Clinical trial results:
Phase II trial of the Btk-inhibitor Ibrutinib in patients with relapsed nodular lymphocyte-predominant Hodgkin Lymphoma (NLPHL)

Summary

EudraCT number	2015-003128-30
Trial protocol	DE
Global end of trial date	20 May 2020

Results information

Result version number	v1 (current)
This version publication date	24 March 2021
First version publication date	24 March 2021

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1776

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02626884
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, German Hodgkin Study Group, 0049 22147888200, ghsg@uk-koeln.de
Scientific contact	Trial Coordination Center, German Hodgkin Study Group, 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	11 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2020
Global end of trial reached?	Yes
Global end of trial date	20 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To establish a novel, non-toxic treatment option for patients with relapsed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL).

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;

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2016
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	15
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to enroll a maximum of 36 eligible patients (stage 1: 15 eligible patients, in case of continuation to stage 2: another 21 eligible patients). We enrolled 16 patients between 26 Aug 2016 and 05 Dec 2018, of whom 1 was not eligible for primary endpoint analysis. Trial was terminated after stage 1, no patients were enrolled in stage 2

Pre-assignment

Screening details:

Main entry criteria: Histollogically proven relapsed nodular lymphocyte-predominant HL; 18-99 years; No prior Btk inhibitor treatment. Main exclusion criteria: Classical HL or composite lymphoma; Concurrent disease which precludes protocol treatment; Pregnancy, 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:

Patients with relapsed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) receive ibrutinib at a dose of 560 mg daily for a maximum of 20 21-day cycles.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	Imbruvica (R)
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients receive continuous 21-day cycles of ibrutinib with a daily dose of 560 mg (i.e. 4 capsules p.d.). The whole dose should be taken at one certain timepoint. Treatment with ibrutinib should be held temporarily, i.e. in case grade IV neutropenia or thrombocytopenia or grade III neutropenia with fever and infection or grade III/IV non-hematological adverse events occur. After recovery from any of such adverse events, ibrutinib should be restarted at full dose after the first occurrence of the event, at 420 mg after the second occurrence of the same event and at 280 mg after the third occurrence of the same event. After the fourth occurrence of the same event, ibrutinib should be discontinued permanently. Ibrutinib treatment must be terminated after a maximum number of 20 cycles.

Number of subjects in period 1	Experimental
Started	16
Start of treatment	16
Completed	9
Not completed	7
Toxicity	1
Progressive disease	3
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Stage 1 (overall period)

Reporting group description: -

Reporting group values	Stage 1 (overall period)	Total	
Number of subjects	16	16	
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)	15	15	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	51.5		
full range (min-max)	29 to 77	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	12	12	
Stage (I-V) of the first diagnosis Units: Subjects			
Stage I	4	4	
Stage II	2	2	
Stage III	6	6	
Stage IV	4	4	
Prior salvage chemotherapy Units: Subjects			
Yes	2	2	
No	14	14	
Prior high-dose chemotherapy Units: Subjects			
Yes	6	6	
No	10	10	
Prior stem cell transplantation Units: Subjects			
Yes	3	3	
No	13	13	
Prior polychemotherapy Units: Subjects			

Yes	5	5	
No	11	11	
Prior ABVD-like therapy Units: Subjects			
Yes	6	6	
No	10	10	
Prior BEACOPP-like therapy Units: Subjects			
Yes	4	4	
No	12	12	
Prior other regimen Units: Subjects			
Yes	2	2	
No	14	14	
Prior targeted therapy Units: Subjects			
Yes	0	0	
No	16	16	
Prior anti-CD20 therapy Units: Subjects			
Yes	6	6	
No	10	10	
Prior radiotherapy Units: Subjects			
Yes	7	7	
No	9	9	
Performance status (ECOG) Units: Subjects			
0: normal activity, no symptoms	14	14	
1: able to work, symptoms apparent	2	2	
Body weight Units: kg			
median	85		
full range (min-max)	69 to 116	-	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) consists of all patients who receive at least one daily dose (partial or full dose) of ibrutinib.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set (SAS) consists of all patients of the FAS who had at least one valid post-baseline safety assessment.

Subject analysis set title	Disease stabilization/response analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The disease stabilization/response anlysis set (DSR) consists of all patients in the FAS who do not have

any major protocol deviation (e.g. violation of inclusion/exclusion criteria) and complete at least six 21-day cycles of single agent ibrutinib unless discontinuation for early disease progression at any time or due to adverse events after at least four cycles of ibrutinib treatment. All patients in the DSR set must have been evaluated for diesease stabilization/response at least once, i.e. at the first planned interim staging according to protocol or earlier in case of disease progression.

Reporting group values	Full analysis set	Safety analysis set	Disease stabilization/response analysis set
Number of subjects	16	16	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	15	14
From 65-84 years	1	1	1
85 years and over	0	0	0
Age continuous Units: years			
median	51.5	51.5	52
full range (min-max)	29 to 77	29 to 77	29 to 77
Gender categorical Units: Subjects			
Female	4	4	4
Male	12	12	11
Stage (I-V) of the first diagnosis Units: Subjects			
Stage I	4	4	4
Stage II	2	2	2
Stage III	6	6	5
Stage IV	4	4	4
Prior salvage chemotherapy Units: Subjects			
Yes	2	2	2
No	14	14	13
Prior high-dose chemotherapy Units: Subjects			
Yes	6	6	5
No	10	10	10
Prior stem cell transplantation Units: Subjects			
Yes	3	3	2
No	13	13	13
Prior polychemotherapy Units: Subjects			
Yes	5	5	4
No	11	11	11
Prior ABVD-like therapy			

Units: Subjects			
Yes	6	6	6
No	10	10	9
Prior BEACOPP-like therapy Units: Subjects			
Yes	4	4	4
No	12	12	11
Prior other regimen Units: Subjects			
Yes	2	2	2
No	14	14	13
Prior targeted therapy Units: Subjects			
Yes	0	0	0
No	16	16	15
Prior anti-CD20 therapy Units: Subjects			
Yes	6	6	6
No	10	10	9
Prior radiotherapy Units: Subjects			
Yes	7	7	7
No	9	9	8
Performance status (ECOG) Units: Subjects			
0: normal activity, no symptoms	14	14	13
1: able to work, symptoms apparent	2	2	2
Body weight Units: kg			
median	85	85	85
full range (min-max)	69 to 116	69 to 116	69 to 116

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Patients with relapsed nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) receive ibrutinib at a dose of 560 mg daily for a maximum of 20 21-day cycles.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) consists of all patients who receive at least one daily dose (partial or full dose) of ibrutinib.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set (SAS) consists of all patients of the FAS who had at least one valid post-baseline safety assessment.

Subject analysis set title	Disease stabilization/response analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The disease stabilization/response anlysis set (DSR) consists of all patients in the FAS who do not have any major protocol deviation (e.g. violation of inclusion/exclusion criteria) and complete at least six 21-day cycles of single agent ibrutinib unless discontinuation for early disease progression at any time or due to adverse events after at least four cycles of ibrutinib treatment. All patients in the DSR set must have been evaluated for diesease stabilization/response at least once, i.e. at the first planned interim staging according to protocol or earlier in case of disease progression.

Primary: Disease stabilization/response rate after six cycles

End point title	Disease stabilization/response rate after six cycles[1]

End point description:

Disease stabilization/response rate after six 21-day cycles of ibrutinib. A complete remission (CR), partial remission (PR), and no change (NC) as treatment response according to the central review evaluation panel (CREP) were counted as disease stabilization, i.e. success for the primary endpoint.
The following cases were counted as failures for the primary efficacy endpoint:
- Progressive disease (PD) confirmed by CREP
- CR/PR/NC could not be confirmed by the CREP.

According to the protocol, the null hypothesis H0: DSR ≤ 70% was to be testes in a 2-stage design. The trial was terminated after stage 1. Thus, only descriptive analyses of the primary endpoint in the stage-1 DSR set were done.

End point type	Primary

End point timeframe:

The first interim staging was conducted after six treatment cycles (within the first week of cycle 7) or earlier in case of suspected progression. Patients who achieve at least disease stabilization according to the CREP continue study treatment.

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: Confirmatory tests could not be carried out, due to the trial termination after stage-1. The analyses were of descriptive nature. 14/15 (93.3%) eligible patients reached a disease stabilization after 6 cycles of ibrutinib (one-sided 95% CI 72.1-100). 1/15 (6.7%) showed a progressive disease.

End point values	Disease stabilization/response analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: patients				
Disease stabilization (CR/CRr, PR, SD)	14			
No disease stabilization	1			

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 to 30 days after end of treatment have to be reported. AEs that occur later than 30 days after the end of treatment have to be reported in case the causality is judged at least as "possible".

Adverse event reporting additional description:

All serious adverse events (SAE) have to be reported as long as the patient is in the trial, independent of the investigator´s opinion whether there is a causal relationship with the study therapy or not.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.2

Reporting groups

Reporting group title	Experimental

Reporting group description:

Patients received continous 21-day cycles of oral ibrutinib, with 560mg/d dose. Dose was to be decreased per recurring occurrence of the same adverse event. Treatment was continued until withdrawal of consent, intolerable toxicity oder after the fourth occurrence of one adverse event.

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Transient ischaemic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis	Additional description: elevated transaminases and increase of cholestasis parameters		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoporosis			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia repair			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nodule	Additional description: Small nodule in arm and leg		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cardiac disorders			
Blood pressure increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Breast pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Arterial fibrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Polyneuropathy	Additional description: Restless leg syndrome and pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	7		
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Hematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Nail injury	Additional description: thin and brittle nails		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Epistaxis			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	15		
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	19		
Respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	22		
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
Eye disorders			
Glaucoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Visual impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	6		
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	6		
Reflux			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain	Additional description: Pain and cramps in legs		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2016	Amendment to the protocol (v2.0), informed consent form (v2.0) (update risk section), description of first and second interim staging in a more detailed way, editorial changes
11 July 2016	Amendment to the SmPC (May 2016), informed consent form (v3.0) (update risk section), spelling correction
21 October 2016	Amendment to the SmPC (August 2016), informed consent form (v4.0) (update risk section), additional informed consent form for patients who have already given consent
08 May 2017	Amendment to the SmPC (February 2017), informed consent form (v5.0) (update risk section), additional informed consent form for patients who have already given consent (second v1.0)
04 October 2017	Amendment to the SmPC (August 2017), informed consent form (v6.0) (update risk section), additional informed consent form for patients who have already given consent (third v1.0)
23 May 2018	Amendment to the SmPC (February 2018), informed consent form (v7.0) (update risk section and update data protection section (DSGVO)), additional informed consent form for patients who have already given consent (fourth v1.0), Declaration of participation and patient inclusion (IVML)
11 March 2019	Amendment to the SmPC (August 2018), informed consent form (V8.9) (update risk section), additional informed consent form for patients who have already given consent (fifth v1.0)
10 September 2019	Amendment for the end of recruitment, Amendment to information in the CT application form, to the protocol (v3.0), changes in conduct or management of the trial (End of recruitment after stage 1)
28 November 2019	Amendment to the SmPC (September 2019), informed consent form (not updated) (update risk section), additional informed consent form for patients who have already given consent (sixth v1.0)

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.

The trial was terminated prematurely after stage 1. Therefore, no confirmatory test could be performed and the analyses were only of descriptive nature.

Notes: