Clinical trial results:
Immunotherapy with CD19 chimeric antigen receptor gene-modified EBV-specific CTLs after stem cell transplant in children with high-risk acute lymphoblastic leukaemia

Summary

EudraCT number	2007-007612-29
Trial protocol	DE GB
Global end of trial date	10 December 2018

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019
Summary attachment (see zip file)	Vaccination to improve the persistence of CD19CAR genemodified T cells in relapsed pediatric acute lymphoblastic leukemia (CD19_Leukemia_2017_31_1087–1095.pdf)

Trial information

Trial identification

Sponsor protocol code	UCL/09/0050

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01195480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Trial Coordinator, CR UK and UCL Cancer Trials Centre, 44 207679 9327, ctc.CD19@ucl.ac.uk
Scientific contact	Trial Coordinator, CR UK and UCL Cancer Trials Centre, 44 207679 9327, ctc.CD19@ucl.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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2016
Global end of trial reached?	Yes
Global end of trial date	10 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the feasibility and safety of adoptive transfer of CD19ζ chimaeric receptor transduced donor-derived EBV-specific cytotoxic T-lymphocytes (EBV-CTL) in patients with high-risk or relapsed B cell precursor acute lymphoblastic leukaemia (BCP-ALL) after allogeneic HSCT.
2. To determine the biological effect of infusion of CD19ζ-transduced EBV-CTL on residual leukaemia as assessed by Minumal Residue Disease (MRD) quantification in the bone marrow.

We conducted a multicenter phase I/II study of donor CD19CAR transduced EBV CTL in pediatric acute lymphoblastic leukaemia (ALL). Patients were eligible pre-emptively if they developed molecular relapse post first stem cell transplant (SCT), or prophylactically post second SCT. An initial cohort showed poor expansion /persistence. We therefore investigated EBV-directed vaccination to enhance expansion/persistence (Leukemia (2017) 31, 1087–1095; doi:10.1038/leu.2017.39)

Protection of trial subjects:

Patient safety was monitored through strict eligibility criteria, regular patient assessments during treatment and follow up, regular review of safety data by Independent Data Monitoring Committee (IDMC) and Trial Management Group (TMG). Treatment of the first 3 patients was staggered by a minimum of 1 month to allow for initial toxicity assessments.
Stopping rules related to trial treatment:
The following stopping rules were defined in protocol:
•Death of a patient after CD19ζ–transduced EBV-CTL therapy that is probably or definitely related to the CD19ζ–transduced EBV-CTL or donor LCL (irradiated EBV transformed lymphoblastic cell lines) vaccination.
•Occurrence of Grade 4 infusional/allergic/anaphylactic/hypoxic/hypotensive toxicity within 24 hours of infusion of CD19ζ–transduced EBV-CTL in 3 patients.
•Occurrence of Grade 4-5 toxicity that may be attributable to CD19-transduced CTL OR Grade III/IV acute GVHD occurring within 12 weeks of infusion in ≥ 14 patients.

The first cohort of 5 trial patients received donor CD19CAR CTL alone. Infusion of CD19CAR T cells was well-tolerated with no significant infusional toxicity. In particular, none of the patients experienced CRS, neurotoxicity or GVHD attributable to CD19CAR CTL. However, although CD19CAR CTL alone were safe, their persistence and anti-leukemic efficacy was limited. Following review of the safety and CTL persistence data by the TMG and IDMC, both advised that the second trial cohort of patients should have vaccination with irradiated, donor-derived LCL along with the CD19CAR CTL to attempt to improve CD19CAR CTL persistence. Five patients were then treated on trial in cohort 2. Both CD19CAR CTL infusion and LCL vaccination were well-tolerated.

Background therapy:

All patients received lymphodepletion consisting of fludarabine on day −5 to − 3 before CD19CAR CTL infusion in order to enhance the expansion of the CD19CAR CTL and break tolerance to residual leukaemic cells.
Patients with detectable residual disease also received cytoreduction with vincristine Day − 9 and dexamethasone −9 to − 3 before infusion of cryopreserved CD19CAR CTL to reduce the leukaemia burden.

Evidence for comparator:

N/A

Actual start date of recruitment	20 August 2012
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: 25
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	4
Children (2-11 years)	20
Adolescents (12-17 years)	3
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May 2012–November 2015, 29 patients were enrolled across six sites in the UK and Germany. 19 were not treated as they remained MRD-negative post SCT (7), donor refused participation (5), died before treatment (6), problems with CTL manufacture (1).

Pre-assignment

Screening details:

- Children with ALL 18 years:

a) in CR but at high risk of relapse post SCT (CD19CAR CTL administered if patient became MRD positive up to 1 year post SCT)
b) patients who had relapsed after 1st SCT (treated with CD19CAR CTL after 2nd SCT following withdrawal of immunosuppression)

- EBV positive & HLA matched donor
- No GVHD ≥2
- No steroids

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Cohort 1: CD19CAR CTL alone

Arm type	Experimental
Investigational medicinal product name	CD19CAR CTL
Investigational medicinal product code	donor EBV-CTL transduced with SFG-CD19-CD3zeta
Other name	CD19 CAR
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The CTL infusion was given over 2 days at a total dose of 2 × 10^8/m2. On day one the first dose of 4 x 10^7/m2 transduced CTL is infused, followed by the second dose of 1.6x 10^8/m2 CTL infused the following day.

Arm title	Cohort 2

Arm description:

Cohort 2: Vaccination with irradiated, donor-derived LCL along with CD19CAR CTL.
An interim analysis of safety and CD19CAR CTL persistence was performed after the patients in cohort 1 received CD19CAR CTLs alone. As the CD19CAR CTL were not detectable in patients post infusion, the TMG and IDMC advised that the second trial cohort should receive vaccination with irradiated, donor derived LCL along with the CD19CAR CTL to attempt to improve CD19CAR CTL persistence.

Arm type	Experimental

Investigational medicinal product name	CD19CAR CTL
Investigational medicinal product code	donor EBV-CTL transduced with SFG-CD19-CD3zeta
Other name	CD19 CAR
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The CTL infusion was given over 2 days at a total dose of 2 × 10^8/m2. On day one the first dose of 4 x 10^7/m2 transduced CTL is infused, followed by the second dose of 1.6x 10^8/m2 CTL infused the following day.

Investigational medicinal product name	Irradiated donor-derived EBV-LCL
Investigational medicinal product code	
Other name	donor-derived LCL
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Vaccination consisted of 3 doses of 5 x 10^6 irradiated (70Gy) donor-derived EBV-lymphoblastoid cell line used to generate CTL and was administered subcutaneously into the thigh (volume 0.3 ml) 2 days prior to CD19 CAR CTL infusion, and then at 4 and 8 weeks after the first infusion of transduced CD19CAR CTL.

Number of subjects in period 1[1]	Cohort 1	Cohort 2
Started	5	5
Completed	5	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Between May 2012–November 2015, 29 patients were enrolled across six sites in the UK and Germany. 19 were not treated as they remained MRD-negative post SCT (7), donor refused participation (5), died before treatment (6), problems with CTL manufacture (1). Therefore a total of 10 patients were treated on the study and included in this analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Cohort 1: CD19CAR CTL therapy alone Cohort 2: Vaccination with irradiated, donor-derived LCL along with CD19CAR CTL therapy	

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	2	
Male	8	8	

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Cohort 1: CD19CAR CTL alone

Reporting group title	Cohort 2

Reporting group description:

Cohort 2: Vaccination with irradiated, donor-derived LCL along with CD19CAR CTL.
An interim analysis of safety and CD19CAR CTL persistence was performed after the patients in cohort 1 received CD19CAR CTLs alone. As the CD19CAR CTL were not detectable in patients post infusion, the TMG and IDMC advised that the second trial cohort should receive vaccination with irradiated, donor derived LCL along with the CD19CAR CTL to attempt to improve CD19CAR CTL persistence.

Primary: Toxicity attributable to CD19CAR transduced CTL

End point title	Toxicity attributable to CD19CAR transduced CTL

End point description:

Since this is a Phase I/II trial only a descriptive analysis of all the variables measured is provided. Adverse event data and corresponding toxicity grades are summarized in the form of tables. The incidence of severe toxicity (defined as combined incidence of Grade 4-5 toxicity that may be attributable to CD19-transduced CTL and Grade III/IV acute GVHD occurring within 12 weeks of infusion) is determined. The predicted incidence for such toxicities in the absence of CTL infusion was 10% and the approach would be considered too unsafe if such toxicities occured in > 30% of treated patients.

End point type	Primary

End point timeframe:

Adverse events within 12 weeks of CD19 CTL infusion (except hypohammaglobulinaemia where incidence is within 1 year of post-SCT)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10	5	5		

Attachments (see zip file)	Max grade AE reported for each

Statistical analyses

Statistical analysis title	Safety analysis

Statistical analysis description:

The incidence of severe toxicity (defined as combined incidence of Grade 4–5 toxicity that may be attributable to CD19CAR CTL within 12 weeks of infusion and Grade III/IV acute GVHD occurring by day 100 post transplant) was determined. A rate of 30% was considered too unsafe.

Comparison groups	Cohort 2 v Cohort 1

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.1 [2]
Method	t-test, 1-sided
Parameter estimate	Descriptive analysis

Notes:

[1] - There is no comparison between cohort 1 (CD19CAR CTL alone) and cohort 2 (CD19CAR CTL and vaccination with donor LCL). An interim analysis on safety and persistence of CD19CAR CTL was performed after 5 patients were treated in cohort 1. CD19CAR CTL were safe but they were undetectable in > 50% of patients by 2 months post-infusion. Therefore subsequent patients (cohort 2) were treated with irradiated donor LCL vaccination in addition to CD19CAR T CTL with the aim to improve CTL persistence.

[2] - The null hypothesis is that toxicity rate P is ≤10% & a one-sided test against the alternative hypothesis P≥30% is performed. Toxicity analysis is published: Leukemia (2017) 31, 1087–1095; doi: 10.1038/leu.2017.39. List of AEs (max Gr/Pt) uploaded.

Primary: Biological efficacy

End point title	Biological efficacy

End point description:

Since this is a Phase I/II trial only a descriptive analysis of all the variables measured will be provided. Biological efficacy as assessed by effect of CD19-transduced CTL on Minimal Residual Disease levels in the bone marrow in the first year post-transduced CTL infusion.Complete response was defined as undetectable MRD, partial response as reduction in MRD level by more than 1 log, stable disease by unchanged MRD, and progressive disease by MRD increased by more than 1 log or frank relapse.

End point type	Primary

End point timeframe:

At 1, 2, 4, 6 and 12 months post CD19CAR CTL infusion.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: CCR, CR, PR, SD, non-responder	5	5		

Attachments (see zip file)	CD19 patient outcome

Statistical analyses

Statistical analysis title	Biological efficacy

Statistical analysis description:

Disease status was assessed by morphology, cytogenetics and qPCR MRD analysis of clone-specific IgH or TCR gene rearrangements with a sensitivity of at least 10− 4 at Euro-MRD reference laboratories in Frankfurt and London on BM samples taken 1 month post CD19CAR CTL infusion. Complete response was defined as undetectable MRD, partial response as reduction in MRD level by > 1 log, stable disease by unchanged MRD, and progressive disease by MRD increased by >1 log or frank relapse.

Comparison groups	Cohort 1 v Cohort 2

Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.1 [4]
Method	Descriptive analysis

Notes:

[3] - Since this is a Phase I/II trial only descriptive analysis of measured variables is provided. There is no comparison between cohort 1 (CD19CAR CTL alone) and cohort 2 (CD19CAR CTL and vaccination with donor LCL). An interim analysis was performed after 5 patients were treated in cohort 1. CD19CAR CTL were safe but undetectable in >50% of patients by 2 months post-infusion. Therefore subsequent patients (cohort 2) were treated with irradiated donor LCL vaccination in addition to CD19CAR T CTL.
[4] - MRD levels post-CTL infusion are analysed. This is a Phase I/II trial where only descriptive analysis of the variables was performed. The analysis is published: Leukemia (2017) 31, 1087–1095; doi: 10.1038/leu.2017.39; patient 'outcome' data uploaded.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 12 weeks of CD19-transduced CTL infusion

Adverse event reporting additional description:

The incidence of severe toxicity (defined as combined incidence of Grade 4-5 toxicity that may be attributable to CD19-transduced CTL and Grade III/IV acute GVHD.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Cohort 1 and 2

Reporting group description: -

Serious adverse events	Cohort 1 and 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Cholecystitis	Additional description: Grade 3		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1 and 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		
GGT increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Infections and infestations Bacterial infection subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Hypoalbuminemia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2011	Following our submission to the European Voluntary Harmonisation Procedure (VHP) committee the protocol and trial-related documents were modified as follows: a) Patients with CD19 negative precursor B cell ALL are not eligible; b) Patients with severe allergy to gentamicin are excluded from receiving vaccination with irradiated donor-derived BLCL c) Patients with 'Known allergy to human serum albumin or DMSO' are excluded d) Addition of the following neurological AEs: ataxia, encephalopathy and seizures. e) Addition of HIV and serological testing for Toxoplasma for donors f) Release criteria tests for both ATMPS have been modified and information on storage, issue and administration of the ATMPs added g) Statement on patient data confidentiality added h) Details on the qPCR used for CD19ζ transgene analysis added i) Long-term patient monitoring extended from 5 to 10 years j) End of trial changed to after 10 years rather than 1 year
27 February 2012	a) The assessment of chronic GVHD has changed from limited/extensive to the new National Institutes of Health (NIH) consensus criteria b) Inclusion criteria text changed from "prednisolone poor or not in molecular remission" to "MRD positive (BCR-ABL/ABL ratio >0.01%) after HR3 block of EsPhALL". c) Addition of "Relapse of infant or Philadelphia-positive in morphological complete remission" to the inclusion criteria. d) Removal of "including normal haemoglobin level and platelet count appropriate for the age/sex of donor" and' Known Allergy to human albumin or DMSO" text from donor inclusion criteria. e) Amended text to reflect change of laboratory site from UCL to GOS for PCR analysis. f) Additional patient identifiers to be collected. g) Sponsor contact details updated.
04 January 2013	The CD3 threshold set in the release criteria for CD19ζ transduced EBV-CTL changed from ≥95% to ≥90% DAPI-ve/CD45+ve cells expressing CD3
11 February 2013	a) Addition of patient group "transplanted in > 3rd CR" to patient inclusion criteria. b) Donor inclusion criterion changed to "Stem cell donors must be EBV sero-positive and HLA matched (8/8 HLA A, B, C and DR at medium resolution typing) or a single antigenic/allelic (7/8) mismatch with the recipient". c) Clarification for patients on the pre-emptive arm to be treated when "BM MRD level >5 x 10-4 "(or BCR-ABL/ABL ratio 0.05% in Ph+ve ALL patients with no IgH MRD marker)'' d) Addition of text to include alternative conditioning regimen for patients on pre-emtive arm to reflect upcoming IBFM ALL protocol e) Text amended in the conditioning regimen in the pre-emptive arm for children under age 2 due to emerging concerns about the toxicity of the busulphan /cyclophosphamide /melphalan conditioning regimen in infants. This has been replaced with an alternate regimen as per the new Interfant protocol guidelines. f) Conditioning regimen for all patients in the prophylaxis arm has been amended to be in line with the chemotherapy conditioning regimen used for patients on the pre-emptive arm by addition of thiotepa and use of serotherapy with ATG rather than Alemtuzumab. g) Updated the NCI Common Terminology Criteria for Adverse Events link from version 4.02 to 4.03 h) Central MRD laboratories will also perform qPCR to look for persistence/homing of CD19ζ transduced EBV-CTL to the bone marrow. i) Additon of 'ANSM' as the new name for French Regulatory Authority.

03 April 2014	a) Protocol changed to state that 5 patients will be treated with the EBV CTL alone (rather than 10 that was originally planned). b) LCL vaccination schedule changed to '2 days prior to CTL infusion and then at 4 and 8 weeks post-CTL infusion'. c) Clarification that the patient card must be given to patients when they are registered to receive the ATMP (i.e. prior to cytoreduction/lymphodepletion). d) Clarification on the follow-up of patients who have discontinued study.
10 December 2018	Protocol changed throughout to state that trial will end 3 years after the last patient alive has been treated with EBV CTL (previously 10 years)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28126984