

Cancer Research UK AML17 Trial: Summary for Patients and Relatives

The AML17 trial was a programme of development for treatment in adult patients, under 60 years of age, with acute myeloid leukaemia (AML). At the time this trial started in 2008, scientific knowledge of the molecular and biological features of this disease, made it no longer possible for a 'one size fits all' treatment approach for patients. As with previous and current AML trials supported by the National Cancer Research Institute AML working group, this trial took the form of a platform trial which allowed questions to be asked at different stages of the patient's treatment pathway. This allowed the trial team to answer several questions at the same time requiring as few extra patients as possible. AML17 also tested the use of targeted therapies where treatment was based upon different genetic features of the disease.

Randomisations mainly focused on new treatments. However other elements of patient experience were also investigated, these are summarised below:

- Complete remission of disease and reasons if patients failed remission,
- Time frame of remission, risk of relapse (disease coming back) and deaths in first complete remission,
- Overall survival,
- Side effects of drugs,
- Supportive care requirements (included: any blood and/or platelet transfusion, antibiotics, antifungals given and/or number of days in hospital,
- Assessment of patient quality of life and assessment of health economics (included: employment, visits to other health care professionals / costs of prescriptions and/or travel to appointments) for patients in the disease monitoring randomisation.

The trial was Sponsored by Cardiff University and opened across the UK, Denmark and New Zealand in April 2009. Projected recruitment was 2,500 to 3000 patients. Each patient's treatment was to be completed within 6 months and patients were followed up for life in the 'routine care' environment. The trial ran for 6.5 years and recruited over 3,500 patients in 138 hospitals.

Several different questions were included in the original design of the trial, some of which were updated as recruitment targets were reached.

The following major questions were proposed:

Different randomisations and treatment courses were given to two separate groups of patients: Acute Promyelocytic (APL) patients and non-APL patients.

APL is a rare sub type of AML which has a unique molecular basis. APL is treated in a very different way from other forms of AML, as it is very sensitive to treatment with All Trans Retinoic Acid (ATRA)

| | | |
|---|----|---|
| 1. For Acute Promyelocytic (APL) patients, which compared: | | |
| Standard chemotherapy Antracycline plus (ATRA) | vs | Chemotherapy free combination of All Trans-retinoic Acid (ATRA) plus Arsenic Trioxide (ATO) |
| Number of patients: 235 | | |
| We discovered the following: | | |
| Quality of life did not differ significantly between the two groups. Data was reported in the number of severe side effects in both groups (57 patients in the ATRA group and 40 patients in the ATRA/ATO group). We found that ATO is a feasible treatment with a high cure rate and low relapse risk. Furthermore, there was a reduction in the amount of time spent as an in-patient. Certain side effects such as hair loss were completely avoided with ATO. | | |
| Impact: | | |
| Although overall survival was not different between arms, ATO was shown to significantly improve survival without relapse. The findings in AML17 contributed to the regulatory approval for ATO as a first line treatment for APL and its approval by NICE (National Institute for Health and Care Excellence). | | |

| | | |
|--|----|---------------------------------------|
| 2. For non-APL patients which compared: | | |
| 4 chemotherapy schedules: | | |
| ADE (Ara C/Daunorubicin (DA) /Etoposide) | vs | ADE plus Mylotarg 3 mg/m ² |
| | or | ADE plus Mylotarg 6 mg/m ² |
| | or | DA plus Mylotarg 3 mg/m ² |
| | or | DA plus Mylotarg 6 mg/m ² |
| Number of patients: 788 | | |
| We discovered the following: | | |
| We saw no significant benefit of using Mylotarg at the higher dose of 6 mg, although there was a possible benefit in the adverse risk patients who have not been shown to benefit from Mylotarg, at the standard dose. The 6 mg/m ² dose did have a detrimental effect with respect to liver toxicity and platelet count recovery, and significantly increased the day 30 and 60 mortality. | | |
| Impact: | | |
| In cases in which a single dose schedule is used, the 3 mg/m ² dose of Mylotarg is adequate. | | |

3. For non-APL patients who have a FLT3 mutation, which compared:

| | | |
|--------------|----|---|
| Chemotherapy | vs | Chemo plus FLT3 inhibitor (CEP 701 or Lestaurtinib) |
|--------------|----|---|

Number of patients randomised: 325

We discovered the following:

There was no overall clinical benefit after adding CEP-701 or Lestaurtinib to standard chemotherapy, although it did prove feasible in younger patients. The improved clinical outcomes seen in patients achieving sustained FLT3 inhibition, encourage continued evaluation of FLT3-directed therapy alongside front-line AML treatment.

Impact:

Future trials may explore further evaluation of FLT3-directed therapy alongside front-line AML treatment.

4. For non-APL patients who lack a FLT3 mutation, and who are not high risk, and who do not have Core Binding Factor leukaemia, which compared:

| | | |
|--------------|----|---|
| Chemotherapy | vs | Chemo plus mTOR inhibition (RAD 001/Everolimus) |
|--------------|----|---|

Number of patients: 339

We discovered the following:

The primary end point was relapse-free survival, however at 5 years there was no difference. The Independent Data Monitoring Committee advised this randomisation to be closed early, owing to excess mortality and there being no evidence of beneficial disease control from mTOR inhibition.

Impact:

The trial arm was closed early.

5. For non-APL high risk patients, which compared:

| | | |
|----------|----|--------------------------|
| FLAG-Ida | vs | Daunorubicin/Clofarabine |
|----------|----|--------------------------|

Number of patients: 311

We discovered the following:

Deaths occurring within 30 days was lower in the Dannorubicin/Clofarabine arm than in the standard FLAG-Ida, however survival was superior in this arm. We concluded that the FLAG-Ida was superior in high-risk patients, despite not delivering more patients to transplant relapse, post-transplant was reduced.

Impact:

FLAG-ida is now established as the most frequently-used regimen for the treatment of relapsed AML.

6. For non-APL patients, which compared:

3 vs 4 courses of consolidation:

| | | |
|--------------|----|-------------------------|
| MACE or HDAC | Vs | MACE/MidAc of HDAC/HDAC |
|--------------|----|-------------------------|

Number of patients: 1017

We discovered the following:

This part of the trial addressed the important question of the optimal amount of chemotherapy needed. Patients given two courses of HDAC consolidation after achieving remission had a reduced risk of relapse compared to just one course. Although this did not result in a significant benefit in overall survival. Survival without relapse was improved.

Impact:

Four courses of consolidation chemotherapy reduces risk of relapse compared to three, but did not result in a significant improvement in survival.

7. For non-APL patients with FLT3 mutation who relapsed:

Treated with Pacritinib on relapse

Number of patients: 30

We discovered the following:

This is the first clinical experience of Pacritinib in patients with AML. Tolerability was encouraging and in the challenging setting of relapsed/primary refractory FLT3 mutated AML, where FLT3 directed monotherapy has seldom achieved complete remission, clinical responses were seen in one-third of evaluable patients. Importantly, several patients were successfully bridged to potentially curative allogenic stem cell transplant.

Impact:

Encouraging results suggest further clinical evaluation of Pacritinib in this setting is warranted.

8. For non-APL patients: To assess the clinical value of minimal residual disease monitoring by randomising patients to be monitored versus not to be monitored, which compared:

| | | |
|---|----|--|
| Monitoring of patients' leukaemia treatment | vs | No monitoring of patients' leukaemia treatment |
|---|----|--|

Number of patients: 400

We discovered the following:

The final randomisation for this trial explored the impact of sensitive and regular monitoring of patient samples. Over 400 patients were randomised to investigate if regularly monitoring patients (every 3 months), using sophisticated laboratory techniques could improve outcomes.

Impact:

This was carried forward into the AML19 trial and the data is currently being analysed.

Clinical Trial Results:

The first results were published in 2015 and additional publications have been completed since the end of the trial, detailed at the end of this summary.

What are the implications of this Trial?

The trial has helped establish ATO as frontline treatment for APL transforming the treatment of this disease. It has established the optimal amount and type of chemotherapy required to prevent relapse in patients who achieve remission and has set a new standard in the treatment of patients who fail to achieve a remission or have other high-risk features. An analysis of response to initial therapy has identified groups of patients who were previously thought to be good risk but in fact have a poor prognosis and this methodology has been integrated into the successor AML19 to improve outcomes.

The AML17 trial has shown that it is possible to deliver several therapeutic advances under the umbrella of a single trial in a rare disease by asking multiple questions at different times in the patient's journey.

The Trial Team are most grateful to patients and their relatives who chose to have their treatment in this trial. As can be seen, the trial has helped us refine and improve the treatment we now offer and provides a new baseline against which to test new treatments.

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&

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&

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Publications:

Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials.

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(14\)70281-5/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70281-5/fulltext)

The Lancet Oncology, Articles, Vol 15, Issue 9, p986-996, August 01, 2014

Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomisation, controlled, phase 3 trial.

The Lancet Oncology, Articles. Volume 15, Issue 13, p1295-1305, October 01, 2015

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(15\)00193-X/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00193-X/fulltext)

A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: Results from the UK NCRI AML17 trial in 1206 patients

Blood. (2015) 125 (25): 3878–3885.

<https://ashpublications.org/blood/article/125/25/3878/34316/A-randomized-comparison-of-daunorubicin-90-mg-m2>

Assessment of Minimal Residual Disease in Standard-Risk AML

The New England Journal of Medicine. February, 2016; 374:422-433

<https://www.nejm.org/doi/full/10.1056/NEJMoa1507471>

An evaluation of the tyrosine kinase inhibitor Pacritinib in patients with relapsed FLT3-mutated acute myeloid leukaemia (the UK NCRI AML17 study)

(Abstract release date: 05/19/16) EHA Library. S. 06/10/16; 133172; P184

[AN EVALUATION OF THE TYROSINE KINASE INHIBITOR PACRITINIB IN... EHA Library. S. Jun 10 2016; 133172 \(ehaweb.org\)](#)

Induction therapy for patients with AML:

Defining the dose of gemtuzumab ozogamicin in combination with induction chemotherapy in acute myeloid leukemia: a comparison of 3 mg/m² with 6 mg/m²

Haematologica. Vol. 101 No. 6 (2016): June, 2016

<https://haematologica.org/article/view/7738>

Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without *NPM1* Mutations

Journal of Clinical Oncology. Vol 36, Issue 15, May 20, 2018

https://ascopubs.org/doi/10.1200/JCO.2017.76.3425?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed

A comparison of FLAG-Ida and daunorubicin combined with Clofarabine in high-risk acute myeloid leukaemia: data from the UK NCRI AML17 Trial

Leukemia. volume 32, pages2693–2697(2018). Published 06 June, 2018

<https://www.nature.com/articles/s41375-018-0148-3>

Attenuated arsenic trioxide plus ATRA therapy for newly diagnosed and relapsed APL: long-term follow-up of the AML17 trial

Blood. 2018 Sep 27;132(13):1452-1454.

<https://pubmed.ncbi.nlm.nih.gov/30097508/>

Addition of the mammalian target of rapamycin inhibitor, Everolimus, to consolidation therapy in acute myeloid leukemia: experience from the UK NCRI AML17 trial:

Haematologica. 2018 Oct; 103(10): 1654–1661.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6165825/>

Defining the Optimal Total Number of Chemotherapy Courses in Younger Patients with Acute Myeloid Leukemia: A Comparison of Three Versus Four Courses.

J Clin Oncol. 2021 Mar 10;39(8):890-901. doi: 10.1200/JCO.20.01170. Epub 2020 Dec 23.

[Defining the Optimal Total Number of Chemotherapy Courses in Younger Patients With Acute Myeloid Leukemia: A Comparison of Three Versus Four Courses | Journal of Clinical Oncology \(ascopubs.org\)](https://ascopubs.org)

Use of samples and data that have been collected as part of the AML17 trial

Collection of **samples** (bone marrow and/or blood samples) during the trial has helped clinicians to assess patients during their treatment and provide the opportunity to change treatment, based on results of analysing of these samples. These samples have been stored in laboratories that were part of the trial. Long-term storage of these samples is only permitted where patients signed a specific patient information sheet “Storage of excess material”.

All trial research on these samples has now been completed, in order to help answer the trial questions, and the trial is now complete. As described in the “Storage of Excess Material” information sheet, at this stage samples will now transfer into Cardiff University’s Biobank (CUBB). Researchers from other institutes may apply to request access to these samples, to further understand this disease, and in some cases other diseases that may be similar.

During the trial, the trial team also collected **data** from patients, in order to answer the questions that are described above. Some of the data, such as patient response to early courses of treatment, directed patient towards their most suitable treatment in later courses. The data has been stored in a secure database throughout the trial, and remains there.

It is the intention of the trial team and Cardiff University to further support research in acute myeloid leukaemia, other blood cancers and other research in general by allowing some access to this trial data. Researchers and research groups may request access to anonymised data, which cannot be used to identify individual patients – details such as initials, name, date of birth, location, etc. will not be shared. Research groups are not allowed to share this data with other researchers without permission from Cardiff University, and are usually required to delete the data after their research is completed. Some examples of this data-sharing are described below:

HARMONY Alliance <https://www.harmony-alliance.eu/>

This European research group are collecting a very large amount of clinical data from as many blood cancer researchers as possible, in order to try and find any signals that will help identify future treatments. There is a strong patient representation within the Harmony Alliance, and Cardiff University is an associate member of the group. Clinical data from AML17 has been shared with Harmony, in an anonymised fashion - so individual patients cannot be identified.

Kronos Bio, Inc.

Kronos Bio are conducting a clinical trial in the United States, and are hoping to use a new clinical trial endpoint, called Measurable Residual Disease (or MRD). Trials in acute myeloid leukaemia usually use survival as their endpoint (measure of success) - this means that trials take a long time to complete and often require many hundreds of patients.

Cardiff University and the AML17 trial team supports the use of new methods like this to conduct clinical trials, as we feel it benefits future patients. To help Kronos conduct their trial effectively, we have shared some data from some AML17 patients – this was anonymised data and only on a small portion of the patients in the trial. Kronos will be required to publish their findings and to delete their AML17 data after this has been done.

Both Harmony and Kronos received data only from patients who did not withdraw their consent from the trial. It is important to understand that **patients are free to withdraw their consent from a clinical trial, even after it has been completed**. If you wish to withdraw from the trial, you should contact your local haematology team where you received your trial treatment, and they will contact the Sponsor.

We will continue to support further advances in the treatment of acute myeloid leukaemia by providing researchers with access to some data and samples – but we will not share data that will allow any patients to be identified, and will only provide the minimum amount of data required for the purpose of the research.