Long-Term Studies Assessing Outcomes of Ibrutinib Therapy in Patients With Del(11q) Chronic Lymphocytic Leukemia

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Abstract

A pooled analysis of 1238 patients with chronic lymphocytic leukemia/small lymphocytic lymphoma from three phase 3 studies found that genomic risk factors were not associated with shorter progression-free survival (PFS) or overall survival for patients treated with ibrutinib. Ibrutinib-treated patients with del(11q) were found to have a longer PFS than those without del(11q). These results suggest less prognostic relevance for certain genomic risk factors with ibrutinib treatment.

Background: Certain genomic features, such as del(11q), expression of unmutated immunoglobulin heavy-chain variable region (*IGHV*) gene, or complex karyotype, predict poorer outcomes to chemotherapy in patients with chronic lymphocytic leukemia (CLL). **Patients and Methods:** We examined the pooled long-term follow-up data from PCYC-1115 (RESONATE-2), PCYC-1112 (RESONATE), and CLL3001 (HELIOS), comprising a total of 1238 subjects, to determine the prognostic significance of these markers in patients treated with ibrutinib. **Results:** With a median follow-up of 47 months, ibrutinib-treated patients had longer progression-free survival (PFS) than patients treated in the comparator arm, regardless of genomic risk factors. Among patients treated with ibrutinib, we found that high-risk genomic features were not associated with shorter PFS (63-75% across all subgroups at 42 months) or overall survival (79-83% across all subgroups at 42 months). Surprisingly, we observed that ibrutinib-treated patients with del(11q) actually had a significantly longer PFS than ibrutinib-treated patients without del(11q) (42-month PFS rate 70% vs. 65%, $P = .02$). **Conclusion:** These analyses not only demonstrate that genomic risk factors previously associated with poor outcomes lose their adverse prognostic significance but also that del(11q) can be associated with a superior PFS with ibrutinib therapy.

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Introduction

In 2000, Döhner and colleagues reported on the prognostic value of fluorescence in situ hybridization analysis for detecting common genomic abnormalities in the leukemia cells of patients with chronic lymphocytic leukemia (CLL).[1] Patients with CLL cells having del(17p) had the worst prognosis, followed by patients with del(11q). Patients with trisomy 12 or del(13q) as the sole genetic abnormality fared significantly better, the latter being comparable to those without detectable genetic abnormalities. This hierarchy was validated by several groups and in prospective chemoimmunotherapy trials, including the Mayo Clinic study and Danish CLL2 Study.[2-4] In addition, complex karyotype, which is partially overlapping with del(17p),[1] has also been associated with relatively short survival.[5,6] Although the treatment of patients with CLL has improved since 2000 owing to the use of anti-CD20 monoclonal antibodies with chemotherapy,[7] the prognostic hierarchy of these genomic abnormalities persists, as evidenced by the outcomes analysis of the Döhner classification in 1585 patients with CLL by the Chronic Lymphocytic Leukemia Research Consortium[8] and by the gene mutation analyses performed in several phase 3 studies (eg, those by the UK and German CLL study groups).[4,9,10]

The mutation status of the immunoglobulin heavy-chain variable region (*IGHV*) gene expressed by CLL cells also has prognostic value. Patients with CLL cells that use unmutated *IGHV* have more aggressive clinical disease associated with enhanced B-cell receptor signaling relative to that of patients with CLL cells that use mutated *IGHV*.[11,12] Evaluation of the outcomes of chemoimmunotherapy regimens, such as fludarabine, cyclophosphamide, and rituximab (FCR), bendamustine and rituximab (BR), or rituximab plus chlorambucil, demonstrated that expression of unmutated *IGHV* has prognostic value independent of cytogenetic abnormalities in defining relatively short progression-free survival (PFS) or overall survival (OS).[4,13-16]

More recently, the treatment of CLL has been transformed by the first-in-class, once-daily inhibitor of Bruton tyrosine kinase, ibrutinib, which was approved for the treatment of patients with CLL, including patients with del(17p). In patients with CLL, the superiority of single-agent ibrutinib with or without CD20 monoclonal antibody over chemotherapy, antibody therapy, or chemoimmunotherapy has been demonstrated in a series of multiple international phase 3 studies.[17-21] Patients who received initial therapy with ibrutinib with or without CD20 monoclonal antibody had a significantly prolonged PFS and OS relative to patients receiving initial therapy with chlorambucil (PCYC-1115/1116, RESONATE-2), chlorambucil plus obinutuzumab (PCYC-1130, iLLUMINATE), BR (Alliance), and FCR (ECOG-ACRIN, E1912).[17,19-21] Moreover, patients with relapsed/refractory CLL, including one-third with del(17p), had significantly longer PFS and OS when treated with ibrutinib than with ofatumumab (PCYC-1112, RESONATE).[18] Finally, patients treated with BR plus ibrutinib had significantly longer PFS than patients treated with BR alone (CLL3001, HELIOS).[22]

We sought to evaluate whether the traditional genomic risk factors prognostic for patients treated with chemoimmunotherapy were associated with better outcomes in patients treated with ibrutinib. To determine this, we pooled data from three phase 3 studies and examined the relative outcomes of patients who had CLL cells with del(11q), unmutated *IGHV*, complex karyotype, or trisomy 12. We did not assess the outcome of patients with del(17p) because such patients were excluded from both the RESONATE-2 and HELIOS studies. Although ibrutinib-treated patients were the focus of this analysis, we also assessed the survival of comparator-treated patients to provide context.

Patients and Methods

Study Design and Participants

Study designs for each of the included phase 3 studies are as described.[17,18,22] Briefly, RESONATE-2 (PCYC-1115) included patients aged $\geq$ 65 years with previously untreated CLL/small lymphocytic lymphoma (SLL) who had Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2 but excluded those with del(17p). RESONATE (PCYC-1112) included patients with CLL/SLL who had received $\geq$ 1 prior line of therapy, were considered inappropriate for treatment with purine analogs, and had ECOG PS 0-1. The HELIOS (CLL3001) study included adult patients with CLL/SLL who had received $\geq$ 1 prior line of systemic therapy and had ECOG PS 0-1 but excluded those with del(17p). The Supplemental Methods in the online version provide additional details on patient eligibility criteria.

Studies were approved by the institutional review boards at each participating institution and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. RESONATE, RESONATE-2, and HELIOS were registered at ClinicalTrials.gov as NCT01578707, NCT01722487, and NCT01611090.

Randomization and Masking

In each of the included studies, patients were randomized 1:1 to the 2 treatment arms. The Supplemental Methods in the online version provide details on patient stratification; RESONATE-2 and RESONATE were open-label studies, and HELIOS was a double-blind study. In all 3 studies, an interactive Web response system assigned a unique treatment code for each patient that assigned treatment and matching study drug kit.

Procedures

In RESONATE-2, patients were randomized to receive ibrutinib 420 mg once daily until progressive disease (PD) or chlorambucil for up to twelve 28-day cycles. In RESONATE, patients were randomized to receive ibrutinib 420 mg once daily until PD or intravenous ofatumumab for up to 24 weeks. In HELIOS, all patients received intravenous BR for up to 6 cycles and were randomized to receive either ibrutinib 420 mg once daily or placebo, starting on day 2 of cycle 1. After completion of BR, single-agent

ibrutinib or placebo was continued until PD. In all of the included studies, crossover to ibrutinib was allowed after PD. Comparator dosing was as described previously.[17,18,22]

Outcomes

Study end points for each of the included phase 3 studies were as previously described.[17,18,22] In this analysis, data from the 3 studies were pooled (ibrutinib pool, comparator pool) and analyzed with respect to *IGHV* mutation status (determined by central laboratory); or presence versus absence of del(11q), complex karyotype, or trisomy 12 (each determined by local laboratories). Positive complex karyotype was defined as the presence of $\geq$ 3 chromosomal abnormalities based on local karyotyping and reported by the investigator; this definition was consistent across the studies. Type of stimulation was not confirmed across local laboratories. High-risk genomic factors examined were del(11q), unmutated *IGHV*, or presence of complex karyotype. In addition, del(11q) and trisomy 12 were analyzed in the prioritized hierarchical classification of Döhner et al.[1] We did not examine the impact of del(17p) because patients with del(17p) were excluded from RESONATE-2 and HELIOS. We determined the PFS, OS, overall response rate, and complete response of ibrutinib-treated patients and the PFS and OS of comparator-treated patients. We noted exposure to treatment, serious adverse events (AEs), and AEs leading to discontinuation or death to report on the impact of genomic risk factors on safety profile. All 3 studies used the same progression and response criteria, which were investigator assessed and were collected consistently across studies.

Statistical Analysis

We included all intent-to-treat patients for efficacy analyses, except for patients with del(17p). We used Kaplan-Meier methods for PFS and OS, and assessed *P* values by log-rank test and hazard ratio (HR). We used a Cox regression model in multivariate analyses to examine risk/prognostic factors associated with PFS and OS (no multiplicity adjustment). The following risk factors were included as individual factors: del(11q), complex karyotype, and/or unmutated *IGHV*. These were also analyzed in patients with 0, any 1, or $\geq$ 2 in these models. For safety analyses, we included all patients who received at least one dose of study drug.

Results

Patients

RESONATE-2, RESONATE, and HELIOS recruited patients between June 2012 and February 2014. Collectively, we evaluated the outcomes of 1238 patients among the 3 studies, including 620 patients treated in the ibrutinib arms and 618 patients treated in the comparator arms. Supplemental Table 1 in the online version provides the baseline characteristics for patients who received ibrutinib in each study; the median age was highest for patients in RESONATE-2 (73 vs. 67 years in RESONATE and 64 years in HELIOS). Patients in RESONATE and HELIOS had received a median of 3 (range, 1-12) and 2 (range, 1-11) prior therapies, respectively. Supplemental Table 2 in the online version provides the baseline clinical characteristics for patients treated with ibrutinib. Of note, patients with unmutated *IGHV*, complex karyotype, or del(11q) had a higher prevalence of bulky disease ($\geq$ 5 cm lymph nodes) than did patients lacking such risk factors. Also, patients with complex karyotype or del(11q) were more heavily pretreated than patients lacking such features. Overall, there were 120 patients in these studies with del(17p); therefore, efficacy outcomes were analyzed for 558 patients treated with ibrutinib and 560 patients treated in the comparator arms without del(17p).

Efficacy Outcomes

With a median follow-up of 47 months (maximum follow-up, 62 months), ibrutinib-treated patients had longer PFS than comparator-treated patients, regardless of genomic risk factors. Patients treated with ibrutinib who had adverse genomic risk markers (del[11q], unmutated *IGHV*, and complex karyotype) did not have a shorter PFS or OS compared to ibrutinib-treated patients lacking such markers (Table 1; Figure 1). Because each individual high-risk factor did not affect outcomes, additional analyses were performed to evaluate if multiple factors affected PFS or OS. For ibrutinib-treated patients, having 1 or $\geq$ 2 risk factors did not have an adverse impact on either PFS (HR [95% confidence interval (CI)]: 1 vs. 0, 0.828 [0.588-1.166], P = .2805; $\geq$ 2 vs. 0, 0.628 [0.414-0.95], P = .0282) or OS (1 vs. 0, 0.976 [0.627-1.518], P = .9127; $\geq$ 2 vs. 0, 0.734 [0.429-1.257], P = .2603). For patients who received the comparator therapies, there was a significant adverse impact for patients who had either 1 or $\geq$ 2 risk factors on both PFS (1 vs. 0, 2.223 [1.755-2.818], P < .0001; $\geq$ 2 vs. 0, 2.672 [2.018-3.537], P < .0001) and OS (1 vs. 0, 1.544 [1.06-2.248], P = .0236; $\geq$ 2 vs. 0, 1.756 [1.129-2.73], P = .0124).

Moreover, ibrutinib-treated patients with del(11q) had statistically longer PFS and may have had a beneficial OS effect, as displayed in the Kaplan-Meier curve, than patients lacking del(11q) (Figure 1; Supplemental Figure 1 in the online version), with 42-month PFS rates of 70% and 65% (HR, 0.70; P = .02) and 42-month OS rates of 83% and 80% (HR, 0.73; P = .14), respectively. Of 147 patients with del(11q) and known *IGHV* status, 87% received unmutated *IGHV* and 13% received mutated *IGHV*. Ibrutinib-treated patients with unmutated *IGHV* had a 42-month PFS rate of 66% versus 75% for those with mutated *IGHV* (HR, 1.17; P = .43). Patients with and without complex karyotype had 42-month PFS rates of 63% and 69%, respectively (HR, 1.02; P = .95). The presence of del(11q), use of unmutated *IGHV*, and complex karyotype were each an adverse prognostic marker associated with decreased PFS in comparator-treated patients (P < .001 for each factor; Figure 1).

Given the large proportion of patients with del(11q) who also had unmutated *IGHV*, we examined the effect of del(11q) on outcomes of patients with unmutated *IGHV*. Within the population of ibrutinib-treated patients with unmutated *IGHV*, 37% had del(11q) CLL. The PFS rate in ibrutinib-treated patients with unmutated *IGHV* with versus without del(11q) at 42 months was 69% versus 63% (HR, 0.72; P = .09), and the 42-month OS rate was 84% versus 79% (HR, 0.67; P = .12), respectively. In a multivariate analysis for PFS for ibrutinib-treated patients, the number of prior therapies was significantly associated with shorter PFS (HR, 0.48 for 0 vs. $\geq$ 1; P < .01), and the presence of del(11q) was significantly associated with longer PFS (HR, 0.71;

Table 1 Efficacy Outcomes in Ibrutinib-Treated Patients by Genomic Subgroups, Excluding Patients With Del(17p)

Outcome	Del(11q)[c]		*IGHV*		Complex Karyotype		Trisomy 12[c]	
	Yes (N = 168)	No (N = 382)	Unmut (N = 334)	Mut (N = 113)	Yes (N = 41)	No (N = 338)	Yes (N = 75)	No (N = 190)
No. for ORR and CR[a]	168	378	334	112	40	337	73	190
ORR[b]								
n (%)	152 (90)	339 (90)	300 (90)	100 (89)	35 (88)	301 (89)	61 (84)	176 (93)
P value (OR)[d]	.78 (1.09)		.87 (1.06)		.73 (0.84)		.03 (0.40)	
CR								
n (%)	46 (27)	105 (28)	104 (31)	28 (25)	8 (20)	88 (26)	24 (33)	42 (22)
P value (OR)[d]	.92 (0.98)		.22 (1.36)		.40 (0.71)		.07 (1.73)	
OS								
42 months (%)	83	80	81	83	79	82	82	80
P value (HR)[d]	.14 (0.73)		.66 (1.12)		.90 (0.95)		.72 (0.89)	
PFS								
42 months (%)	70	65	66	75	63	69	69	69
P value (HR)[d]	.02 (0.70)		.43 (1.17)		.95 (1.02)		.94 (1.02)	

Abbreviations: CR = complete response; HR = hazard ratio; *IGHV* = immunoglobulin heavy-chain variable region; mut = mutated; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; unmut = unmutated.
[a]Excludes patients without measurable disease at baseline.
[b]Including CR, CR with incomplete blood-count recovery, nodular partial response, partial response, and partial response with lymphocytosis.
[c]Del(11q) and trisomy 12 were analyzed in the prioritized hierarchical classification of Döhner et al.[1]
[d]*P* values show the statistical comparison between patients with versus without these genomic features.

$P = .04$; Figure 2). A multivariate analysis for OS in ibrutinib-treated patients demonstrated that shorter OS was associated with a greater number of prior therapies (HR, 0.43; $P < .01$ for 0 vs. ≥ 1) and β_2-microglobulin level > 3.5 mg/L (HR, 1.78; $P = .04$). Although the presence of del(11q) was associated with a better OS within ibrutinib-treated patients versus those without del(11q), the difference was not significant ($P = .18$; Supplemental Figure 2 in the online version). In comparator-treated patients, male sex, unmutated *IGHV*, and bulky disease ≥ 5 cm were each independently associated with a significantly shorter PFS and OS ($P < .05$). In addition, del(11q), complex karyotype, and serum β_2-microglobulin level > 3.5 mg/L were all associated with a significantly shorter PFS ($P < .05$; Supplemental Figure 3 in the online version), and ECOG PS ≥ 1, cytopenia, and elevated lactate dehydrogenase were each associated with a significantly shorter OS ($P < .05$).

Genomic risk factors were not associated with inferior overall response rates or rates of complete response in ibrutinib-treated patients (Table 1). Of note, ibrutinib-treated patients with versus without trisomy 12 CLL had significantly lower overall response rate (84% vs. 93%; $P = .03$) but trended toward a higher rate of complete response (33% vs. 22%; $P = .07$).

Safety

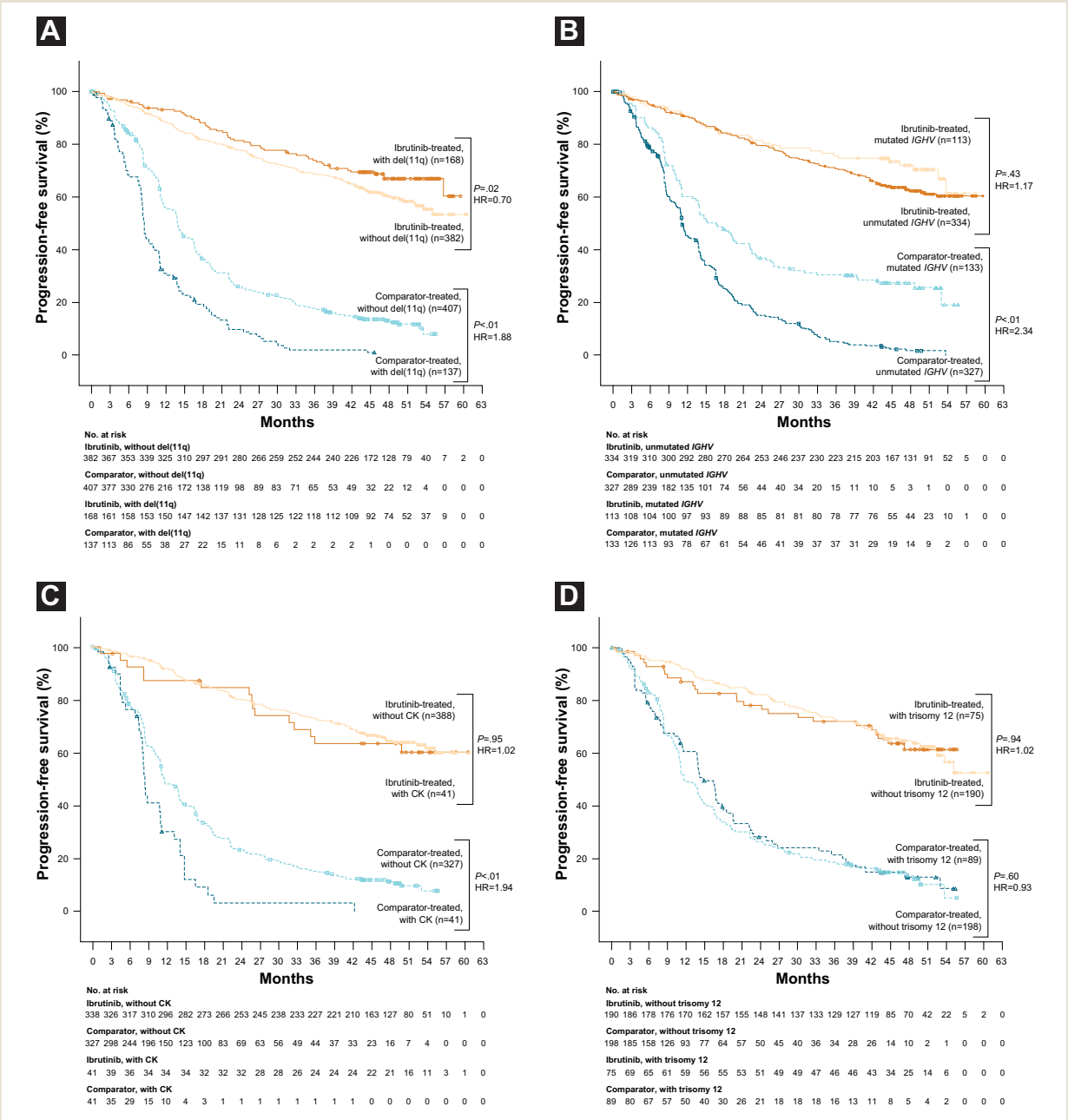
For RESONATE-2, RESONATE, and HELIOS, median ibrutinib exposure (47, 45, and 47 months, respectively) and rates of serious AEs by subgroup (63-70%) varied across studies with up to 62 months of treatment (Supplemental Table 3 in the online version); genomic risk factors did not notably alter the dose-limiting or severe/serious AEs.

Discussion

Advances in therapy can challenge the prognostic significance of disease features previously associated with adverse outcome. Here we examined pooled data from more than 600 patients treated with ibrutinib and found that genomic risk factors associated with poor outcomes with chemotherapy-based regimens (ie, del[11q], unmutated *IGHV*, or complex karyotype) lost their relative prognostic value. Importantly, there was significantly longer PFS and a beneficial effect on OS, as displayed in the Kaplan-Meier curve in ibrutinib-treated patients with del(11q), indicating that del(11q) actually may be associated with better outcomes with ibrutinib therapy, thereby inverting its historical prognostic significance. This finding is consistent with original trends noted in previously published analyses of the original trials.[23-25] However, this pooled analysis of long-term data provides power to detect significant differences. Previous studies of the German CLL Study Group found that the small subset of patients with CLL who have del(11q) and who receive mutated *IGHV* can experience prolonged survival with FCR.[13] However, most patients with del(11q) receive therapy with unmutated *IGHV* (87% of evaluable patients in this analysis), which is associated with a shorter PFS.[13] The superior outcomes of ibrutinib-treated patients with del(11q) versus standard chemoimmunotherapy is further supported by the recent E1912 study of ibrutinib plus rituximab versus FCR; in a subgroup analysis for PFS, ibrutinib plus rituximab was superior to FCR independent of the presence/absence of del(11q).[20]

The initial efficacy and tolerability of ibrutinib in patients with CLL were demonstrated in a single-arm phase 1b/2 study (PCYC-1102/1103) in patients with treatment-naive or relapsed/refractory disease.[26,27] In a recent 5-year report of this study, durable responses to ibrutinib were reported, including in

Figure 1 Progression-Free Survival in Ibrutinib- and Comparator-Treated Patients by Genomic Subgroup. Genomic Subgroups Are (A) Del(11q) Status, (B) *IGHV* Mutation Status, (C) Presence of Complex Karyotype, and (D) Trisomy 12 Status

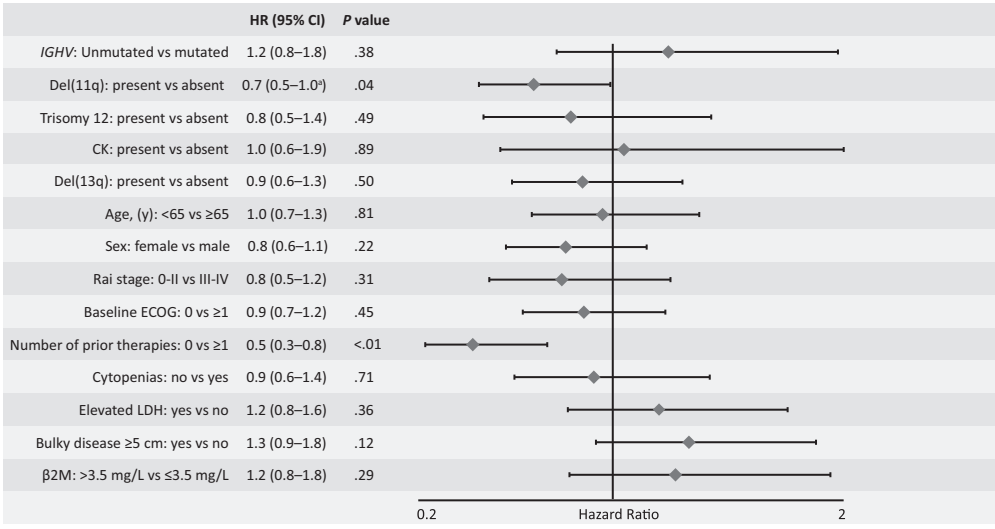


Abbreviations: CK = complex karyotype; HR = hazard ratio; *IGHV* = immunoglobulin heavy-chain variable region.

patients with del(17p), del(11q), or use of unmutated *IGHV*.[28] Data for these relapsed/refractory patients demonstrated the highest risk for shortened survival in patients with del(17p), followed by those with del(11q), consistent with the Döhner hierarchy. The shortened survival of patients with del(11q) in this earlier phase 1b/2 study may have been related to the fact that such patients in particular had received more rounds of prior therapy (75% of patients with del[11q] received ≥ 3 prior therapies)[28] and that having had multiple prior therapies was associated with inferior outcomes to therapy in general. This is supported by a multivariate analysis, in which only del(17p) had adverse independent prognostic impact on the PFS or OS of patients treated with ibrutinib and del(11q) was not independently prognostic.[28]

In retrospective reviews of patients with CLL treated with ibrutinib-based regimens, complex karyotype has been found to be prognostic of inferior outcomes.[29,30] However, in one of these studies, 17 of the 21 patients with complex karyotype also had del(17p); this proportion was not reported for the other study. The

Figure 2 Multivariate Analysis of Progression-Free Survival in Ibrutinib-Treated Patients



Abbreviations: β2M = beta-2-microglobulin; CI = confidence interval; CK = complex karyotype; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; *IGHV* = immunoglobulin heavy-chain variable region; LDH = lactate dehydrogenase. [a]Upper CI range is 0.99.

high frequency of del(17p) in patients with complex karyotype may explain why del(17p), rather than complex karyotype, was an independent prognostic factor for shortened PFS in PCYC-1102/1103.[31] Two of the 3 studies in the current pooled analysis excluded patients with del(17p) as part of the eligibility criteria; therefore, this patient population was excluded because of limited sample size. Exclusion of these patients with del(17p) in this analysis may have improved the results with complex karyotype, although complex karyotype remained a significant prognostic factor for shortened PFS for patients who received comparator therapy but not for patients treated with ibrutinib, in both univariate and multivariate analyses. It has been previously reported that patients with del(17p) without complex karyotype have had optimal outcomes after chemoimmunotherapy[32]; however, this could not be evaluated in the current analysis with ibrutinib as patients with del(17p) CLL were excluded. The local, rather than central, determination of complex karyotype status is a limitation of this analysis. However, the 5-year report of PCYC-1102/1103 reflects complex karyotype that was assessed centrally, and is consistent with the current findings that complex karyotype is not an independent prognostic factor for poor outcomes with ibrutinib.[28] The relatively good outcomes of ibrutinib-treated patients with complex karyotype compared to patients treated with standard chemotherapy is further supported by a recent phase 3 study led by the Alliance for Clinical Trials in Oncology, in which complex karyotype did not seem to portend adverse outcomes in patients treated with ibrutinib or ibrutinib plus rituximab, in contrast to what was observed with BR therapy.[21]

Although conclusions are based on analyses of available follow-up to date, it is unlikely that the effect of ibrutinib treatment in mitigating the poor prognostic impact of these genomic risk factors will be reversed with longer follow-up. Further, the comparators' single-agent chemotherapy, antibody therapy, and BR therapy were analyzed by pooling comparator arms across studies to provide context to the ibrutinib data; however, this limits interpretation of outcomes in the pooled comparator analysis of PFS and OS.

Conclusion

With the advent of ibrutinib therapy, traditional genomic adverse factors in CLL appear to lose their significance with regard to survival. These findings challenge the assumption that such markers are invariably associated with poor outcomes independent of the type of therapy, and they should be considered when defining the type of treatment for patients with CLL. Importantly, the prognostic relevance of del(11q) appears reversed with ibrutinib therapy, where del(11q) apparently portends a relatively long PFS.

Clinical Practice Points

- Certain genomic features, including del(11q), complex karyotype, and expression of unmutated *IGHV*, are prognostic for relatively poor outcomes to chemotherapy-based treatment in patients with CLL.
- Ibrutinib, a first-in-class, once-daily inhibitor of Bruton tyrosine kinase, is approved for the initial treatment of patients with CLL/SLL, including patients with del(17p).
- In a pooled analysis, the accepted genomic risk factors of unmutated *IGHV*, complex karyotype, and del(11q) were not associated with shorter PFS or OS for patients with CLL treated with ibrutinib.
- Ibrutinib-treated patients who had CLL with del(11q) were also found to have a longer PFS than similarly treated patients without del(11q), suggesting that del(11q) may be prognostic of better outcomes with ibrutinib therapy, thus inverting the prognostic significance of del(11q) observed with traditional therapies for CLL.

- These findings suggest that the prognostic power of such markers is dependent on the type of therapy and should be considered when defining treatment strategies for patients with CLL.

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Supplemental Data

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Supplemental Data

Supplemental Methods

Key Patient Eligibility Criteria

RESONATE-2

- Age ≥ 65 years.
- Previously untreated CLL or SLL requiring therapy.
- ECOG PS ≤ 2.
- Absolute neutrophil count ≥ 1000 cells/μL.
- Platelet count ≥ 50,000/μL.
- Adequate liver and kidney function.
- Excluded if chromosome 17p13.1 deletion present.

RESONATE

- CLL or SLL requiring therapy who received ≥ 1 previous therapy.
- Inappropriate for purine analog treatment due to a short progression-free interval after chemoimmunotherapy or because of coexisting illnesses, age ≥ 70 years, or chromosome 17p13.1 deletion.
- ECOG PS < 2 (on 0-5 scale).
- Absolute neutrophil count ≥ 750 cells/μL.
- Platelet count ≥ 30,000 cells/μL.
- Adequate liver and kidney function.
- Excluded if warfarin or strong CYP3A4/5 inhibitors required.

HELIOS

Inclusion criteria

- Age ≥ 18 years.
- CLL or SLL requiring therapy.
- Relapsed or refractory disease after ≥ 1 previous lines of systemic therapy consisting of ≥ 2 cycles of a chemotherapy-containing regimen.
- ECOG PS 0-1.
- Measurable lymph node disease (> 1.5 cm) by CT scan.
- Absolute neutrophil count ≥ 1×10^9 cells/L.
- Platelet count ≥ 50×10^9 cells/L.
- Adequate liver and kidney function.

Exclusion criteria

- Presence of del(17p) (del[17p] in ≥ 20% of blood or bone marrow cells examined by fluorescence in situ hybridization).
- Prior treatment with ibrutinib or other Bruton tyrosine kinase inhibitors, refractory disease or relapse within 24 months with a previous bendamustine-containing regimen, or hematopoietic stem-cell transplantation.
- Central nervous system leukemia or lymphoma.
- Richter transformation.
- History of stroke, intracranial hemorrhage, or clinically significant cardiovascular disease within 6 months before randomization.
- Requirement for concurrent anticoagulation with warfarin or other vitamin K antagonists or strong CYP3A4 or CYP3A5 inhibitors.

Stratification

RESONATE-2

- ECOG PS (0-1 vs. 2).
- Rai stage (0–II vs. III–IV).

RESONATE

- Resistance to purine analog chemoimmunotherapy (yes vs. no).
- Del(17p) status (yes vs. no).

HELIOS

- Purine analog refractory status (yes vs. no).
- Number of prior lines of therapy (1 vs. > 1).

Abbreviations: CLL = chronic lymphocytic leukemia; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; PS = performance status; SLL = small lymphocytic lymphoma.

Supplemental Table 1 Key Baseline Characteristics in Ibrutinib-Treated Patients by Study

Characteristic	RESONATE-2 (N = 136)	RESONATE (N = 195)	HELIOS (N = 289)
Age (y), median (range)	73 (65-89)	67 (30-86)	64 (31-86)
Male sex	88 (65)	129 (66)	193 (67)
ECOG PS			
0	61 (45)	79 (41)	125 (43)
1	62 (46)	116 (59)	164 (57)
2	13 (10)	0	0
No. of Prior Treatment Regimens			
0	136 (100)	0	0
1	0	35 (18)	140 (48)
≥2	0	160 (82)	149 (52)
Rai stage III/IV, n/N (%)	68/136 (50)	109/195 (56)	99/256 (39)
Bulky disease ≥ 5 cm	54 (40)	124 (64)	168 (58)
ALC ($\times 10^9$/L), median (range)	51 (1-383)	30 (<1-468)	27 (<1-502)
β2M > 3.5 mg/L, n/N (%)	85/126 (67)	153/183 (84)	189/281 (67)
Unmutated *IGHV*, n/N (%)	58/101 (57)	98/134 (73)	210/259 (81)
Trisomy 12, n/N (%)	23/112 (21)	22/138 (16)	57 (20)
Complex karyotype, n/N (%)	6/93 (6)	39/153 (25)	18 (6)
Del(11q), n/N (%)	29/130 (22)	63/190 (33)	87 (30)
Del(17p)	0[a]	60 (31)	2 (1)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ALC = absolute lymphocyte count; β2M = beta-2-microglobulin; ECOG = Eastern Cooperative Oncology Group; *IGHV* = immunoglobulin heavy-chain variable region; PS = performance status.
[a]Two patients in RESONATE-2 had unknown del(17p) status.

Supplemental Table 2 Key Baseline Characteristics in Ibrutinib-Treated Patients by Genomic Subgroup

Characteristic	*IGHV*		Trisomy 12		Complex Karyotype		Del(11q)	
	Unmut	Mut	Yes	No	Yes	No	Yes	No
No. of patients	366	125	102	346	63	364	179	30
Age (y)								
Median (range)	66.5 (30-89)	70 (41-87)	70.5 (40-89)	67 (30-85)	69 (40-83)	67 (30-89)	67 (30-89)	68 (31-87)
≥65 y	215 (59)	96 (77)	72 (71)	222 (64)	45 (71)	232 (64)	108 (60)	281 (65)
ECOG PS								
0	154 (42)	60 (48)	46 (45)	145 (42)	23 (37)	153 (42)	72 (40)	190 (44)
1	210 (57)	60 (48)	50 (49)	195 (56)	40 (63)	202 (56)	105 (59)	229 (53)
2	2 (1)	5 (4)	6 (6)	6 (2)	0	9 (3)	2 (1)	11 (3)
Rai stage III/IV	150/343 (44)	65/122 (53)	34 (33)	165 (48)	26 (41)	168 (46)	78 (44)	190 (44)
Bulky disease ≥ 5 cm	238 (65)	48 (39)	47 (47)	207 (60)	44 (71)	209 (58)	124 (69)	218 (51)
ALC ($\times 10^9$/L), median (range)	36 (0-459)	40 (1-502)	27 (0-459)	37 (0-468)	37 (1-241)	31 (0-468)	42 (1-376)	31 (0-502)
β2M > 3.5 mg/L, n/N (%)	253/351 (72)	92/118 (78)	76/97 (78)	245/331 (74)	44/61 (72)	264/344 (77)	125/172 (73)	295/408 (72)
Del(17p)	32 (9)[a]	12 (10)	12 (12)	32 (9)	22 (35)	26 (7)	11 (6)	48 (11)
No. of prior therapies, median (range)	1 (0-11)	1 (0-12)	1 (0-7)	2 (0-11)	2 (0-12)	2 (0-11)	2 (0-11)	1 (0-9)
≥ 3 prior therapies	93 (25)	39 (31)	24 (24)	111 (32)	31 (49)	106 (29)	59 (33)	116 (27)

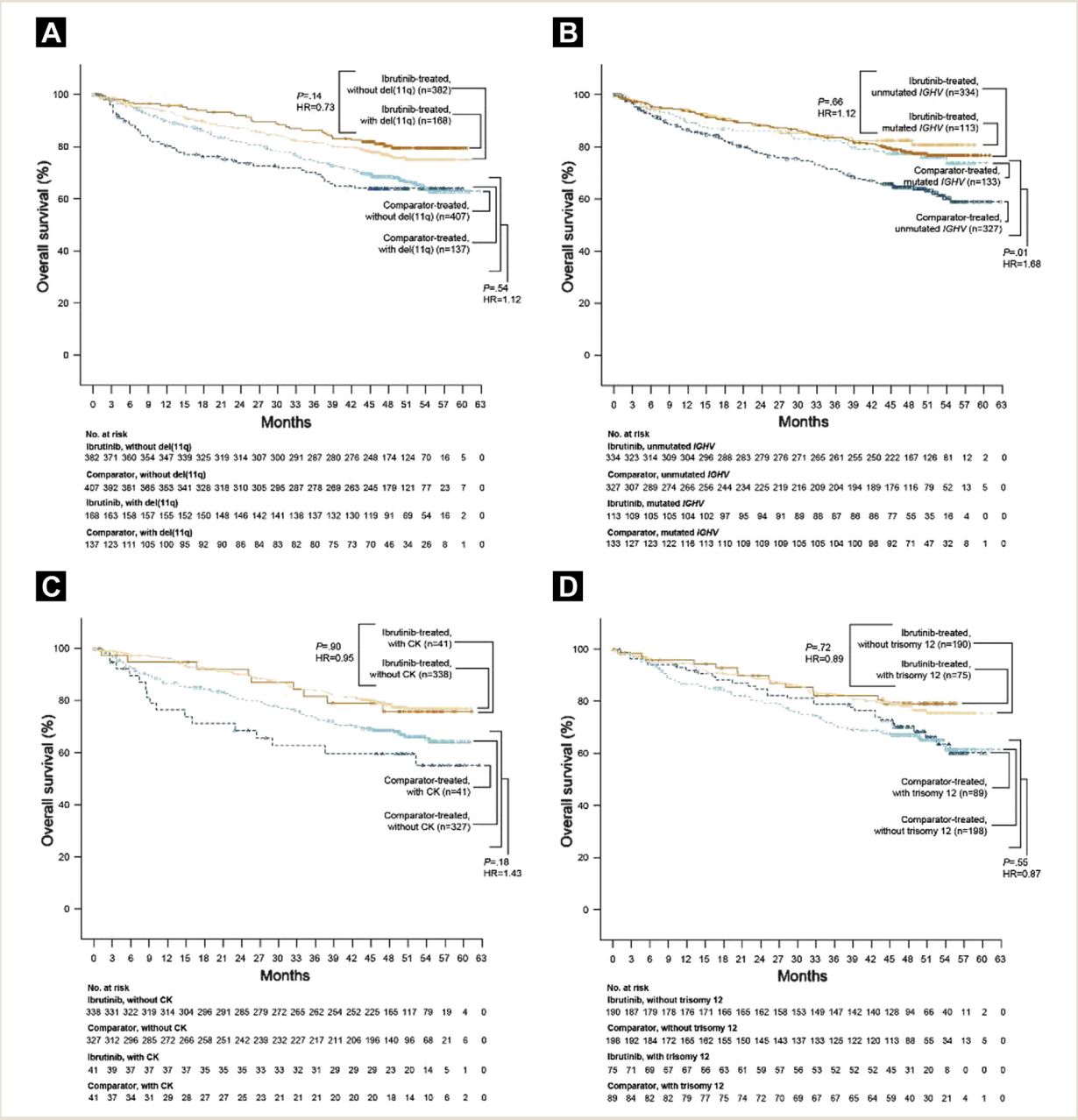
Data are presented as n (%) unless otherwise indicated.
Abbreviations: ALC = absolute lymphocyte count; β2M = beta-2-microglobulin; ECOG = Eastern Cooperative Oncology Group; *IGHV* = immunoglobulin heavy-chain variable region; mut = mutated; PS = performance status; unmut = unmutated.
[a]One patient with unmutated *IGHV* status had unknown del(17p) status.

Supplemental Table 3 Safety Profile in Ibrutinib-Treated Patients by Genomic Subgroup, Excluding Patients With Del(17p)

	IGHV		Trisomy 12		Complex Karyotype		Del(11q)	
Safety Profile	**Unmut**	**Mut**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
No. of patients	333	113	73	190	41	336	168	380
Months of exposure, median (range)	47 (< 1-60)	48 (1-58)	46 (1-57)	47 (< 1-62)	50 (1-62)	47 (1-61)	48 (1-61)	47 (< 1-62)
Grade 3/4 AEs	285 (86)	96 (85)	65 (89)	155 (82)	33 (80)	286 (85)	143 (85)	319 (84)
Serious AEs	221 (66)	75 (66)	46 (63)	123 (65)	27 (66)	216 (64)	118 (70)	245 (64)
AEs leading to dose modification	88 (26)	23 (20)	18 (25)	52 (27)	8 (20)	83 (25)	38 (23)	100 (26)
AEs leading to discontinuation	63 (19)	30 (27)	18 (25)	41 (22)	7 (17)	70 (21)	30 (18)	87 (23)
AEs leading to death	32 (10)	11 (10)	5 (7)	21 (11)	5 (12)	24 (7)	12 (7)	41 (11)

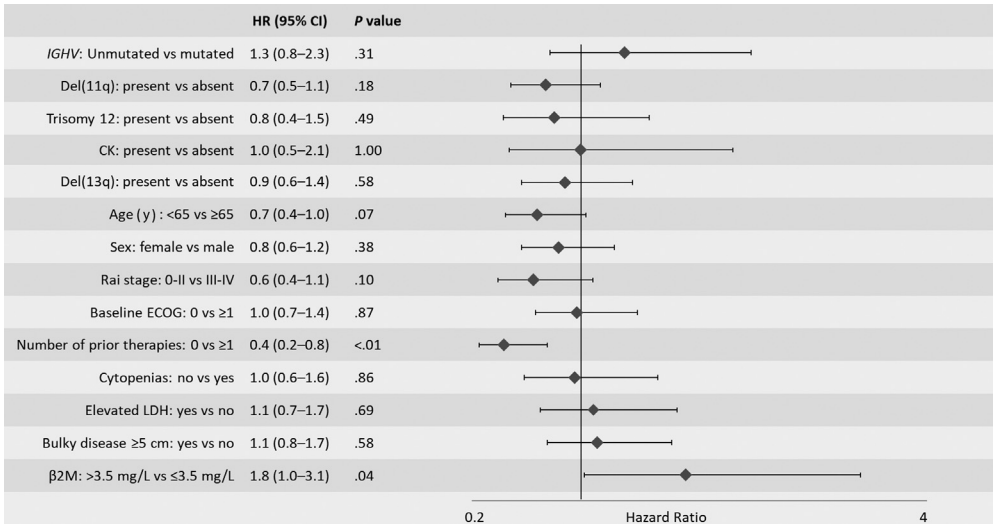
Data are presented as n (%) unless otherwise indicated.
Abbreviations: AE = adverse event; IGHV = immunoglobulin heavy-chain variable region; mut = mutated; unmut = unmutated.

Supplemental Figure 1 **Overall Survival in Ibrutinib- and Comparator-Treated Patients. Patients Were Divided by Genomic Subgroups by (A) Del(11q) Status, (B) *IGHV* Mutation Status, (C) Presence of Complex Karyotype (CK), and (D) Trisomy 12 Status**



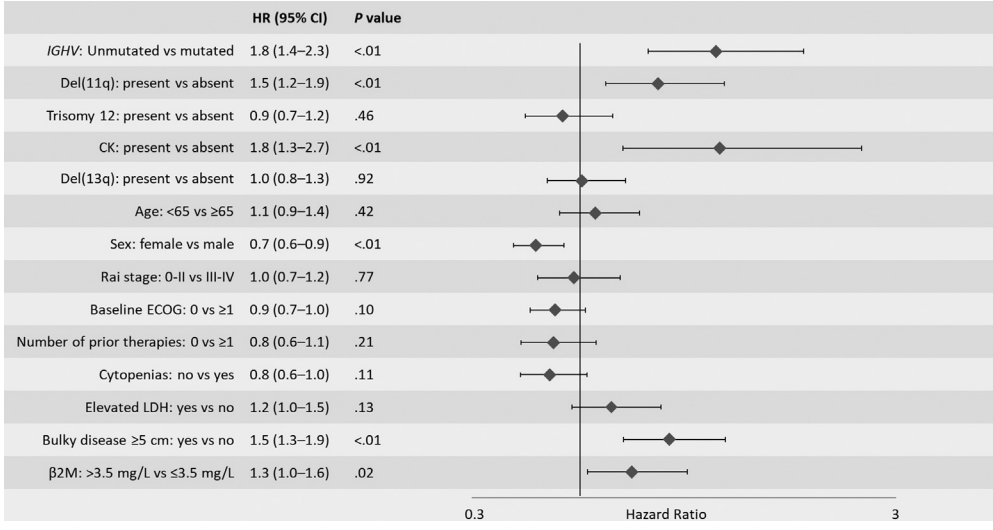
Abbreviations: HR = hazard ratio; IGHV = immunoglobulin heavy-chain variable region.

Supplemental Figure 2 Multivariate Analysis of Overall Survival in Ibrutinib-Treated Patients



Abbreviations: β2M = beta-2-microglobulin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IGHV = immunoglobulin heavy-chain variable region; LDH = lactate dehydrogenase.

Supplemental Figure 3 Multivariate Analysis of Progression-Free Survival in Comparator-Treated Patients



Abbreviations: β2M = beta-2-microglobulin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IGHV = immunoglobulin heavy-chain variable region; LDH = lactate dehydrogenase.