HHS Public Access

Author manuscript

Clin Lymphoma Myeloma Leuk. Author manuscript; available in PMC 2021 February 18.

Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2020 March ; 20(3): 174–183.e3. doi:10.1016/j.clml.2019.10.009.

Prognostic Testing and Treatment Patterns in Chronic Lymphocytic Leukemia in the Era of Novel Targeted Therapies: Results From the informCLL Registry

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Abstract

informCLL is the first United States-based registry of patients with chronic lymphocytic leukemia that initiated enrollment after approval of novel targeted agents. Prognostic/predictive testing rates and chronic lymphocytic leukemia treatment selection with availability of novel agents have not been previously investigated in clinical practice. Results from this interim analysis demonstrate that prognostic/predictive testing was infrequently used to guide treatment selection, potentially inhibiting beneficial outcomes for patients.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 20, No. 3, 174-83 ª 2019 The Authors. Published by Elsevier Inc.

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The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figure and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2019.10.009.

Introduction: The therapeutic landscape for chronic lymphocytic leukemia (CLL) has significantly shifted with the approval of novel agents. Understanding current prognostic testing and treatment practices in this new era is critical. Beginning enrollment in 2015, informCLL is the first United States-based real-world, prospective, observational registry that initiated enrollment after approval of novel agents.

Patients and Methods: Eligible patients were age ≥ 18 years, started CLL treatment within 30 days of enrollment, and provided consent. For this planned interim analysis, treatments were classified into 5 groups: ibrutinib, chemoimmunotherapy, chemotherapy, immunotherapy, and other novel agents.

Results: Frequency of prognostic testing and treatment patterns are reported among 840 patients (459 previously untreated; 381 relapsed/refractory), enrolled largely (96%) from community practice settings. Testing for chromosomal abnormalities by fluorescence in situ hybridization, *TP53* mutation, or *IGHV* mutation status occurred infrequently among all patients (31%, 11%, and 11%, respectively). Chemoimmunotherapy was the most common treatment in previously untreated patients (42%), whereas ibrutinib was the most common treatment among relapsed/refractory patients (51%). Of patients who tested positive for del(17p) or *TP53* mutation, 34% and 26% received chemoimmunotherapy, respectively. Among patients who did not have fluorescence in situ hybridization or *TP53* mutation testing prior to enrollment, 33% and 32% received chemoimmunotherapy, respectively.

Conclusion: Our findings indicate that prognostic testing rates were poor, and approximately one-third of high-risk patients (del[17p] and *TP53)* received chemoimmunotherapy, which is not aligned with current CLL treatment recommendations. This represents an opportunity to educate and alert health care professionals about the necessity of prognostic testing to guide optimal CLL treatment decisions.

Keywords

Chemoimmunotherapy; Ibrutinib; Novel agents; Prognostic marker; Real-world registry

Introduction

Treatment of chronic lymphocytic leukemia (CLL) has changed significantly with approval of novel targeted therapies.[1–4] Additionally, a deeper understanding of factors influencing disease prognosis has also advanced the treatment paradigm. Although available treatments and tools for risk stratification once proved limited in their effectiveness, especially for elderly patients with comorbidities or patients with high-risk features, selection of newer therapies based on results of prognostic testing has allowed for more robust outcomes for patients.[5]

Whereas data from clinical trials are essential for moving the field forward and for approval of new CLL-directed therapies, interrogating how these findings influence day-to-day clinical practice represents a significant opportunity to identify previously unrecognized barriers to optimal medical care in the community. In addition, assessment of outcomes in patients receiving care in community practices based on current guidelines and approved therapies is of value.

This report describes an interim analysis from the informCLL registry, the first United States (US)-based prospective registry initiating enrollment after the approval of novel agents for CLL treatment. The registry was designed to characterize treatment patterns in previously untreated patients or those with relapsed/refractory CLL and observe corresponding outcomes over extended follow-up. Here we evaluate rates of prognostic biomarker testing and treatment patterns in clinical practice in the modern era of novel agents and examine their consistency with current treatment guidelines.

Biomarker testing is critical for informing treatment decisions for individual patients, as the results are prognostic and could be predictive as well. Results from interphase fluorescence in situ hybridization (FISH; testing for chromosome 17p deletion [del(17p)], 11q deletion [del(11q)], 13q deletion [del(13q)], and trisomy 12) and sequencing for mutations in tumor protein p53 (*TP53*) and for immunoglobulin heavy chain variable (*IGHV*) somatic hypermutation status provide insight into a patient's risk stratification and their potential response to CLL therapies.[6] The value of testing has been increasingly recognized, and prognostic models and diagnostic guidelines have recently updated their recommendations to include it when making treatment considerations.[7–10]

In terms of treatment patterns, a limitation of published data from the ConnectCLL real-world registry was its collection prior to availability of novel targeted agents or updated guidelines.[11,12] Therefore, it is of importance to determine if current testing patterns have been influenced by the approval of novel agents and/or align with guidelines. The International Workshop on CLL updated their guidelines in 2018 to recommend molecular-genetic testing not only for clinical trials, but also for routine clinical practice.[10] These guidelines note that patients with del(17p) or *TP53* mutations have poorer outcomes and do not respond well to chemotherapy/chemoimmunotherapy, and they emphasize the prognostic value of *IGHV* mutational status testing.[10] It is important to understand whether current practices reflect these updated guidelines.

Patients and Methods

Registry Objective

The primary objective of the informCLL registry is to describe current treatment patterns among patients who are initiating a new line of treatment with novel therapies, including approved oral kinase inhibitors or other approved CLL therapies/regimens as first- or later-line therapy, and explore the associations with baseline patient characteristics, health care resource utilization, and clinical outcomes.

Study Design

Beginning enrollment in October 2015, informCLL (PCYC-1134; NCT02582879) is a US-based, 200-center, prospective, observational registry of patients with CLL or small lymphocytic lymphoma (SLL) who initiated treatment with a US Food and Drug Administration (FDA)-approved CLL/SLL therapy/regimen, including an approved oral kinase inhibitor or BCL-2 inhibitor. informCLL was conducted in accordance with the Declaration of Helsinki, and its approval was obtained from the independent ethics

committee or institutional review board for each participating center. Therapy had to occur prior to or within 30 days of entering the registry. All treatment decisions were made at the sole discretion of the treating physician in accordance with their usual practices; no treatments were recommended or provided. Patients were given the choice to withdraw consent and discontinue participation in the registry at any time. The registry was co-sponsored by Pharmacyclics LLC, an AbbVie Company, and Janssen, and was designed by the co-sponsors in collaboration with investigators of the Steering Committee. Data were collected by investigators and their research teams. Pharmacyclics LLC, an AbbVie Company, confirmed accuracy of the data and compiled them for analysis. All authors had full access to the data and interpreted the data. All authors contributed to revisions and final approval of the manuscript and made the decision to submit the manuscript for publication.

Patient Population

Eligible patients were enrolled at the time of presentation for a routine clinic visit; no specific clinic visits were required as part of participation in this registry. Patients who were prescribed oral kinase inhibitors approved at the time of enrollment (eg, inhibitors of Bruton's tyrosine kinase [ibrutinib] or PI3Kδ [idelalisib]), BCL-2 inhibitors (eg, venetoclax), or other FDA-approved CLL therapies/regimens by their physician were invited to participate in the registry around the time of treatment decision. Key inclusion criteria included patients who were ≥ 18 years old with a clinical diagnosis of CLL/SLL per published diagnostic criteria,[13] initiation of treatment within ± 30 days of enrollment, available documentation on previous CLL/SLL treatment and duration of response in medical records (relapsed/refractory patients only), and ability to: provide written informed consent, complete patient-reported outcome questionnaire, provide information on survey questionnaire, and provide a blood sample at the time of enrollment. Patients were excluded if they had been diagnosed with any B-cell malignancy other than CLL/SLL, had a < 6-month life expectancy, or were currently receiving treatment in an interventional clinical trial at the time of enrollment. Patients who enrolled in an interventional clinical trial after enrollment could remain in the registry.

Treatment Groups

CLL treatments received by patients at the time of registry enrollment were categorized as follows: ibrutinib (single agent or in combination); chemoimmunotherapy (includes anti-CD20 monoclonal antibodies such as rituximab, obinutuzumab, or ofatumumab in combination with chemotherapy [eg, bendamustine + rituximab, obinutuzumab + chlorambucil, or fludarabine + cyclophosphamide + rituximab]); chemotherapy (chlorambucil, bendamustine, fludarabine, cyclophosphamide, doxorubicin, gemcitabine, vincristine, or any other chemotherapy [as single agent or in combination]); immunotherapy (anti-CD20 monoclonal antibodies: rituximab, obinutuzumab, ofatumumab [with or without steroids]); or other novel agents such as: idelalisib (single agent or in combination), venetoclax (single agent or in combination), or other novel CLL therapies.

Assessments

All assessments were performed at routine clinical encounters by the prescribing physician. Data were collected at predetermined time points or by referencing the information routinely

recorded in the medical record for purposes of the registry. Information collected included demographics, laboratory testing, relevant medical history and comorbidities, available diagnostic/prognostic testing, CLL/SLL treatment initiated at enrollment, indication for treatment, and concomitant medications. Data were collected at enrollment (baseline), 3 months, 6 months, and then every 6 months thereafter for a minimum of 24 months or until early discontinuation (owing to loss to follow-up, withdrawal from the registry, or death).

Statistical Analysis

Reported here are data from a pre-planned annual interim analysis of the first 840 patients enrolled in the registry from October 2015 to February 2018. Patient demographics, clinical characteristics, and treatment groups were described at baseline by line of therapy and initial treatment at enrollment. Prognostic testing information was collected from patients who were tested at enrollment. CLL treatments received at the time of enrollment were grouped and are described above in Treatment Groups.

Evaluation of potential factors associated with FISH testing was done using logistic regression analyses per methods previously described.[11] Variables used for univariate and multivariate analyses included: time from initial CLL diagnosis to treatment at enrollment, age, gender, race, insurance, Eastern Cooperative Oncology Group performance status, Rai stage, previously untreated versus relapsed/refractory, comorbidities, institution type (community or academic), previous malignancy, and US geographic region. Variables identified as significant at the $P < .15$ level based on univariate regression modeling were tested using stepwise multivariable logistic regression to identify the independent characteristics associated with FISH testing.

Statistical analyses were performed using Statistical Analysis Software (SAS) Version 9.4 or higher.

Data-sharing Statement

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Results

Baseline Demographics and Disease Characteristics

Of 840 enrolled patients at the time of interim analysis, 459 (55%) were previously untreated, and 381 (45%) had relapsed/refractory disease (Table 1). Community-based practices (centers not affiliated with teaching/academic institutions) enrolled the majority of patients compared with academic institutions (96% vs. 4%, respectively). The median follow-up was 9.4 months (range, 0.03–24.9 months) at the time of this analysis.

A summary of patient demographics and clinical characteristics at enrollment by line of therapy is listed in Table 1 and by groups based on initial CLL treatment at enrollment in Supplemental Tables 1 and 2 (in the online version). Patients had a median age of 70 years (range, 34–95 years). Previously untreated patients were slightly younger compared with

relapsed/refractory patients (69 vs. 71 years, respectively). For all patients, the median time from initial diagnosis prior to first treatment at registry enrollment was 41 months (range, < 1–446 months).

Rai staging data were available from 485 (58%) patients who were assessed at enrollment. Rai stage ≥ III was observed in 45% of previously untreated patients and 57% of relapsed/refractory patients (Table 1). A physical exam was conducted in 303 (36%) of patients for whom Rai staging was not assessed at enrollment. The frequency of patients presenting with baseline comorbidities was similar between previously untreated and relapsed/refractory patients (95% and 96%, respectively). Among all patients, hypertension and type 2 diabetes were the most common comorbidities observed (64% and 23%, respectively). Previous malignancy was observed in 204 (24%) patients, with a similar frequency between previously untreated patients and relapsed/refractory patients (24% and 25%, respectively).

Prognostic Testing and Treatment Patterns in Practice

FISH, *TP53* mutation, and *IGHV* somatic hypermutation testing were performed infrequently across all patients at registry enrollment (n = 262 [31%]; n = 89 [11%]; and n = 94 [11%], respectively) (Figure 1). FISH testing was performed in approximately one-third of patients overall, with significantly higher rates observed in previously untreated versus relapsed/refractory patients (36% vs. 26%; $P = .0007$). Of 262 patients with available FISH testing, 70 (27%) had del(17p), 76 (29%) had del(11q), 158 (60%) had del(13q), and 75 (29%) had trisomy 12 (Figure 2). Del(17p) was slightly higher in previously untreated versus relapsed/refractory patients (29% vs. 23%), whereas del(11q) was slightly lower (27% vs. 32%, respectively). Rates of del(13q) and trisomy 12 were similar between the 2 groups (60% vs. 60% and 28% vs. 30%, respectively).

Testing for *TP53* mutation was performed in a small minority of all patients (89/840; 11%) and was slightly higher in previously untreated (54/459; 12%) compared with relapsed/refractory patients (35/381; 9%) (Figure 1). The rate of patients with mutated *TP53* was the same for previously untreated (14/54; 26%) and relapsed/refractory patients (9/35; 26%) among patients who were tested (Figure 2).

Testing for *IGHV* somatic hypermutation was infrequent (94/840; 11%) with similar testing rates among previously untreated (55/459; 12%) and relapsed/refractory patients (39/381; 10%) (Figure 1). Among the low number of patients with *IGHV* mutational status testing, unmutated *IGHV* was reported in 69 (73%) of all 94 patients tested (Figure 2).

Factors Associated With Performing Prognostic Marker Testing

To determine factors associated with performing FISH testing, univariate then multivariate analyses were performed. In the univariate logistic regression analysis, the following 8 of 12 potential factors were found to be associated at a $P < .15$ level with performing FISH testing in all patients: lesser time from initial diagnosis to treatment at enrollment; gender (more likely male); lower Eastern Cooperative Oncology Group performance status; higher Rai stage; no prior line of therapy, presence of comorbidities, or previous malignancy; and geographic region within the US (other census-defined regions more likely than west). Assessed with multivariate modeling, the variables found significant in predicting FISH

testing regardless of line of therapy were shorter time from initial diagnosis to treatment at enrollment and positive history of previous malignancy (Table 2). Given the low number of patients with *TP53* and *IGHV* mutational status testing (n = 89 and n = 94, respectively), regression model analyses did not produce meaningful conclusions.

Treatment Patterns

Treatment patterns overall and by line of therapy are listed in Table 3. Overall, ibrutinib was the most common treatment (44%) regardless of line of therapy at enrollment. Of patients receiving ibrutinib, most were treated with single-agent ibrutinib compared with ibrutinib-based combination therapies (96% vs. 4%, respectively). Chemoimmunotherapy was the next most common treatment prescribed for approximately one-third of all patients, and the most common regimen used was bendamustine + rituximab (19%).

Chemoimmunotherapy was more common in previously untreated patients compared with relapsed/refractory patients (42% vs. 23%), whereas ibrutinib was more frequently used in relapsed/refractory versus previously untreated patients (51% vs. 39%) (Table 3). For patients < 65 years old, chemoimmunotherapy (bendamustine + rituximab and fludarabine + cyclophosphamide + rituximab) was the most common treatment (53%) in previously untreated patients, and ibrutinib was the most common treatment (55%) in relapsed/refractory patients (see Supplemental Figure 1 in the online version). Ibrutinib was the most common treatment in patients ≥ 65 years old regardless of line of therapy (43% in first-line and 49% in relapsed/refractory, respectively) (see Supplemental Figure 1 in the online version).

Across all patients with available prognostic testing information, ibrutinib was the most common treatment for high-risk patients with del(17p), *TP53* mutation, or unmutated *IGHV* (54%, 65%, and 43%, respectively) (Figure 3). Unexpectedly, chemoimmunotherapy was also frequently prescribed among patients in this high-risk population, with rates of 34% for patients with del(17p), 26% for patients with *TP53* mutation, and 42% in patients with unmutated *IGHV*.

For patients who did not undergo FISH, *TP53*, or *IGHV* somatic hypermutation testing or those with unavailable biomarker data (69%, 89%, and 89%, respectively), ibrutinib was the most common treatment (44%, 44%, and 45%, respectively). Chemoimmunotherapy was prescribed among approximately one-third of patients despite unknown molecular-genetic risk status (33%, 32%, and 33%, respectively).

Discussion

The informCLL registry is the first prospective observational registry for patients with CLL in the era of approved novel targeted therapies. As such, the registry did not influence initial assessments, prognostic biomarker testing, or treatment decisions, and the data collected reflect physician decisions. This interim analysis provides important insight into the current practices for the treatment of CLL, especially with respect to prognostic marker testing. We conclude from these results that current clinical practice is not keeping pace with recommendations and guidelines for prognostic marker testing and subsequent selection of

appropriate therapy.[10,14] These data present an opportunity to highlight the relevance of this critical issue. Given the importance of targeted agents for the treatment of high-risk patients, this lack of prognostic marker testing and the less than expected use of novel agents is a potentially significant missed opportunity for treating patients with the most appropriate therapies.

Patients were largely enrolled from community-based practices; therefore, findings are based on a generalizable patient population that would likely be encountered during routine clinical practice as opposed to the more stringently selected patients enrolled in clinical trials or in other retrospective non-trial studies. The demographics of patients enrolled in informCLL were consistent with other community-based real-world reports,[12] with the median age of patients enrolled being 70 years, indicating an elderly population.[12] Del(17p) was observed in 27% of patients among those who were tested regardless of line of therapy. Although this rate is higher than what would be expected,[15] it underscores the high-risk population enrolled in informCLL and may suggest that patients who underwent FISH testing in this setting were somehow clinically different than those who were not tested prior to first-line or subsequent therapy initiation.

Although the International Workshop on CLL guidelines were only recently updated in 2018 to more explicitly include testing in routine clinical practice, other guidelines and prognostic models have recommended prognostic biomarker testing for risk stratification for several years.[7–9,16] Therefore, it was unexpected that in the present analysis, prognostic marker testing occurred in such a low percentage of patients, regardless of line of therapy. Even more surprising, rates reported here for FISH testing (31%) were even lower than those reported from the ConnectCLL registry (2010 to 2014, era prior to introduction of novel agents into clinical practice), which showed that 49% of patients had FISH testing and 6% had testing for *IGHV* mutational status at enrollment in the registry.[11] Patients enrolled in ConnectCLL included a higher proportion from academic institutions compared with informCLL, which may explain the differences in prognostic testing rates observed between the 2 registries.[11] However, it does not appear that routine prognostic marker testing is being adopted rapidly. In our multivariate analysis, only 2 factors were found to be significantly associated with FISH testing: shorter time from initial diagnosis to treatment and positive history of previous malignancy. Therefore, our regression analysis indicates that lack of testing is not isolated to key groups with specific access barriers (eg, age, race, and insurance status) but rather is a pervasive problem in the community practice setting. Given the impact that test results can have on treatment decisions for patients, it is critical to continue to educate physicians on the importance of selecting the appropriate and potentially life-saving intervention that can be guided by prognostic testing.

As the use of novel targeted agents continues to increase for CLL, we observed that ibrutinib was commonly prescribed (44%) among all patients. When examining by treatment line and age, chemoimmunotherapy was the most common treatment in previously untreated younger patients (< 65 years), whereas the majority of relapsed/refractory older patients (≥ 65 years) received ibrutinib. This demonstrates that chemoimmunotherapy appeared to remain the primary selection for first-line therapy at the time of this analysis, which may be in part owing to the approval of novel targeted agents for first-line treatment occurring after

enrollment began and because the rate of adoption of newly approved medications in the community practice may be slower than academic centers. As evidence recently presented from phase III studies demonstrates improved outcomes for patients treated with novel agent-based regimens compared with chemoimmunotherapy in the first-line setting,[17–20] data from this registry may allow for examination of changing prescribing trends for first-line treatment over time as clinical trial data continue to emerge.

In the high-risk groups of patients with del(17p) and mutated *TP53*, surprisingly 34% and 26% of patients received chemoimmunotherapy combinations, respectively. This finding was concerning in that it contradicts consensus guidelines based on data from several clinical studies,[13,15] which do not recommend chemoimmunotherapy for these high-risk patients owing to poor disease and survival outcomes with this treatment strategy.[21,22] This is important to highlight because there are robust data demonstrating that targeted agents such as ibrutinib, idelalisib, and venetoclax are quite active in these high-risk molecular/genetic subtypes.[1,23–25] In addition, more than 40% of tested patients with unmutated *IGHV* also received chemoimmunotherapy, despite decreased efficacy with chemoimmunotherapy in this patient population[14] and data indicating that ibrutinib is able to overcome the negative impact of unmutated *IGHV*.[26,27] For patients with unknown risk status, approximately one-quarter received chemoimmunotherapy. We estimate that based on reported rates of del(17p), mutated *TP53*, and unmutated *IGHV* unmutated seen within informCLL, this represents approximately 50 potential patients for whom a more appropriate therapy could have been selected. Therefore, failure to test for prognostic factors prior to CLL therapy selection can result in life-changing consequences for patients.

Like other real-world registries, the informCLL registry relies on site-reported data that are subject to data coding limitations, missing data, and data entry error. However, aggressive data querying, robust query resolution, and validation of each individual site prior to the interim analysis were conducted to ensure data accuracy. Analyses with registry data typically have biases associated with uncontrolled and/or undetectable confounders, unlike randomized controlled trials. For example, a higher percentage of previously untreated del(17p) patients (29%) was observed versus what is typically expected in clinical trials (7%–10%),[15,21] although this is consistent when benchmarking against other “real-world” publications (21%–37%).[28–30] The percentage of patients with relapsed/refractory CLL and del(17p) is also consistent with other real-world reports.[12] High-risk patients may have presented with more symptoms or aggressive disease; therefore, testing may have been disproportionality high in these patients. Additionally, the small numbers of patients tested could have identified a higher proportion of patients with del(17p) than if all enrolled patients had been tested. These limitations should be non-differential and similarly apply to patients across all groups and cause minimal bias.

Conclusion

These interim prospective observational registry data from informCLL indicate that even with the approval of novel agents and updated guidelines, low rates of prognostic biomarker testing may lead to suboptimal therapy choices for patients with unknown risk status. In addition, we note that the presence of high-risk features (del(17p) and *TP53*) is

unfortunately not translating to choosing the optimal therapy for these patients. Therefore, we have highlighted the importance of using prognostic testing to inform CLL treatment decisions and lead to robust outcomes for patients. informCLL will continue to follow patients and collect clinical outcomes of CLL treatments, providing further insights into changing trends in CLL treatment choices in the community setting as novel targeted agents continue to gain approval for different treatment settings and patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the patients who participated in this study, and their supportive families, as well as the investigators, sub-investigators, and coordinators at each of the study sites. This study was sponsored by Pharmacyclics LLC, an AbbVie Company, and Janssen. Editorial support was provided by Emily Chastain, PhD, an employee of Pharmacyclics LLC, an AbbVie Company. This registry was co-sponsored by Pharmacyclics, LLC, an AbbVie Company, and Janssen, LP.

Disclosure

ARM reports consultancy/advisory role with AbbVie, Astra Zeneca, Celgene, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; and research funding from AbbVie, LOXO, Pharmacyclics LLC, an AbbVie Company, Regeneron, Sunesis, and TG Therapeutics. JCB reports honoraria from Janssen; consultancy/advisory role with AbbVie, AstraZeneca, Bayer, Genentech, Gilead, Pharmacyclics LLC, an AbbVie Company, and Sandoz; and research funding from AbbVie, Oncternal Therapeutics, and Pharmacyclics LLC, an AbbVie Company. NG reports honoraria from Astra Zeneca, Bristol-Myers Squibb, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, SGN, TG Therapeutics; consultancy/advisory role with Celgene, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, SGN, and TG Therapeutics; research funding from Celgene, Genentech, Janssen, Pharmacyclics LLC, an AbbVie Company, SGN, and TG Therapeutics; and speakers' bureau for Astra Zeneca, Bristol-Myers Squibb, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, and SGN. JMP reports consultancy/advisory role with Gilead and Pharmacyclics LLC, an AbbVie Company. DB reports honoraria from AbbVie, Genentech, Teva, and TG Therapeutics; consultancy/advisory role with AbbVie, AstraZeneca, Genentech, Novartis, Pharmacyclics LLC, an AbbVie Company, Teva, and TG Therapeutics; and research funding from AbbVie, AstraZeneca, BeiGene, DTRM, Genentech, and TG Therapeutics. KK reports stock ownership in AbbVie, Agios, and Celgene; and speakers' bureau for Celgene, Pharmacyclics LLC, an AbbVie Company, and Takeda. RI reports employment with Pharmacyclics LLC, an AbbVie Company; and stock ownership in AbbVie; patents, royalties, or other intellectual property with Express Scripts. DI and CIA report employment with Pharmacyclics LLC, an AbbVie Company; and stock ownership in AbbVie. SU reports employment with Pharmacyclics LLC, an AbbVie Company, and Protagonist Therapeutics; and stock ownership in AbbVie. MS reports employment with Johnson & Johnson; and stock ownership in AbbVie, Bristol-Myer Squibb, and Johnson & Johnson. JH reports employment with Janssen and Boehringer Ingelheim; and stock ownership in Johnson and Johnson. NG reports employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; and travel expenses from Pharmacyclics LLC, an AbbVie Company. JPS reports honoraria and research funding from, and consultancy/advisory role with AbbVie, Acerta, Astra Zeneca, Celgene, Genentech, Gilead, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics.

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Clinical Practice Points

- informCLL is the only US-based, observational, prospective registry of patients with CLL that initiated enrollment post-FDA approval of novel targeted agents.
- Prognostic/predictive testing results of biomarkers associated with risk status are crucial for the appropriate selection of treatment.
- Results from this early interim analysis indicate that rates of prognostic marker testing occurred in a low percentage of patients with CLL regardless of line of therapy, which is consistent with data reported from prior registries that gathered information before the approval of novel agents.
- Logistic regression analysis demonstrated that testing deficiencies could not be attributed to a single factor or factors (eg, age, race, insurance status) but rather were ubiquitously observed among all patient factors.
- Approximately one-third of tested patients with either deletion 17p or *TP53* mutation and 42% with unmutated *IGHV* received chemoimmunotherapy combinations against the recommendation of current CLL treatment guidelines.
- These real-world data indicate that, with the approval of novel agents and updated guidelines, the frequency of prognostic biomarker testing remains suboptimal; this provides a critical opportunity to highlight the importance of testing results to inform CLL treatment decisions and facilitate optimal clinical outcomes for patients.

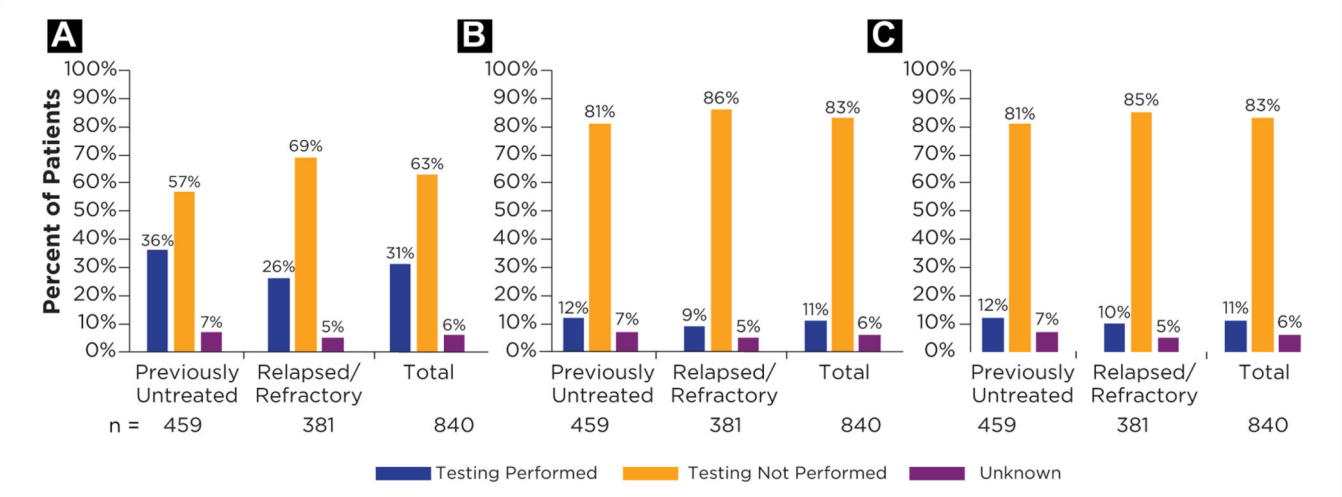
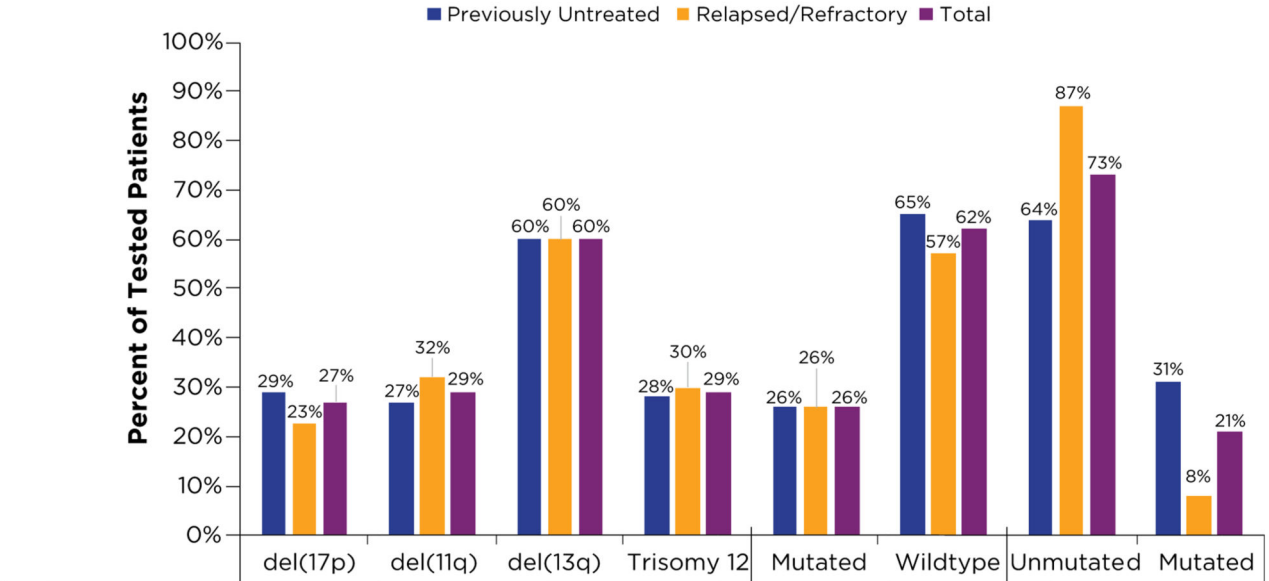


Figure 1. Frequency of Prognostic Biomarker Testing for FISH (A), *TP53* Mutational Status (B), and *IGHV* Mutational Status (C) Are Shown by Line of Therapy and All Patients

Abbreviations: FISH = fluorescence in situ hybridization; *IGHV* = immunoglobulin heavy-chain variable region gene; *TP53* = tumor protein p53 gene.



