Received: 1 August 2018 | Revised: 13 August 2018 | Accepted: 15 August 2018

DOI: 10.1002/ajh.25259

WILEY AJH

RESEARCH ARTICLE

Single-agent ibrutinib versus chemoimmunotherapy regimens for treatment-naïve patients with chronic lymphocytic leukemia: A cross-trial comparison of phase 3 studies

Tadeusz Robak[1] | Jan A. Burger[2] | Alessandra Tedeschi[3] | Paul M. Barr[4] | Carolyn Owen[5] | Osnat Bairey[6] | Peter Hillmen[7] | David Simpson[8] | Sebastian Grosicki[9] | Stephen Devereux[10] | Helen McCarthy[11] | Steven E. Coutre[12] | Hang Quach[13] | Gianluca Gaidano[14] | Zvenyslava Maslyak[15] | Don A. Stevens[16] | Carol Moreno[17] | Devinder S. Gill[18] | Ian W. Flinn[19] | John G. Gribben[20] | Ahmad Mokatrin[21] | Mei Cheng[21] | Lori Styles[21] | Danelle F. James[21] | Thomas J. Kipps[22] | Paolo Ghia[23]

[1]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland

[2]The University of Texas MD Anderson Cancer Center, Houston, Texas

[3]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

[4]Wilmot Cancer Institute, University of Rochester Cancer Center, Rochester, New York

[5]Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada

[6]Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[7]The Leeds Teaching Hospitals, St. James's Institute of Oncology, Leeds, UK

[8]North Shore Hospital, Auckland, New Zealand

[9]School of Public Health, Silesian Medical University, Katowice, Poland

[10]King's College Hospital, NHS Foundation Trust, London, UK

[11]Royal Bournemouth Hospital, Bournemouth, UK

[12]Stanford University School of Medicine, Stanford, California

[13]St. Vincent's Hospital, University of Melbourne, Melbourne, Australia

[14]Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

[15]Institute of Blood Pathology and Transfusion Medicine of the Academy of Medical Sciences of Ukraine, Lviv, Ukraine

[16]Norton Cancer Institute, Louisville, Kentucky

[17]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[18]Princess Alexandra Hospital, Brisbane, Australia

[19]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee

[20]Barts Cancer Institute, Queen Mary University of London, London, UK

[21]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, California

[22]University of California San Diego, Moores Cancer Center, La Jolla, California

[23]Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milan, Italy

Correspondence
Prof. Tadeusz Robak, MD, PhD, Department of Hematology, Medical University of Lodz, 93-510 Lodz, Ul Ciolkowskiego 2, Poland,
Email: robaktad@csk.umed.lodz.pl

Funding information
Pharmacyclics LLC, an AbbVie Company

Abstract

Chemoimmunotherapy (CIT) and targeted therapy with single-agent ibrutinib are both recommended first-line treatments for chronic lymphocytic leukemia (CLL), although their outcomes have not been directly compared. Using ibrutinib data from the RESONATE-2 (PCYC-1115/1116) study conducted in patients ≥65 years without del(17p), we performed a cross-trial comparison with CIT

data from published phase 3 studies in first-line treatment of CLL. Progression-free survival (PFS), overall survival (OS), and safety data for ibrutinib (median follow-up 35.7 months) were evaluated alongside available CIT data. CIT regimens included: fludarabine + cyclophosphamide + rituximab (CLL8, CLL10), bendamustine + rituximab (CLL10), obinutuzumab + chlorambucil and rituximab + chlorambucil (CLL11), and ofatumumab + chlorambucil (COMPLEMENT-1). Median age across studies was 61-74 years, with older populations receiving ibrutinib, obinutuzumab + chlorambucil, or rituximab + chlorambucil. Median follow-up varied across studies/regimens (range 14.5-37.4 months). Among all patients, PFS appeared longer with ibrutinib relative to CIT and OS appeared comparable. Relative to CIT studies that similarly excluded patients with del(17p) (CLL10) or enrolled older/less-fit patients (CLL11), PFS appeared favorable for ibrutinib in high-risk subgroups, including advanced disease, bulky lymph nodes, unmutated *IGHV* status, and presence of del(11q). Grade ≥ 3 infections ranged from 9% (ofatumumab + chlorambucil) to 40% (fludarabine + cyclophosphamide + rituximab), and was 25% with ibrutinib. Grade ≥ 3 neutropenia was 12% for ibrutinib and 26%-84% for CIT. Although definitive conclusions cannot be made due to inherent limitations of cross-trial comparisons, this report suggests that ibrutinib has a favorable benefit/risk profile and may potentially eliminate the need for chemotherapy in some patients. Randomized, comparative studies are needed to support these findings.

1 | INTRODUCTION

The treatment landscape for chronic lymphocytic leukemia (CLL) has rapidly expanded in recent years with the addition of anti-CD20 monoclonal antibody-based chemoimmunotherapy (CIT), a standard first-line treatment for CLL patients without del(17p) or *TP53* mutations.[1–3] Findings from the pivotal phase 3 CLL8 international trial conducted by the German CLL Study Group demonstrated longer median progression-free survival (PFS) with fludarabine, cyclophosphamide, and rituximab (51.8 months) vs fludarabine and cyclophosphamide (32.8 months) in physically fit patients (median age 61 years) with previously untreated CLL.[4] However, tolerability to fludarabine-based CIT is limited due to toxicities that include infections and myelosuppression, both of which can be frequent and severe.[4–7] Furthermore, relapse is common over time and inferior efficacy has been noted in several subgroups of patients with certain high-risk disease factors (eg, unmutated immunoglobulin heavy variable [*IGHV*] gene status).[4,8,9] In older patients or in those not considered suitable for fludarabine-based CIT, the addition of anti-CD20 antibodies such as rituximab, obinutuzumab, or ofatumumab, in combination with chlorambucil, have shown improved outcomes over chlorambucil single-agent therapy,[10,11] leading to their approval in both the US and EU for patients with previously untreated CLL. Bendamustine plus rituximab has also shown efficacy as first-line treatment in patients with CLL,[12] particularly among older patients (>65 years).[6]

Advances in CLL research have also led to the development of several highly effective targeted agents, including ibrutinib.[13] Ibrutinib, a first-in-class, once-daily oral inhibitor of Bruton tyrosine kinase (BTK), is approved in the US and EU for the first-line treatment of patients with CLL. The efficacy of single-agent ibrutinib in CLL has been demonstrated in multiple phase 2 and phase 3 studies conducted in patients with relapsed/refractory CLL as well as in previously untreated patients.[14–16] The approval of ibrutinib as a first-line therapy for CLL was based on the results of a multicenter, randomized phase 3 study (RESONATE-2/PCYC-1115) that evaluated single-agent ibrutinib vs chlorambucil in older treatment-naive patients (aged ≥65 years) with CLL without del(17p).[16] In the primary analysis of RESONATE-2 (median follow-up, 18.4 months), ibrutinib resulted in significantly prolonged PFS, with 84% reduction in risk of progression or death and longer overall survival (OS) compared with chlorambucil. All patients in PCYC-1115 were allowed to enroll in an extension study (PCYC-1116) that is still ongoing.

At the time the RESONATE-2 trial was initiated (2013), single-agent chlorambucil was still considered the standard of care for a treatment-naïve CLL population deemed not suitable for fludarabine-based treatment. Therefore, the benefit of ibrutinib in the context of more aggressive, currently recommended CIT therapies that include an anti-CD20 agent remains to be established. To date, there are no published head-to-head randomized clinical trials comparing ibrutinib and CIT in the first-line CLL setting. Thus, despite the inherent limitations of heterogeneity in patient populations, a cross-trial comparison of available randomized, phase 3 data can provide potentially useful insight to clinicians treating patients with CLL and inform future research directions. Using additional follow-up data for ibrutinib (median 35.7 months) from the ongoing extension study of RESONATE-2, we conducted a cross-trial comparison of outcomes from published phase 3 studies of CIT regimens in the first-line CLL treatment setting.[4,6,10,11]

2 | METHODS

2.1 | Procedures

A targeted literature search was conducted to identify published phase 3, randomized controlled studies of CIT in treatment-naïve patients with CLL. The study designs, patient characteristics, dosing and treatment durations, and clinical efficacy and safety outcomes

from the CIT studies identified were evaluated alongside the study design and clinical data from RESONATE-2 of ibrutinib. Reporting of clinical outcomes, including PFS and OS data and toxicities, was limited by the availability of CIT data reported in the published literature. Subgroup analyses of PFS by baseline factors, including age, disease stage, bulky disease, *IGHV* mutation status, fluorescence in situ hybridization (FISH) cytogenetics, and β_2 microglobulin levels from RESONATE-2, were summarized alongside the CIT regimens where published subgroup data were available. For the safety analysis, only the adverse events (AEs) common to both ibrutinib and CIT were considered.

2.2 | Statistical analysis

Due to a lack of available patient-level data from the published CIT studies and differences in study designs and patient eligibility criteria, no formal cross-study comparative statistical testing was performed. Descriptive statistics, including median (range) for continuous variables and proportions for discrete variables, were reported for baseline characteristics, CIT completion rates, and AEs. Data reflect all included patients as reported in each publication, with no additional adjustments made. Kaplan-Meier plots for PFS and OS for ibrutinib and the CIT regimen arms were summarized, in addition to medians and landmark estimates obtained using Kaplan-Meier methods, where published data were available.[4,6,10,11] The magnitude of PFS benefit by baseline subgroups reported by the forest plot of hazard ratios (HRs) from the RESONATE-2 study (ibrutinib vs chlorambucil) were presented alongside the HRs for PFS benefit in CIT regimens for which published HR data were available.

3 | RESULTS

The CIT regimens identified in the search were as follows: fludarabine, cyclophosphamide, and rituximab (studies CLL8, CLL10); bendamustine plus rituximab (CLL10); obinutuzumab plus chlorambucil (CLL11); and ofatumumab plus chlorambucil (COMPLEMENT-1). Details of the RESONATE-2 and CIT study designs and patient eligibility are described in each of the primary publications.[4,6,10,11,16] Briefly, RESONATE-2 randomized patients aged ≥65 years without del(17p) to receive ibrutinib (*n* = 136) or chlorambucil (*n* = 133).[16] Eligible patients could enroll in a separate extension study of open-label ibrutinib (PCYC-1116) for continuing treatment and follow-up after PCYC-1115 study closure.[17] Among the available CIT phase 3 studies, two included fludarabine-based therapies: the CLL8 study, which randomized patients aged 30-81 years with an ECOG performance status of 0-1 to receive fludarabine, cyclophosphamide, and rituximab (*n* = 408, median age 61) or fludarabine and cyclophosphamide (*n* = 409, median age 61)[4] and the CLL10 study, which randomized patients aged 54-69 with an ECOG performance status of 0-2 to receive bendamustine and rituximab (*n* = 279, median age 61) or fludarabine, cyclophosphamide, and rituximab (*n* = 282, median age 62).[6]

CLL10, like PCYC-1115, excluded patients with del(17p). Both CLL8 and CLL10 included patients with low comorbidity, defined as a Cumulative Illness Rating Scale (CIRS) score up to 6 and a creatinine clearance of at least 1.17 mL/s (70.1 mL/min), though some patients with decreased creatinine clearance were enrolled in CLL8.[4,6] The third study, CLL11, was a three-group study designed to assess the efficacy of chlorambucil alone and in combination with the anti-CD20 antibodies obinutuzumab (GA101) and rituximab.[10] In this study, patients aged 39-90 years (median age 73) were randomized to receive: obinutuzumab plus chlorambucil (*n* = 333), rituximab plus chlorambucil (*n* = 330), or chlorambucil alone (*n* = 118). Patients in this study were required to have clinically meaningful comorbidity, defined as a CIRS score greater than 6 or a creatinine clearance of 30-69 mL/min. In the fourth study included in this report, COMPLEMENT-1, patients aged 35-92 years (median age 69) with an ECOG performance score of 0-2 who were considered not suitable for fludarabine-based treatment were randomized to receive anti-CD20 monoclonal antibody ofatumumab plus chlorambucil (*n* = 221) or chlorambucil alone (*n* = 226).[11] The planned dosage for ibrutinib and each CIT dosing schedule are included in Supporting Information Table S1.[4,6,10,11,16] All studies, with the exception of RESONATE-2 and CLL10, allowed patients with del(17p) to enroll.

As described in the primary publications, each study was approved by an independent ethics committee or institutional review board at their respective institutions and/or conducted according to the Declaration of Helsinki, and all patients provided written informed consent.[4,6,10,11,16] All trials were registered with ClinicalTrials.gov: NCT01722487 and NCT01724346 (PCYC-1115/1116), NCT00281918 (CLL08), NCT00769522 (CLL10), NCT01010061 (CLL11), NCT00748189 (COMPLEMENT-1).[4,6,10,11,16,17]

A summary of baseline demographics and disease characteristics for patients by study and treatment is shown in Supporting Information Table S2.[4,6,10,11,16] The median age of patients across the studies ranged from 61 to 74 years, with older patients enrolled in the studies with ibrutinib and chlorambucil-based CIT and younger patients enrolled in the studies with bendamustine and fludarabine-based CIT (Supporting Information Table S2). The percentage of patients with unmutated *IGHV* gene status was lower in the ibrutinib treatment arm (43%) than in the CIT arms (range 55%-68%). In general, patients treated with bendamustine or fludarabine-based CIT regimens had lower comorbidity (eg, lower CIRS scores, higher creatinine clearance), whereas those treated with ibrutinib or chlorambucil-based CIT therapies had higher comorbidity (Supporting Information Table S2).

The median duration of follow-up reported for the CLL8 study (fludarabine, cyclophosphamide, and rituximab vs fludarabine and cyclophosphamide) was 37.2 months.[4,5] The median duration of follow-up was reported by treatment arm in the remaining studies and was 35.7 months for ibrutinib, 36.0 months for bendamustine plus rituximab, 37.4 months for fludarabine, cyclophosphamide, and rituximab,[6] 14.5 months for obinutuzumab plus chlorambucil,[10] 15.3 months for rituximab plus chlorambucil,[10] and 28.9 months for ofatumumab plus chlorambucil.[11]

Among the studies that enrolled older or less-fit patients (RESONATE-2, CLL11, COMPLEMENT-1), treatment with ibrutinib appeared to be associated with longer PFS than chlorambucil plus anti-CD20-based CIT based on a superimposed display of the Kaplan-Meier curves (Figure 1A).[10,11] Patients treated with ibrutinib also appeared to have longer PFS than younger, more-fit patients treated

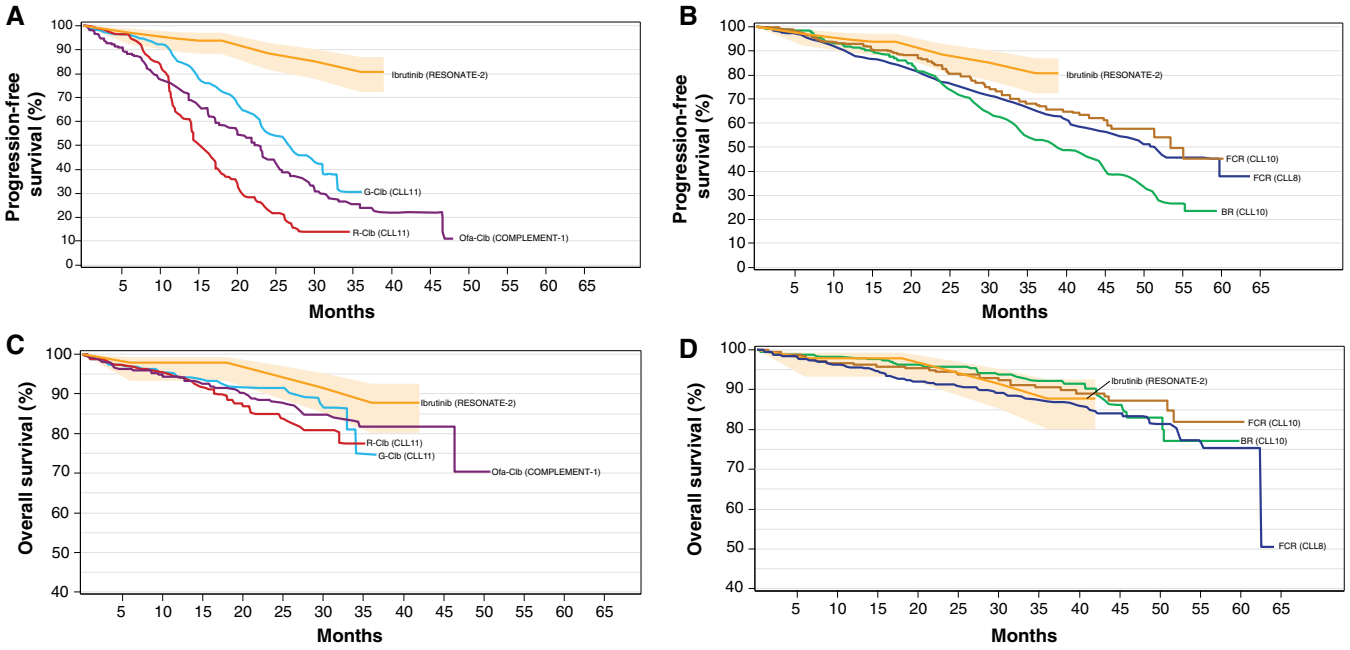

FIGURE 1 Progression-free survival and overall survival for ibrutinib and comparator studies. Progression-free survival (A) and overall survival (C) for ibrutinib from RESONATE-2/PCYC-1116 (ongoing extension study) and studies in older patients or patients with comorbidities (CLL11, COMPLEMENT-1[10,11]) and progression-free survival (B) and overall survival (D) for ibrutinib and studies in younger patients (CLL8, CLL10[4,6]). Shaded area represents 95% confidence band with ibrutinib. BR, bendamustine plus rituximab; Clb, chlorambucil; FCR, fludarabine, cyclophosphamide, and rituximab; G, obinutuzumab; Ofa, ofatumumab; R, rituximab.

with bendamustine plus rituximab or with fludarabine-based CIT (Figure 1B).[4,6]

Among the studies that excluded patients with del(17p) (RESONATE-2 and CLL10), PFS rates for baseline subgroups appeared more favorable with ibrutinib relative to bendamustine- and fludarabine-based CIT regimens from CLL10, particularly in subgroups with other high-risk features, including advanced disease, bulky lymph nodes, unmutated *IGHV* status, and presence of del(11q) (Table 1).[6] Ibrutinib treatment was associated with a PFS rate at 3 years of >80% in both patients with mutated (83.8%) and unmutated (83.6%) *IGHV* status, whereas lower 3-year PFS rates were associated with bendamustine and rituximab (42.8%) and fludarabine, cyclophosphamide, and rituximab (59.1%) in patients with unmutated *IGHV* status (Table 1). The 3-year PFS rate with ibrutinib in patients with del(11q) (93.0%) was also notably higher relative to patients with del(11q) treated with bendamustine and rituximab and fludarabine, cyclophosphamide, and rituximab (14.2 and 56.8%). Based on the side-by-side display of HRs by baseline subgroups in a forest plot, the magnitude of PFS benefit with ibrutinib over chlorambucil appeared greater than that seen with regimens with anti-CD20 antibodies plus chlorambucil over chlorambucil alone, including in high-risk subgroups (Figure 2).[10,16]

Among all the studies with an older or less-fit population, ibrutinib appeared to show a more favorable OS relative to the chlorambucil-based CIT regimens including ofatumumab, rituximab, or obinutuzumab (Figure 1C).[10,11] The OS with ibrutinib also appeared comparable to more intensive CIT regimens in studies that included younger, more fit patients (Figure 1D).[4,6]

The median treatment duration for patient's receiving daily ibrutinib (34.1 months) was considerably longer than the approximate median treatment duration for patients receiving CIT (range 5.2-6 months) (Table 2).[4,6,10,11] Fewer patients in the fludarabine-based CIT regimens (74% in CLL8 and 71% in CLL10)[4,6] completed 6 courses of CIT compared with patients in the bendamustine plus rituximab regimen (81%)[6] or chlorambucil-based regimens (range 81%-89%).[10,11] In the CLL10 study, the proportion of patients receiving all six treatment cycles of fludarabine, cyclophosphamide, and rituximab was considerably lower for older patients (>65 years, 57%) than for younger patients (≤65 years, 76%).

The rate of grade ≥ 3 AEs for ibrutinib (73%) was similar to the overall rate reported with obinutuzumab plus chlorambucil (70%) despite a much longer treatment period (Table 2). Rates of grade ≥ 3 AEs were highest in the fludarabine- and bendamustine-based treatment arms (range 76%-94%), and lowest in the rituximab plus chlorambucil and ofatumumab plus chlorambucil groups (55% and 50%, respectively). In the older patient population (>65 years), single-agent ibrutinib was associated with lower rates of grade ≥ 3 cytopenias than the rates associated with fludarabine- and bendamustine-based CIT (Table 2). Reporting of grade 3 or higher cytopenias by grade showed substantially lower rates of grade 3 and grade 4 neutropenia or thrombocytopenia with ibrutinib, relative to fludarabine- or bendamustine-based CIT regimens (Supporting Information Table S3).[6] Grade ≥ 3 infection rates with ibrutinib were similar to those with bendamustine plus rituximab (Table 2). When restricting the period of follow-up for ibrutinib to the first 6 months of treatment (similar to the treatment duration reported for CIT), the rate of reported grade ≥ 3 AEs was 48% overall, 13% for infections, 6% each for neutropenia and anemia, and 1% for thrombocytopenia (Supporting Information Table S4).

TABLE 1 PFS by subgroups from studies that excluded patients with del(17p)

	RESONATE-2 (PCYC-1115/1116 ongoing extension study) Ibrutinib (*n* = 136)		CLL10[6] Bendamustine, rituximab (*n* = 279)		CLL10[6] Fludarabine, cyclophosphamide, rituximab (*n* = 282)	
	Median, months (95% CI)	3-year rate (95% CI)	Median, months (95% CI)	3-year rate (95% CI)	Median, months (95% CI)	3-year rate (95% CI)
All patients	NR[a] (NE)	80.9% (72.2-87.1)	41.7 (34.9-45.3)	54.5% (47.9-61.1)	55.2 (NE)	69.6% (63.8-75.4)
Age						
>65 years	NR (NE)	80.9% (72.2-87.1)	48.5 (34.6-52.0)	56.8% (46.0-67.6)	NR (NE)	69.1% (58.6-79.6)
≤65 years			38.5 (33.1-44.8)	52.9% (44.5-61.2)	53.6 (NE)	69.8% (62.8-76.8)
Binet stage						
A	NR (NE)	87.8% (66.8-95.9)	43.1 (NE)	61.2% (46.5-75.8)	55.2 (NE)	72.4% (60.3-84.5)
B	NR (NE)	82.4% (68.8-90.4)	33.3 (27.8-44.8)	44.2% (33.9-54.6)	NR (NE)	69.6% (60.4-78.8)
C	NR (NE)	77.4% (62.3-87.1)	44.6 (38.0-51.3)	61.2% (51.0-71.3)	53.6 (NE)	67.9% (58.3-77.4)
Lymph node size[b]						
<5 cm	NR (NE)	79.8% (67.0-88.0)		63.4% (55.8-70.9)		72.1% (65.8-78.4)
≥5 cm	NR (NE)	83.9% (70.4-91.6)		31.4% (19.0-43.8)		57.5% (43.1-71.9
IGHV mutation status						
Mutated	NR (NE)	83.8% (67.3-92.4)	55.4 (NE)	77.5% (67.8-87.1)		82.4% (75.1-89.6)
Unmutated	NR (NE)	83.6% (70.8-91.1)	33.6 (30.3-38.4)	42.8% (34.5-51.1)		59.1% (50.6-67.6)
FISH cytogenetics						
Del(11q)	NR (NE)	93.0% (74.7-98.2)	25.3 (23.5-30.3)	14.2% (3.4-25.0)	37.8 (31.5-45.5)	56.8% (43.7-70.0)
Trisomy 12	NR (25.2-NE)	71.5% (47.1-86.1)		70.7% (51.4-90.0)		69.4% (52.5-86.4)
Normal	NR (NE)	79.0% (63.4-88.5)		63.7% (51.8-75.6)		70.6% (59.0-82.2)
Del(13q)	NR (NE)	84.2% (69.7-92.1)		66.4% (56.7-76.0)		76.9% (68.8-85.0)

FISH, fluorescence in situ hybridization; NE, not estimable, NR, not reached.
[a] Median follow-up duration 35.7 months for ibrutinib.
[b] For RESONATE-2, the cutoff was lymph node <5 cm or ≥5 cm. For CLL10, the cutoff was lymph node not present or ≤5 cm or >5 cm.

4 | DISCUSSION

Previous results of the RESONATE-2 study demonstrated a significant benefit in survival with ibrutinib over chlorambucil in treatment-naïve patients with CLL,[16,17] and ibrutinib is recommended as a first-line treatment for older or less-fit patients in this setting.[3] In this cross-trial analysis of first-line regimens, with median follow-up ranging from 14.5 months to 37.4 months, single-agent ibrutinib appeared to be associated with longer PFS relative to published phase 3 data for CIT. In studies with older patients, ibrutinib was associated with both longer PFS and OS than CIT regimens with anti-CD20 antibodies plus chlorambucil. Single-agent ibrutinib was also associated with longer PFS and comparable OS relative to the more intensive fludarabine- and bendamustine-based CIT regimens from studies that included younger, more-fit patients. In addition, ibrutinib was associated with a generally more favorable safety profile, despite the longer reporting period for AE data, with notably lower rates of severe cytopenias, particularly relative to fludarabine- and bendamustine-based CIT.

In this cross-study analysis, treatment with ibrutinib was associated with particularly favorable PFS outcomes with high rates of PFS at 3 years among patient subgroups with high-risk factors such as advanced disease, bulky lymph nodes, unmutated *IGHV* status, and presence of del(11q). PFS rates in these subgroups appeared favorable with ibrutinib relative to both the fludarabine- and bendamustine-based CIT regimens from the CLL10 study, which, like RESONATE-2, excluded patients with del(17p).

PFS by subgroup for ibrutinib was also reported alongside the PFS for CIT regimens from the CLL11 study that included older or less-fit patients. Again, a favorable benefit with ibrutinib was apparent among all patients and among high-risk patient subgroups with

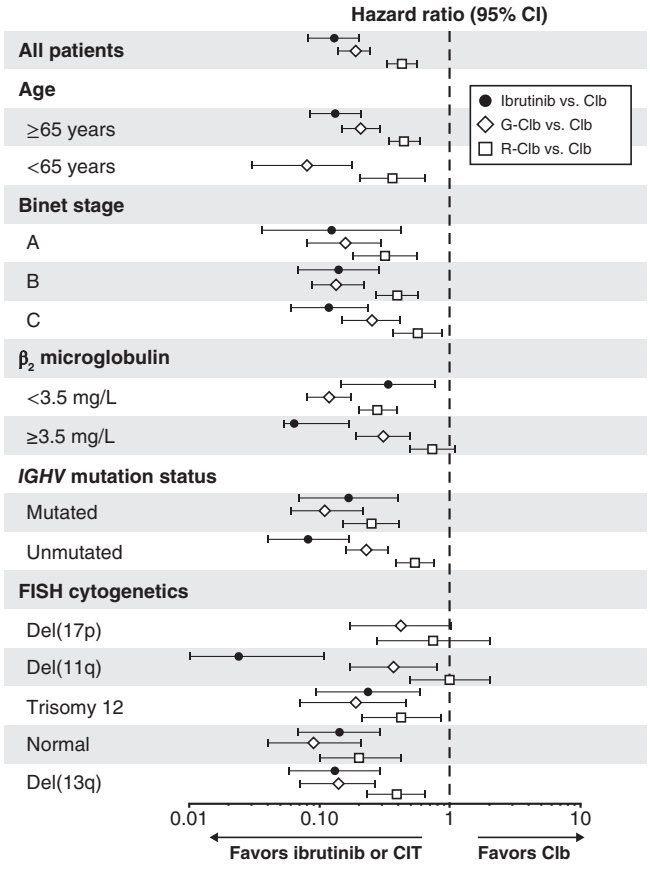

FIGURE 2 Forest plot of hazard ratios for PFS with ibrutinib from RESONATE-2 (PCYC-1115)[16] and obinutuzumab plus chlorambucil, and rituximab plus chlorambucil from CLL11.[10] The display of HRs shows that the magnitude of PFS benefit of ibrutinib vs chlorambucil was generally greater than that seen with the anti-CD20 monoclonal antibodies plus chlorambucil vs chlorambucil, particularly in high-risk patient subgroups. Dosing for chlorambucil in RESONATE-2: 0.5 mg/kg (max 0.8 mg/kg) days 1 and 15 of each 28-day cycle (total 12). Dosing for chlorambucil in CLL11: 0.5 mg/kg on days 1 and 15 of each 28-day cycle (total 6). CI, confidence interval; CIT, chemoimmunotherapy; Clb, chlorambucil; FISH, fluorescence in situ hybridization; G, obinutuzumab; PFS, progression-free survival; R, rituximab.

advanced age, elevated beta-2 microglobulin, unmutated *IGHV* status, and del(11q), suggesting that first-line treatment with ibrutinib appears to overcome the negative prognostic effects of several high-risk features that are typically associated with poorer outcomes with CIT regimens.

These findings are consistent with the results of a previously conducted network meta-analysis of 15 randomized controlled trials in the first-line CLL setting, including ibrutinib data from the primary analysis of the RESONATE-2 study (median follow-up 18.4 months).[18] Results of the network meta-analysis demonstrated a benefit in PFS, as well as OS, with ibrutinib over CIT in overall and fludarabine-ineligible populations, with particular efficacy demonstrated in subgroups with del(11q) or unmutated *IGHV* status. A similar benefit in high-risk groups has been noted in previous studies of relapsed/refractory patients with CLL treated with ibrutinib as a single agent or in combination with CIT.[15,19,20] A recent pooled analysis of 1238 patients from 3 clinical studies of ibrutinib in CLL as a single agent or in combination with CIT also noted favorable PFS and OS with ibrutinib, regardless of the presence of genomic risk factors, including unmutated *IGHV* status and del(11q).[21] Notably, among ibrutinib-treated patients in the pooled analysis, del(11q) was associated with a trend of longer PFS and OS compared with those without del(11q). This is in contrast with standard first-line CIT with fludarabine, cyclophosphamide, and rituximab, which has shown worse outcomes in patients with several high-risk features.[6,8,22] Together these data suggest that targeting intracellular B-cell signaling by BTK inhibition with ibrutinib may be particularly beneficial in patients with features traditionally considered high-risk, such as unmutated *IGHV* and del(11q), who may not be expected to respond well to standard CIT with fludarabine or bendamustine. Of note, the number of patients with unmutated *IGHV* status in the cross-trial analysis was lower in the ibrutinib group than in the CIT groups; however, for patients treated with ibrutinib in RESONATE-2, the PFS plot was superimposable when we considered unmutated and mutated cases separately.

It should also be noted, however, that some patients benefit remarkably from first-line treatment with fludarabine, cyclophosphamide, and rituximab. According to an updated survival analysis from the CLL8 study, with a median follow up of 5.9 years, median PFS was 56.8 months and median OS was not reached following treatment with fludarabine-cyclophosphamide-rituximab.[5] Furthermore, a follow-up analysis of the phase 2 MD Anderson Cancer Center study (N = 300) noted long-term benefit in patients with mutated *IGHV* status, with the PFS curve plateauing, and no relapse beyond 10 years in 14% of all patients (42 of 300 patients).[9] Many patients, however, may not be able to complete the full course of fludarabine-based CIT for reasons that include tolerability, which was exemplified by the lower completion rates of planned CIT cycles for the fludarabine-based CIT regimens noted in this analysis.[4,6] Fludarabine- and bendamustine-based CIT are frequently associated with hematologic toxicity,[4,6,12] and cytopenias can be persistent, lasting more than 3 months in 19% of patients treated with fludarabine CIT in particular.[7] Severe infections are also common with fludarabine-based CIT, particularly in older patients.[4,6] In the CLL10 study, the rates of infections and cytopenias were higher with fludarabine-cyclophosphamide-rituximab vs bendamustine-rituximab, and were generally more pronounced among older patients.[6] Despite the longer treatment duration, the rate of cytopenias in older, previously untreated patients treated with once-daily ibrutinib were considerably lower than the rates reported in CLL10, and the rate of infections was similar to the rate reported with bendamustine-rituximab. Further, when looking at AE rates during similar treatment exposure periods across studies (first 6 months), the rates of cytopenias and infections were lowest with ibrutinib. The rate of cytopenias with ibrutinib reported with longer-term follow-up on RESONATE-2 appeared consistent with the rates reported at primary analysis (with median treatment duration 17.4 months), suggesting that the prevalence of cytopenias do not increase with continued ibrutinib treatment.[16] Rather, as shown in a separate analysis of the RESONATE-2 study data, severe cytopenias decreased over time during 3 years of ibrutinib treatment.[23] Of note, treatment-specific clinical AEs of interest, such as atrial fibrillation and hypertension with ibrutinib or infusion-related reactions with an anti-

TABLE 2 Treatment exposure and summary of select grade ≥ 3 AEs across studies

	RESONATE-2 (PCYC-1115/1116 ongoing extension) Ibrutinib (*n* = 135)	CLL10[6] Bendamustine, rituximab (*n* = 278)	CLL10[6] Fludarabine, cyclophosphamide, rituximab (*n* = 279)	CLL8[4] Fludarabine, cyclophosphamide, rituximab (*n* = 404)[a]	CLL11[10] Obinutuzumab, chlorambucil (*n* = 336)	CLL11[10] Rituximab, chlorambucil (*n* = 321)	COMPLEMENT-1[11] Ofatumumab, chlorambucil (*n* = 217)
Median treatment duration, months	34.1	6[b]	6[b]	5.2[b]	6[b]	6[b]	6[b]
Treatment completion rates	N/A	225/279 (81%)	199/282 (71%)	298/404 (74%)	273/336 (81%)	286/321 (89%)	177/217 (82%)
Overall grade ≥ 3 AEs	99 (73%)	234 (84%)	261 (94%)	309 (76%)	235 (70%)	117 (55%)	109 (50%)
Grade ≥ 3 infections		74 (27%)	111 (40%)	103 (25%)	40 (12%)	44 (14%)	20 (9%)
≤65 years[c]	—	47 (27%)[c]	70 (35%)[c]	—	—	—	—
>65 years	34 (25%)	27 (25%)[d]	41 (48%)[d]	—	—	—	—
Grade ≥ 3 cytopenias							
Neutropenia	—	164 (59%)	235 (84%)	136 (34%)	111 (33%)	91 (28%)	56 (26%)
≤65 years[c]	—	89 (52%)[d]	159 (82%)[d]	—	—	—	—
>65 years[c]	16 (12%)	65 (61%)[e]	76 (88%)[e]	—	—	—	—
Thrombocytopenia	—	40 (14%)	60 (22%)	30 (7%)	35 (10%)	10 (3%)	10 (5%)
≤65 years[c]	—	17 (10%)[d]	34 (18%)[d]	—	—	—	—
>65 years[c]	5 (4%)	23 (21%)[e]	26 (30%)[e]	—	—	—	—
Anemia	—	29 (10%)	38 (14%)	22 (5%)	14 (4%)	12 (4%)	10 (5%)
≤65 years[c]	—	15 (9%)[d]	26 (13%)[d]	—	—	—	—
>65 years[c]	9 (7%)	14 (13%)[e]	12 (14%)[e]	—	—	—	—

Data reported as *n* (%) or *n*/*N* (%) unless otherwise indicated.
BR, bendamustine and rituximab; FCR, fludarabine, cyclophosphamide, and rituximab; N/A, not applicable.
[a] Grade 3-4 AEs reported for CLL8 FCR.
[b] Median treatment duration was approximated using the median number and length of cycles; mean number of cycles reported for CLL8 FCR.
[c] Data collected only for CLL10.
[d] FCR, *n* = 193; BR, *n* = 171.
[e] FCR, *n* = 86; BR, *n* = 107.

CD20 antibody plus chlorambucil, could not be compared here, but should also be considered.

The findings in this analysis must be interpreted cautiously given the numerous limitations of cross-trial comparisons, including, but not limited to, differences in the study designs, eligibility criteria, and patient populations. In these CLL studies, differences in baseline comorbidity (which can also influence dose intensity), age, disease state, and cytogenetic and genomic features must all be considered. We also acknowledge that OS outcomes are particularly difficult to compare across studies given the variables that may affect survival, including differences in allowance of cross-over in the study designs or variations in access to subsequent (second-line) therapies, including with targeted agents, during the time the studies were conducted. While no statements of statistical superiority can be made on the basis of this broad comparative analysis of ibrutinib and CIT regimens, the results of these findings are of potential value to clinicians who are faced with an increasing array of treatment options for CLL. Our analysis provides evidence that ibrutinib may be favorable to chlorambucil-based therapies in patients unfit for more aggressive CIT regimens, but results are needed from phase 3 studies directly comparing ibrutinib-containing therapy with fludarabine- and bendamustine-based CIT before ibrutinib can be routinely recommended in patients fit for aggressive CIT. Ongoing randomized studies in first-line CLL are currently evaluating ibrutinib alone or in combination with rituximab vs bendamustine and rituximab (NCT01886872) or fludarabine, cyclophosphamide, and rituximab (NCT02048813, ISRCTN01844152/Eudra-CT2013-001944-76), and ibrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab (NCT02264574). These studies will help further explore and confirm the role of ibrutinib as a first-line treatment for CLL.

ACKNOWLEDGMENTS

We thank the patients who participated in these studies and their supportive families, as well as the investigators and clinical research staff from the study centers. This analysis was supported by Pharmacyclics LLC, an AbbVie Company. The authors thank Simona Baculea, MSc, PhD (Janssen-Cilag Ltd, UK), Suzy Van Sanden, PhD (Janssen Pharmaceutica NV, Belgium), Thomas Webb, MSc (Janssen Ltd, UK), and Yingxin Xu, PharmD, PhD (formerly at Evidera), for their contributions to the systematic literature review, identification of studies, and conceptualization of key research questions. Medical writing was provided by Sarah Mizne, PharmD, and was funded by Pharmacyclics LLC, an AbbVie Company.

CONFLICT OF INTEREST

TR: research funding from Pharmacyclics LLC, an AbbVie Company. JAB: honoraria and travel expenses from Janssen; consultancy/advisory role for Gilead, Janssen, and Pharmacyclics LLC, an AbbVie Company; research funding from Pharmacyclics LLC, an AbbVie Company. AT: consultancy/advisory role for AbbVie, Gilead, and Janssen-Cilag S.p.A.; speakers' bureau for Janssen. PMB: consultancy/advisory role for AbbVie, Celgene, Genentech, Gilead, Merck, Novartis, Seattle Genetics, and Verastem. CO: honoraria from AbbVie, AstraZeneca, Celgene, Gilead, Janssen, Lundbeck, Merck, and Roche; consultancy/advisory role for Roche; research funding from Gilead, Pharmacyclics LLC, an AbbVie Company, and Roche. OB: consultancy/advisory role for AbbVie; research funding from Janssen. PH: honoraria, consultancy/advisory role, and research funding from AbbVie, Janssen, and Pharmacyclics LLC, an AbbVie Company; travel expenses from AbbVie and Janssen. DS: honoraria from Celgene, Janssen, Merck Sharp & Dohme, and Roche; research funding from AbbVie, Acerta, Amgen, BeiGene, Merck Sharp & Dohme, Pharmacyclics LLC, an AbbVie Company, Roche, and Sanofi; travel expenses from Bristol-Myers Squibb, Celgene, and Novartis. SG, ZM: no relevant conflicts of interest to disclose. SD consultancy/advisory role for AbbVie, Bristol-Myers Squibb, Janssen, and GlaxoSmithKline; speakers' bureau for Gilead, and Janssen. HM: honoraria and travel expenses from AbbVie, Janssen, Novartis, and Roche; consultancy/advisory role for Janssen. SEC: honoraria from Janssen and Pharmacyclics LLC, an AbbVie Company; consultancy/advisory role for AbbVie, BeiGene, and Janssen; research funding from AbbVie, Acerta, Gilead, Janssen, and Pharmacyclics LLC, an AbbVie Company. HQ: honoraria and consultancy/advisory role for Amgen, Celgene, Janssen-Cilag, and Takeda; research funding from Amgen and Celgene. GG: honoraria from AbbVie, Amgen, Gilead, Janssen, MorphoSys, and Roche: consultancy/advisory role for AbbVie, Amgen, Gilead, Janssen, and Roche. DAS: consultancy/advisory role for Bayer. CM: consultancy/advisory role for AbbVie, Janssen, and Pharmacyclics LLC, an AbbVie Company. DSG: speakers bureau and travel expenses from Janssen. IWF: institution received research funding from Agios, ArQule, BeiGene, Calithera, Celgene, Constellation, Curis, Forma, Forty Seven, Genentech, Gilead, Incyte, Infinity, Janssen, KITE, Merck, Novartis, Pfizer, Pharmacyclics LLC, an AbbVie Company, Portola, Seattle Genetics, Takeda, TG Therapeutics, Trillium, and Verastem. JGG: honoraria and consultancy/advisory role for Janssen and Pharmacyclics LLC, an AbbVie Company; research funding from Janssen. AM, MC, LS: employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie. DFJ: employment with Pharmacyclics LLC, an AbbVie Company, and husband employment with AbbVie; stock ownership by self/husband with AbbVie; patents/royalties/other intellectual property with AbbVie. TJK: consultancy/advisory role for AbbVie, Celgene, Genentech-Roche, Gilead, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, Genentech-Roche, Oncternal, Pharmacyclics LLC, an AbbVie Company. PG: honoraria and consultancy/advisory role for AbbVie, Acerta, BeiGene, Gilead, Janssen, Roche, and Sunesis; research funding from AbbVie, Gilead, Janssen, and Novartis; speakers' bureau for Gilead.

AUTHOR CONTRIBUTIONS

The sponsor collected the RESONATE-2 study data, contributed to the analysis and interpretation of the data, and contributed to the drafting, review, and final approval of the manuscript for submission. The corresponding author and sponsor designed the analysis. TR, LS, and DFJ conceived and/or designed the work that led to the submission. LS and DFJ acquired data, and all authors had access to and interpreted the raw data. All authors carefully reviewed and revised drafts of the manuscript and approved the final version. TR had full access to all of the data and final responsibility to submit for publication.

ORCID

Tadeusz Robak http://orcid.org/0000-0002-3411-6357

REFERENCES

1. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. *Am J Hematol*. 2017;92(9):946-965.
2. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v78-v84.
3. ESMO Guidelines Committee. eUpdate – chronic lymphocytic leukaemia treatment recommendations 2017; http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations. Accessed March 30, 2018.
4. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.
5. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215.
6. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
7. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008;112(4):975-980.
8. Rossi D, Terzi-di-Bergamo L, De Paoli L, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. *Blood*. 2015;126(16):1921-1924.
9. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
10. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
11. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet*. 2015;385(9980):1873-1883.
12. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German chronic lymphocytic leukemia study group. *J Clin Oncol*. 2012;30(26):3209-3216.
13. Robak T, Stilgenbauer S, Tedeschi A. Front-line treatment of CLL in the era of novel agents. *Cancer Treat Rev*. 2017;53:70-78.
14. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
15. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014;15(1):48-58.
16. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
17. Coutre S, Tedeschi A, Robak T, et al. Survival adjusting for crossover: phase 3 study of ibrutinib vs chlorambucil in older patients with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma. *Haematologica*. 2018;103(6):e249-e251.
18. Xu Y, Fahrbach K, Dorman E, et al. Front-line treatment of patients with chronic lymphocytic leukemia: a systematic review and network meta-analysis. *J Comp Eff Res*. 2018;7(5):421-441.
19. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
20. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol*. 2016;17(2):200-211.
21. Kipps TJ, Fraser G, Coutre SE, et al. Integrated analysis: outcomes of ibrutinib-treated patients with chronic lymphocytic leukemia/ small lymphocytic leukemia (cll/sll) with high-risk prognostic factors [abstract]. *Hematol Oncol*. 2017;35(suppl 2):109-111.
22. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123(21):3247-3254.
23. Tedeschi A, Owen CJ, Robak T, et al. Prolonged improvement in patient-reported outcomes (PROs) and well-being in older patients with treatment-naïve (TN) chronic lymphocytic leukemia treated with ibrutinib (Ibr): 3-year follow-up of the RESONATE-2 study [abstract]. *Blood*. 2017;130(suppl 1):1746.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Robak T, Burger JA, Tedeschi A, et al. Single-agent ibrutinib versus chemoimmunotherapy regimens for treatment-naïve patients with chronic lymphocytic leukemia: A cross-trial comparison of phase 3 studies. *Am J Hematol*. 2018;93:1402–1410. https://doi.org/10.1002/ajh.25259