Clinical trial results:
CD19-TARGETING 3RD GENERATION CAR T CELLS FOR REFRACTORY B CELL MALIGNANCY – A PHASE II TRIAL

Summary

EudraCT number	2016-004043-36
Trial protocol	SE
Global end of trial date	14 January 2022

Results information

Result version number	v1 (current)
This version publication date	19 April 2023
First version publication date	19 April 2023

Trial information

Trial identification

Sponsor protocol code	004:TCELL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03068416
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University
Sponsor organisation address	Dag Hammarskjöldsväg 20, Uppsala, Sweden, 751 85
Public contact	Jamileh Hashemi, Department of Immunology, Genetics and Pathology , Uppsala University, Sweden, 0046 186110203, jamileh.hashemi@igp.uu.se
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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	07 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the feasibility and safety of two administrations of CAR T cells to patients with disseminated B cell lymphoma or leukemia.
- To evaluate long-term toxicity of CAR T cells by an extended follow-up period (12-24 months) when patients are analyzed even if they have
  progressed in their disease and/or received another therapy.
- To evaluate whether two courses of gemcitabine given in association with CAR T cells can increase the effect of CAR T cell therapy.

Protection of trial subjects:

The main serious risks for patients treated with CAR T cells are fever, cytokine release syndrome, dyspnea, Platelet count decreased and risk of infection due to low immunoglobulin level. The patients have been closely monitored and tocilizumab (anti-IL6R) was successfully used to limit cytokine release syndrome.

Background therapy:

The study protocol included bridging therapy of the treating clinician’s choice. Prior CAR T-cell injection, the patients may treated with chemotherapy and/or radiotherapy for 4-8 weeks to reduce the tumour burden and control the disease. Thereafter the patients are preconditioned for 3 days with Fludarabine and Cyclophosphamide. CAR T-cell injection followed by 2 cycles of gemcitabine (800 mg/m2) in order to suppress myeloid derived suppressor cells (MDSC) thought to hamper CAR T-cell function).

Evidence for comparator:

No comparator was used.

Actual start date of recruitment	10 April 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	1
Adults (18-64 years)	12
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 2017-2020 in Sweden. The trial site was in Uppsala but some patients were referred to by other hospitals.

Pre-assignment

Screening details:

24 patinets met eligibility criteria. Four of 28 (4/28) recruited patients failed to receive treatment. Main reason for failing screening of three patients was too short expected survival that would result in patients not surviving long enough for the CAR T cells to be manufactured. It was not possible to manufacture CAR T cell for one (1) patient.

Pre-assignment period milestones

Number of subjects started	28[1]
Number of subjects completed	24

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 4

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Enrollmnet is defined as patients randomised to a treatment arm. Pre-assignment is the screening period prior to initiation of treatment.

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:

Blinding was not applicable.

Arms

Arm title	CAR-T cells

Arm description:

Two doses CAR-T cells infusion in patients who did not respond or relapsed after initial response and two courses of gemcitabine in association with CAR-T cells.

Arm type	Experimental
Investigational medicinal product name	CAR T cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2x10e8 cells/m2

Number of subjects in period 1	CAR-T cells
Started	24
Completed	24

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	24	24	
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)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	12	12	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
median	63		
full range (min-max)	14 to 77	-	
Gender categorical			
Female Male			
Units: Subjects			
Female	13	13	
Male	11	11	

Subject analysis sets	
Subject analysis set title	Received CART treatment
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Started treatment with CAR T	
Subject analysis set title	One week
Subject analysis set type	Full analysis
Subject analysis set description: Protein Levels meaured 1 week after treatment	
Subject analysis set title	Three weeks
Subject analysis set type	Full analysis
Subject analysis set description: Protein levels measured three weeks after treatment	

Reporting group values	Received CART treatment	One week	Three weeks
Number of subjects	24	24	24
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	63	63	
full range (min-max)	14 to 77	14 to 77	
Gender categorical			
Female Male			
Units: Subjects			
Female	13		
Male	11		

End points

End points reporting groups

Reporting group title	CAR-T cells
Reporting group description:	
Two doses CAR-T cells infusion in patients who did not respond or relapsed after initial response and two courses of gemcitabine in association with CAR-T cells.	
Subject analysis set title	Received CART treatment
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Started treatment with CAR T	
Subject analysis set title	One week
Subject analysis set type	Full analysis
Subject analysis set description:	
Protein Levels meaured 1 week after treatment	
Subject analysis set title	Three weeks
Subject analysis set type	Full analysis
Subject analysis set description:	
Protein levels measured three weeks after treatment	

Primary: Tumor response measured as best response and over all response

End point title	Tumor response measured as best response and over all response[1]
End point description:	
Patients received two administrations of CAR T cells are grouped as overall responder and best responder at 1 month after the first CAR-T infusion. Tunor metrics totalt structural burden (V total) for the pre-therapy scan (t0) and post therapy scan (t1) are presented.	
End point type	Primary
End point timeframe:	
From study inclusion to the end of study participation	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It is one-arm study therefore statistical analysis has not been presented.

End point values	CAR-T cells			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Number of patinets				
Overall respone	9			
Best response	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Determination of tumor size and the tumor marker CD19

End point title	Determination of tumor size and the tumor marker CD19

End point description:

End point type	Secondary

End point timeframe:

From treatment to maximum 24 months post treatment

End point values	CAR-T cells	Received CART treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24			
Units: ml				
median (full range (min-max))	34.7 (4.0 to 219.9)	17.6 (3.4 to 202.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Determination of the level CAR T cell in blood

End point title	Determination of the level CAR T cell in blood

End point description:

Patients who received two administrations of CAR T cells (14 patients) were divided in two groups as increased vs not increased CAR T copy number in blood. Only 4 out of the 14 patients who got 2 doses had an increase of CAR-Ts in their blood after the second infusion.

End point type	Secondary

End point timeframe:

From treatment to maximum 24 months post treatment

End point values	Received CART treatment	One week	Three weeks	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	14	14	
Units: Copy number				
arithmetic mean (standard deviation)				
Not increased CAR T cell	2379.349 (± 3146.384)	1269.0323 (± 1567.2802)	260.831 (± 430.951)	
Increased CAR T cell	97.9 (± 79.6)	157.93 (± 108.70)	310.366 (± 357.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Determination of the of the presence of immunological markers in blood and biopsies

End point title	Determination of the of the presence of immunological markers in blood and biopsies

End point description:

Protein levels found in plasma of patients, before CAR T infusion, after one week and three weeks of CAR T treatment.

End point type	Secondary

End point timeframe:

From treatment to maximum 24 months post treatment

End point values	CAR-T cells	One week	Three weeks	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	24	24	24	
Units: NPX				
arithmetic mean (standard error)				
TNFRSF9	-0.3567 (± 0.6191)	-0.7712 (± 0.4819)	-1.6148 (± 0.4694)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Enrollment to last visit (maximum 24 months post CAR T cell infusion)	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 24 (54.17%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events			
Investigations			
Creatinine increased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
White blood cell decreased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headeache			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	7 / 24 (29.17%)			
occurrences causally related to treatment / all	14 / 14			
deaths causally related to treatment / all	0 / 0			
Generalized edema				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Throat pain				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	4 / 24 (16.67%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhea				

subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomach pain				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	3 / 24 (12.50%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusion				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucinations				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Bladder infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device-related infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection Suspicion			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Unknown infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cath-a-port			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection Bronchial			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 24 (45.83%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal-cell cancer			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Tumor in left leg			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
General disorders and administration site conditions			
Common cold			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Edema			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Fever			

subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Flu like symptoms subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Neurological pain right arm subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Immune system disorders			
Cytokine release syndrome subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Investigations			
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Decreased leukocytes subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Hypogammaglobulenemi subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 5		
White blood cell decreased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	 3 / 24 (12.50%) 3		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		
Eye disorders dry eye subjects affected / exposed occurrences (all) Glaucoma subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 2 1 / 24 (4.17%) 1		
Hepatobiliary disorders			

Portal vein thrombosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Redness under both eyes			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthtralgia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Discomfort left eyebrow			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Groin discomfort			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Muscle strain left thigh			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Herpes simplex reactivation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2019	(1) The number of patients has been changed to "<25" from "<15". This change is motivated by the fact that although CD19-CAR T cell therapy is now approved within the EU and will be available as standard care therapy in Sweden, the introduction of this therapy into Swedish hospitals will take time. For many patients it will then be too late. Since we still have virus left from the batch used for production and also have financing for treating more patients we would like to do that. (2) Following the possibility to include 10 more patients the planned trial period has been extended with one year and the trial time table has been extended with one year for the last patient in and last patient out.

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/36575477