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ORIGINAL REPORT

Multivariable Model for Time to First Treatment in Patients With Chronic Lymphocytic Leukemia

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ABSTRACT

Purpose
The clinical course for patients with chronic lymphocytic leukemia (CLL) is diverse; some patients have indolent disease, never needing treatment, whereas others have aggressive disease requiring early treatment. We continue to use criteria for active disease to initiate therapy. Multivariable analysis was performed to identify prognostic factors independently associated with time to first treatment for patients with CLL.

Patients and Methods
Traditional laboratory, clinical prognostic, and newer prognostic factors such as fluorescent in situ hybridization (FISH), *IGHV* mutation status, and ZAP-70 expression evaluated at first patient visit to MD Anderson Cancer Center were correlated by multivariable analysis with time to first treatment. This multivariable model was used to develop a nomogram—a weighted tool to calculate 2- and 4-year probability of treatment and estimate median time to first treatment.

Results
There were 930 previously untreated patients who had traditional and new prognostic factors evaluated; they did not have active CLL requiring initiation of treatment within 3 months of first visit and were observed for time to first treatment. The following were independently associated with shorter time to first treatment: three involved lymph node sites, increased size of cervical lymph nodes, presence of 17p deletion or 11q deletion by FISH, increased serum lactate dehydrogenase, and unmutated *IGHV* mutation status.

Conclusion
We developed a multivariable model that incorporates traditional and newer prognostic factors to identify patients at high risk for progression to treatment. This model may be useful to identify patients for early interventional trials.

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INTRODUCTION

The clinical course of chronic lymphocytic leukemia (CLL) is highly diverse; some patients have indolent disease, never needing treatment, whereas others have aggressive disease, requiring treatment at initial presentation. Once patients require treatment, subsequent clinical outcomes typically reflect aggressiveness of disease, including response to first-line therapy, first remission duration, response to treatment for relapsed disease and subsequent remission duration, and overall survival. Prognostic factors, including clinical and laboratory features, have been correlated with clinical outcomes.[1,2] Newer prognostic factors include chromosome abnormalities identified by fluorescent in situ hybridization (FISH),[3] immunoglobulin heavy chain variable gene (*IGHV*) mutation status,[4,5] and leukemia cell expression of ZAP-70[6,7] and CD38.[5,8] It is important to clearly define the clinical end point for analysis and not assume the same factors apply across all clinical end points.

The standard of CLL care is observation for patients who do not have 1996 National Cancer Institute–Working Group (NCI-WG)/IWCLL 2008 indications for treatment.[9,10] No clinical trial has demonstrated an impact of early intervention on clinical outcome, particularly overall survival. Furthermore, there currently is no curative treatment with an acceptable toxicity profile.

Multivariable analyses and models to correlate independent prognostic factors, including traditional clinical and laboratory parameters and newer prognostic factors, with time to first treatment could be used to identify high-risk patients for progressive disease and shortened time to first treatment. Such

Table 1. Patient Characteristics and Univariable Analyses for Time to First Treatment

Characteristic	No. of Patients	Median	Range	No. of Patients Treated	Hazard Ratio*	*P*
Age, years	930	59	30-89	232	0.99	.0893
ALC, K/μL	922	14.7	1-319	232		
Ln (ALC), /μL	922			232	1.50	< .001
Hemoglobin, gm/dL	921	14	6.9-17.6	232	0.92	.0451
Platelet, K/μL	920	209	17-961	232	0.15	.0483
Beta-2 microglobulin, mg/L	909	2.2	0.7-10.6	231	1.30	< .001
Lactate dehydrogenase, IU/L	913	487	69-5,008	230	2.46	< .001
Creatinine, mg/dL	915	1	0.2-9.9	231	1.13	.1644
Albumin, gm/dL	914	4.4	2.6-9.3	231	0.82	.3186
Bone marrow lymphocytes, %	670	53	1-95	183	1.02	< .001
IgG, mg/dL	876	892	85-7,000	222	1.01	.6191
IgA (mg/dL)	868	124	4-2,370	218	0.84	.0227
IgM (mg/dL)	866	47	4-1,340	219	1.01	.8828
Spleen size, cm	926	0	0-15	232	1.15	.0015
Liver size, cm	926	0	0-7	230	1.33	< .001
Cervical LN size, cm†	929	0	0-11	232	1.47	< .001
Axillary LN size, cm†	928	0	0-5	231	1.55	< .001
Inguinal LN size, cm†	929	0	0-5	232	1.60	< .001
Time from diagnosis to MDACC, months	929	3.4	0-428	231	0.98	.7637

