Clinical trial results:
Ibrutinib and Standard Immuno-Chemotherapy (R-CHOEP-14) In Younger, High-Risk Patients with Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2017-003256-22
Trial protocol	DE
Global end of trial date	23 December 2023

Results information

Result version number	v1 (current)
This version publication date	05 January 2025
First version publication date	05 January 2025

Trial information

Trial identification

Sponsor protocol code	UKM17_0017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03399513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Münster, Germany, 48149
Public contact	Coordinating investigator, Universitätsklinikum Münster, Norbert.Schmitz@ukmuenster.de
Scientific contact	Coordinating investigator, Universitätsklinikum Münster, Norbert.Schmitz@ukmuenster.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	15 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2023
Global end of trial reached?	Yes
Global end of trial date	23 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the 2-year progression-free survival (PFS) achieved with ibrutinib in combination with immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (R-CHOEP) in newly diagnosed, younger patients (age 18-60 years) with diffuse large B-cell lymphoma (DLBCL) and age-adjusted International Prognostic Index (aaIPI) 2 or 3.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

The test product ibrutinib was administered in combination with standard immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (R-CHOEP).

Evidence for comparator:

A secondary objective for efficacy was to compare patients from this single-arm study with patients from the previous R-MegaCHOEP phase III trial (Schmitz et al., Lancet Oncol 2012).

Actual start date of recruitment	01 June 2018
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

40 patients were registered for this study from June 2018 until December 2023 at 9 study sites in Germany.

Pre-assignment

Screening details:

Each patient's eligibility was verified during a screening visit. Informed consent was obtained prior to any clinical procedures that are performed solely for study-related purposes.

Period 1

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

Arms

Arm title	Ibrutinib + R-CHOEP

Arm description:

Patients treated with ibrutinib in combination with immunochemotherapy 8 x R-CHOEP.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was administered at a dose of 560 mg (4 x 140 mg capsules orally once daily) from day 1 to day 112 or max. until day 14 of cycle 8 of R-CHOEP. R-CHOEP was administered every 2 weeks for 8 cycles.

Number of subjects in period 1	Ibrutinib + R-CHOEP
Started	40
Completed	34
Not completed	6
Death due to lymphoma	4
Death due to other reason	1
Death due to salvage therapy following r/r disease	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	40	40	
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)	40	40	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	20	20	
Male	20	20	
LDH > UNV Units: Subjects			
Yes	38	38	
No	2	2	
ECOG > 1 Units: Subjects			
Yes	8	8	
No	32	32	
Stage III/ IV Units: Subjects			
Yes	39	39	
No	1	1	
aaIPI Units: Subjects			
01	1	1	
02	33	33	
03	6	6	
Extranodal involvement Units: Subjects			
Yes	35	35	
No	5	5	
Extranodal involvement > 1 Units: Subjects			
Yes	23	23	

No	17	17	
Bulky disease Units: Subjects			
Yes	24	24	
No	16	16	
B symptoms Units: Subjects			
Yes	18	18	
No	22	22	
BM involvement Units: Subjects			
Yes	6	6	
No	34	34	
Diagnosis of lymphoma according to primary pathology Units: Subjects			
DLBCL, NOS	29	29	
High-grade B-cell lymphoma (HGBCL), NOS	7	7	
HGBCL with MYC and BCL2 and/or BCL6 rearrangements	4	4	
Diagnosis of lymphoma according to reference pathology Units: Subjects			
DLBCL, NOS	32	32	
HGBCL, NOS	1	1	
HGBCL with MYC and BCL2 and/or BCL6 rearrangements	1	1	
T-cell/histiocyte-rich large B-cell lymphoma	1	1	
PMBCL	1	1	
Burkitt lymphoma	2	2	
Follicular lymphoma grade 1/2	1	1	
Not available	1	1	

End points

End points reporting groups

Reporting group title	Ibrutinib + R-CHOEP
Reporting group description:	
Patients treated with ibrutinib in combination with immunochemotherapy 8 x R-CHOEP.	

Primary: PFS (Progression free survival)

End point title	PFS (Progression free survival)[1]
End point description:	

End point type	Primary
End point timeframe:	
After 24 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: The primary analysis was to determine the 2-year PFS-rate with 95% confidence interval using a Kaplan-Meier curve.

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	83 (71 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	

End point type	Secondary
End point timeframe:	
After 24 months	

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	83 (71 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (EFS)

End point title	Event-free survival (EFS)

End point description:

End point type	Secondary

End point timeframe:

After 24 months

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	83 (71 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission (CR) rate

End point title	Complete remission (CR) rate

End point description:

End point type	Secondary

End point timeframe:

Response of therapy

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	70 (53 to 83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial remission (PR) rate

End point title	Partial remission (PR) rate

End point description:

End point type	Secondary

End point timeframe:

Response of therapy

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	22 (11 to 38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) (CR+PR)

End point title	Overall response rate (ORR) (CR+PR)

End point description:

End point type	Secondary

End point timeframe:

Response of therapy

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	92 (80 to 98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression rate

End point title	Progression rate

End point description:

End point type	Secondary

End point timeframe:

Response of therapy

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (confidence interval 95%)	2 (1 to 13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate

End point title	Relapse rate

End point description:

End point type	Secondary

End point timeframe:

Relapse-rate for patients with response CR

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percent				
number (confidence interval 95%)	14 (4 to 33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Administration of R-CHOEP and Ibrutinib

End point title	Administration of R-CHOEP and Ibrutinib

End point description:

End point type	Secondary

End point timeframe:

Course of therapy

End point values	Ibrutinib + R-CHOEP			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
Complete therapy	43			
Early termination of Ibrutinib	25			
Early termination of R-CHOEP and Ibrutinib	32			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The documentation of adverse events (AEs) started with first study treatment after patient inclusion and ended 100 days after the last application of ibrutinib or any component of R-CHOEP (whichever was applied last).

Adverse event reporting additional description:

In this study, AEs were documented in the eCRF according to predefined categories per therapy cycle. All serious AEs were reported here as serious adverse events (SAEs) and all AEs with CTC grade 3 or higher as non-SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 40 (65.00%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			

subjects affected / exposed	4 / 40 (10.00%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Microangiopathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myopericarditis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Haemolysis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Thrombocytopenia				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	8 / 40 (20.00%)			
occurrences causally related to treatment / all	6 / 11			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	5 / 40 (12.50%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea exertional				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Disorientation				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
COVID-19				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Fungaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 40 (2.50%)		
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 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events subjects affected / exposed	40 / 40 (100.00%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 10		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all)	22 / 40 (55.00%) 76 5 / 40 (12.50%) 6 30 / 40 (75.00%) 106 19 / 40 (47.50%) 64 24 / 40 (60.00%) 68		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 3 / 40 (7.50%) 3 5 / 40 (12.50%) 6		
Infections and infestations Infection subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2018	Inclusion criteria of the protocol have been amended: The eligible primary diagnoses for inclusion of the patient were changed according the new WHO classification of malignant lymphomas (Swerdlow et al., 2016): DLBCL (NOS) or High-grade B-cell Lymphoma with MYC and BCL2 and/or BCL6 rearrangements or High-grade B-cell lymphoma, NOS. In addition, the following was modified in the protocol: Dose modification for the chemotherapy CHOEP was listed in the protocol, SAE reporting was changed.
05 September 2018	The time of administration of ibrutinib was specified in the protocol.
19 June 2019	Safety data from the updated Investigator's brochure of ibrutinib regarding the interaction with other medicinal products (moderate CYP3A inhibitors) was added to the protocol. Prephase treatment was revised in the protocol allowing for prolonging prephase treatment for a maximum of seven days of prednisolone at the investigators discretion and adequate medical reason. Prophylaxis of infections was revised with regard to acyclovir, levofloxacin and the prophylaxis and treatment of fungal infections was addressed in the protocol.
25 March 2020	Safety data from the updated Investigator's brochure of ibrutinib regarding precautions and warnings in case of bleeding-related events, cardiac arrhythmias, lymphocytosis, cerebrovascular accidents and other safety observations were added to the protocol. The handling of complaints regarding the trial medication (Product Quality Complaint (PQC)) was included in the protocol.
30 April 2020	Safety data from the updated Investigator's brochure of ibrutinib regarding precautions and warnings in case of bleeding-related events, leukostasis, hypertension, lymphocytosis, cerebrovascular accidents and other safety observations were added to the protocol. A clarification regarding reporting of pregnancy was added.
12 April 2021	The number of patients in the study was adjusted.
24 August 2021	Safety data from the updated Investigator's brochure of ibrutinib regarding precautions and warnings in case of cardiac arrhythmias and cardiac failure and other safety observations were added to the protocol.
30 June 2022	Administrative changes in the study were implemented in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported