Clinical trial results:
Targeted Natural Killer (NK) cell based adoptive immunotherapy for the treatment of patients with Non-Small Cell Lung Cancer (NSCLC) after radiochemotherapy (RCT)

Summary

EudraCT number	2008-002130-30
Trial protocol	DE
Global end of trial date	07 May 2018

Results information

Result version number	v1 (current)
This version publication date	16 May 2020
First version publication date	16 May 2020

Trial information

Trial identification

Sponsor protocol code	NSCLC-TKD/IL-2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Iniv. Prof. Dr. med. Stephanie Combs, Klinikum rechts der Isar der TUM Klinik für RadioOnkologie und Strahlenterapie, 0049 (0)8941404501, StephanieElisabeth.Combs@mri.tum.de
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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	26 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to examine whether an adjuvant treatment with TKD/IL-2-activated, patient-derived NK cells following definitive RCT is feasible and effective. Comparison of progression-free survival between treatment and control group A control arm with standard radiochemotherapy (Cisplatin/Vinorelbine) is part of this study, because Pfister et al (2007) could demonstrate that lung cancer patients with an Hsp70 membrane expression had a poorer clinical outcome with respect to overall survival when compared to their Hsp70 membrane counterparts. Therefore, all historic data on overall survival of lung cancer patients are the result of a mixture of Hsp70 positive and negative patients and median overall survival of Hsp70 positive lung cancer patients is not known.

Protection of trial subjects:

The conduct of this clinical study met the local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP).
Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy:

Standard of care.

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	11
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pre-screening processes were in place for all patients. 16 patients were randomised between 27.11.2014 and 08.08.2016.

Pre-assignment

Screening details:

Patients must have all screening evaluations performed prior to the first dose of study drug and must meet all inclusion and none of the exclusion criteria. The patients must be thoroughly informed about all aspects of the study, all evaluations as required per protocol and all regulatory requirements for informed consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TKD/IL-2 Activated NK_Cells

Arm description:

The group of Hsp70 positive subjects received Hsp70-peptide TKD/IL-2 activated, autologous NK cells (somatic cell therapy, plasma derived medicinal product, IMP) subsequent to standard RCT. Patients underwent leukapheresis of 3-4 hours before each treatment cycle to collect lymphocytes. A defined number of lymphocytes were activated for 3-5 days with GMP grade Hsp70-peptide TKD (Bachem) plus low dose IL-2 (100 IU/ml; Proleukin, Chiron) at a cell density of 10x106 cells.
Patients were to be treated with NK therapy every 2-6 weeks on study visits (V) 2, V3, V4, and V5.

Arm type	Experimental
Investigational medicinal product name	TKD_NK
Investigational medicinal product code	
Other name	TKD/IL-2 Activated NK_Cells
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The group of Hsp70 positive subjects received Hsp70-peptide TKD/IL-2 activated, autologous NK cells (somatic cell therapy, plasma derived medicinal product, IMP) subsequent to standard RCT.
Patients underwent leukapheresis of 3-4 hours before each treatment cycle to collect lymphocytes. A defined number of lymphocytes were activated for 3-5 days with GMP grade Hsp70-peptide TKD (Bachem) plus low dose IL-2 (100 IU/ml; Proleukin, Chiron) at a cell density of 10x106 cells. On day 3-5 the TKD/IL-2 activated, autologous NK cells were washed twice in Ringer's Lactate solution, re-suspended in 500 ml of Ringer's Lactate/0.1%HSA and re-infused into the patient intravenously over 30-60 min using a stem cell infusion set.
Patients were to be treated with NK therapy every 2-6 weeks on study visits (V) 2, V3, V4, and V5.

Arm title	Standard RCT

Arm description:

The group of Hsp70 positive subjects received best supportive care following their standard RCT.

Arm type	Best supportive care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	TKD/IL-2 Activated NK_Cells	Standard RCT
Started	8	8
Completed	4	4
Not completed	4	4
Study closed	1	-
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	-
Lost to follow-up	-	1
Tumor progression	1	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	62.8		
standard deviation	± 6.8	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	9	9	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized subjects who received at least one dose of sudy mdeication.

Reporting group values	ITT		
Number of subjects	15		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 63.1 ± 7.0		
Gender categorical Units: Subjects			
Female Male	7 8		

End points

End points reporting groups

Reporting group title	TKD/IL-2 Activated NK_Cells

Reporting group description:

The group of Hsp70 positive subjects received Hsp70-peptide TKD/IL-2 activated, autologous NK cells (somatic cell therapy, plasma derived medicinal product, IMP) subsequent to standard RCT. Patients underwent leukapheresis of 3-4 hours before each treatment cycle to collect lymphocytes. A defined number of lymphocytes were activated for 3-5 days with GMP grade Hsp70-peptide TKD (Bachem) plus low dose IL-2 (100 IU/ml; Proleukin, Chiron) at a cell density of 10x106 cells.
Patients were to be treated with NK therapy every 2-6 weeks on study visits (V) 2, V3, V4, and V5.

Reporting group title	Standard RCT

Reporting group description:

The group of Hsp70 positive subjects received best supportive care following their standard RCT.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consists of all randomized subjects who received at least one dose of sudy mdeication.

Primary: Progression free survival - PFS

End point title	Progression free survival - PFS

End point description:

End point type	Primary

End point timeframe:

From time of randomisation to 18 months follow-up. The point estimate of PFS is given for 12 months.

End point values	TKD/IL-2 Activated NK_Cells	Standard RCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[1]	8		
Units: percent				
number (confidence interval 95%)	67 (19 to 90)	33 (5 to 68)		

Notes:

[1] - One patient excluded from ITT

Statistical analyses

Statistical analysis title	Comparison of PFS

Statistical analysis description:

One-sided log-rank test

Comparison groups	TKD/IL-2 Activated NK_Cells v Standard RCT

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	3.45

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

All patients survived 18 months after treatment

End point type	Secondary

End point timeframe:

From time of randomisation to 18 months follow-up.

End point values	TKD/IL-2 Activated NK_Cells	Standard RCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[2]	8		
Units: patients	7	8		

Notes:

[2] - One patient excluded from ITT

Statistical analyses

No statistical analyses for this end point

Secondary: Response to treatment

End point title	Response to treatment

End point description:

End point type	Secondary

End point timeframe:

From time of randomisation to 18 months follow-up.

End point values	TKD/IL-2 Activated NK_Cells	Standard RCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[3]	8		
Units: Patients				
irCR	1	0		
irPR	1	1		
irSD	1	1		
irPD	3	5		

Notes:

[3] - One patient excluded from ITT, one patient dropped out before V3

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life

End point title	Quality of life

End point description:

Quality of life is measured by the QLQ-C30 score

End point type	Secondary

End point timeframe:

Visit 1 to Visit 9.

End point values	TKD/IL-2 Activated NK_Cells	Standard RCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[4]	8		
Units: score				
arithmetic mean (standard deviation)				
Visit 1	67.4 (± 16.7)	74.2 (± 21.5)		
Visit 6	92.5 (± 4.1)	82.6 (± 14.6)		
Visit 7	87.0 (± 6.2)	75.0 (± 18.8)		
Visit 8	77.8 (± 19.6)	72.6 (± 26.3)		
Visit 9	84.5 (± 9.8)	78.4 (± 20.3)		

Notes:

[4] - One patient was excluded from the ITT set

Statistical analyses

No statistical analyses for this end point

Secondary: NK activation

End point title	NK activation

End point description:

Percent increase of CD94+ NK cells considering successful re-infusions only.

End point type	Secondary

End point timeframe:

Visit 2, visit 3, visit 4, visit 5

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Percent increase of CD94+ NK cells				
arithmetic mean (standard deviation)				
Visit 2	100 (± 36)			
Visit 3	143 (± 109)			
Visit 4	103 (± 43)			
Visit 5	116 (± 56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity

End point title	Toxicity

End point description:

Toxicity measured according to NCI CTCAE v4.0

End point type	Secondary

End point timeframe:

18 months

End point values	TKD/IL-2 Activated NK_Cells	Standard RCT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[5]	8		
Units: Patients				
Grade 3	3	1		

Notes:

[5] - One patient excluded from ITT

Statistical analyses

Statistical analysis title	Toxicity

Statistical analysis description:

Comparison of number of patients with toxicity throughout the study between the two study groups. Only toxicities of grade 3 were observed.

Comparison groups	TKD/IL-2 Activated NK_Cells v Standard RCT

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were documented in the timeframe from signed informed consent till the end of the follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	TKD/IL-2 Activated NK_Cells

Reporting group description:

The group of Hsp70 positive subjects received Hsp70-peptide TKD/IL-2 activated, autologous NK cells (somatic cell therapy, plasma derived medicinal product, IMP) subsequent to standard RCT. Patients underwent leukapheresis of 3-4 hours before each treatment cycle to collect lymphocytes. A defined number of lymphocytes were activated for 3-5 days with GMP grade Hsp70-peptide TKD (Bachem) plus low dose IL-2 (100 IU/ml; Proleukin, Chiron) at a cell density of 10x106 cells.
Patients were to be treated with NK therapy every 2-6 weeks on study visits (V) 2, V3, V4, and V5.

Reporting group title	Standard RCT

Reporting group description:

The group of Hsp70 positive subjects received best supportive care following their standard RCT.

Serious adverse events	TKD/IL-2 Activated NK_Cells	Standard RCT	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
local swelling			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TKD/IL-2 Activated NK_Cells	Standard RCT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	3 / 8 (37.50%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
metastatic pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Performance status decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Blood potassium decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Leukopenia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Burning mouth syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Coeliac disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Irritable bowel syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Neck pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
sensation of heaviness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	3	
Syphilis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

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.

Based of the slower than expected recruitment and current standard of care for NSCLC as recommended at this time (e.g. NCCN guidelines, 2018) the clinical trial was terminated prematurely.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30747241