Clinical Trial Protocol

Therapy of Nodal Follicular Lymphoma (WHO grade 1/2) in Clinical Stage I/II using Response Adapted Involved Site Radiotherapy in Combination with Gazyvaro

GAZAI Trial

(**GAZ**yvaro and response **A**dapted **I**nvolved-site Radiotherapy)

A trial of the German Low Grade Lymphoma Study Group

in the Competence Network Malignant Lymphomas

Code: GAZAI

EudraCT No.: 2016-002059-89

Phase: non-controlled, open, national multi-center phase II trial

Version: 1.2 (06.10.2017)

GCP Statement: The study will be conducted in compliance with Good Clinical Practices (ICH-GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

CONFIDENTIAL: This protocol contains confidential information and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of the Principal Investigator/ Coordinating Investigator.

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[1] the actual list of reference sites is available on the homepage of the KML (http://www.lymphome.de/Projekte/Referenzpathologie/Institute.jsp)

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The trial will be conducted in 30 national sites (15 Radiation Oncology; 15 Hematology&Oncology) at 15 locations. The sites will be specified in a separate document.

TABLE OF CONTENT

SYNOPSIS

Title

Therapy of early stage nodal Follicular Non-Hodgkin Lymphoma (WHO grade 1/2) in clinical stage I/II using response adapted involved site radiotherapy in combination with Gazyvaro

GAZAI trial (**Gazyvaro** and response **A**dapted **I**nvolved-site Radiotherapy)

Phase

Phase II trial

Sponsor

Ruprecht-Karls-University Heidelberg, Medical Faculty, represented by the University Hospital Heidelberg and its Commercial Director Dipl. Volkswirtin Irmtraut Gürkan, Im Neuenheimer Feld 672, 69120 Heidelberg

Coordinating Principal Investigator / Leiter der klinischen Prüfung

Prof. Dr. med. Klaus Herfarth, Dept. Radiation Oncology, INF 400, 69120 Heidelberg, Germany

Financing

Non-commercial clinical investigation under co-funding of the Roche Pharma AG.

Indication

Stage I or stage II (Ann Arbor) nodal follicular Non-Hodgkin Lymphoma grade 1 or grade 2

Study population

Inclusion criteria

- Centrally reviewed CD20-positive follicular lymphoma grade 1/2 based on WHO classification (2016)
- Untreated (radiation-, chemo- or immunotherapy) nodal lymphoma (including involvement of Waldeyer´s ring)
- Age: ≥18 years
- ECOG: 0-2
- Stage: clinical stage I or II (Ann Arbor classification)
- Risk profile: Largest diameter of the lymphoma ≤ 7 cm (sectional images)
- Written informed consent and willingness to cooperate during the course of the trial
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows: Hemoglobin ≥ 9.0 g/dL; absolute neutrophil count ≥ 1.5 × 10^9/L, Platelet count ≥ 75 × 10^9/L
- Capability to understand the intention and the consequences of the clinical trial
- Adequate contraception for men and women of child-bearing age during therapy and 18 months thereafter
- Patients with non-active hepatitis B infection (HBsAg neg/HBcAB pos/HBV DNA neg) under 1-year require prophylactic anti-viral therapy (e.g. Entecavir®) possible (see also

5.6. Prior and Concomitant Disease)

Exclusion criteria

- Extra nodal manifestation
- Secondary cancer in the patient's medical history (exclusion: basalioma, spinalioma, melanoma in situ, bladder cancer T1a, non-metastasized solid tumor in constant remission, which was diagnosed >3 years ago
- Concomitant diseases: congenital or acquired immune-deficiency syndromes, active infections including viral hepatitis (serology positive for HBsAg or HBcAb in combination positive HBV DNA), uncontrolled concomitant diseases including significant cardiovascular or pulmonary disease (see also 5.6. Prior and Concomitant Disease)
- Severe psychiatric disease
- Pregnancy / lactation
- Known hypersensitivity against Gazyvaro (Obinutuzumab) or drugs with similar chemical structure or any other additive of the pharmaceutical formula of the study drug
- Participation in another interventional trial or follow-up period of a competing trial which can influence the results of this current trial
- Creatinine > 1.5 times the upper limit of normal (ULN) (unless creatinine clearance normal), or calculated creatinine clearance < 40 mL/min
- AST or ALT > 2.5 × ULN
- Total bilirubin ≥ 1.5 × ULN
- INR > 1.5 × ULN
- PTT or aPTT > 1.5 × the ULN

Background

Large field radiation therapy has proven to be superior to more limited fields radiation in early stage follicular lymphoma in prolonging PFS (ARO 98-01 trial, personal communication M. Engelhard)

The MIR trial showed, that at least in the short time follow-up, the addition of MabThera to a small-field radiation therapy in conventional dosage can lead to at least equal results concerning the PFS as compared to the historic large field data of the ARO 98-01 trial. However, the toxicity has been shown to be lower (Herfarth et al. 2014).

The metabolic CR rate as demonstrated by FDG-PET was identified as a prognostic marker for freedom of recurrence in advanced stage of follicular lymphoma (Trotman et al. 2011 PRIMA trial).

Immune modulating radiation therapy alone using a low-dose of 2 x 2 Gy (LDRT) has been shown to be effective in inducing CR in about 60% of follicular lymphoma in a prospective trial (Haas et al 2003) or 48% in the British FORT trial (Hoskin et al. 2014). It can be speculated that a CR-repsonse to LDRT identifies specific subtypes of follicular lymphoma. Also, it is not known whether a combination of LDRT with anti-CD20 antibody therapy may enhance the CR-rate.

The goal of the current trial is a further reduction of the radiation dose in patients with a good response to a combination of LDRT and anti-CD20 immunotherapy. The shift from MabThera to Gazyvaro might lead to an even more effective treatment, which can be proven by the morphological response in week 7 and the MRD eradication in comparison to the MIR trial. Patients with insufficient response (no metabolic CR) after LDRT will receive an additional radiation dose of 36 Gy adding up to the total dose 40 Gy of the MIR trial.

Objectives

Primary

Evaluation of the rate of metabolic CR after low-dose involved site radiotherapy in combination with Gazyvaro (Obinutuzumab) in early stage nodal follicular lymphoma in order to avoid conventional full dose IF radiotherapy.

Secondary

Efficacy and safety of a response adapted radiation dose treatment schedule.

Endpoints

Primary

- Metabolic complete response (CR) in week 18 in patients with remaining macroscopic lymphoma after initial diagnostic biopsy judged by FDG-PET/CT

Secondary

- Morphologic CR, PR, SD, PD in week 7, week 18 and month 6 in patients with initially remaining lymphoma judged by CT/MRI
- Historical comparison of the morphologic response with MIR data (using MabThera); the comparison of the CR rate in week 7 allow for a comparison of the two different anti-CD20 antibodies. Based on the patient numbers a matched pair analysis will be not be possible
- Progression-free survival (PFS) of all treated patients (2 years after individual treatment start)
- Toxicity (NCI-CTC criteria, version 4.03) of all patients
- Relapse rate and pattern of recurrence of all treated patients at all follow-up visits.
- Overall survival (OS) of all treated patients (2 years)
- Quality of life according EORTC QLQ C30 and FACT-Lym questionnaires at inclusion and in week 18, month 12, and 24 (all treated patients)
- MRD response: initially, week 18, months 6, 12, 18 and 24 (all treated patients). MRD is evaluated by the laboratory of C. Pott (Kiel) using at least the markers: t(14:18) PCR for MBR, 3'mbr, 5'mcr and MCR; clonal IGH rearrangements (FR1-3); clonal IGL rearrangements (IGK and Kappa-KDE)

Additional Scientific program

- Genetic profiling of responders and non-responders (coordinated by W. Klapper, Kiel)

Design of the trial

Open, non-controlled, national multi-center phase II trial

Study medication: Gazyvaro (Obinutuzumab)

Duration and dosing:

1000 mg Obinutuzumab i.v. flat dose weekly in weeks 1-4 and week 8, week 12, week 16

(pharmacokinetics based on [1])

week	1	2	3	4	5	6	7	8	9	12	16
Gazyvaro (1000 mg i.v.)	X (day 1)	X (day 8)	X (day 15)	X (day 22)				X (day 1 of week 8)		X (day 1 of week 12)	X (day 1 of week 16)
IS-RT									2x2 Gy		

Radiation therapy

- Involved site radiotherapy of the involved lymph node regions: 2 x 2 Gy in week 9 on two consecutive days (after 5th administration of Gazyvaro)
- Salvage radiotherapy if there is no metabolical CR **and** morphological PR/CR at week 18: additional 18 x 2 Gy (5x2 Gy/week) starting from week 20 (without Gazyvaro)

Number of patients

Due to the descriptive character of the trial, no assessment of any formal statistical hypotheses is performed. The calculation of the number of patients is primarily based on the aspects of practicability and precision of the results. The following calculations are based on the intention-to-treat (ITT) population. Since the strength of the results for the primary endpoint may be weakened due to early drop-outs (as described later), the number of patients needed should be high enough to compensate for potential drop-outs. Primary endpoint is the rate of metabolic CR in week 18 in patients with initially remaining lymphoma judged by FDG-PET/CT. Based on the morphologic CR rate of 37-84% after 2 x 2 Gy documented in the literature and in face of a lack of data for metabolic CR after 2x2 Gy, a CR rate of 60% is assumed. If fifty patients enter the FDG-PET/CT and the observed metabolic CR rate amounts to 60%, the half width of the asymptotic two-sided 95% confidence interval amounts to about ± 13.5%.
Based on the experience of the MIR trial, a general drop-out rate of 10% is assumed, and about 30% of the included patients will not have remaining lymphoma after initial surgery to prove the histology. In addition, we expect an additional drop-out rate of about 15% after the initial FDG-PET due to stage-shifting to a stage III/IV disease.
These considerations lead to the following calculation:
If 93 patients are being recruited, about 15% will drop out due to a stage-shift to higher stages after FDG-PET (79 patients remaining). Of these 79 patients, about 30% will have no remaining PET positive lymphoma after initial surgery (according to the experiences in the MIR trial). Therefore, 55 patients would start therapy with the goal of reaching the primary endpoint assessment. Assuming a drop-out rate of 10%, 50 patients will be available for final assessment of the primary endpoint.
The number of n=93 represents the upper limit of the patients to be included. This number of definitively included patients might drop during the trial, if, e.g., less patients show a stage-shift or more patients show remaining lymphoma.

Statistical analysis

Trial data are evaluated by applying methods of descriptive data analysis:
Rate of metabolic CR in week 18 after initiation of the therapy of each patient as relative frequency including the two-sided 95% confidence interval according to Wilson. (ITT and PP populations).
PFS and OS at 2 years after initiation of the therapy of each patient will be analyzed using the Kaplan-Meier method and the two-sided 95% confidence intervals according to Greenwood (ITT and PP populations).
Quality of life will be evaluated according to the evaluation guide of the two questionnaires.

(ITT and PP populations).
Toxicity will be evaluated for frequency and intensity (safety population).

Length of the clinical trial and milestones

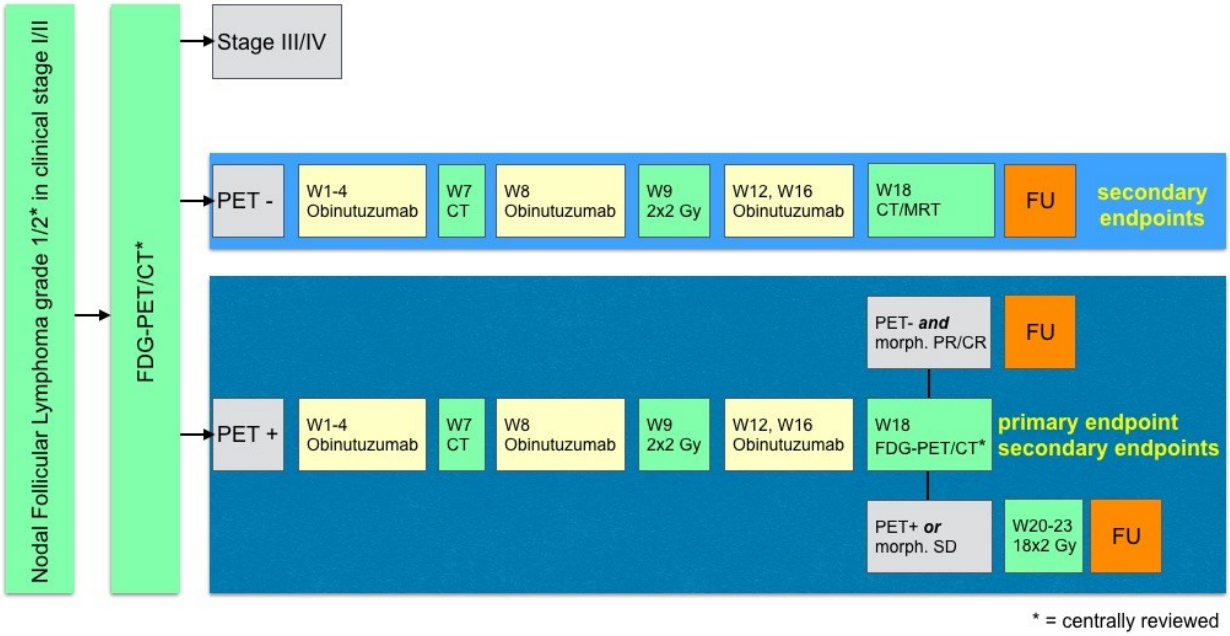
Length of the clinical phase:	5.5 years (66 months)
Start of trial preparation:	Q1 2015
FPI (First Patient In):	Q4 2017
LPI (Last Patient In):	Q1 2021
LPO (Last Patient Out):	Q3 2023
DBL (Data Base Lock):	Q1 2024
Completion of the statistical analysis:	Q2 2024
Completion of the trial report:	Q3 2024

STUDY FLOW CHART

Two stage Screening:

a) Histology and CT or MRI: centrally approved follicular lymphoma grade 1/2 in clinical stage I/II (max. 93 patients)

b) FDG-PET/CT: exclusion of stage III/IV patients (approx.. 15%= 14 patients)
Inclusion of max 79 patients: ca. 70% (=55 patients with remaining lymphoma); approx. 30% (=24 patients with metabolic CR)
Drop-out-rate: approx. 10% (analyzable for primary endpoint 50 patients with remaining PET positive lymphoma)



PET-pos (PET+):	PET positive residual lymphoma
PET-neg. (PET-):	metabolic CR
W:	week
FU:	Follow-up examinations
morph. SD:	morphological SD

STUDY SCHEDULE

	R/S *	Base line	Monotherapy Gazyvaro				Staging CT	Combined Therapy Gazyvaro +Radiation				Staging FDG-PET/CT	(Salvage)				Follow-up				
			Week														Month				
Visits from 1. Gazyvaro			**1**	**2**	**3**	**4**	**7**	**8**	**9**	**12**	**16**	**18**	**20**	**21**	**22**	**23/ 24**	**6**	**12**	**18**	**24**	**30**
Window: ± days (d)/weeks (w)				2d	2d	2d	1w	3d		3d	3d	1w	1w				2w	2w	2w	2w	2w
Informed consent	**S**	**X**																			
Hepatitis[11]/HIV[12]/ pregnancy testing (serum)[20]	**R**	**X**																			
Pregnancy test (serum / urine) [22]			**X**[21]			**X**[21]		**X**[21]		**X**[21]	**X**[21]										
Biopsy(R)/reference pathology.(R)[7]	**R**	**X**																			
Previous medical history and current status[3]	**R**	**X**					**X**					**X**					**X**	**X**	**X**	**X**	**X**
ECOG	**S**	**X**										**X**					**X**	**X**	**X**	**X**	**X**
Gazyvaro i.v. [5]	**S**		**X**	**X**	**X**	**X**		**X**		**X**	**X**										
Radiation IS[6] (2Gy/day)	**S**								**X**[6]												
Salvage RT [6] (36 Gy)	**S**												(**X**	**X**	**X**	**X**)					
Diff. blood count[10]	**R**	**X**	**X**[2]	**X**[2]	**X**[2]		**X**	**X**[2]		**X**[2]	**X**[2]	**X**					**X**	**X**	**X**	**X**	**X**
Clin. chemistry[4]; LDH	**R**	**X**					**X**					**X**					**X**	**X**	**X**	**X**	**X**
Albumin, immunoglobulins, immunefixation[15]; ß2-Microglobulin	**R**	**X**																			**X**
FDG-PET/CT	**S**	**X**[13]										**X**[14]									

	R/S *	Base line	Monotherapy Gazyvaro				Staging CT	Combined Therapy Gazyvaro +Radiation				Staging FDG-PET/CT	(Salvage)				Follow-up				
			Week														Month				
Visits from 1. Gazyvaro			1	2	3	4	7	8	9	12	16	18	20	21	22	23/ 24	6	12	18	24	30
Window: ± days (d)/weeks (w)				2d	2d	2d	1w	3d		3d	3d	1w	1w				2w	2w	2w	2w	2w
CT/MRI[16]	R	X					CT[17]					X[19]					X	X	X	X	X
Bone marrow aspiration	R	X																			
Additional examination based on involved sites.[8]	R	X																			X
MRD[9] EDTA-blood (10 ml) STRECK-tube (10 ml)	S	X[1]										X					X	X	X	X	
QLQ (EORTC QLQ-C30; FACT Lym)	S	X[1]										X						X		X	
AEs (CTCAE)	S/R		X	X	X	X	X	X		X	X	X	X[18]				X	X	X	X	X
Support medication		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X

*R = Routine, S = trial specific

[1] before therapy

[2] before each infusion of Gazyvaro

[3] Weight, height, comorbidities, medication, physical examination including lymph node status, FLIPI

[4] Na, K, AST/ALT, Bilirubine total, AP, creatinine: all baseline-values older than 4 weeks before first Gazyvaro infusion.

[5] as described in synopsis

[6] Irradiation: Dosage according ICRU 50

Week 9: IS-Radiation Total dose: 4 Gy
Single dose: 2 Gy per day on two consecutive days

Salvage RT on remaining lymphoma (after positive FDG-PET/CT week 18) from week 20 (until week 23 or 24): total dose 36 Gy, single dose 2 Gy, 5 fractions per week
There is no salvage RT in case of metabolic CR and morphologic PR

[7] Fine needle aspiration is not acceptable. Biopsy specimens should be sent to the reference pathologists as early as possible. Histology must be not older than 6 months

[8] TSH, fT3/fT4 in case of cervical involvement

[9] MRD-diagnostic via Prof. Dr. Ch. Pott, Kiel

[10] differential blood cell count: hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes

[11] HBV-Testing: at least HBsAG-status and HBcAb-status

[12] Hepatitis/HIV screening can be dispensed if values not older than 3 months exists; pregnancy testing in blood serum

[13] FDG-PET/CT after trial inclusion (initial FDG-PET/CT): it can be dropped if there is an existing FDG-PET/CT not older than 4 months and performed under the requested conditions. (central review of these images in Heidelberg)
[14] PET/CT in week 18 if there was initially PET positive remaining lymphoma
[15] Serum electrophoresis: albumin, M-component
[16] CT/MRI: head/neck, thorax/ abdomen/ pelvis incl. inguinal region), if necessary additional ultrasound. staging procedures not older than 4 months.
[17] CT of the involved region as planning CT
[18] in case of salvage RT from week 20
[19] CT/MRI only, in week 18 in patients with PET negative initially enlarged lymph nodes
[20] Pregnancy test (serum) in all women with childbearing potential (including tubal ligation)
[21] Pregnancy test (serum or urine) in all women with childbearing potential (including tubal ligation); In case of a positive urine pregnancy test, dosing will be delayed, until patient's status is determined by a serum pregnancy test.
[22] Additionally, pregnancy test (serum or urine) in all women with childbearing potential (including tubal ligation) if menstruation is overdue more than 2 weeks during the follow up period up to month 24.

LIST OF TABLES

ABREVIATIONS

ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse Event
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
ATC	Anatomical-Therapeutic-Chemical Code, part of WHO-DRL (Drug Reference List)
BDSG	Bundesdatenschutzgesetz
BfS	Bundesamt für Strahlenschutz (Federal Radiation Safety Agency)
BOB	Bundesoberbehörde
CDC	Complement-dependent cytotoxicity
CLL	Chronic lymphocytic leukemia
CMR	Complete Metabolic Response
CRF	Case Report Form
CR	Complete Remission
CRu	unconfirmed Complete Remission
CS	clinical stage
CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Curriculum Vitae
D	Day
DBL	Data Base Lock
DICOM	Digital Imaging and Communications in Medicine
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
EF	Extended field
ENT	Ears nose throat
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life questionnaire
FD	Financial Disclosure
FDG-PET	^{18}F-Fluor-Desoxy-Glucose Positron-Emissions Tomography
FL	Follicular Lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
FPI	First Patient In
FU	Follow-up visit
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Ordinance (GCP-Verordnung)
GLSG	German Low-Grade Lymphoma Study Group
Gy	Gray, Energy dose (J/kg)
IB	Investigator´s Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH GCP	ICH harmonized tripartite guideline on GCP
ICRU 50	International Committee on Radiation Units and Measurements 50
ICSR	Individual Case Safety Report
IF	Involved field
IMBI	Institute for Medical Biometry and Informatics
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IRR	Infusion related reaction
IS	Involved site
ISF	Investigator Site File
ISRCTN	International Standard Randomized Controlled Trial Number
ITT	Intention To Treat
KKS	Coordination Centre for Clinical Trials (Koordinierungszentrum für Klinische Studien)
LDRT	Low dose radiation therapy
LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LPO	Last Patient Out
LPI	Last Patient In
MedDRA	Medical Dictionary for Regulatory Activities
MPD	Metabolic Progressive Disease
MRD	minimal residual disease
MRI	Magnetic resonance imaging
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PD	Progressive Disease
PEI	Paul-Ehrlich-Institute
PFS	Progression-free survival
PI	Principal Investigator
PMR	Partial Metabolic Response
PP	per-Protocol
RF	Regional field
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Steering Committee
SmPC	Summary of Product Characteristics
SPD	Sum of the products of the greatest diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TLI	Total lymphatic irradiation
TMF	Trial Master File

TNI	Total nodal irradiation
TSH	Thyroid stimulating hormone
W	Week
WHO	World Health Organization

SUMMARY

Extended field or total nodal irradiation had been the gold standard for early stage follicular lymphoma for a long time in Germany. An *involved field* (IF) irradiation has been favored due to the toxicity of large field irradiation in other countries (e.g. USA). However, smaller irradiation fields have been accompanied with an increased risk of recurrence [2, 3]. A combination of *involved field* irradiation with the anti-CD20 antibody Rituximab (MIR trial) has led to similar efficacy results compared to the large field irradiation but with markedly reduced side effects [4].

Haas et al. showed in a prospective trial, that a low dose radiation therapy (LDRT) can lead to a complete remission in up to 60% in follicular lymphoma [5]. This is presumed to result from immune modulatory effects induced by LDRT. The effectiveness of LDRT could also be demonstrated in another prospective, randomized British trial (FORT trial [6]: 2 x2 Gy vs. 12 x 2 Gy) with a CR rate of 40% after 2 x 2 Gy (60% after 12 x 2 Gy). Currently, it is unknown, which patients need a higher radiation dose and which not.

A metabolic complete remission (CR) is an important prognostic marker for progression-free survival. According to the results of the PRIMA trial, CR is a very strong predictive parameter if the CR is established using FDG-PET [7].

In the present GAZAI trial, patients with early stage nodular follicular lymphoma will be treated in a combined approach of immunotherapy with an anti-CD20 antibody and small field (involved site) irradiation as in the MIR trial. In GAZAI, the fully humanized anti-CD20 antibody Obinutuzumab (GAZYVARO) will be used, which showed a high efficacy in combination with bendamustin in patients with follicular lymphoma refractory to Rituximab (GADOLIN trial) [8]. In addition, the radiation dose will be limited to 2 x2 Gy in responding patients. A dose build-up to a total of 40 Gy (dose in the MIR trial) will be performed in case of failure to achieve a complete CR based on a FDG-PET in week 18.

Primary endpoint of the trial is the rate of CR (based on FDG-PET/CT) after Obinutuzumab and 2x2 Gy IS radiotherapy in week 18. Secondary endpoints are the morphological CR rate in week 7, week 18 and month 6, the PFS, the toxicity, the recurrence rate, the recurrence pattern, overall survival and quality of life.

1 INTRODUCTION

1.1 Background

Follicular lymphomas (FL) are B cell lymphomas characterized by CD20 expression and quite often by a t(14;18)(q32;q21) translocation. Based on the increasing amount of centroblasts, FL is categorized in grade 1, 2 or 3. FL grade 3 is a heterogeneous group of lymphomas. Grade 3b FLs clinically present more like aggressive lymphomas and are usually treated accordingly. Follicular lymphoma is the second most frequent non-Hodgkin lymphoma entity in the US and in Europe (30% of all NHL and about 70% of indolent lymphomas). Most patients present with an advanced stage at the time of diagnosis. Only about 15-30% of the patients with FL initially present in an early stage (stage I or II according to the Ann Arbor classification). The natural course is usually slowly advancing with a relatively long survival, especially in the early stages. Due to this behavior, a watch and wait concept (withholding therapy till progression) is being favored for the advanced stages and partly also for the early stages [9] [10].

1.1.1 Radiation therapy and extension of the target volume

Radiation therapy alone has been the gold standard for patients in the early stages. Long lasting remissions and the potential chance for cure were the main arguments supporting this approach. However, there was no consensus about the extent of the radiation fields (target volumes). Table 1 summarizes the results of several international experiences with a longer follow-up [2, 11-22]. These are mostly retrospective analyses with only a few exceptions [15, 17, 18]. Involved field, extended field and total lymphatic irradiation (TLI) were used in these series. The 10-years freedom-from-recurrence rates were 38%-72% and the overall survival rates 50%-78% with a median survival of more than 12 years.

Table 1: Results of radiotherapy in larger patient series with early stage FL (f/u = follow-up; IF = Involved field, RF = regional field; EF = Extended field; TLI = total lymphatic irradiation; TNI = total nodal irradiation)

Autor		Median f/u [years]	Proportion stage I [%]	RF surv 10 J [%]	OS 10 J. [%]	RT Volume
Soubeyran, 1988 [12]	103	8,3	44	49	56	IF/RF
Lawrence, 1988 [14]	93	9	50	48	69	IF/EF/TLI
Mac Manus, 1996 [2]	177	7,7	41	44	64	IF/RF/EF/TLI
Stuschke, 1997 [18]	117	5,5	51	59 (5J)	86 (5J)	EF/TLI
Wilder, 2001 [20]	80	19	41	72 (I); 38 (II)	70 (I); 58 (II)	IF/RF/EF
Ott, 2003 [21]	58	8,75	40	64	69	IF/EF/TNI/TLI
Neumann, 2003 [22]	103	4	61	48	51	IF/EF/TNI

A prospective German trial included 117 early stage FL patients between 1986 and 1993. These patients were only treated by large field irradiation techniques (EF and TLI). 41% showed a recurrence after 8 years of follow-up. Risk for infield-field nodal relapse was significantly lower in adjuvant irradiated than in non-irradiated regions at least in stage I patients – suggestive of a necessity to evaluate large field irradiation under controlled conditions. However, this kind of treatment was accompanied with an increased risk of toxicity: 23% of the patients showed grade 3 / 4 toxicity [18].

The successor trial ARO98-01 evaluated TLI and a modified EF irradiation in a randomized comparison. The recruitment of 202 patients was completed in 2007 and the final results have not been published yet. However, interim analyses showed a significant difference of the PFS and most recurrences occurred outside the radiation field [3].

1.1.2 Radiation dose

Most of the trials listed in Table 1 used radiation doses of 30 Gy or more. In the German trial

published by Stuschke 1997, 26 Gy were mandatory for areas of possible microscopic disease and 36 Gy to macroscopic disease. In a multiviariate analysis, a deviation of more than 20% of this dose proved to be a highly significant negative prognostic factor for recurrence [18].

In a 2011 published prospective British trial, the dose effect was evaluated in a randomized fashion in 361 patients with indolent lymphoma [23]. Patients received either 20 x 2 Gy or 12 x 2 Gy involved field radiotherapy. There was no difference in the local or systemic lymphoma control reported after median follow up of 5 years. However, some reservations have to be made: The patient cohort was very heterogeneous regarding the histology (40% non-follicular grade 1/2), the stage and pretreatment (30% were treated for recurrence), and the thoroughness of follow-up examinations (radiological and only clinical examinations were allowed) [23]. Despite this, 24 Gy has was recommended as a standard dose in England since the results of this study were published[24]. The German radiation oncology community is more concerned with the problems of the trial and has more confidence in the above mentioned data of Stuschke et al. suggesting a minimal dose of 36 Gy to macroscopic tumor sites [18].

However, low dose radiation therapy (LDRT) has shown long lasting effects. Ganem et al. published retrospective data about a low dose radiation therapy of follicular lymphomas in 1994 [25]. Twenty-seven patients with advanced disease were treated with 2 x 2 Gy over 3 days. A CR was achieved in 37%. More patients with low-grade lymphoma (according to the Working formulation) were treated subsequently using the 2 x2 Gy scheme as published in 2001 by Girinsky et al.: Of 48 patients, 80% were pretreated with at least 2 different chemotherapy schedules in their past medical history. A total of 135 sites were treated using 2 x 2 Gy and this resulted in a 51% CR rate. Positive predictors were a lymphoma <5cm, less previous chemotherapies, and an age < 65 years [26].
Based on these data, a prospective multicenter phase 2 trial with 109 patients and recurrent indolent lymphoma was initiated and published by Haas et al in 2003 [5]. They reported a response rate of 92% and a CR rate of 61% (72% in patients without previous therapy). The local PFS in patients who achieved a CR was 75% after 2 years. The median local PFS was at 42 months.
Luthy et al. treated 33 patients with advanced or recurrent indolent lymphoma also using the 2 x 2 Gy schedule [27]. They described a CR rate of even 84%. However, they also reported 23% infield recurrences after a time of 9 months (median). Achievement of CR was not a positive predictor.

In summary, the CR rates after 2 x 2 Gy irradiation ranged between 37 and 84% (Table 2)

Table 2: Response (PR/CR) und rate of CR after 2 x 2 Gy IF radiotherapy (based on Luthy et al. [27]

Author	n	Total response [%]	CR [%]
Ganem, 1994 [25]	27	89	37
Sawyer, 1997 [28]	11	94	38
Girinsky, 2001 [26]	48	81	57
Johannsson, 2002 [29]	22	87	65
Haas, 2003 [5]	109	92	61
Luthy, 2008 [27]	33	95	84
Hoskin, 2014 [6]	243	80	48

The mode of action of 2 x 2 Gy is not completely understood. An induction of the p53 pathway is discussed [30]. Knoops et al. looked at lymph node biopsies before and after LDRT. They found an

upregulation of p53 expression in 10 of 15 samples. An increase of the p53 immuno-staining from 5% to >80% was seen in 7 samples [31]. This effect was observed primarily in the follicular lymphoma cells and not in T-cells or endothelial cells visible. In vivo imaging lead to the speculation, that LDRT neutralizes anti-apoptotic effects of the characteristic bcl-2 overexpression in follicular lymphoma cells [32].

The British FORT trial prospectively tested 12 x 2 Gy against 2 x 2 Gy in the treatment of indolent lymphomas in a randomized fashion. Recruitment was stopped shortly before the end of the trial was reached due to the superiority of the 24 Gy arm (freedom from local progression after 2 years 93.7% vs. 80.4%) [33]. The CR rate was 40% after LDRT (total response rate 74%) and 60% after 24 Gy (total response rate 81%). For follicular lymphomas, the final results showed a CR rate of 48% after LDRT and 68% after 24 Gy ($p = 0.0096$). There were significantly more recurrences (n=70) in the LDRT arm after a median follow-up time of 26 months as compared to the standard 24 Gy arm (21 recurrences; HR 3.42; $p<0.0001$) [6]. However, this trial also has some major weaknesses [34]:

The inferiority regarding the PFS could have been strengthened by a possible imbalance between the two arms: There was no differentiation between follicular lymphoma grade 1, 2, 3a or 3b. A central review of the pathology confirmed only in 60% a follicular or a marginal zone lymphoma. There was no central pathological review in 20% of the patients and other lymphomas (also aggressive lymphomas) or no lymphoma at all were diagnosed in the other cases. It was not stratified after the size of the lesion. There was also no maximal size limitation and different response rates in relation to the size were not discussed. No difference in the PFS was seen in a subgroup analysis of all patients (4 Gy and 24 Gy), but there was no information about the effect of the different doses in respect to the size of the lesion. There was no information about previous and following treatments. In the staging and follow-up procedures, 3D imaging was not mandatory, conventional x-ray and clinical evaluations only were also allowed. It is not clear, how many of these patients were evaluated only clinically without 3D imaging. Unfortunately, there was also no information about the best response status of the patients with recurrence.

In summary, the FORT trial showed some effectiveness after LDRT, but it is not clear whether the difference between LDRT and 24 Gy was as large as published considering the above mentioned weaknesses.

1.1.3 Chemotherapy and radiation therapy

In the 70ties and 80ties, several trials addressed the possibility that relapse control could be improved by a combination of radiation therapy with systemic chemotherapy [35-38]. The sequential application of COP or CHOP-B and IF radiation therapy showed an improvement of the recurrence-free survival but not of the overall survival compared with historical data [39]. An update of the data revealed a 10 years recurrence free survival of 72%, which is superior to historical controls [40]. However, 22% of the patients developed a neutropenia grade IV and there were 14 secondary malignancies.

1.1.4 Immunotherapy using an anti-CD20-Antibody (MabThera / Rituximab)

In early and advanced stage CD20 positive follicular lymphoma, the use of the anti-CD20 antibody Rituximab has been evaluated as monotherapy or in combination with chemotherapy in several trials. The effectiveness of Rituximab without chemotherapy was tested in the SAKK 35/09 trial using two different dose schedules (4x vs. 8x) [41]. Most of the 202 included patients had an advanced disease, only 15% had a clinical stage I or II according to the Ann Arbor classification. Thirty-eight percent of the patients of the 8x arm showed a CR during follow-up. The highest CR rate was achieved in patients without previous chemotherapy in their medical history and 8 cycles of MabThera (52%) [41]. However, there was no plateau of the PFS curve in the long-term follow-up. The above-mentioned best subgroup had a PFS of 70% after 2 years and 45% after 5 years (median PFS 43 months) [42].

