Trial Results Report[1]

Name of Sponsor/Company: **Goethe University Frankfurt**	Individual Study Table: [2] Not applicable	*For national authority use only*
Name of Finished Product: Atriance Oncaspar		
Name of Active Substance: Nelarabine PEG-Asparaginase		

Title of Study[3]
Treatment optimization in adult patients with newly diagnosed acute lymphoblastic leukemia or lymphoblastic lymphoma by individualized, targeted and intensified treatment - a phase IV-trial with a phase III-part to evaluate safety and efficacy of nelarabine in T-ALL/T-LBL patients

Approvals of subsequent changes according to § 10 paragraph 1 GCP Regulation (GCP-V)

- 20.06.2017: Change in the delivery and labeling of the investigational medicinal product Nelarabine
- 18.11.2020: Protocol V2 Amendment 1 dated 04.09.2020, Pat.-Info dated 04.09.2020, SmPC
- 05.04.2022: GMP (change to delivery of single vials instead of kits with 6 vials)
- 14.03.2024: Protocol V3 Amendment 2 dated 27.02.2024, Shortening of the post-treatment observation period and an additional questionnaire for patient self-documentation of cognitive function

Investigators
"Leiter der Klinischen Prüfung" according to german drug law: Dr. Nicola Gökbuget

Study centre(s)
82 study centers in Germany

Publication (reference)
n.a.

Studied period (years): date of first enrolment, date of last completed4
24.08.2016–05.12.2024

Phase of development
Phase IV with a phase III part

[1] § 42b AMG (german drug law), according to ICH E3
[2] Referring to Part of the Dossier (Volume, Page)
Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich
[3] Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren
[4] Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/ Studienabbrüche unter Angabe der Gründe aufgeführt werden

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Objectives

Main objective:
To improve event free survival (EFS), remission duration (RD), disease free survival (DFS) and overall survival (OS) compared with the previous trial GMALL 07/2003

Secondary objectives:
1. To evaluate the role of CNS radiation and the role of chemotherapy alone in high risk ALL in molecular remission by randomised evaluation
R1: CNS rad + i.th. vs i.th. alone
R2: SCT vs chemotherapy in pts with molCR
2. To evaluate the feasibility of the entire treatment concept (i.e. adherence to schedule, administration of single and combination chemotherapy, maintenance therapy)
3. To evaluate feasibility and tolerability of nelarabine (IMP) as part of consolidation treatment in T-ALL
4. To perform prospective and concomitant monitoring of comorbidities and specifically defined serious adverse events
5. To evaluate an innovative overall approach to optimize treatment of a rare, biologically diverse disease by use of subgroup specific targeted and experimental substances within the main trial and in associated studies
6. To set up an interlinked biomaterial bank to prospectively evaluate molecular genetic risk factors and carry out scientific accompanying projects

Methodology
This protocol is a therapy optimization study. The drugs have already been used many times in this or similar combinations and are not the subject of the study as individual substances. The study examines the overall concept when implemented within standard of care of ALL patients.
Stem cell transplantation is also performed according to general standards. The protocol describes the indications for SCT. The actual performance of SCT is not the subject of the study.
Nelarabine is investigational drug. Nelarabine is used during consolidation therapy for patients with T-ALL outside of its approval in first-line therapy. Nelarabine is provided free of charge as an investigational drug for this treatment situation.
Due to the feasibility study of asparaginase maintenance therapy, PEG-asparaginase was also defined as an investigational drug. PEG-asparaginase is prescribed as part of standard of care and is not provided.

Number of patients (planned and analysed)
900 patients planned. 1023 were included; 1009 started with therapy; 979 were evaluable for study therapy and therefore analysed.

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Diagnosis and main criteria for inclusion

- Acute lymphoblastic leukemia (all subtypes except burkitt leukemia, blasts in BM ≥ 25%
  or
  Lymphoblastic lymphoma (B- or T-lineage), blasts in BM <25%
- Age: ≥ 18 - ≤ 55 years
- Written Informed consent to participate in the study and the GMALL registry
- Women of childbearing potential (WOCBP) and male sexual partners of WOCBP must be willing to use an effective method of contraception (Pearl-Index < 1%) during the study and at least 6 months thereafter

Main Exclusion Criteria:

- Serious complications (leukemia associated) or concomitant diseases, such as
  - severe uncontrollable complications (leukemia associated), i.e. sepsis, pneumonia with hypoxia, shock, bleeding at diagnosis
  - renal insufficiency, if not caused by leukemia
  - severe impairment of heart or liver function (if not caused by leukemic infiltration)
  - severe obstructive or restrictive pulmonary disease
  - known HIV infection or other uncontrolled infections
  - any other condition that compromises the patient's eligibility for intensive treatment as described by the study protocol
- Late relapse of childhood leukemia or concurrent malignancy
- Previous cytostatic treatment
  - ALL directed (exceptions: standard prephase, application of steroids ≤ 7 days, once-only application of vincristine, cyclophosphamide or other substances as emergency medical intervention)
  - directed to other malignancies within the last 10 years before diagnosis of ALL
- Pregnancy or breastfeeding
- Severe psychiatric disease or any severe concomitant condition under which the patient's understanding of importance and consequences of study participation and/or compliance and therapy according to study protocol cannot be expected
- At diagnosis: participation in another trial that interferes with the antileukemic treatment (exceptions: trials aiming at supportive care, defined accompanying GMALL trials, and at a later timepoint trials with experimental substances, i. e. in case of molecular treatment failure)

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Test product, dose and mode of administration, batch number

Subjects: Patients aged 18 to 55 yrs of both sexes with newly diagnosed T-ALL or T-LBL, treated within the standard risk arm of GMALL 08/2013
For the first 10 pts: Unlabeled test product Nelarabine (provided by GSK)
Batch-Numbers: C711145, C703586, C737288
For the remaining 147 pts: Atriance® market product (provided by Novartis)
Batch-Numbers: C792047, C756887, C802042, C803531, C836376, C836612, BN8R, LIVI, KN3K, W97S, PL6Y, PL7B, MP4C, UM8T, UM8S, KZ5707, MC5932
Administration: c.i.v., 2 h
Cycle 1: 1500 mg/m² d 1, 3, 5, week 24
Cycle 2: 1500 mg/m² d 1, 3, 5, week 32

Duration of treatment

The duration of intensive treatment of an individual patient with ALL is at maximum 41 weeks, followed by maintenance therapy up to a total duration of 2.5 years. Duration of treatment for patient with LBL is at maximum 41 weeks.

Reference therapy, dose and mode of administration, batch number

N/A

Criteria for evaluation:

Efficacy:

The primary endpoint of the study is the improvement of event-free survival in comparison to a historical control group. Secondary endpoints are time to consolidation I for randomisation I and disease-free survival for randomisation II.

Safety:

Safety information (AEs, SAEs) will be summarized by descriptive statistics. Proportion of patients who died during or after induction therapy during the first 61 days will be described.

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Statistical methods

The primary objective of the study is the improvement of event-free survival in comparison to a historical control group, given by patients of the GMALL 07/2003 study. Primary endpoint is therefore event-free survival (EFS), defined as time from first day of study treatment to relapse, treatment failure (partial remission or worse), occurrence of a second malignant tumour or death from any cause, whichever occurs first. The first day of study treatment is defined by the date of first administration of study medication. A formal interim analysis of the primary endpoint will take place at the end of the recruitment phase (which is expected to be 5 years after study start).

Secondary objectives will be evaluated in randomised comparisons (randomisation I and II) on an alpha-level of 5% separately for each hypothesis. No adjustment according to multiple testing will be applied. The objective of randomisation I is the improvement of CNS prophylaxis, defined by the reduction in time to start of consolidation due to omitting cranial radiation. The objective of randomisation II aims to check whether stem cell transplantation can be replaced by chemotherapy for HR patients with molecular remission to improve disease free survival. Thus, secondary endpoints are

- time to consolidation I (randomisation I)
- disease-free survival (randomisation II)

The secondary endpoint time to consolidation I is defined as time from start of induction I treatment to start of consolidation I. Start of induction I and consolidation I, respectively, is defined as the day of first administration of chemotherapy drug.

The secondary endpoint disease-free survival is defined as time from date of randomisation II to relapse, molecular relapses, death, secondary malignancies or last date in remission.

Summary – Conclusions:

Efficacy Results:

Primary Endpoint

Event-free survival evaluation is performed by a comparison with the preceding study GMALL 07/2003 (historical control). The main analysis consists of the test of the (null) hypothesis

$$H_0: \lambda_{GMALL\ 07/2003} = \lambda_{GMALL\ 08/2013}$$

where $\lambda_{(.)}$ denotes the hazard rate of EFS in the respective population. The interim analysis is triggered by the occurrence of 198 EFS events and is performed with significance threshold 0.1%.

The evaluation of the primary endpoint is based on the full analysis set, i. e. all evaluable patients included in the study. Data lock point for this analysis was 25th October 2022.
The historical control has been accrued between 2003 and 2011 and consists of 2492 patients with available additional information age, sex, risk group, immunophenotype (line), subtype, PH status, t(4;11) status and leukocyte count. We excluded patients with subtype “unknown” from the historical control because subtype information was available for all GMALL 08/2013 patients. This

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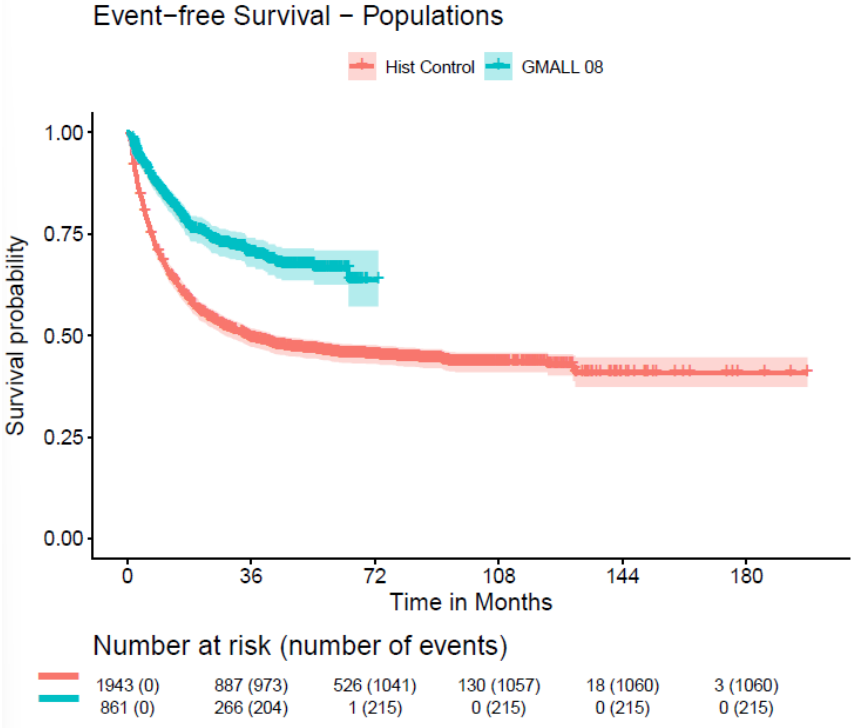
leaves us with 1943 patients. There were no LBL patients in the historical control, therefore LBL patients were also excluded from the GMALL 08/2013 population for this analysis.

The following table illustrates the categorical and nominal baseline characteristics of the study population and the historical control:

Variable	Levels	Hist (n/%)	Study (n/%)	All (n/%)
Gender	female	756 (39%)	338 (39%)	1094 (39%)
	male	1187 (61%)	523 (61%)	1710 (61%)
Risk	Standard risk	849 (44%)	372 (43%)	1221 (44%)
	High risk	632 (33%)	317 (37%)	949 (34%)
	PH+	462 (24%)	172 (20%)	634 (23%)
Line	B	1609 (83%)	638 (74%)	2247 (80%)
	T	334 (17%)	223 (26%)	557 (20%)
Subtype	c/prae-B	1425 (73%)	557 (65%)	1982 (71%)
	Pro-B	184 (10%)	81 (9%)	265 (9%)
	Mature T	25 (1%)	41 (5%)	66 (2%)
	Early T	181 (9%)	80 (9%)	261 (9%)
	Thymic/cortical T	128 (7%)	102 (12%)	230 (8%)

The unadjusted EFS probabilities between both populations are illustrated by Kaplan-Meier survival curves:



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Result for primary endpoint: The two-sided log-rank (chi-squared) test for the evaluation of the primary endpoint was performed. The resulting p-value is < 0.001. Consequently, the null hypothesis of equality of hazard rates can be rejected.

Secondary Endpoint for Randomisation I

The secondary objective under consideration in randomisation I is improvement of CNS prophylaxis by reduction of time to consolidation I by omitting cranial radiation. The comparison will be performed via a two-sided Mann-Whitney U-test. The corresponding analysis population consists of all patients which had a CR before consolidation I started with consolidation I as stated in the protocol.

Patients are eligible for randomisation I, if they have

- C/B-pre-ALL (PH negative) OR
  B-LBL AND
- no initial CNS problems

Randomisation I takes place after stratification I. Patients are randomised into

1. Arm 1: Intrathecal therapy & cranial radiation
2. Arm 2: Intrathecal therapy w/o cranial radiation

while stratifying for risk groups (SR vs HR according to stratification I).

Data lock point for the analysis of randomisation I was on 10th March 2023. The analysis population includes 422 CR patients with the following characteristics:

Variable	Levels	Arm 2, n=241	Arm 1 (incl. Radiation), n=241
Induction I – Consolidation II	Median (min, max)	75 (54 – 135)	76 (55 – 163)
Risk Groups	Standard risk (SR)	127 (59%)	133 (64%)
	High risk (HR)	88 (41%)	74 (36%)
Gender	female	79 (37%)	103 (50%)
	male	136 (63%)	104 (50%)
Disease	ALL	210 (98%)	201 (97%)
	LBL	4 (2%)	6 (3%)
	other	1 (1%)	0 (0%)
Line	B	214 (100%)	207 (100%)
	Missing	1 (1%)	0 (0%)
Leukocytes	< 30000	158 (74%)	152 (73%)
	≥ 30000	56 (26%)	53 (26%)
	Missing	1 (1%)	2 (1%)
CD20	< 20%	136 (63%)	136 (66%)
	≥ 20%	78 (36%)	70 (34%)

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	Missing	1 (1%)	1 (1%)
Age	Median (min, max)	34 (18 – 55)	32 (18 – 55)

The time from induction I (defined by first day of Vincristin) to consolidation I (defined by first day of Methotrexate) between the two treatment arms in the analysis population were investigated. The two-sided Mann-Whitney U test on the analysis population was performed to test the null of location shift (different from 0).

Result for randomisation I: The resulting p-value is 0.344 which is larger than the significance threshold α=0.049. Consequently, the null hypothesis of a nonzero location shift in the time from induction to consolidation between the two treatment arms cannot be rejected.

Secondary Endpoint for Randomisation II:

The secondary endpoint of randomisation II is disease-free survival (DFS) since randomisation II. DFS will be compared between the two treatment arms. A two-sided log-rank test is applied to test the null hypothesis of no difference in DFS between the two treatment arms at significance level α=20%. Number of events per treatment arm will be tabulated, the resulting p-value of the log-rank test will be reported. To visualize disease-free survival per treatment arm Kaplan-Meier estimates will be provided.

The investigation randomises patients into

1. Arm 1: Chemotherapy
2. Arm 2: Stem-cell therapy (SCT), which is the standard therapy

Patients are eligible for randomisation II, if

- they are high risk (stratification I)
- they have confirmed molecular and cytological CR at week 9 (before remission)
- donor is available

Data lock point for the analysis of randomisation II was on 17th March 2023. The ITT population includes all patients included in randomisation II as they have been treated. The number of patients was 96 and their basic characteristics are illustrated in the following table.

Variable	Levels	Arm 2, n=48	Arm 1 (SCT), n=48
Risk Groups	Standard risk	0 (0%)	2 (4%)
	High risk	48 (100%)	46 (96%)
Gender	female	18 (38%)	18 (38%)
	male	30 (63%)	30 (63%)
Age	Median (min, max)	31 (18 – 55)	30.5 (18 – 54)
Actual Therapy	Chemotherapy	43 (90%)	10 (21%)
	SCT	3 (6%)	38 (79%)
	Missing	2 (4%)	0 (0%)
DFS Event	No	35 (73%)	37 (77%)
	Yes	13 (27%)	11 (23%)

The DFS probabilities between both treatment arms by Kaplan-Meier survival curves:

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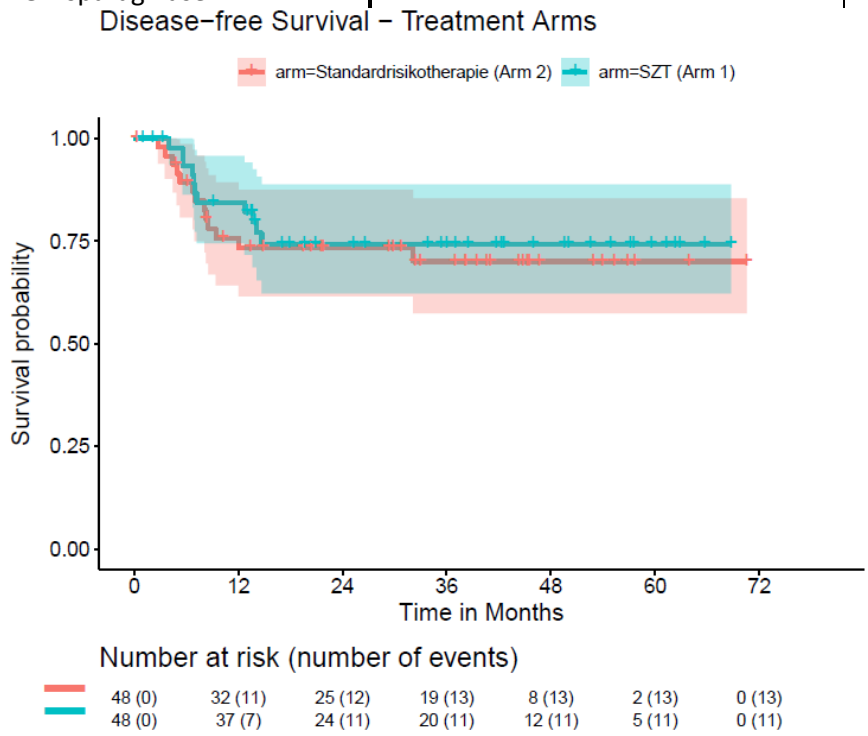

The two-sided log-rank (chi-squared) test for the evaluation of the secondary endpoint was performed.

Result for randomisation II: The resulting p-value is 0.611. Consequently, we cannot reject the null hypothesis that both treatment arms have the same hazard rates.

Summary – Conclusions:

Safety Results:

All patients with start of study therapy (N=1009) are included. Only non-serious AEs as defined per protocol with frequency threshold ≥ 5% during complete therapy.

SOC	Event Term	Number of subjects affected	Event term occurrences all
Blood and lymphatic disorders	Anemia	93 (9%)	240
	Febrile Neutropenia	108 (11%)	147
Gastrointestinal disorders	Diarrhea	64 (6%)	75
	Nausea	107 (11%)	151
	Mucositis	503 (50%)	638
	Fatigue	194 (19%)	334

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General disorders and administration site conditions	Fever	52 (5%)	66
Immune system disorders	Allergic reaction	106 (11%)	143
Infections and infestations	Infection	583 (58%)	1059
Investigations	Blood bilirubin increased	589 (58%)	1111
	Fibrinogen decreased	357 (35%)	674
	Lipase increased	136 (13%)	181
	Neutrophil count decreased	270 (27%)	409
	Platelet count decreased	404 (40%)	1013
	White blood cell decreased	301 (30%)	525
	Transaminase increased	733 (73%)	2101
Metabolism and nutrition disorders	Hyperglycemia	86 (9%)	159
	Hypertriglyceridemia	204 (20%)	476
	Hypoalbuminemia	132 (13%)	183
Nervous system disorders	Headache	53 (5%)	70
	Paresthesia	65 (6%)	113
Renal and urinary disorders	Acute or chronic kidney injury	57 (6%)	64
AE of special interest (No CTCAE criteria)	Antithrombin deficiency	523 (52%)	1513
	Immunoglobulin deficiency	58 (6%)	115
Vascular disorders	Thrombosis	106 (11%)	125

The following list contains all SAEs (as defined per protocol) reported in the context of the trial:

SOC	Event Term	Number of subjects affected	Event term occurrences all
Blood and lymphatic system disorders	Intracerebral hemorrhage	1	1
	Neutropenia	1	1
	Febrile neutropenia	1	1
	Prolonged Thrombopenia	1	1
Cardiac disorders	Cardiac arrest	2	2
	Left ventricular dysfunction	1	1
Eye disorders	Sicca-Syndrome	1	1
Gastrointestinal disorders	Duodenal perforation	1	1
	Enterocolitis	2	2
	Bleeding	1	1
	Mallory-Weiß-Syndrome	1	1

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	Generalized mucositis	1	1
	Ileus	1	1
	Mucositis oral	5	5
	Sigmadivertikulosis	1	1
	Pancreatitis	8	8
General disorders and administration site conditions	Infusion related reaction	2	2
	Pain	1	1
Hepatobiliary disorders	Cirrhosis of the liver	1	1
	Elevation of blood bilirubin and transaminase	1	1
	Liver parenchyma damage	1	1
	Steatosis	1	1
	Hepatopathy	1	
	Liver abscess	1	1
Immune system disorders	Allergic reaction	2	2
	Anaphylactic reaction to Etoposid	1	1
	Anaphylaxis	6	6
	Hemolytic-uremic syndrome	1	1
	Hypophysitis	1	1
	Suspected HLH	1	1
Infections and infestations	Abdominal infection	1	1
	Appendicitis	1	1
	Appendicitis perforated	1	1
	Bone infection	1	1
	Catheter related infection	1	1
	Device related infection	1	1
	Encephalitis infection	1	1
	Endocarditis infective	1	1
	Fungal infection	1	1
	Generalized Mucormycosis	1	1
	Hepatic infection (Morganella morganii)	1	1
	Hepatitis viral	1	1
	Disseminated Aspergillosis	1	1
	Empyem cerebral	1	1
	Fungal pneumonia or atypical pneumonia	1	1
	Hepatolienal Candidiasis	1	1
	Infection (Fusarium petroliphilum)	1	1
	Meningoenzephalitis (HHV6)	1	1
	Necrotizing fasciitis	1	1

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	PCJ-Pneumonia	1	1
	Pneumonia with Covid-19	1	1
	Septic shock	5	6
	Soft tissue infection	2	2
	Viral infection SARS CoV-2	78	81
	Respiratory infection	1	1
	Reactivation of CMV, CMV- pneumonia	1	1
	Invasive mycosis of the lungs	1	1
	Lung infection	7	7
	Lung infection (fungal)	1	1
	Lung infection with ARDS	1	1
	Lymph gland infection	1	1
	Meningitis bacterial (E. Coli)	1	1
	Mucormycosis	2	2
	Influenza A virus infection	1	1
	Pneumocystis jirovecii Pneumonia	1	1
	Pneumogenic sepsis	1	1
	Pneumonia	2	2
	Sepsis	70	73
	Sepsis 3MRGN (E-Coli)	1	1
	Septic cardiomyopathy	1	1
	Wound infection	1	1
	Febrile infection	1	1
	Viral infection (varizella)	1	1
Injury, poisoning and procedural complications	Abdominal soft tissue necrosis	1	1
Investigations	CPK increased	1	1
	Creatinine increased	1	1
	Platelet count decreased	1	1
Metabolism and nutrition disorders	Hyperglycemia	3	3
	Hypoglycemia	1	1
	Hyponatremia	2	2
	Diabetic ketoacidosis	1	1
Musculoskeletal and connective tissue disorders	Arthritis	1	1
	Aseptic necrosis of bone	1	1
	Avascular necrosis	3	3
	Femur necrosis both sides	1	1
	Osteonecrosis	26	27
	Osteoporosis	1	1

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	Osteonecrosis of femoral head both sides	1	1
	Rhabdomyolyse	9	9
	Soft tissue necrosis lower limb	1	1
	Spondylodiscitis	1	1
	Osteonecrosis of femoral head right side	1	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Papillary thyroid carcinoma	1	1
Nervous system disorders	Cerebral vasospasm	1	1
	Depressed level of consciousness	1	1
	Edema cerebral	1	1
	Encephalopathy	2	2
	Intracranial hemorrhage	10	10
	Ischemia cerebrovascular (suspected)	1	1
	Leukoencephalopathy	3	3
	Nelarabine associated Guillain Barre Syndrom	1	1
	JC infection	1	1
	Tetraparesis	1	1
	Unclear neurological symptom complex	1	1
	Polyneuropathy	2	2
	Reversible posterior leukoencephalopathy syndrome	1	1
	Seizure	4	4
	Somnolence	1	1
	Subdural hematoma	1	1
	Incomplete cauda equina syndrome	1	1
	Double vision	1	1
	Reduction of vigilance, coordination disorder, disorientation	1	1
Psychiatric disorders	Delirium	2	2
	Depression	1	1
	Delirium and psychotic Symptoms	1	1
	Epileptical attack	1	1
	Psychosis	1	1
	Suicide attempt	1	1
Renal and urinary disorders	Acute kidney injury	29	30
	Increased creatinine, renal failure	1	1
	Prolongation of MTX-level decrease	1	1

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	Renal failure	6	6
	Renal failure/insufficiency	1	1
	Renal insufficiency	1	1
	Acute renal failure	5	5
Respiratory, thoracic and mediastinal disorders	Adult respiratory distress syndrome	3	3
	Adult respiratory distress syndrome, lung infection	1	1
	Bronchopulmonary hemorrhage	1	1
	Hypoxia	1	1
	Pleural effusion	1	1
	Pneumonitis	3	3
	Pneumothorax	1	1
	Respiratory failure	3	3
Vascular disorders	Thromboembolic event	9	9
	Hygroma	1	1
	Brain vein thrombosis	1	1
	Lung artery embolism	1	1
	Subsegmental pulmonary embolism	1	1
	Hygroma	1	1

33 patients died during or after induction therapy during the first 61 days, 32 ALL patients and 1 LBL patient.

Conclusions:

Overall GMALL trial 08/2013 was completed as scheduled. It yielded extraordinarily good overall results and a significant improvement compared to the previous study generation.
The primary endpoints of randomization I and II were not met. Further analyses of secondary and exploratory endpoints are ongoing to decide on the future role of CNS irradiation and stem cell transplantation in the GMALL protocols.
No unexpected side effects were observed in this large multicenter trial.

I hereby confirm that the data in the results report are collected properly and are correct.

Date of report: 2.12.2025

Print name: Dr.N.Gökbuget

Signature: Dr.N.Gökbuget