



## 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:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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 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 10<sup>6</sup> 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..

|                                       |                       |
|---------------------------------------|-----------------------|
| <b>Number of subjects in period 1</b> | 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   | 14      |  |  |
| full range (min-max)   | 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 <sup>[1]</sup>  |
| P-value                                 | < 0.05 <sup>[2]</sup> |
| 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

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### 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