



## Clinical trial results: T-cell therapy in combination with vemurafenib for BRAF mutated metastatic melanoma

### Summary

EudraCT number	2014-001419-38
Trial protocol	DK
Global end of trial date	31 December 2018

### Results information

Result version number	v1 (current)
This version publication date	18 January 2020
First version publication date	18 January 2020

### Trial information

#### Trial identification

Sponsor protocol code	MM1414
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02354690
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Inge Marie Svane
Sponsor organisation address	Borgmester Ib Juuls Vej 25C, Herlev, Denmark, 2730
Public contact	Inge Marie Svane, National Center for Cancer Immune Therapy, 0045 38689339, inge.marie.svane@regionh.dk
Scientific contact	Inge Marie Svane, National Center for Cancer Immune Therapy, 0045 38689339, 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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

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

Protection of trial subjects:

Patients were treated according to best practice.

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:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	11
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All patients were included in Denmark from November 2014 to April 2018.

### Pre-assignment

Screening details:

Main inclusion criteria were metastatic melanoma with a tumor available for surgical resection and another measurable lesion according to RECIST. Performance status should be 0 or 1 without significant co-morbidities.

### Period 1

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

### Arms

Arm title	T cell therapy with vemurafenib pretreatment
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Arm description:

7 days before tumor harvest, patients will begin taking vemurafenib until admission for lymphodepleting chemotherapy followed by TIL infusion and interleukin-2.

Vemurafenib: Patients will start treatment in a dose of 960 BID 7 days before tumor harvest and ends at the day of admission (day -8).

Lymphodepleting chemotherapy regimen consisting of cyclophosphamide 60 mg/kg for 2 days and fludarabine 25 mg/m<sup>2</sup> for 5 days (constitutes day -7 to -1 of admission).

TIL infusion: A tumor is surgically removed in order to isolate, activate and expand tumor infiltrating lymphocytes (TIL) to high numbers. In vitro preparation usually takes 4-6 weeks using the young TIL method.

On day 0 patients receive an infusion of TIL (1x10<sup>9</sup>-2x10<sup>11</sup> cells).

Interleukin-2 is administered according to the decrescendo regimen (18 MIU/m<sup>2</sup> for 6 hours, 18 MIU/m<sup>2</sup> for 12 hours, 18 MIU/m<sup>2</sup> for 24 hours followed by 4,5 MIU/m<sup>2</sup> for another 3 x 24 hours)

Arm type	Experimental
Investigational medicinal product name	Tumor Infiltrating Lymphocytes
Investigational medicinal product code	
Other name	TIL
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

One-time intravenous infusion of 5x10<sup>9</sup> to 2x10<sup>11</sup> cultured autologous tumor infiltrating lymphocytes

<b>Number of subjects in period 1</b>	T cell therapy with vemurafenib pretreatment
Started	13
Received T cell infusion	12
Completed	12
Not completed	1

Disease progression	1
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## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	2	2	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	7	7	
M stage			
M stage according to the AJCC melanoma 7th edition classification			
Units: Subjects			
M1a	1	1	
M1b	1	1	
M1c	11	11	

## End points

### End points reporting groups

Reporting group title	T cell therapy with vemurafenib pretreatment
Reporting group description:	
7 days before tumor harvest, patients will begin taking vemurafenib until admission for lymphodepleting chemotherapy followed by TIL infusion and interleukin-2.	
Vemurafenib: Patients will start treatment in a dose of 960 BID 7 days before tumor harvest and ends at the day of admission (day -8).	
Lymphodepleting chemotherapy regimen consisting of cyclophosphamide 60 mg/kg for 2 days and fludarabine 25 mg/m2 for 5 days (constitutes day -7 to -1 of admission).	
TIL infusion: A tumor is surgically removed in order to isolate, activate and expand tumor infiltrating lymphocytes (TIL) to high numbers. In vitro preparation usually takes 4-6 weeks using the young TIL method.	
On day 0 patients receive an infusion of TIL (1x10e9-2x10e11 cells).	
Interleukin-2 is administered according to the decrescendo regimen (18 MIU/m2 for 6 hours, 18 MIU/m2 for 12 hours, 18 MIU/m2 for 24 hours followed by 4,5 MIU/m2 for another 3 x 24 hours)	

### Primary: Number of reported adverse events

End point title	Number of reported adverse events <sup>[1]</sup>
End point description:	
From start of treatment until 24 weeks after T cell infusion	
End point type	Primary
End point timeframe:	
0-40 weeks	
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 assessment of the endpoint is descriptive and due to the single arm design no statistics are to be performed.	

End point values	T cell therapy with vemurafenib pretreatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: adverse events				
Grade 1-2	89			
Grade 3-4	35			
Total	124			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Treatment related immune responses

End point title	Treatment related immune responses
End point description: Measurable anti-tumor reactive T cells in the infusion product	
End point type	Secondary
End point timeframe: 0-24 weeks	

<b>End point values</b>	T cell therapy with vemurafenib pretreatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Participants				
Infusion product contains reactive T cells	10			
Reactive T cells not found in infusion product	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective response rate

End point title	Objective response rate
End point description: Complete or partial response according to RECIST1.1.	
End point type	Secondary
End point timeframe: Up to 12 months	

<b>End point values</b>	T cell therapy with vemurafenib pretreatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Response				
Complete response	1			
Partial response	8			
Stable disease	3			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

End point title	Overall survival
End point description: Overall survival (OS), defined as the time from the start of treatment to death, will be described with the Kaplan-Meier curve.	
End point type	Secondary
End point timeframe: Up to 40 months	

<b>End point values</b>	T cell therapy with vemurafenib pretreatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Months				
median (full range (min-max))				
Median overall survival	28.8 (5.2 to 39.9)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival

End point title	Progression-free survival
End point description: Progression-free survival (PFS), defined as the time from start of treatment to disease progression, relapse or death due to any cause, whichever is earlier, will be described with the Kaplan-Meier curve.	
End point type	Secondary
End point timeframe: Up to 40 months	

<b>End point values</b>	T cell therapy with vemurafenib pretreatment			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Months				
median (full range (min-max))				
Median progression-free survival	4.8 (2.5 to 36.1)			



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment to 24 weeks after T cell infusion.

Adverse event reporting additional description:

Adverse events were collected continually and as a minimum systematically at baseline, each treatment visit and at follow-up visits until 24 weeks after T cell infusion.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia without neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis	Additional description: Related to prior systemic anti-cancer treatment		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Pancreatitis			
alternative assessment type: Non-systematic			

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: 0 %

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia without neutropenia		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	12 / 12 (100.00%)		
occurrences (all)	14		
Immune system disorders			
Rhinitis atrophic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	10		
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hallucination			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			

subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all)  Neutropenia subjects affected / exposed occurrences (all)  Lymphopenia subjects affected / exposed occurrences (all)  Thrombocytopenia subjects affected / exposed occurrences (all)	12 / 12 (100.00%) 12  12 / 12 (100.00%) 13  12 / 12 (100.00%) 13  12 / 12 (100.00%) 13		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Eye disorders 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)  Constipation subjects affected / exposed occurrences (all)	9 / 12 (75.00%) 9  2 / 12 (16.67%) 2  1 / 12 (8.33%) 1		

Oral mucositis subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 5		
Hepatobiliary disorders Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)  Petechiae subjects affected / exposed occurrences (all)  Alopecia subjects affected / exposed occurrences (all)  Vitiligo subjects affected / exposed occurrences (all)  Dry skin subjects affected / exposed occurrences (all)  Papilloma subjects affected / exposed occurrences (all)  Actinic keratosis subjects affected / exposed occurrences (all)  Hyperkeratosis subjects affected / exposed occurrences (all)  Photosensitivity subjects affected / exposed occurrences (all)	12 / 12 (100.00%) 14  1 / 12 (8.33%) 1  12 / 12 (100.00%) 12  1 / 12 (8.33%) 1  4 / 12 (33.33%) 4  1 / 12 (8.33%) 1  1 / 12 (8.33%) 1  5 / 12 (41.67%) 5		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	10 / 12 (83.33%) 10		
Infections and infestations Infection subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 5		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2017	Prolongation of inclusion period due to slow accrual.
31 December 2018	Description of follow-up was changed to allow for early closure of the trial.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported