Clinical trial results:
Prospective, explorative trial for the detection of circulating cell-free tumor DNA in the plasma of patients with gastrointestinal stromal tumors (GIST) harboring activating mutations of CKIT or PDGFRA pre/post surgery or pre/under treatment with a tyrosine kinase inhibitor or progressive disease irrespective of current or planned Treatment. An open-label, non-randomized, multicenter phase IIIb clinical trial

Summary

EudraCT number	2011-002544-27
Trial protocol	DE
Global end of trial date	14 October 2015

Results information

Result version number	v1 (current)
This version publication date	13 September 2020
First version publication date	13 September 2020
Summary attachment (see zip file)	GIST-Clinical_Cancer_Research (CF-DNA-GIST_IJC_2019.pdf)

Trial information

Trial identification

Sponsor protocol code	CSTI571BDE78T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462994
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Professor Dr. med. Nikolas von Bubnoff , Klinikum rechts der Isar, Klinik und Poliklinik für Innere Medizin III , +49 761 270 33210,
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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	12 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 October 2015
Global end of trial reached?	Yes
Global end of trial date	14 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Goal of the study is to investigate whether tumor-specific CKIT or PDGFRA DNA fragments can be detected and quantified in the plasma of patients with active GIST as defined as GIST lesions that can be measured by diagnostic imaging.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP). Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy:

Medical treatment will be given according to the clinical trial centers' routine with TKI such as imatinib or sunitinib. The medication is standard medication, which can vary between study centers. The information on which medication is administered, dose and duration of medical treatment will be collected and captured on the CRF at baseline and each time the patient presents in the hospital for follow-up visits.

Evidence for comparator:

n.a.

Actual start date of recruitment	24 January 2012
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: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	22
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted multicentric single-centre in Germany between 24.01.2012 (first patient recruited) and 14.10.2015 (last patient completed).

Pre-assignment

Screening details:

During screening it will be assessed whether the patient meets all inclusion and no exclusion criteria. Each patient screened will be captured on the subject screening list. Patients were enrolled to the study, if eligibility was confirmed. After Screening, a total of 35 patients were included in the study.

Period 1

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

Blinding implementation details:

This is a single-arm not blinded study.

Arms

Arm title	GIST trial

Arm description:

Single arm for detection of circulating tumor DNA in the plasma of patients with GIST pre/post surgery and pre/under neoadjuvant or palliative medical treatment with a tyrokiniase inhibitors (TKI) like imatinib or sunitinib or in progressive disease irrespective of therapy.

Arm type	Experimental
Investigational medicinal product name	Imatinib
Investigational medicinal product code	CAS 152459-95-5
Other name	SUB25387
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg /day for 12 months

Investigational medicinal product name	Sunitinib
Investigational medicinal product code	557795-19-4
Other name	SUB22321
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50 mg per day for 4 weeks

Number of subjects in period 1	GIST trial
Started	35
Completed	11
Not completed	24
Adverse event, serious fatal	5

Consent withdrawn by subject	8
Developed NSCLC	1
Organizational reasons	3
Lost to follow-up	4
Protocol deviation	3

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Single Arm

Reporting group values	Overall Trial	Total	
Number of subjects	35	35	
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)	22	22	
From 65-84 years	13	13	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55.2		
standard deviation	± 12.8	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	19	19	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Eight patients were excluded from the ITT set due to missing baseline plasma samples. Another two patients were excluded from the ITT set since they showed no measureable lesions at baseline (due to no CT/MRI).

Reporting group values	ITT		
Number of subjects	25		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	22		
From 65-84 years	13		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	61,9		
standard deviation	±		
Gender categorical			
Units: Subjects			
Female	12		
Male	13		

End points

End points reporting groups

Reporting group title	GIST trial

Reporting group description:

Single arm for detection of circulating tumor DNA in the plasma of patients with GIST pre/post surgery and pre/under neoadjuvant or palliative medical treatment with a tyrokiniase inhibitors (TKI) like imatinib or sunitinib or in progressive disease irrespective of therapy.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Eight patients were excluded from the ITT set due to missing baseline plasma samples. Another two patients were excluded from the ITT set since they showed no measureable lesions at baseline (due to no CT/MRI).

Primary: Detection of tumor-specific DNA

End point title	Detection of tumor-specific DNA

End point description:

Percentage of patients with histologically proven GIST, measurable lesions in imaging, and activating CKIT and PDGFRA mutation, where detection of tumor-specific DNA encoding for mutated CKIT or PDGFRA is possible in the plasma at least at one time point.
The detection rate was 64% with exact 95%CI of (42.5%, 82.0%).

End point type	Primary

End point timeframe:

Throughout the study (up to 2 years)

End point values	GIST trial	ITT	ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	25[1]	25	25	
Units: Patients				
Detection possible	16	16	16	
Detection not possible	9	9	9	

Notes:

[1] - This analysis was performed on the ITT set.

Statistical analyses

Statistical analysis title	Detection Rate

Statistical analysis description:

The detection rate for the primary endpoint was 64.0% and the two-sided exact 95% CI was (42.5%, 82.0%).

Comparison groups	ITT v ITT
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Detection rate
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.425
upper limit	0.82

Notes:

[2] - Detection rate in the primary endpoint including exact 95% CI.

Secondary: Amount of tumor

End point title	Amount of tumor

End point description:

The Spearman's correlation coefficient between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and the amount of tumor as assessed by diagnostic imaging was 0.187 (p=0.044).

End point type	Secondary

End point timeframe:

Throughout the study.

End point values	GIST trial	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25[3]			
Units: mimimeter				
arithmetic mean (standard deviation)	77.1 (± 61.1)	77.1 (± 61.1)		

Notes:

[3] - This endpoint was analyzed on the ITT set.

Statistical analyses

No statistical analyses for this end point

Secondary: Response to therapy

End point title	Response to therapy

End point description:

Response was coded in increasing manner starting with complete response. The Spearman correlation coefficient between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and the response to therapy (surgery and/or therapy with a TKI) as assessed by diagnostic imaging was 0.092 (p=0.269). Differences in the amount of tumor-DNA measured for patients with response and progression could not be shown (Mann-Whitney U test: p=0.549).

End point type	Secondary

End point timeframe:

Throughout the study

End point values	GIST trial	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25[4]			
Units: Response				
arithmetic mean (standard deviation)	2.88 (± 1.17)	2.88 (± 1.17)		

Notes:

[4] - This endpoint was calculated on the ITT set.

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse or progression

End point title	Relapse or progression

End point description:

Relapse or progression =1, else 0. The variable was used for calculation of Spearman's correlation coefficient (0.050; p=0.551) between the amount of tumor specific CKIT or PDGFRA DNA in plasma samples and relapse or progression of disease as assessed by diagnostic imaging showed no correlation between the
variables.

End point type	Secondary

End point timeframe:

Throughout the trial

End point values	GIST trial	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25[5]			
Units: Relapse				
arithmetic mean (standard deviation)	0.42 (± 0.50)	0.42 (± 0.50)		

Notes:

[5] - This analysis was performed on the ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor flair

End point title	Tumor flair

End point description:

The percentage of patients with transient increase of tumor specific CKIT or PDGFRA DNA in the plasma („tumor flare") after starting a medical treatment with a TKI was calculated. This percentage is 0%, as no such patients existed. This calculation was done on the subset of 8 patients who did not have TKI at screening, but received it during study conduct and who have L-PCR measurements both pre and (1-5 days) post TKI.

End point type	Secondary

End point timeframe:

Up to 5 days post TKI.

End point values	GIST trial	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8[6]	25		
Units: Patients				
tumor flair	0	0		
no tumor flair	8	8		

Notes:

[6] - This analysis was done on the set of 8 patients who did not have TKI at screening.

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity of L-PCR

End point title	Sensitivity of L-PCR

End point description:

Comparison of the sensitivity of L-PCR for specific CKIT or PGDFRA mutations: sensitivity, specificity, PPR, NPR, and accuracy were calculated using diagnostic imaging as a "gold standard". All available time points were used. Sensitivity was 71.9%, specificity was 28.0%, PPR was 43.8%, NPR was 56.1%, accuracy was 47.3%. As only two patients had mutations in exon 9 and one patient in PDGFRA18, this analysis does not distinguish between the different types of mutations.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	GIST trial	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25[7]			
Units: Lab tests				
Lab negative and no response	46	46		
Lab negative but response	59	59		
Lab positive but no response	18	18		
Lab positive and response	23	23		

Notes:

[7] - 146 valid lab/response pairs were available for analysis resulting from 25 patients

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study duration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Overal trial

Reporting group description: -

Serious adverse events	Overal trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 35 (17.14%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Investigations			
ECOG performance status worsened			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
General physical health deterioration			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 35 (2.86%)		
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	Overal trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 35 (54.29%)		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Eye disorders			
Periorbital oedema			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	11		
Constipation			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	6		
Alopecia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 35 (5.71%)		
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