# Clinical trial results:
# Bloodwise and NCRI Working Group Pick a Winner Programme (LI-1) Trial

## Summary

| | |
|---|---|
| EudraCT number | 2011-000749-19 |
| Trial protocol | GB DK |
| Global end of trial date | 27 May 2024 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 August 2024 |
| First version publication date | 10 August 2024 |
| Summary attachment (see zip file) | BCT100 publication (BCT100 paper_BJH_2023.pdf)<br>AC220 arm publication (AC220 paper_LI1_Blood Advances_2021.pdf)<br>Tosedostat publication (Li1 Tosedostat BJHaem March 2021.pdf)<br>Vosaroxin arms publication (BLOOD608117_Vosaroxin LI1.pdf)<br>Sapacitabine publication (leu201538_sapacitabine publication.pdf)<br>Lenalidomide publication post print (Copland_Manuscript Lenalidomide Revised_BJH_clean.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | SPON934-11 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN40571019 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Cardiff University |
| Sponsor organisation address | 30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE |
| Public contact | Ian Thomas, Cardiff University, 02920 745397, thomasif@cf.ac.uk |
| Scientific contact | Ian Thomas, Cardiff University, 02920 745397, thomasif@cf.ac.uk |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No | No |

| | |
|---|---|
| 1901/2006 apply to this trial? | |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 May 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 May 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 May 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare standard treatment, low-dose Ara-C against the available novel approaches:
•Sapacitabine
•LD Ara-C combined with AC220
•LD Ara-C combined with vosaroxin
•Vosaroxin only

During the course of the Programme other novel therapies became available, and were added to the trial design via protocol amendment.
•LD Ara-C combined with ganetespib
•LD Ara-C combined with Tosedostat
•LD Ara-C combined with Selinexor
•LD Ara-C combined with Lenalidomide
•LD Ara-C combined with BCT100

Protection of trial subjects:

Addition of novel agents was via protocol amendment, requiring approval from competent authority and ethics committee. Independent scientific review was also conducted on behalf of the Sponsor, prior.

Standard processes were in place throughout the trial to capture Serious Adverse Events in line with relevant regulations, and the clinical trial unit SOPs.

In this feasibility trial additional pharmacovigilance arrangements were in place - this included communication with investigators on a regular basis to monitor events, beyond the formal data capture via the Patient Record Book. This enhanced pharmacovigilance data did not form part of the formal database, but was in place to allow rapid review of data following introduction of a novel agent.

Background therapy:

Standard treatment at trial outset was defined as Ara-C 20 mg bd by subcutaneous injection daily on days 1-10 (20 doses) to be repeated at 28 to 42 day intervals. This schedule had been confirmed as standard of care in these patients, following a previous NCRI AML trial, AML14.

Most arms of the trial sought to compare this standard of care against a treatment with a novel agent combined with low-dose Ara-C. As such, low-dose Ara-C could be considered to be the background treatment for the trial.

In 2 comparisons however, the novel agents were administered as monotherapy - sapacitabine only and vosaroxin only. Patients allocated to these treatment arms did not receive low-dose Ara-C.

Evidence for comparator:

A substantial majority of patients diagnosed with AML or high risk MDS are elderly and either decline, or are not considered fit for, intensive treatment. Until 2010, there was no established treatment for these patients. As part of the NCRI/LRF AML14 trial, low dose Ara-C (LD Ara-C) was compared with hydroxyurea. The trial was closed early because low dose Ara-C was significantly superior. Although an 18% remission rate was observed, the overall survival was still poor at 5 months. Benefit was limited to patients who achieved remission, which therefore became the major objective against which to assess

new treatments in the LI1 trial.

Justifications for investigation of the novel treatment options were included in the different versions of the trial protocol.

| | |
|---|---|
| Actual start date of recruitment | 01 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 180 |
| Country: Number of subjects enrolled | Denmark: 22 |
| Worldwide total number of subjects | 202 |
| EEA total number of subjects | 22 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 3 |
| From 65 to 84 years | 199 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment occurred across all sites, with a total of xxx patients enrolled. Recruitment started in the UK on 1st December 2011.

### Pre-assignment

Screening details:

Screening was undertaken prior to enrolment, to ensure subjects met all of the protocol inclusion criteria and none of the exclusion criteria. Some arms within the trial had specific criteria associated with them - depending on the availability of options at site, and across the trial, subjects could still enter other arms of the trial.

### Period 1

| | |
|---|---|
| Period 1 title | Treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | LD Ara-C |

Arm description:

Standard of care

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The aim for all treatments throughout the trial was to administer 4 courses. If the patient was benefitting after 4 courses, treatment could continue until disease progression

Ara-C 20mg bd by subcutaneous injection daily on days 1-10 (20 doses) to be repeated at 28042 day intervals

| | |
|---|---|
| **Arm title** | Lenalidomide |

Arm description:

LD Ara-C was administered as per standard of care in combination with lenalidomide.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide was administered orally once daily in a flat 10mg dose for 21 days, where day 1 was day 1 of LD Ara-C. This course was repeated after a 2-week rest period and continued for four courses (therefore repeated every 5 weeks).

| **Number of subjects in period 1** | LD Ara-C | Lenalidomide |
|---|---|---|
| Started | 102 | 100 |
| Completed | 102 | 100 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | LD Ara-C |
| Reporting group description: | |
| Standard of care | |
| Reporting group title | Lenalidomide |
| Reporting group description: | |
| LD Ara-C was administered as per standard of care in combination with lenalidomide. | |

| Reporting group values | LD Ara-C | Lenalidomide | Total |
|---|---|---|---|
| Number of subjects | 102 | 100 | 202 |
| Age categorical | | | |
| Age by age ranges as described in the trial protocol | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| 60-64 | 1 | 2 | 3 |
| 65-69 | 8 | 4 | 12 |
| 70-74 | 27 | 29 | 56 |
| 75-79 | 32 | 28 | 60 |
| 80+ | 34 | 37 | 71 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 39 | 46 | 85 |
| Male | 63 | 54 | 117 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Survival |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Analyses are by intention-to-treat. Time-to-event outcomes were analysed using the log-rank test, Kaplan-Meier survival curves. Hazard ratios and 95% confidence interval were calculated using the statistics from the log-rank test | |

| Reporting group values | Survival | | |
|---|---|---|---|
| Number of subjects | 202 | | |
| Age categorical | | | |
| Age by age ranges as described in the trial protocol | | | |
| Units: Subjects | | | |

| | | | |
|---|---|---|---|
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| 60-64 | 3 | | |
| 65-69 | 12 | | |
| 70-74 | 56 | | |
| 75-79 | 60 | | |
| 80+ | 71 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 85 | | |
| Male | 117 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | LD Ara-C |
| Reporting group description: | |
| Standard of care | |
| Reporting group title | Lenalidomide |
| Reporting group description: | |
| LD Ara-C was administered as per standard of care in combination with lenalidomide. | |
| Subject analysis set title | Survival |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Analyses are by intention-to-treat. Time-to-event outcomes were analysed using the log-rank test, Kaplan-Meier survival curves. Hazard ratios and 95% confidence interval were calculated using the statistics from the log-rank test | |

### Primary: Overall survival

| | |
|---|---|
| End point title | Overall survival |
| End point description: | |
| Overall survival is a common endpoint in trials of this nature | |
| End point type | Primary |
| End point timeframe: | |
| From trial entry to date of death or date last seen | |

| End point values | LD Ara-C | Lenalidomide | Survival | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 102 | 100 | 202[1] | |
| Units: days | | | | |
| number (not applicable) | 102 | 100 | 202 | |

Notes:

[1] - Not applicable

| | |
|---|---|
| **Attachments (see zip file)** | Lenalidomide publication/Copland_Manuscript Lenalidomide |

### Statistical analyses

| **Statistical analysis title** | 2-year overall survival |
|---|---|
| Statistical analysis description: | |
| Survival is reported as % alive at 2 years in each arm | |
| Comparison groups | Lenalidomide v LD Ara-C |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.719 [3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Notes:

[2] - Time-to-event outcomes were analysed using the log-rank test, Kaplan-Meier survival curves. Hazard ratios and 95% confidence interval were
calculated using the statistics from the log-rank test

[3] - Hazard ratios and 95% confidence interval in the attached publication were calculated using the statistics from the log-rank test

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported for the arms available in the final version of the protocol. Evens for LDAC v LDAC+ lenalidomide are reported for the entire period of the randomisation

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | LDAC +/- len |

Reporting group description:

Important note: patients are followed up until death. Not all deaths are related to trial treatment. Number of deaths in this arm does not reflect the toxicity of the treatments.

| **Serious adverse events** | LDAC +/- len | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 202 (3.96%) | | |
| number of deaths (all causes) | 202 | | |
| number of deaths resulting from adverse events | | | |
| Blood and lymphatic system disorders | | | |
| All Blood and Lymphatic | Additional description: Events for this SOC are summarised below. A detailed SAE summary across all SOCs is attached separately.<br><br>A list of deaths coded by type is all included. Therefore, deaths related or not to SAEs is recorded as 0 below. | | |
| subjects affected / exposed | 8 / 202 (3.96%) | | |
| occurrences causally related to treatment / all | 5 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | LDAC +/- len | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 202 / 202 (100.00%) | | |
| Blood and lymphatic system disorders | | | |
| All Blood and Lymphatic | Additional description: AEs are summarised in the publication uploaded. | | |
| subjects affected / exposed | 202 / 202 (100.00%) | | |
| occurrences (all) | 202 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 April 2012 | Addition of ganetespib to the protocol in line with the trial design. The date given is for MHRA approval in the UK. |
| 09 April 2013 | Addition of tosedostat, removal of sapacitabine from the protocol in line with the trial design. The date given is for MHRA approval in the UK. |
| 09 January 2014 | Addition of Selinexor, removal of LDAC + vosaroxin from protocol. The date given is for MHRA approval in the UK. |
| 02 July 2014 | Addition of tablet formulation of AC220, update to eligibility, clarification of sampling, stats analysis. The date given is for MHRA approval in the UK. |
| 17 October 2014 | Maintain daily dose of tosedostat at 120mg. Confirmation of re-opening of ganetespib randomisation. The date given is for MHRA approval in the UK. |
| 18 December 2014 | Temporary suspension of LD Ara-C + selinexor randomisation. The date given is for MHRA approval in the UK. |
| 07 May 2015 | Change of CI, Addition of Lenalidomide, supportive measures for Ganetespib, addition of Co-ordinators, Update of safety information for Selinexor and clarification of safety review process and RSI. The date given is for MHRA approval in the UK. |
| 17 February 2016 | Re-opening of selinexor option, clarification of lenalidomide schedule. The date given is for MHRA approval in the UK. |
| 15 April 2016 | Urgent safety measure, closing ganetespib randomisation following withdrawal of company support. The date given is for MHRA approval in the UK. |
| 25 April 2018 | Removal of Tosedostat and Selinexor, and addition of BCT-100. The date given is for MHRA approval in the UK. |
| 10 August 2018 | Updated information in regards to BCT-100. The date given is for MHRA approval in the UK. |
| 15 November 2019 | Closure of two arms (Lenalidomide & AC220) due to the full recruitment target being met. The date given is for MHRA approval in the UK. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In this novel trial design, control patients are used for each arm that is contemporaneously available at the time of entry as outlined in the PubMed link below. Upload of results by arm is therefore not possible within this functionality.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/21734235