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Title: Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: Results of the Phase III NCRI FLAIR Trial

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Introduction:
The gold standard chemoimmunotherapy (CIT) in previously untreated CLL is the combination of fludarabine, cyclophosphamide and rituximab (FCR). Ibrutinib (Ibr), the first irreversible inhibitor of Bruton's tyrosine kinase approved for CLL, has improved outcomes in numerous clinical trials compared to different CIT.

Methods:
FLAIR (ISRCTN01844152) is an ongoing, phase III, multicentre, randomised, controlled, open, parallel group trial for previously untreated CLL requiring therapy according to the IWCLL 2008 guidelines funded by Cancer Research UK, Janssen and AbbVie. Patients over 75 years or with >20% 17p deleted cells were excluded. Participants were randomised on a 1:1 basis to receive 6 cycles of FCR (oral fludarabine 24mg/m^2/day for 5 days, oral cyclophosphamide 150mg/m^2/day for days with IV rituximab [375 mg/m^2 on day 1/2 of cycle 1; 500 mg/m^2 on day 1 of cycles 2-6]) every 28-days or IR (Ibrutinib [420mg/day] plus rituximab [6 doses as for FCR]) given for up to 6 years with stratification by disease stage, age, gender and centre. The primary endpoint was to assess whether IR was superior to FCR in terms of PFS. Secondary endpoints included overall survival, attainment of undetectable MRD; response to therapy; safety and toxicity; health-related quality of life and cost-effectiveness. A formal interim analysis was planned when 191 events were observed in both arms or 109 events in the FCR arm alone with a p-value of 0.005 leading to reporting of the trial. Here we report the results after this planned interim.

Results:
A total of 771 patients were randomised on FLAIR (385 to FCR and 386 to IR) from 113 UK Centres between 19/9/14 and 19/7/18. The data was locked on 24/5/21. 73.3% were male, median age was 62 years (33.6% >65yo) and 45.1% were Binet Stage C. IGHV data was available for 728/771 (94.4%) patients with 53.2% IGHV unmutated (≥98% homology to germline), 40.5% IGHV mutated and 6.3% Subset 2. Hierarchical FISH testing revealed 0.4% 17p del, 15.4% 11q del, 12.3% +12, 29.7% normal and 35% 13q del with 7.1% failed. The arms were well-balanced for disease variables with no significance differences. Median follow-up was 52.7 months. IR had a superior PFS compared to FCR (Median PFS not reached for IR versus 67 months for FCR; HR: 0.44; p<0.001; see Figure). The PFS was significantly better for IR in IGHV unmutated patients (HR: 0.41; p<0.001), but not for IGHV mutated at this follow-up (HR: 0.66; p=0.179). There was no difference in overall survival between the two arms (HR: 1.01; p=0.956) with a total of 29 deaths in FCR arm (including 4

from CLL, 3 Richter's [RT], 3 AML/MDS, 3 COVID-19 and 2 cardiac) and 30 in the IR arm (including 3 CLL, 1 RT, 0 AML/MDS, 3 COVID-19 and 8 cardiac). Second line treatment has been given to 59 patients after FCR (including 38 BTKi, 7 venetoclax+R [venR], 4 BendamustineR [BR] and 3 CHOP-R [RT]) and 21 after IR (7 FCR, 5 venR, 1 BR, 1 CHOP-R [RT], 1 ABVD [Hodgkin's]). Therefore for CLL progression after FCR 88.1% of patients have received targeted therapies. The survival with FCR in FLAIR is significantly improved compared to FCR previous NCRI trials (ADMIRE and ARCTIC) which had the same inclusion criteria, the same Centres and identical FCR schedule, but prior to the wide availability of targeted therapy in relapse (recruited between 2009 and 2012). The 4 year overall survival for FCR in FLAIR was 94.5% compared to 84.2% for FCR between 2009 and 2012. SAE's were reported in 53.7% of patients in FCR and 53.4% in IR. Notable differences for SAE's by organ class for FCR vs IR: infections in 33.6% of patients vs 27.1%; blood and lymphatic in 19.8% vs 10.7% of patients; and cardiac in 1.1% vs 8.3% of patients. Across the trial there were 11 sudden or cardiac deaths: 9 IR and 2 FCR. Further analysis indicated that 8 of the 9 sudden deaths in the IR patients had a history of hypertension or cardiac disease all of whom were taking ACE-inhibitors at trial entry. Neither of the sudden deaths in the FCR arm had a prior cardiac or hypertensive history or treatment. There were 6 cases of secondary MDS/AML in the FCR arm and 1 in the IR arm.

Conclusion:
Ibrutinib plus rituximab resulted in a superior PFS compared to FCR. There was no difference in overall survival but this appeared to be due to the crossover to targeted therapy in the patients progressing after FCR.