Clinical trial results:
JeRiCHO (JAK-inhibition in recurrent classical Hodgkin Lymphoma): A phase II, open-label, prospective, non-randomized, multicenter clinical trial with the JAK-inhibitor ruxolitinib in patients with relapsed or refractory Hodgkin Lymphoma (HL).

Summary

EudraCT number	2013-003369-33
Trial protocol	DE
Global end of trial date	30 June 2019

Results information

Result version number	v1 (current)
This version publication date	25 June 2020
First version publication date	25 June 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1698

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02164500
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus Magnus-Platz, Köln, Germany, 50923
Public contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center of the German Hodgkin Study Group (GHSG), German Hodgkin Study Group (GHSG), 0049 22147888200, ghsg@uk-koeln.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	20 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the objective response rate (complete response + partial response) of ruxolitinib in patients with relapsed or refractory classical Hodgkin lymphoma

Protection of trial subjects:

Written informed consent prior to study entry; 2-stage design with comprehensive interim risk-benefit assessment and formal futility criterion after stage 1; standardized dose reduction in case of adverse events

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	8
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment for stage 1 was open between 28 Oct 2015 and 12 May 2017. It was planned to enroll 12 response-eligible patients in stage 1. We enrolled 14 patients, of whom 2 were not eligible for primary endpoint analysis. The trial was terminated after stage-1 analysis. No patients were enrolled in stage 2.

Pre-assignment

Screening details:

Main inclusion criteria: Relapsed or refractory histologically confirmed cHL that is progressing or active and requires treatment after ≥ 1 appropriate therapy including ASCT if eligible; Age ≥ 18 years; ECOG ≤ 2; adequate organ function. Main exclusion criteria: Relevant concurrent disease; pregnancy or lactation.

Period 1

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

Arms

Arm title	Experimental

Arm description:

Continuous 28-day cycles of ruxolitinib until disease progression, withdrawal of consent or intolerable toxicity

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakavi (R)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ruxolitinib was applied twice a day (approximately 12 hours apart: morning and night) with a starting dose of 25 mg per application. Ruxolitinib dose was to be decreased (5 mg bid steps) per standardized dosing paradigm in case of adverse events. Ruxolitinib tablets were administered orally without regards to food in an outpatient setting. The dosage strength was 5 mg/tablet ruxolitinib (free base equivalent). Ruxolitinib was dispensed on day 1 of each cycle by the study center personnel. Patients were provided with an adequate supply of ruxolitinib for self-administration at home.

Number of subjects in period 1	Experimental
Started	14
Start of ruxolitinib treatment	14
Completed	12
Not completed	2
cHL diagnosis disconfirmed	2

Baseline characteristics

Reporting groups

Reporting group title	Stage 1

Reporting group description: -

Reporting group values	Stage 1	Total	
Number of subjects	14	14	
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)	8	8	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	2	
Male	12	12	
ECOG performance status Units: Subjects			
ECOG 0	2	2	
ECOG 1	11	11	
ECOG 2	1	1	
Prior ASCT Units: Subjects			
No	6	6	
Yes	8	8	
Prior allogeneic SCT Units: Subjects			
No	12	12	
Yes	2	2	
Prior brentuximab vedotin Units: Subjects			
No	1	1	
Yes	13	13	
Number of prior HL therapies Units: Therapy lines			
median	3		
full range (min-max)	2 to 11	-	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Continuous 28-day cycles of ruxolitinib until disease progression, withdrawal of consent or intolerable toxicity

Primary: Objective response rate (ORR) after 2 cycles by central review

End point title	Objective response rate (ORR) after 2 cycles by central

End point description:

Objective response was defined as complete or partial remission in the centrally reviewed PET/CT-based restaging after 2 cycles of ruxolitinib. The primary endpoint was to be analyzed per-protocol, excluding patients who received less than 2 cycles ruxolitinib unless due to progressive disease.

End point type	Primary

End point timeframe:

PET/CT-based restaging was to be performed at day 26-30 of the second cycle (last day of cycle +/- 2 days).

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: According to the trial protocol, the null hyothesis H0: ORR ≤ 5% was to be tested in a 2-stage design. The trial was terminated after stage 1 although the required responders were observed (1 responder required, 2 responders observed). Thus, only descriptive analyses of the primary endpoint in the stage-1 per-protocol population were done.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	12[2]			
Units: Subjects				
Objective response (complete or partial remission)	2			
No objective response (no change or progression)	10			

Notes:

[2] - Per-protocol analysis excluding 2 patients due to disconfirmation of cHL diagnosis

Statistical analyses

No statistical analyses for this end point

Secondary: Best response

End point title	Best response

End point description:

End point type	Secondary

End point timeframe:

From the restaging after two cycles onwards, restagings with a modality at the investigator’s discretion (local standard of care) were to be performed every three months until end of study treatment.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Complete remission	0			
Partial remission	3			
No change	3			
Progressive disease	7			
Not done	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was analyzed according to Kaplan-Meier.

End point type	Secondary

End point timeframe:

Progression-free survival was calculated for each patient as time between the date of completion of staging and the date of first progression, relapse or death or, in cases of continuing response, the date of the last documented follow-up.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: months				
median (confidence interval 95%)	3.6 (1.9 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed from start of study treatment up until the 28-day follow-up visit or the start of a new HL therapy, whichever occurred first.

Adverse event reporting additional description:

Expected AEs of CTCAE grades 3/4 were assessed on the therapy administration CRFs by predefined CTCAE categories. Unexpected and serious AEs were assessed on specific forms and coded according to MedDRA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.2

Reporting groups

Reporting group title	Experimental

Reporting group description:

Patients received continuous 28-day cycles of oral ruxolitinib, with 25 mg bid (approximately 12 hours apart: morning and night) as starting dose. Ruxolitinib dose was to be decreased (5 mg bid steps) per standardized dosing paradigm in case of adverse events. Treatment was continued until disease progression, withdrawal of consent or intolerable toxicity.

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paresis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Febrile infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General physical health deterioration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary hesitation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		

Cardiac disorders Cardiac disorder alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Blood and lymphatic system disorders Leukopenia alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Respiratory, thoracic and mediastinal disorders Respiratory tract disorder alternative dictionary used: CTCAE 4.0 subjects affected / exposed occurrences (all)	 2 / 14 (14.29%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2016	Updated ICF, implementation of regulatory authority and ethics committee authorizations
19 September 2016	Amendment of dose reduction section due to changes in SmPC of ruxolitinib
22 February 2018	Amendment of the frequency of side effects due to changes in SmPC of ruxolitinib

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 May 2017	Recruitment of stage 1 completed	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was terminated after stage 1 due to slow recruitment and low response rates/PFS in line with protocol guidance although required responders were observed (1 required, 2 observed). Only descriptive analysis in stage-1 population were done.

Notes: