Second results from the FLAIR trial

These results were presented at the European Hematology Association conference in June 2022

This document is a plain English summary of the presentation.
A link to the summary presented at the conference is at the end of this document

Conclusion: For people having their first treatment for CLL, ibrutinib with venetoclax is better than ibrutinib alone.

Why was the research needed?

For people having their first treatment for chronic lymphocytic leukaemia (CLL), the traditional treatment is chemotherapy (usually the combination of fludarabine, cyclophosphamide and rituximab, called FCR). Ibrutinib and venetoclax are relatively new (compared to chemotherapy) targeted cancer drugs. Previous studies suggested ibrutinib would work well for treatment of CLL. Small studies of people whose CLL had come back suggested that treatment with the combination of ibrutinib and venetoclax also worked well.

What were the main questions studied?

The FLAIR trial studied whether taking ibrutinib with venetoclax is better than ibrutinib alone for people having their first treatment for CLL. Results from this part of the trial were presented at the conference in June 2022 and are summarised here.

Who took part in the trial?

This part of the study opened in July 2017. 523 adults (younger than 76 years) having their first treatment for CLL took part. Results presented here are for 274 participants who have completed two years follow up. They joined the trial between July 2017 and March 2019 at 83 hospitals in the UK.

Of those who took part, three quarters were men, and a third were older than 65 years. Most participants (93%) were tested for the Immunoglobulin Variable Heavy chain gene (IgVH). For half (48%) this was unmutated (meaning they are higher risk than if IgVH was mutated). Participants were similar in the two treatment groups.

What happened during the study?

For everyone who took part, their doctor considered both study treatments were appropriate. As FLAIR was a randomised trial, the decision about which treatment each person received was decided by chance, rather like tossing a coin. This process is called randomisation. A

computer chose which treatment each participant received. Neither they nor their doctor were able to choose.

What treatments did the participants receive?

136 participants had ibrutinib with venetoclax (I+V), and 138 had ibrutinib alone (I). Ibrutinib was given as 3 capsules taken at the same time each day (total dose 420mg). For I+V, venetoclax was added after two months of taking ibrutinib. The dose of venetoclax was increased over 5 weeks to reach 400mg per day, taken as four tablets after breakfast.

Control of CLL was checked with blood and bone marrow tests. If these tests showed their CLL was well controlled participants could stop treatment. The earliest they could stop was after two years of treatment.

What side effects and other problems did the participants have?

Overall, 40% of the participants had serious side effects, and this was similar in both groups (42% for I+V; 38% for I). The groups were also similar in the type of side effects. These included serious infections (15% for I+V; 20% for I) and high blood pressure or heart problems (12% for I+V; 8% for I).

In the first year after joining the trial non-serious side effects were common. Some were different between the groups. People in the I+V group were more likely to have diarrhoea than those in the I group (53% for I+V; 29% for I), and more likely to have anaemia (29% for I+V; 17% for I). They were also more likely to have low white cells (36% for I+V; 9% for I), and low platelets (24% for I+V; 14% for I).

What were the results of the trial?

Before starting treatment people with CLL have leukaemia cells in their blood and bone marrow. This is called minimal residual disease (MRD) positive. After treatment, some people will have no detectable leukaemia cells. This is called MRD negative.

After two years of treatment, in the I+V group 65% of participants were MRD negative in their bone marrow (89/136) and 71% were MRD negative in their blood (97/136). No participants in the I group were MRD negative in either their bone marrow or blood. After two years, 40% (54/136) of participants in the I+V group stopped their treatment as they met the MRD criteria for stopping treatment.

After nine months, most participants had some response to their treatment (either complete or partial). This was similar between the two groups (120/136, 88% for I+V; 119/138, 86% for I). Complete response (CR) at 9 months was more frequent in the I+V group (81/136, 60% for I+V;
11/138, 8% for I).

How has this study helped people with CLL?

This study found that for people having their first treatment for CLL, the combination of ibrutinib and venetoclax is better than ibrutinib alone for reducing detectable leukaemia cells in both bone marrow and blood after two years of treatment.

Who were the researchers who did this study?

The trial team was led by Professor Peter Hillmen, and supported by the Leeds Institute of Clinical Trials Research.

Summary of the conference presentation is available here:

https://library.ehaweb.org/eha/2022/eha2022-congress/357009/peter.hillmen.the.combination.of.ibrutinib.plus.venetoclax.results.in.a.high.html

Trial registration number: ISRCTN018