Clinical trial results:
Dendritic cell vaccination in patients with Lynch Syndrome or colorectal cancer with MSI

Summary

EudraCT number	2008-005584-33
Trial protocol	NL
Global end of trial date	02 November 2020

Results information

Result version number	v1 (current)
This version publication date	04 December 2020
First version publication date	04 December 2020

Trial information

Trial identification

Sponsor protocol code	KUN2009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01885702
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands, 6525 GA
Public contact	Prof. dr. N. Hoogerbrugge, Radboudumc, department of Human Genetics, 0031 2466205, nicoline.hoogerbrugge@radboudumc.nl
Scientific contact	Prof. dr. I.J.M. de Vries, Radboudumc, department of Tumor Immunology, 0031 2455750, 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	02 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2015
Global end of trial reached?	Yes
Global end of trial date	02 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate the safety and feasibility of vaccination with frameshift-derived neoantigen-loaded DC.

Protection of trial subjects:

Adverse events are 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, will be 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.

All AEs 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:

Colorectal cancer is one of the most common types of cancer in the western world. Surgery offers the only change for cure. Approximately 50% of patients eventually develop distant metastases for which no curative treatment is available, with the exception of a small subgroup of patients with resectable metastases. The results of systemic treatment improve progression free survival by about 2 years, but there remains a need for more effective treatment.

Evidence for comparator: -

Actual start date of recruitment	15 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	4 Years
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)	22
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

- All individuals were HLA-A2.1 positive
- Patients who had any malignancy, more than 5 years previously, were also eligible
- WHO performance status 0-1
- Absence of autoimmune diseases, an active viral infection or allergy to shell fish
- No concomitant immunosuppressive drug usen
- No pregnancy or lactation
- No laboratory abnormalities

Pre-assignment

Screening details:

There was no run-in period for this trial.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lynch syndrome patients with MSI CRC

Arm description:

CRC patients, who are known to carry a germline MMR-gene mutation (Lynch syndrome) and patients with an MSI-positive CRC and yet unknown or negative MMR-gene mutation status

Arm type	Experimental
Investigational medicinal product name	Vaccination with dendritic cells loaded with CEA-derived and frameshift mutation-derived neopeptides
Investigational medicinal product code	
Other name	moDC vaccine
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subdermal use

Dosage and administration details:

DC vaccination with DC loaded with KLH and tumor-associated peptide CEA and frameshift-derived neopeptides will be administered three times on day 0, 7 and 14. DC will be simultaneously administered intradermally (i.d.) in the upper leg and intravenously (i.v.). This regime is comparable to our previous trials in colorectal cancer patients. We aim to inject 10 and 20 x 106 cells intradermal and intraveneously, respectively.

Arm title	Carriers of a germline MMR-gene mutation

Arm description:

Persons (n=20) who are known to be carrier of a germline MMR-gene mutation with no signs of disease yet or were more than 5 years beyond primary CRC resection at the time of the study . These latter persons know that they have a life-time risk for CRC up to 70% because of a germline mutation in one of the MMR-genes, are highly motivated to participate in studies that may lead to risk reduction, because they experienced colorectal cancer and death with close relatives.

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Number of subjects in period 1	Lynch syndrome patients with MSI CRC	Carriers of a germline MMR-gene mutation
Started	3	20
Inclusion of 5 patients to open Arm B	3	0 [1]
Completed	3	20

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This milestone is applicable to arm A only. In arm B all 20 planned patients were included.

Baseline characteristics

Reporting groups	
Reporting group title	Lynch syndrome patients with MSI CRC
Reporting group description:	
CRC patients, who are known to carry a germline MMR-gene mutation (Lynch syndrome) and patients with an MSI-positive CRC and yet unknown or negative MMR-gene mutation status	
Reporting group title	Carriers of a germline MMR-gene mutation
Reporting group description:	
Persons (n=20) who are known to be carrier of a germline MMR-gene mutation with no signs of disease yet or were more than 5 years beyond primary CRC resection at the time of the study . These latter persons know that they have a life-time risk for CRC up to 70% because of a germline mutation in one of the MMR-genes, are highly motivated to participate in studies that may lead to risk reduction, because they experienced colorectal cancer and death with close relatives.	

Reporting group values	Lynch syndrome patients with MSI CRC	Carriers of a germline MMR-gene mutation	Total
Number of subjects	3	20	23
Age categorical			
Age 18-75 years			
Units: Subjects			
Adults (18-64 years)	3	19	22
From 65-84 years	0	1	1
Age continuous			
Age 18-75 years			
Units: years			
median	47	51	
full range (min-max)	46 to 48	29 to 65	-
Gender categorical			
Units: Subjects			
Female	1	7	8
Male	2	13	15
Germline mutation			
Germline mutation			
Units: Subjects			
MLH1	1	9	10
MSH2	1	7	8
MSH6	1	3	4
PMS2	0	1	1

End points

End points reporting groups

Reporting group title	Lynch syndrome patients with MSI CRC

Reporting group description:

CRC patients, who are known to carry a germline MMR-gene mutation (Lynch syndrome) and patients with an MSI-positive CRC and yet unknown or negative MMR-gene mutation status

Reporting group title	Carriers of a germline MMR-gene mutation

Reporting group description:

Persons (n=20) who are known to be carrier of a germline MMR-gene mutation with no signs of disease yet or were more than 5 years beyond primary CRC resection at the time of the study . These latter persons know that they have a life-time risk for CRC up to 70% because of a germline mutation in one of the MMR-genes, are highly motivated to participate in studies that may lead to risk reduction, because they experienced colorectal cancer and death with close relatives.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The first objective of this study is to evaluate safety and feasibility of vaccination with frameshift-derived neoantigen-loaded DC.

Subject analysis set title	Feasibility
Subject analysis set type	Full analysis

Subject analysis set description:

The first objective of this study is to evaluate safety and feasibility of vaccination with frameshift-derived neoantigen-loaded DC.

Subject analysis set title	Induction of antigen-specific T cells
Subject analysis set type	Full analysis

Subject analysis set description:

The secondary objectives of the study are to evaluate whether peptide-loaded DC can induce or enhance an immune response to tumor-associated antigen CEA and specific frameshift-derived neoantigens in the study population

Primary: Safety

End point title	Safety[1]

End point description:

AEs are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational treatment. All AEs occurring during the study, whether or not definitely attributable to the immunization procedure, will be 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.
All AEs 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.

End point type	Primary

End point timeframe:

From inclusion until any occured AE has been abated, or until a stable situation has been reached.

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: For this safety endpoint no statistical analysis were performed.

End point values	Lynch syndrome patients with MSI CRC	Carriers of a germline MMR-gene mutation	Safety	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	20	23	
Units: Nr of pts with safe DC administration				
Safety	3	19	22	

Attachments (see zip file)	Safety and feasibility description/Safety and feasibility

Statistical analyses

No statistical analyses for this end point

Primary: Feasibility

End point title	Feasibility[2]

End point description:

Individuals were included during the periode from February 2012 until January 2014 (arm A). And during the period from January 2014 until November 2014 (arm B).

End point type	Primary

End point timeframe:

From February 2012 until January 2014 (arm A). And from January 2014 until November 2014 (arm B).

Notes:

[2] - 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: For this feasibility endpoint no statistical analysis were performed.

End point values	Lynch syndrome patients with MSI CRC	Carriers of a germline MMR-gene mutation	Feasibility	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	20	23	
Units: Nr of patients eventually included				
Feasibility	3	20	23	

Attachments (see zip file)	Safety and feasibility description/Safety and feasibility

Statistical analyses

No statistical analyses for this end point

Secondary: Induction of antigen-specific T cells

End point title	Induction of antigen-specific T cells

End point description:

Patients were vaccinated intravenously and intradermally 3 times every week with DC loaded with CEA-derived and frameshift mutation-derived neopeptides. After the 3 vaccinations a DTH was performed,

from which biopsies will be taken for T cell analysis. If no relapse occurs, we will repeat this cycle two more times with a 6 months interval.

End point type	Secondary

End point timeframe:

During the period of 3 DC vaccination cycles (if no relapse occurs).

End point values	Lynch syndrome patients with MSI CRC	Carriers of a germline MMR-gene mutation	Induction of antigen-specific T cells	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	20	23	
Units: Yes or No				
Induction of antigen-specific T cells	3	17	20	

Statistical analyses

Statistical analysis title	Paired t-tests

Statistical analysis description:

Descriptive statistics of the immunological responses for the treated group were calculated using SPSS® Statistics version 20.0 software (SPSS Inc., Chicago, IL, USA) and Graphpad Prism 5.03 (GraphPad Software, Inc., San Diego, CA, USA). Statistical significance was evaluated using the log-rank test and was defined as P< 0.05. Paired t-tests were performed to evaluate immunologic responses before and after vaccination.

Comparison groups	Lynch syndrome patients with MSI CRC v Carriers of a germline MMR-gene mutation v Induction of antigen-specific T cells
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[3] - Immunogical responses were studied before and after vaccination. Therefore, the subjects in this analysis are 46 (two times 23 patients).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From study inclusion until disappearence of an AE. All AEs will be followed until they have abated, or until a stable situation has been reached.

Adverse event reporting additional description:

All AEs occurring during the study, whether or not definitely attributable to the vaccines, will be recorded. Any CTCAE 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. All AEs will be followed until they have abated.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Any toxicity (overall patients)

Reporting group description:

Any adverse event.

Serious adverse events	Any toxicity (overall patients)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 2		

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

Non-serious adverse events	Any toxicity (overall patients)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)		
General disorders and administration site conditions			

Flu-like symptoms	Additional description: Flu-like symptoms include fever, fatigue, chills, body aches, malaise, loss of appetite and headache.		
alternative assessment type: Systematic			
subjects affected / exposed	23 / 23 (100.00%)		
occurrences (all)	23		
Injection site reaction	Additional description: An injection site reaction is characterized by erythema at the site of injection and an asymptomatic temporary nodal swelling of 1-2 cm. This always disappeared after a few days to a week.		
alternative assessment type: Systematic			
subjects affected / exposed	19 / 23 (82.61%)		
occurrences (all)	19		
Infections and infestations			
Lung infection	Additional description: Definition: A disorder characterized by an infectious process involving the lungs, including pneumonia.		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2013	Despite a number of measures, the inclusion of the first 5 patients (arm A) has been delayed. As a result, the inclusion criteria have been broadened and patients have been approached from a larger area (more hospitals) to participate in the study. Nevertheless, we were unable to include the required 5 patients. Therefore, only 3 patients were included. DC vaccinations in these first 3 patients were safe and no CTCAE grade 3-4 toxicity was observed. Consequently, we amended the protocol and asked for permission to start with the enrollment of of the Lynch syndrome carriers (arm B) after treatment of 3 in stead of 5 patients in arm A. This amendment was accepted by the medical ethical committee and we started with patient recruitment in arm B of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Despite a number of measures, the inclusion of the first 5 patients (arm A) failed. Therefore, only 3 patients were included.

Notes: