

## ORIGINAL ARTICLE

# Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease

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## ABSTRACT

**BACKGROUND**

The combination of ibrutinib and venetoclax has been shown to improve outcomes in patients with chronic lymphocytic leukemia (CLL) as compared with chemoimmunotherapy. Whether ibrutinib–venetoclax and personalization of treatment duration according to measurable residual disease (MRD) is more effective than fludarabine–cyclophosphamide–rituximab (FCR) is unclear.

**METHODS**

In this phase 3, multicenter, randomized, controlled, open-label platform trial involving patients with untreated CLL, we compared ibrutinib–venetoclax and ibrutinib monotherapy with FCR. In the ibrutinib–venetoclax group, after 2 months of ibrutinib, venetoclax was added for up to 6 years of therapy. The duration of ibrutinib–venetoclax therapy was defined by MRD assessed in peripheral blood and bone marrow and was double the time taken to achieve undetectable MRD. The primary end point was progression-free survival in the ibrutinib–venetoclax group as compared with the FCR group, results that are reported here. Key secondary end points were overall survival, response, MRD, and safety.

**RESULTS**

A total of 523 patients were randomly assigned to the ibrutinib–venetoclax group or the FCR group. At a median of 43.7 months, disease progression or death had occurred in 12 patients in the ibrutinib–venetoclax group and 75 patients in the FCR group (hazard ratio, 0.13; 95% confidence interval [CI], 0.07 to 0.24;  $P < 0.001$ ). Death occurred in 9 patients in the ibrutinib–venetoclax group and 25 patients in the FCR group (hazard ratio, 0.31; 95% CI, 0.15 to 0.67). At 3 years, 58.0% of the patients in the ibrutinib–venetoclax group had stopped therapy owing to undetectable MRD. After 5 years of ibrutinib–venetoclax therapy, 65.9% of the patients had undetectable MRD in the bone marrow and 92.7% had undetectable MRD in the peripheral blood. The risk of infection was similar in the ibrutinib–venetoclax group and the FCR group. The percentage of patients with cardiac severe adverse events was higher in the ibrutinib–venetoclax group than in the FCR group (10.7% vs. 0.4%).

**CONCLUSIONS**

MRD-directed ibrutinib–venetoclax improved progression-free survival as compared with FCR, and results for overall survival also favored ibrutinib–venetoclax. (Funded by Cancer Research UK and others; FLAIR ISRCTN Registry number, ISRCTN01844152; EudraCT number, 2013-001944-76.)

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\*A complete list of the trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on December 10, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2310063

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**C**HRONIC LYMPHOCYTIC LEUKEMIA (CLL) has an age-adjusted incidence rate of 6 per 100,000 persons. Two key pathophysiological pathways in CLL cells, proliferation mediated through B-cell receptor (BCR) signaling and resistance to apoptosis due to overexpression of B-cell lymphoma 2 (Bcl-2), lead to the accumulation of these cells, with tissue infiltration and immune dysfunction. Bruton's tyrosine kinase (BTK) is a key mediator of BCR signaling. Ibrutinib, an orally bioavailable, irreversible BTK inhibitor, blocks BCR signaling, thus preventing CLL-cell proliferation, migration, and adhesion.<sup>1</sup> Venetoclax, an orally bioavailable small-molecule inhibitor of Bcl-2, results in CLL-cell apoptosis.<sup>2</sup>

Because ibrutinib and venetoclax have discrete modes of action and different toxic effects, their combination is rational and has been investigated.<sup>3</sup> Synergy has been noted in preclinical models,<sup>4</sup> and CLL-cell mobilization by ibrutinib should render tumor cells more susceptible to venetoclax.<sup>5</sup> We previously assessed ibrutinib plus venetoclax in patients with relapsed–refractory CLL, with the duration of therapy defined by the time to undetectable measurable residual disease (MRD),<sup>6</sup> and found that the combination was efficacious and safe.

Toxicity limits the duration of chemoimmunotherapy, but with ibrutinib–venetoclax, no cumulative toxicity has been described. However, continuous therapy (e.g., with a BTK inhibitor) results in emerging resistance. Time-limited therapy is desirable to prevent resistance, allow immune recovery, and reduce costs. The GLOW<sup>7,8</sup> and CAPTIVATE<sup>5</sup> studies assessed 1 year of fixed-duration ibrutinib–venetoclax with compelling efficacy. Patients have differential responses to therapy, with some having rapid disease eradication and others having a slow response. The continuation of treatment for a defined period beyond the attainment of undetectable disease should result in deep responses and improve outcomes, prolong remission, and possibly cure. The FLAIR trial used an individualized duration of ibrutinib–venetoclax that is double the time taken to achieve undetectable MRD.

The FLAIR trial initially compared ibrutinib plus rituximab with fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated patients with CLL who were candidates for chemoimmunotherapy.<sup>9</sup> In 2017, FLAIR was adapted to include both ibrutinib monotherapy and ibrutinib–venetoclax with therapy duration

defined according to MRD. An interim analysis of ibrutinib monotherapy as compared with ibrutinib–venetoclax showed superiority of ibrutinib–venetoclax in achieving undetectable MRD.<sup>10,11</sup> Here, we present the results of a planned interim analysis comparing MRD-guided ibrutinib–venetoclax with FCR.

## METHODS

### TRIAL DESIGN AND PATIENTS

FLAIR is a phase 3, multicenter, open-label, parallel-group, randomized, controlled, adaptive trial platform involving patients with previously untreated CLL.<sup>12</sup> Patients were recruited from 96 hospitals in the United Kingdom (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Key inclusion criteria included previously untreated CLL or small lymphocytic lymphoma, with patients considered by the treating clinician to be fit for treatment with FCR. Key exclusion criteria were Richter's transformation, central nervous system involvement, and symptomatic cardiac disease. Also excluded were patients in whom more than 20% of CLL cells had chromosome 17p deletion, as identified by fluorescence in situ hybridization (FISH). Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix. Patients provided written informed consent.

The trial was performed in accordance with the principles of the Declaration of Helsinki. The ethics committee at each participating institution approved the protocol (available at NEJM.org). An independent data monitoring and ethics committee reviewed safety data throughout the trial until the interim analysis. The legal sponsor of the trial, the University of Leeds, was represented by the Leeds Cancer Research UK Clinical Trials Unit, which was responsible for data collection and medical review. The authors designed the trial; all the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors contributed to drafting the manuscript, and no one else contributed to writing the manuscript.

Ibrutinib was provided by Janssen, and venetoclax was provided by AbbVie. Unrestricted educational grants from Janssen, Pharmacyclics, and AbbVie supported trial coordination and laboratory studies; these companies had no other role in the trial.

### RANDOMIZATION AND PROCEDURES

Patients were assigned (in a 1:1:1 ratio) to receive FCR, ibrutinib monotherapy, or ibrutinib–venetoclax with the use of a minimization algorithm with a random element. Full details are provided in the Supplementary Appendix.

FCR was repeated every 28 days for six cycles in the absence of disease progression or unacceptable toxic effects. Ibrutinib was administered orally at a dose of 420 mg per day for 8 weeks before the initiation of venetoclax at a dose of up to 400 mg per day (see the Supplementary Appendix for details). Patients continued ibrutinib–venetoclax for a total of 6 years, unless the MRD stopping rules were reached or disease progression or unacceptable toxic effects occurred. The MRD stopping rules were based on an algorithm (Fig. S2 in the Supplementary Appendix).

### ASSESSMENTS AND END POINTS

The primary end point comparing MRD-guided ibrutinib–venetoclax with FCR was progression-free survival, defined as the time from randomization to progressive disease or death from any cause. Data from patients without an event were censored at the last follow-up. We have previously reported the results of an interim analysis comparing MRD-guided ibrutinib–venetoclax with ibrutinib monotherapy, with the primary end point being undetectable MRD within 2 years after randomization.

Secondary end points were overall survival, the proportion of patients with undetectable MRD at 9 months after randomization and longitudinally, the pattern of MRD relapse and retreatment, response to therapy (according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia) at 9 months after randomization and longitudinally, safety, toxic effects, health-related quality of life, and cost-effectiveness. The hierarchy of cytogenetic abnormalities was assessed, and progression-free survival among patients with various cytogenetic aberrations was analyzed. Adverse events were assessed at the start of each treatment cycle (see the Supplementary Appendix for details).

### STATISTICAL ANALYSIS

The interim analysis of progression-free survival comparing MRD-guided ibrutinib–venetoclax with FCR was conducted when either 50% of the total required events of disease progression or death had been observed (116 events) or 69 events had

been observed in the FCR group. The data-cutoff date was May 22, 2023. To ensure that an overall significance level of 5% was maintained for this comparison, the O'Brien and Fleming alpha-spending function was used with prespecified boundaries of 0.005 for the interim analysis and 0.048 for the final analysis.<sup>13</sup> The results of the interim analysis were considered to be significant ( $P \leq 0.005$ ). Therefore, the independent data monitoring and ethics committee recommended conducting the full analysis of primary and secondary end points.

For the primary end point, we estimated summaries of time to event according to treatment group using the Kaplan–Meier method, with corresponding 95% confidence intervals estimated by means of the Hall–Wellner method. We made comparisons between the randomly assigned groups using the Cox proportional-hazards model, with adjustment for the minimization factors (excluding trial center), to estimate hazard ratios and 95% confidence intervals. Details of secondary end-point and predefined subgroup analyses are provided in the Supplementary Appendix. No adjustment for multiple comparisons across the secondary end points was performed; results are reported with 95% confidence intervals, without *P* values, and the confidence intervals should not be used in place of hypothesis testing or to infer definitive treatment effects.

## RESULTS

### PATIENTS

Between July 20, 2017, and March 24, 2021, a total of 523 patients underwent randomization (260 in the ibrutinib–venetoclax group and 263 in the FCR group) (Fig. S3). Demographic and clinical characteristics were well balanced, including immunoglobulin heavy-chain variable region (*IGHV*) mutational status and cytogenetic abnormalities detected by means of FISH (Table 1). The median age of the patients was 62 years (interquartile range, 56 to 67); 163 (31.2%) were older than 65 years of age, and 373 (71.3%) were men. The representativeness of the trial population is shown in Table S1; the percentage of Black patients (2% of the trial population) was lower than the overall percentage of Black persons in the United Kingdom. Seven patients (1.3%) had chromosome 17p deletion (3 in the ibrutinib–venetoclax group and 4 in the FCR group). One patient in the ibrutinib–venetoclax

<b>Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*</b>			
<b>Characteristic</b>	<b>Ibrutinib–Venetoclax (N = 260)</b>	<b>FCR (N = 263)</b>	<b>Total (N = 523)</b>
<b>Age</b>			
Median (IQR) — yr	62 (55–67)	62 (57–67)	62 (56–67)
<b>Distribution — no. (%)</b>			
≤65 yr	179 (68.8)	181 (68.8)	360 (68.8)
>65 yr	81 (31.2)	82 (31.2)	163 (31.2)
<b>Sex — no. (%)</b>			
Male	186 (71.5)	187 (71.1)	373 (71.3)
Female	74 (28.5)	76 (28.9)	150 (28.7)
<b>Race or ethnic group — no. (%)†</b>			
White	233 (89.6)	240 (91.3)	473 (90.4)
Mixed: White and Black Caribbean or African	2 (0.8)	0	2 (0.4)
Other mixed background	1 (0.4)	1 (0.4)	2 (0.4)
Asian: Indian, Pakistani, or Bangladeshi	4 (1.5)	4 (1.5)	8 (1.5)
Other Asian background	1 (0.4)	1 (0.4)	2 (0.4)
Black: Caribbean or African	3 (1.2)	2 (0.8)	5 (1.0)
Other Black background	4 (1.5)	1 (0.4)	5 (1.0)
Other ethnic group	2 (0.8)	0	2 (0.4)
Not stated	10 (3.8)	14 (5.3)	24 (4.6)
<b>WHO performance-status score — no. (%)‡</b>			
0	181 (69.6)	181 (68.8)	362 (69.2)
1	69 (26.5)	69 (26.2)	138 (26.4)
2	8 (3.1)	8 (3.0)	16 (3.1)
Missing data	2 (0.8)	5 (1.9)	7 (1.3)
<b>Binet stage — no. (%)§</b>			
Progressive A or B	151 (58.1)	152 (57.8)	303 (57.9)
C	109 (41.9)	111 (42.2)	220 (42.1)
<b>B symptoms — no. (%)¶</b>			
Yes	128 (49.2)	121 (46.0)	249 (47.6)
No	130 (50.0)	136 (51.7)	266 (50.9)
Missing data	2 (0.8)	6 (2.3)	8 (1.5)
Median creatinine clearance (range) — ml/min	83.0 (40.0–231)	79.0 (37.0–247)	82.0 (37.0–247)
Median $\beta_2$ -microglobulin concentration (range) — mg/liter**	4.00 (1.90–14.3)	4.00 (1.70–13.1)	4.00 (1.70–14.3)
<b>Duration of CLL — mo††</b>			
Mean	37.9±44.9	33.7±34.0	35.8±40.0
Median (range)	23.3 (0.1–263)	21.4 (0.0–162)	22.8 (0.0–263)
<b>IGHV mutation status — no. (%)</b>			
Mutated	93 (35.8)	80 (30.4)	173 (33.1)
Unmutated	123 (47.3)	138 (52.5)	261 (49.9)
BCR subset 2 mutated	10 (3.8)	6 (2.3)	16 (3.1)
BCR subset 2 unmutated	3 (1.2)	7 (2.7)	10 (1.9)
Not available	31 (11.9)	32 (12.2)	63 (12.0)

**Table 1. (Continued)**

Characteristic	Ibrutinib–Venetoclax (N=260)	FCR (N=263)	Total (N=523)
Hierarchical genetic abnormalities — no. (%)			
TP53 deletion	1 (0.4)	0	1 (0.2)
ATM deletion	45 (17.3)	50 (19.0)	95 (18.2)
Trisomy 12	57 (21.9)	29 (11.0)	86 (16.4)
Normal karyotype	52 (20.0)	69 (26.2)	121 (23.1)
13q deletion	87 (33.5)	100 (38.0)	187 (35.8)
Undetermined	18 (6.9)	15 (5.7)	33 (6.3)

\* Plus–minus values are means  $\pm$ SD. The intention-to-treat population included all the patients who had undergone randomization. Percentages may not total 100 because of rounding. BCR denotes B-cell receptor, CLL chronic lymphocytic leukemia, FCR fludarabine–cyclophosphamide–rituximab, and IQR interquartile range.

† Race or ethnic group was reported by the patient.

‡ World Health Organization (WHO) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increased disability.

§ Binet stages indicate the degree of advancement of CLL and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.

¶ B symptoms consist of night sweats, unexplained fever (temperature  $>38^{\circ}\text{C}$ ), or loss of more than 10% of body weight.

|| Data were missing for 1 patient in the ibrutinib–venetoclax group.

\*\* Data were missing for 24 patients (12 in each group).

†† Data were missing for 70 patients (28 in the ibrutinib–venetoclax group and 42 in the FCR group).

group had chromosome 17p deletion in more than 20% of CLL cells on central laboratory assessment.

Of 239 patients in the FCR group who received at least one treatment cycle, 159 (66.5%) received 6 cycles. In the ibrutinib–venetoclax group, the median number of treatment cycles received was 27 (range, 2 to 72) for ibrutinib and 25 (range, 1 to 70) for venetoclax (Table S2). Dose modifications consisting of reductions, delays, and omissions were reported for 143 patients (55.0%) in the ibrutinib–venetoclax group and 144 (54.8%) in the FCR group (Table S3). Dose modifications were reported for 34 patients (13.1%) and 80 patients (30.8%) receiving ibrutinib–venetoclax up to 12 months and 12 to 24 months after randomization, respectively (Table S4). Early discontinuation of treatment was reported in 58 of 252 patients (23.0%) in the ibrutinib–venetoclax group and 62 of 239 patients (25.9%) in the FCR group. Reasons for discontinuation are detailed in Tables S5 and S6.

The duration of ibrutinib–venetoclax therapy was determined according to the MRD-directed approach, with 146 of 260 patients stopping treatment owing to MRD stopping rules after 24 to 60 months of ibrutinib–venetoclax treatment (Table S7 and Fig. S4). Kaplan–Meier estimates

of the percentage of patients who had stopped treatment by specific time points are as follows: by 24 months, 28.9%; by 36 months, 58.0%; and by 60 months, 78.4%. Five patients restarted ibrutinib–venetoclax and were alive and progression-free at the last follow-up.

A total of 42 patients in the FCR group received treatment after progression or withdrawal. Of these 42 patients, 35 received targeted therapies (13 received acalabrutinib, 11 received venetoclax-based therapy, 9 received ibrutinib, and 1 each received idelalisib and zanubrutinib), 6 received chemoimmunotherapy, and 1 received an allogeneic bone marrow transplant. In the ibrutinib–venetoclax group, 5 patients received subsequent therapies. One each received acalabrutinib, alemtuzumab, ibrutinib, pirtobrutinib, and chemoimmunotherapy.

#### EFFICACY

After a median follow-up of 43.7 months (interquartile range, 35.1 to 51.5), disease progression or death had occurred in 12 patients (4.6%) in the ibrutinib–venetoclax group and 75 (28.5%) in the FCR group. The estimated 3-year progression-free survival was 97.2% (95% confidence interval [CI], 94.1 to 98.6) with ibrutinib–venetoclax and

76.8% (95% CI, 70.8 to 81.7) with FCR. Annual progression-free survival estimates are provided in Table S8. The hazard ratio for disease progression or death (ibrutinib–venetoclax vs. FCR) was 0.13 (95% CI, 0.07 to 0.24;  $P < 0.001$ ) (Fig. 1A). Results for progression-free survival also favored ibrutinib–venetoclax as compared with FCR in patients with unmutated *IGHV* (hazard ratio for disease progression or death, 0.07; 95% CI, 0.02 to 0.19) (Fig. 1B) but not in those with mutated *IGHV* (hazard ratio, 0.54, 95% CI, 0.21 to 1.38) (Fig. 1C). In a subgroup analysis, the benefit of ibrutinib–venetoclax with respect to progression-free survival was seen across all subgroups except patients with mutated *IGHV* (Figs. S5 and S6).

Death occurred in 9 patients (3.5%) in the ibrutinib–venetoclax group and 25 (9.5%) in the FCR group. The 3-year overall survival was 98.0% (95% CI, 95.2 to 99.2) with ibrutinib–venetoclax and 93.0% (95% CI, 88.9 to 95.6) with FCR. Annual overall survival estimates are provided in Table S9. The hazard ratio for death (ibrutinib–venetoclax vs. FCR) was 0.31 (95% CI, 0.15 to 0.67) (Fig. 2A). Results for overall survival appeared to favor ibrutinib–venetoclax as compared with FCR in patients with unmutated *IGHV* (hazard ratio for death, 0.23; 95% CI, 0.06 to 0.81) (Fig. 2B) but not in those with mutated *IGHV* (hazard ratio, 0.61, 95% CI, 0.20 to 1.82) (Fig. 2C). Subgroup analyses suggested benefit of ibrutinib–venetoclax with respect to overall survival across all subgroups except patients with mutated *IGHV* (Figs. S7 and S8).

The percentage of patients with undetectable MRD in bone marrow at 2 years was 52.4% (95% CI, 45.9 to 58.9) in the ibrutinib–venetoclax group and 49.8% (95% CI, 43.2 to 56.5) in the FCR group (Fig. S9A). The percentage at 5 years was 65.9% (95% CI, 59.5 to 72.3) and 49.8% (95% CI, 43.2 to 56.5), respectively. The median time to first undetectable MRD in peripheral blood was 12.0 months (95% CI, 11.5 to 17.3) with ibrutinib–venetoclax and 8.9 months (95% CI, 8.5 to 9.1) with FCR (Fig. S9B). The percentage of patients with undetectable MRD in peripheral blood at 1 year was 47.5% (95% CI, 41.2 to 53.7) in the ibrutinib–venetoclax group and 66.0% (95% CI, 60.0 to 72.1) in the FCR group. The percentage at 5 years was 92.7% (95% CI, 88.1 to 97.3) and 67.9% (95% CI, 61.9 to 73.9), respectively. Annual estimates of undetectable MRD are provided in Tables S10 and S11.

At 9 months after randomization, undetectable MRD in bone marrow was attained in 108 patients (41.5%; 95% CI, 35.5 to 47.8) in the ibrutinib–venetoclax group and 127 (48.3%; 95% CI, 42.1 to 54.5) in the FCR group (Table S12). The cumulative incidence of MRD negativity in peripheral blood increased throughout ibrutinib–venetoclax treatment but not with FCR (Table S13). Undetectable MRD in bone marrow at any time was reported in 161 patients (61.9%) in the ibrutinib–venetoclax group and 106 (40.3%) in the FCR group. Similarly, undetectable MRD in peripheral blood at any time was reported in 223 patients (85.8%) in the ibrutinib–venetoclax group and 160 (60.8%) in the FCR group. The adjusted odds ratio of having undetectable MRD at any time (ibrutinib–venetoclax vs. FCR) was 2.03 (95% CI, 1.43 to 2.89) in bone marrow and 3.91 (95% CI, 2.55 to 6.00) in peripheral blood.

At 9 months after randomization, an overall response had occurred in 225 patients (86.5%; 95% CI, 81.8 to 90.4) in the ibrutinib–venetoclax group and 201 patients (76.4%; 95% CI, 70.8 to 81.4) in the FCR group. Similar results occurred for complete response: 154 patients (59.2%; 95% CI, 53.0 to 65.3) in the ibrutinib–venetoclax group and 129 patients (49.0%; 95% CI, 42.9 to 55.3) in the FCR group (Table S14). The adjusted odds ratio (ibrutinib–venetoclax vs. FCR) was 2.00 (95% CI, 1.26 to 3.16) for overall response and 1.51 (95% CI, 1.07 to 2.14) for complete response.

#### SAFETY

Of 491 patients in the safety population, 450 (91.6%) reported at least one adverse event. The most common grade 3 to 5 adverse events occurring within 1 year after randomization were neutropenia (in 26 of 252 patients [10.3%] in the ibrutinib–venetoclax group and in 113 of 239 patients [47.3%] in the FCR group), anemia (in 2 [0.8%] and in 37 [15.5%], respectively), and thrombocytopenia (in 5 [2.0%] and in 24 [10.0%]) (Table 2). Common adverse events of any grade were fatigue (in 39 patients [15.5%] in the ibrutinib–venetoclax group and in 117 [49.0%] in the FCR group) and neutropenia (in 49 [19.4%] and in 140 [58.6%], respectively) (Table 2). A total of 15 grade 3 adverse events involving febrile neutropenia occurred in 13 patients (5.4%) in the FCR group; none occurred in the ibrutinib–venetoclax group. Common adverse events after 1 year in the ibrutinib–venetoclax group are shown in Table S15.

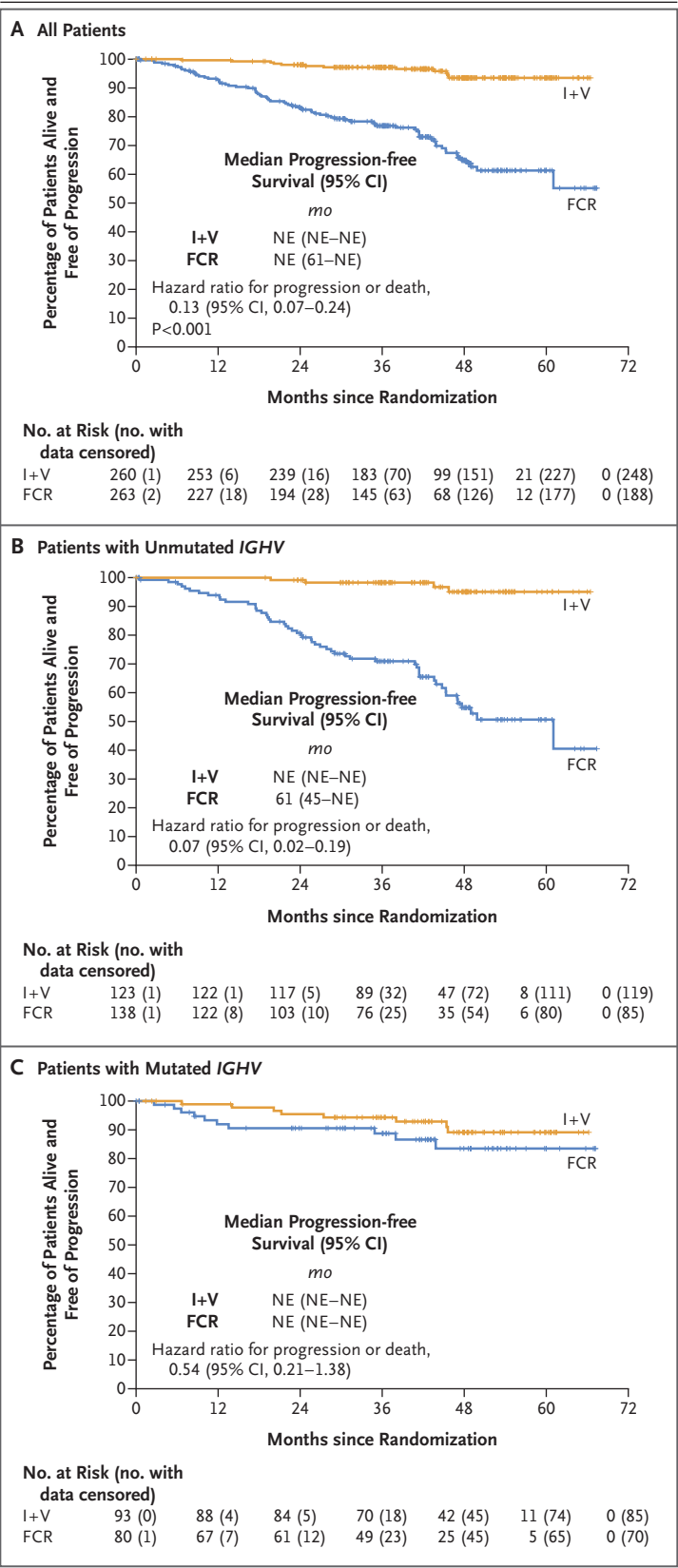
**Figure 1. Progression-free Survival.**

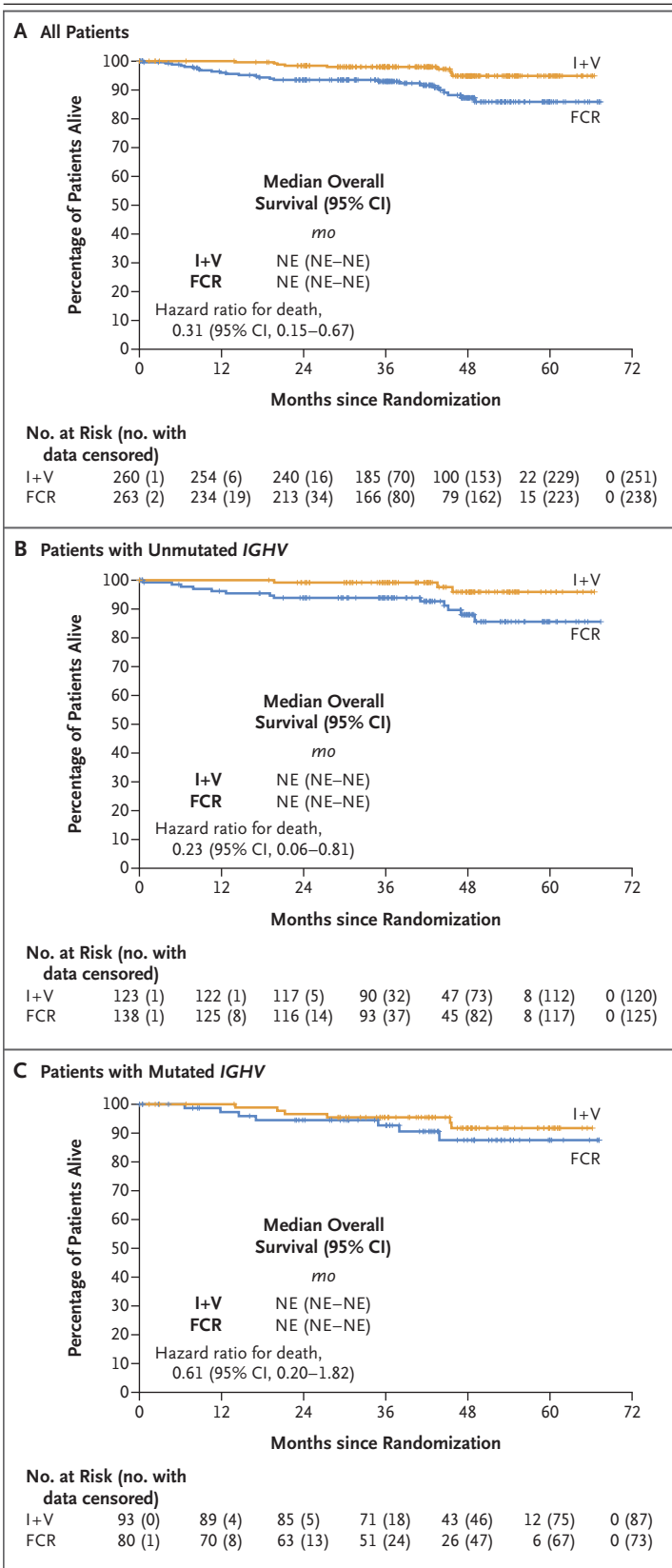
Ibrutinib–venetoclax (I+V) was superior to fludarabine–cyclophosphamide–rituximab (FCR) with respect to progression-free survival in the total population (Panel A). Ibrutinib–venetoclax had a greater effect on progression-free survival among patients with unmutated *IGHV* (Panel B) than among those with mutated *IGHV* (Panel C). Tick marks indicate censored data. NE denotes could not be estimated.

During the trial, 80 adverse events involving hypertension occurred in 34 patients (13.5%) in the ibrutinib–venetoclax group, and 14 such events occurred in 4 patients (1.7%) in the FCR group. A total of 62 adverse events involving atrial fibrillation or arrhythmia occurred in 34 patients (13.5%) in the ibrutinib–venetoclax group, and 9 such events occurred in 4 patients (1.7%) in the FCR group. Granulocyte colony-stimulating factor was used in 56 of 260 patients (21.5%) in the ibrutinib–venetoclax group and in 149 of 263 patients (56.7%) in the FCR group.

A total of 416 serious adverse events were reported in 252 patients at any time: 194 events in 123 patients in the ibrutinib–venetoclax group and 222 events in 129 patients in the FCR group (Table S16). The most common serious adverse events were infections and infestations, which occurred in 101 patients (56 in the ibrutinib–venetoclax group and 45 in the FCR group). Serious adverse events involving the blood and lymphatic systems occurred in a higher percentage of patients in the FCR group than in the ibrutinib–venetoclax group (31.0% vs. 5.2%). Cardiac serious adverse events occurred in a higher percentage of patients in the ibrutinib–venetoclax group than in the FCR group (10.7% vs. 0.4%). A total of 23 adverse events of special interest (including major hemorrhage and tumor lysis syndrome) were reported in 21 patients (18 in the ibrutinib–venetoclax group and 3 in the FCR group). Eight major hemorrhages were reported (5 in the ibrutinib–venetoclax group and 3 in the FCR group). In the ibrutinib–venetoclax group, clinical tumor lysis syndrome was reported in 1 patient, and biochemical tumor lysis syndrome was reported in 14 patients; all cases resolved when managed according to the protocol.

Death occurred in 8 patients who received ibrutinib–venetoclax and 23 who received FCR (Table S17). Local investigators determined that death was probably related to treatment in 1 of





**Figure 2. Overall Survival.**

Ibrutinib–venetoclax had an apparent benefit with respect to overall survival in the total population (Panel A). Ibrutinib–venetoclax had a greater effect on overall survival among patients with unmutated *IGHV* (Panel B) than among those with mutated *IGHV* (Panel C). Tick marks indicate censored data.

8 patients in the ibrutinib–venetoclax group and 6 of 23 patients in the FCR group. The most common causes in the FCR group were infections (in 10 patients [43%], 2 of whom died from coronavirus disease 2019 [Covid-19]) and secondary cancers (in 8 patients [35%]). Sudden unexplained or cardiac death occurred in 2 patients in the FCR group. The causes in the ibrutinib–venetoclax group were infections (in 3 patients, 2 of whom died from Covid-19), sudden unexplained or cardiac death (in 3 patients), and secondary cancers (in 2 patients). Of the 3 cases of sudden unexplained or cardiac death in the ibrutinib–venetoclax group, 2 occurred after the end of treatment (35 days and 411 days later) and were considered by local investigators to be probably unrelated to treatment.

A total of 24 secondary cancers occurred in 17 patients in the ibrutinib–venetoclax group, and 45 secondary cancers occurred in 34 patients in the FCR group (Table S18). Myelodysplastic syndrome or acute myeloid leukemia developed in 1 patient in the ibrutinib–venetoclax group and 8 patients in the FCR group. Richter’s transformation developed in 4 patients in the FCR group and 1 patient in the ibrutinib–venetoclax group. The incidence of other cancers per 100 patient-years was 2.6 (95% CI, 2.4 to 2.8) in the ibrutinib–venetoclax group and 5.4 (95% CI, 5.1 to 5.7) in the FCR group (hazard ratio, 0.43; 95% CI, 0.23 to 0.77) (Table S19).

**DISCUSSION**

In this cohort of the FLAIR trial in which patients with previously untreated CLL were randomly assigned to receive ibrutinib–venetoclax, ibrutinib monotherapy, or FCR, we found that MRD-guided ibrutinib–venetoclax was superior to FCR with respect to progression-free survival (97.2% vs. 76.8% at 3 years); results for overall survival also favored ibrutinib–venetoclax over FCR (98.0% vs. 93.0% at 3 years). The results appear better than those in previous studies of



**Table 2. Adverse Events, According to Maximum Grade, within 1 Year after Randomization (Safety Population).\***

Adverse Event	Ibrutinib–Venetoclax (N=252)				FCR (N=239)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
	<i>number of patients (percent)</i>							
Acute kidney injury	0	0	0	0	4 (1.7)	3 (1.3)	0	0
Anemia	24 (9.5)	2 (0.8)	0	0	50 (20.9)	33 (13.8)	4 (1.7)	0
Atrial fibrillation or arrhythmia	10 (4.0)	2 (0.8)	0	0	4 (1.7)	0	0	0
Constipation	8 (3.2)	1 (0.4)	0	0	60 (25.1)	0	0	0
Cough	4 (1.6)	0	0	0	45 (18.8)	4 (1.7)	0	0
Diarrhea	58 (23.0)	2 (0.8)	0	0	46 (19.2)	6 (2.5)	0	0
Dyspnea	10 (4.0)	0	0	0	22 (9.2)	3 (1.3)	1 (0.4)	0
Fatigue	38 (15.1)	1 (0.4)	0	0	108 (45.2)	9 (3.8)	0	0
Febrile neutropenia	0	0	0	0	0	13 (5.4)	0	0
Fever	5 (2.0)	0	0	0	57 (23.8)	17 (7.1)	0	0
Headache	10 (4.0)	0	0	0	31 (13.0)	1 (0.4)	0	0
Hemolysis or hemolytic anemia	0	0	0	0	3 (1.3)	3 (1.3)	0	0
Hypertension	6 (2.4)	6 (2.4)	0	0	3 (1.3)	1 (0.4)	0	0
Infections and infestations, other	1 (0.4)	0	0	0	0	3 (1.3)	0	0
Infusion-related reaction	0	0	0	0	64 (26.8)	2 (0.8)	1 (0.4)	0
Lung infection	0	0	0	0	3 (1.3)	3 (1.3)	1 (0.4)	0
Lymphocyte count decreased	4 (1.6)	0	0	0	4 (1.7)	4 (1.7)	4 (1.7)	0
Nausea	43 (17.1)	3 (1.2)	0	0	138 (57.7)	1 (0.4)	0	0
Neutropenia	23 (9.1)	16 (6.3)	10 (4.0)	0	27 (11.3)	53 (22.2)	60 (25.1)	0
Other	24 (9.5)	7 (2.8)	0	0	26 (10.9)	7 (2.9)	0	1 (0.4)
Platelet count decreased	39 (15.5)	3 (1.2)	2 (0.8)	0	65 (27.2)	16 (6.7)	8 (3.3)	0
Rash	26 (10.3)	1 (0.4)	0	0	66 (27.6)	5 (2.1)	0	0
Sepsis	0	0	0	0	0	10 (4.2)	4 (1.7)	0
Skin infections	2 (0.8)	0	0	0	3 (1.3)	3 (1.3)	0	0
Taste alteration or loss of appetite	4 (1.6)	0	0	0	30 (12.6)	0	0	0
Upper respiratory infection	6 (2.4)	1 (0.4)	0	0	24 (10.0)	8 (3.3)	0	0
Vomiting	15 (6.0)	1 (0.4)	0	0	65 (27.2)	5 (2.1)	0	0

\* The safety population included all the patients who had undergone randomization and received at least one treatment cycle. Shown are adverse events of any grade that occurred in at least 10% of the patients in either treatment group and adverse events of grade 3 or higher that occurred in at least 1% of the patients in either treatment group.

ibrutinib monotherapy or venetoclax, as monotherapy or in combination with anti-CD20.<sup>14,15</sup>

The MRD-driven approach in the FLAIR trial led 28.9% of the patients in the ibrutinib–venetoclax group to stop therapy by 2 years, and 58.0% had stopped therapy by 3 years. No plateau was seen in achievement of undetectable MRD in peripheral blood, which suggests that continued therapy informed by MRD is justified. In the CAPTIVATE study,<sup>16</sup> the duration of ibrutinib–

venetoclax was defined by MRD (either 12 months or 24 months); among those who received a course of 15 to 24 months, 77% had undetectable MRD in peripheral blood.

In the GLOW study,<sup>7,8</sup> ibrutinib–venetoclax was given for 12 months in all patients, and 54.7% had undetectable MRD in peripheral blood 3 months after the end of therapy. In the FLAIR trial, 47.5% had undetectable MRD in peripheral blood after 12 months of ibrutinib–venetoclax,

but this value increased to 92.7% with continued therapy, which suggests that 12 months of ibrutinib–venetoclax is insufficient for many patients. In the GLOW study, 80.5% of the patients in the ibrutinib–venetoclax group were progression-free after 30 months. In the GAIA–CLL13 trial, patients received 12 months of either venetoclax–obinutuzumab or ibrutinib–venetoclax–obinutuzumab (IVO), with ibrutinib continued for up to 3 years if MRD was detectable at 12 months. At 15 months, undetectable MRD in peripheral blood was attained in 86.5% of the patients receiving venetoclax–obinutuzumab and 92.2% of those receiving IVO; 3-year progression-free survival was 87.7% and 90.5%, respectively.<sup>15</sup> In our trial, progression-free survival for MRD-guided ibrutinib–venetoclax was 97.2% at 3 years.

The positive outcome of the FLAIR trial appeared most marked in patients with *IGHV*-unmutated CLL, with substantial improvements in progression-free and overall survival. However, a benefit was not observed in patients with *IGHV*-mutated CLL. MRD-defined ibrutinib–venetoclax resulted in better outcomes than FCR in all conventional cytogenetic subgroups, with particularly marked improvement in patients with *ATM*-deleted CLL.

The combination of ibrutinib and venetoclax was associated with no new safety concerns. Cardiac arrhythmias remain a concern. In an earlier cohort of the FLAIR trial,<sup>9</sup> sudden deaths were reported more frequently with ibrutinib–rituximab than with FCR. An amendment incorporated stricter monitoring of cardiac-associated risk factors that were identified in the earlier FLAIR report. In the current trial, more cases of atrial fibrillation and hypertension were reported in the ibrutinib–venetoclax group than in the FCR group (findings that were consistent with previous findings), but these results did not translate into an increased risk of sudden death. Whether these findings illustrate the effect of changes in the management of hypertension and cardiac side effects cannot be ascertained. Severe infections were more commonly reported with FCR than with ibrutinib–venetoclax. Tumor lysis syndrome was more common in the ibrutinib–venetoclax group, but only a single clinical case was reported.

The CLL treatment landscape has been trans-

formed by targeted drugs. Continuous BTK inhibitor therapy has improved outcomes in patients with CLL. Fixed-duration venetoclax in combination with obinutuzumab or ibrutinib has also been shown to improve patient outcomes. However, only trends toward improvement in overall survival have been seen as compared with chlorambucil and obinutuzumab. These approaches are based on the principle that “one size fits all,” and therapy is not individualized on the basis of response. Using MRD to define the duration of ibrutinib–venetoclax treatment, as in the FLAIR trial, may result in improved outcomes, allowing the individualization of therapy based on response in real time.

Trials that are stopped early for efficacy may overestimate effect size.<sup>17</sup> However, with stringent, predefined stopping rules<sup>18</sup> and reporting of a significant proportion of required events,<sup>19</sup> stopping early should have a negligible effect on estimates. Patients in the FLAIR trial will continue to be followed until the final analysis.

In this trial, MRD-guided ibrutinib–venetoclax, including individualized treatment duration beyond undetectable MRD, resulted in significant improvement in progression-free survival and an apparent benefit with respect to overall survival among patients with previously untreated CLL. Benefits appeared to be particularly marked in patients who tend to have poorer outcomes with standard treatments (e.g., those with unmutated *IGHV* and certain genetic abnormalities).

Supported by a grant (C18027/A15790) from Cancer Research UK; by unrestricted educational grants from Janssen, Pharmaceutics, and AbbVie that supported trial coordination and laboratory studies; and by a grant (C7852/A25447) for Core Clinical Trials Unit Infrastructure from Cancer Research UK.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the patients at centers throughout the United Kingdom whose participation made this trial possible; the members of the U.K. National Cancer Research Institute Hematological Oncology Study Group and all the principal investigators, subinvestigators, and local center staff for their dedication and commitment to recruiting patients to the trial; the members of the trial steering committee and data monitoring and ethics committee; the staff of the Clinical Trials Research Unit at the University of Leeds for their contribution to the successful running of the trial; the laboratory team at the Hematological Malignancy Diagnostic Service, St. James's University Hospital, where central laboratory analysis was performed; and the staff of the UK CLL Trials Biobank, University of Liverpool, for their collaboration.

## APPENDIX

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