Clinical trial results:
Treatment of patients with metastatic melanoma (AJCC stage IV or III unresectable) with the PDE-inhibitor Tadalafil:
A Pilot Trial for “Proof of Principle”

Summary

EudraCT number	2011-003273-28
Trial protocol	DE
Global end of trial date	30 January 2015

Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022
Summary attachment (see zip file)	TaMeDermReport (Report_TaMeV2clear.pdf)

Trial information

Trial identification

Sponsor protocol code	Derm-NCT001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospital Heidelberg
Sponsor organisation address	INF 672, Heidelberg, Germany, 69123
Public contact	Skin Cancer Center, Department of Dermatology, Universtiy Hospital Heidelberg, +49 62215638503, jessica.hassel@med.uni-heidelberg.de
Scientific contact	Skin Cancer Center, Department of Dermatology, Universtiy Hospital Heidelberg, +49 62215638503, jessica.hassel@med.uni-heidelberg.de

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	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2015
Global end of trial reached?	Yes
Global end of trial date	30 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immune response as assessed by number of CD8+ cells in fresh tumor tissue by FACS

Protection of trial subjects:

Medication contraindicated with the oral intake of Tadalafil were prohibited, e.g. nitrates, ketoconazole/itraconazole, chlarithromycin/erythromycin, ritonavir and other CYP3A metabolized drugs, rifampicin, Phenobarbital, Phenytoin, Carbamazepin and other CYP3A inductors, alpha-blocker like doxazosin.
Safety laboratory assessments were performed.

Background therapy:

Any medication which is considered necessary for the patient’s welfare, and which was not expected to interfere with the evaluation of the study drug, might have been given at the discretion of the investigator.
Treatment with other cytokines, cytotoxic agents (e.g. chemotherapy) or hormone therapies (e.g. corticosteroids) was not allowed. Exceptions were hormone replacement therapy or oral contraceptives.

Evidence for comparator:

Not applicable (no comparator)

Actual start date of recruitment	04 October 2011
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	Germany: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	8
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Inclusion of 12 patients:
• Age: 18-75 years
• Histologically proven metastatic melanoma,
• Measurable disease
• ECOG 0-2
• At least one prior treatment for metastatic disease
• No medical contraindication to biopsy
• Willingness and ability to understand the informed consent and the QoL Questionnaire
• WOCBP: effective contraception

Pre-assignment

Screening details:

Screening examinations were performed after obtaining informed consent in writing.

Period 1

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

Blinding implementation details:

no blinding

Arms

Arm title	Tadalafil

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tadalafil
Investigational medicinal product code	GO4BE08
Other name	Cialis (Product name)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40, 20, 10 or 5mg administered once daily p.o.

Number of subjects in period 1	Tadalafil
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Therapy

Reporting group description: -

Reporting group values	Therapy	Total	
Number of subjects	12	12	
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)	8	8	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	6	6	
Male	6	6	

End points

End points reporting groups

Reporting group title	Tadalafil

Reporting group description: -

Primary: Immune Response

End point title	Immune Response[1]

End point description:

Stable disease was achieved in 3/12 patients (25%). Details of cellular immune response are displayed in fig. 5 of the report atteched as PDF file.

End point type	Primary

End point timeframe:

After 4 weeks of treatment a biopsy from acutaneous metastasis was taken to evaluate number of CD8+ cells in fresh tumor tissue by FACS

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: There was no control group, no statistical analysis was performed

End point values	Tadalafil			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients with stable				
stable disease yes	3			
stable disease no	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate

End point title	Response rate

End point description:

End point type	Secondary

End point timeframe:

From start of treatment until progression of disease or death

End point values	Tadalafil			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: months				
median (full range (min-max))	4.6 (0.7 to 7.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Other immune response parameters

End point title	Other immune response parameters

End point description:

Number of CD4+ and CD8+ cells in tumor tissue by IHC and proliferation of CD8+ lymphocytes in peripheral blood mononuclear cells by FACS.
Details

End point type	Secondary

End point timeframe:

4 weeks after start of therapy

End point values	Tadalafil			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability

End point title	Tolerability

End point description:

As the treatment was tolerated very well with only 13% grade 3/4 adverse events the recommended dose is 40mg.
One patient in the 10 mg dose-cohort experienced headaches that were resistant to pain medication and developed into a Grade 3 AE. The administration of the study medication was then reduced by 50% to 5 mg tadalafil daily.

End point type	Secondary

End point timeframe:

During treatment period

End point values	Tadalafil			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients				
No change in treatment	11			
Dose reduction	1			
Stop of medication	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment (8 weeks)

Adverse event reporting additional description:

All patients experienced at least one adverse event (AE) with a median number of 7.5 (1– 12) AEs per patient. A total of 84 AEs were recorded during the study, 11 of 84 AEs (13.1%) of grade 3–4. 6 of 84 (7.1%) severe AEs (SAEs) were registered in three patients. The most frequently reported AE was vomiting/nausea (8.3%).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tadalafil

Reporting group description: -

Serious adverse events	Tadalafil		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of pleura			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tadalafil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Nervous system disorders			

Nervous system disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	10		
General disorders and administration site conditions			
General disorders and administraton site conditions	Additional description: All AEs in this SOC		
subjects affected / exposed	12 / 12 (100.00%)		
occurrences (all)	24		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	12 / 12 (100.00%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	7		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All AEs in this SOC		
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	9		

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.

In the section on non-serious adverse events, the number 'subjects affected' was not available. Instead, the maximum possible value was entered. However, as one AE may occur several times in one individual, the actual number might have been lower.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28932631