Clinical trial results:
Phase II Trial of Ipilimumab in Patients with advanced melanoma and spontaneous preexisting immune response to NY-ESO-1

Summary

EudraCT number	2009-016631-35
Trial protocol	DE
Global end of trial date	03 June 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	NCT-2009-11-02-53

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ruprecht-Karls-University Heidelberg, Medical Faculty
Sponsor organisation address	Im Neuenheimer Feld 672, Heidelberg, Germany,
Public contact	Principal Investigator, NCT Heidelberg, ++49 6221567229, Dirk.Jaeger@med.uni-heidelberg.de
Scientific contact	Principal Investigator, NCT Heidelberg, ++49 6221567229, Dirk.Jaeger@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	08 May 2017
Is this the analysis of the primary completion data?	Yes

Primary completion date	
Global end of trial reached?	Yes
Global end of trial date	03 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immune-related Disease Control Rate irDCR (irCR, irPR, irSD) according to the immune-related response criteria (see Appendix 1) in patients with spontaneous preexisting NY-ESO-1 immune response treated with ipilimumab.

Protection of trial subjects:

- regular DMC meetings
- adherence to all ethical and legal reqirement

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	16
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

- Signed Written Informed Consent must be obtained before performing protocol-related procedures that are not part of standard patient care.
- Target Population

Histologic diagnosis of malignant melanoma; unresectable Stage III melanoma or Stage IV melanoma; Measurable/evaluable disease (as per mWHO criteria), within 28 days before first dose of

Period 1

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

Arms

Arm title	single arm study

Arm description:

single arm study

Arm type	single arm study
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

10 mg/kg of ipilimumab intravenously

Number of subjects in period 1	single arm study
Started	25
Completed	4
Not completed	21
Unacceptable toxicities	9
Progression of disease	12

Baseline characteristics

Reporting groups	
Reporting group title	Main Period

Reporting group description: -

Reporting group values	Main Period	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
From 18-44 years	2	2	
From 45-64 years	14	14	
65 years and older	9	9	
Age continuous Units: years			
arithmetic mean	60.7		
full range (min-max)	36 to 80	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	20	20	
Ethnic Origin Units: Subjects			
Caucasian/white	25	0	
BMI categorical Units: Subjects			
Underweight	1	1	
Normal Weigth	6	6	
Overweight	16	16	
Obese	1	1	
Severly Obese	1	1	
Tumor diagnosis Units: Subjects			
Unresectable stage III melanoma	3	3	
Stage IV melanoma	22	22	
BMI continuous Units: kg/m^2			
arithmetic mean	26.4		
full range (min-max)	17.3 to 39.5	-	

End points

End points reporting groups

Reporting group title	single arm study
Reporting group description:	
single arm study	
Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Including all enrolled patients who have taken at least one dose of trial treatment	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of the ITT population with at least one postscreening/baseline tumour assessment and no major protocol deviations	

Primary: Immune-related disease control rate (irDCR)

End point title	Immune-related disease control rate (irDCR)
End point description:	
irDCR was defined as the total number of patients whose immune-related best overall response (irBOR) was irCR, irPR, or irSD	
End point type	Primary
End point timeframe:	
For all patients, tumor measurements could be determined at week 12, 16 (optional) 24, 28 (optional), 36, 40 (optional), and 48.	

End point values	ITT set	Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: Patients with irDCR	13	13		

Statistical analyses

Statistical analysis title	Descriptive Analysis ITT
Statistical analysis description:	
Number of patients with irDCR	
Comparison groups	ITT set
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	observed percentage
Point estimate	52

Statistical analysis title	Descriptive Analysis Per Protocol
Statistical analysis description: Number of patients with irDCR	
Comparison groups	Per protocol set
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	observed percentage
Point estimate	61.9

Secondary: Disease Control Rate according to RECIST	
End point title	Disease Control Rate according to RECIST
End point description: Disease Control includes CR, PR or SD	
End point type	Secondary
End point timeframe: At end of induction (week 12)	

End point values	ITT set	Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: DCR	11	11		

Statistical analyses

Statistical analysis title	Descriptive Analysis ITT
Statistical analysis description: Number of patients with DCR	
Comparison groups	ITT set
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	observed percentage
Point estimate	44

Statistical analysis title	Descriptive Analysis Per Protocol
Statistical analysis description: Number of patients with DCR	
Comparison groups	Per protocol set
Number of subjects included in analysis	21

Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	observed percentage
Point estimate	52.4

Secondary: Progression-free survival according to irRC

End point title	Progression-free survival according to irRC

End point description:

End point type	Secondary

End point timeframe:

First study treatment date until documented tumor progression date or date of death. PFS data were censored on the date of the last tumor assessment on study for patients who do not have a progressive disease and who do not die while on study.

End point values	ITT set	Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: Months				
number (not applicable)				
Median	7.8	7.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival according to RECIST

End point title	Progression-free survival according to RECIST

End point description:

End point type	Secondary

End point timeframe:

First study treatment date until documented tumor progression date or date of death. PFS data were censored on the date of the last tumor assessment on study for patients who do not have a progressive disease and who do not die while on study.

End point values	ITT set	Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: Months				
number (confidence interval 95%)	2.9 (2.5 to 8.1)	2.9 (2.5 to 8.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Including the survival follow up until January 2017

End point values	ITT set	Per protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	21		
Units: Months				
number (not applicable)				
Median	22.7	32.8		
1-year event free rate	0.668	0.747		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

+AEs will be recorded for a total of 10 weeks after the last administration of the investigational agent

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Safety set

Reporting group description: -

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 25 (52.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		

deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune colitis			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Appendicitis perforated			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Peripheral coldness			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Skin operation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	10 / 25 (40.00%)		
occurrences (all)	10		
General physical health deterioration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Mucosal dryness			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	2 / 25 (8.00%)		

occurrences (all)	2		
Pyrexia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	6		
Reproductive system and breast disorders			
Genital blister			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Oedema genital			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Blood cortisol decreased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
C-reactive protein increased			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hepatic enzyme increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Dyspnoea exertional			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Epistaxis			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Increased bronchial secretion			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Pulmonary pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Carotid artery stenosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	8 / 25 (32.00%)		

occurrences (all)	8		
Hypoaesthesia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Visual acuity reduced			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Visual impairment			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Abdominal tenderness			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Anal haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Autoimmune colitis				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences (all)	3			
Diarrhoea				
subjects affected / exposed	11 / 25 (44.00%)			
occurrences (all)	11			
Dry mouth				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Eructation				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	4 / 25 (16.00%)			
occurrences (all)	4			
Gastrointestinal pain				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Haematochezia				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	5 / 25 (20.00%)			
occurrences (all)	5			
Noninfective gingivitis				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Retching				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Stomatitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Vomiting				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences (all)	3			

Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Polyuria subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Hepatobiliary disorders Autoimmune hepatitis subjects affected / exposed occurrences (all) Hepatitis subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 1 / 25 (4.00%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Dyshidrotic eczema subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed	 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1 2 / 25 (8.00%) 2 1 / 25 (4.00%) 1 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2 1 / 25 (4.00%)		

occurrences (all)	1		
Night sweats			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Pain of skin			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Post inflammatory pigmentation change			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Pruritus generalised			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	8		
Rash generalised			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Rash papular			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Vitiligo			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		

Back pain subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5		
Bone pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Muscle tightness subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Musculoskeletal discomfort subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Neck pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6		
Pain in jaw subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Endocrine disorders Autoimmune thyroiditis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Hypophysitis subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Dehydration subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Infections and infestations Appendicitis perforated subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Erysipelas subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Folliculitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Fungal infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Herpes zoster subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Infection subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Skin infection subjects affected / exposed	1 / 25 (4.00%)		

occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2010	following the recommendations of the IEC the description of the statistical methods was improved without changing of the overall study conduct (Protocol version 1.3).
20 December 2011	the protocol was changed to enhance the recruitment: now patients could be recruited irrespective of a preceding failure of the standard chemo therapy (Protocol version 2.0).
31 March 2015	update of the Reference Safety Information without change of the safety profile of the participants (Protocol version 2.2).
07 April 2015	update of the Reference Safety Information without change of the safety profile of the participants (Protocol version 2.3).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 November 2014	the toxicity based stop criterion as defined in the protocol (30% toxicity) was reached and recruitment was stopped immediately. The risk-benefit-ratio remained untouched. The DMC recommended continuing the recruiting, which was continued 6.2.2015.	06 February 2015

Notes:

Limitations and caveats

None reported