



## 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
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#### 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  $\geq 56$  years and having a first diagnosis of a B precursor 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
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Arm description:

All patients who received 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), administered as intravenous infusion over an hour. The dose for the three cycles were as follow:

Cycle 1: Day 1 0.8mg/m<sup>2</sup>; day 8 and day 15 0.5mg/m<sup>2</sup>

Cycle 2 and 3: day 1, 8 and 15 dose of 0.5mg/m<sup>2</sup>

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 received 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 <sup>[1]</sup>
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
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### Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	All patients with study treatment
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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 occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 0 / 0		
Vascular disorders Venooclusive disease alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 0 / 0		
Surgical and medical procedures Kyphoplasty alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 0 / 0		
Nervous system disorders Presyncope alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 0 / 0		
Blood and lymphatic system disorders Thrombocytopenia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 0 / 0		
Febrile neutropenia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 45 (2.22%) 0 / 1 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 and fibrosis 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 %

<b>Non-serious adverse events</b>	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			

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

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

Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
mucositis oral alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 8		
Nausea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 45 (15.56%) 8		
Stomach pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3		
Epistaxis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 7		
Renal and urinary disorders Acute kidney injury alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 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	9 / 45 (20.00%)		
occurrences (all)	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 version 1.4: <ul style="list-style-type: none"><li>- Prophylaxis: MTX dose changed from 15mg to 12mg</li><li>- Clarification of asparaginase preparation: E.Coli asparaginase</li><li>- Addition of Leukovorin-Rescue after HD-MTX according to GMALL recommendation</li></ul>
31 October 2019	Main modifications of protocol version 1.5: <ul style="list-style-type: none"><li>- Updates in the synopsis related to prephase and study treatment;</li><li>- Update of cycle sequence (Ind I - III, Cons I + II, re-induction, Cons III - V, maintenance);</li><li>- Data collection times adjusted (KMPs);</li><li>- Changes in the days of the therapy cycles</li><li>- The remission assessment was changed to the end of consolidation therapy 3 and 5 (before start of maintenance);</li><li>- Updating the characterization of disease progression</li><li>- Adverse events: progression and relapse of the disease under study was considered as an outcome not as an AE.</li></ul>
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: <ul style="list-style-type: none"><li>- patients aged 75 or older;</li><li>- contraindications for intensive consolidation chemotherapy and/or severe comorbidities</li></ul> Exclusion criteria added: <ul style="list-style-type: none"><li>- COVID-19 infection at diagnosis</li></ul> therapy: <ul style="list-style-type: none"><li>- Standard of care - chemotherapy cycles consolidation I + II, reinduction, consolidation III - V omitted</li><li>- Start of maintenance week 12</li><li>- Duration of maintenance: 20 months</li><li>- Changes in the programming of intra-tax injections and remissions assessments.</li></ul> 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>