Clinical trial results:
A therapy and pharmacokinetics study of temsirolimus in patients with refractory and recidivated primary CNS lymphoma.

Summary

EudraCT number	2009-011277-33
Trial protocol	DE
Global end of trial date	15 December 2014

Results information

Result version number	v1 (current)
This version publication date	17 December 2022
First version publication date	17 December 2022

Trial information

Trial identification

Sponsor protocol code	PZNSL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00942747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Hindenburgdamm 30, Berlin, Germany, 12200
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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	16 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2014
Global end of trial reached?	Yes
Global end of trial date	15 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess efficacy of Temsirolimus in patients with refractory and recidivated primary CNS lymphoma

Protection of trial subjects:

Study conduct followed International Conference on Harmonization Guidelines for Good Clinical Practice, including written informed consent and data monitoring. Baseline assessments included physical and neurologic examination, cranial magnetic resonance imaging (spinal on clinical suspicion only), and ophthalmologic and CSF examination. Safety assessments included physical examinations, adverse event monitoring, and laboratory parameter changes before each infusion. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Response assessment was performed after 4 weeks and every 8 weeks thereafter. Additionally, response assessment was recommended at each time point when progression was suspected. After discontinuing therapy, patients completed an end-of-treatment visit 30 days after their last temsirolimus dose. In patients with PR or CR, remission status was evaluated every 3 months.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Germany: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	0
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between September 2009 and November 2014, 37 patients were enrolled at four German centers .

Pre-assignment

Screening details:

The vast majority of patients had intermediate- or high-risk disease according to the Memorial Sloan Kettering Cancer Center score. Patients had received a median of one prior therapy comprising HDMTX in all patients and high-dose cytarabine in 11. Two patients were pretreated with WBRT, three patients with HD-ASCT, and four patients with both.

Period 1

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

Arms

Arm title	Temsirolimus Arm

Arm description:

Among the first three patients who were given 25 mg temsirolimus, two had grade 3 toxicity (one patient had diarrhea, thrombocytopenia, and leukopenia with pneumonia; one patient had pneumonia). Thus, an additional three patients were treated with the same dose. In these patients, no grade 3 to 4 toxicity was observed, and there was a PR in one patient. Thus, per protocol, the study was continued with 75 mg temsirolimus once per week.

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

Dosage and administration details:

In the first stage, patients were treated with temsirolimus 25 mg intravenously once per week with clemastine premedication. In case of Common Toxicity Criteria grades 3 to 4 toxicity, three additional patients were to be treated with the same dose. If no Common Toxicity Criteria grades 3 to 4 toxicity were observed, all following patients were treated with 75 mg once per week.

Number of subjects in period 1	Temsirolimus Arm
Started	37
Completed	37

Baseline characteristics

Reporting groups	
Reporting group title	Temsirolimus Arm

Reporting group description:

Among the first three patients who were given 25 mg temsirolimus, two had grade 3 toxicity (one patient had diarrhea, thrombocytopenia, and leukopenia with pneumonia; one patient had pneumonia). Thus, an additional three patients were treated with the same dose. In these patients, no grade 3 to 4 toxicity was observed, and there was a PR in one patient. Thus, per protocol, the study was continued with 75 mg temsirolimus once per week.

Reporting group values	Temsirolimus Arm	Total	
Number of subjects	37	37	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	70		
full range (min-max)	22 to 83	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	18	18	
MSKCC score			
MSKCC, Memorial Sloan Kettering Cancer Center			
Units: Subjects			
score 1	2	2	
score 2	29	29	
score 3	6	6	
No. of previous treatment regimens			
Units: Subjects			
1-2	29	29	
3-5	8	8	
Lymphoma localization			
Units: Subjects			
Parenchymal only	30	30	
Meningeal only	4	4	
Combined	3	3	
ECOG performance status			
ECOG, Eastern Cooperative Oncology Group			
Units: Score			
median	2		
full range (min-max)	0 to 2	-	
Median time since last pretreatment			
Units: months			
median	3.9		
standard deviation	± 0	-	

End points

End points reporting groups

Reporting group title	Temsirolimus Arm

Reporting group description:

Among the first three patients who were given 25 mg temsirolimus, two had grade 3 toxicity (one patient had diarrhea, thrombocytopenia, and leukopenia with pneumonia; one patient had pneumonia). Thus, an additional three patients were treated with the same dose. In these patients, no grade 3 to 4 toxicity was observed, and there was a PR in one patient. Thus, per protocol, the study was continued with 75 mg temsirolimus once per week.

Primary: Patients responding rate to treatment

End point title	Patients responding rate to treatment[1]

End point description:

Response assessment was performed after 4 weeks and every 8 weeks thereafter. Additionally, response assessment was recommended at each time point when
progression was suspected. After discontinuing therapy, patients completed an end-of-treatment visit 30 days after their last temsirolimus dose. In patients with PR or CR, remission status was evaluated every 3 months. Survival data were collected every 3 months for up to 2 years from start of study treatment or until study closure.
CR, complete response;
uCR, unconfirmed CR;
PD, progressive disease;
PR, partial remission;
Overall response rate (ORR) of 54% (95% CI, 37% to 71%)
SD; stable disease

End point type	Primary

End point timeframe:

48 months

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: This was a phase II a two stage design using single-agent temsirolimus in patients. The second stage of the trial was planned to enroll 25 additional patients. After termination of this study stage, the therapy was considered ineffective if fewer than four patients responded. Since there was only one arm and one stage, comparison between groups was not possible.

End point values	Temsirolimus Arm			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects				
CR	5			
uCR	3			
PD	5			
SD	7			
no response evaluation	5			
PR	12			

Statistical analyses

No statistical analyses for this end point

Secondary: CSF Penetration of Temsirolimus

End point title	CSF Penetration of Temsirolimus

End point description:

Fourteen blood/CSF pairs were collected in nine patients:
10 pairs in five patients in the 25-mg cohort and four pairs in four patients in the 75-mg cohort.

End point type	Secondary

End point timeframe:

48months

End point values	Temsirolimus Arm			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: ng/ml				
number (not applicable)				
25mg cohort	292			
75mg cohort	484			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free survival

End point title	Progression Free survival

End point description:

End point type	Secondary

End point timeframe:

48 months

End point values	Temsirolimus Arm			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
arithmetic mean (full range (min-max))				
PFS	2.1 (1.1 to 30)			

Attachments (see zip file)	PFS Fig 2(A)/PFSandOSGraph.pdf

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:

60months

End point values	Temsirolimus Arm			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: months				
arithmetic mean (full range (min-max))	3.7 (1.5 to 5.8)			

Attachments (see zip file)	OS Fig.2 (B)/PFSandOSGraph.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity All Grades

End point title	Toxicity All Grades

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Temsirolimus Arm			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Subjects				
Thrombocytopenia	23			
Anemia	22			
Leukopenia	22			

Hyperglycemia	31			
Transaminases elevation	16			
Fatigue	16			
Skin toxicity	13			
Infection	12			
Creatinine elevation	11			
Stomatitis	10			
Nausea	5			
Vomiting	2			
Diarrhea	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 years	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	3.0
Reporting groups	
Reporting group title	Temsirolimus Arm
Reporting group description: Temsirolimus Arm	

Serious adverse events	Temsirolimus Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 37 (56.76%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events			
Investigations			
Hyperglycemia			
subjects affected / exposed	11 / 37 (29.73%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Transaminases elevation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Creatinine elevation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
cerebral bleeding			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 37 (21.62%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Anemia			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
tumor progression			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin toxicity			

subjects affected / exposed	3 / 37 (8.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection	Additional description: pneumonia in two patients and GI infection with sepsis, sepsis without focus,		
subjects affected / exposed	7 / 37 (18.92%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 4		
Stomatitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)		
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	Temsirolimus Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 37 (54.05%)		
Investigations			
Hyperglycemia			
subjects affected / exposed	20 / 37 (54.05%)		
occurrences (all)	20		
Transaminases elevation			
subjects affected / exposed	15 / 37 (40.54%)		
occurrences (all)	15		
Creatinine elevation			
subjects affected / exposed	10 / 37 (27.03%)		
occurrences (all)	10		
Blood and lymphatic system disorders			

Thrombocytopenia subjects affected / exposed occurrences (all) Anemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 15 / 37 (40.54%) 15 18 / 37 (48.65%) 18 20 / 37 (54.05%) 20		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 14 / 37 (37.84%) 14 5 / 37 (13.51%) 5		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all)	 1 / 37 (2.70%) 1		
Skin and subcutaneous tissue disorders Skin toxicity subjects affected / exposed occurrences (all)	 10 / 37 (27.03%) 10		
Infections and infestations Infection subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all)	 5 / 37 (13.51%) 5 10 / 37 (27.03%) 10		
Metabolism and nutrition disorders Vomiting subjects affected / exposed occurrences (all)	 2 / 37 (5.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2011	new protocol version 2.1 : adjustment of schedule and dosage, the process organization to the termination criteria

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.

limitation was the preferential inclusion of elderly patients whose initial treatment is frequently not according to the current standards used in younger patients. Generalization of our results should thus be viewed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26976424