Clinical trial results:
A Phase 2 open label study to investigate the efficacy of autologous EBV-specific T-cells for the treatment of patients with aggressive extranodal NK/T-cell lymphoma (ENKTCL).

Summary

EudraCT number	2013-004380-31
Trial protocol	GB DE
Global end of trial date	05 September 2018

Results information

Result version number	v1 (current)
This version publication date	02 August 2019
First version publication date	02 August 2019

Trial information

Trial identification

Sponsor protocol code	CM-2013-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01948180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cell Medica Inc.
Sponsor organisation address	7505 Fannin Street, Suite 200, Houston, United States,
Public contact	Clinical Trials Information, Cell Medica Ltd., 0044 02075544070, info@cellmedica.co.uk
Scientific contact	Clinical Trials Information, Cell Medica Ltd., 0044 02075544070, info@cellmedica.co.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 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2018
Global end of trial reached?	Yes
Global end of trial date	05 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall response rate per independent endpoint assessment.

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	15
EEA total number of subjects	6

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)	12
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

54 subjects screened. 38 of 54 were screening failures. 16 of 54 screened subjects entered treatment phase, 1 died before receiving first dose. Remaining 15 patients were treated with CMD-003.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Patients with measurable disease according to international consensus standards as defined by the 2014 Lugano Criteria at baseline.

Arm type	Experimental
Investigational medicinal product name	CMD-003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Treatment consisted of 2×107 CD3+ cells/m2 administered on Day 1 and Day 15 as intravenous infusions over a 1 to 10 minute period through either a peripheral or an existing central line. An infusion set with a standard blood filter (pore size no smaller than 170 microns) could be used, per institutional standard operating procedures. To ensure the entire CMD-003 product was infused, the bag was rinsed with a volume of sterile saline solution at the end of the infusion.

Arm title	Group B

Arm description:

Patients with no measurable disease at baseline.

Arm type	Experimental
Investigational medicinal product name	CMD-003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Treatment consisted of 2×107 CD3+ cells/m2 administered on Day 1 and Day 15 as intravenous infusions over a 1 to 10 minute period through either a peripheral or an existing central line. An infusion set with a standard blood filter (pore size no smaller than 170 microns) could be used, per institutional standard operating procedures. To ensure the entire CMD-003 product was infused, the bag was rinsed with a volume of sterile saline solution at the end of the infusion.

Number of subjects in period 1	Group A	Group B
Started	10	5
Completed	2	0
Not completed	8	5
Sponsor's Decision	-	2
Disease Progression	7	2
Received Other Treatment	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Patients with measurable disease according to international consensus standards as defined by the 2014 Lugano Criteria at baseline.	
Reporting group title	Group B
Reporting group description:	
Patients with no measurable disease at baseline.	

Reporting group values	Group A	Group B	Total
Number of subjects	10	5	15
Age categorical Units: Subjects			
≤ 60 years	7	5	12
> 60 years	3	0	3
Gender categorical Units: Subjects			
Female	5	1	6
Male	5	4	9
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	3	0	3
Black or African American	0	1	1
White	4	3	7
Other	1	0	1
Not Reported	2	0	2
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	6	5	11
Not Reported	3	0	3
Weight Units: kg			
arithmetic mean	74.0	79.4	
standard deviation	± 14.17	± 10.55	-
Height Units: cm			
arithmetic mean	169.1	175.2	
standard deviation	± 7.64	± 8.77	-

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Patients with measurable disease according to international consensus standards as defined by the 2014 Lugano Criteria at baseline.	
Reporting group title	Group B
Reporting group description:	
Patients with no measurable disease at baseline.	
Subject analysis set title	Group A MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
For efficacy endpoints: ORR, CRR, response duration, TTR, and PFS were only presented for patients assigned to Group A (patients with measurable disease) who received at least one dose with a formal response determined at the week 8 visit or later (modified intent-to-treat (MITT) population).	
Subject analysis set title	Group A/B MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Combined MITT population for group A and B	
Subject analysis set title	Safety Population Overall
Subject analysis set type	Full analysis
Subject analysis set description:	
Overall Safety Population (Group A and Group B)	

Primary: Overall Response Rate

End point title	Overall Response Rate[1]
End point description:	
Overall Response Rate: The ORR was defined as the percentage of evaluable patients with measurable disease whose best response was either a CR or a PR according to the Lugano 2014 criteria and central independent radiological review	
End point type	Primary
End point timeframe:	
12 months	

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: Due to the small sample size, only a descriptive analysis and documentation of data listings of this endpoint was specified.