	Patients				
	No.	%	Univariable Comparison	Hazard Ratio*	*P*
Sex					
Male	566	61	*v* female	1.38	.023
Female	364	39			
Rai stage			II-IV *v* 0-I	1.98	< .001
0	334	36			
I	472	51			
II	77	8			
III-IV	47	5			
No. of involved node sites					
0	370	40			
1	186	20	*v* 0	2.05	< .001
2	169	18	*v* 0	2.39	< .001
3	204	22	*v* 0	4.25	< .001
ECOG performance status			1-2 *v* 0	1.15	.2863
0	600	64.5			
1	321	34.5			
2	9	1			
Hierarchic FISH category					
17p deletion	35	4	*v* 13q del	3.96	< .001
11q deletion	77	9	*v* 13q del	2.72	.001
+ 12	145	17	*v* 13q del	1.81	.002
Negative	229	27	*v* 13q del	1.11	.596
13q deletion	349	42			
Metaphase karyotype					
Complex	62	10	*v* diploid	2.10	< .001
Single abnormality	56	9	*v* diploid	1.34	.259
Diploid	501	81			
IGHV mutation status					
Unmutated	314	42			
Mutated	403	55	*v* unmutated	0.28	< .001
Discordant	19	3	*v* unmutated	0.67	.339
CD38 expression					
Positive (≥ 30%)	189	25	*v* negative	1.62	.0015
Negative (< 30%)	562	75			
ZAP-70					
IHC positive	274	46	*v* negative	2.62	< .001
Flow positive (≥ 20%)	142	35	*v* negative	2.96	< .001
Positive flow or IHC	345	46	*v* negative	3.82	< .001
Negative	409	54			

Abbreviations: ALC, absolute lymphocyte count; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescent in situ hybridization; flow, flow cytometry; Ig, immunoglobulin; *IGHV*, immunoglobulin heavy chain variable gene; IHC, immunohistochemistry; LN, lymph node; Ln, natural log; MDACC, MD Anderson Cancer Center.

*Cox proportional hazards regression models.

†LN size is estimate of diameter of largest LN palpated in each region.

multivariable models could be used to identify high-risk patients for early intervention trials. In addition, such models could identify high-risk patients for whom an aggressive follow-up and monitoring plan would be appropriate and would also be helpful in discussions with patients regarding their risk for progression as well as treatment planning.

We performed an analysis to identify traditional and newer prognostic factors independently associated with time to first CLL treatment for patients who do not have an indication for treatment at time of evaluation. Furthermore, we developed a weighted multivariable model using the significant prognostic factors as a tool to identify high-risk patients with shorter time to first treatment.

PATIENTS AND METHODS

Patients

Patients provided written informed consent according to institutional review board guidelines. We identified 930 previously untreated patients who presented to MD Anderson Cancer Center (MDACC) between January 2004 and December 2009, were not recommended for first-line treatment at initial visit, and were evaluated for traditional clinical and laboratory prognostic factors and one or more of the newer prognostic factors including *IGHV* mutation status, chromosome abnormalities by FISH analysis, and ZAP-70 expression by flow cytometry and/or immunohistochemistry (IHC). At initial evaluation, date of CLL diagnosis was recorded, and the time-to-event end point was defined as time from first MDACC visit to first CLL treatment. There was no restriction for time from diagnosis to presentation to MDACC. All patients had more than 2 months of treatment-free follow-up from initial MDACC evaluation, and physicians were to conform to 1996 NCI-WG guidelines for initiating treatment. This was done to develop a model that best correlated with time to first treatment for patients who do not have an indication for treatment at the time of evaluation. Follow-up was either by visits to MDACC or communication with referring physicians, including faxed documentation of blood counts, physical examinations, and time to first treatment. Clinical and laboratory evaluation at first MDACC visit included history and physical examination, standard clinical laboratory evaluation, and bone marrow biopsy and aspirate; evaluation for ZAP-70 by flow cytometry was performed on blood sent to the CLL Research Consortium in San Diego, CA.[11]

Traditional prognostic factors and clinical and laboratory variables included sex; age; Rai stage; Eastern Cooperative Oncology Group performance status; physical examination with evaluation of number of involved lymph node sites (cervical, axillary, and inguinal), measurement (largest diameter) of cervical, axillary, inguinal lymph nodes, and measurement of liver and spleen size; WBC count; absolute lymphocyte count; hemoglobin level; platelet count; beta-2 microglobulin; lactate dehydrogenase (LDH); creatinine; albumin; and quantitative immunoglobulin (Ig) levels (IgG, IgA, and IgM). Bone marrow aspirate and biopsy were taken to confirm the diagnosis by flow cytometry and characterization of CD38 expression; morphologic examination of marrow to estimate percent bone marrow lymphocytes; and standard metaphase karyotype. Metaphase karyotype for each patient was performed in the MDACC clinical laboratory by the GTL (Giemsa, Trypsin, Leischmans) staining with unstimulated lymphocytes from marrow. Karyotype was categorized as complex (> one chromosome abnormality in > one metaphase), single abnormality (one chromosome abnormality in > one metaphase), or diploid. FISH analysis for 17p deletion, 11q deletion, trisomy 12, and chromosome 13q deletion was performed on bone marrow by the MDACC clinical laboratory using a Vysis multicolor probe panel (Abbott Laboratories, Abbott Park, IL) designed to provide simultaneous detection of the 11q22.3 (*ATM* gene) region of chromosome 11, 17p13.1 (*TP53* gene) region of chromosome 17, alpha satellite, centromeric region of chromosome 12 (D12Z3), D13S319 locus (located between RB1 and D13S25 loci) in the 13q14.3 region of chromosome 13, and 13q34 region (*LAMP1* gene) near the subtelomere of chromosome 13q in two hybridizations (two and three probes per hybridization, respectively). A total of 200 interphase cells were analyzed for each probe. Positive patient cases were those with 5% or more of cells with the abnormality. Patients' FISH results were categorized according to the Dohner hierarchy.[3]

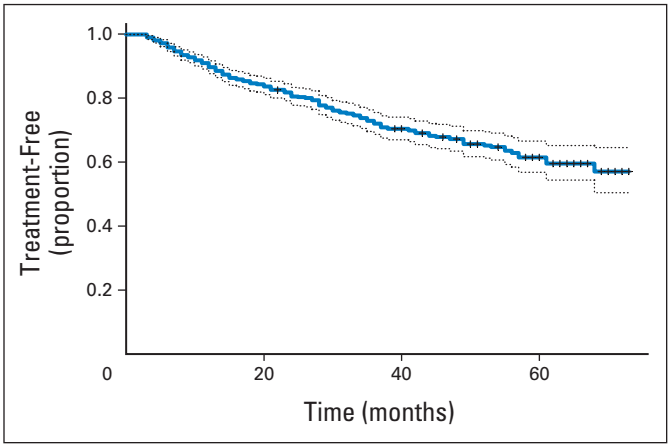

Fig 1. Time to first treatment (N = 930). Previously untreated patients with chronic lymphocytic leukemia who presented to MD Anderson Cancer Center from January 2004 through December 2009 had traditional clinical and laboratory features as well as newer prognostic factors characterized. Patients who did not require treatment within first 3 months of evaluation and had 3 months or more of follow-up were included in analyses of time to first treatment. Kaplan-Meier estimate of treatment-free survival is shown with 95% CI.

IGHV mutation status was characterized by direct sequencing method, and patients were categorized as unmutated (*IGHV* ≥ 98% germline homology) or mutated (< 98% homology).[11,12] There were 208 patients who had *IGHV* mutation status performed by both the CLL Research Consortium and MDACC molecular laboratory. There were 19 discordant patient cases among the 208 patient cases.

ZAP-70 expression was characterized by two methods. Flow cytometry (n = 405; 20% cut point) was performed on blood samples by the CLL Research Consortium, as previously described.[11] Also, IHC (n = 599) was performed on bone marrow sections by the MDACC clinical laboratory.[13] A patient case was considered positive if the majority of neoplastic cells showed

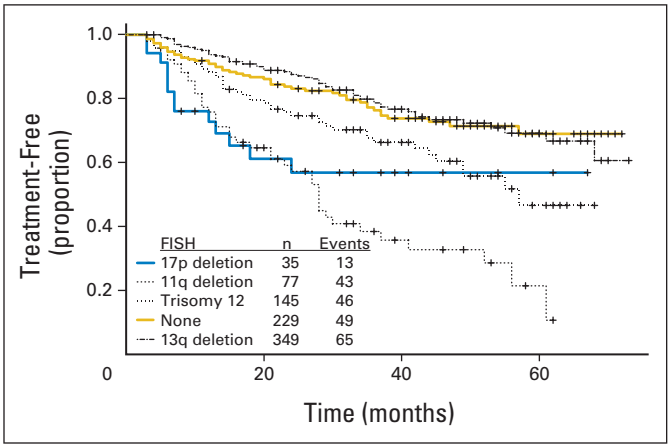

Fig 2. Time to first treatment by fluorescent in situ hybridization (FISH; n = 835). Previously untreated patients with chronic lymphocytic leukemia had bone marrow aspirate samples evaluated for chromosome abnormalities by FISH at initial presentation to MD Anderson Cancer Center. Patients were observed for time to first treatment. Kaplan-Meier estimates of treatment-free survival are shown for each of following FISH categories according to Dohner hierarchic categorization: 17p deletion, 11q deletion, trisomy 12, no abnormality, and 13q deletion as sole abnormality.

faint to moderate cytoplasmic staining. Admixed T cells were regarded as an internal control, because these cells showed strong ZAP-70 expression. In samples with equivocal staining or minimal amounts of disease, ZAP-70 stain was repeated and/or additional IHC stains were used to clarify the degree of B- and T-cell infiltration.

Statistical Methods

Patient characteristics were summarized using frequency (percentage) for categorical and median and range for continuous variables. The primary outcome, time to first treatment, was defined as the time interval between the date of presentation to MDACC and date of first CLL treatment. Patients who did not receive any treatment were censored at their last confirmed treatment-free follow-up date. The Kaplan-Meier method was used to estimate the distribution of time to first treatment, and the log-rank test was performed to compare patient subgroups. Univariable and multivariable Cox proportional hazards regression models were fit to assess associations between patient characteristics and time to first treatment. The proportional hazards assumption was assessed using the method of Grambsch et al.[14] For the multivariable model, stepwise variable selection was used. Initially, variables were added one by one to the Cox regression model and were kept in the model if *P* values were less than .10. After each variable was added, variables already in the model were removed if *P* values were greater than .05. This process continued until every variable in the model was significant at the .05 level. After the stepwise selection was completed, potential interactions among covariates in the model were assessed before deriving the final fitted model. A classification and regression tree (CART) analysis was conducted to help identify the interaction effects between covariates. The final Cox model was internally validated using two methods. First, patients were randomly entered into a testing set; the other half were included in the validation set. For validation, the testing set was used to derive the multivariable Cox proportional hazards model, which was then applied to the validation set. The *P* values of the Cox model based on the validation set were visually compared with those for the full data set. All covariates except diameter of largest palpated cervical lymph node remained statistically significant. Second, in the bootstrapping method, the same multivariable Cox model was fitted 1,000 times using bootstrap samples; the percentage of times each covariate was statistically significant ranged from 65% to 98%. Finally, a nomogram was constructed using characteristics that were significantly associated with time to first treatment in the multivariable Cox model, as described by Kattan et al.[15] All *P* values were two sided and deemed statistically significant if less than .05. All statistical analyses were conducted in SAS (SAS Institute, Cary, NC) and S-Plus (Statistical Sciences, Seattle, WA).

RESULTS

There were 930 patients included in these analyses; median age was 59 years (range, 30 to 89 years); two thirds were male; 65% had unmutated *IGHV* status; and 17p and 11q deletion (high-risk cytogenetic features) were noted in 4% and 9% of individuals, respectively (Table 1). Median time from diagnosis to presentation to MDACC was 3.4 months (range, 0 to 428 months). Median follow-up time was 26

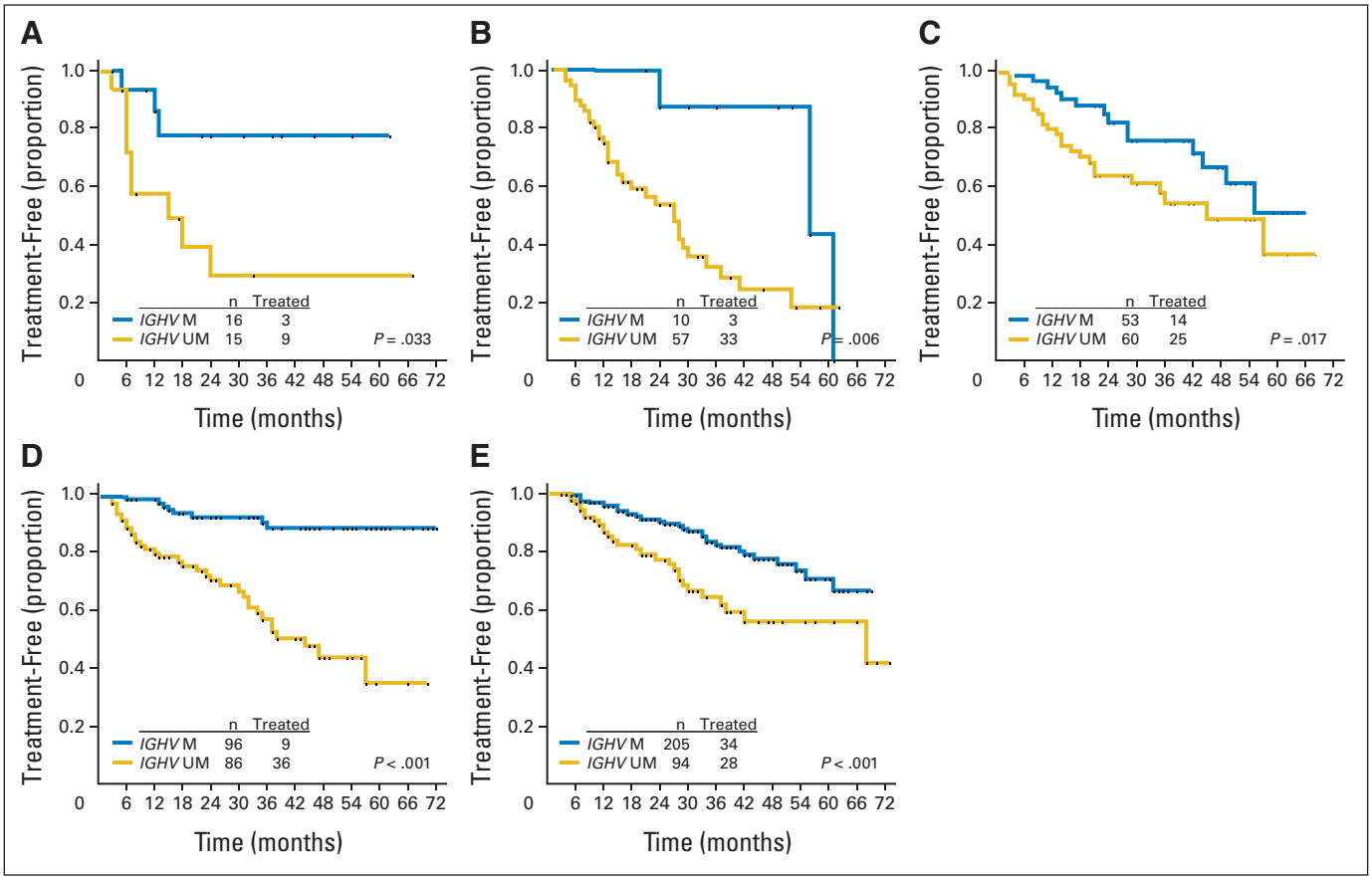

Fig 3. Time to first treatment by (A-E) *IGHV* mutation status and (F-J) ZAP-70 expression for each fluorescent in situ hybridization (FISH) category. Previously untreated patients with chronic lymphocytic leukemia had bone marrow samples evaluated for chromosome abnormalities by FISH, *IGHV* mutation status, and ZAP-70 expression by flow cytometry or immunohistochemistry at initial presentation to MD Anderson Cancer Center. Patients were observed for time to first treatment. Kaplan-Meier estimates of treatment-free survival are shown for (A-E) unmutated (UM; gold) versus mutated (M; blue) *IGHV* status or (F-J) positive (Pos; gold) versus negative (Neg; blue) ZAP-70 expression for each FISH category.

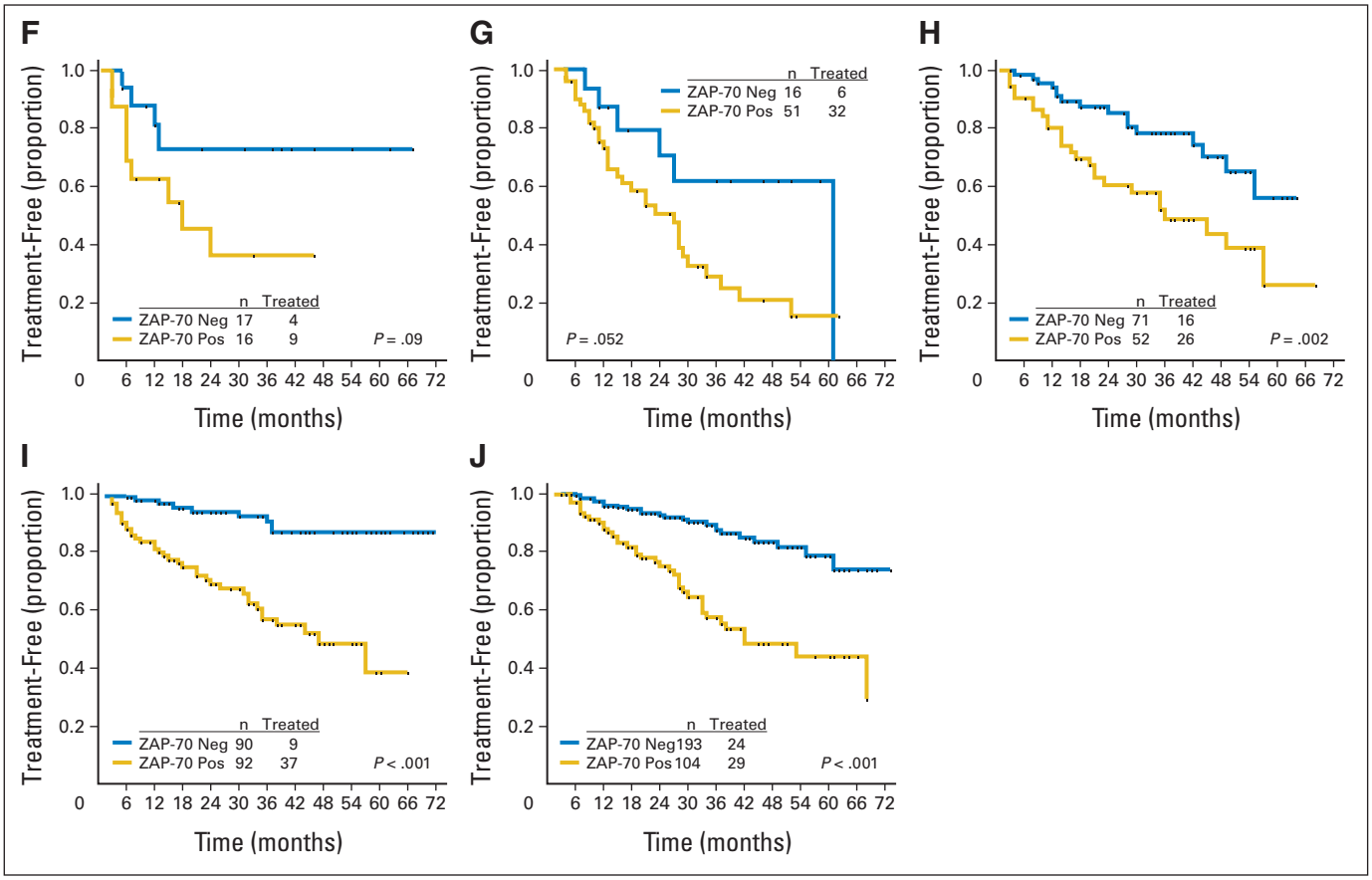

Fig 3. (continued).

months (range, 3 to 73 months); 869 patients were alive at last follow-up; 42 patients were treatment free and censored at time of death. Median time to treatment for all patients has not been reached (Fig 1). For the 232 patients who began therapy (Fig 1), median time to first treatment was 16 months (range, 3 to 68 months); 80% of patients began treatment at MDACC according to NCI-WG indications to initiate treatment.

Univariable analyses identified both traditional and new prognostic factors associated ($P < .05$) with shorter time to first treatment, including the following: higher absolute lymphocyte count; lower hemoglobin, platelet count, and IgA level; higher beta-2 microglobulin and LDH; greater percent bone marrow lymphocytes and number of involved lymph node sites; increased spleen, liver, and lymph node size; advanced Rai stage; presence of 11q deletion or 17p deletion; unmutated *IGHV* status; expression of ZAP-70 by either flow cytometry or IHC; expression of CD38 (> 30%); and complex metaphase karyotype (Table 1).

The presence of chromosome abnormalities by FISH analysis identified high-risk categories, including patients with 17p deletion or 11q deletion with shorter time to first treatment (Fig 2). Furthermore, 70% of patients with 11q deletion required treatment within 4 years (Fig 2).

Patients with unmutated *IGHV* had shorter time to first treatment (Table 1). Of note, there were 208 patients who had *IGHV* mutation status determined by both the MDACC clinical laboratory and CLL Research Consortium, of whom 19 were discordant. Time to first treatment for discordant patients was most consistent with patients who had unmutated *IGHV* (Table 1; data not shown); therefore, in all other analyses, *IGHV* discordant patients were combined with the unmutated *IGHV* group.

ZAP-70 expression was evaluated by flow cytometry and IHC (Table 1); 28% of patients were discordant by these methods (Appendix Table A1, online only). ZAP-70 expression by flow cytometry and IHC correlated with shorter time to first treatment (Table 1).[11] ZAP-70 expression was not included in the multivariable analysis for time to first treatment because of the lack of standardized testing in the community.

IGHV mutation status was correlated with time to first treatment for each FISH category (Fig 3A; Appendix Table A2, online only). Interestingly, there were significant differences in separation of the curves depending on FISH category. Similar to *IGHV* mutation status, there was clear separation in curves by ZAP-70 expression, with positive patient cases having shorter time to first treatment for each FISH category (Fig 3B; Appendix Table A2).

Patients with unmutated *IGHV* and ZAP-70 expression had the shortest time to first treatment, with a median of approximately 30 months (Appendix Fig A1, online only). Twenty-two percent of patients were discordant regarding *IGHV* mutation status and ZAP-70 expression; 12% were *IGHV* unmutated but ZAP-70 negative, and 10% were *IGHV* mutated but ZAP-70 positive (Appendix Table A3, online only). Times to first treatment for discordant patients were statistically significantly different from the concordant

Table 2. Multivariable Cox Proportional Hazards Model for Time to First Treatment*

Characteristic	Hazard Ratio	*P*
IGHV mutation status (unmutated or discordant *v* mutated)	10.68	< .001
Diameter of largest palpated cervical LN, cm	1.32	< .001
FISH category†		
11q del *v* 13q del, + 12, or none	1.86	.001
17p del *v* 13q del, + 12, or none	2.12	.01
No. of involved LN sites (3 *v* < 3)	1.64	.004
Lactate dehydrogenase, IU/L/100		
IGHV mutated	2.36	.002
IGHV unmutated or discordant	1.07	.14

Abbreviations: FISH, fluorescent in situ hybridization; *IGHV*, immunoglobulin heavy chain variable gene; LN, lymph node.
*No. of patients, 687; No. treated, 193.
†By Dohner hierarchic categorization.

patients when compared individually; however, when compared with one another, time to first treatment was not different (Appendix Fig A1, online only).

A multivariable Cox proportional hazards model for time to first treatment was developed with 687 patients (74%) who had complete data available for the fitted covariates (Table 2). The following patient characteristics were independently associated with shorter time to first treatment: three involved lymph node sites, increased size (diameter) of largest cervical lymph node, elevated serum LDH, presence of either 17p deletion or 11q deletion by FISH, and unmutated *IGHV* gene. The size (largest diameter) of the largest cervical lymph node and serum LDH were included as continuous variables; all others were categorical. A CART analysis was conducted to assess the interaction effects between covariates (Appendix Fig A2, online only). On the basis of the CART analysis, a potential interaction between *IGHV* mutation status and LDH was suggested; for patients with mutated *IGHV*, the impact of LDH was greater than for patients with unmutated *IGHV*. The fitted multivariable Cox model was validated and confirmed by two methods: first, generating testing and validation sets, and second, bootstrap resampling (details in Statistical Methods). This multivariable model was developed into a nomogram to estimate 2- and 4-year treatment-free probability and median treatment-free survival (Fig 4). This nomogram provides a visual depiction of the relative contribution of each prognostic factor to the total point score and, thus, the weight of factors regarding risk for requiring first treatment. The formula for calculating the total point score is as follows: [I(No. of lymph node sites involved = 3) × 7.370 + I(FISH = 11q del) × 9.312 + I(FISH = 17p del) × 11.285 + (diameter of largest cervical lymph node in cm) × 4.172 + (LDH/100) × I([*IGHV* gene = mutated] × 5.000 + (LDH ÷ 100) × I(*IGHV* gene = unmutated) × 1.065] + 35.467. The indicator function (I) is equal to 1 if the statement in the parentheses is true and is equal to 0 otherwise. The total point scores ranged from 0 to 87.4 points, with a median of 21.0.

DISCUSSION

A multivariable model for time to first treatment was developed, which was used to generate a nomogram to calculate a weighted likelihood for requiring first treatment and estimate individuals' time to first treatment. To our knowledge, this is the first such multivariable model using traditional and newer prognostic factors and time tofirst treatment as the clinical end point. Other analyses have attempted to evaluated the relative contribution of multiple prognostic factors to

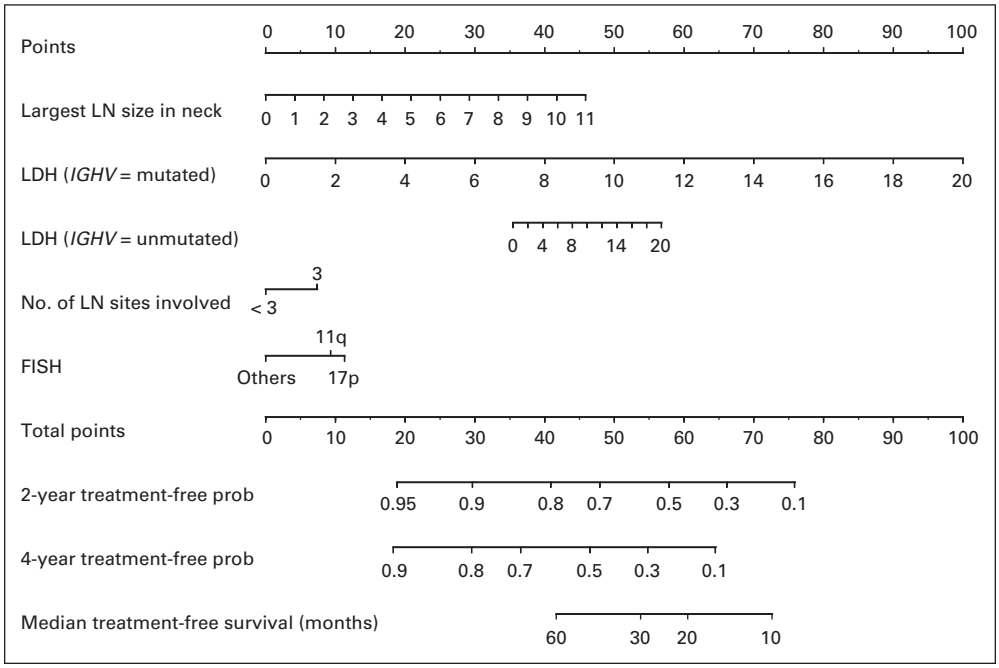

Fig 4. Nomogram for time to first treatment. Nomogram used by totaling points identified at top scale for each of four independent variables. Point score for lactate dehydrogenase (LDH) identified based on *IGHV* mutation status. This summed point score then identified on total point scale to identify 2- and 4-year treatment-free probability (prob) and estimate treatment-free survival. Fluorescent in situ hybridization (FISH) was categorized by Dohner hierarchic categorization. LN, lymph node.

time to first treatment[16-23]; however, none have evaluated traditional and newer prognostic factors in the same model for time to first treatment. This model was possible only with prolonged follow-up and is relevant particularly for early-stage patients who did not have NCI-WG[9] or IWCLL[10] indications for initial therapy. Median time from initial CLL diagnosis to prognostic factor evaluation was 3.4 months; this model incorporated both fixed characteristics such as *IGHV* mutation status and features that evolve with progression of disease such as number of involved nodal sites, size (diameter) of the largest cervical lymph node, LDH, and acquisition of new chromosome abnormalities by FISH. Of note, these features were distinct compared with previously reported characteristics associated with overall survival from initial MDACC presentation for untreated patients with CLL.[1]

This analysis has several strengths. First, the patient population was well characterized regarding traditional and newer prognostic factors, and follow-up was consistent and continuously updated. The patient population was an unselected, untreated, relatively recently diagnosed group who did not require treatment at presentation. Another strength of this analysis is that it is a multivariable model, which incorporates both traditional clinical and laboratory parameters as well as newer prognostic factors to identify characteristics independently associated with time to first treatment. This model includes prognostic factors that are evaluable and can be obtained by reference laboratories in the community such as *IGHV* mutation status.

This analysis has some weaknesses. First, there are likely unknown prognostic factors affecting outcome not accounted for in this analysis. Another weakness is that it is a single-center study of a referral population. As a referral population, patients included in this analysis were younger than those seen in general community practice. Median age for this population was 59 years, whereas median age for diagnosis of CLL in the general population is 72 years. Notably, in both univariable and multivariable analyses for time to first treatment, age was not a significant factor, suggesting that age is not as relevant in evaluating this end point. Standardizing the methodology for characterizing ZAP-70 expression by flow cytometry has been problematic. Although IHC can be readily performed, there is potential subjectivity in readout, which may relate to experience of the hematopathologist and may introduce bias. These issues may provide insight into the reason for the 28% discordance between these two methods reported. Therefore, this variable was not included in the multivariable model.

Among the total 930 patients, 687 patients with complete covariate information were included in the final fitted Cox model. To assess for potential selection bias, we compared the 687 patients with complete data with those patients with at least one covariate missing ($n = 243$). The results indicated that there was no significant difference between these two cohorts regarding any of the covariates fitted in the multivariate Cox model, with P values ranging from 0.10 to 0.88. Finally, there is subjectivity in this model introduced by measuring the largest diameter of largest cervical lymph node by physical examination. Finally, although 80% of patients in this analysis had treatment initiated at MDACC, there is still subjectivity in evaluating and identifying when patients develop an indication to begin treatment.

Further evaluation of this model will require validation in an independent population. Our prior work identified traditional prognostic factors associated with overall survival for untreated patients presenting to MDACC[1] as well as clinical end points associated with first therapy.[2] These models were validated in independent data sets.[23-25] We did not identify a test group to internally validate this model. The strength of the model and number of independent variables that can be evaluated depends on the total number of patients included in the analysis and on the number of events (in this case, patients requiring treatment). Our multivariable model identified six independent characteristics from a total of 687 patients in the final model, 193 of whom required treatment.

There are many potential applications for this model, particularly in identifying patients at high risk for early progression. This model allows us to identify patients with a high likelihood of requiring treatment within 2 to 4 years; these patients would be candidates for clinical trials of interventions to delay time to first treatment with chemoimmunotherapy. Such interventions would be low risk, such as vaccines or immune-modulating agents. This model will allow us to generate expected over observed ratios to evaluate such interventions. With clinically effective early intervention, this model may become obsolete, and new models may need to be generated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

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