



Clinical trial results: T cell therapy in combination with peginterferon for metastatic malignant melanoma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001420-29 |
| Trial protocol | DK |
| Global end of trial date | 17 August 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 14 November 2018 |
| First version publication date | 14 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | MM1413 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02379195 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Center for Cancer Immune Therapy, Herlev Hospital |
| Sponsor organisation address | Herlev Ringvej 75, Herlev, Denmark, 2730 |
| Public contact | Center for Cancer Immune Therapy, Center for Cancer Immune Therapy, +45 38683868, inge.marie.svane@regionh.dk |
| Scientific contact | Center for Cancer Immune Therapy, Center for Cancer Immune Therapy, +45 38683868, inge.marie.svane@regionh.dk |

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 | 17 August 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 August 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 August 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate toxicity (according to CTCAE version 4.0) and feasibility

Protection of trial subjects:

Palliative medications as needed

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 June 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 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) | 16 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

All patients were screened in Denmark between November 2014 and May 2017.

Pre-assignment

Screening details:

Patients were screened in a two-stage model. For inclusion for surgery patients were screened with blood samples, PET/CT scan of the body and MRI of the brain. A total of 23 patients were included for surgery. 12 patients were enrolled for treatment with T-cell therapy.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | TIL + IFNa |

Arm description:

The patients are admitted to hospital day -8 and receive lymphodepleting chemotherapy (cyclophosphamide and fludarabine) on day -7 to day -1.

The TILs are infused on day 0 and Interleukin-2 therapy are administered on day 0 to day 5.

Interleukin-2 are administered in an i.v. continuous decrescendo regimen starting approximately 6 hours after TIL infusion with a duration of approximately 5 days

Subcutaneous injections of peginterferon alpha 2b are administered three time (day -2, day 7 and day 14)

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tumor-infiltrating lymphocytes |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Maximum number of expanded TILs ($20-200 \times 10^9$) are infused intravenously once

| | |
|------------------|---------|
| Arm title | Surgery |
|------------------|---------|

Arm description:

Patients enrolled for surgery, but did not receive treatment.

| | |
|---|---------|
| Arm type | Surgery |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | TIL + IFNa | Surgery |
|---------------------------------------|------------|---------|
| Started | 12 | 11 |
| Completed | 12 | 0 |
| Not completed | 0 | 11 |
| Consent withdrawn by subject | - | 1 |
| Progression/clinical deterioration | - | 4 |
| Did not progress after surgery | - | 5 |
| Removed tumor was not melanoma | - | 1 |

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 | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Adults (18-70) | 23 | 23 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 10 | |
| Male | 13 | 13 | |

End points

End points reporting groups

| | |
|--|------------|
| Reporting group title | TIL + IFNa |
| Reporting group description: | |
| The patients are admitted to hospital day -8 and receive lymphodepleting chemotherapy (cyclophosphamide and fludarabine) on day -7 to day -1. | |
| The TILs are infused on day 0 and Interleukin-2 therapy are administered on day 0 to day 5. | |
| Interleukin-2 are administered in an i.v. continuous decrescendo regimen starting approximately 6 hours after TIL infusion with a duration of approximately 5 days | |
| Subcutaneous injections of peginterferon alpha 2b are administered three time (day -2, day 7 and day 14) | |
| Reporting group title | Surgery |
| Reporting group description: | |
| Patients enrolled for surgery, but did not receive treatment. | |

Primary: Tolerability and feasibility

| | |
|--|---|
| End point title | Tolerability and feasibility ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| 3 years | |
| 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: The primary endpoint is tolerability and feasibility. The treatment was both tolerable and feasible. Statistical analysis on this endpoint is not feasible. | |

| End point values | TIL + IFNa | Surgery | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 11 | | |
| Units: Tolerable | | | | |
| number (not applicable) | 12 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median overall survival

| | |
|------------------------|--|
| End point title | Median overall survival ^[2] |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Median overall survival is only provided for the treatment arm.

| End point values | TIL + IFNa | | | |
|-------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 11.75 (0.13 to 27.33) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Median progression-free survival

| | |
|-----------------|---|
| End point title | Median progression-free survival ^[3] |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Median overall survival is only provided for the treatment arm.

| End point values | TIL + IFNa | | | |
|-------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: months | | | | |
| median (full range (min-max)) | 2.8 (0.13 to 18.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Immune response

| | |
|-----------------|--------------------------------|
| End point title | Immune response ^[4] |
|-----------------|--------------------------------|

End point description:

Anti-tumor reactive T-cells in the infusion product

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

4 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Median overall survival is only provided for the treatment arm.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | TIL + IFNa | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Cell | | | | |
| number (not applicable) | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

| | |
|-----------------|--------------------------------------|
| End point title | Overall response rate ^[5] |
|-----------------|--------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3 years

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Median overall survival is only provided for the treatment arm.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | TIL + IFNa | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: Percent | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

November 2014 - August 2018

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | TIL + IFNa |
|-----------------------|------------|

Reporting group description:

The patients are admitted to hospital day -8 and receive lymphodepleting chemotherapy (cyclophosphamide and fludarabine) on day -7 to day -1.

The TILs are infused on day 0 and Interleukin-2 therapy are administered on day 0 to day 5.

Interleukin-2 are administered in an i.v. continuous decrescendo regimen starting approximately 6 hours after TIL infusion with a duration of approximately 5 days

Subcutaneous injections of peginterferon alpha 2b are administered three time (day -2, day 7 and day 14)

| Serious adverse events | TIL + IFNa | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 1 | | |
| Nervous system disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow toxicity | Additional description: After treatment patient's bone marrow recovered, but subsequently the patient developed low platelet counts, low leukocyte counts and anemia. No abnormalities were found on bone marrow biopsy and counts normalized spontaneously. | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Candida infection | Additional description: Patient had oral- and oesophageal candidiasis leading to short-term hospitalization. | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | TIL + IFNa | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | | |
| Investigations | | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | | |
| occurrences (all) | 6 | | |

| | | | |
|--|---|--|--|
| Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all) | 12 / 12 (100.00%) 12 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed ^[1] occurrences (all) | 12 / 12 (100.00%) 12 11 / 11 (100.00%) 11 | | |
| Ear and labyrinth disorders Hearing impairment subjects affected / exposed occurrences (all) | 5 / 12 (41.67%) 5 | | |
| Eye disorders Anterior uveitis subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Mucositis management subjects affected / exposed occurrences (all) | 12 / 12 (100.00%) 12 8 / 12 (66.67%) 8 11 / 12 (91.67%) 11 6 / 12 (50.00%) 6 7 / 12 (58.33%) 7 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--|--|--|
| Dyspnea subjects affected / exposed occurrences (all) | 12 / 12 (100.00%) 12 | | |
| Pulmonary oedema subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all) | 6 / 12 (50.00%) 6 | | |
| Petechiae subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 4 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | Additional description: Myalgia/arthralgia | | |
| subjects affected / exposed occurrences (all) | 8 / 12 (66.67%) 8 | | |
| Infections and infestations Infection subjects affected / exposed occurrences (all) | 7 / 12 (58.33%) 7 | | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Twelve patients were exposed to chemotherapy, but one patient died few days after and alopecia was not yet recorded for this patient.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 27 November 2014 | Amended to not having to wait 6 weeks between treating study subjects. |
| 14 December 2015 | Amended to change principal investigator. |
| 15 March 2016 | Amended to allow for enrollment of more patients. |
| 11 July 2017 | Amended to prolong study period. |

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.

Only twelve patients were treated.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29688262>