



## Clinical trial results:

**A double-blind, placebo-controlled, randomized, multicenter phase II trial to assess the efficacy of temsirolimus added to standard primary therapy in elderly patients with newly diagnosed AML**

### Summary

EudraCT number	2011-002365-37
Trial protocol	DE
Global end of trial date	26 April 2017

### Results information

Result version number	v1 (current)
This version publication date	06 October 2021
First version publication date	06 October 2021

### Trial information

#### Trial identification

Sponsor protocol code	3066K1-1165
-----------------------	-------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01611116
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Goethe University
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt am Main, Germany, 60590
Public contact	Prof Christian Brandts, MD, Lead PI, J.W. Goethe University Hospital, 0049 69 6301 7104, Christian.brandts@kgu.de
Scientific contact	Prof Christian Brandts, MD, Lead PI, J.W. Goethe University Hospital, 0049 69 6301 7104, Christian.brandts@kgu.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	21 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2016
Global end of trial reached?	Yes
Global end of trial date	26 April 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Run-in part; To determine the optimal temsirolimus dose and schedule for the main part of the study  
Main part: To compare the median Event Free Survival (EFS) And the EFS probability of all AML patients between the temsirolimus and the control group

\* EFS defined as: Time interval from day 1 of study treatment until treatment failure, relapse from CR or CRi, or death from any cause, whichever occurs first. The time point at which the patient is resistant to therapy or survives induction without a CR, CRi or morphologic leukemia-free state will be recorded.

Protection of trial subjects:

Data safety monitoring board to decide on optimal dose for main part as well as on serious adverse events with unclear relation to the study drug

Background therapy:

Induction I (7+3):

Cytarabine	100mg/m <sup>2</sup> /24hrs i.v.	day 1-7
Daunorubicin	60mg/m <sup>2</sup> i.v.	day 3-5

Induction II (HAM elderly) for patients with PR or treatment failure:

Cytarabine (HD-AraC)	1g/m <sup>2</sup> /3hrs i.v. (2 x daily)	day 1, 3, 5
Mitoxantrone	10mg/m <sup>2</sup> i.v.	day 3-5

Consolidation I (high-dose cytarabine):

Cytarabine (HD-AraC) 1g/m<sup>2</sup>/3hrs i.v. (2 x daily) day 1, 3, 5

Consolidation II (high-dose cytarabine):

Cytarabine (HD-AraC) 1g/m<sup>2</sup>/3hrs i.v. (2 x daily) day 1, 3, 5

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 June 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: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	9
From 65 to 84 years	24
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patient were recruited by treating physician/investigator upon relevant diagnosis at the hospital

### Pre-assignment

Screening details:

additional screening procedures compared to standard diagnostics: informed consent,  
laboratory test: troponin T / troponin I, CK, CK-MB, NT-proBNP

### Period 1

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

Blinding implementation details:

Randomized not controlled, 3 experiemental arms with different doselevels (cohort 1; cohort 2; cohort 3)

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1

Arm description:

temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

<b>Arm title</b>	Cohort 2
------------------	----------

Arm description:

temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

<b>Arm title</b>	Cohort 3
------------------	----------

Arm description:

temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cohort 1: temsirolimus 12.5mg on day -1 of each chemotherapy cycle

Cohort 2: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle

Cohort 3: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2	Cohort 3
Started	5	17	11
DLT (cohort 1; cohort 2; cohort 3)	3	9	7
Completed	3	9	7
Not completed	2	8	4
Consent withdrawn by subject	1	2	-
Physician decision	1	2	-
pt died before 1st dose was administered	-	-	1
Lost to follow-up	-	1	-
Lack of efficacy	-	1	3
Protocol deviation	-	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Run-in part
Reporting group description: -	

Reporting group values	Run-in part	Total	
Number of subjects	33	33	
Age categorical			
All patients enrolled in the run-in part regardless of evaluability			
Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	24	24	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	14	14	
Male	19	19	

### Subject analysis sets

Subject analysis set title	Run-in part
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients enrolled in the run-in part regardless of evaluability	

Reporting group values	Run-in part		
Number of subjects	33		
Age categorical			
All patients enrolled in the run-in part regardless of evaluability			
Units: Subjects			
Adults (18-64 years)	9		
From 65-84 years	24		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	14		
Male	19		

## End points

### End points reporting groups

Reporting group title	Cohort 1
Reporting group description: temsirolimus 12.5mg on day -1 of each chemotherapy cycle	
Reporting group title	Cohort 2
Reporting group description: temsirolimus 12.5mg on day -1 and day 8 of each chemotherapy cycle	
Reporting group title	Cohort 3
Reporting group description: temsirolimus 25mg on day -1 and day 8 of each chemotherapy cycle	
Subject analysis set title	Run-in part
Subject analysis set type	Per protocol
Subject analysis set description: All patients enrolled in the run-in part regardless of evaluability	

### Primary: Optimal temsirolimus dose and schedule

End point title	Optimal temsirolimus dose and schedule <sup>[1]</sup>
End point description: According to the definition in the protocol, dose level / mode of application in cohort I and cohort II could be evaluated as being safe. Eleven patients were enrolled in cohort III. Due to a simultaneous patient screening, seven evaluable patients were eventually included. Two DLTs were observed: Mucositis oral grade 3 and Mucositis/colitis grade 3 with suspected relationship. Multiple incidences of mucositis grade 3 both in cohort II (1 DLT and 1 not evaluable patient with SAE mucositis oral grade 3 with suspected relationship to study drug) and cohort III suggest that temsirolimus may cause increased mucosal toxicity when administered in combination with 7+3 standard therapy. After reassessing the risk benefit ratio, the co-ordinating investigator in line with the data safety monitoring board decided not to enroll any additional patients in cohort III thus giving priority to the patients' safety over formal requirements of the 3+3 design.	
End point type	Primary
End point timeframe: Run-in part	

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: Only descriptive analysis!

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4 <sup>[2]</sup>	9 <sup>[3]</sup>	7 <sup>[4]</sup>	
Units: ng	12500	12500	25000	

Notes:

[2] - Dose: 12,5 mg

[3] - Dose: 12,5 mg

[4] - Dose: 25 mg

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From enrolment until 30 days following last dose of study treatment or 42 days after last dose of study treatment (for neutropenia and thrombocytopenia)

Adverse event reporting additional description:

Not applicable

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4.03
--------------------	------

### Reporting groups

Reporting group title	Run-in part
-----------------------	-------------

Reporting group description: -

Serious adverse events	Run-in part		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	3		
Cardiac disorders			
Heart failure	Additional description: Not applicable		
subjects affected / exposed	4 / 29 (13.79%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Intracranial hemorrhage	Additional description: Epidural hematoma		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction	Additional description: dyspnea, facial rash, fever + shivering		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal mucositis	Additional description: Not applicable		



subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal hemorrhage	Additional description: Peranal bleeding		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Not applicable		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspiration	Additional description: Not applicable		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Lung infection	Additional description: Not applicable		
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: Sepsis in neutropenia		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypernatremia	Additional description: Not applicable		
subjects affected / exposed	1 / 29 (3.45%)		
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 %

<b>Non-serious adverse events</b>	Run-in part		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)		
Vascular disorders			
Hematoma			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	7		
Phlebitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Edema face			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Edema limbs			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	17		
Fatigue			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	5		
Fever			
subjects affected / exposed	17 / 29 (58.62%)		
occurrences (all)	26		
Infusion related reaction			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Infusion site extravasation			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Injection site reaction			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Localized edema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Multi-organ failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 29 (13.79%)</p> <p>6</p> <p>5 / 29 (17.24%)</p> <p>5</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>3 / 29 (10.34%)</p> <p>3</p>		
<p>Immune system disorders</p> <p>Allergic reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 29 (27.59%)</p> <p>18</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pleural effusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pneumonitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary edema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sore throat</p>	<p>7 / 29 (24.14%)</p> <p>9</p> <p>10 / 29 (34.48%)</p> <p>12</p> <p>16 / 29 (55.17%)</p> <p>18</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>4 / 29 (13.79%)</p> <p>4</p> <p>2 / 29 (6.90%)</p> <p>2</p>		

subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 6		
Psychiatric disorders			
Agitation			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Confusion			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Delirium			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Investigations			
Investigations - Other, specify (CRP)	Additional description: CRP increase		
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	5		
Investigations - Other, specify (TPZ)	Additional description: TPZ decrease		
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	8		
Weight loss			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
White blood cell decreased			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Syncope subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3  12 / 29 (41.38%) 12  1 / 29 (3.45%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)  Febrile neutropenia subjects affected / exposed occurrences (all)  Thrombotic thrombocytopenic purpura subjects affected / exposed occurrences (all)	8 / 29 (27.59%) 8  12 / 29 (41.38%) 20  1 / 29 (3.45%) 2		
Eye disorders Vitreous hemorrhage subjects affected / exposed occurrences (all)  Dry eye subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2  2 / 29 (6.90%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Bloating	4 / 29 (13.79%) 5		

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Colitis			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	11		
Diarrhea			
subjects affected / exposed	19 / 29 (65.52%)		
occurrences (all)	22		
Dry mouth			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Mucositis oral			
subjects affected / exposed	21 / 29 (72.41%)		
occurrences (all)	23		
Nausea			
subjects affected / exposed	8 / 29 (27.59%)		
occurrences (all)	10		
Oral hemorrhage			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Oral pain			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Stomach pain			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	11 / 29 (37.93%)		
occurrences (all)	19		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		

Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Purpura			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	5		
Skin ulceration			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Infections and infestations			
Infections and infestations - Other, specify (CRP)	Additional description: CRP increased		
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Bladder infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Catheter related infection			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	6		
Lip infection			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	7		
Lung infection			

subjects affected / exposed	7 / 29 (24.14%)		
occurrences (all)	7		
Mucosal infection			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	7		
Papulopustular rash			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Skin infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Tooth infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Hyperglycemia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Hyperkalemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Hypokalemia			
subjects affected / exposed	18 / 29 (62.07%)		
occurrences (all)	25		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2013	<p>Study design</p> <ul style="list-style-type: none"><li>• Increase of number of patients in run-in part</li><li>• Implementation of dose-escalating study design with three consecutive cohorts</li><li>• Definition of Dose Limiting Toxicity</li><li>• Changes in definition of non-hematological DLT</li><li>• Changes in definition of evaluability for DLT assessment</li></ul> <p>Definition of Dose Limiting Toxicity</p> <ul style="list-style-type: none"><li>• Changes in definition of non-hematological DLT</li><li>• Changes in definition of evaluability for DLT assessment</li></ul> <p>Treatment</p> <ul style="list-style-type: none"><li>• Modification of scheme of run-in part</li><li>• Modification of treatment schedule for induction chemotherapy</li><li>• Modification of treatment schedule for induction II chemotherapy</li><li>• Modification of treatment schedule for consolidation chemotherapy I and II</li></ul> <p>Dose modification and delays of temsirolimus / placebo</p> <ul style="list-style-type: none"><li>• Dose modifications for non-hematological toxicity</li><li>• Instructions for safety evaluations and dose modification in patients with cardiac disorders</li><li>• Instructions for dose modification in patients with mucositis</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 July 2012	Interruption of accrual after two SUSAR (Heart failure) in order to re-evaluate patient safety	05 September 2013

Notes:

### Limitations and caveats

None reported