Chronic lymphocytic leukemia therapy guided by measurable residual disease

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ABSTRACT:

Background:

Ibrutinib (I) and venetoclax (V) improve chronic lymphocytic leukemia (CLL) outcomes compared to chemo-immunotherapy. We hypothesized I+V is more effective than fludarabine-cyclophosphamide-rituximab (FCR), and personalizing treatment duration, using measurable residual disease (MRD), would optimize outcomes.

Methods:

FLAIR, a phase III, multicenter, randomized, controlled, open-label platform trial for untreated CLL, compared I+V and I, to FCR. In I+V, after 2m I, V was added for up to 6y of therapy. The duration of I+V was defined by MRD assessed in peripheral blood (PB) and bone marrow (BM) and was double the time to undetectable MRD (uMRD). The primary endpoint was PFS for I+V vs FCR, reported herein. Key secondary endpoints were OS, response, MRD and safety.

Results:

523 participants were randomized to FCR or I+V. At median 43.7m, there were 87 progressions (75 FCR, 12 I+V). The hazard ratio (HR) for PFS for I+V vs FCR is 0.13 (95% confidence interval [CI], 0.07-0.24; P<0.0001). There were 34 deaths (25 FCR, 9 I+V). The HR for OS for I+V vs FCR is 0.31 (95%CI, 0.15-0.67). At 3y, 58.0% I+V participants stopped therapy due to uMRD. After 5y of I+V, 65.9% and 92.7% participants were BM and PB uMRD, respectively. Infection rates were similar. There were more cardiovascular events with I+V (10.7%) vs FCR (0.4%).

Conclusion:

MRD-directed I+V improved PFS and favored OS compared to FCR. (Trial Registration number: ISRCTN01844152 and EudraCT, 2013-001944-76.)

INTRODUCTION

Chronic 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 their accumulation 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 (BTKi), blocks BCR signalling preventing CLL-cell proliferation, migration, and adhesion.[1] Venetoclax, an orally bioavailable small-molecule inhibitor of Bcl-2, results in CLL-cell apoptosis.[2]

Since ibrutinib and venetoclax have discrete modes of action and different toxicities their combination is rational and has been investigated.[3] Synergy is noted in pre-clinical models,[4] and CLL cell mobilization by ibrutinib should render tumor cells more susceptible to venetoclax.[5] We previously assessed ibrutinib plus venetoclax (I+V) in relapsed-refractory CLL, where the duration of therapy was defined by time to achieve undetectable measurable residual disease (uMRD),[6] demonstrating the combination was efficacious and safe.

Toxicity limits the duration of chemo-immunotherapy but with I+V, no cumulative toxicity has been described. However, continuous therapy (e.g., with a BTKi) results in emergent resistance. Time-limited therapy is desirable to prevent resistance, allow immune recovery, and reduce costs. GLOW[7,8] and CAPTIVATE[9] assessed 1y of fixed duration I+V with compelling efficacy. Patients have differential responses to therapy with some experiencing rapid disease eradication and others responding slowly. The continuation of treatment for a defined period beyond the attainment of undetectable disease should result in deep responses and optimize outcomes, prolong remission and possibly cure. FLAIR utilized an individualized duration of I+V that is double the time taken to achieve uMRD.

FLAIR initially compared ibrutinib and rituximab (IR) with fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated patients with CLL who were fit for chemo-immunotherapy.[9] FLAIR was adapted in 2017, to include ibrutinib monotherapy (I) and ibrutinib plus venetoclax (I+V) with therapy duration defined by MRD. An interim analysis of I vs I+V showing superiority of I+V in achieving uMRD has been reported.[11,12] Herein, we present results of a planned interim analysis comparing MRD-guided I+V with FCR.

METHODS

STUDY DESIGN AND PARTICIPANTS

FLAIR is a phase III, multicenter, randomized, controlled, open-label, parallel group, multi-arm adaptive trial platform in patients with previously untreated CLL,[13] recruiting from 96 UK hospitals (Appendix).

Key inclusion criteria included treatment-naive CLL/small lymphocytic lymphoma, considered fit for FCR. Key exclusion criteria were Richter transformation, CNS involvement and symptomatic cardiac disease. Patients with greater than 20% CLL cells having deletion chromosome 17p deletion identified by fluorescence in-situ hybridisation (FISH) were excluded. Detailed inclusion and exclusion criteria in Appendix. Participants provided written informed consent.

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

RANDOMIZATION AND PROCEDURES

Participants were assigned (1:1:1) to treatment with either FCR, I or I+V using a minimisation algorithm with a random element. Full details in Appendix.

FCR was repeated every 28d for six cycles in the absence of disease progression or toxicity requiring cessation. Ibrutinib was administered orally at a dose of 420mg/day for 8w before the initiation of venetoclax up to 400mg/day (see Appendix for details). Participants continued I+V for a total of 6y, unless the MRD stopping rules were reached, toxicity required cessation, or disease progression. The MRD stopping rules were based on an algorithm (Appendix Figure S2).

ASSESSMENTS AND ENDPOINTS

The primary endpoint comparing MRD-guided I+V with FCR was progression-free survival, defined as time from randomization to progressive disease or death (any cause). Participants without an event were censored at last follow-up. We have previously reported the results of interim analysis comparing MRD-guided I+V with I with the primary endpoint proportion of participants with uMRD within 2y post-randomisation. Secondary endpoints were overall survival, the proportion of participants with uMRD at 9m post-randomization and longitudinally, pattern of MRD relapse and retreatment, response to therapy (IWCLL criteria) at 9m post-randomization and longitudinally, safety, toxicity, health-related quality of life and cost-effectiveness. The hierarchy of cytogenetic abnormalities was assessed and progression-free survival for various cytogenetic aberrations were analysed. Adverse events were assessed at the start of each treatment cycle (see Appendix for details).

STATISTICAL ANALYSIS

The interim analysis of progression-free survival comparing MRD-guided I+V with FCR was conducted when either 50% of total required progression-free survival events were observed (116 events) or 69 events were observed in FCR. The cut-off 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 bounds of 0.005 for interim and 0.048 for final analysis, respectively.[14] The results of the interim analysis were considered significant (P≤0.005). Therefore, the independent data monitoring committee recommended conducting the full analysis of primary and secondary endpoints. For the primary endpoint, we estimated summaries of time to event per treatment group using the Kaplan-Meier method with corresponding 95% CIs estimated using the Hall-Wellner method. We made comparisons between the allocated groups using the Cox proportional hazards model adjusted for the minimization factors, excluding center, to estimate HRs and 95% CIs. Details of secondary endpoint and predefined subgroup analyses are in the Appendix. No plan to adjust for multiple comparisons across the secondary endpoints was planned; results are reported with 95% CIs, without p values; 95% CI intervals should not be used in place of hypothesis testing and to infer definitive treatment effects.

RESULTS

PARTICIPANTS

Between July 20, 2017, and March 24, 2021, 523 patients were randomly assigned (Appendix, Fig. S3) (263 FCR, 260 I+V). Patient and disease characteristics were well balanced including immunoglobulin heavy chains (*IGHV*) mutational status and cytogenetic abnormalities by FISH (Table1). The median age was 62y (IQR 56-67), 163 (31.2%) were over 65y, 373 (71.3%) were male. The participant sample is representative of epidemiological studies and supports generalizability of findings (Appendix, Table S1).

Seven participants (1.3%) had 17p deletion (four FCR, three I+V). One I+V participant had greater than 20% 17p deletion on central laboratory assessment.

159 FCR participants (66.5%) received 6 cycles. The median number of 28-day ibrutinib cycles received was 27 (range, 2-72) and venetoclax was 25 (range, 1-70) (Appendix, Table S2). Dose modifications consisting of reductions, delays and omissions were reported for 144 (54.8%) FCR and 143 (55.0%) I+V participants (Appendix, Table S3). Dose modifications were reported for 34 (13.1%) and 80 (30.8%) participants receiving I+V up to 12m and 12-24m post-randomization, respectively (Appendix, Table S4). 62 FCR participants (25.9%) and 58 I+V participants (23.0%) discontinued treatment early. Reasons for discontinuation are detailed in Appendix, Table S5-S6.

Duration of I+V was as per MRD-directed approach with 146 out of 260 participants stopping treatment due to MRD stopping rules after 24m-60m I+V treatment (Appendix, Table S7, Figure S3). 65 participants stopped treatment at 24m, 61 at 36m and 20 at 48-60m. Five participants restarted I+V and were alive and progression-free at last follow up.

Forty-two FCR participants received treatment after progression or withdrawal. 35 received targeted therapies (ibrutinib (n=9), acalabrutinib (n=13), zanubrutinib (n=1), venetoclax-based therapy (n=11) and idelalisib (n=1)), 6 chemo-immunotherapy and 1 an allogeneic bone marrow transplant. In I+V, 5 participants received subsequent therapies. One each received ibrutinib, acalabrutinib, pirtobrutinib, chemo-immunotherapy and alemtuzumab.

EFFICACY

After a median follow-up of 43.7m (IQR. 35.1-51.5), 75 (28.5%) FCR and 12 (4.6%) I+V participants had disease progression or died. The estimated 3y progression-free survival was 76.8% (95%CI, 70.8-81.7) for FCR and 97.2% (95%CI 94.1-98.6) for I+V. Annual progression-free survival estimates are in Appendix, Table S8. The HR for progression-free survival for participants randomized to I+V vs. FCR was 0.13 (95%CI, 0.07-0.24;P<0.0001;

Fig.1A). Results for progression-free survival also favored I+V compared with FCR in *IGHV* unmutated-CLL (HR 0.07, 95%CI, 0.02-0.19; Fig.1B), but not *IGHV* mutated-CLL (HR 0.54, 95%CI, 0.21-1.38, Fig.1C). In a subgroup analysis, the benefit of I+V on progression-free survival was seen across all subgroups except mutated *IGHV* (Appendix, Fig.S5-S6).

25 (9.5%) FCR and 9 (3.5%) I+V participants died. The 3y overall survival was 93.0% (95%CI, 88.9-95.6) for FCR and 98.0% (95%CI, 95.2-99.2) for I+V. Annual overall survival estimates are in Appendix, Table S9. The HR for overall survival for participants randomized to I+V vs. FCR was 0.31 (95%CI, 0.15-0.67 Fig.2A). The overall survival appeared to favor I+V compared with FCR in *IGHV* unmutated-CLL (HR 0.23, 95%CI, 0.06-0.81; Fig.2B), but not *IGHV* mutated-CLL (HR 0.61, 95%CI, 0.20-1.82; Fig.2C). Subgroup analyses suggested benefit of I+V on overall survival was seen across all subgroups except mutated *IGHV* (Appendix, Fig.S7-S8).

The 2y bone marrow uMRD rate was 52.4% (95% CI, 45.9-58.9) for I+V and 49.8% (95%CI, 43.2-56.5) for FCR (Appendix, Fig.S9A). The 5y bone marrow uMRD rate was 65.9% (95%CI, 59.5-72.3) for I+V and 49.8% (95%CI, 43.2-56.5) for FCR. Median time to first peripheral blood uMRD was 9m (95%CI, 8.5-9.1) for FCR and 12m (95%CI, 11.5-17.3) for I+V participants (Appendix, Fig. S9B). The 5y peripheral blood uMRD rate was 67.9% (95%CI, 61.9-73.9) for FCR and 92.7% (95%CI, 88.1-97.3) for I+V. Annual uMRD estimates are in Appendix, Table S10-S11.

At 9m post randomization, 108 (41.5%, 95%CI, 35.48-47.79) I+V participants attained bone marrow uMRD versus 127 (48.3%, 42.11-4.51) for FCR (Appendix, Table S12). The cumulative incidence of MRD negativity in peripheral blood increased throughout I+V treatment but not for FCR (Appendix, Table S13). 106 (40.3%) FCR and 161 (61.9%) I+V participants had bone marrow uMRD at any time. Similarly, 160 (60.8%) FCR and 223 (85.8%) I+V participants had peripheral blood uMRD at any time. The adjusted odds ratio of

becoming uMRD at any time for I+V vs FCR was 2.03 (95%CI, 1.43-2.89) in bone marrow and 3.91 (95%CI, 2.55-6.00;P<0.001) in peripheral blood.

At 9m post-randomization, 201 (76.4%, 95%CI, 70.82-81.42) FCR and 225 (86.5%; 95%CI, 81.78-90.44) I+V participants achieved an overall response. Similar results are seen for complete response; 129 (49.0%, 95%CI, 42.86-55.26) FCR and 154 (59.2%, 95%CI, 52.99-65.26) I+V (Appendix, Table S14). The adjusted odds ratio of response rate for I+V compared to FCR was 2.00 (95%CI, 1.26-3.16;) and for complete response was 1.51 (95%CI, 1.07-2.14).

SAFETY

Of 491 participants in the safety population, 450 (91.6%) reported at least one adverse event. The most common grade 3-5 adverse events occurring within 1y of randomization were neutropenia (113 [47.3%] FCR, 26 [10.3%] I+V); anemia 37 [15.5%] FCR, 2 [0.8%] I+V and thrombocytopenia (24 [10.2%] FCR, 5 [2.0%] I+V) (Table 2). Common adverse events of any grade were fatigue (117 [49.0%] FCR, 39 [15.5%] I+V) and neutropenia (140 [58.6%] FCR, 49 [19.4%] I+V) (Table 2). 15 febrile neutropenia grade 3 adverse events occurred in 14 (5.4%) FCR participants, and none in I+V. Common adverse events after 1y in I+V are in Appendix, Table S15. 14 hypertension adverse events occurred in 4 (1.7%) FCR participants compared to 80 adverse events in 34 (13.5%) I+V. Nine atrial fibrillation/arrhythmia/flutter adverse events occurred in 4 (1.7%) FCR participants, compared to 62 adverse events in 34 (11.1%) I+V participants. Granulocyte colony stimulating factor was used in 91 (34.6%) FCR and 56 (21.5%) I+V participants.

416 serious adverse events were reported from 252 participants at any time: 222 from 129 FCR participants and 194 from 123 I+V participants (Appendix, Table S16). The most common serious adverse event was infection and infestations, experienced by 101 participants (45 FCR; 56 I+V). More serious adverse events were reported in blood and

lymphatic system for FCR compared to I+V (31.0% vs 5.2%). More cardiac serious adverse events were reported for I+V compared to FCR (10.7% vs 0.4%). 23 adverse events of special interest (included major hemorrhage and tumor lysis syndrome) were reported in 21 participants (18 I+V, 3 FCR). Eight major hemorrhages were reported (3 FCR, 5 I+V). Clinical and biochemical tumor lysis syndrome was reported in 1 and 14 participants receiving I+V, respectively. All cases resolved.

Twenty-three FCR participants and 8 treated with I+V died (Appendix, TableS16). Six (26.1%) of the 23 deaths for FCR and 1 of the 8 deaths for I+V were assessed by local investigator to be probably related to treatment. The most common causes with FCR were infections (10, 43.5%), two of which were COVID-19, and secondary malignancies (8, 34.8%). The most common causes in I+V were infections (3), two of which were COVID-19, sudden unexplained or cardiac death (3), and secondary malignancies (2). Two sudden unexplained or cardiac deaths occurred in FCR participants and 3 in I+V. However, 2 of these in I+V occurred at 35d and 411d after treatment end and were considered probably unrelated to treatment by local investigator.

Thirty-four FCR participants and 17 I+V have experienced a total of 45 and 24 secondary malignancies, respectively (Appendix, Table S18). 8 FCR participants have developed myelodysplastic syndrome or acute myeloid leukaemia compared to one I+V participant. Four FCR participants developed Richter's transformation compared to one I+V. The incidence of other cancers per 100 participant-years was 5.4 (95%CI, 5.11-5.68) in FCR and 2.6 (95%CI, 2.4-2.79) in I+V (HR 0.43, 95%CI, 0.23-0.77; Appendix, Table S19).

DISCUSSION

In this phase of FLAIR in which patients were randomized to I+V, I and FCR, we found that MRD guided I+V is superior to FCR in obtaining progression-free survival (97.2% vs 76.8% at 3y) and favors overall survival (98.0% alive vs 93.0% at 3y) for previously untreated CLL.

The results are favorable compared to previous studies of ibrutinib monotherapy or venetoclax, as monotherapy, or in combination with anti-CD20.[15,16] The MRD-driven approach in FLAIR led to 28.9% and 58.0% of participants in I+V stopping therapy at 2y and 3y, respectively. No plateau was seen in achievement of peripheral blood uMRD, suggesting that continued therapy informed by MRD is justified. In the CAPTIVATE MRD-guided study,[17] the duration of I+V was defined by MRD (either 12m or 24m) and, among those who received a 15-24m course 77% achieved peripheral blood uMRD.

I+V was given in GLOW[7,8] for 12m in all participants and 54.7% achieved peripheral blood uMRD 3m after the end of therapy. In FLAIR 47.5% became peripheral blood uMRD after 12m of I+V but this increased to 92.7% with continued therapy suggesting that 12m I+V is insufficient for many. In GLOW, 80.5% I+V participants were progression-free after 30m. In GCLLSG CLL13, venetoclax-obinutuzumab (VO) was given for 12m or the venetoclax-obinutuzumab-ibrutinib (IVO) combination for 12m with ibrutinib continued for up to 3y if MRD was detectable at 12m. 86.5% receiving VO were peripheral blood uMRD and 92.2% of IVO were peripheral blood uMRD at 15m with 3 year progression-free survival of 87.7% and 90.5%, respectively.[16] The progression-free survival for MRD guided I+V in FLAIR compared favorably with 97.2% progression-free at 3y.

The positive outcome of FLAIR appears most marked in *IGHV* unmutated CLL with significant improvements in progression-free and overall survival. However, a benefit was not yet observed in *IGHV* mutated CLL. MRD-defined I+V is favored compared to FCR for outcomes in all conventional cytogenetic sub-groups, with particularly marked improvement in *ATM*-deleted CLL.

The combination of I+V was associated with no new safety concerns. Cardiac arrhythmias remain a concern. In an earlier cohort of FLAIR[19], sudden deaths were reported for IR compared to FCR. An amendment incorporated stricter monitoring of cardiac associated risk factors identified in earlier FLAIR report. Consistent with previous findings, more cases of

atrial fibrillation and hypertension were reported in I+V but this did not translate into increased sudden death rates. Whether these findings illustrate the impact of changes made for management of hypertension and cardiac side effects cannot be ascertained. Severe infections were more commonly reported in FCR as compared to I+V. Tumor lysis syndrome was more common in I+V but only a single clinical case was reported.

The CLL treatment landscape has been transformed by targeted drugs. Continuous BTKi therapy has improved outcomes in CLL. Fixed duration venetoclax in combination with obinutuzumab or ibrutinib also improve patient outcomes. However, only trends towards improvement in overall survival have been seen compared to chlorambucil and obinutuzumab. These approaches are based on the principle that ‘one size fits all‘ and therapy is not individualized based on response. Using MRD to define duration of I+V treatment, as in FLAIR, results in improved outcomes, allowing the individualization of therapy based on response in real time.

Trials that stopped early for efficacy may overestimate effect size.[20] However, with stringent, predefined stopping rules[21] and a significant proportion of required events are reported,[22] stopping early should have negligible effect on estimates. FLAIR will continue to follow-up participants until final analysis.

MRD-guided I+V, as delivered in FLAIR, including individualized treatment duration beyond uMRD, resulted in significant improvements in progression-free survival and an apparent benefit in overall survival in patients with previously untreated CLL, particularly in subsets of patients with poorer outcomes to standard treatments (e.g., unmutated IgVH genes, certain other genetic lesions).

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

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References

1. de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012;119(11):2590-4. DOI: 10.1182/blood-2011-11-390989.

2. Herman SE, Mustafa RZ, Jones J, Wong DH, Farooqui M, Wiestner A. Treatment with Ibrutinib Inhibits BTK- and VLA-4-Dependent Adhesion of Chronic Lymphocytic Leukemia Cells In Vivo. Clin Cancer Res 2015;21(20):4642-51. DOI: 10.1158/1078-0432.CCR-15-0781.

3. Jain N, Keating M, Thompson P, et al. Ibrutinib and Venetoclax for First-Line Treatment of CLL. The New England journal of medicine 2019;380(22):2095-2103. DOI: 10.1056/NEJMoa1900574.

4. Anderson MA, Deng J, Seymour JF, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. Blood 2016;127(25):3215-24. DOI: 10.1182/blood-2016-01-688796.

5. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood 2022;139(22):3278-3289. DOI: 10.1182/blood.2021014488.

6. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2019;37(30):2722-2729. DOI: 10.1200/JCO.19.00894.

7. Niemann CU, Munir T, Moreno C, et al. Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus

Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): The Glow Study. Blood 2022;140(Supplement 1):228-230. DOI: 10.1182/blood-2022-156070.

8. Kater AP, Owen C, Moreno C, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence 2022;1(7):EVIDoa2200006. DOI: doi:10.1056/EVIDoa2200006.

9. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. The New England journal of medicine 2018;378(13):1211-1223. DOI: 10.1056/NEJMoa1715519.

10. Gregory WM, Twelves CJ, Bell R, et al. Characterizing and quantifying the effects of breast cancer therapy using mathematical modeling. Breast Cancer Res Treat 2016;155(2):303-11. DOI: 10.1007/s10549-016-3684-4.

11. Hillmen P, Pitchford A, Bloor A, et al. S145: THE COMBINATION OF IBRUTINIB PLUS VENETOCLAX RESULTS IN A HIGH RATE OF MRD NEGATIVITY IN PREVIOUSLY UNTREATED CLL: THE RESULTS OF THE PLANNED INTERIM ANALYSIS OF THE PHASE III NCRI FLAIR TRIAL. HemaSphere 2022;6:46-47. DOI: 10.1097/01.Hs9.0000843472.57904.29.

12. Munir T, Pitchford A, Bloor A, et al. Combination of Ibrutinib Plus Venetoclax with MRD-Driven Duration of Treatment Results in a Higher Rate of MRD Negativity in IGHV Unmutated Than Mutated CLL: Updated Interim Analysis of FLAIR Study. Blood 2022;140(Supplement 1):231-233. DOI: 10.1182/blood-2022-170463.

13. Howard DR, Hockaday A, Brown JM, et al. A platform trial in practice: adding a new experimental research arm to the ongoing confirmatory FLAIR trial in chronic lymphocytic leukaemia. Trials 2021;22(1):38. DOI: 10.1186/s13063-020-04971-2.

14. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35(3):549-56. (In eng).

15. Al-Sawaf O, Zhang C, Lu T, et al. Minimal Residual Disease Dynamics after Venetoclax-Obinutuzumab Treatment: Extended Off-Treatment Follow-up From the Randomized CLL14 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(36):4049-4060. (In eng). DOI: 10.1200/jco.21.01181.

16. Eichhorst B, Niemann CU, Kater AP, et al. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. The New England journal of medicine 2023;388(19):1739-1754. DOI: 10.1056/NEJMoa2213093.

17. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia: Primary Analysis Results From the Minimal Residual Disease Cohort of the Randomized Phase II CAPTIVATE Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2021;39(34):3853-3865. DOI: 10.1200/JCO.21.00807.

18. Al-Sawaf O, Robrecht S, Zhang C, et al. S145: VENETOCLAX-OBINUTUZUMAB FOR PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA: 6-YEAR RESULTS OF THE RANDOMIZED CLL14 STUDY. Hemasphere 2023;7(Suppl) (In eng). DOI: 10.1097/01.HS9.0000967492.06443.0a.

19. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2023;24(5):535-552. DOI: 10.1016/S1470-2045(23)00144-4.

20. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. Jama 2010;303(12):1180-7. (In eng). DOI: 10.1001/jama.2010.310.

21. Korn EL, Freidlin B, Mooney M. Stopping or reporting early for positive results in randomized clinical trials: the National Cancer Institute Cooperative Group experience from 1990 to 2005. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27(10):1712-21. (In eng). DOI: 10.1200/jco.2008.19.5339.

22. Freidlin B, Korn EL. Stopping clinical trials early for benefit: impact on estimation. Clinical trials (London, England) 2009;6(2):119-25. (In eng). DOI: 10.1177/1740774509102310.

Figures

Figure 1:

(A) Progression-free survival, all participants

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

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

Figure 2

(A) Overall survival, all participants

(B) Overall survival, participants with unmutated IGHV

(C) Overall survival, participants with mutated IGHV

Tables

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

	FCR (n=263)	I+V (n=260)	Total (n=523)
Age			
Median (IQR)	62 (57-67)	62 (55-67)	62 (56-67)
=< 65 years	181 (68.8%)	179 (68.8%)	360 (68.8%)
> 65 years	82 (31.2%)	81 (31.2%)	163 (31.2%)
Sex			
Male	187 (71.1%)	186 (71.5%)	373 (71.3%)
Female	76 (28.9%)	74 (28.5%)	150 (28.7%)
Ethnicity			
White	240 (91.3%)	233 (89.6%)	473 (90.4%)
Mixed - White and Black Caribbean, African	0 (0.0%)	2 (0.8%)	2 (0.4%)
Other mixed background	1 (0.4%)	1 (0.4%)	2 (0.4%)
Asian – Indian, Pakistani, Bangladeshi	4 (1.5%)	4 (1.5%)	8 (1.6%)
Other Asian background	1 (0.4%)	1 (0.4%)	2 (0.4%)
Black – Caribbean, African	2 (0.8%)	3 (1.2%)	5 (1.0%)
Other Black background	1 (0.4%)	4 (1.5%)	5 (1.0%)
Other ethnic group	0 (0.0%)	2 (0.8%)	2 (0.4%)
Not stated	14 (5.3%)	10 (3.9%)	24 (4.6%)
WHO performance status			
0	181 (68.8%)	181 (69.6%)	362 (69.2%)
1	69 (26.2%)	69 (26.5%)	138 (26.4%)
2	8 (3.1%)	8 (3.1%)	16 (3.1%)
Missing	5 (1.9%)	2 (0.8%)	4 (0.8%)
Binet Stage			
Progressive A or B	152 (57.8%)	151 (58.1%)	303 (57.9%)
C	111 (42.2%)	109 (41.9%)	220 (42.1%)
B Symptoms			
Yes	121 (46.0%)	128 (49.2%)	249 (47.6%)
Missing	6 (2.3%)	2 (0.8%)	8 (1.5%)
Creatinine clearance (mL/min)			
Median (range)	79.0 (37.0, 247)	83.0 (40.0, 231)	82.0 (37.0, 247)
Missing	0	1	1
ß2 microglobulin concentration (mg/L)			
Median (range)	4.00 (1.70, 13.1)	4.00 (1.90, 14.3)	4.00 (1.70, 14.3)
Missing	12	12	24
Duration of CLL (months)			
Mean (s.d.)	33.7 (34.0)	37.9 (44.9)	35.8 (40.0)
Median (range)	21.4 (0.00, 162)	23.3 (0.10, 263)	22.8 (0.00, 263)

	FCR (n=263)	I+V (n=260)	Total (n=523)
Missing	42	28	70
VH mutation status			
Mutated	80 (30.4%)	93 (35.8%)	173 (33.1%)
Unmutated	138 (52.5%)	123 (47.3%)	261 (49.9%)
Subset 2 / Mutated	6 (2.3%)	10 (3.8%)	16 (3.1%)
Subset 2 / Unmutated	7 (2.7%)	3 (1.2%)	10 (1.9%)
Not available	32 (12.2%)	31 (11.9%)	63 (12.0%)
Hierarchical genetic abnormalities			
TP53 deletion	0 (0.0%)	1 (0.4%)	1 (0.2%)
ATM deletion	50 (19.0%)	45 (17.3%)	95 (18.2%)
Trisomy 12	29 (11.0%)	57 (21.9%)	86 (16.4%
Normal karyotype	69 (26.2%)	52 (20.0%)	121 (23.1%)
13q deletion	100 (38.0%)	87 (33.5%)	187 (35.8%)
Undetermined	15 (5.7%)	18 (6.9%)	33 (6.3%)

Table 2: AEs in the Safety Population, According to Maximum Grade

	FCR (n=239)				I+V (n=252)			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Acute kidney injury	4 (1.7%)	3 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anemia	50 (20.9%)	33 (13.8%)	4 (1.7%)	0 (0%)	24 (9.5%)	2 (0.8%)	0 (0%)	0 (0%)
Atrial fibrillation/Arrythmia	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	10 (4.0%)	2 (0.8%)	0 (0%)	0 (0%)
Constipation	60 (25.1%)	0 (0%)	0 (0%)	0 (0%)	8 (3.2%)	1 (0.4%)	0 (0%)	0 (0%)
Cough	45 (18.8%)	4 (1.7%)	0 (0%)	0 (0%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	46 (19.2%)	6 (2.5%)	0 (0%)	0 (0%)	58 (23%)	2 (0.8%)	0 (0%)	0 (0%)
Dyspnea	22 (9.2%)	3 (1.3%)	1 (0.4%)	0 (0%)	10 (4%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	108 (45.2%)	9 (3.8%)	0 (0%)	0 (0%)	38 (15.1%)	1 (0.4%)	0 (0%)	0 (0%)
Febrile neutropenia	0 (0%)	13 (5.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	57 (23.8%)	17 (7.1%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Haemolysis / Haemolytic anaemia	3 (1.3%)	3 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Headache	31 (13%)	1 (0.4%)	0 (0%)	0 (0%)	10 (4%)	0 (0%)	0 (0%)	0 (0%)
Hypertension	3 (1.3%)	1 (0.4%)	0 (0%)	0 (0%)	6 (2.4%)	6 (2.4%)	0 (0%)	0 (0%)
Infections and infestations - Other	0 (0%)	3 (1.3%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Infusion related reaction	64 (26.8%)	2 (0.8%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung infection	3 (1.3%)	3 (1.3%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lymphocyte count decreased	4 (1.7%)	4 (1.7%)	4 (1.7%)	0 (0%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)
Nausea	138 (57.7%)	1 (0.4%)	0 (0%)	0 (0%)	43 (17.1%)	3 (1.2%)	0 (0%)	0 (0%)
Neutropenia	27 (11.3%)	53 (22.2%)	60 (25.1%)	0 (0%)	23 (9.1%)	16 (6.3%)	10 (4%)	0 (0%)
Other	26 (10.9%)	7 (2.9%)	0 (0%)	1 (0.4%)	24 (9.5%)	7 (2.8%)	0 (0%)	0 (0%)
Platelet count decreased	65 (27.2%)	16 (6.7%)	8 (3.3%)	0 (0%)	39 (15.5%)	3 (1.2%)	2 (0.8%)	0 (0%)
Rash	66 (27.6%)	5 (2.1%)	0 (0%)	0 (0%)	26 (10.3%)	1 (0.4%)	0 (0%)	0 (0%)

	FCR (n=239)				I+V (n=252)			
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Sepsis	0 (0%)	10 (4.2%)	4 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin infections	3 (1.3%)	3 (1.3%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Taste alteration/loss of appetite	30 (12.6%)	0 (0%)	0 (0%)	0 (0%)	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)
Upper respiratory infection	24 (10%)	8 (3.3%)	0 (0%)	0 (0%)	6 (2.4%)	1 (0.4%)	0 (0%)	0 (0%)
Vomiting	65 (27.2%)	5 (2.1%)	0 (0%)	0 (0%)	15 (6%)	1 (0.4%)	0 (0%)	0 (0%)

Grade 1-2 in ≥10% of participants and Grade 3-5 in ≥1% of participants in the safety population.