Clinical trial results:
Adoptive cell therapy across cancer diagnoses

Summary

EudraCT number	2017-002323-25
Trial protocol	DK
Global end of trial date	04 December 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	AA1720

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03296137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev Hospital
Sponsor organisation address	Ib Juuls vej 1, Herlev, Denmark, 2730
Public contact	Principal investigator, Center for cancer immune therapy, +45 36686467, anders.kverneland@regionh.dk
Scientific contact	Principal investigator, Center for cancer immune therapy, +45 36686467, anders.kverneland@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	04 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to determine the feasibility and safety of adoptive cell therapy in combination with checkpoint inhibition across different metastatic solid cancers.

Protection of trial subjects:

Patients were constantly monitored for safety and general condition. Treatable conditions where treated when appropiate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
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	Denmark: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	22
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Metastatic cancer disease
Exhausted standard therapies
Good performance status and vital organ function

Pre-assignment

Screening details:

Metastasis avaliable for safe resection. Acceptable vital organ function including kidney, lung, liver and heart. Acceptable performance status.

Period 1

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

Arms

Arm title	TIL therapy

Arm description:

The study design included:
1) ipilimumab (3 mg/kg) 2 weeks before tumor removal
2) Surgical resection of tumor tissue for expansion of tumor-infiltrating lymphocytes (TILs) in vitro
3) Conditioning chemotherapy with cyclophosphamide (60 mg/kg x 2) and fludarabine-phosphate (25 mg/m2 x 5)
4) Infusion of in vitro expanded TILs
5) Nivolumab (3 mg/kg) at day -2, 12, 26 and 40 relative to TIL infusion
6) Stimulation with low dose IL-2 (2 MIU x1 s.c.) for 14 days

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Sendoxan
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg x 2 at day -7 and -6 relative to TIL infusion

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at least 14 days before surgical tumor resection for TIL generation

Investigational medicinal product name	Fludarabine phophate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25 mg/m2 x 5 at day -5, -4, -3, -2 and -1 relative to TIL infusion.

Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	
Other name	Interleukin-2
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

2 million international units daily at day 0 to day 13 relative to TIL infusion

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at day -2, 12, 26 and 40 relative to TIL infusion

Investigational medicinal product name	Tumor infiltration lymphocytes
Investigational medicinal product code	
Other name	TILs, adoptive cell therapy, autologous cell product
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The cell product is generated from in vitro expansion of autologous tumor infiltrating lymphocytes. The expansion consists of an initial step with IL-2 media and a second step with IL-2, anti-CD3 and feeder cells. between 5 x 10e9 and 150 x 10e9 cells are infused into the patient.

Number of subjects in period 1	TIL therapy
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	TIL therapy

Reporting group description: -

Reporting group values	TIL therapy	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
39-66	25	25	
Age continuous Units: years			
median	54		
full range (min-max)	39 to 66	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	11	11	

End points

End points reporting groups

Reporting group title	TIL therapy

Reporting group description:

The study design included:
1) ipilimumab (3 mg/kg) 2 weeks before tumor removal
2) Surgical resection of tumor tissue for expansion of tumor-infiltrating lymphocytes (TILs) in vitro
3) Conditioning chemotherapy with cyclophosphamide (60 mg/kg x 2) and fludarabine-phosphate (25 mg/m2 x 5)
4) Infusion of in vitro expanded TILs
5) Nivolumab (3 mg/kg) at day -2, 12, 26 and 40 relative to TIL infusion
6) Stimulation with low dose IL-2 (2 MIU x1 s.c.) for 14 days

Subject analysis set title	TIL therapy
Subject analysis set type	Full analysis

Subject analysis set description:

The protocol is a phase I-II clinical trial andthe results will be analysed in a qualitative manner.

Primary: Tolerability and feasibility of TIL therapy with CPI addition

End point title	Tolerability and feasibility of TIL therapy with CPI addition[1]

End point description:

Patients in which the TIL expansion and following therapy was possible

End point type	Primary

End point timeframe:

Whole trial period

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 clinical trial is an exploratory phase I-II clinical trial with a relative low number of patients. The stastical power to analyse such a small and heterogenous data set is very limited and the analysis will instead be qualiative.

End point values	TIL therapy			
Subject group type	Subject analysis set			
Number of subjects analysed	31[2]			
Units: 25	25			

Notes:

[2] - Unsuccesful in 6 patients that underwent surgery

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

RECIST v1.1.

End point type	Secondary

End point timeframe:

6 months after treatment

End point values	TIL therapy			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: 25				
PR	2			
SD	5			
PD	18			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of therapy until trial discontinuation

Adverse event reporting additional description:

CTCAE v4

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	TIL therapy

Reporting group description: -

Serious adverse events	TIL therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Refractory causes by alloimmunization		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chylos	Additional description: Swelling of the neck due to surgical removal of metastastic lymph node		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis	Additional description: In vena jugularis after insertion of central venous catheter		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Colitis	Additional description: Immune therapy related adverse event		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Cough	Additional description: Fever and cough. Spontanous remission		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bilirubin excretion disorder	Additional description: Due to progression in liver metastases		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress	Additional description: Acute reaction and T-cell infusion. Transfered to ICU for intubation. Returned after 4 days.		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis	Additional description: Infection after insertion of ureteric stent insertion.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Addison's disease	Additional description: Addisons crisis. Patient with adenocorticocarcinoma and in mitotane therapy.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Febrile neutropenia	Additional description: After discharge recurrent neutropenia and onset of fever		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection	Additional description: After initial discharge after TIL therapy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	TIL therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Vascular disorders			
Thrombosis	Additional description: In central venous catheter		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	25 / 25 (100.00%)		
occurrences (all)	27		
Thrombocytopenia			
subjects affected / exposed	22 / 25 (88.00%)		
occurrences (all)	22		
Anaemia			
subjects affected / exposed	22 / 25 (88.00%)		
occurrences (all)	22		
General disorders and administration site conditions			

Nausea subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Fatigue subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6		
Performance status decreased subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 9		
Vomiting subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Immune system disorders Febrile neutropenia subjects affected / exposed occurrences (all)	Additional description: Due to cell therapy and IL-2 therapy 16 / 25 (64.00%) 18		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4		
Hepatobiliary disorders Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Renal and urinary disorders Hyponatraemia subjects affected / exposed occurrences (all)	Additional description: Cyclophosphamide induced 2 / 25 (8.00%) 2		
Cystitis haemorrhagic subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Psychiatric disorders			

Hallucination subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Infections and infestations Infection in an immunocompromised host subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The patients are late stage cancer patients with many accompanying comorbidities. The study design consists of many different drugs and the individual contribution to effacacy and safety is difficult to assess.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34607899