



## Clinical trial results:

### A randomized phase IIa study: natural dendritic cells for immunotherapy of chemo-naïve 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:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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  |

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

We screened 44 chemotherapy-naïve 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 |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | mDC arm |
|------------------|---------|

Arm description:

CD1c+ mDC vaccinations (2–5 × 10<sup>6</sup> 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 × 10<sup>6</sup> cells per injection; arm A)

|                  |         |
|------------------|---------|
| <b>Arm title</b> | pDC arm |
|------------------|---------|

Arm description:

pDC vaccinations (1–3 × 10<sup>6</sup> 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 × 10<sup>6</sup> cells; arm B)

|                  |         |
|------------------|---------|
| <b>Arm title</b> | combiDC |
|------------------|---------|

Arm description:

combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 10<sup>6</sup> 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 × 10<sup>6</sup> cells; arm C)

| <b>Number of subjects in period 1</b> | 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:<br>CD1c+ mDC vaccinations (2–5 × 10 <sup>6</sup> cells per injection; arm A)             |         |
| Reporting group title   | pDC arm |
| Reporting group description:<br>pDC vaccinations (1–3 × 10 <sup>6</sup> cells; arm B)                                 |         |
| Reporting group title   | combiDC |
| Reporting group description:<br>combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 10 <sup>6</sup> cells; arm C) |         |

| Reporting group values                | mDC arm    | pDC arm   | combiDC    |
|---------------------------------------|------------|-----------|------------|
| Number of subjects                    | 7          | 7         | 7          |
| Age categorical<br>Units: Subjects    |            |           |            |
| Adults (18-64 years)                  | 2          | 2         | 3          |
| From 65-84 years                      | 5          | 5         | 4          |
| Age continuous<br>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<br>Units: Subjects |            |           |            |
| Female                                | 0          | 0         | 0          |
| Male                                  | 7          | 7         | 7          |
| Baseline PSA<br>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<br>Units: Subjects    |       |  |  |
| Adults (18-64 years)                  | 7     |  |  |
| From 65-84 years                      | 14    |  |  |
| Age continuous<br>Units: years        |       |  |  |
| geometric mean                        |       |  |  |
| full range (min-max)                  | -     |  |  |
| Gender categorical<br>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:<br>CD1c+ mDC vaccinations (2–5 × 10 <sup>6</sup> cells per injection; arm A)   |  |
| Reporting group title   | pDC arm  |
| Reporting group description:<br>pDC vaccinations (1–3 × 10 <sup>6</sup> cells; arm B)   |  |
| Reporting group title   | combiDC  |
| Reporting group description:<br>combined CD1c+ mDC and pDC vaccinations (combiDC; 3–8 × 10 <sup>6</sup> cells; arm C)   |  |
| Subject analysis set title  | Immunological response after mDC vaccinations    |
| Subject analysis set type   | Per protocol                                     |
| Subject analysis set description:<br>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:<br>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:<br>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:<br>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:<br>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 progression-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 progression-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

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported