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Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with *TP53* aberrations: a pooled analysis from four clinical trials

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Summary

TP53 aberrations [del(17p) or *TP53* mutation] predict poor survival with chemoimmunotherapy in patients with chronic lymphocytic leukaemia (CLL). We evaluated long-term efficacy and safety of first-line ibrutinib-based therapy in patients with CLL bearing *TP53* aberrations in a pooled analysis across four studies: PCYC-1122e, RESONATE-2 (PCYC-1115/16), iLLUMINATE (PCYC-1130) and ECOG-ACRIN E1912. The pooled analysis included 89 patients with *TP53* aberrations receiving first-line treatment with single-agent ibrutinib ($n = 45$) or ibrutinib in combination with an anti-CD20 antibody ($n = 44$). All 89 patients had del(17p) (53% of 89 patients) and/or *TP53* mutation (91% of 58 patients with *TP53* sequencing results available). With a median follow-up of 49.8 months (range, 0.1–95.9), median progression-free survival was not reached. Progression-free survival rate and overall survival rate estimates at four years were 79% and 88%, respectively. Overall response rate was 93%, including complete response in 39% of patients. No new safety signals were identified in this analysis. Forty-six percent of patients remained on ibrutinib treatment at last follow-up. With median follow-up of four years (up to eight years), results from this large, pooled, multi-study data set suggest promising long-term outcomes of first-line ibrutinib-based therapy in patients with *TP53* aberrations.

Registered at ClinicalTrials.gov (NCT01500733, NCT01722487, NCT02264574 and NCT02048813).

Keywords: chronic lymphocytic leukaemia, ibrutinib, *TP53* mutation, del(17p), first-line.

Introduction

Chronic lymphocytic leukaemia (CLL) is a heterogeneous disease with a variable clinical course, influenced by the diversity of genomic features inherent to the malignant CLL clone.^{1,2} In particular, the presence of *TP53* aberrations is a strong prognosticator of progressive disease (PD), progression-free survival (PFS) and overall survival (OS) in patients with CLL.^{1,2} *TP53* aberrations can arise through deletion of the *TP53* locus on chromosome 17 [del(17p)] or via mutations in the *TP53* gene, which encodes the tumour suppressor protein p53.³ Loss of functional p53 results in DNA repair disruption, inability of cell cycle arrest to occur normally in response to DNA damage and failure of normal

apoptosis to take place in response to DNA damage.³ Patients with CLL/small lymphocytic lymphoma (SLL) and *TP53* aberrations experience inferior outcomes with chemoimmunotherapy compared with patients without *TP53* aberrations.^{4–7} Moreover, the prevalence of *TP53* aberrations is increased in the relapsed/refractory setting relative to untreated patients as a result of selective expansion of chemoimmunotherapy-refractory *TP53*-aberrant subclones,^{8,9} highlighting the need to re-analyse *TP53* aberration status before each line of therapy to guide treatment selection.

Ibrutinib, a once-daily Bruton's tyrosine kinase (BTK) inhibitor, is the only targeted therapy to demonstrate both a significant PFS benefit (RESONATE, RESONATE-2, iLLUMINATE, Alliance A041202, ECOG-ACRIN E1912 and HELIOS) and OS

benefit (RESONATE, RESONATE-2, ECOG-ACRIN E1912 and HELIOS) in multiple randomised phase 3 studies in both previously untreated and relapsed/refractory CLL/SLL.^{10–15} Previous reports of single-agent ibrutinib or ibrutinib-based combination therapy have demonstrated favourable PFS benefit in patients with *TP53* aberrations in both the first-line and relapsed/refractory settings.^{10,14–17}

Given the poor outcomes in patients with *TP53* aberrations who receive chemimmunotherapy as first-line treatment, this predictive biomarker should be assessed before making treatment decisions in CLL.^{1,3,18,19} Although ibrutinib has demonstrated efficacy in study-specific subgroup analyses, there are limited data on long-term outcomes in patients with *TP53* aberrations treated with first-line ibrutinib.²⁰ Therefore, we performed a pooled analysis across four phase 2 and 3 studies to evaluate the long-term efficacy and safety of first-line ibrutinib-based therapy in patients with CLL bearing *TP53* aberrations.

Materials and methods

Pooled analysis

The pooled analysis included patients with *TP53* aberrations who received single-agent ibrutinib in PCYC-1122e (NCT01500733)²¹ or RESONATE-2 (PCYC-1115/16; NCT01722487)²² or an ibrutinib-based combination therapy with an anti-CD20 antibody in iLLUMINATE (PCYC-1130; NCT02264574)¹⁴ or ECOG-ACRIN E1912 (NCT02048813).¹² Detailed methods for each study were previously reported and baseline characteristics from each study are shown in Table S1. Briefly, in PCYC-1122e, patients with previously untreated CLL/SLL with *TP53* aberrations received single-agent oral ibrutinib (420 mg once daily) until PD or unacceptable toxicity.²¹ In RESONATE-2, patients aged ≥ 65 years with previously untreated CLL/SLL without del(17p) were randomised in a 1:1 ratio to receive single-agent oral ibrutinib (420 mg once daily) until PD or unacceptable toxicity, or up to 12 cycles of chlorambucil (0.5 mg/kg, increased up to 0.8 mg/kg as tolerated, on days 1 and 15 of each 28-day cycle).²² In iLLUMINATE, patients with previously untreated CLL/SLL aged ≥ 65 years or < 65 years with either co-existing conditions or del(17p)/*TP53* mutation were randomised 1:1 to receive ibrutinib (420 mg once daily) until PD or unacceptable toxicity plus six cycles of obinutuzumab (100 mg on day 1, 900 mg on day 2 and 1 000 mg on days 8 and 15 in cycle 1, then 1 000 mg on day 1 of each 28-day cycle) or six cycles of chlorambucil (0.5 mg/kg on days 1 and 15 of each 28-day cycle) plus obinutuzumab (as described for the ibrutinib plus obinutuzumab arm).¹⁴ In ECOG-ACRIN E1912, patients with previously untreated CLL/SLL aged ≤ 70 years without del(17p) were randomised 2:1 to receive ibrutinib (420 mg once daily) until PD or unacceptable toxicity plus rituximab (50 mg/m² on day 1 of cycle 2, 325 mg/m² on day 2 of cycle 2 and 500 mg/m² on day 1 of cycles 3 through 7)

or to six cycles of fludarabine (25 mg/m² on days 1–3) plus cyclophosphamide (250 mg/m² on days 1–3) plus rituximab (50 mg/m² on day 1 of cycle 1, 325 mg/m² on day 2 of cycle 1 and 500 mg/m² on day 1 of cycles 2 through 6).¹²

Each study protocol was approved by institutional review boards or independent ethics committees at participating institutions. Each study was conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines from the International Conference on Harmonisation. All patients provided written informed consent prior to screening.

Assessment of *TP53* aberrations

In the PCYC-1122e, RESONATE-2 and iLLUMINATE studies, fluorescence *in situ* hybridisation (FISH) testing for del(17p) was performed using a standard panel of probes for CLL. Testing was performed locally for PCYC-1122e and RESONATE-2 (or centrally in cases for which local results were unavailable) and centrally in iLLUMINATE. In the ECOG-ACRIN E1912 study, FISH testing was performed locally in accordance with each institute's standards. For PCYC-1122e, RESONATE-2 and iLLUMINATE, assessment of *TP53* mutations was performed centrally per European Research Initiative on Chronic Lymphocytic Leukemia (ERIC) guidelines.²³ For ECOG-ACRIN E1912, *TP53* mutation assessment was performed centrally at the Mayo Clinic, and mutations were identified per Mayo Clinic standard methods.

Outcomes

Clinical outcomes evaluated were PFS by investigator assessment, OS, overall response rate (ORR), complete response (CR) rate and safety. PFS and OS were estimated using the Kaplan–Meier method. ORR was assessed by investigators per 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines²⁴ in all four studies, and included CR, CR with incomplete haematological recovery, and partial response. Time on study was calculated based on the follow-up time of OS using reverse Kaplan–Meier estimates.

Data sharing statement

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

Results

Patients

The pooled analysis included 89 patients with *TP53* aberrations receiving first-line treatment with single-agent ibrutinib ($n = 45$) or ibrutinib in combination with an anti-CD20

antibody ($n = 44$). Median age was 65 years (range, 33–87) and 69% of patients were male (Table I). All patients had del(17p) and/or *TP53* mutation. Of 89 patients, 47 (53%) had del(17p); of the 58 patients with *TP53* sequencing results available, 53 (91%) had a *TP53* mutation. Among 16 patients with del(17p) who had *TP53* sequencing results available, 11 had both del(17p) and *TP53* mutations.

Median follow-up for all patients in the pooled analysis was 49.8 months (range, 0.1–95.9). At the time of analysis, 46% of patients ($n = 41$) continued to receive ibrutinib treatment, 35% ($n = 31$) of patients received ibrutinib for more than five years and 22% ($n = 20$) received ibrutinib for more than six years.

Efficacy

With a median follow-up of 49.8 months (up to 95.9 months), median PFS was not reached [95% CI: 67.3 months to not estimable (NE)] in the overall pooled population. The estimated four-year PFS rate was 79% (95% CI: 68–87; Figure 1A). For the 47 patients who had del(17p) only or *TP53* mutation only, median PFS was not reached (95% CI: 60.0 months to NE). For the 11 patients who had both del(17p) and *TP53* mutations, median PFS was 42.8 months (95% CI: 7.2 months to NE). For the 31 patients who had del(17p) and unknown *TP53* mutation status, median PFS was not reached (95% CI: 66.8 months to NE). In the overall pooled population, the four-year OS rate was 88% (95% CI: 78–93) (Figure 1B). Most patients (83/89) achieved a response, resulting in an ORR of 93% (95% CI: 86–98), including 39% who achieved a CR (Table II).

Table I. Baseline characteristics.

Characteristic	All patients $n = 89$
Median age (range), years	65 (33–87)
Age ≥ 65 years, n (%)	46 (52)
Male, n (%)	61 (69)
Rai stage, n (%)	
0–II	42 (47)
III/IV	47 (53)
Bulky disease (≥ 5 cm),* n (%)	33 (38)
Median lactate dehydrogenase level (range), [†] U/l	233 (52–2 568)
Unmutated IGHV, [‡] n (%)	60 (69)
Del(17p), n (%)	47 (53)
<i>TP53</i> mutation, [§] n (%)	53 (91)
Del(17p) and <i>TP53</i> mutation, [¶] n (%)	11 (69)

*Data available for 88 patients.

[†]Data available for 63 patients.

[‡]Data available for 87 patients.

[§]*TP53* sequencing results available for 58 patients.

[¶]Data available for 16 patients with del(17p) and *TP53* sequencing results.

Safety

At the time of analysis, the median duration of ibrutinib treatment was 45.9 months (range, 0.1–95.5; Table III). In the overall pooled population ($n = 89$), the prevalence of most grade ≥ 3 adverse events (AEs) of clinical interest was highest during the first year of ibrutinib treatment and generally decreased thereafter (Figure 2). Similarly, the prevalence of any-grade AEs of clinical interest, including hypertension, atrial fibrillation, infection and bleeding, generally declined over time; for example, hypertension occurred in 26/89 (29%), 24/81 (30%), 16/76 (21%), 10/57 (17%) and 5/41 (12%) patients in years 0–1, >1–2, >2–3, >3–4 and >4, respectively. Eighteen patients (20%) had a secondary malignancy, most commonly non-melanoma skin cancer ($n = 12$; 13%). Other secondary malignancies included melanoma ($n = 2$), prostate cancer ($n = 2$), plasma cell myeloma ($n = 1$) and unknown/neoplasm type not specified ($n = 4$).

Ibrutinib discontinuation and subsequent therapy

The most common primary reason for ibrutinib discontinuation was PD (Table III), with a total of 18 patients (20%). Three of the 18 patients had both del(17p) and *TP53* mutations and four of the 18 patients had *TP53* mutations in the absence of del(17p); the remaining 11 patients had del(17p), but *TP53* mutation data were not available. AEs were the primary reason for ibrutinib discontinuation in nine patients (10%), including three deaths (septic shock, sepsis without neutropenia and sudden death; Table III). Median duration of ibrutinib treatment for patients who discontinued because of an AE was 30.9 months (range, 0.2–71). Atrial fibrillation led to ibrutinib discontinuation in two patients. AEs leading to ibrutinib discontinuation in one patient each were anaemia, haemoptysis, platelet count decrease, pneumonia, rash, septic shock and death (cause unknown).

In the three studies (63 patients) that collected data for Richter's transformation, two transformations were noted as the PD event; time to transformation for these two patients was 0.4 months and 15.2 months.

The most common subsequent therapies initiated after discontinuing ibrutinib due to PD were novel agents (venetoclax-based regimens, $n = 11$; phosphoinositide 3 kinase inhibitor, $n = 1$; acalabrutinib, $n = 1$), chemoimmunotherapy ($n = 9$) and other ($n = 5$).

Discussion

Results from this large, pooled, multi-study dataset suggest a promising long-term outcome of first-line ibrutinib-based therapy in patients with CLL bearing *TP53* aberrations, with high estimated PFS (79%) and OS (88%) rates at four years and a median PFS that was not reached at the time of analysis. These results in the pooled population of patients with *TP53* aberrations are broadly consistent with long-term PFS

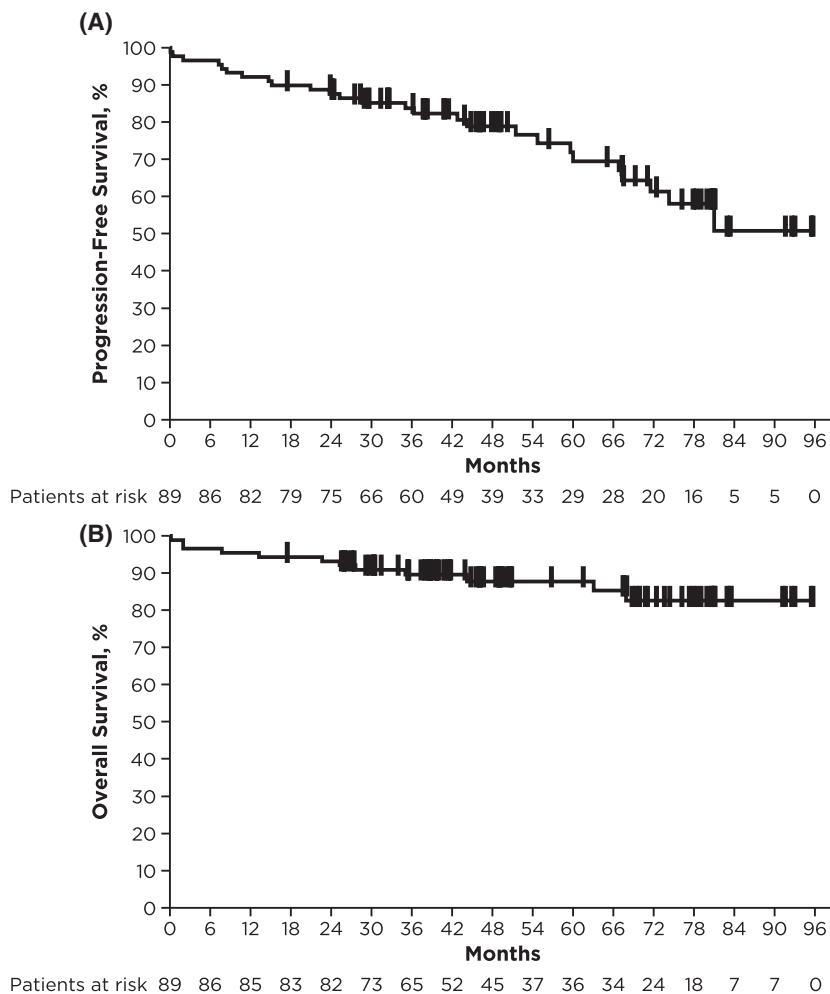


Fig 1. Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival^a in patients with *TP53* aberrations receiving first-line ibrutinib-based therapy. ^aThe patient who had the longest follow-up died at 96 months, resulting in an artefact for estimating median OS; this patient’s data were suppressed from the plot to correctly represent the population for which the median OS is not estimable.

and OS rates reported with ibrutinib-based therapy in the overall CLL patient populations in each of the included studies.^{10,12,14,17} The outcomes observed with first-line ibrutinib in this study are substantially better than those reported for patients with CLL bearing *TP53* aberrations treated with first-line chemoimmunotherapy, with three-year PFS and OS rates of only 18% and 38%, respectively, with fludarabine, cyclophosphamide and rituximab (FCR).⁷ With a median follow-up of more than five years, median PFS and OS with FCR were 11 months and 33 months respectively.²⁵ In the randomised Alliance study for patients with del(17p) treated with ibrutinib with or without rituximab, the median PFS was not reached compared to seven months for patients treated with bendamustine and rituximab ($P < 0.001$).¹⁵ In addition, there were more grade ≥ 3 haematological AEs with bendamustine and rituximab compared to the ibrutinib regimens.¹⁵ Despite the poor prognosis of patients with *TP53* aberrations treated with chemoimmunotherapy, data from the prospective, observational informCLLTM registry

Table II. Investigator-assessed overall response rate.

	All patients <i>n</i> = 89
ORR, <i>n</i> (%) [95% CI]	83 (93) [86–98]
CR, <i>n</i> (%) [95% CI]	35 (39) [29–50]
Best overall response, <i>n</i> (%)	
CR	35 (39)
PR	48 (54)
PR-L	1 (1)
Stable disease	2 (2)
Not available	3 (3)

CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis.

(*n* = 840) showed that chemotherapy and chemoimmunotherapy continue to be commonly used as first-line treatment in these patients, including 34% of those with

del(17p) and 36% with *TP53* mutations.²⁶ Given the favourable long-term survival data observed with ibrutinib-based therapy in our study, ibrutinib should be considered over chemoimmunotherapy as first-line therapy for patients with *TP53* aberrations. While four-year PFS rates with ibrutinib are higher than those reported after four years of follow-up with venetoclax and obinutuzumab (53%) in previously untreated patients with CLL and *TP53* aberrations,²⁷ it is difficult to make direct comparisons because of differences in the treatment schedules (continuous and fixed duration). Nonetheless, data from this analysis support guideline recommendations to use ibrutinib as first-line treatment for this group of high-risk patients.¹⁹

It remains unclear whether the presence of both del(17p) and *TP53* mutations (i.e. biallelic *TP53* disruption) is associated with poorer clinical outcomes than the presence of

del(17p) or *TP53* mutation alone in patients with CLL. Genomic profiling of 277 patients with CLL suggested that patients with biallelic *TP53* disruption had poorer OS than those with monoallelic disruption or wildtype *TP53*.²⁸ In the RESONATE study of single-agent ibrutinib in patients with relapsed/refractory CLL, patients with both del(17p) and *TP53* mutations trended toward shorter PFS compared with those who had neither del(17p) nor *TP53* mutations.¹⁰ Although only 11 patients with both del(17p) and *TP53* mutations were identified in the current pooled analysis, median PFS with first-line ibrutinib-based therapy appeared to be shorter for these patients than for patients with del(17p) only or *TP53* mutation only. These findings are similar to a previous study of patients with CLL and *TP53* aberrations.²⁹ Nonetheless, median PFS with first-line ibrutinib in this subgroup was still substantially longer than what has been reported with chemoimmunotherapy (43 months vs 11 months).²⁵ The BTK inhibitor zanubrutinib has also been evaluated in patients with CLL and a del(17p) mutation in a non-randomized cohort ($n = 109$ patients) of an open-label, multicentre, phase 3 study. The 18-month PFS rate with zanubrutinib was 88.6%^{30,31}; however, the long-term efficacy of zanubrutinib in del(17p) patients remains to be assessed. Long-term outcomes in patients with del(17p) mutation are important to inform expectations for treatment with BTK inhibitors.

Although our study has limitations inherent to pooled analyses, it represents a relatively large population of patients with CLL and *TP53* aberrations treated with a BTK inhibitor in the first-line setting. In addition, our analysis has the longest treatment follow-up for BTK inhibitors in such patients to date. Future studies with uniform, centralised testing of both del(17p) and *TP53* mutations may further aid in optimising the treatment and management of patients with CLL and *TP53* aberrations.

With a median follow-up of four years, first-line ibrutinib-based treatment resulted in sustained efficacy with

Table III. Patient disposition and treatment exposure.

	All patients $n = 89$
Treatment regimen, n (%)	
Single-agent ibrutinib	45 (51)
Ibrutinib plus anti-CD20 antibody	44 (49)
Median duration of ibrutinib therapy (range), months	45.9 (0.1–95.5)
Reason for ibrutinib discontinuation, n (%)	
Progressive disease	18 (20)
Study termination by sponsor	10 (11)
Adverse event	9 (10)
Withdrawal by patient	6 (7)
Death	3 (3)*
Investigator decision	2 (2)†
Remaining on ibrutinib at time of analysis, n (%)	41 (46)

*Causes of death were septic shock, sepsis without neutropenia and sudden death (presumed cardiac cause).

†One patient discontinued due to scheduled surgery.

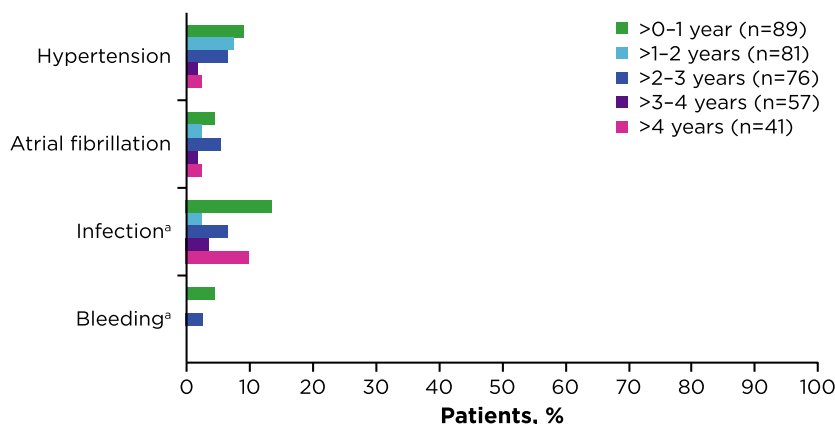


Fig 2. Prevalence of grade ≥ 3 adverse events of clinical interest by yearly interval. ^aCombined terms. Infection was identified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class term for Infections and infestations. Bleeding was identified using the Standardised MedDRA Query for Haemorrhage, excluding laboratory terms. [Colour figure can be viewed at wileyonlinelibrary.com]

high PFS and OS rates in patients with CLL and *TP53* aberrations, a population with historically poor outcomes. No new safety signals were identified in this analysis. Although patients with *TP53* aberrations remain at risk for disease progression, first-line treatment with ibrutinib has meaningfully improved the poor prognosis in this high-risk population.

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Author contributions

JNA and IEA designed the study in collaboration with the study sponsor. JNA, TS, AW, CM, SMO and IEA collected data. JPD and GK confirmed the accuracy of the data, interpreted the data and compiled it for analysis. JL performed the statistical analyses. All authors had full access to the data, contributed to data interpretation and attest to the accuracy of the data. All authors contributed to the manuscript preparation and approved the final version of the manuscript for submission.

Conflicts of interest

JNA: honoraria from AstraZeneca, Janssen, and AbbVie; consulting/advisory role for AstraZeneca, Pharmacyclics LLC, an AbbVie Company, BeiGene, AbbVie, Genentech, TG Therapeutics, Ascentage, ADC Therapeutics and Epizyme; research funding from Celgene, Genentech, AstraZeneca, TG Therapeutics and Janssen; and speakers bureau for AbbVie, Janssen, Pharmacyclics LLC, an AbbVie Company, AstraZeneca and BeiGene. TS: honoraria from Vanderbilt University, Cornell University, Eastside Health Network, Emory University, University of Nebraska, Columbia University, Memorial Sloan Kettering, Coalition for Physician Well-Being, Washington Hospital, Nevada Physician Wellness Coalition, St. Christopher's Hospital for Children, American Society for Nephrology, Lankenau Medical Center, Physicians' Education

Resource, Adventist Health Care, Advocate Health Care, Vancouver Physician Staff Association, Advent Health Care and Hospital for Special Surgery; research funding from Genentech, Pharmacyclics LLC, an AbbVie Company and AbbVie; and patents/royalties/other intellectual property with Mayo Clinic. AW: research funding from Pharmacyclics LLC, an AbbVie Company, Acerta, Merck, Nurix, Verastem and Genmab; and patents/royalties/other intellectual property with National Institutes of Health. CM: consulting/advisory role for Janssen, AbbVie, BioGene and AstraZeneca; research funding from AbbVie and Janssen; and speakers bureau for AbbVie and Janssen. SMO: consulting or advisory role for Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen, Aptose Biosciences, Vaniyam Group, AbbVie, Alexion, Verastem, Eisai, Juno Therapeutics, Vida Ventures, Autolus, Johnson & Johnson, Merck, Bristol Myers Squibb, Gilead, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics, Pfizer, NOVA Research Company and Sunesis; and research funding from Kite, Regeneron, Acerta, Gilead, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics, Pfizer, Caribou and Sunesis. JL: employment with AbbVie and Summit Therapeutics; and stock or other ownership with AbbVie, Summit Therapeutics, Gilead, Vertex Pharmaceuticals, ALX Oncology, I-Mab Biopharma, Surface Oncology, Moderna, Trillium Therapeutics, Pfizer, Novavax, BioMarin, Oncternal Therapeutics, Iovance Biotherapeutics, Fate Therapeutics, BeiGene, TG Therapeutics and Arbutus Biopharma. GK: employment with Pharmacyclics LLC, an AbbVie Company, AbbVie and Bristol Myers Squibb; stock or other ownership with AbbVie, Bristol Myers Squibb, Moderna, Dynavax and Inovio; and travel/accommodations/expenses from Bristol Myers Squibb. JPD: employment with Pharmacyclics LLC, an AbbVie Company; and stock or other ownership with AbbVie. IEA: nothing to disclose.

Supporting Information

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

Table SI. Baseline characteristics by study.

References

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for diagnosis, indications for treatment, response assessment and supportive management of chronic lymphocytic leukemia. *Blood*. 2018;131:15.
2. Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med*. 2020;383:460–73.
3. Campo E, Cymbalista F, Ghia P, Jäger U, Pospisilova S, Rosenquist R, et al. *TP53* aberrations in chronic lymphocytic leukemia: an overview of the clinical implications of improved diagnostics. *Haematologica*. 2018;103:1956–68.
4. Byrd JC, Gribben JG, Peterson BL, Grever MR, Lozanski G, Lucas DM, et al. Select high-risk genetic features predict earlier progression following chemoimmunotherapy with fludarabine and rituximab in chronic

- lymphocytic leukemia: justification for risk-adapted therapy. *J Clin Oncol*. 2006;**24**:437–43.
5. Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Döhner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;**123**:3247–54.
 6. Thompson PA, Tam CS, O'Brien SM, Wierda WG, Stingo F, Plunkett W, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;**127**:303–9.
 7. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, 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**:1164–74.
 8. Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature*. 2015;**526**:525–30.
 9. Rossi D, Khiabani H, Spina V, Ciardullo C, Brusca A, Famà R, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. *Blood*. 2014;**123**:2139–47.
 10. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, et al. Final analysis from RESONATE: up to 6 years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;**94**:1353–63.
 11. Burger JA, Barr PM, Robak T, Owen C, Ghia P, Tedeschi A, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;**34**:787–98.
 12. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;**381**:432–43.
 13. Fraser GAM, Chanan-Khan A, Demirkan F, Santucci Silva R, Grosicki S, Janssens A, et al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leuk Lymphoma*. 2020;**61**:3188–97.
 14. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;**20**:43–56.
 15. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;**379**:2517–28.
 16. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol*. 2016;**17**:1409–18.
 17. Ahn IE, Farooqui MZH, Tian X, Valdez J, Sun C, Soto S, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. *Blood*. 2018;**131**:2357–66.
 18. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. Version 2.2021. Plymouth Meeting, PA, National Comprehensive Cancer Network, 2021.
 19. Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;**32**:23–33.
 20. Ahn IE, Tian X, Wiestner A. Ibrutinib for chronic lymphocytic leukemia with TP53 alterations. *N Engl J Med*. 2020;**383**:498–500.
 21. Farooqui MZH, Valdez J, Martyr S, Aue G, Saba N, Niemann CU, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol*. 2015;**16**:169–76.
 22. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;**373**:2425–37.
 23. Malcikova J, Tausch E, Rossi D, Sutton LA, Soussi T, Zenz T, et al. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation. *Leukemia*. 2018;**32**:1070–80.
 24. Hallek M, Cheson B, Catavsky D. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase in peripheral blood lymphocytes. *Blood*. 2012;**119**:5348.
 25. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;**127**:208–15.
 26. Mato AR, Barrientos JC, Ghosh N, Pagel JM, Brander DM, Gutierrez M, et al. Prognostic testing and treatment patterns in chronic lymphocytic leukemia in the era of novel targeted therapies: results from the informCLL registry. *Clin Lymphoma Myeloma Leuk*. 2020;**20**:174–83.e173.
 27. Al-Sawaf O, Zhang C, Robrecht S, Tandon M, Panchal A, Fink A-M, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study. Presented at: EHA2021 Virtual; June 9–17, 2021. Abstract S146.
 28. Yu L, Kim HT, Kasar SN, Benien P, Du W, Hoang K, et al. Survival of Del17p CLL depends on genomic complexity and somatic mutation. *Clin Cancer Res*. 2017;**23**:735–45.
 29. Brieghel C, Aarup K, Torp MH, Andersen MA, Yde CW, Tian X, et al. Clinical outcomes in patients with multi-hit TP53 chronic lymphocytic leukemia treated with ibrutinib. *Clin Cancer Res*. 2021;**27**:4531–8.
 30. Brown JR, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Efficacy and safety of Zanubrutinib in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): follow-up results from arm C of the SEQUOIA (BGB-3111-304) trial. *Blood*. 2020;**136**:11–2.
 31. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. *Haematologica*. 2020;**106**:2354–63.