Clinical trial results:
A randomized phase IIa study: natural dendritic cells for immunotherapy of chemo-naive metastatic castration-resistant prostate cancer patients

Summary

EudraCT number	2012-002531-29
Trial protocol	NL
Global end of trial date	06 March 2019

Results information

Result version number	v1 (current)
This version publication date	04 June 2020
First version publication date	04 June 2020
Summary attachment (see zip file)	Westdorp et al JITC 2019 (Westdorp et al JITC 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	NaturalDCformCRPC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02692976
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein 26, Nijmegen, Netherlands,
Public contact	Radboudumc, Radboud University Medical Centre Nijmegen, 0031 243617600, Jolanda.deVries@radboudumc.nl
Scientific contact	Radboudumc, Radboud University Medical Centre Nijmegen, 0031 243617600, 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	06 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2019
Global end of trial reached?	Yes
Global end of trial date	06 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show immunologic efficacy of tumor-peptide loaded natural DC in mCRPC patients

Protection of trial subjects:

The investigator will inform the subjects and the CCMO if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the CCMO, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

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 occurring during the study, whether or not definitely attributable to the immunization procedure (suspected), 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.

A serious adverse event is any untoward medical occurrence or effect that results in death or is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- 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 serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) will be reported via ToetsingOnline to the CCMO.

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	01 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 21

Worldwide total number of subjects	21
EEA total number of subjects	21

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)	7
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

We screened 44 chemotherapy-naive CRPC patients. Patients with rising PSA were closely monitored. Patients were screened for study eligibility as soon as patients met the criteria for CRPC. Twenty-two of the screened patients were HLA-A-*0201. One of these patients was excluded because a second primary malignancy was detected.

Period 1

Period 1 title	Baseline characteristics (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	mDC arm

Arm description:

CD1c+ mDC vaccinations (2–5 × 106 cells per injection; arm A)

Arm type	Experimental
Investigational medicinal product name	Tumor antigen peptide-loaded blood-derived dendritic cell product for use in prostate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Other use

Dosage and administration details:

Intranodal administration. CD1c+ mDC vaccinations (2–5 × 106 cells per injection; arm A)

Arm title	pDC arm

Arm description:

pDC vaccinations (1–3 × 106 cells; arm B)

Arm type	Experimental
Investigational medicinal product name	Tumor antigen peptide-loaded blood-derived dendritic cell product for use in prostate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Other use

Dosage and administration details:

Intranodal administration. pDC vaccinations (1–3 × 106 cells; arm B)

Arm title	combiDC

Arm description:

combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 106 cells; arm C)

Arm type	Experimental

Investigational medicinal product name	Tumor antigen peptide-loaded blood-derived dendritic cell product for use in prostate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Other use

Dosage and administration details:

Intranodal administration. Combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 106 cells; arm C)

Number of subjects in period 1	mDC arm	pDC arm	combiDC
Started	7	7	7
Completed	7	7	7

Baseline characteristics

Reporting groups	
Reporting group title	mDC arm
Reporting group description:	
CD1c+ mDC vaccinations (2–5 × 106 cells per injection; arm A)	
Reporting group title	pDC arm
Reporting group description:	
pDC vaccinations (1–3 × 106 cells; arm B)	
Reporting group title	combiDC
Reporting group description:	
combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 106 cells; arm C)	

Reporting group values	mDC arm	pDC arm	combiDC
Number of subjects	7	7	7
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	3
From 65-84 years	5	5	4
Age continuous Units: years			
geometric mean	67.9	69.4	66.3
full range (min-max)	60 to 78	59 to 82	53 to 74
Gender categorical Units: Subjects			
Female	0	0	0
Male	7	7	7
Baseline PSA Units: ug/l			
median	10	6.3	38
full range (min-max)	4.6 to 260	2.6 to 19	3.7 to 120

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	14		
Age continuous Units: years			
geometric mean			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	0		
Male	21		

Baseline PSA			
Units: ug/l			
median			
full range (min-max)	-		

Subject analysis sets

Subject analysis set title	Immunological response after mDC vaccinations
Subject analysis set type	Per protocol

Subject analysis set description:

Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.

Subject analysis set title	Immunological response after pDC vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.

Subject analysis set title	Immunological response after combiDC vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.

Reporting group values	Immunological response after mDC vaccinations	Immunological response after pDC vaccination	Immunological response after combiDC vaccination
Number of subjects	7	7	7
Age categorical			
Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	14		
Age continuous			
Units: years			
geometric mean	67.9		
full range (min-max)	53 to 82		
Gender categorical			
Units: Subjects			
Female	0		
Male	21		
Baseline PSA			
Units: ug/l			
median	10		
full range (min-max)	2.6 to 260		

End points

End points reporting groups

Reporting group title	mDC arm
Reporting group description:	
CD1c+ mDC vaccinations (2–5 × 106 cells per injection; arm A)	
Reporting group title	pDC arm
Reporting group description:	
pDC vaccinations (1–3 × 106 cells; arm B)	
Reporting group title	combiDC
Reporting group description:	
combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 106 cells; arm C)	
Subject analysis set title	Immunological response after mDC vaccinations
Subject analysis set type	Per protocol
Subject analysis set description:	
Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.	
Subject analysis set title	Immunological response after pDC vaccination
Subject analysis set type	Per protocol
Subject analysis set description:	
Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.	
Subject analysis set title	Immunological response after combiDC vaccination
Subject analysis set type	Per protocol
Subject analysis set description:	
Paired t-tests were performed to evaluate immunological responses before and after vaccination and independentsamples t-tests (Mann-Whitney U tests) were used to evaluate differences between groups.	

Primary: Tetramer/dextramer-positive (dm+) and IFN-γ-producing (IFN-γ+) antigen specific T cells

End point title	Tetramer/dextramer-positive (dm+) and IFN-γ-producing (IFN-γ+) antigen specific T cells
End point description:	
Both tetramer/dextramer-positive (dm+) and IFN-γ-producing (IFN-γ+) antigen specific T cells were detected more frequently in skin biopsies of patients with radiological non-progressive disease (5/13 patients; 38%) compared to patients with progressive disease (0/8 patients; 0%). In these patients with vaccination enhanced dm+ and IFN-γ+ antigen-specific T cells median rPFS was 18.8 months (n = 5) vs. 5.1 months (n = 16) in patients without IFN-γ-producing antigen-specific T cells (p = 0.02).	
End point type	Primary
End point timeframe:	
Primary endpoint was the immunological response after DC vaccination, which was monitored in peripheral blood and in T cell cultures of biopsies of post-treatment delayed-type hypersensitivity-skin tests.	

End point values	mDC arm	pDC arm	combiDC	Immunological response after mDC vaccinations
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	7	7	7	7
Units: radiological profression-free survival				

median (full range (min-max))				
rPFS (dm+ and IFN-γ+)	23.6 (12.0 to 24.3)	18.8 (18.8 to 18.8)	12.0 (12.0 to 12.0)	23.6 (12.0 to 24.3)
rPFS (dm- or IFN-γ-)	3.4 (3.4 to 24.8)	8.6 (3.4 to 23.9)	4.0 (3.2 to 9.7)	3.4 (3.4 to 24.8)

End point values	Immunological response after pDC vaccination	Immunological response after combiDC vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: radiological profression-free survival				
median (full range (min-max))				
rPFS (dm+ and IFN-γ+)	18.8 (18.8 to 18.8)	12.0 (12.0 to 12.0)		
rPFS (dm- or IFN-γ-)	8.6 (3.4 to 23.9)	4.0 (3.2 to 9.7)		

Statistical analyses

Statistical analysis title	Paired t-tests and independent-samples t-tests

Statistical analysis description:

Paired t-tests were performed to evaluate immunological responses before and after vaccination and independent-samples t-tests (Mann-Whitney U tests) were used to evaluate group differences. Statistical significance: defined as $p < 0.05$ (two-tailed significance level). Time-to-event data were evaluated using the Kaplan-Meier method. Statistical significance was evaluated using the two-sided log-rank test; defined as $p < 0.05$. Differences between treatment arms were evaluated using one-way ANOVA.

Comparison groups	Immunological response after mDC vaccinations v Immunological response after pDC vaccination v Immunological response after combiDC vaccination
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 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	4.0
Reporting groups	
Reporting group title	Any toxicity
Reporting group description: -	
Reporting group title	Flu-like symptoms
Reporting group description: Flu-like symptoms include fever, fatigue, chills, body aches, malaise, loss of appetite and headache.	

Serious adverse events	Any toxicity	Flu-like symptoms	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
number of deaths (all causes)	8	8	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Ruptured type A acute aortic dissection	Additional description: Patient (pDC-07) had stable disease according to RECIST 1.1 and PCWG2 criteria. At 10.7 months after apheresis patient deceased due to a ruptured type A acute aortic dissection. Finally, concluded as non-related to the ATMP product.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Any toxicity	Flu-like symptoms	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	10 / 21 (47.62%)	
General disorders and administration site conditions			
Any vaccine-related toxicity			
subjects affected / exposed	21 / 21 (100.00%)	10 / 21 (47.62%)	
occurrences (all)	21	10	

Flu-like symptoms	Additional description: Flu-like symptoms include fever, fatigue, chills, body aches, malaise, loss of appetite and headache.		
subjects affected / exposed	21 / 21 (100.00%)	10 / 21 (47.62%)	
occurrences (all)	21	10	

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? No

Limitations and caveats

None reported