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Title:

Measurable Residual Disease-Guided Therapy for Chronic Lymphocytic Leukemia

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ABSTRACT

BACKGROUND

Ibrutinib-venetoclax improves CLL outcomes as assessed by achieving undetectable measureable residual disease (MRD) as compared to chemoimmunotherapy. In this follow up, we determined if ibrutinib-venetoclax is more likely to improve progression-free survival and overall survival than ibrutinib alone or fludarabine-cyclophosphamide-rituximab (FCR).

METHODS

In this phase III, multicenter, randomized-controlled, open-label trial, patients were randomized to receive ibrutinib+venetoclax, ibrutinib alone, or FCR. The primary endpoint for ibrutinib-venetoclax vs ibrutinib was uMRD (sensitivity 10^{-4}) in BM at two years after initiation of therapy and for ibrutinib-venetoclax vs FCR was progression-free survival. A powered secondary endpoint for ibrutinib-venetoclax vs ibrutinib was progression-free survival. Other secondary endpoints were overall survival, MRD, iwCLL response and safety.

RESULTS

786 patients were randomized to receive FCR, ibrutinib or ibrutinib-venetoclax. Within two-years, 299 participants achieved uMRD in BM: 127/263 FCR (48.3%), 0/263 ibrutinib (0%) and 172/260 ibrutinib-venetoclax (66.2%) ($p<0.001$). At a median of 62.2 months, disease progression or death had occurred in 112 FCR, 59 ibrutinib and 18 ibrutinib-venetoclax participants. 5-year progression-free survival was 58.1% with FCR, 79.0% with ibrutinib and 93.9% with ibrutinib-venetoclax.

Hazard ratio (HR) for progression-free survival was: 0.13 (95% CI, 0.08 to 0.21, p<0.001) for ibrutinib-venetoclax vs FCR; 0.29 (95% CI, 0.17 to 0.49, p<0.001) for ibrutinib-venetoclax vs ibrutinib, and 0.44 (95% CI, 0.32 to 0.60) for ibrutinib vs FCR. Deaths occurred in 76: 39 FCR, 26 ibrutinib,11 ibrutinib-venetoclax. HR for overall survival was: 0.26 (95% CI, 0.13 to 0.50) for ibrutinib-venetoclax vs FCR; 0.41 (95% CI, 0.20 to 0.83) for ibrutinib-venetoclax vs ibrutinib and 0.64 (95% CI, 0.39 to 1.05) for ibrutinib vs FCR. Fifteen patients had sudden/cardiac deaths: 4 FCR, 8 ibrutinib, 3 ibrutinib-venetoclax.

CONCLUSION:

With extended follow-up and increased enrollment, CLL patients treated with ibrutinib-venetoclax had higher rates of uMRD, extended progression-free survival and increased overall survival than those treated with ibrutinib alone or FCR.
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INTRODUCTION

Chronic lymphocytic leukemia (CLL) affects approximately 4.6 per 100,000 persons.[1] In CLL, malignant B cells proliferate autonomously through B-cell receptor (BCR) dependent signalling using Bruton's tyrosine kinase (BTK) and fail to undergo apoptosis due in part to overexpression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2). Ibrutinib, an oral BTK inhibitor, blocks BCR signalling, thus reducing CLL-cell proliferation, migration and adhesion. Venetoclax is an oral small-molecule inhibitor of Bcl-2, leading to CLL cell apoptosis.

Continuous BTK inhibitor therapy leads to improved outcomes but can induce resistance and toxicity. Due to their discrete modes of action, the combination of ibrutinib and venetoclax has been studied in pre-clinical models and clinical trials[2]. GLOW and CAPTIVATE trials studied ibrutinib-venetoclax 15 months fixed-duration combination, leading to improved progression-free survival.[3,4] In relapsed-refractory CLL, ibrutinib-venetoclax combination using eradication of detectable measurable residual disease (MRD) to guide duration of therapy, demonstrated that individualizing therapy was feasible.[5]

The FLAIR trial was adapted to include ibrutinib monotherapy and ibrutinib-venetoclax combination using MRD-guided duration of therapy, comparing it to FCR in previously untreated CLL patients. Ibrutinib-venetoclax reported superiority to FCR previously in progression-free and overall survival.[6] Here, we present the pre-planned analysis comparing MRD-guided ibrutinib-venetoclax with ibrutinib and FCR with extended follow-up.

METHODS

TRIAL DESIGN AND PATIENTS:

FLAIR is a phase III, multicenter, open-label, parallel-group, randomized, controlled, adaptive trial platform involving patients with previously untreated CLL (see Figure S1).[7] Patients were recruited from 99 hospitals in the United Kingdom (see the Appendix).

Key inclusion criteria included previously untreated CLL or small lymphocytic lymphoma requiring treatment; considered fit for FCR, between 18 and 75 years of age. Key exclusion criteria were Richter's transformation, symptomatic cardiac disease and >20% 17p deletion assessed by FISH. For detailed inclusion and exclusion criteria see the Appendix. Participants provided written informed consent.

The trial was performed in accordance with the Declaration of Helsinki. A national ethics committee and institutional review boards approved the protocol. An independent data monitoring committee reviewed safety throughout the trial. The trial sponsor, the University of Leeds, was responsible for data collection and medical review. The authors designed the trial, vouch for the accuracy and completeness of the data, and adherence to the protocol (available at NEJM.org). All the authors contributed to drafting the manuscript. No one who is not an author contributed to writing the manuscript.

RANDOMIZATION AND PROCEDURES

Participants were randomly assigned (1:1:1) to receive FCR, ibrutinib or ibrutinib-venetoclax with the use of a computer-generated minimization algorithm with a random element. For full details see the Appendix.

FCR was repeated every 28 days for six cycles. Ibrutinib monotherapy was administered orally 420 mg/day for six years. In the ibrutinib-venetoclax group, ibrutinib was administered orally 420 mg/day for 8 weeks before venetoclax was incrementally escalated to 400 mg/day over 5 weeks. Participants continued ibrutinib-venetoclax or ibrutinib for 6 years, unless the MRD stopping rules were met or unacceptable toxicity or disease progression occurred. The MRD stopping rules were based on an algorithm (Fig S2 in Appendix) so that patients received therapy for twice the duration of time taken to achieve first uMRD in blood. At the end of six years, participants in either ibrutinib group were allowed to enrol on the STATIC trial (ISRCTN51675454), stop ibrutinib or receive other standard therapy. STATIC is currently recruiting UK FLAIR participants who received six years of ibrutinib, randomized to continuous or intermittent therapy with ibrutinib.

ASSESSMENTS AND ENDPOINTS

The primary endpoint comparing MRD-guided ibrutinib-venetoclax with ibrutinib was uMRD in the bone marrow within 2 years after randomization. The primary endpoint comparing MRD-guided ibrutinib-venetoclax with FCR was progression-free survival. A powered secondary endpoint comparing MRD-guided ibrutinib-venetoclax with ibrutinib was progression-free survival.

Other secondary endpoints were overall survival, the proportion of participants with uMRD at 9 months after randomization and longitudinally, pattern of MRD relapse and retreatment, response to therapy (according to the IWCLL criteria), safety and toxicity, health-related quality of life, and cost-effectiveness. The hierarchy of cytogenetic abnormalities was assessed.

STATISTICAL ANALYSIS

The final analysis of the primary endpoint was conducted when the final participant reached two years post-randomization. All reported p-values were two sided. To ensure an overall significance level of 5% for this comparison allowing for interim analysis, the O'Brien and Fleming alpha-spending function[8] was used. The results of the final analysis were significant if P≤0.048. The final analysis of the powered secondary endpoint was conducted when the required number of events had been observed (disease progression or death; 90 events overall, or 56 events in ibrutinib group). The data cut-off date was November 4, 2024.

For the primary endpoint, we compared the proportion of participants with uMRD in the bone marrow within two years post-randomization. We made comparisons using a binary logistic penalized regression model with adjustment for the minimization factors (excluding trial center). For the powered secondary endpoint, we estimated time to event summaries using the Kaplan-Meier method. We made comparisons using the Cox proportional hazards model, with similar adjustment. Further details of analysis, primary and secondary endpoints, and pre-defined subgroup analyses are in the 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, 786 patients underwent randomization (260 ibrutinib-venetoclax, 263 ibrutinib and 263 FCR) (Fig. 1). Demographic and clinical characteristics were well balanced, including immunoglobulin heavy-chain variable region (IGHV) mutational status and cytogenetic abnormalities (Table 1). The median age was 62 years (IQR, 56 to 67); 247 (31.4%) >65 years. The representativeness of participants as a reflection of the distribution of patient characteristics in the general population is shown in Table S1. Blacks are underrepresented in the study.

159 of 239 (66.5%) participants who received at least one FCR cycle completed 6 cycles (Table S3). 57 ibrutinib and 10 ibrutinib-venetoclax participants completed 6 years of treatment. At the time of data cut-off, 82 patients were recruited on the STATIC trial having completed 6 years of ibrutinib on this study. In FLAIR, the median number of ibrutinib monotherapy treatment cycles received was 62 (range, 1 to 79) whereas the median number of ibrutinib-venetoclax cycles received was 27 (range, 2 to 79). Dose modifications consisting of reductions, delays and omissions were reported for 157 (60.4%) ibrutinib-venetoclax, 156 (59.3%) ibrutinib and 152 (57.8%) FCR participants (Tables S4, S5 and S6). Early discontinuation of treatment was reported in 22.6% ibrutinib-venetoclax group, 37.7% ibrutinib group and 25.9% FCR group (Tables S7 and S8). The duration of ibrutinib-venetoclax was determined according to the MRD-directed approach, with 157 of 260 participants stopping treatment owing to MRD stopping rules after 24 to 60 months of ibrutinib-venetoclax (Fig. S3 and Table S10, overall and by IGHV mutation status). Thirteen participants

in the ibrutinib-venetoclax arm (5%) have restarted treatment with recurrence of detectable MRD.

50 FCR, 13 ibrutinib and 5 ibrutinib-venetoclax participants received treatment for clinical disease progression (not just the appearance of MRD positivity), mostly targeted therapies (Table S11).

EFFICACY

Within two-years, 299 participants achieved uMRD in BM: 172/260 ibrutinib-venetoclax (66.2%), 0/263 ibrutinib (0%) and 127/263 FCR (48.3%) (p<0.001).

After a median follow-up of 62.2 months (IQR 53.8 to 71.7), disease progression or death had occurred in 18 (6.9%) ibrutinib-venetoclax, 59 (22.4%) ibrutinib and 112 (42.6%) FCR participants, respectively. The estimated 5-year progression-free survival was 93.9% (95%CI, 90.9 to 96.9) with ibrutinib-venetoclax, 79.0% (95%CI, 73.8 to 84.2) with ibrutinib and 58.1% (95%CI, 51.7 to 64.5) with FCR. Annual progression-free survival estimates are provided in Table S12. HR for progression-free survival (ibrutinib-venetoclax vs. ibrutinib) was 0.29 (95%CI, 0.17 to 0.49; P<0.001); (ibrutinib-venetoclax vs. FCR) was 0.13 (95%CI, 0.08 to 0.21; P<0.001) and (ibrutinib vs FCR) was 0.44 (95%CI, 0.32 to 0.60) (Fig. 2A).

In participants with unmutated IGHV, progression-free survival was longer in patients treated with ibrutinib-venetoclax than ibrutinib alone (HR for PFS, 0.20; 95%CI, 0.08 to 0.48; Fig. 2B) or FCR (HR, 0.07; 95%CI, 0.03 to 0.15; Fig. 2B). In participants with mutated IGHV, progression-free survival with ibrutinib-venetoclax was similar to

ibrutinib (HR, 0.51; 95%CI, 0.24 to 1.08; Fig. 2C), but was longer than FCR (HR, 0.36; 95%CI, 0.18 to 0.76; Fig. 2C). Ibrutinib and FCR were similar in the mutated IGHV group (HR, 0.73; 95%CI, 0.39 to 1.37; Fig. 2C). Progression-free survival outcomes in subgroups are shown in Figs. S4 and S5. 76 of 129 FCR group and 13 of 157 ibrutinib-venetoclax group had recurrence of detectable MRD during follow up after testing undetectable MRD in peripheral blood.

Death occurred in 11 (4.2%) ibrutinib-venetoclax, 26 (9.9%) ibrutinib and 39 (14.8%) FCR participants. The estimated 5-year overall survival was 95.9% (95% CI, 93.4 to 98.4) with ibrutinib-venetoclax, 90.5% (95% CI, 86.8 to 94.2) with ibrutinib and 86.5% (95% CI, 82.0 to 91.0) with FCR. Annual overall survival estimates are provided in Table S13. The HR for death comparing ibrutinib-venetoclax vs ibrutinib was 0.41 (95%CI, 0.20 to 0.83), was 0.26 (95%CI, 0.13 to 0.50) for ibrutinib-venetoclax vs FCR, and was 0.64 (95%CI, 0.39 to 1.05) for ibrutinib vs FCR (Fig. 3A). Results for overall survival favored ibrutinib-venetoclax compared with ibrutinib in unmutated IGHV (HR for death, 0.30; 95%CI, 0.08 to 1.08) (Fig. 3B), but was similar in patients with mutated IGHV (HR for death, 0.74; 95%CI, 0.28 to 1.93) (Fig. 3C). Overall survival in subgroups is plotted in Figs. S6 and S7.

Overall survival appeared longer with ibrutinib-venetoclax than FCR in unmutated IGHV (HR 0.16; 95%CI, 0.05 to 0.55) (Fig. 3B), but was similar in mutated IGHV (HR 0.46, 95%CI, 0.19 to 1.11) (Fig. 3C). Results for overall survival were similar for ibrutinib and FCR in both unmutated IGHV (HR 0.63; 95%CI, 0.30 to 1.33) (Fig. 3B) and mutated IGHV (HR 0.62, 95%CI, 0.26 to 1.45) (Fig. 3C).

66.2% (95%CI, 60.05 to 71.88) ibrutinib-venetoclax participants achieved BM uMRD, 0% (95%CI, 0.00 to 1.39) with ibrutinib and 48.3% (95%CI, 42.11 to 54.51) for FCR. The percentage with uMRD in peripheral blood at 2 years was 73.1% (95%CI, 67.25 to 78.37) for ibrutinib-venetoclax, 0% (95%CI, 0.00 to 1.39) for ibrutinib and 60.8% (95%CI, 54.65 to 66.71) for FCR. The median time to first peripheral blood uMRD was 13.0 months (95%CI, 11.7 to 17.6) with ibrutinib-venetoclax, not relevant with ibrutinib because no patient achieved uMRD status, and 8.9 months (95%CI, 8.5 to 9.1) with FCR (Fig. S8). MRD rates at other time points are shown in Tables S13, S14 and S16. The median duration of therapy with ibrutinib-venetoclax was 35 months (95% CI, 24 to 36) overall, 25 months (95% CI, 24 to 36) in unmutated IGHV and 48 months (95% CI, 25 to not estimable) in mutated IGHV (Fig. S3, S10).

At 9 months after randomization, overall response occurred in 87.7%, 87.1% and 77.6% in the ibrutinib-venetoclax, ibrutinib and FCR groups, respectively (Table S18).

SAFETY

742 of 756 (98.1%) in the safety population reported at least one adverse event. The most common grade 3 to 5 adverse events within 1 year after randomization was neutropenia (70/257 [27.2%] for ibrutinib-venetoclax, 17/260 ibrutinib [6.5%] and 113/239 FCR [47.3%]. (Table 2). Common adverse events of any grade were fatigue in 98 [38.1%] ibrutinib-venetoclax, 91 [35%] ibrutinib and 117 [49.0%] FCR) participants, and neutropenia (101 [40.1%], 29 [11.2%] and 141 [59%], respectively) (Table 2). Grade 3 adverse events involving febrile neutropenia occurred in 15 (6.3%) FCR participants; 1 (0.4%) for ibrutinib; 5 (1.9%) for ibrutinib-venetoclax. All

the adverse events reported are summarised in Table S19-S21. Common adverse events after 1 year in the ibrutinib and ibrutinib-venetoclax groups are shown in Table S20 and S21. Hypertension was reported in 17.1% ibrutinib-venetoclax, 20.8% ibrutinib and 1.7% FCR participants. Atrial fibrillation or arrhythmia occurred in 35 (13.6%) ibrutinib-venetoclax, 33 (12.7%) ibrutinib and 6 (1.7%) FCR participants.

657 serious adverse events have been reported from 390 participants at any time (Table S22). Commonest serious adverse events were infections, reported in 172 participants (61 ibrutinib-venetoclax, 66 ibrutinib and 45 FCR). Cardiac serious adverse events occurred more frequently for the ibrutinib and ibrutinib-venetoclax groups compared to FCR (10.4% vs. 10.9% vs. 0.4%). 14 major hemorrhages were reported (5 ibrutinib-venetoclax, 6 ibrutinib and 3 FCR). In the ibrutinib-venetoclax group, clinical tumor lysis syndrome was reported in 1 participant, and biochemical tumor lysis syndrome in 14 participants; all cases resolved.

Eleven deaths were seen in participants treated with ibrutinib-venetoclax, 25 with ibrutinib and 37 with FCR (Table S23). The most common causes of death for FCR were infections (11 participants, 3 of whom died from Covid-19), secondary cancers (8 participants), sudden death (4 participants). The most common causes for ibrutinib were sudden death (8 participants) and infection (6 participants, including 2 Covid-19). The most common causes in the ibrutinib-venetoclax group were infections (3 participants, including 2 Covid-19), sudden death (3 participants), and secondary cancers (2 participants).

36 secondary cancers occurred in 24 ibrutinib-venetoclax, 40 in 33 ibrutinib and 65 in 47 FCR participants (Table S24). Myelodysplastic syndrome or acute myeloid leukemia developed in 13 participants (1 ibrutinib-venetoclax, 1 ibrutinib and 11 FCR). Richter's transformation developed in 6 participants (3 FCR, 1 ibrutinib and 2 ibrutinib-venetoclax). The incidence of other cancers per 100 patient-years was 2.8 for ibrutinib-venetoclax, 3.2 for ibrutinib and 5.5 for FCR. The HR for other cancers (ibrutinib-venetoclax vs. ibrutinib) was 0.76 (95%CI, 0.45 to 1.30); (ibrutinib-venetoclax vs. FCR) was 0.46 (95%CI, 0.28 to 0.76) and (ibrutinib vs FCR) was 0.62 (95%CI, 0.40 to 0.97) (Table S25).

DISCUSSION

In this analysis of FLAIR, we observed that ibrutinib-venetoclax led to high rates of uMRD in peripheral blood (73.1% vs 0% at 2 years). This benefit extended beyond MRD, with ibrutinib-venetoclax demonstrating a continuing improvement in progression-free (93.9% vs 79.0% at 5 years) and overall survival (95.9% vs 90.5% at 5 years). Progression-free (93.9% vs 58.1% at 5 years) and overall survival (95.9% vs 86.5% at 5 years) remained higher with ibrutinib-venetoclax and ibrutinib when compared to FCR. These results for MRD-guided ibrutinib-venetoclax are favorable as compared with those in previous studies of untreated CLL patients with continuous BTKi and fixed duration options using venetoclax in combination with BTKi or obinutuzumab.[4,9-17]

48.3%, 56.3% and 68.1% participants stopped ibrutinib-venetoclax at 2, 3 and 4 years respectively following MRD-guided rules set in the trial. No plateau was seen in achieving uMRD in blood, as 92.7% of participants achieved this with continued ibrutinib-venetoclax. Ongoing marrow MRD responses may be expected, but this was not tested if uMRD in the blood was achieved more than 3 years from baseline. The rates (54.5% vs 38.5% at 12 months) and median time (12 months vs. 18 months) of achieving uMRD were better in the unmutated IGHV group compared to the mutated IGHV group.[3] Similar findings were reported in the CAPTIVATE and GLOW trials, though relapse at MRD level were more common in the unmutated IGHV group after fixed duration ibrutinib-venetoclax.[4,16] In FLAIR, MRD responses are more durable than reported in fixed-duration ibrutinib-venetoclax, possibly due to the personalized approach and longer exposure to ibrutinib-venetoclax. Prolonging ibrutinib-venetoclax treatment by one year in the detectable MRD cohort in

CAPTIVATE improved the uMRD responses from 31% to 66% in marrow.[18] In the intention-to treat population with fixed duration venetoclax-obinutuzumab in the CLL14 trial, 3 months post-treatment uMRD rates were 75.5% in blood and 56.9% in marrow but 5 years after treatment it was only 7.9% in blood.[18,19]

In this study, MRD-guided ibrutinib-venetoclax continued to show improved progression-free and overall survival over ibrutinib alone. The ibrutinib group results in FLAIR, showing estimated 5-year progression-free and overall survival of 79.0% and 90.5% respectively, are comparable to ibrutinib treated groups in E1912, A01402 and RESONATE-2, acalabrutinib monotherapy in ELEVATE-TN (72% and 84% respectively) and zanubrutinib in SEQUOIA (78.5% and 85.8% respectively).[9,11-14] Ibrutinib monotherapy in FLAIR showed improved progression-free survival over FCR consistent with reported outcomes in E1912 study. With the caveats of cross-trial comparisons, the results from MRD-guided ibrutinib-venetoclax suggests improved survival outcomes over continuous BTK inhibitors. Prospective comparison of the ibrutinib-venetoclax time-limited treatment duration vs continuous BTK inhibitors is needed to definitively address the relative activity.

Fixed duration therapy utilizing venetoclax combination with BTK inhibitors or obinutuzumab have improved outcomes compared to chemo-immunotherapy but no head-to-head trial comparison to continuous BTKi is available.[15-18,20] The undetectable MRD, progression-free and overall survival outcomes of unmutated IGHV CLL sub-group with MRD-guided ibrutinib-venetoclax in FLAIR suggest that this group benefits the most from this approach. The magnitude of survival difference is not as stark in the IGHV mutated CLL sub-group over ibrutinib, with only a trend

for improvement due to the slow nature of relapse observed in this sub-group. The outcomes are comparable to fixed-duration approaches at this follow-up, but differences may emerge with longer follow-up.[4,15-17,19,20]. Predictors of time to uMRD beyond IGHV status, particularly within the mutated subgroup, are under evaluation and may guide future individualization of therapy; upcoming results from CLL17 may also help address this question.

MRD-guided duration of ibrutinib-venetoclax is longer than other fixed duration combinations and is further complicated by the need for real-time MRD analysis. While the improvements in outcomes observed with this individualized approach suggests the validity of MRD-guided therapy in untreated CLL, we acknowledge that prolonged therapy duration itself may contribute to efficacy. Distinguishing the relative contributions of treatment duration versus MRD guidance represents an important future research question. Cost benefit and toxicity analyses, particularly in comparison to fixed duration therapies are ongoing within FLAIR and will be reported in future updates.

No new safety concerns emerged with MRD-guided ibrutinib-venetoclax. Cardiac arrhythmias remain a concern with ibrutinib, and more cases of atrial fibrillation and hypertension were reported in the ibrutinib-venetoclax group and ibrutinib group than in the FCR group, but these results did not translate into an increased risk of sudden death. In FLAIR, careful management of hypertension and optimization of cardiovascular risk factors helped to deliver longer duration of ibrutinib-venetoclax without increasing the risk of cardiac complications. These findings should also be

interpreted in the context of the relatively young trial population, in whom longer term follow up is essential to evaluate the potential for functional cure.

In conclusion, using MRD to define the duration of ibrutinib-venetoclax treatment, as in the FLAIR trial, continued to show improvements in uMRD, PFS compared to treatment with ibrutinib and FCR, and OS compared to treatment with FCR, (especially for those with unmutated IGHV), allowing the individualization of therapy based on response in real time. Additional follow up is required to determine the durability of uMRD and its relationship with long-term survival off therapy.

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

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FIGURES

Figure 1:

Randomization, Treatment, and Follow-up.

Figure 2:

(A) Progression-free survival, all participants

(B) Progression-free survival, participants with unmutated IGHV

(C) Progression-free survival, participants with mutated IGHV

Figure 3

(A) Overall survival, all participants

(B) Overall survival, participants with unmutated IGHV

(C) Overall survival, participants with mutated IGHV

Table 1: Characteristics of the Participants at Baseline (Intention-to-Treat Population)

	FCR (n=263)	I (n=263)	I+V (n=260)	Total (n=786)
Median Age (IQR) - yr	62 (57 - 67)	62 (56 - 67)	62 (55 - 67)	62 (56 - 67)
Age group				
=< 65 years	181 (68.8%)	179 (68.1%)	179 (68.8%)	539 (68.6%)
> 65 years	82 (31.2%)	84 (31.9%)	81 (31.2%)	247 (31.4%)
Gender				
Male	187 (71.1%)	186 (70.7%)	186 (71.5%)	559 (71.1%)
Female	76 (28.9%)	77 (29.3%)	74 (28.5%)	227 (28.9%)
Binet Stage				
Progressive A or B	154 (58.6%)	153 (58.2%)	154 (59.2%)	461 (58.7%)
C	109 (41.4%)	110 (41.8%)	106 (40.8%)	325 (41.3%)
Ethnicity				
White	240 (91.3%)	241 (91.6%)	235 (90.4%)	716 (91.1%)
Other	1 (0.4%)	1 (0.4%)	3 (1.2%)	5 (0.6%)
Asian	5 (1.9%)	8 (3.0%)	5 (1.9%)	18 (2.3%)
Black	3 (1.1%)	4 (1.5%)	7 (2.7%)	14 (1.8%)
Not available	14 (5.3%)	9 (3.4%)	10 (3.8%)	33 (4.2%)
WHO performance status				
0	181 (68.8%)	187 (71.1%)	181 (69.6%)	549 (69.8%)
1	69 (26.2%)	70 (26.6%)	69 (26.5%)	208 (26.5%)
2	8 (3.0%)	5 (1.9%)	8 (3.1%)	21 (2.7%)
Missing	5 (1.9%)	1 (0.4%)	2 (0.8%)	8 (1.0%)
B Symptoms				
Yes	121 (46.0%)	126 (47.9%)	128 (49.2%)	375 (47.7%)
No	133 (50.6%)	136 (51.7%)	130 (50.0%)	399 (50.8%)
Missing	9 (3.4%)	1 (0.4%)	2 (0.8%)	12 (1.5%)
Creatinine clearance (mL/min)	79.0 (37.0, 247)	80.1 (41.0, 260)	83.0 (40.0, 231)	81.0 (37.0, 260)
Missing	3	1	1	5
ß2 microglobulin concentration (ß2m) (mg/L)	4.00 (1.70, 13.1)	4.10 (1.70, 17.9)	4.00 (1.90, 14.3)	4.00 (1.70, 17.9)
Missing	16	17	12	45
Duration of CLL (months)				
Mean (s.d.)	33.4 (33.9)	36.2 (37.9)	37.9 (44.6)	35.9 (39.2)
Median (range)	21.3 (0.00, 162)	27.5 (0.33, 241)	23.7 (0.00, 263)	24.9 (0.00, 263)
Missing	43	30	22	95
VH Mutation Status				
Mutated	82 (31.2%)	87 (33.1%)	97 (37.3%)	266 (33.8%)
Unmutated	139 (52.9%)	129 (49.0%)	123 (47.3%)	391 (49.7%)
Not available	28 (10.6%)	24 (9.1%)	24 (9.2%)	76 (9.7%)
BCR Subset 2 Mutated	6 (2.3%)	15 (5.7%)	11 (4.2%)	32 (4.1%)
BCR Subset 2 Unmutated	8 (3.0%)	8 (3.0%)	5 (1.9%)	21 (2.7%)
Hierarchical genetic abnormalities				
TP53 deletion	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.1%)
ATM deletion	50 (19.0%)	36 (13.7%)	45 (17.3%)	131 (16.7%)
Trisomy 12	29 (11.0%)	45 (17.1%)	57 (21.9%)	131 (16.7%)
Normal karyotype	69 (26.2%)	64 (24.3%)	52 (20.0%)	185 (23.5%)
13q deletion	100 (38.0%)	106 (40.3%)	89 (34.2%)	295 (37.5%)
Undetermined	15 (5.7%)	12 (4.6%)	16 (6.2%)	43 (5.5%)

* Borderline TP53 deletions, defined as a deletion detected in 7–19% of lymphocytes scored, were reported in seven participants. Of these, four were allocated to the FCR arm (with TP53 deletion detected in 7%, 10%, 13%, and 13% of lymphocytes), two to the ibrutinib–venetoclax arm (deletion in 9% and 10% of lymphocytes), and one to the ibrutinib-only arm (deletion in 7% of lymphocytes). One participant assigned to the ibrutinib–venetoclax arm was found to have both a TP53 deletion (89%) and a TP53 mutation (VAF 97%), but had been included in the trial [due to a discrepancy between local and central laboratory findings].

Table 2: AEs in the Safety Population, According to Maximum Grade AE, adverse events.

	FCR (n=239)				I (n=260)				I+V (n=257)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Abdominal pain/bloating	21 (8.8%)	0 (0%)	0 (0%)	0 (0%)	15 (5.8%)	1 (0.4%)	0 (0%)	0 (0%)	37 (14.4%)	0 (0%)	0 (0%)	0 (0%)
Anemia	50 (20.9%)	33 (13.8%)	5 (2.1%)	0 (0%)	52 (20%)	11 (4.2%)	1 (0.4%)	0 (0%)	61 (23.7%)	16 (6.2%)	2 (0.8%)	0 (0%)
Arthralgia/Arthritis	10 (4.2%)	0 (0%)	0 (0%)	0 (0%)	49 (18.8%)	2 (0.8%)	0 (0%)	0 (0%)	56 (21.8%)	1 (0.4%)	0 (0%)	0 (0%)
Bruising/bleeding	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	78 (30%)	1 (0.4%)	0 (0%)	0 (0%)	85 (33.1%)	0 (0%)	0 (0%)	0 (0%)
Constipation	60 (25.1%)	0 (0%)	0 (0%)	0 (0%)	23 (8.8%)	0 (0%)	0 (0%)	0 (0%)	29 (11.3%)	2 (0.8%)	0 (0%)	0 (0%)
Cough	47 (19.7%)	4 (1.7%)	0 (0%)	0 (0%)	25 (9.6%)	0 (0%)	0 (0%)	0 (0%)	23 (8.9%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	46 (19.2%)	6 (2.5%)	0 (0%)	0 (0%)	66 (25.4%)	1 (0.4%)	0 (0%)	0 (0%)	114 (44.4%)	3 (1.2%)	0 (0%)	0 (0%)
Dyspepsia	9 (3.8%)	0 (0%)	0 (0%)	0 (0%)	30 (11.5%)	0 (0%)	0 (0%)	0 (0%)	33 (12.8%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	108 (45.2%)	9 (3.8%)	0 (0%)	0 (0%)	89 (34.2%)	2 (0.8%)	0 (0%)	0 (0%)	97 (37.7%)	1 (0.4%)	0 (0%)	0 (0%)
Fever	59 (24.7%)	18 (7.5%)	0 (0%)	0 (0%)	22 (8.5%)	2 (0.8%)	0 (0%)	0 (0%)	23 (8.9%)	2 (0.8%)	0 (0%)	0 (0%)
Headache	31 (13%)	1 (0.4%)	0 (0%)	0 (0%)	40 (15.4%)	2 (0.8%)	0 (0%)	0 (0%)	39 (15.2%)	2 (0.8%)	0 (0%)	0 (0%)
Infusion related reaction	65 (27.2%)	2 (0.8%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Mouth ulcers	11 (4.6%)	0 (0%)	0 (0%)	0 (0%)	29 (11.2%)	1 (0.4%)	0 (0%)	0 (0%)	38 (14.8%)	1 (0.4%)	0 (0%)	0 (0%)
Nausea	138 (57.7%)	1 (0.4%)	0 (0%)	0 (0%)	40 (15.4%)	0 (0%)	0 (0%)	0 (0%)	93 (36.2%)	3 (1.2%)	0 (0%)	0 (0%)
Other	31 (13%)	9 (3.8%)	1 (0.4%)	1 (0.4%)	81 (31.2%)	13 (5%)	0 (0%)	0 (0%)	65 (25.3%)	16 (6.2%)	0 (0%)	0 (0%)
Platelet count decreased	65 (27.2%)	16 (6.7%)	8 (3.3%)	0 (0%)	44 (16.9%)	1 (0.4%)	1 (0.4%)	0 (0%)	55 (21.4%)	8 (3.1%)	5 (1.9%)	0 (0%)
Rash	67 (28%)	6 (2.5%)	0 (0%)	0 (0%)	74 (28.5%)	8 (3.1%)	0 (0%)	0 (0%)	82 (31.9%)	5 (1.9%)	0 (0%)	0 (0%)
Upper respiratory infection	26 (10.9%)	8 (3.3%)	0 (0%)	0 (0%)	31 (11.9%)	2 (0.8%)	0 (0%)	0 (0%)	22 (8.6%)	5 (1.9%)	0 (0%)	0 (0%)
Vomiting	66 (27.6%)	5 (2.1%)	0 (0%)	0 (0%)	17 (6.5%)	0 (0%)	0 (0%)	0 (0%)	35 (13.6%)	2 (0.8%)	0 (0%)	0 (0%)
White blood cell decreased	28 (11.7%)	53 (22.2%)	60 (25.1%)	0 (0%)	12 (4.6%)	4 (1.5%)	13 (5%)	0 (0%)	31 (12.1%)	38 (14.8%)	32 (12.5%)	0 (0%)

This table shows the 20 most incident adverse events. In the appendix we provide adverse events reported at Grade 1-2 in ≥10% of participants and Grade 3-5 in ≥1% of participants in the safety population in the first year of treatment yearly subsequently up to six years.