Clinical trial results:
mRNA-transfected dendritic cell vaccination in high risk uveal melanoma patients

Summary

EudraCT number	2008-001974-33
Trial protocol	NL
Global end of trial date	01 April 2016

Results information

Result version number	v1 (current)
This version publication date	10 June 2020
First version publication date	10 June 2020
Summary attachment (see zip file)	Publication Ophthalmology 2016 (Bol et al Ophthalmology 2016.pdf)

Trial information

Trial identification

Sponsor protocol code	08/014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00929019
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein 26, Nijmegen, Netherlands,
Public contact	Prof. dr. Jolanda de Vries, Radboudumc, department of Tumor Immunology, 0031 243655750, Jolanda.deVries@radboudumc.nl
Scientific contact	Prof. dr. Jolanda de Vries, Radboudumc, department of Tumor Immunology, 0031 243655750, Jolanda.deVries@radboudumc.nl

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	01 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2016
Global end of trial reached?	Yes
Global end of trial date	01 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The first objective is to study the efficacy of autologous mRNA-transfected monocyte-derived DC in terms of progression free survival (PFS) in high-risk uveal melanoma patients.

Protection of trial subjects:

Adverse events were defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational treatment. All adverse events (AE) occurring during the study, whether or not definitely attributable to the immunization procedure, were recorded. Any CTC-grade 4 or other serious, life-threatening or fatal adverse event occurring within 28 days of receiving the last treatment must be reported within 24 hours to the study coordinator.

A serious adverse event is any untoward medical occurrence or effect that results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the accredited CMO that approved the protocol, according to the requirements of that CMO.

Follow-up of adverse events:
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	18
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Uvea melanoma patients with a loss of chromosome 3 (monosomy 3; high-risk uvea melanoma), with an interval since local treatment <12 months, were included in this trial.

Pre-assignment

Screening details:

Additional inclusion criteria were UM expressing the melanoma-associated antigens gp100, age 18-75 years, and WHO performance status 0 or 1. Patients with distant metastases, serious concomitant disease or a history of a second malignancy we were excluded. HLA-A*02:01-positive patients were vaccinated, negative patients served as a control group.

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	All included patients

Arm description:

DC vaccinated patients

Arm type	Experimental
Investigational medicinal product name	DC vaccination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate, Concentrate for solution for injection/infusion
Routes of administration	Intradermal use, Intravenous use

Dosage and administration details:

DC vaccination with DC loaded with KLH and transfected with mRNA encoding gp100 and tyrosinase will be administered three times on day 0, 14 and 28. DC will be simultaneously administered intradermally (i.d.) in the upper leg and intravenously (i.v.) 10 and 20 x 106 cells, respectively.
This regime is comparable to our previous trials in melanoma patients. The reason why we choose for this vaccination strategy is that it is shown in preclinical models that it may be beneficial to combine different routes of administration: depending on the localization of the tumor, intravenous or intradermal may be preferential for visceral and non-visceral metastases, respectively. Furthermore, to date our most promising clinical data are obtained in a group of stage IV melanoma patients vaccinated i.d. and i.v..

Number of subjects in period 1	All included patients
Started	23
Completed	18
Not completed	5
Lack of efficacy	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	23	23	
Age categorical			
Inclusion criteria included human leukocyte antigen (HLA)-A*02:01 positivity, interval since local treatment <12 months, and age 18 to 75 years.			
Units: Subjects			
Adults (18-64 years)	18	18	
From 65-84 years	5	5	
Age continuous			
Units: years			
geometric mean	56		
full range (min-max)	31 to 69	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	12	12	
T stage			
T stage of uvea melanoma.			
Units: Subjects			
T stage	23	23	
Tumor size			
Mean tumor size			
Units: mm			
geometric mean	14		
full range (min-max)	7 to 23	-	

Subject analysis sets

Subject analysis set title	Tumor-specific T cells in skin biopsies
Subject analysis set type	Per protocol

Subject analysis set description:

Descriptive statistics of the immunological response and patient survival data will include means, standard deviations and medians for both groups. Survival of patients will be presented as Kaplan-Meier plots.

Subject analysis set title	No tumor-specific T cells in skin biopsies
Subject analysis set type	Per protocol

Subject analysis set description:

Number of patients without induction of tumor-specific T cells in skin biopsies upon dendritic cell vaccination.

Reporting group values	Tumor-specific T cells in skin biopsies	No tumor-specific T cells in skin biopsies	
Number of subjects	17	6	

Age categorical			
Inclusion criteria included human leukocyte antigen (HLA)-A*02:01 positivity, interval since local treatment <12 months, and age 18 to 75 years.			
Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years geometric mean full range (min-max)			
Gender categorical Units: Subjects			
Female Male			
T stage			
T stage of uvea melanoma.			
Units: Subjects			
T stage	23		
Tumor size			
Mean tumor size			
Units: mm geometric mean full range (min-max)	 14 7 to 23		

End points

End points reporting groups

Reporting group title	All included patients
Reporting group description: DC vaccinated patients	
Subject analysis set title	Tumor-specific T cells in skin biopsies
Subject analysis set type	Per protocol
Subject analysis set description: Descriptive statistics of the immunological response and patient survival data will include means, standard deviations and medians for both groups. Survival of patients will be presented as Kaplan-Meier plots.	
Subject analysis set title	No tumor-specific T cells in skin biopsies
Subject analysis set type	Per protocol
Subject analysis set description: Number of patients without induction of tumor-specific T cells in skin biopsies upon dendritic cell vaccination.	

Primary: Tumor-specific T cells in the skin tests

End point title	Tumor-specific T cells in the skin tests
End point description:	
End point type	Primary
End point timeframe: After a cycle of DC vaccinations skin tests were performed after each vaccination cycle, and the presence and functionality of tumor-specific T cells induced by DC vaccination were analyzed	

End point values	All included patients	Tumor-specific T cells in skin biopsies	No tumor-specific T cells in skin biopsies	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	17	6	
Units: yes or no				
Tumor-specific T cells in the skin tests	17	17	6	

Statistical analyses

Statistical analysis title	Description of tumor-specific T cells in biopsies
Statistical analysis description: Percentage of tumor-specific T cells in biopsies upon dendritic cell vaccination. Tumor-specific T cells in the skin tests were present in 17 patients (74%), demonstrating the effectiveness of these type of vaccines.	
Comparison groups	All included patients v Tumor-specific T cells in skin biopsies v No tumor-specific T cells in skin biopsies

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	Not applicable
Parameter estimate	Not applicable

Notes:

[1] - Not applicable.

[2] - Not applicable.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AE) occurring during the study, whether or not definitely attributable to the immunization procedure, will be recorded. All adverse events will be followed until they have abated, or until a stable situation has been reached.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Flu-like symptoms

Reporting group description: -

Serious adverse events	Flu-like symptoms		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Flu-like symptoms		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 23 (91.30%)		
General disorders and administration site conditions			
Flu-like symptoms			
subjects affected / exposed	21 / 23 (91.30%)		
occurrences (all)	21		
Erythema at injection site			
subjects affected / exposed	20 / 23 (86.96%)		
occurrences (all)	20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 June 2015	Because of low accrual rates, mainly caused by the rarity of the tumor, older age at diagnosis, HLA restriction, and the increase of eye-conserving treatments interfering with the availability of tumor material for genetic testing, the trial was stopped prematurely. Still, 23 patients received at least 1 cycle of adjuvant DC vaccination and were considered evaluable.	-

Notes:

Limitations and caveats

None reported