Clinical trial results:
Profile of soluble and cellular biomarkers and of functional imaging during antiangiogenic therapies in cancer patients

Summary

EudraCT number	2008-008852-18
Trial protocol	AT
Global end of trial date	04 October 2014

Results information

Result version number	v1 (current)
This version publication date	17 October 2020
First version publication date	17 October 2020

Trial information

Trial identification

Sponsor protocol code	PRAEMARKERAAT08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01507740
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
Public contact	Priv.Doz. Dr. Andreas Pircher, Medical University Innsbruck, University Hospital for Internal Medicine V, +43 (0)512/ 504-24003,
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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	04 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2014
Global end of trial reached?	Yes
Global end of trial date	04 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Biomarker evaluation under antiannagiogenic therapy with Nexavar, Sutent and Avastin. Eligible patients are suffering from hepatocellular carcinoma, non small cell lung cancer, renal cell cancer and colorectal cancer routinely treated with the abov mentioned antiangiogenic agents.

Protection of trial subjects:

Laboratory examinations were part of the routine blood sampling and CT scans were performed as depended by clinical requirements. Functional imaging with dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) was preplanned at study inclusion and at the time point of disease progression.

Background therapy:

NSCLC patients were treated with bevacizumab monotherapy (maintenance therapy), RCC patients were treated either with sorafenib or sunitinib monotherapy, HCC patients were treated with sorafenib monotherapy.

Evidence for comparator:

No comparators have been used in this trial.

Actual start date of recruitment	26 October 2009
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	Austria: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	9
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between November 2009 and July 2012 22 patients were included in this academic non-interventional pilot study.
Patients with HCC (hepatocellular cancer), RCC (renal cell cancer) and NSCLC (non-small cell lung cancer) treated either with sorafenib, sunitinib or bevacizumab were eligible.

Pre-assignment

Screening details:

An already ongoing antiangiogenic therapy was required for study inclusion (baseline analysis). Only patients with confirmed benefit (disease stabilization) from antiangiogenic could be included, while primary resistant patients were not part of the study.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Treatment group

Arm description:

2 NSCLC patients were treated with bevacizumab monotherapy (maintenance therapy), RCC patients were treated either with sorafenib (1 patient) or sunitinib (6 patients) monotherapy,13 HCC patients were treated with sorafenib monotherapy.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	H-C-687
Other name	Sutent
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

Tablets of 50mg were given daily for 4 weeks followed by an intervall of 2 weeks with no therapy.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

2x 400mg daily

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15mg/ kg every 3 weeks.

Number of subjects in period 1	Treatment group
Started	22
Completed	22

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment goup

Arm description:

During the response interval under monotherapy with antiangiogenic drugs periodical measurements at intervals of 3-7 weeks (according to local standards) were performed.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

Tablets of 50mg were given daily for 4 weeks followed by an intervall of 2 weeks with no therapy.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

2x 400mg daily.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15mg/ kg every 3 weeks.

Number of subjects in period 2	Treatment goup
Started	22
Completed	20
Not completed	2
Lost to follow-up	2

Period 3

Period 3 title	Progression
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment group

Arm description:

NSCLC patients were treated with bevacizumab monotherapy (maintenance therapy), RCC patients were treated either with sorafenib or sunitinib monotherapy, HCC patients were treated with sorafenib monotherapy.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

Tablets of 50mg were given daily for 4 weeks followed by an intervall of 2 weeks with no therapy.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Gastroenteral use

Dosage and administration details:

2x 400mg daily

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15mg/ kg every 3 weeks.

Number of subjects in period 3	Treatment group
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	22	22	
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)	9	9	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65		
standard deviation	± 10.00	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	18	18	

End points

End points reporting groups

Reporting group title	Treatment group
Reporting group description:	
2 NSCLC patients were treated with bevacizumab monotherapy (maintenance therapy), RCC patients were treated either with sorafenib (1 patient) or sunitinib (6 patients) monotherapy,13 HCC patients were treated with sorafenib monotherapy.	
Reporting group title	Treatment goup
Reporting group description:	
During the response interval under monotherapy with antiangiogenic drugs periodical measurements at intervals of 3-7 weeks (according to local standards) were performed.	
Reporting group title	Treatment group
Reporting group description:	
NSCLC patients were treated with bevacizumab monotherapy (maintenance therapy), RCC patients were treated either with sorafenib or sunitinib monotherapy, HCC patients were treated with sorafenib monotherapy.	

Primary: TEM

End point title	TEM
End point description:	
The aim of the present study was to generate a profile of possible mechanisms of resistance in patients with renal cell cancer (RCC), hepatocellular cancer (HCC) and non-small cell lung cancer (NSCLC) treated with sunitinib, sorafenib or bevacizumab thereby comparing and correlating changes in tumor endothelial markers (TEM) to disease progression. TEM have been shown to be selectively expressed by tumor endothelial cells and to have important biological functions (e.g. Robo4 inhibits VEGFR2 signaling). Therefore, we analyzed Robo4, Clec14 and ECSCR expression levels in PBMC, which decreased significantly at disease progression	
End point type	Primary
End point timeframe:	
Baseline- Progression	

End point values	Treatment group	Treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Expression				
median (full range (min-max))				
Robo4	1.29 (0.06 to 16.28)	0.46 (0.12 to 5.12)		
Clec14	1.64 (0.12 to 17.01)	0.91 (0.06 to 21.16)		
ECSCR	1.45 (0.04 to 18.02)	0.57 (0.06 to 8.67)		

Statistical analyses

Statistical analysis title	Robo4 expression

Statistical analysis description:

Robo4 expression decreased significantly from baseline to disease progression.

Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.04
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Clec14 expression
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.09
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ECSCR expression
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.009
Method	Wilcoxon (Mann-Whitney)

Primary: Circulating cell populations

End point title	Circulating cell populations

End point description:

The aim of the present study was to generate a profile of possible mechanisms of resistance in patients with renal cell cancer (RCC), hepatocellular cancer (HCC) and non-small cell lung cancer (NSCLC) treated with sunitinib, sorafenib or bevacizumab thereby comparing and correlating changes in circulating cell populations to disease progression.
Levels of CECs (circulating endothelial cells) and CEPs (circulating progenitor cells) are indicative of high vascular turnover and potential candidates for monitoring antiangiogenic therapies.
Additionally CD45-CD31+ and VEGFR2+CEC cell populations were measured.

End point type	Primary

End point timeframe:

Baseline- Progression

End point values	Treatment group	Treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: cells per milliliter				
median (full range (min-max))				
CEC	11.88 (0.00 to 111.20)	40.00 (13.56 to 135.40)		
CD45-CD31+	2360 (154 to 9239)	3021 (38 to 11535)		
CEP	4.63 (0.00 to 27.68)	35.44 (13.94 to 150.90)		
VEGFR2+CEC	48.28 (7.50 to 145.80)	13.54 (3.62 to 62.28)		

Statistical analyses

Statistical analysis title	CEC level
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CD45-CD31+ level
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	CEP level
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	VEGFR2+CEC
Comparison groups	Treatment group v Treatment group

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Primary: Cytokine levels

End point title	Cytokine levels

End point description:

The aim of the present study was to generate a profile of possible mechanisms of resistance in patients with renal cell cancer
(RCC), hepatocellular cancer (HCC) and non-small cell lung cancer (NSCLC) treated with sunitinib, sorafenib or bevacizumab thereby comparing and correlating changes in angiogenic growth factors to disease progression. We measured serum levels of proangiogenic
cytokines at baseline and disease progression and found that VEGF, PDGF, PlGF and HGF increased during the course of therapy. In contrast, we observed that cytokines like sVEGFR2, DKK3, MIG and ICAM decreased during the course of therapy.

End point type	Primary

End point timeframe:

Baseline- Progression

End point values	Treatment group	Treatment group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[1]	18[2]		
Units: pg per milliliter				
median (full range (min-max))				
VEGF	155 (53 to 381)	189 (67 to 698)		
sVEGFR2	179 (98 to 391)	135 (32 to 267)		
PlGF	4 (1 to 21)	8 (2 to 38)		
PDGF	656 (232 to 1034)	690 (532 to 1146)		
DKK3	4754 (1510 to 8758)	4347 (1335 to 8278)		

Notes:

[1] - For PIGF 17 subjects and for PDGF 19 subjects were analysed.

[2] - For PIGF 17 subjects and for PDGF 19 subjects were analysed.

Statistical analyses

Statistical analysis title	Serum concentration of VEGF
Comparison groups	Treatment group v Treatment group

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.04
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Serum concentration of sVEGFR2
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.08
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Serum concentration of PIGF
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Serum concentration of PDGF
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.06
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Serum concentration of DKK3
Comparison groups	Treatment group v Treatment group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.08
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline- Progression	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03
Reporting groups	
Reporting group title	Treatment group

Reporting group description: -

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)		
Immune system disorders			
Leukopenia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	11 / 22 (50.00%)		
occurrences (all)	11		
Stomatitis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26956051