Clinical trial results:
CD20-Immunotargeting in Stage IV Melanoma Patients - A Prospective, Open Label, Two-Period Pilot Study to Evaluate Overall Tumor Responsive Rate

Summary

EudraCT number	2010-023277-19
Trial protocol	AT
Global end of trial date	28 January 2015

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	CD20 Immunotargeting of Melanoma

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01376713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Waehringer Guertel 18-20, Vienna, Austria,
Public contact	UD Dr. Stephan Wagner, Medical University of Vienna, Department of Dermatology , 0043 14040077050, stephan.wagner@meduniwien.ac.at
Scientific contact	UD Dr. Stephan Wagner, Medical University of Vienna, Department of Dermatology , 0043 14040077050, stephan.wagner@meduniwien.ac.at

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	01 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2013
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the overall disease control rate according to criteria of RECIST v. 1.1

Protection of trial subjects:

Exclusion of:
Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)
• Other past or current malignancy.
• Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment
• History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae
• HIV positive
• Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to enrolement, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.
• Significant concurrent, uncontrolled medical condition
• Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.
• Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result
• Screening laboratory values:
hemoglobin < 8g/dL
platelets <70 x 109/L
leukocytes <1.5 x 109/L
creatinine >2.0 times upper normal limit
total bilirubin >1.5 times uppertotal bilirubin >1.5 times upper normal limit
ALT >2.5 times upper normal limit
alkaline phosphatase >2.5 times upper normal limit
• Pregnant or lactating women.

Efficacy, safety and laboratory assessments on a regular basis:
MRI/CT, physical examination, ECOG, weight, 12-lead ECG, adverse events and concomitant therapy evaluation, hematology (hemoglobin, hematocrit, RBC, WBC + differentials), chemistry (ASAT, ALAT, alkaline phosphatase, total bilirubin, creatinine), serum pregnancy testing;

Background therapy:

In this study, all concomitant medications were allowed, with the exception of:
• treatment with any known marketed drug substance or experimental therapy within 5 terminal half lives or 4 weeks prior to enrollment, whichever is longer;
• currently participating in any other interventional trials;

Evidence for comparator:

not applicable

Actual start date of recruitment	21 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the population that is routinely treated for melanoma at the study sites.

Pre-assignment

Screening details:

Screening procedures for the study were performed from day -28 until day 0 before administration of study medication. Screening assessments were performed only after the patient has signed the informed consent form. Inclusion and exclusion criteria were checked accordingly at the screening visit.

Period 1

Period 1 title	Arm A (Monotherapy) - Stage 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	Arm A - Stage 1

Arm description:

Initially, 10 eligible patients will be treated with ofatumumab (1000 mg) alone. Tumor imaging is planned at wk 4 (screening for rapid disease progression), 8, 16 and 24. Follow-up starts at wk 24. If interim analysis shows that at least 1 confirmed overall response (CR, PR) occurs, the study will proceed to Arm A stage 2. If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression will have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC (Arm A - Rescue Arm)

Arm type	Experimental
Investigational medicinal product name	Arzerra
Investigational medicinal product code	Ofatumumab
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab will be administered at a dose of 1000mg iv weekly (+/- 2 days) for 8 weeks and q4w (+/- 1 week) for another 16 weeks.

Number of subjects in period 1	Arm A - Stage 1
Started	10
confirmed overall response, CR/PR	0 [1]
Completed	8
Not completed	2
Adverse event, serious fatal	1
death after disease progression	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Sequential study design - no patient enroled. For saving the xml-file, a number has to be entered. The information of no enrolment is given under non-completion reason.

Period 2

Period 2 title	Arm A - Stage 1 - Rescue Arm
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Arm title	Arm A - Stage 1 Rescue Arm

Arm description:

If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression will have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC.

Arm type	Experimental
Investigational medicinal product name	Arzerra
Investigational medicinal product code	Ofatumumab
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients with disease progression received at least three cycles of Ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg Dacarbazine.

Investigational medicinal product name	Dacarbazine medac
Investigational medicinal product code	Dacarbazine
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients with disease progression received at least three cycles of Ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg Dacarbazine.

Number of subjects in period 2	Arm A - Stage 1 Rescue Arm
Started	8
Completed	7
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Monotherapy) - Stage 1

Reporting group description:

Initially, 10 eligible patients shall be treated with ofatumumab (1000 mg) alone. Tumor imaging was planned at wk 4 (screening for rapid disease progression), 8, 16 and 24. Follow-up started at wk 24. If interim analysis shows that at least 1 confirmed overall response oc-curs, the study should proceed to Arm A stage 2. If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression should have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC.

Reporting group values	Arm A (Monotherapy) - Stage 1	Total	
Number of subjects	10	10	
Age categorical			
Patients have to be older than 18 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)	5	5	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	2	
Male	8	8	

End points

End points reporting groups

Reporting group title	Arm A - Stage 1

Reporting group description:

Initially, 10 eligible patients will be treated with ofatumumab (1000 mg) alone. Tumor imaging is planned at wk 4 (screening for rapid disease progression), 8, 16 and 24. Follow-up starts at wk 24. If interim analysis shows that at least 1 confirmed overall response (CR, PR) occurs, the study will proceed to Arm A stage 2. If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression will have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC (Arm A - Rescue Arm)

Reporting group title	Arm A - Stage 1 Rescue Arm

Reporting group description:

If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression will have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC.

Primary: Evaluation of overall disease control rate according to criteria of RECIST v. 1.1 (measurable disease))

End point title	Evaluation of overall disease control rate according to criteria of RECIST v. 1.1 (measurable disease))[1]

End point description:

Efficacy criterion.

The primary objective of this study is to evaluate the overall disease control rate according to criteria of RECIST v. 1.1. The primary endpoint disease control, is tested with Simon Two Stage Designs. The primary analysis is based on the full analysis set comprising all patients that received at least one dose of the study drug. Patients for which the primary endpoint is not available will be considered as treatment failures in this analysis. The one sided type I error rate for each of the hypothesis tests (H0A , H0B) is set to 0.05.

End point type	Primary

End point timeframe:

Disease control according to RECIST v. 1.1 criteria until week 24 (measurable disease).

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: no further statistical sub-analysis

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[2]	6[3]		
Units: Extent of response or disease				
Disease control rate (CR, PR, SD)	6	4		
Progressive Disease (PD)	4	2		

Notes:

[2] - please see data below, subject analysis sets

[3] - 1 patient not analyzable

Statistical analyses

No statistical analyses for this end point

Primary: Evaluation of overall disease control rate according to ir-RC (overall response)

End point title	Evaluation of overall disease control rate according to ir-RC (overall response)[4]

End point description:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Evaluation by immune-related response criteria (ir-RC). This method of evaluation of the overall response is referred to in the Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria (Clin Cancer Res 2009;15(26) December 1, 2009. The ir-RC evaluation was not implemented in the clinical study protocol issued in 2010.

End point type	Primary

End point timeframe:

Disease control according to immune-related response criteria until week 24 (overall response).

Notes:

[4] - 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: no further statistical sub-analysis

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[5]	8		
Units: Extent of response or disease				
Disease control rate (CR, PR, SD)	2	1		
Progressive disease (PD)	8	7		

Notes:

[5] - SD in 2 patients

Statistical analyses

No statistical analyses for this end point

Primary: Evaluation of overall disease control rate according to criteria of RECIST v. 1.1 (overall response)

End point title	Evaluation of overall disease control rate according to criteria of RECIST v. 1.1 (overall response)[6]

End point description:

End point type	Primary

End point timeframe:

Disease control according to RECIST v. 1.1 criteria until week 24 (overall response).

Notes:

[6] - 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: no further statistical sub-analysis

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[7]	8[8]		
Units: Extent of response or disease				
Disease Control Rate (CR, PR, SD)	1	1		
Progressive disease (PD)	9	7		

Notes:
[7] - SD in 1 patient
[8] - SD in 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of progression-free survival (PFS) - RECIST v1.1 (overall response)

End point title	Assessment of progression-free survival (PFS) - RECIST v1.1 (overall response)

End point description:

End point type	Secondary

End point timeframe:
First day of treatment until first documentation of disease progression or death, whichever occurs first.

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[9]	1[10]		
Units: Surrogate Endpoint				
Months	5	5		

Notes:
[9] - for patients with disease control only
[10] - for patients with disease control only

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) - RECIST v1.1 (overall response)

End point title	Overall survival (OS) - RECIST v1.1 (overall response)

End point description:

End point type	Secondary

End point timeframe:
Every three months (+/- 1 month) until all patients have died or are lost to follow up.

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[11]	8[12]		
Units: Surrogate endpoint	11	11		

Notes:

[11] - given as mean value in months

[12] - given as mean value in months

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of progression-free survival (PFS) - ir-RC (overall response)

End point title	Assessment of progression-free survival (PFS) - ir-RC (overall response)

End point description:

Efficacy endpoint

End point type	Secondary

End point timeframe:

First day of treatment until first documentation of disease progression or death, whichever occurs first.

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: months				
months	22	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) - ir-RC (overall response)

End point title	Overall survival (OS) - ir-RC (overall response)

End point description:

End point type	Secondary

End point timeframe:

Every three months (+/- 1 month) until all patients have died or are lost to follow up.

End point values	Arm A - Stage 1	Arm A - Stage 1 Rescue Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	8		
Units: months				
months	22	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Induction (week 1-8 qw) until Follow-up visit (3 months post treatment)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Arm A (Monotherapy) - Stage 1

Reporting group description:

Stage 1: Treatment with Ofatumumab (1000 mg) only.

Tumor imaging is planned at wk 4 (screening for rapid disease progression), 8, 16 and 24. Follow-up starts at wk 24. If interim analysis shows that at least 1 confirmed overall response occurs, the study will proceed to Arm A stage 2. If ofatumumab at the 1000 mg dose is well tolerated, patients with disease progression will have the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose of 2000 mg in combination with 1000 mg DTIC.

Reporting group title	Arm A - Stage 1 - Rescue Arm

Reporting group description:

Patients with disease progression who have well tolerated the Ofatumumab treatment well, had the opportunity to receive at least 3 cycles of ofatumumab q4w at an increased dose (2000 mg) in combination with DTIC (1000mg).

Serious adverse events	Arm A (Monotherapy) - Stage 1	Arm A - Stage 1 - Rescue Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	1 / 8 (12.50%)	
number of deaths (all causes)	2	7	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Acute coronary syndrome	Additional description: Possible relation to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Hypertension	Additional description: Probable relation to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia	Additional description: possible relation to study drug		

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erysipelas	Additional description: resulting in Sepsis, not related vs.probable related to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A (Monotherapy) - Stage 1	Arm A - Stage 1 - Rescue Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	2 / 8 (25.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites	Additional description: unlikely related to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Incoordination	Additional description: possible relation to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Sinus tachycardia	Additional description: probable relation to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Anemia	Additional description: possible relation to study drug		
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Immune system disorders			
Urticarial rash	Additional description: certain relation to study drug		
subjects affected / exposed	5 / 10 (50.00%)	0 / 8 (0.00%)	
occurrences (all)	5	0	
Eye disorders			

Retinal detachments and defects	Additional description: unlikely related to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Anal fissure	Additional description: unlikely related to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastroesophageal reflux disease	Additional description: possible relation to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension	Additional description: unlikely related to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erysipelas	Additional description: not related to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Exanthem	Additional description: possible relation to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal artery stenosis	Additional description: unlikely related to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Influenza	Additional description: not related to study drug		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pneumonia	Additional description: assessed as possible to probable relation to study drug		
subjects affected / exposed	2 / 10 (20.00%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Pneumococcal infection	Additional description: possibly related to study drug		
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2011	Addition of clinical trial site: Prof.Dr.Klemens Rappersberger Rudolfstiftung, Department for Dermatology and Venerology
13 March 2014	Release of safety warning by GSK Pharma GmbH with respect to risk of HBV reactivation after administration of Arzerra. The warning states that HBV reactivation can occur in patients receiving CD20-directed cytolytic antibodies (including Arzerra), resulting in some cases in fulminant hepatitis, hepatic failure, and death. As a consequence GSK recommends the screening of all patients for HBV infection prior starting Arzerra i.v treatment by measuring HBsAg and HBcAb. Moreover patients with a prior HBV infection who are at risk of HBV reactivation shall be monitored properly.

Notes:

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.

not applicable

Notes: