Clinical trial results:
PHASE I/IIa AdCD40L IMMUNOGENE THERAPY FOR MALIGNANT MELANOMA PATIENTS WITH DISSEMINATED DISEASE

Summary

EudraCT number	2010-023103-94
Trial protocol	SE
Global end of trial date	28 January 2016

Results information

Result version number	v1 (current)
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	002:CD40L

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01455259
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University
Sponsor organisation address	Rudbeck laboratory Dag Hammarskjoldsvag 20, Uppsala, Sweden, 751 85
Public contact	Thomas Tötterman, Uppsala university, 46 0186114184, thomas.totterman@igp.uu.se
Scientific contact	Thomas Tötterman, Uppsala university, 46 0186114184, thomas.totterman@igp.uu.se

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	28 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2016
Global end of trial reached?	Yes
Global end of trial date	28 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1 - To evaluate the feasibility of repeated intra-tumor AdCD40L injections of malignant melanoma patients with metastases by studying tolerance and toxicity.

Part 2 - To evaluate the feasibility of repeated local treatment of cyclophosphamide preconditioned malignant melanoma patients with metastases by studying the tolerance and toxicity during and after repeated cycles of AdCD40L injections.

Protection of trial subjects:

The patients were treated accordingly to protocol. Symptoms of disease or adverse events were handled as per hospital routine to minimize risk or pain of all study patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	19
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in at Uppsala university hospital in Sweden.

Pre-assignment

Screening details:

Patients that had failed all conventional treatments as per national directives at Uppsala University Hospital during the trial period could be screened for participation in the trial. In total, 43 patients were screened and 30 patients were enrolled and treated with at least one dose of AdCD40L.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	AdCD40L

Arm description:

Four intratumoral injections of AdCD40L given one week apart (n=6) +/- in combination with cyclophosphamide preconditioning (300mg/m2; n=15) prior to the first and last AdCD40L dose +/- one local radiotherapy (n=9).

Arm type	Experimental
Investigational medicinal product name	AdCD40L
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intratumoral use

Dosage and administration details:

2.5x10e11 VP

Number of subjects in period 1	AdCD40L
Started	30
Completed	20
Not completed	10
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Adverse event, non-fatal	6
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	11	11	
Gender categorical Units: Subjects			
Female	16	16	
Male	14	14	

End points

End points reporting groups

Reporting group title	AdCD40L

Reporting group description:

Four intratumoral injections of AdCD40L given one week apart (n=6) +/- in combination with cyclophosphamide preconditioning (300mg/m2; n=15) prior to the first and last AdCD40L dose +/- one local radiotherapy (n=9).

Primary: Safety

End point title	Safety[1]

End point description:

End point type	Primary

End point timeframe:

DLT was determined from the first treatment to final follow-up for the individual patient

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: There were no dose limiting toxicities due to drug related AEs in the study. No statistical calculation was performed due to this descriptive study.

End point values	AdCD40L			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: DLT				
number (not applicable)				
DLT	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect accordingly to RECIST at 9 weeks follow-up.

End point title	Effect accordingly to RECIST at 9 weeks follow-up.

End point description:

Radiology evaluation accordingly to RECIST criteria

End point type	Secondary

End point timeframe:

9 weeks post treatment initiation

End point values	AdCD40L			
Subject group type	Reporting group			
Number of subjects analysed	22[2]			
Units: RECIST				
number (not applicable)				
Stable disease	10			
Progressive disease	12			
Partial response	0			
Complete response	0			

Notes:

[2] - 8 of 30 patients could not be evaluated at 9 weeks post treatment initiation

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from initiation of treatment to final follow-up for the individual patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All patients receiving at least 1 injection of AdCD40L.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fracture left humerus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Stroke, cerebral hemorrhage			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Acute hemorrhage esofagotracheal stent			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
General deterioration	Additional description: General deterioration due to tumor swelling/progression		

subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Progressive disease			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
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	30 / 30 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pain	Additional description: Pain at tumor site		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	13 / 30 (43.33%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	14		
Flu like symptoms	Additional description: Dyspnea, transpiration, shivering, fever, chills, headache		
subjects affected / exposed	20 / 30 (66.67%)		
occurrences (all)	26		
General deterioration	Additional description: General deterioration due to progressive tumor growth, swelling, weight loss		
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	14		
Immune system disorders			
Autoimmune skin reaction	Additional description: Vitiligo		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Pneumothorax			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hoarseness			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Confusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Injection or biopsy-related injury			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	9		
Fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
Neuropathy peripheral	Additional description: Neuropathy, decreased sensitivity		
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Vertigo			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	9		
Gastroenteritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Hepatobiliary disorders			
Liver function test abnormal			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	26		
Liver enlargement			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders Muscle pain subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 3		
Infections and infestations Infection subjects affected / exposed occurrences (all)	 11 / 30 (36.67%) 13		
Metabolism and nutrition disorders Hypoalbuminemia subjects affected / exposed occurrences (all) Anorexia subjects affected / exposed occurrences (all)	 5 / 30 (16.67%) 5 4 / 30 (13.33%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	Inclusion of various solid malignancies (n=6) in addition to malignant melanoma (n=15).

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/27031851