UniversitätsKlinikum Heidelberg

Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** TaMe (Derm-NCT001)	*(For National Authority Use only)*
Name of (Finished) Product: Cialis®		**Name of Active Ingredient:** Tadalafil	
EudraCT-Nr.: 2011-003273-28	**BfArM Vorlage-Nr.:**	**Ethik Antrags-Nr.:** AFmo- 417/2011	

SYNOPSIS

Title of Study:
Treatment of patients with metastatic melanoma (AJCC stage IV or III unresectable) with the PDE-inhibitor Tadalafil: A Pilot Trial for "Proof of Principle"

Investigators:
Principle Investigator: Prof. Dr. med. J. Hassel

Study Centre(s):
National Center for Tumor Diseases/Department of Dermatology
University Hospital Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg

Publication (reference):
Hassel JC, Jiang H, Bender C, Winkler J, Sevko A, Shevchenko I, Halama N, Dimitrakopoulou-Strauss A, Haefeli WE, Jäger D, Enk A, Utikal J, Umansky V. Tadalafil has biologic activity in human melanoma. Results of a pilot trial with Tadalafil in patients with metastatic Melanoma (TaMe). Oncoimmunology. 2017 May 16;6(9):e1326440. [IF 7,644]

Study period: **date of first enrolment: Mar 2012** **date of last completed: Jan 2015**		**Study Phase: IIa**

Objectives:
Primary Outcome measures:
- immune response as assessed by number of CD8+ cells in fresh tumor tissue by FACS

Secondary outcome measures:
- response rate and disease control rate according to irRC and RECIST
- Other immune response parameters as number of CD4+ and CD8+ cells in tumor tissue by IHC and proliferation of CD8+ lymphocytes in peripheral blood mononuclear cells by FACS
- Tolerability
- Optimal dosing schedule for tadalafil
- Treatment-related side effects
- Progression-free survival at 8 weeks of treatment
- Quality of life

UniversitätsKlinikum Heidelberg

Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** TaMe (Derm-NCT001)	*(For National Authority Use only)*
Name of (Finished) Product: Cialis®		**Name of Active Ingredient:** Tadalafil	
EudraCT-Nr.: 2011-003273-28	**BfArM Vorlage-Nr.:**	**Ethik Antrags-Nr.:** AFmo- 417/2011	

Methodology:
Dose de-escalation cohort study:
The study was an open label, monocenter phase IIa clinical trial which was designed as a pilot project in order to establish the biological effect, optimal biological dose, efficacy and tolerability of Cialis® as palliative treatment of metastatic melanoma. Patients were treated subsequently in cohorts characterized by different doses (40mg - 20mg – 10mg – 5mg) to analyze dosage dependent effects. Dose deescalation was performed in order to determine dose levels for thresholds of efficacy, whereas previous studies with Tadalafil showed that dosages up to 40mg per day are tolerable.

Number of patients (planned and analysed):
12

Diagnosis and main criteria for inclusion:
Criteria for inclusion:
- Age: 18-75 years
- Histologically proven metastatic melanoma, clinical stage IV or III unresectable (AJCC 2010)
- Measurable disease
- ECOG performance status of 0-2
- At least one prior treatment for metastatic disease
- No medical contraindication to biopsy of target lesion
- Willingness and ability to understand the informed consent and the quality of life questionnaires and to give signed written informed consent
- WOCBP: effective contraception

Test product, dose and mode of administration, batch number:
Cialis® p.o. once daily. Dose: 40mg/d in cohort 1, 20mg/d in cohort 2, 10mg/d in cohort 3, 5mg/d in cohort 4

Batch numbers (charge): 20mg (A945012, A945012, A945012, A970989, C057493, C089043), 5mg (C077842, C110783, C202379, C316044)

Duration of treatment:
8 weeks

Reference therapy, dose and mode of administration, batch number:
none

Name of Sponsor/Company: Universitätsklinikum Heidelberg	Sponsor-Code of Study: TaMe (Derm-NCT001)	*(For National Authority Use only)*
Name of (Finished) Product: Cialis®	**Name of Active Ingredient:** Tadalafil	
EudraCT-Nr.: 2011-003273-28	**BfArM Vorlage-Nr.:**	**Ethik Antrags-Nr.:** AFmo- 417/2011

Criteria for evaluation: (efficacy, safety)

Assessments of biologic effect: Prior and after 4 weeks of treatment with Cialis® a biopsy from acutaneous metastasis is taken to evaluate tumor infiltrating lymphocytes histopathologically and by FACS.
Assessments of efficacy: Whole body tumor assessment will be performed before begin of treatment and after 8 weeks. Methods comprise whole body CT scans and Brain MRI as well as digital photography and lymph node ultrasound for assessment of target lesions on skin and lymph nodes. Response evaluation will be performed according to immune-related response criteria (irRC) and the standard RECIST criteria.
Assessment of safety: The incidence and grading of adverse events and abnormal laboratory test results will be performed according to CTC-Criteria.

Statistical methods:

Descriptive statistics, X2, student t-test, Kaplan–Meier analysis, log rank testing, unpaired two-tailed Student's t test

Substantial Amendement and trial holds:

The trial was conducted as planned, there were no substantial amendments. Only the recruitment time (03/12-01/15) was longer than planned because of new competing phase 3 trials with PD-1 antibodies especially nivolumab..

Summary – Conclusions:

Efficacy Results:

- Clinical: Stable disease was achieved in 3/12 patients (25%). Median progression-free survival was 4.6 months (range 0.7–7.1), median overall survival (OS) 8.5 months (range 2.7–23.7) (see attached manuscript: Hassel et al, 2017)

Table 1. Patient characteristics and treatment outcome.

ID	Stage	Mutation status	Age (years)	Gender	Tadalafil dosage	Elevated serum LDH (yes/no)[1]	Best response (irRC)	Previous therapies	PFS (months)	OS (months)
01	M1c	wt	75	Male	40 mg	yes	PD	DTIC, Ipi, P/C	2.2	2.8
02	M1b	wt	64	Male	40 mg	no	SD	DTIC	4.3	13.2
03	M1c	wt	55	Male	40 mg	yes	PD	DTIC, Ipi	1.8	4.6
04	M1c	V600E	48	Female	20 mg	no	PD	Ipi	1.8	15.9
05	M1c	wt	70	Male	20 mg	yes	PD	DTIC, Ipi	1.8	8.8
06	M1c	V600	33	Male	20 mg	yes	PD	DTIC, Ipi, BRAF-I	0.7	5.0
07	M1c	wt	61	Male	10 mg	yes	PD	DTIC, Ipi, P/C, T/G, trofosfamide	1.8	2.7
08	M1c	V600E	60	Female	10 mg	no	SD	Ipi	3.0	6.3
10	M1a	NRas	70	Female	10 mg	no	PD	Ipi/Nivo	1.8	23.7+
11	M1c	D594N	58	Female	5 mg	yes	PD	none (CI Ipi)	1.9	22.2+
14	M0	V600E	68	Female	5 mg	no	SD	ECT, Ipi	7.1	20.8+
15	M1a	NRas	75	Female	5 mg	no	PD	DTIC	2.1	8.2
									Median: 4.6	*Median: 8.5*

Abbreviations (alphabetical order): BRAF-I = BRAF inhibitor, CI = contraindication, DTIC = dacarbazine, ECT = Electrochemotherapy, Ipi = Ipilimumab, irRC: immune-related response criteria, LDH: lactate dehydrogenase, Nivo = Nivolumab, OS = overall survival, P/C = Paclitaxel/Carboplatin, PFS = progression free survival, PD = progressive disease, SD = stable disease, T/C = Treosulfan/Gemcitabin, wt = wildtype;
[1]at the start of treatment.

- Immunomodulatory: Stable patients displayed significantly higher numbers of CD8+ TIL in the center of metastases before treatment as compared with progressive patients. Upon therapy, they showed increased expression of

Name of Sponsor/Company: Universitätsklinikum Heidelberg		Sponsor-Code of Study: TaMe (Derm-NCT001)	*(For National Authority Use only)*
Name of (Finished) Product: Cialis®		**Name of Active Ingredient:** Tadalafil	
EudraCT-Nr.: 2011-003273-28	**BfArM Vorlage-Nr.:**	**Ethik Antrags-Nr.:** AFmo- 417/2011	

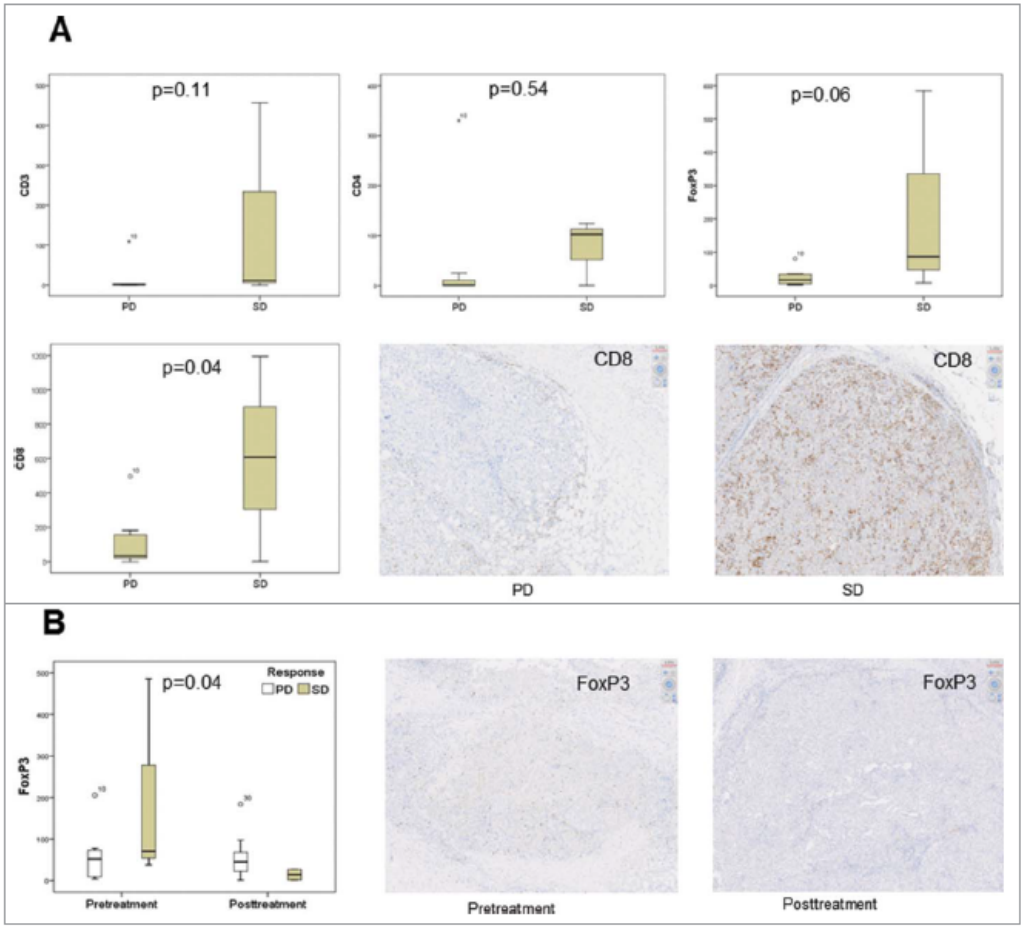

Figure 5. Tissue specimens before and after 4 weeks of treatment were immunohistochemically analyzed for their infiltration with T cells (CD3, CD8, FOXP3, PD-1), B cells (CD20) and macrophages (CD163). Computer-assisted analysis revealed a significantly higher number of infiltrating T cells, especially of the $CD8^+$ phenotype, in stable patients pretreatment in the center of the metastases ($p = 0.036$) (A). After 4 weeks of treatment with tadalafil, no significant changes could be seen between stable and progressive patients with the exception of a drop in the infiltration with regulatory T cells ($p = 0.044$; Fig. 5B) (PD — progressive disease; SD — stable disease; *y* axis in box plots — mean cells/mm^2).

Safety Results:

every patient in the study experienced one or more adverse events (AEs) with a median number of 7.5 (1–12) AEs per patient (Table S1). 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 AEs included vomiting/nausea (8.3%) and headache, fatigue and weight loss (3.6%) (Fig. 2). 15 of 84 (17.9%) AEs were thought to be treatment-related. One patient in the 10 mg dose-cohort experienced headaches that were resistant to pain medication and developed into a Grade 3 AE. All six recorded SAEs were related to the underlying disease and disease progression, e.g., anasarca and ascites. There were no treatment-related deaths.

Name of Sponsor/Company: Universitätsklinikum Heidelberg	Sponsor-Code of Study: TaMe (Derm-NCT001)	*(For National Authority Use only)*
Name of (Finished) Product: Cialis®	**Name of Active Ingredient:** Tadalafil	
EudraCT-Nr.: 2011-003273-28	**BfArM Vorlage-Nr.:**	**Ethik Antrags-Nr.:** AFmo- 417/2011

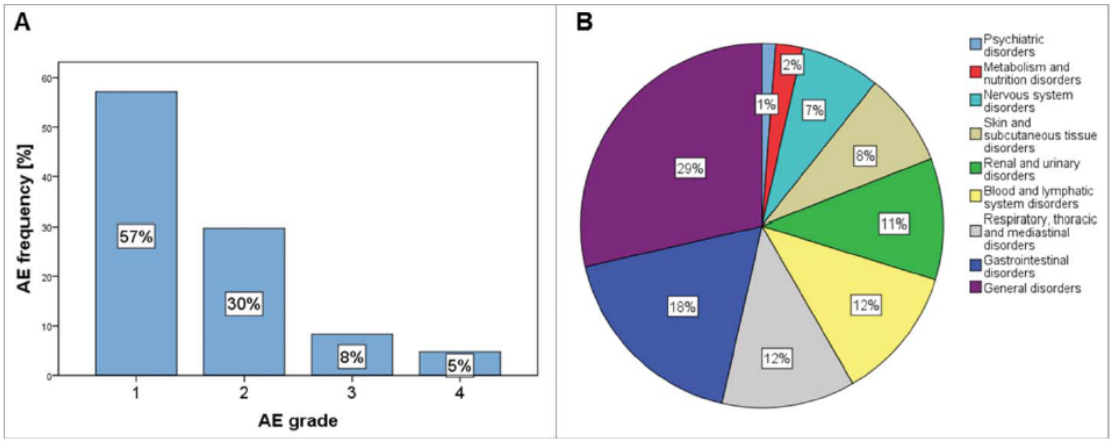

Figure 2. Adverse events: frequency of adverse events according to toxicity grades CTCAE4.0 criteria (A) and affected organ systems (B).

Optimal dosing schedule for tadalafil: patients with SD and longer PFS were seen in all dosis cohorts from 5mg to 40mg tadalafil. As the treatment was tolerated very well with only 13% grade 3/4 adverse events the recommended dose is 40mg.

Quality of life:
Quality of life (QoL) was assessed using the SF-12TM Health Survey (SF-12) questionnaire at baseline, 4 and 8 weeks of treatment (Table S2). Data are complete except one missing score (last time point of patient 6), which could not be assessed due to rapid disease progression and death of the patient. SF-12 physical (PCS) and mental component scores (MCS) varied greatly among patients over the course of the trial. Comparing PCS and MCS at screening to the 4 week time point, we noted a minor decrease by a mean of 2.1 (range ¡11.0 to 19.1) points and 0.8 points (range ¡2.1 to 27.9), respectively (Fig. S1). There was no statistically significant difference in QoL between stable and progressive patients (Pearson correlation: p D 0.231 for PCS; p D 0.672 dor MCS) nor depending on the number of AE (Pearson correlation: p D 0.594 for PCS, p D 0.630 for MCS).

Conclusion
The results of this pilot trial indicate that the PDE-5 inhibitor tadalafil has the potential to improve clinical outcome of advanced melanoma patients by enhancing antitumor immunity and highlights its potential application in combined melanoma immunotherapy (see Hassel et al, 2017).

Date of report: 22.07.2022