CLL SUPPORT
Helping people affected by CLL and SLL

New results from the FLAIR trial

These results were published in December 2023
(a link to the article is at the end of this document)
This document is a plain English summary of the article.

For people having their first treatment for CLL, ibrutinib with venetoclax is better than chemotherapy (fludarabine, cyclophosphamide and rituximab, FCR): Results of the FLAIR trial.

Why was the research needed?

For people having their first treatment for chronic lymphocytic leukaemia (CLL), the chemotherapy that works best is the combination of fludarabine, cyclophosphamide and rituximab (called FCR). Ibrutinib and venetoclax are relatively new targeted cancer drugs (compared to chemotherapy), which previous studies suggested would work well for treatment of CLL.

What were the main questions studied?

The trial studied whether ibrutinib with venetoclax is better than FCR for people having their first treatment for CLL. It also studied whether using blood and bone marrow tests to measure the CLL level, and using the result of these tests to decide how long each person took ibrutinib with venetoclax, gave the best results. This is called measurable residual disease (MRD) guided treatment.

The FLAIR trial is also studying (i) whether ibrutinib with rituximab (another targeted drug called a monoclonal antibody) is better than FCR, and (ii) whether taking ibrutinib alone is better than taking ibrutinib with venetoclax. Links to plain English summaries of results from these parts of the trial are at the end of this document.

Who took part in the trial?

Participants joined this part of the study between July 2017 and March 2021. 523 adults (younger than 76 years) having their first treatment for CLL took part at 96 hospitals in the UK. Results presented here use data collected up to 23 May 2023. At that time participants had been in the study for, on average, 3 years 6 months.

Of those who took part, three quarters were men (which was to be expected as CLL is more common in men), and a third were older than 65 years. Most participants (83%) were tested

for the Immunoglobulin Variable Heavy chain gene (IgVH). For half this was unmutated (meaning they are higher risk than if IgVH was mutated). Participants were similar in the two treatment groups at the start of the study.

What happened during the study?

For everyone who took part, their doctor considered both study treatments were an appropriate treatment. 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?

260 participants had ibrutinib with venetoclax (I+V), and 263 had FCR. Ibrutinib was given as three capsules taken at the same time each day. For the first eight weeks ibrutinib was taken on its own. After eight weeks, venetoclax was started at a low dose and increased over five weeks to four tablets after breakfast each day. Treatment continued for up to six years. 146 participants (56%) stopped their I+V treatment before six years, based on their blood and bone marrow tests. Of these, five restarted their I+V treatment.

FCR was given as tablets of fludarabine, and cyclophosphamide taken for five days every four weeks. Each four weeks of treatment is called a cycle. On the first day of each cycle rituximab was given as a drip into the vein. FCR was given for six cycles.

What side effects and other problems did the participants have?

Overall, half the participants had serious side effects, and this was similar in both groups (49% on I+V; 54% on FCR).

There were some differences between the treatment groups in the type of side effects. People in the I+V group had fewer blood and lymphatic complications (5% on I+V; 31% on FCR). People in both groups had similar levels of infection (22% for I+V; 19% for FCR). Those in the I+V group had more heart and blood pressure problems (11% on I+V; 1% on FCR). Eight people had serious bleeding (5 on I+V; 3 on FCR).

51 people developed another cancer, 17 were on I+V and 34 on FCR. Of these, nine people developed a second blood cancer (either myelodysplastic syndrome or acute myeloid leukaemia), one was on I+V and eight were on FCR. Five people developed Richter's transformation, one was on I+V and four on FCR.

What were the results of the trial?

Participants in the I+V group had better Progression-Free Survival (PFS) than those in the FCR group. PFS is the time between joining the trial and either CLL getting worse or death. After 3 years, in the I+V group 97% (252/260) were alive and their CLL had not got worse,

compared with 77% (202/263) in the FCR group. Those in the FCR group had an 87%% higher risk of either their CLL getting worse or dying, than those in the I+V group.

Those in the I+V group also had better overall survival. To date, in the I+V group 3.5% people have died (9/260) compared with 9.5% (25/263) in the FCR group. Cause of death for those on I+V was Richter's transformation (1 death), COVID-19 (2 deaths), other infections (1 deaths), second cancer (not blood cancer) (1 death), heart attack (3 deaths). For FCR, cause of death was CLL (4 deaths), Richter's transformation (2 deaths), second blood cancer (3 deaths), COVID-19 (2 deaths), other infections (8 deaths), second cancer (not blood cancer) (2 deaths), heart attack (2 deaths) and other causes (2 deaths).

Some participants needed a second treatment for their CLL; of those in the I+V group 2% (5/260) had a second treatment, compared with 16% (42/263) in the FCR group. Of the 42 who had a second treatment in the FCR group, for 35 participants this included a targeted cancer drug.

How has this study helped people with CLL?

This study found that for people having their first treatment for CLL, I+V was better than FCR for increasing the time to either first progression or death, and for increasing overall survival.

In FLAIR, these results are better than in previous studies of either ibrutinib alone or ibrutinib with venetoclax where everyone had treatment for the same length of time. This suggests that using blood and bone marrow results to help decide how long to continue treatment for each person (MRD guided treatment) should become usual practice.

Who were the researchers who did this study?

The trial team was led by Professor Peter Hillmen and supported by the Leeds Cancer Research UK Clinical Trials Unit.

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Trial registration number: ISRCTN01844152

The article can be accessed here:

Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease | NEJM

Links to plain English summaries of other FLAIR results

(i) Is ibrutinib with rituximab better than FCR

https://cllsupport.org.uk/first-results-from-the-flair-trial/

(ii) Is ibrutinib alone better than ibrutinib with venetoclax

https://cllsupport.org.uk/wp-content/uploads/2023/02/FLAIR-second-results.pdf