Clinical trial results:
An open label phase II study to evaluate the efficacy and safety of Inotuzumab Ozogamicin for Induction Therapy followed by a conventional chemotherapy based consolidation and maintenance therapy In patients aged 56 years and older with Acute Lymphoblastic leukemia (ALL).

Summary

EudraCT number	2016-004836-39
Trial protocol	DE
Global end of trial date	27 October 2023

Results information

Result version number	v1 (current)
This version publication date	14 November 2024
First version publication date	14 November 2024

Trial information

Trial identification

Sponsor protocol code	Initial-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03460522
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Goethe University
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt am Main, Germany,
Public contact	Medizinische Klinik II, Goethe Universität, 0049 6963016365, goekbuget@em.uni-frankfurt.de
Scientific contact	Medizinische Klinik II, Goethe Universität, 0049 6963016365, goekbuget@em.uni-frankfurt.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	30 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2023
Global end of trial reached?	Yes
Global end of trial date	27 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
To evaluate the efficacy of an inotuzumab ozogamicin induction therapy, defined as the number of patients being alive in first remission one year after start of induction therapy.

Protection of trial subjects:

The study was performed in accordance with the requirements of the current German drug law ("Arzneimittelgesetz"), the current legal provisions regarding data protection, and the principals of Good Clinical Practice.
Study personnel handled all patient data in a strictly confidential way.
To prevent the identification of a person to whom study data belong, study data were pseudonymized by means of the patient identification number.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2017
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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	23

From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in 06/13/2018, last patient out 08/02/2024 (MM/DD/YYYY)

Pre-assignment

Screening details:

Screening was conducted to verify that the inclusion criteria for the study were met. The unifying characteristics of the patient were age of ≥56 years and having a first diagnosis of a B precusor ALL(+CD22).

Period 1

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

Blinding implementation details:

N.A. (open-label single-arm phase II study)

Arms

Arm title	Inotuzumab Ozogamicin Induction Therapy

Arm description:

All patients who receveid 2 or more cycles of inotuzumab ozogamicin therapy.

Arm type	open label single arm study
Investigational medicinal product name	Inotuzumab ozogamicin
Investigational medicinal product code	
Other name	BESPONSA®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

Inotuzumab ozogamicin (PF-05208773), administrated as intravenous infusion over an hour. The dose for the three cycles were as follow:
Cycle 1: Day 1 0.8mg/m2; day 8 and day 15 0.5mg/m2
Cycle 2 and 3: day 1, 8 and 15 dose of 0.5mg/m2

Number of subjects in period 1	Inotuzumab Ozogamicin Induction Therapy
Started	45
Completed	43
Not completed	2
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
Adults (56-64 years)	23	23	
Adults (65-84 years)	22	22	
Gender categorical Units: Subjects			
Female	23	23	
Male	22	22	

Subject analysis sets

Subject analysis set title	Evaluable patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The population for the primary efficacy analysis by intention-to-treat (ITT) consists of all enrolled patients. Patients, who withdraw informed consent, are considered as screening failure due to violation of eligibility criteria, and patients who died prior to the first day of study intervention will not be included. This population is defined as full analysis set (FAS).

Reporting group values	Evaluable patients		
Number of subjects	43		
Age categorical Units: Subjects			
Adults (56-64 years)	23		
Adults (65-84 years)	20		
Gender categorical Units: Subjects			
Female	22		
Male	21		

End points

End points reporting groups

Reporting group title	Inotuzumab Ozogamicin Induction Therapy

Reporting group description:

All patients who receveid 2 or more cycles of inotuzumab ozogamicin therapy.

Subject analysis set title	Evaluable patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The population for the primary efficacy analysis by intention-to-treat (ITT) consists of all enrolled patients. Patients, who withdraw informed consent, are considered as screening failure due to violation of eligibility criteria, and patients who died prior to the first day of study intervention will not be included. This population is defined as full analysis set (FAS).

Primary: Event-free survival (EFS) at one year

End point title	Event-free survival (EFS) at one year[1]

End point description:

End point type	Primary

End point timeframe:

12 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: Only descriptive analysis.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: percent	88			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment phase + follow up	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	All patients with study treatment
Reporting group description:	
All patients who received any infusion of the investigational drug.	

Serious adverse events	All patients with study treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 45 (51.11%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	1		
Investigations			
LDH increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Transfusion reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Subarachnoid haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Venoocclusive disease				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Kyphoplasty				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Presyncope				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

General disorders and administration site conditions			
Fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cysts ans fibroses in the gl. left parotid			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haemorrhage			

alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural effusion				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute Cystitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchial infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
bloodstreaminfection with E.coli, multiresistent				

alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
SARS-CoV-2 infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	4 / 45 (8.89%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever of Unknown Origin				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperbilirubinaemia				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients with study treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)		
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 45 (44.44%)		
occurrences (all)	30		
alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
AST, GOT increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 45 (42.22%)		
occurrences (all)	32		
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 45 (26.67%)		
occurrences (all)	14		
GGT increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	13		
GOT/GPT increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Lipase increased			

alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	11		
Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	28 / 45 (62.22%)		
occurrences (all)	58		
Platelet count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	36 / 45 (80.00%)		
occurrences (all)	83		
White blood cell count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	38 / 45 (84.44%)		
occurrences (all)	79		
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	10		
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
thromboembolic event			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	6		
Antithrombin III decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	17		
Nervous system disorders			

Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia/Hemoglobin			
alternative assessment type: Non-systematic			
subjects affected / exposed	32 / 45 (71.11%)		
occurrences (all)	78		
Febrile neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
General disorders and administration site conditions			
Edema limbs			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 45 (31.11%)		
occurrences (all)	18		
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	11		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	7		
Ascites			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	6		

Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
mucositis oral			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	8		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)		
occurrences (all)	8		
Stomach pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	7		
Renal and urinary disorders			
Acute kidney injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Bone pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Infections and infestations			
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypercalcaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	8		
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 45 (46.67%)		
occurrences (all)	49		
Hyperuricaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	9		
Hypoalbuminaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	5		
Hypocalcaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Hypokalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 45 (20.00%)		
occurrences (all)	19		
Hypophosphataemia			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2018	Modifications of Protocol version1.4: - Prophylaxis: MTX dose changed from 15mg to 12mg - Clarification of asparaginase preparation: E.Coli asparaginase - Addition of Leukovorin-Rescue after HD-MTX according to GMALL recommendation
31 October 2019	Main modifications of protocol version 1.5: - Updates in the sypnose related to prephase and study treatment; - Update of cycle sequence (Ind I - III, Cons I + II, re-induction, Cons III - V, maintenance); - Data collection times adjusted (KMPs); - Changes in the days of the therapy cycles - The remission assessment was changed to the end of consolidation therapy 3 and 5 (before start of maintenance); - Updating the characterization of disease progression - Adverse events: progression and relapse of the disease under study was considered as an outcome not as an AE.
31 October 2022	The duration of the trial(8 years instead of 5), the statistics, the inclusion criteria, the rationale and the risk-benefit ratio were adapted accordingly as well as the time-schedule and the treatment plan. Inclusion criteria replaced: - patients aged 75 or older; -contraindications for intensive consolidation chemotherapy and/or severe comorbidities Exclusion criteria added: - COVID-19 infection at diagnosis therapy: -Standard of care - chemotherapy cycles consolidation I + II, reinduction, consolidation III - V omitted - Start of maintenance week 12 - Duration of aintenance: 20 months - Changes in the programming of intra-tax injections and remissions assessments. Updated definition of molecular response and time-dependent endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37883727