Tested Patients, n*	FISH	*TP53*	*IGHV*
Previously Untreated	164	54	55
Relapsed/Refractory	98	35	39
Total	262	89	94

Figure 2. Proportion of Tested Patients With Specific Genetic Abnormality and/or Molecular Mutations Are Shown by Line of Therapy and All Patients

n* represents the number of patients with available testing results.

Abbreviations: del(17p) = chromosome 17p deletion; del(11q) = chromosome 11q deletion; del(13q) = chromosome 13q deletion; FISH = fluorescence in situ hybridization; *IGHV* = immunoglobulin heavy-chain variable region gene; *TP53* = tumor protein p53 gene.

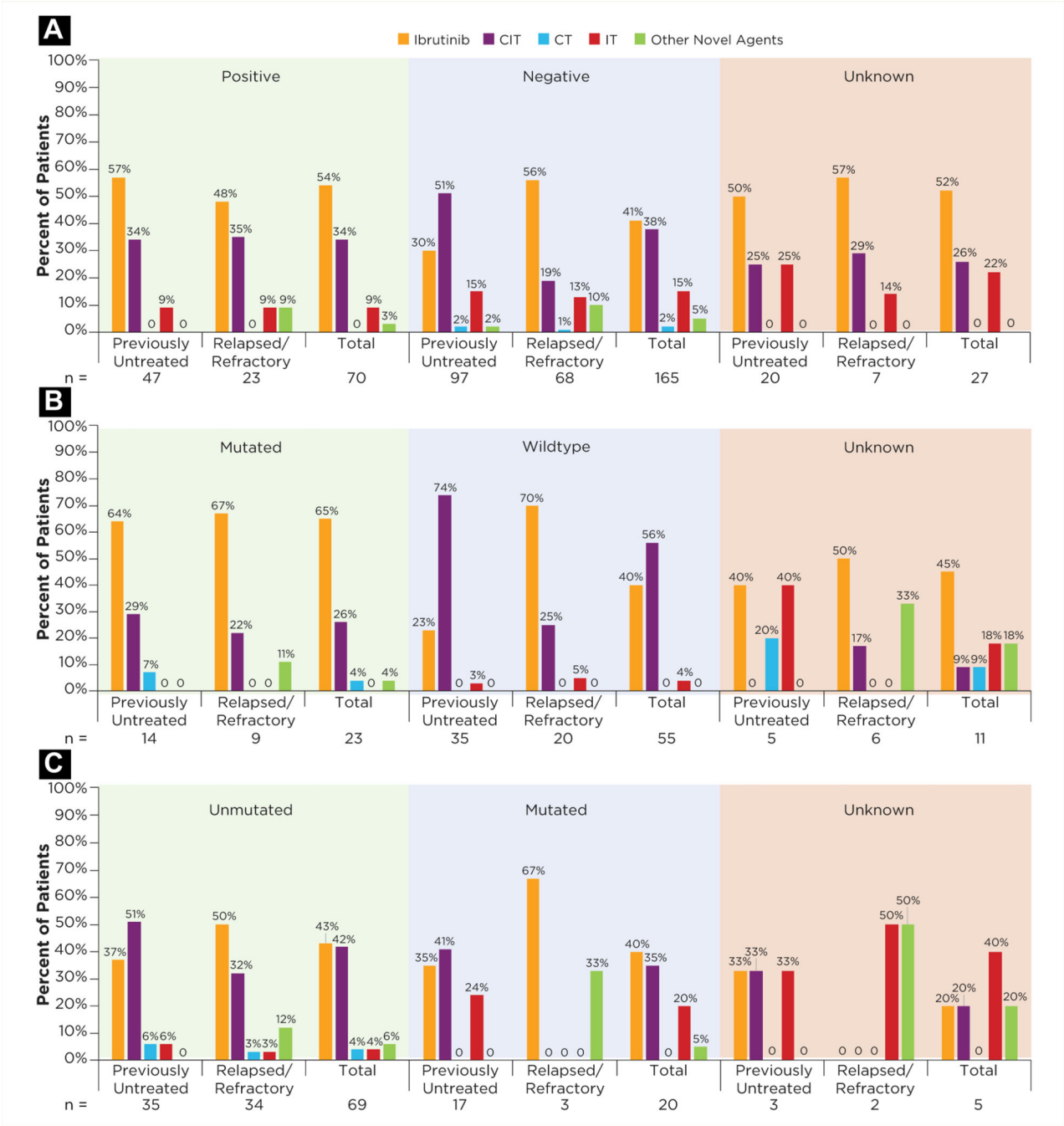


Figure 3. Percentage of Patients Receiving Specific Treatment Are Shown by Line of Therapy and All Patients for Prognostic Biomarker Status for del(17p) (A), *TP53* Mutation (B), and *IGHV* Mutation (C)

Abbreviations: CIT = chemoimmunotherapy; CT = chemotherapy; del(17p) = chromosome 17p deletion; *IGHV* = immunoglobulin heavy-chain variable region gene; IT = immunotherapy; *TP53* = tumor protein p53 gene.

Table 1

Patient Demographics and Clinical Characteristics at Enrollment

Demographics	**Previously Untreated (n = 459), n (%)**[a]	**Relapsed/Refractory (n = 381), n (%)**	**Total (N = 840), n (%)**[a]
Median age (range), y	69 (38–95)	71 (34–95)	70 (34–95)
Male	293 (64)	244 (64)	537 (64)
White	421 (92)	348 (91)	769 (92)
ECOG performance status			
0	201 (44)	155 (41)	356 (42)
1	204 (44)	173 (45)	377 (45)
2	28 (6)	33 (9)	61 (7)
3	3 (0.7)	6 (2)	9 (1)
4	0	0	0
Not specified	22 (5)	14 (4)	36 (4)
Missing	1 (0.2)	0	1 (0.1)
Rai staging done at enrollment			
No	142 (31)	161 (42)	303 (36)
Not specified	28 (6)	23 (6)	51 (6)
Missing	1 (0.2)	0	1 (0.1)
Yes	288 (63)	197 (52)	485 (58)
Rai stage[b]			
0	34 (12)	16 (8)	50 (10)
I	49 (17)	23 (12)	72 (15)
II	69 (24)	28 (14)	97 (20)
III	56 (19)	46 (23)	102 (21)
IV	74 (26)	66 (34)	140 (29)
Median time from initial diagnosis to treatment at registry enrollment (range), mos	18 (<0.1–212)	80 (0.4–446)	41 (<0.1–446)
Comorbidities	438 (95)	364 (96)	802 (95)
Hypertension	291 (63)	245 (64)	536 (64)
Diabetes mellitus	112 (24)	82 (22)	194 (23)

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Demographics	Previously Untreated (n = 459), n (%)[a]	Relapsed/Refractory (n = 381), n (%)	Total (N = 840), n (%)[a]
Connective tissue disease	88 (19)	67 (18)	155 (19)
Pulmonary issues/COPD	53 (12)	48 (13)	101 (12)
Atrial fibrillation	37 (8)	45 (12)	82 (10)
Institution type			
Community	133 (96)	113 (97)	144 (96)
Academic	5 (4)	4 (3)	6 (4)
Insurance status at enrollment[c,d]			
Public[e]	331 (72)	304 (80)	635 (76)
Private[f]	166 (36)	123 (32)	289 (34)
United States geographic region of clinical site			
Midwest	80 (17)	54 (14)	134 (16)
Northeast	78 (17)	77 (20)	155 (18)
South	228 (50)	194 (51)	422 (50)
West	73 (16)	56 (15)	129 (15)
Previous malignancy[b]			
Yes[g]	109 (24)	95 (25)	204 (24)
No	348 (76)	286 (75)	634 (76)

Abbreviations: COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group.

[a] One patient missing available data.

[b] Based on patients with Rai staging assessed.

[c] Patients may have had more than one type of insurance so the sum of the total may be more than 100%.

[d] Does not include patients with insurance listed as “none” or “other.”

[e] Includes Medicare, Medicaid, military-based, and exchange-based coverage (through the Health Insurance Marketplace or state-based exchanges that were established as part of the Affordable Care Act of 2010).

[f] Includes employer-based, American Association of Retired Persons (AARP), self-pay, and private insurance.

[g] History of malignancies other than CLL/SLL.

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Table 2

Independent Predictors of Performing FISH Test at Enrollment

Factor	Odds Ratio	95% Confidence Interval	*P*
Time from initial diagnosis to treatment at enrollment			.0015
≤18 months	1	–	
>18 to ≤36 months	0.6152	0.3798–0.9827	.0456
>36 months	0.5497	0.3952–0.7638	.0004
Previous malignancy			.0129
No	1	–	
Yes	1.5445	1.0960–2.1716	

Abbreviations: FISH = fluorescence in situ hybridization.

Table 3

Treatment Groups and Common Treatment Regimens

	Previously Untreated (n = 459), n (%)	Relapsed/Refractory (n = 381), n (%)	Total (N = 840), n (%)
Ibrutinib – single agent or in combination	180 (39)	193 (51)	373 (44)
Chemoimmunotherapy	193 (42)	89 (23)	282 (34)
BR	93 (20)	63 (17)	156 (19)
GC	43 (9)	12 (3)	55 (7)
FCR	44 (10)	9 (2)	53 (6)
Other	13 (3)	5 (1)	18 (2)
Chemotherapy	8 (2)	10 (3)	18 (2)
Bendamustine	4 (1)	2 (1)	6 (1)
Chlorambucil	1 (<1)	5 (1)	6 (1)
Other	3 (1)	3 (1)	6 (1)
Immunotherapy – single agents	71 (16)	56 (15)	127 (15)
Rituximab	42 (9)	34 (9)	76 (9)
Obinutuzumab	27 (6)	17 (5)	44 (5)
Other	2 (<1)	5 (1)	7 (1)
Other novel agents –single agent or in combination	7 (2)	33 (9)	40 (5)
Idelalisib	1 (<1)	13 (3)	14 (2)
Venetoclax	0	18 (5)	18 (2)
Other	6 (1)	2 (<1)	8 (1)

Abbreviations: BR = bendamustine + rituximab; GC = obinutuzumab + chlorambucil; FCR = fludarabine + cyclophosphamide + rituximab.