# Effect of targeted treatment on IGHV subset #2 and #8 patients in CLL: Comparison of MRD directed Ibrutinib plus Venetoclax treatment to the Ibrutinib and FCR arms of the FLAIR Trial

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Surita Dalal[1,2], Jane Shingles[1], Sean Girvan[3], David Cairns[3], Nichola Webster[1,2], Andrew Rawstron[1], Darren Newton[2], Sue Bell[3], Natasha Greatorex[3], Anna Hockaday[3], Sharon Jackson[3], David Phillips[3], David Stones[3], David Allsup[4], Adrian Bloor[5], Anita Sarma[6], Abraham Varghese[6], Peter Hillmen[2] and Talha Munir[6]

[1]HMDS, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Leeds Institute of Medical Research, University of Leeds, Leeds, UK; [3]Leeds Cancer Research UK CTU, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; [4]Castle Hill Hospital, Cottingham, Hull, UK; [5]Haematology and Transplant Unit, Christie Hospital NHS Foundation Trust, Manchester, UK; [6]Department of Haematology, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

## 1. Introduction

- Somatic hypermutation (SHM) status of the immunoglobulin heavy chain variable (IGHV) gene is a key independent prognostic marker in CLL.
- Approximately one third of CLL B-cell receptor (BcR) immunoglobulins (IG) display highly homologous variable heavy complementarity-determining region 3 (VH CDR3), and can be assigned to distinct subsets, with virtually identical or stereotyped BcR IG.
- Subset #2 (S#2) predominantly utilizes the IGHV3-21 gene segment, is the most common subset in CLL and is characterised by poor clinical outcome, irrespective of SHM status[2]. Subset #8 (S#8), defined by the use of IGHV4-39 gene segment, is associated with clinically aggressive disease and high risk of Richter's transformation (RT)[3]
- FLAIR has reported improved Progression-Free Survival (PFS) and Overall Survival with MRD directed ibrutinib and venetoclax (I+V) compared to Fludarabine, Cyclophosphamide, Rituximab (FCR) in CLL[4]. However, the synergistic effect of I+V on S#2 and S#8 patients (pts) is poorly understood.

Aim: To examine 5-yr PFS in S#2 pts, comparing MRD-directed I+V to Ibrutinib (I & IR) and FCR arms of FLAIR. Report on RT in S#8.

## 2. Methods

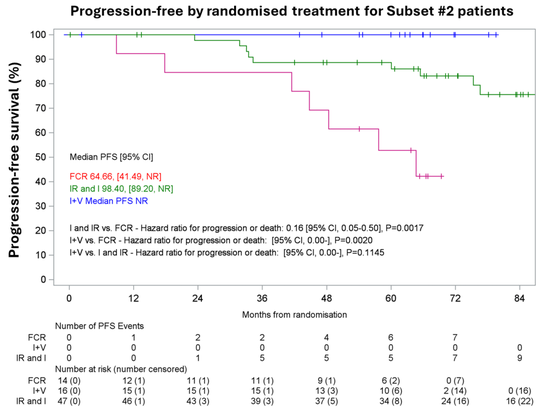
- FLAIR (ISRCTN01844152) is an ongoing phase III, multicentre, randomised, controlled, open-label trial in previously untreated CLL pts. Pts enrolled on the FLAIR Trial were ≤75 years, considered fit for FCR were randomised to receive I+V, I, IR or FCR. Pts with >20% chrom.17p deletion were excluded.
- Somatic hypermutation status was determined by PCR amplification of *IGHV-IGHD-IGHJ* gene rearrangements using IGHV leader/FR1/JH primers. Bidirectional Sanger sequencing was analysed using IMGT/V-Quest and the ARResT/AssignSubsets tool.
- Group comparisons were made using the Cox proportional hazards model, adjusted for minimisation factors, excluding centre, to estimate HRs & 95% CIs. Log-rank test was used to estimate p-value where HR was zero (zero progression events in one or more treatment arms).

## 3. Results

### CLL Subset #2 and PFS

- 1172 pts were randomly assigned to receive I+V (n=260), I&IR (n=263 & 386) or FCR (n=263). Median follow up 58mth (63mth I+V; 51mth I&IR; 56mth FCR).
- 77 pts (6.6%) were assigned to CLL S#2 (n=16 I+V; n=47 I&IR; n=14 FCR).

A significant difference in PFS was observed between S#2 pts treated with I&IR and I+V compared to FCR (p=0.002 and 0.002 respectively) but not between I+V and I&IR (p=0.115). The 5yr PFS for S#2 patients was 100% for I+V, 88.9% for I&IR and 52.7% for FCR.

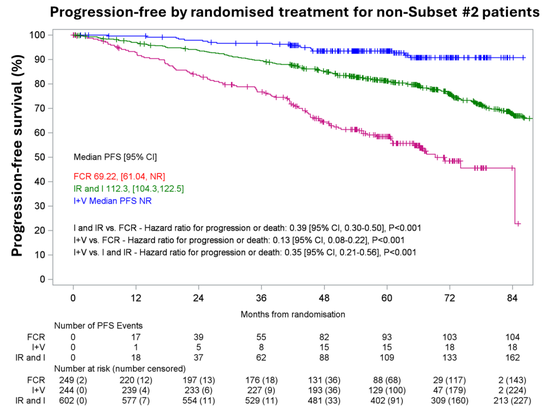



### CLL non-Subset #2 and PFS

- Of the 1,095 non-S#2 pts, 244 received treatment with I+V, 602 with I&IR, and 249 with FCR.

A significant difference in PFS was observed between non-S#2 pts treated with I&IR and I+V compared to FCR (p<0.001 for both) and between I+V and I&IR (p<0.001). The 5yr PFS for non-S#2 patients was 93.5% for I+V, 80.2% for I&IR and 58.5% for FCR.

- **Overall, there was no significant difference in PFS between non-S#2 and S#2 pts (p=0.3).**




### CLL Subset #8 and Richter's transformation

- 8 pts (<1%) were assigned to CLL S#8 (n=4 I+V; n=2 I&IR; n=2 FCR). All 8 pts were 100% *IGHV* unmutated.

Overall, 12/1172 patients (1%) on FLAIR were reported to have undergone RT (I+V n=2; I&IR n=6; FCR n=4). However, none of these patients were CLL S#8.

## 4. Conclusions

- **FLAIR trial has shown that targeted treatment is highly effective at mitigating the poor outcome previously associated with CLL subset #2 patients.**
- **Marked responses have been achieved with MRD-directed I+V therapy, with no disease progressions reported so far among subset #2 patients in this treatment arm.**
- **Overall PFS for subset #2 patients was similar to their non-subset #2 counterparts.**
- **No CLL subset #8 patients in the FLAIR trial have developed Richter's transformation to date.**

## References

[1]Agathangelidis *et al*., Blood, 2012. [2]Baliakas *et al*, Blood. 2015. [3]Rossi *et al*, Hematol Oncol. 2009. [4]Munir *et al*, N Engl J Med. 2024

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## Contacts

s.dalal@leeds.ac.uk
tmunir@nhs.net