Title: Ibrutinib plus venetoclax with MRD-directed duration of treatment is superior to FCR and is a new standard of care for previously untreated CLL: Report of the Phase III UK NCRI FLAIR study

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Introduction:
Ibrutinib (I), irreversible Btk inhibitor, and venetoclax (V), Bcl-2 inhibitor, both improve CLL outcomes in numerous trials compared to chemoimmunotherapy. I and V target two key pathophysiological pathways in CLL suggesting possible synergy. This is supported by *in vitro* studies and by Phase II trials in which I+V results in high proportions of measurable residual disease (MRD) negativity. A Phase III trial comparing I+V with chlorambucil-obinutuzumab led to the approval of I+V given for 15 months (mo). However, mathematical disease modelling and Phase II studies favor defining treatment duration according to individual patient sensitivity to I+V. We hypothesized that I+V is more effective than FCR in CLL and that treatment duration personalised using MRD response would optimize outcome.

Methods:
FLAIR (ISRCTN01844152) is an ongoing, phase III, multicentre, randomised, controlled, open, parallel group trial for untreated CLL. FLAIR was adapted in 2017 to add 2 arms, I monotherapy and I+V compared to FCR. Here we report the planned analysis of I+V vs FCR. In I+V after 2 months I, V was added with a 4-week dose escalation to 400mg/day and then I+V for up to 6 years. The duration of I+V was defined by MRD. PB MRD was assessed at 12 months and then 6 monthly and if negative, was repeated after 3 months and at 6 months in PB and BM. If all were MRD neg, then the initial MRD neg PB was considered the time to MRD negativity, and duration of therapy was double that period. Thus, treatment duration was 2 to 6 years. The primary endpoint for I+V vs FCR was PFS. Key secondary endpoints presented are OS, IWCLL response, MRD and safety. Appropriate endpoints were analysed by CLL prognostic sub-groups.

Results:
523 patients were randomised to FCR (n=263) and I+V (n=260) from 96 UK Centers from 07/20/2017 to 03/24/2021. Data-lock on 05/23/2023. 71.3% male, median age 62 yrs (31.2% >65yo) and 40.9 % Binet Stage C. IGHV unmutated (≥98% homology to germline) in 56.9%, 37.6% IGHV mutated and 5.5% Subset 2. Hierarchical FISH: 20.6% 11q del, 20.1% trisomy 12, 27.8% normal and 31.4% 13q del.
At a median 43.7 months there are 87 progressions - 75 FCR and 12 I+V. The hazard ratio (HR) for PFS for I+V vs FCR is 0.13 (95% CI: [0.07, 0.24]; p<0.0001) (Fig). This result was consistent

for gender, age or stage. At 3 years 2.8% had progressed on I+V compared to 23.2% on FCR. There have been 34 deaths (25 FCR and 9 I+V) resulting in improved overall survival for I+V vs FCR: HR 0.31 (95% CI: [0.15, 0.67]; p=0.0029)[Fig]. At 3 years 2.0% of I+V pts had died compared to 7.0% for FCR.

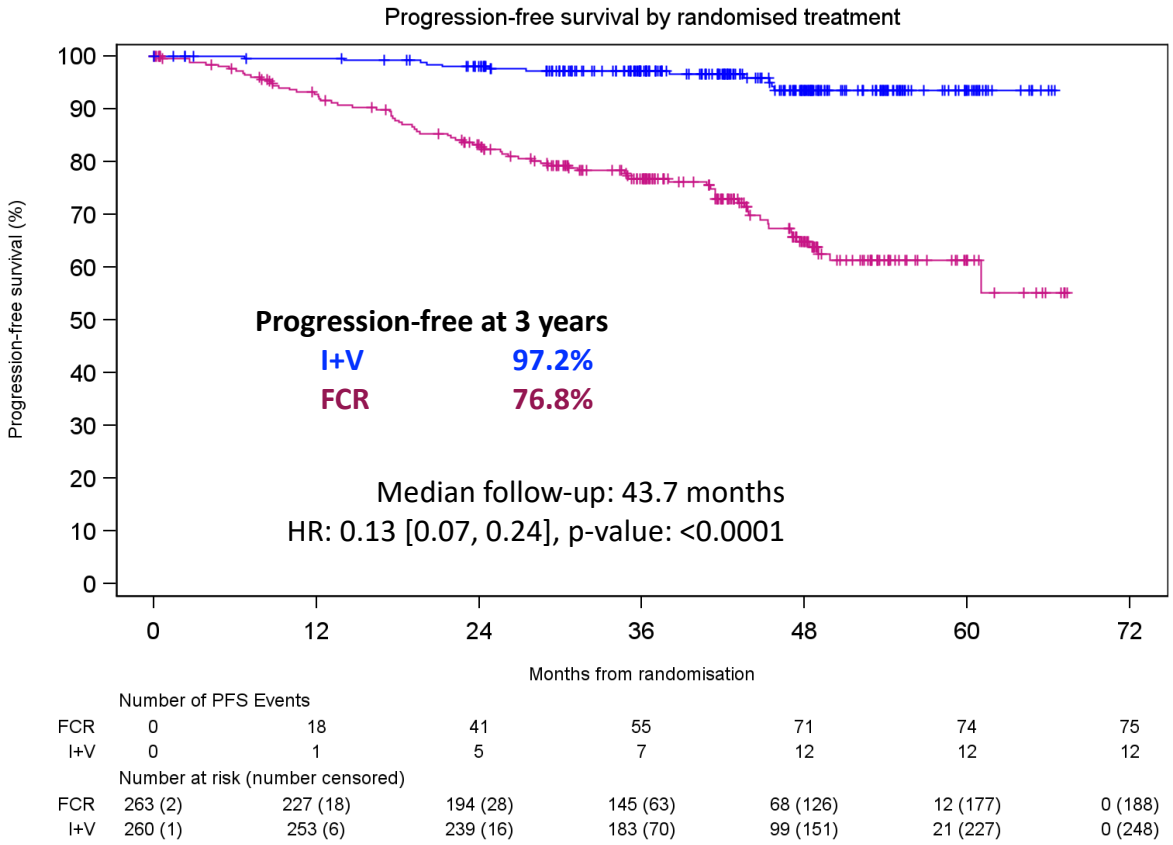
At 9 months (3 months post-FCR) more FCR pts became MRD neg in BM compared to I+V (48.3% vs 41.5%). However, with continued I+V more pts became MRD neg: the odds of MRD negativity at any time for I+V vs FCR were 2.03 (95% CI: [1.43, 2.89]; P<0.001) in BM and 3.91 (95% CI: [2.55, 6.00]; P<0.001) in PB. After 5 years of I+V 68% were BM MRD negative and 90.6% in PB. At 2 years 93/260 (35.8%) I+V pts stopped therapy due to the MRD stopping rules. At 9 months a higher proportion achieved an overall response for I+V; FCR 76.4% (95% CI: [70.82%, 81.42%]) and I+V 86.5% (95% CI: [81.78%, 90.44%]). CR rates of 49.0% (95% CI: [42.86%, 55.26%]) for FCR and 59.2% (95% CI: [52.99%, 65.26%]) for I+V. This difference was greater for best response at any time: ORR 83.7% (95% CI: [78.62%, 87.91%]) for FCR vs 95.4% (95% CI: [92.08%, 97.59%]) for I+V; CR 71.5% (95% CI: [65.61%, 76.86%]) for FCR vs 92.3% (95% CI: [88.37%, 95.24%])) for I+V. The odds ratios estimate to achieve CR with I+V vs FCR is 1.51 (95% CI: [1.07, 2.14]; p<0.05). Responses and outcomes by FISH and IGHV will be presented.

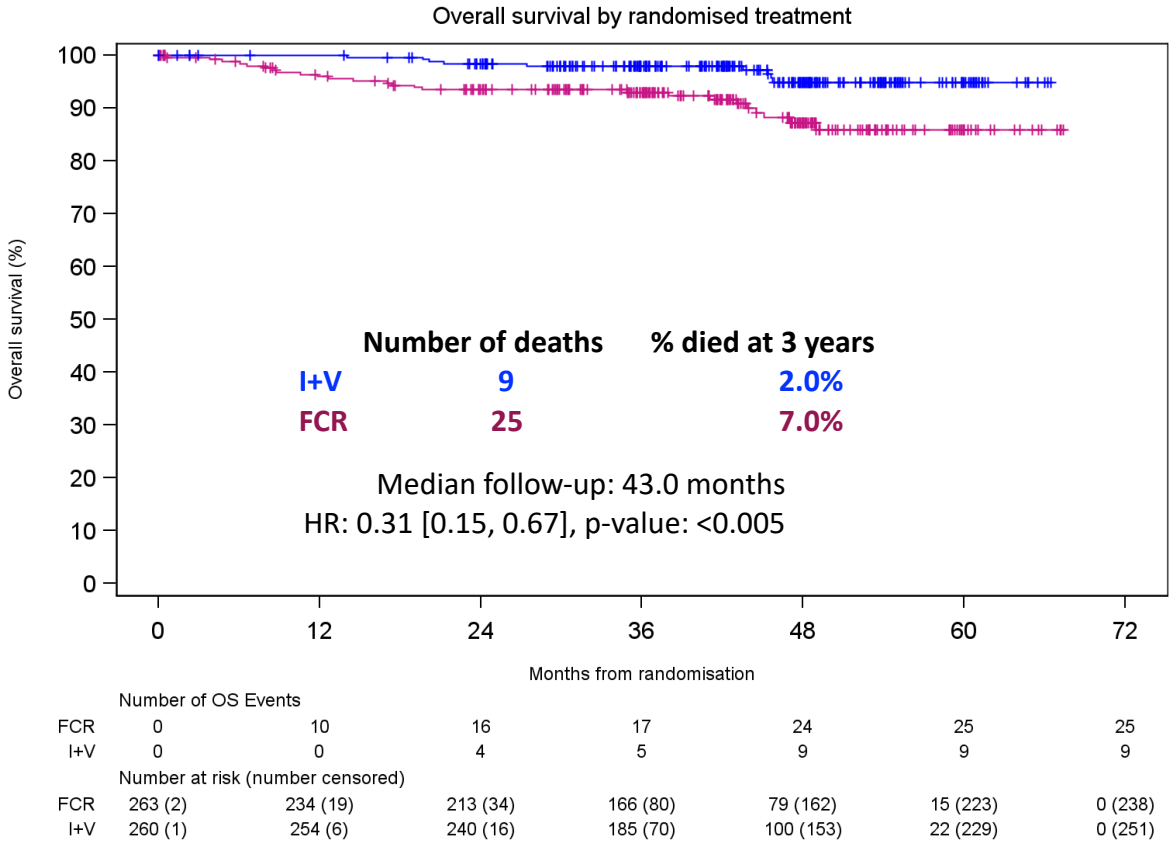
SAEs were reported in 252 (51.3%) pts (129 FCR vs 123 I+V). Notable SAEs by organ class for FCR vs I+V: infections in 18.8% of FCR pts vs 22.2% for I+V; blood and lymphatic in 31% vs 5%; and cardiac in 0.4% vs 10.7%. 4 pts had sudden or cardiac deaths – 2 FCR and 2 I+V. 69 other cancers were diagnosed (45 in FCR, 24 in I+V) in 51 pts (34 FCR, 17 I+V). The incidence of other cancers per 100 pt-years is greater for FCR than I+V; 5.4 (95% CI: [5.11, 5.68]) vs. 2.6 (95% CI: [2.40, 2.79]). There were 7 cases of secondary MDS/AML with FCR and 1 with I+V.

Conclusion:

Ibrutinib plus venetoclax significantly improved progression-free and overall survival compared to FCR in untreated CLL. The remarkable outcomes for I+V indicate that directing the duration of I+V according to individual MRD response maximizes outcomes. The results in FLAIR are dramatically better than in any previous Phase III CLL trial indicating that I+V with the treatment guided by MRD is a new gold standard for CLL treatment.

Figure:


Progression-free survival by randomised treatment
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
Progression-free at 3 years
I+V 97.2%
FCR 76.8%
Median follow-up: 43.7 months
HR: 0.13 [0.07, 0.24], p-value: <0.0001
0
12
24
36
48
60
72
Months from randomisation
Number of PFS Events
FCR 0 18 41 55 71 74 75
I+V 0 1 5 7 12 12 12
Number at risk (number censored)
FCR 263 (2) 227 (18) 194 (28) 145 (63) 68 (126) 12 (177) 0 (188)
I+V 260 (1) 253 (6) 239 (16) 183 (70) 99 (151) 21 (227) 0 (248)


Overall survival by randomised treatment
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Number of deaths % died at 3 years
I+V 9 2.0%
FCR 25 7.0%
Median follow-up: 43.0 months
HR: 0.31 [0.15, 0.67], p-value: <0.005
0
12
24
36
48
60
72
Months from randomisation
Number of OS Events
FCR 0 10 16 17 24 25 25
I+V 0 0 4 5 9 9 9
Number at risk (number censored)
FCR 263 (2) 234 (19) 213 (34) 166 (80) 79 (162) 15 (223) 0 (238)
I+V 260 (1) 254 (6) 240 (16) 185 (70) 100 (153) 22 (229) 0 (251)