End point values	Group A MITT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Subjects				
Responders	5			
Nonresponders	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

The CRR was defined as the percentage of evaluable patients with measurable disease who experienced a CR, as their best overall response.

End point type	Secondary

End point timeframe:

12 months

End point values	Group A MITT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Subjects				
Responders	3			
Nonresponders	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of Response is defined as the response duration time in days from Complete Response or Partial Response until lymphoma progression or death as a result of any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Duration of study

End point values	Group A MITT			
Subject group type	Subject analysis set			
Number of subjects analysed	8[2]			
Units: days (estimated mean)	159			

Notes:

[2] - Median not reached

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

TTR was defined as the time in days from study entry (Day 1 of CMD-003 dosing) until the precise date of a CR or PR, whichever occurred first. This was applicable only to evaluable patients with measurable disease.

End point type	Secondary

End point timeframe:

Duration of study

End point values	Group A MITT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Days				
median (inter-quartile range (Q1-Q3))	204.0 (74.0 to 271.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

PFS was defined as the time from study entry until lymphoma progression or death as a result of any cause, whichever occurred first. The date of progression was defined as the first date of documentation of PD.

End point type	Secondary

End point timeframe:

Duration of study

End point values	Group A MITT			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: days (estimated median)	251			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival

End point title	Disease-Free Survival

End point description:

DFS was measured from time of occurrence of disease-free state or attainment of a CR to disease recurrence or death, whichever occurred first. Applicable to patients regardless of measurable disease status in the study.

End point type	Secondary

End point timeframe:

Duration of study

End point values	Group A MITT	Group A/B MITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	13		
Units: days				
median (confidence interval 95%)	121.5 (59.0 to 184.0)	306.0 (59.0 to 410.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the time from study entry until death as a result of any cause. This definition was applicable to patients regardless of measurable disease status in the study.

End point type	Secondary

End point timeframe:

Duration of study

End point values	Group A/B MITT	Safety Population Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13[3]	15[4]		
Units: days (estimated mean)	371	351		

Notes:

[3] - Median not reached

[4] - Median not reached

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of first study product dose until 30 days after last study product dose. SAEs were recorded at every study visit for up to one year.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

All subjects treated were considered eligible for safety evaluation.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Gait disturbance			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Peripheral swelling			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Laryngeal inflammation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
White blood cell count decreased			

subjects affected / exposed occurrences (all) Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Facial paralysis subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 4 / 15 (26.67%) 5 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Gastrointestinal disorders Diarrhoea			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Gastritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin odour abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3		
Back pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Arthralgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Cellulitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		
Device related infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Otitis media acute subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Metabolism and nutrition disorders			

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2014	Principal changes to allow additional salvage therapies, patients with NK/T cutaneous lesions, and to allow patients to receive HSCT after 8-week follow-up. Other changes made for clarification and consistency.
09 September 2014	Administrative Amendment – Replaced references to Cheson 2007 with 2014 along with corresponding response table in Appendix F.
05 November 2014	The main areas clarified are exclusion of women of child bearing potential; withdrawals and discontinuations alignment; extend safety monitoring of first few patients immediately post cell administration; addition of 30 month assessment to capture data out to 2 years after last study dose. Various minor edits.
20 November 2015	Increase starting material volume to 200 mL and provided general guidance for autologous blood donation to promote safe blood collection for the patient. Clarify in-line filtration for IP infusion sets, update prohibited medications to include G-CSF and HDAC inhibitors frequently used in this patient population. Added option for patient's extra tumor tissue to be tested by centralized pathology lab, when possible.
06 June 2016	Change screening phase eligibility criteria to exclude patients who have failed 3 or more prior chemotherapy regimens or is considered to have Asparaginase refractory disease and increase life expenctancy to 4 months. Limit treatment phase eligibility to patients with active disease as assessed by imaging, clinical signs or elevated EBV DNA viral load. Also exclude patients with significant liver dysfunction. Allow investigator to decide best salvage treatment option (salvage not mandatory), instead of requiring gemcitabine as the only salvage option, prior to starting CMD-003 treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported