



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) AC220 arm publication (AC220 paper_LI1_Blood Advances_2021.pdf) Tosedostat publication (Li1 Tosedostat BJHaem March 2021.pdf) Vosaroxin arms publication (BLOOD608117_Vosaroxin LI1.pdf) Sapacitabine publication (Ieu201538_sapacitabine publication.pdf) Lenalidomide publication post print (Copland_Manuscript Lenalidomide Revised_BJH_clean.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON934-11
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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

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
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Arm title	LD Ara-C
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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
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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
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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. Events for LDAC v LDAC+ lenalidomide are reported for the entire period of the randomisation

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	1
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Reporting groups

Reporting group title	LDAC +/- len
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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 SOC's is attached separately.		
	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>