



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
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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
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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]
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End point description:

End point type	Secondary
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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]
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End point description:

Anti-tumor reactive T-cells in the infusion product

End point type	Secondary
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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]
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End point description:

End point type	Secondary
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	TIL + IFNa
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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/arthritis		
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>