



## Clinical trial results:

### A phase II study to evaluate safety and efficacy of combined treatment with ipilimumab and intratumoral interleukin-2 in pretreated patients with stage IV melanoma

#### Summary

EudraCT number	2010-019033-98
Trial protocol	DE
Global end of trial date	23 June 2015

#### Results information

Result version number	v1 (current)
This version publication date	29 October 2021
First version publication date	29 October 2021
Summary attachment (see zip file)	Adverse Events Information (AEs_Attachment_TUE-01.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	BMS-TUE-01
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01480323
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University Hospital Tuebingen
Sponsor organisation address	Geissweg 3, Tuebingen, Germany, 72076
Public contact	PD Dr. med. Benjamin Weide, University Hospital Tuebingen, +49 7071 / 2985748, benjamin.weide@med.uni-tuebingen.de
Scientific contact	Prof. Dr. Michael Bamberg , University Hospital Tuebingen, +49 7071 / 298216, michael.bamberg@med.uni-tuebingen.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	24 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2014
Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of the trial was to assess the efficacy of the combined treatment with ipilimumab and intratumoral IL-2 based on the Disease Control Rate according to immune-related Response Criteria (irDCR) at week 12

Protection of trial subjects:

Before the beginning of the study, approval of the responsible Independent Ethics Committee (IEC) was obtained. The responsible IEC of the coordinating investigator was the ethics committee of medical faculty of the University of Tuebingen. The study was approved on 27.10.2011. Protocol Amendment 1 was approved on 08.04.2013 by the responsible IEC. The regulatory basis of the conduct of this study consisted of the Declaration of Helsinki (in its current version), the AMG (German Medicinal Products Act), in particular Sections 40-42 in the current versions, and the principles of the proper conduct of clinical trials (ICH GCP). In accordance with the AMG, the sponsor had taken out insurance for all subjects who gave consent to participation in the clinical trial. The Investigator provided adequate information to the subject prior to subject signing the informed consent. The Institute provided an information sheet to the subjects and prepared it in accordance with the Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) for the purpose of obtaining informed consent. In addition to this written information, the Investigator informed the subject verbally.

Background therapy:

Concomitant systemic or local anti-cancer medications or treatments were prohibited in this study while receiving study treatment. Furthermore the following therapies during the study were prohibited:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other CTLA-4 inhibitors or agonists
- CD137 agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

Evidence for comparator: -

Actual start date of recruitment	16 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

<b>Subjects enrolled per age group</b>	
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)	15
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 15 patients from 1 site (Tuebingen Center for Dermato-Oncology, Investigator: PD Dr. med. Benjamin Weide) were enrolled from February 2012 to July 2014.

### Pre-assignment

Screening details:

In part 1 of this study 15 patients were enrolled from 1 site. 14 of 15 patients met all inclusion criteria and did not meet one of the exclusion criteria. All 15 patients were analysed for safety and efficacy evaluations. Due to the results of the second interim analysis no patients were enrolled in part 2 of the study.

### Period 1

Period 1 title	Ipilimumab with intratumoral IL-2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Arm title	Treatment arm
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Arm description:

The treatment arm consisted of ipilimumab infusions (3mg/kg) every 3 weeks (days 2, 23, 44,65) for a total of four doses in combination with intralesional IL-2 at a dosage of 9 MIU distributed between all injected metastases proportionally to the respective lesion size at treatment days 1,4, 8, 11, 15, 18, 22 and 25.

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	BMS-734016
Other name	Yervoy
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Each patient should have received ipilimumab at days 2, 23, 44 and 65 of the induction phase at a dosage of 3 mg/kg as an infusion. Infusions were given over 90 minutes (not bolus or IV push)

Investigational medicinal product name	IL-2
Investigational medicinal product code	
Other name	Proleukin, Aldesleukin
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Proleukin® S administration at a dosage of 9 MIU was planned at days 1, 4, 8, 11, 15, 18, 22 and 25 by intratumoral injections. The total daily dose was distributed between all selected soft-tissue metastases up to a maximum of 5. The total daily dose of 9 MIU IL-2 was distributed proportionally according to lesion sizes. Injections should have been guided by sonography for deep soft tissue metastases to ensure the intratumoral route of application

<b>Number of subjects in period 1</b>	Treatment arm
Started	15
Completed	10
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Lack of efficacy	2

## Baseline characteristics

### Reporting groups

Reporting group title	Ipilimumab with intratumoral IL-2
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Reporting group description: -

Reporting group values	Ipilimumab with intratumoral IL-2	Total	
Number of subjects	15	15	
Age categorical			
The median age at registration was 54 years.			
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)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	9	9	

## End points

### End points reporting groups

Reporting group title	Treatment arm
Reporting group description: The treatment arm consisted of ipilimumab infusions (3mg/kg) every 3 weeks (days 2, 23, 44,65) for a total of four doses in combination with intralesional IL-2 at a dosage of 9 MIU distributed between all injected metastases proportionally to the respective lesion size at treatment days 1,4, 8, 11, 15, 18, 22 and 25.	
Subject analysis set title	Treatment arm
Subject analysis set type	Full analysis
Subject analysis set description: Ipilimumab + IL-2	

### Primary: Disease Control Rate according to immune-related Response Criteria (irDCR) at week 12

End point title	Disease Control Rate according to immune-related Response Criteria (irDCR) at week 12 <sup>[1]</sup>
End point description: The primary endpoint of this study was the Disease Control rate according to immune-related Response Criteria (irDCR) at week 12. irDCR at week 12 represents the sum of patients with an overall response (irCR or irPR or irSD) divided by the total number of patients, who were evaluable for efficacy. According to the definition of the evaluable set (see section 8.1) 15 patients were evaluable for the primary endpoint. 3 of the 15 patients (20.0%) showed irSD at week 12 and 10 of the 15 patients (66.7%) showed irPD at week 12. For 2 of the 15 patients (13.3%) the end of treatment visit including tumor assessment was performed before week 12 due to progressive disease requiring another systemic treatment (Table 4). Therefore the irDCR at week 12 amounts to 20.0%:	
End point type	Primary
End point timeframe: 12 weeks	
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: Statistical analysis can be found in the attached publication	

End point values	Treatment arm	Treatment arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: 20	15	15		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Immune –related Overall Response Rate (irORR) at week 12

End point title	Immune –related Overall Response Rate (irORR) at week 12
End point description: Immune –related Overall Response Rate (irORR) at week 12 is defined as the sum of patients with an Overall Response (irPR or irCR) at week 12, divided by the total number of patients who were evaluable for efficacy. Since none of the 15 evaluable patients showed irCR or irPR at week 12 (Table 4), the irORR at week 12 was 0%	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Treatment arm	Treatment arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: percentage of patients				
number (not applicable)	15	15		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Immune-related Best Overall Response Rate (irBORR)

End point title	Immune-related Best Overall Response Rate (irBORR)
End point description:	
Immune-related Best Overall Response Rate (irBORR) is defined as number of patients whose irBOR was irCR (Complete Response) or irPR (Partial Response), divided by the total number of patients who were evaluable for efficacy. Of the 15 evaluable patients none of them showed irCR or irPR as Best Response. Therefore the irBORR is 0%.	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Treatment arm	Treatment arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: percentage of patients				
number (not applicable)	15	15		

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR at week 12 according to modified WHO criteria (mWHO)

End point title	ORR at week 12 according to modified WHO criteria (mWHO)
End point description:	
This secondary endpoint represents the sum of patients with an overall response (CR or PR) according to modified WHO criteria) at week 12, divided by the total number of patients, who were evaluable for efficacy. 15 patients were evaluable for the analysis. 1 of the 15 patients (6.67%) showed SD (Stable Disease) according to mWHO criteria at week 12 and	



12 of the 15 patients (80.0%) showed PD according to mWHO at week 12. For 2 of the 15 patients (13.3%) the end of treatment visit including tumor assessment was performed before week 12 due to progressive disease requiring another systemic treatment. Since none of the 15 evaluable patients showed CR or PR (according to mWHO) at week 12, the ORR at week 12 according to modified WHO criteria was 0%.

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Treatment arm	Treatment arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: percentage of patients				
number (not applicable)	15	15		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

Adverse events were assessed at each visit during the treatment period and at week 52

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Adverse event reporting additional description:

Safety laboratory tests had to be documented at the pre-study visit, at days 1, 8, 15, 22, 29, 44, and 65 of the treatment period and at week 12.

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Assessment type	Systematic
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### Dictionary used

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Dictionary name	NCI CTCAE
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Dictionary version	4
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Frequency threshold for reporting non-serious adverse events: 4 %

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### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Information regarding Adverse Events and Serious AEs can be found in the attached file

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

After analysis of the first 15 patients , an unsatisfactory efficacy (irDCR at week 12: 20.0%) became aware. Therefore the second part of the study involving additional 24 patients was omitted.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/2800845>