



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, clarithromycin/erythromycin, ritonavir and other CYP3A metabolized drugs, rifampicin, Phenobarbital, Phenytoin, Carbamazepin and other CYP3A inducers, 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 attached 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

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