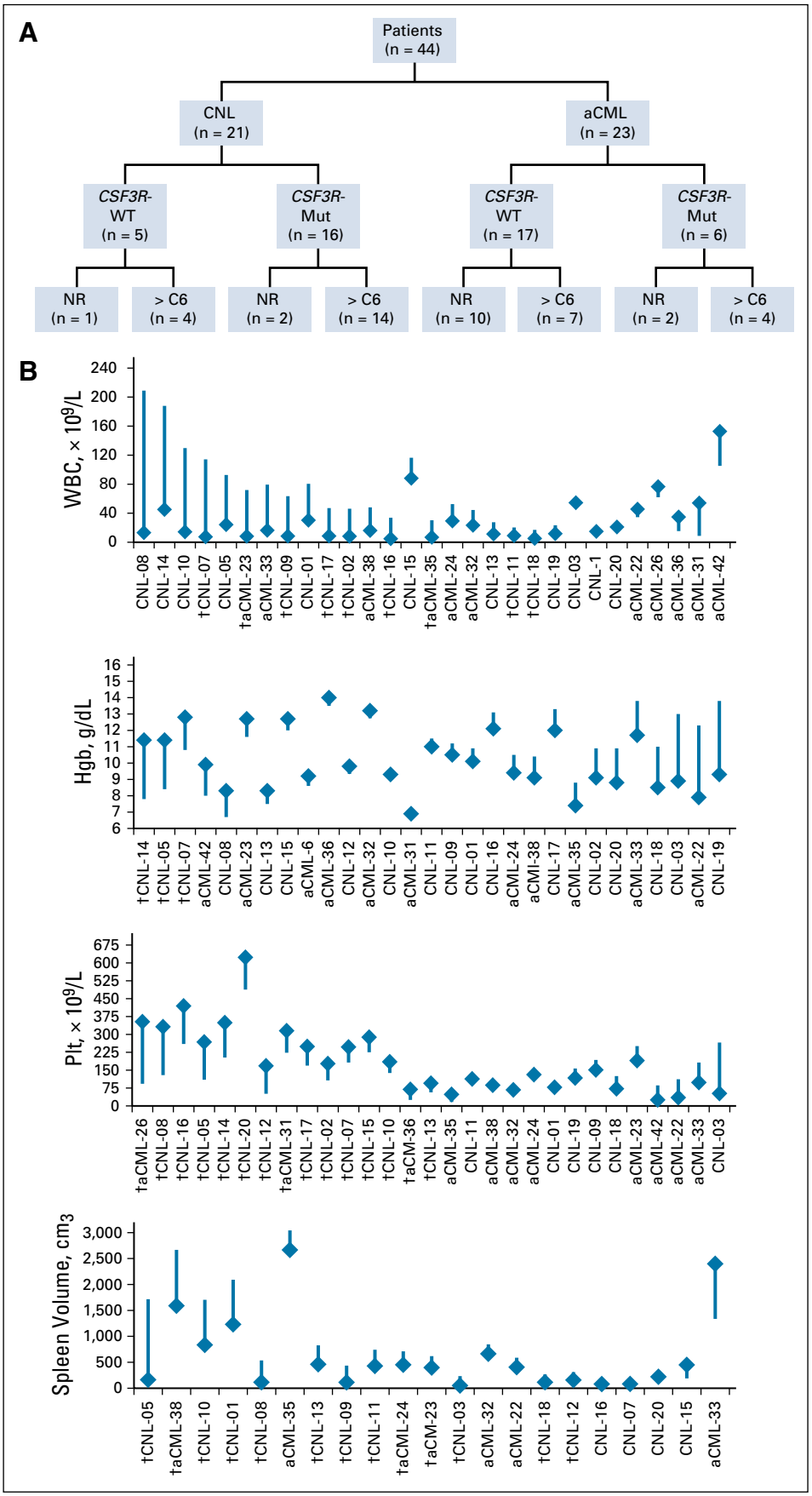

FIG 1. (A) Schematic of 44 patients enrolled by diagnosis and *CSF3R* mutation status. Mut, *CSF3R*-T618I (n = 20), -T615A (n = 1), or -T640N (n = 1); WT, *CSF3R*–wild type; NR, nonresponder, 15 of 44 (34.1%) withdrew from study before the end of cycle 6; > C6, patients reached the end of cycle 6, 29 of 44 (65.9%). (B) Waterfall plot of absolute change of various hematologic parameters according to individual patients. Numbering of patients is arbitrarily based on the order presented in the heat map by mutation profile in Figure 2. The flat end of the line represents baseline value and the diamond-head end represents the end of cycle 6 value. Presented in this manner, both minimal and significant changes can be assessed on an individual basis. (†) Incidences of complete normalization of WBC, hemoglobin (Hgb) increases by > 2 g/dL, platelet (Plt) increases by > 30 × 10^9/L, and spleen volume reduction by ≥ 35%. aCML, atypical chronic myeloid leukemia; CNL, chronic neutrophilic leukemia.

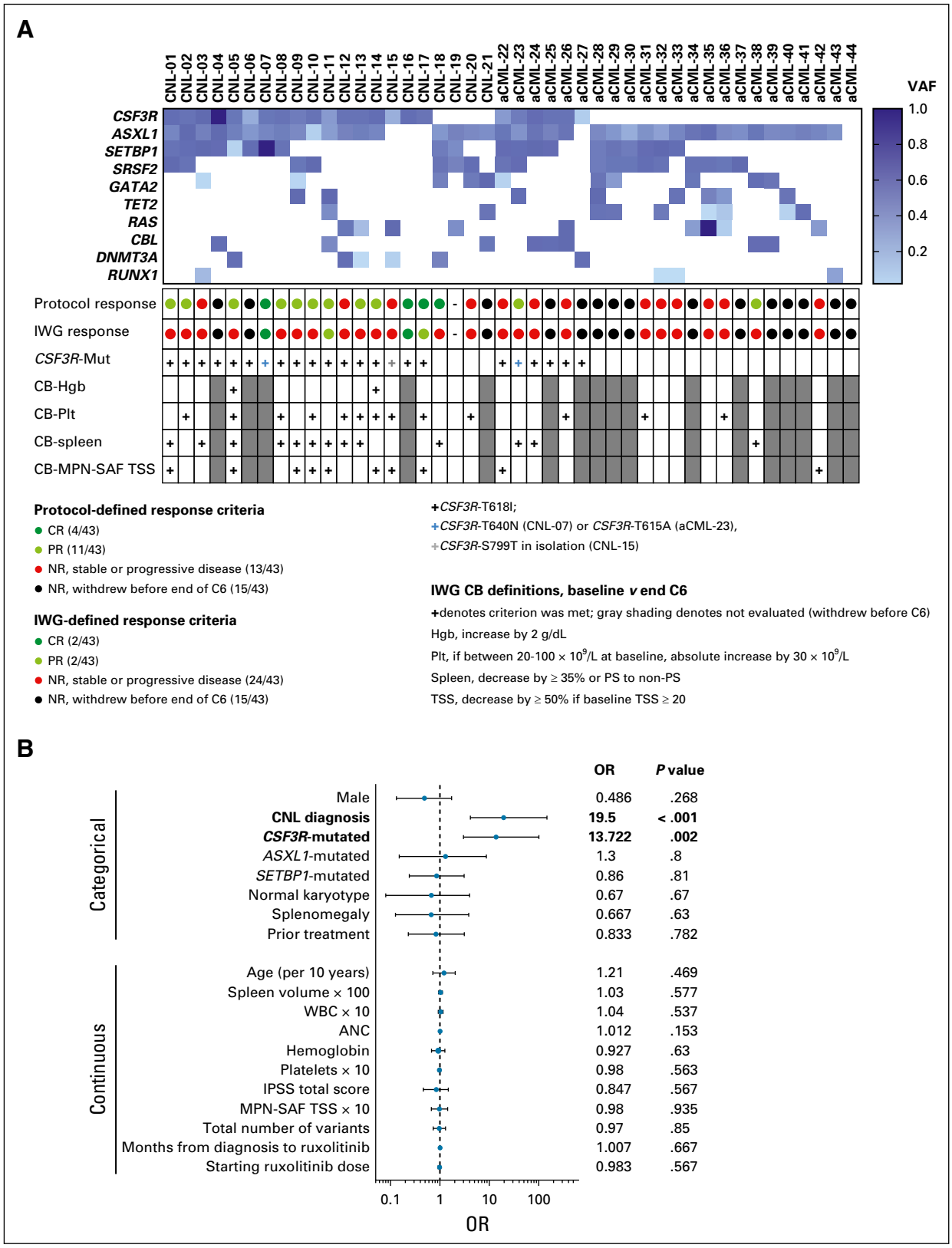

FIG 2. (A) Summary figure of patients according to mutation profile, response assessment, and clinical benefit (CB). The heat map displays the 11 most commonly mutated genes in this study population according to variant allele frequency (VAF; darkest blue 100% and white 0%). The protocol-defined and International Working Group (IWG)–defined response assessments are color-coded by response. *CSF3R*-T618I mutation status is indicated as well as other pertinent *CSF3R* variants. CB was assessed by IWG criteria with (continued on following page)

4) genetic correlates of hematologic responses, and 5) 2-year overall survival (OS).

Response Criteria and Study Assessments

Because of the lack of validated response criteria for CNL and aCML, we designed response criteria using end point analyses considered clinically relevant in MPNs generally and taking into account that treatment with ruxolitinib and other JAK inhibitors is associated with hematologic adverse events of anemia and thrombocytopenia. We defined CR as normalization of WBC count and absolute neutrophil count (ANC), no evidence of granulocytic hyperplasia (CNL) or granulocytic dysplasia (aCML), and normal spleen by ultrasonography measurement (< 250 cm^3)[17] or by palpation. There is excellent correlation of spleen volume estimates using prolate ellipsoid method by ultrasonography and calculations by computed tomography.[18] In patients who are not in CR, PR requires $> 50\%$ reduction of WBC, ANC, and granulocytic hyperplasia or dysplasia and $> 25\%$ reduction in spleen volume or palpable spleen length from the left midcostochondral line. Quantifying marrow dysplasia proved challenging among pathologists, so when a less-subjective criterion was not met for CR (eg, normalization of marrow cellularity or WBC/ANC), the patient was determined not to have a CR. Marrow cellularity and myeloid:erythroid ratio are measures of granulocytic hyperplasia. Details of response criteria are listed in the Data Supplement. All responses were assessed by an adjudication committee (J.G., M.M.N.D., S.T.O.), including the principal investigator (K-H.D.). We also evaluated clinical benefit as defined by MDS/MPN IWG.[16] The data cutoff date was October 17, 2018.

Molecular Analyses

DNA from blood cells was sequenced using a custom panel of 76 genes recurrently mutated in leukemia (QIAseq; Qiagen, Hilden, Germany; Data Supplement). The lower limit of detection is 2% variant allele frequency (VAF), and the average coverage is 2,000×. After sequencing on the Illumina (San Diego, CA) NextSeq500, data were aligned against the hg19 reference genome. A custom bioinformatics analysis pipeline integrating multiple established variant calling tools (FreeBayes [arXiv, Cornell Univeristy, Ithaca, NY], MuTect2 [Broad Institute, Cambridge, MA], and Scalpel [http://scalpel.sourceforge.net/index.html]) and variant annotation tools (Oncotator, Broad Institute, Cambridge, MA) was used. The inter-run coefficient of variation of replicate sampling is 8%.

Statistical Analysis

For sample size calculation, we considered ruxolitinib promising if it demonstrated ORR of $\geq 30\%$.[19] Other studies have considered this an acceptable ORR for investigational therapies in hematologic malignancies.[20,21] The null hypothesis was 10% ORR, given that CNL and aCML are rare diseases with no best available therapy for comparison. On the basis of Simon's 2-stage minimax design, 25 evaluable patients would provide 80% power at 5% significance level with an interim analysis on the availability of primary end point data for the first 15 patients. If 1 or 0 patients responded, the trial was stopped for futility. If ≥ 2 patients responded, accrual to the second stage was expanded to 25 patients. The study was subsequently amended to allow enrollment to 44 patients, because approximately one-third of the patients could not reach the end of cycle 6, a time point for evaluation of secondary end points. We report the primary end point (ORR) on the first 25 patients, and the ORR and other end points on the basis of the 44 enrolled patients. Summary statistics were used to describe demographic and clinical characteristics. To compare the baseline characteristics for patients, we used Kruskal-Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Kaplan-Meier plot and log-rank test were used to visualize and compare 2-year OS between groups. Median follow-up was estimated using the reverse Kaplan-Meier method. Statistical analysis was performed using R 3.5.3, IBM SPSS Statistics 21 (SPSS, Armonk, NY), and GraphPad Prism 8 (GraphPad Software, San Diego, CA).

RESULTS

Patient Characteristics

At the time of data cutoff, 21 patients with CNL and 23 patients with aCML were enrolled. Patient characteristics are presented in Table 1. The median age was 73 years

FIG 2. (Continued). one modification.[16] We added the CB criterion of decrease in spleen volume by $\geq 35\%$ (used in myelofibrosis pivotal studies).[34] CB was not evaluated in patients who had a complete response (CR) by IWG criteria or in patients who withdrew before the end of cycle 6 (denoted by gray shading). (B) Forest plot for the unadjusted odds ratio (OR) and 95% CI obtained from univariate logistic regression models, with some continuous variables scaled in units of 10 or 100 to produce reasonable range of ORs. Data separated by categorical and continuous variables. Analyses on 43 evaluable patients were performed based on various demographic and disease characteristics and also starting doses of ruxolitinib. Boldface indicates variables that were found to be statistically significant. We also explored the adjusted effects, potential confounders, and effect modifiers using multivariable logistic regression models. Multivariable models were not presented because diagnosis is the single dominating risk factor for response, even after controlling for other important risk factors (ie, *CSF3R* mutation status and spleen volume). Although *CSF3R* mutation and spleen volume showed individual confounding effects, the estimated effect of diagnosis from a multivariable logistic regression model with both covariates included was very close to that from the univariate model. aCML, atypical chronic myeloid leukemia; ANC, absolute neutrophil count; C6, cycle 6; CNL, chronic neutrophilic leukemia; Hgb, hemoglobin; MPN-SAF, myeloproliferative neoplasm symptom assessment form; NR, no response; Plt, platelet; PR, partial response; PS, palpable spleen; TSS, total symptom score.

TABLE 2. Change in Disease Characteristics, Baseline *v* End of Cycle 6

Characteristic	All Patients[a] (n = 29)	CNL (n = 18)	aCML (n = 11)	*P*[b]	*CSF3R*–Wild Type (n = 11)	*CSF3R*-Mutant (n = 18)	*P*[b]
WBC, absolute median change (range), × 10^9/L	−23.5 (−195.9 to 47.4)	−33.5 (−195.9 to 2.6)	−21.2 (−63.7 to 47.4)	**.053**[b]	−8.5 (−63.0 to 47.4)	−38.3 (−195.9 to 14.5)	**.028**[b]
WBC, % median change (range) × 10^9/L	−62.5 (−93.7 to 513.6)	−68.3 (−93.7 to 14.4)	−44.3 (−88.6 to 513.6)	**.053**[b]	−40.7 (−79.3 to 513.6)	−74.9 (−93.7 to 23.4)	**.031**[b]
ANC, absolute median change (range) × 10^9/L	−16.7 (−189.1 to 27.5)	−29.8 (−189.1 to 3.6)	−10.7 (−51.6 to 27.5)	**.043**[b]	−6.5 (−51.6 to 27.5)	−33.0 (−189.1 to 13.8)	**.022**[b]
ANC, % median change (range) × 10^9/L	−68.1 (−94.3 to 317.0)	−70.6 (−94.3 to 24.0)	−42.8 (−90.2 to 317.0)	.065[b]	−27.6 (−83.3 to 317.0)	−74.0 (−94.3 to 27.7)	**.028**[b]
Hemoglobin, absolute mean change (SD), g/dL	−0.5 (2.0)	−0.4 (2.2)	−0.6 (1.8)	.848	−1.0 (1.8)	−0.1 (2.1)	.292
Hemoglobin, % mean change (SD), g/dL	−2.0 (19.5)	−0.7 (21.6)	−4.1 (16.0)	.653	−7.6 (16.0)	1.5 (21.0)	.226
Platelet, absolute median change (range) × 10^9/L	38.0 (−214.0 to 260.0)	64.0 (−214.0 to 203.0)	−8.0 (−84.0 to 260.0)	.096[b]	11.0 (−84.0 to 135.0)	56.0 (−214.0 to 260.0)	.216[b]
Platelet, % median change (range) × 10^9/L	28.0 (−80.5 to 279.6)	34.9 (−80.5 to 229.4)	−10.3 (−70.9 to 279.6)	.418[b]	14.5 (−70.9 to 176.0)	41.5 (−80.5 to 279.6)	.208[b]
Spleen reduction ≥ 35%,[c] no, No. (%)	8 (38.1)	4 (28.6)	4 (57.1)	.346	5 (71.4)	3 (21.4)	**.056**
Spleen reduction ≥ 35%,[c] yes, No. (%)	13 (61.9)	10 (71.4)	3 (42.9)		2 (28.6)	11 (78.6)	
Spleen volume, absolute median change (range), cm^3	−219.7 (−1,553.8 to 1,061.4)	−249.7 (−1,553.8 to 259.9)	−219.7 (−1078.9 to 1,061.4)	.941[b]	−112.3 (−1,078.9 to 1,061.4)	−287.2 (−1,553.8 to −14.0)	.179[b]
Spleen volume, % median change (range), cm^3	−39.8 (−90.6 to 137.0)	−43.4 (−90.6 to 137.0)	−31.2 (−40.4 to 79.4)	**.052**[b]	−12.4 (−49.5 to 137.0)	−41.8 (−90.6 to −14.6)	**.014**[b]
MPN-SAF TSS,[d] absolute median change (range)	−4.0 (−37.0 to 8.0)	−4.5 (−37.0 to 7.0)	−3.0 (−25.0 to 8.0)	.514[b]	−2.5 (−25.0 to 7.0)	−4.0 (−37.0 to 8.0)	.599[b]
MPN-SAF TSS,[d] % median change (range)	−31.2 (−100.0 to 700.0)	−38.9 (−100.0 to 700.0)	−20.7 (−83.3 to 100.0)	.461[b]	−15.6 (−83.3 to 700.0)	−42.3 (−100.0 to 150.0)	.255[b]
MPN-SAF TSS ≥ 20,[d] absolute median change (range)	−10.5 (−37.0 to 3.0)	−17.0 (−37.0 to 3.0)	−6.0 (−25.0 to 0.0)	.350[b]	−10.0 (−25.0 to 0.0)	−11.0 (−37.0 to 3.0)	.462[b]
MPN-SAF TSS ≥ 20,[d] % median change (range)	−33.8 (−100.0 to 10.3)	−42.3 (−100.0 to 10.3)	−20.7 (−83.3 to 0.0)	.350[b]	−32.3 (−83.3 to 0.0)	−42.3 (−100.0 to 10.3)	.463[b]
IPSS, absolute median change (range)	0.0 (−3.0 to 2.0)	−1.0 (−3.0 to 2.0)	0.0 (−2.0 to 2.0)	.163[b]	0.0 (−2.0 to 2.0)	−1.0 (−3.0 to 2.0)	.137[b]
IPSS, % median change (range)	0.0 (−100.0 to 200.0)	−41.7 (−100.0 to 200.0)	0.0 (−100.0 to 100.0)	.369[b]	0.0 (−100.0 to 200.0)	−41.7 (−100.0 to 100.0)	.153[b]

NOTE. A negative value denotes a reduction and a positive value denotes an increase in the mean or median change of the variable evaluated.

Abbreviations: aCML, atypical chronic myeloid leukemia; ANC, absolute neutrophil count; CNL, chronic neutrophilic leukemia; IPSS, International Prognostic Scoring System; MPN-SAF TSS, myeloproliferative neoplasm symptom assessment form, total symptom score; SD, standard deviation.

[a]Twenty-nine of 44 patients reached the end of cycle 6, the primary end point analyses at which these variables are evaluated.

[b]Kruskal-Wallis test for non-normally distributed, continuous variables. For other variables, *t* test for normally distributed, continuous variables; Fisher's exact test for percentage spleen reduction. Bolded *P* values indicate significant or marginally significant differences.

[c]For spleen volume, only those patients who had 3 dimensions measured by ultrasonography and complete data at baseline *v* end of cycle 6 were evaluated.

[d]For MPN-SAF TSS, only those patients who answered all 10 questions and had complete data at baseline *v* end of cycle 6 were evaluated. TSS ≥ 20 indicates those patients who had a baseline TSS score ≥ 20, whereby clinical benefit could be evaluated per International Working Group response criteria.

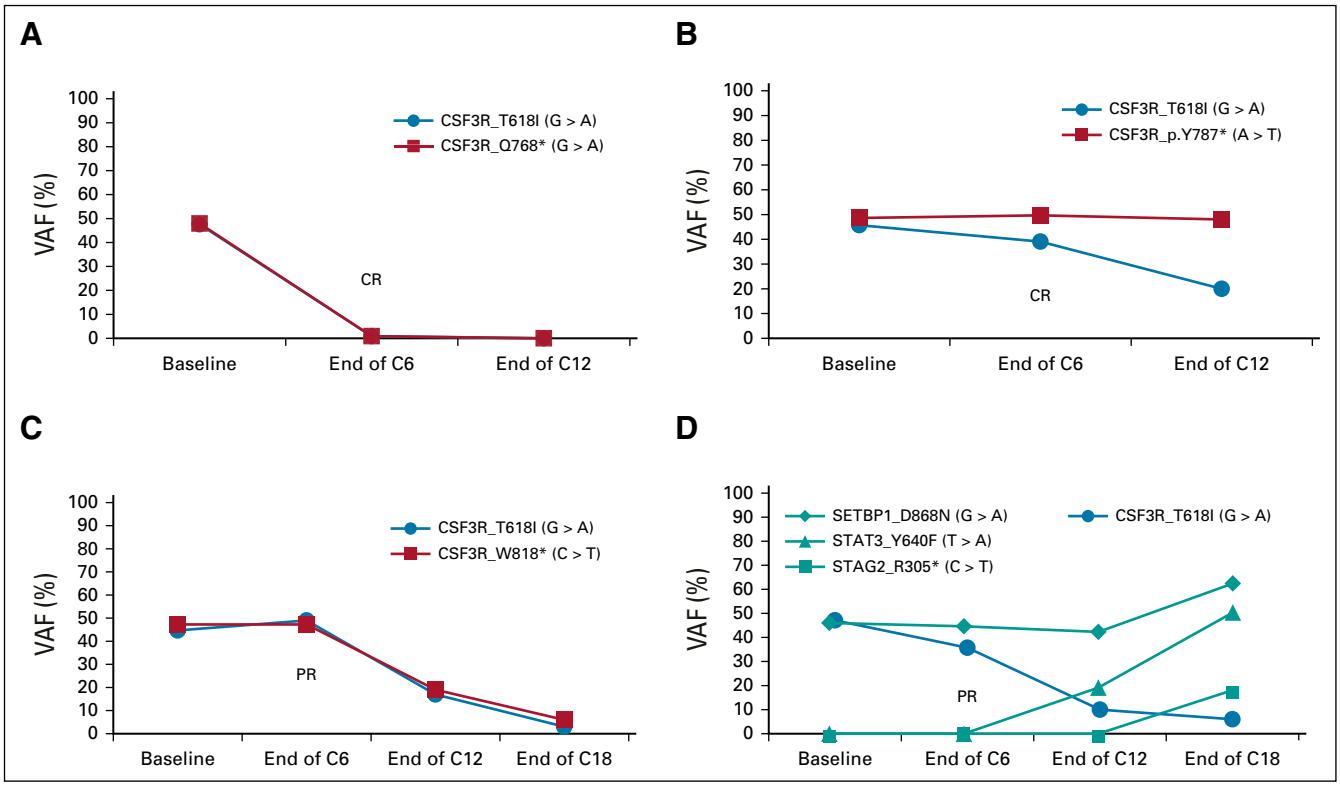

FIG 3. Different patterns of *CSF3R*-mutation variant allele frequency (VAF) changes over time with ruxolitinib. The status of the patient and cycle they reached as of data cutoff are indicated. (A) CNL-16, on study C19. (B) CNL-17, on study C16. (C) CNL-05, on study C43. (D) CNL-08, off study C19. C, cycle; CNL, chronic neutrophilic leukemia; CR, complete response; PR, partial response.

(range, 43-92 years). Patients with CNL were older (median, 74 years) than patients with aCML (median, 67 years; $P = .026$). As expected, *CSF3R* membrane-proximal and transmembrane mutations were more common in CNL (76%) than in aCML (26%; $P = .002$). The median WBC/ANC, hemoglobin, and platelet count at baseline were not statistically different (Table 1). Other clinical characteristics are summarized in Table 1, and ruxolitinib dosing is summarized in the Data Supplement.

Efficacy Analyses

For the first 15 patients in stage 1, 5/15 (33%) responded, allowing us to move on to stage 2 of the Simon's design. Eight of the first 25 patients responded (32%; 8 PR and 0 CR). By diagnosis, ORR was 58% (7/12) in the CNL group and 8% (1/13) in the aCML group ($P = .011$). By *CSF3R* mutation status, ORR was 54% (7/13) in the *CSF3R*-mutated group and 8% (1/12) in the *CSF3R*–wild type group ($P = .030$). Although 25 patients will achieve adequate power for the primary end point, we enrolled 44 patients to allow a reasonable number of patients to reach the end of cycle 6 for evaluation of secondary end points. The data for the first 25 patients are provided in the Data Supplement.

In Table 1, we summarize overall study outcomes for all 44 patients except for ORR, which we reported for 43 patients because one patient (CNL-19) had a suboptimal bone marrow biopsy specimen at the end of cycle 6 and had a normal spleen volume at baseline. The adjudication committee deemed this case not evaluable for response. Among 43 patients evaluable for response, ORR was 35% (11 PR [9 CNL, 2 aCML] and 4 CR [CNL]). The Data Supplement summarizes the adjudicated CR cases.

Figure 1A provides a schematic of patients according to diagnosis, *CSF3R* mutation status, and disposition on study. Figure 1B depicts absolute changes in WBC, hemoglobin, platelet count, and spleen volume, and Table 2 summarizes median or mean change of these and other variables in patients who reached the end of cycle 6. Ruxolitinib produced greater reduction of median WBC/ANC in patients with CNL (*v* patients with aCML) and in *CSF3R*-mutated patients (*v* *CSF3R*–wild type patients). Spleen volume reduction $\geq 35\%$ occurred more frequently in *CSF3R*-mutant patients (79% *v* 29% *CSF3R*–wild type patients; $P = .056$), but this did reach statistical significance. Overall, ruxolitinib therapy reduced mean hemoglobin and improved median platelet count (-0.5 [$\pm$ 2.0 standard deviation] and +38 [range, -214 to 260], respectively).

In Fig 2A, we summarize baseline mutation profile and individual responses. Comprehensive mutation data are

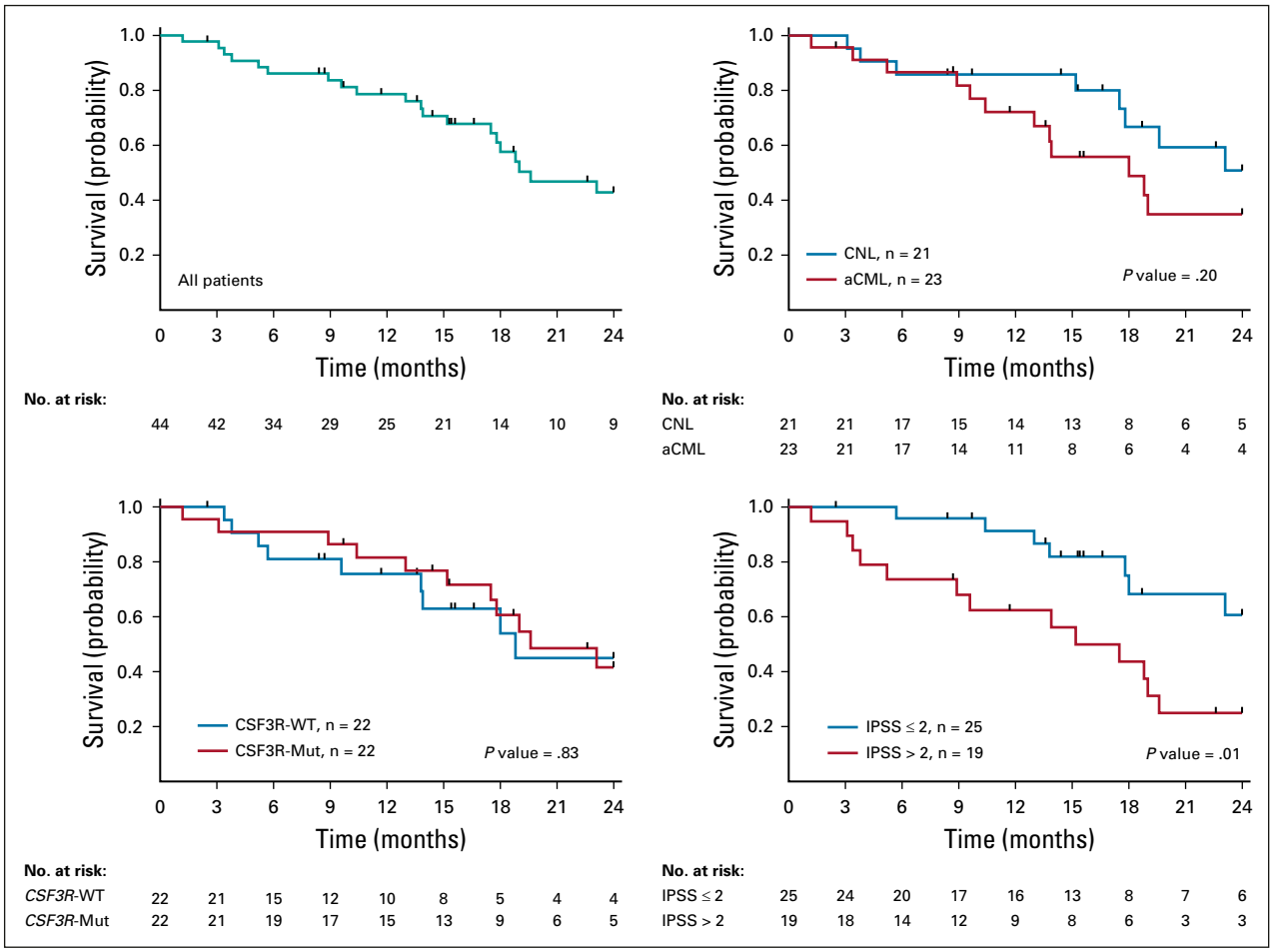

FIG 4. Kaplan-Meier curves estimating probability of survival for all patients and subgroup analyses as indicated. The *P* values from log-rank (Mantel-Cox) tests are indicated on the graph. We currently have 2-year data for all 44 patients enrolled. For those with longer-term data, we censored the data at 2 years. Six patients were also censored on the date they underwent hematopoietic stem-cell transplantation. aCML, atypical chronic myeloid leukemia; CNL, chronic neutrophilic leukemia; IPSS, International Prognostic Scoring System; Mut, mutation; WT, wild type.

provided in the Data Supplement. The mean baseline VAF of *CSF3R*-T618I was 0.44 (range, 0.09 to 0.89). Characteristics of compound mutations are summarized in the Data Supplement. We observed a higher frequency of *DNMT3A* mutations in CNL (24%) compared with aCML (4.3%). In contrast, *TET2* and *RAS* mutations were more frequent in aCML (26% and 30%, respectively) compared with CNL (9.5% and 9.5%, respectively). *ASXL1* and *SETBP1* mutations were present in 89% and in 46% of patients, respectively, with no difference between CNL versus aCML.

Two patients attained CR by protocol-defined and IWG-defined criteria.[16] In patients who did not obtain CR by IWG-defined criteria at the end of cycle 6, we performed clinical benefit analyses according to IWG criteria as defined in Figure 2A.[16] Overall, 85% (23/27) of patients fulfilled criteria for ≥ 1 category of clinical benefit(s). In Figure 2B, univariate analyses were performed according to response by protocol-defined criteria. CNL diagnosis and *CSF3R* mutations were strongly correlated with response. No other variables were significantly correlated with response, including karyotype, number of mutations, and *ASXL1* or *SETBP1* mutations.

Patterns of Mutant *CSF3R*-T618I Allele Frequency Changes

Figure 3 shows examples of changes in *CSF3R*-T618I VAF during treatment. Two patients had CR with early VAF reduction (CNL-16, CNL-17). One patient had a PR at the end of cycle 6 but with continued treatment achieved a CR that correlated with VAF reduction (CNL-05). CNL-08 had a PR that tracked with progressive *CSF3R*-T618I reduction but developed disease progression with expansion of *CSF3R*-T618I–negative cells harboring *STAT3*-Y640F and *STAG2*-R305*. Although 2 patients with CR (CNL-16, CNL-17) maintained responses through cycle 19 and cycle 16 as of data cutoff, the other 2 patients with CR (CNL-07, CNL-18) maintained response for < 1 year. CNL-07 had early

TABLE 3. Grade ≥ 3 Adverse Events Occurring in ≥ 2 Patients

Adverse Event	All Patients (N = 44)
General	
Fatigue	**4 (9.1)**
Back pain	2 (4.5)
Neurocognitive function	
Delirium	2 (4.5)
Cardiovascular system	
Heart failure	**3 (6.8)**
Respiratory system	
Upper respiratory infection	**3 (6.8)**
Lung infection	**4 (9.1)**
Pneumonitis	**4 (9.1)**
Immune system/infection	
Skin infection	2 (4.5)
Decreased lymphocytes	**3 (6.8)**
Urinary tract infection	**3 (6.8)**
Bleeding	
Hematoma	2 (4.5)
Other	
Death	2 (4.5)
Hematologic	
Anemia	**15 (34.1)**
Platelet count decreased	**6 (13.6)**
Leukocytosis	**5 (11.4)**

NOTE. Data presented as No. (%). Boldface indicates adverse events occurring in more than 5% of patients.

progression with expansion of *STAT3*-D427G– and *CBL*-W408C–mutant cells. The mean absolute VAF change for patients with *CSF3R*-T618I, -T615A, or -T640N was −0.26 for CR, −0.05 for PR, and +0.01 for no response, with 8% inter-run coefficient of variation (Data Supplement).

Survival

Survival data were collected from the start of study drug and were censored on the day of hematopoietic stem-cell transplantation for 6 patients or last follow-up. All patients who did not die or proceed to transplant were followed for at least 2 years (median follow-up, 38.4 months). Median OS for all patients was 18.8 months (95% CI, 15.3 to 25.2 months). By response, median survival was 15.6 months for nonresponders and 23.1 months for responders. We expect the responders to have longer median survival because they had to survive at least 6 cycles of treatment to be evaluated as a potential responder. Figure 4 summarizes 2-year OS. Patients with lower International Prognostic Scoring System score as defined in Table 1 survived longer.[22] Disease duration before study participation was not considered in survival analysis.

Treatment Status at the Data Cutoff Point and Safety Assessment

At data cutoff, 39 patients were off study. The main reasons for study discontinuation were disease progression with or without blastic transformation (n = 15) or provider preference, usually due to lack of clinical benefit (n = 11; Data Supplement). Thirty-one patients have died. The most common cause of death was disease progression (n = 13). Other causes of death are listed in the Data Supplement.

Because AEs of all grades with ruxolitinib have been reported previously,[23,24] we focused on grade ≥ 3 AEs (Table 3). Fifty-five percent of patients experienced at least 1 grade ≥ 3 nonhematologic AE. Except 1 case of nutritional weight gain, no other nonhematologic grade ≥ 3 AEs were considered related or probably related to ruxolitinib. The expected hematologic AEs with ruxolitinib include anemia and thrombocytopenia. Grade ≥ 3 anemia and thrombocytopenia were observed in 34% and 14% of patients, respectively, occurring as a treatment effect or related to disease. In patients who experienced progressive leukocytosis, this was related to discontinuation of hydroxyurea and primary resistance or disease progression due to secondary resistance. All other grade ≥ 3 AEs were considered expected and/or were not related to ruxolitinib; therefore, no new serious AEs were identified.

DISCUSSION

Studies in cell lines, primary colony assays, and in vivo models suggest ruxolitinib targets signaling downstream of oncogenic *CSF3R*.[3,12,13] Our clinical study provides evidence that ruxolitinib is a treatment option for a subset of patients with CNL and aCML. ORR by protocol-defined criteria for the first 25 patients was 32% (8/25 with PR). Previous experience with ruxolitinib in CNL and aCML has been limited to case reports with variable responses.[25-29] Some responses are associated with allele burden reduction.[27,28] Our data are consistent with these anecdotal experiences, including the observation that hematologic responses occur more often in CNL than in aCML. When evaluated by *CSF3R* mutation status, the *CSF3R* mutation effect was confounded by the strong association with CNL diagnosis (Fig 2B). We did not observe a high frequency of grade 3-4 anemia, as noted in patients with myelofibrosis treated with ruxolitinib, and actually observed increases in platelet counts in selected patients, a treatment benefit not typically experienced with hydroxyurea, the drug most commonly used to control proliferative myeloid neoplasms.

The majority of patients did not experience CR or PR and eventually succumbed to disease-related complications, but the potential for durable CR (including a molecular CR [CNL-16]) and IWG-defined clinical benefits is noteworthy. Two patients (CNL-16 and -17) with CR by protocol-defined criteria for > 1 year (and ongoing) presented with lower-risk features, suggesting that ruxolitinib may be

more effective early in disease pathogenesis. These patients had mild/no cytopenias, had mild leukocytosis, lacked splenomegaly and overt symptoms, and had no other co-occurring mutations recurrently mutated in CNL and aCML. In the primary care setting, where neutrophilia may be ignored or attributed to reactive causes, increased awareness of the possibility of CNL may facilitate earlier diagnosis and therapy, when the disease could be more responsive to ruxolitinib. However, additional studies are required to determine whether early treatment could alter the natural history of CNL, whether combination therapies can improve ORR in CNL/aCML, and whether patients with durable responses could achieve long-term eradication of mutant cells. MEK inhibition in *CSF3R*-mutated CNL,[30] *CSF3R*–wild type aCML,[31] or MDS-MPN overlap neoplasms[32] is another potential therapeutic consideration. In recent years, examples have emerged in chronic myeloid neoplasms indicating that complete responses, which are generally infrequent with noncytotoxic therapies, are not required for survival benefit (MDS/azacitidine[33] and myelofibrosis/ruxolitinib[34]). Thus, novel therapies should be investigated for survival benefit even if they infrequently induce complete responses.

We highlight 2 novel genetic characteristics in this study population. First, we observed 3 patients with *CSF3R*-S799T. This variant occurs in the cytoplasmic domain and has uncertain oncogenic potential. In variant 3 *CSF3R* transcript, this site corresponds to S772, which is part of a motif that regulates receptor endocytosis. An S772A substitution results in increased cell surface expression,[35] but it is not clear how a conserved substitution S772T would alter function. In one case, *CSF3R*-S799T occurred at $< 5\%$ VAF, and in the other 2 cases, after 6 cycles of ruxolitinib, *CSF3R*-S799T VAF was reduced from 12% to 0% (compound_T618I, CNL-13) and 21% to 0% (in isolation, CNL-15). CNL-15 was not evaluated in the *CSF3R*-mutated group, but these data suggest some degree of direct sensitivity to ruxolitinib, or alternatively, the S799T mutation exists in a clone sensitive to ruxolitinib by virtue of other genetic drivers. Second, *ASXL1* and *SETBP1* mutation status did not correlate with responses, but our sample size is too small to make definitive conclusions. Mutations in *ASXL1* and *SETBP1* are considered disease-modifying mutations and are associated with shortened survival in CNL and aCML.[1,36] Anecdotally, we note that the two CR responses lasting $>$ 1year harbored no *ASXL1* or *SETBP1* mutations (CNL-16 and -17). Meanwhile, PR responses can be durable for $>$ 40 cycles even with these mutations, for example, CNL-05 (*ASXL1* and *SETBP1* mutations) and CNL-11 (*ASXL1* mutation). We expect that the spectrum of responses we observed within the *CSF3R*-mutant subset can be at least partially explained by co-occurring mutations, which awaits additional preclinical and clinical modeling in larger studies.

In summary, our study offers evidence supporting the clinical efficacy of ruxolitinib in one-third of patients with CNL and aCML and provides new insights on genetic features of CNL and aCML in the context of ruxolitinib therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy of Ruxolitinib in Patients With Chronic Neutrophilic Leukemia and Atypical Chronic Myeloid Leukemia

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Consulting or Advisory Role: Blueprint Medicines, Gilead Sciences, Aptose Biosciences, MolecularMD, Beta Cat Pharmaceuticals, CTI BioPharma, GRAIL, Third Coast Therapeutics, Baxalta, Aileron Therapeutics, ALLCRON Pharma, Cepheid, Celgene, Monojul, Vivid Biosciences, The RUNX1 Research Program, Patient True Talk, Enliven Therapeutics, VB Therapeutics
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Jeffrey W. Tyner
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