1.1.5 Combination of anti-CD20-antibody and radiation therapy

The MIR trial was a multi-center phase II trial investigating the combination of Rituximab with *involved field* radiotherapy in FL stage I/II patients [43]. The recruitment of 85 patients was finished in 2010. The final clinical results were presented on the annual meeting of the European Society of Therapeutic Radiation Oncology (ESTRO) 2014 in Vienna [4]: The effectiveness was comparable with the superior arm of the ARO98-01 trial (TLI) but with a lower morbidity profile. The PFS rate after 2 years was 86%. The CR rate after 4 cycles of MabThera (without radiation) was 29% in patients with macroscopic disease at inclusion. Best morphologic response was reached at month 6 with a CR rate of 79%. The final results are going to be published after integration of the scientific MRD data.

1.1.6 FDG-PET for staging and response evaluation

The sensitivity and specificity of a FDG-PET examination for staging purposes is very high [44-46]. Tskamoto describes a sensitivity of 91% in 193 regions with involvement of follicular lymphoma [45]. Only the involvement of the duodenum in 3 patients was not detected. Elstrom et al. reported of similar results (sensitivity 98% in 42 patients) [46]. A sensitivity of 98% and a specificity of 94% were presented by Wöhrer et al. in 62 patients with different grades of follicular lymphoma. These were lower if conventional staging methods were used (sensitivity 95%, specificity 80%) [44]. Luminari et al. looked at the consequences of an FDG-PET in 142 patients of the FOLL05 trial who were primarily staged by CT: Based on the FDG-PET, 32% more involved lymph node regions were detected(46/146). Less involved regions were diagnosed in 11%. A stage shift into a more advanced stage was diagnosed in 11% due to the FDG-PET [47].

The Cheson criteria of 2007 recommend FDG-PET for response evaluation in patients with Hodgkin`s lymphoma or aggressive lymphomas [48, 49]. In these days, there was no statement for the use of FDG-PET for staging and response evaluation in indolent lymphomas due to the lack of consequences. However, it was recommended for clinical trials if the primary endpoint would be CR [48]. The current update from 2014 [50] includes now the use of FDG-PET for staging also for follicular lymphomas to avoid an “under staging” (up staging in 8-41%). The 5-PS score is recommended for interpretation of the results. The inclusion of FDG PET for staging also for follicular lymphoma was also based on the results of the PRIMA trial: A positive FDG-PET in the response evaluation showed to be a highly negative predictive value [7, 51]. Patients, who were PET negative after induction chemotherapy had a significant higher PFS after 42 months than PET positive patients (71% vs. 33%; $p<0.001$). The PET signal was an independent prognostic marker. Similar observation were made in the Italian FOLL05 trial [52]: PET negative patients had a significant superior PFS after 3 years compared to PET positive patients (66% vs. 35%, $p<0.001$). Looking only at the morphologic changes via CT, the prognostic difference between CR and non-CR was much weaker (3-years PFS 63% vs. 51%; $p=0.04$). The prognostic value was highest in case of a negative FDG-PET and a morphological PR in the CT scan [52].

1.2 Rational for the Current Trial Concept

The MIR trial has shown that the radiation volumes could be significantly reduced without compromising the effectiveness of the historical large field irradiation. The toxicity of the combined approach of an anti-CD20 antibody and an *involved field* radiotherapy was much lower than the historical data of large field irradiation. Therefore, the combination of an anti-CD20 antibody with small field irradiation of the involved sites will probably become the new standard in the treatment of early stage nodal follicular lymphoma grade 1 and grade 2.

Low dose radiation therapy

After the reduction of the radiation field, a marked reduction of the radiation dose should be tested prospectively: the combination of an anti-CD20 antibody and low dose radiation therapy (LDRT). Although the FORT trial resulted in an inferiority of LDRT compared to higher dose irradiation, it also showed effectiveness in part of the patients with follicular lymphoma (CR rate 48%).

In the GAZAI trial, the concept of LDRT with 2x2 Gy will for the first time be evaluated prospectively in a homogenous cohort of newly diagnosed, non-pretreated, and strictly examined FL grade 1 / 2 stage I/II patients. All diagnoses will be confirmed by central histological review. Involved-site irradiation will be combined with immunotherapy with an improved anti-CD20 antibody (Gazyvaro) with the aim to control occult systemic disease and prevent distant relapse. Additionally, there will be a precisely defined salvage option for those patients who do not achieve CR after the combined LDRT and antibody treatment. These patients will receive additional radiation therapy with 36 Gy (5x2 Gy/week) adding up to a total of 40 Gy which was the established dose of the MIR trial. This salvage dose is, therefore, response adapted for those patients who do not sufficiently respond to LDRT.

Role of FDG-PET

The routine staging diagnostic procedures using CT/MRI will be augmented by a FDG-PET/CT examination in the GAZAI trial. The total radiation dose will then be defined response adapted by a second FDG-PET.

Since the sensitivity and specificity of FDG-PET is higher compared to sole morphological imaging, all patients will get an initial FDG-PET/CT. This has to be performed at least 5 weeks after a surgical procedure (e.g. lymph node sampling) for minimizing the risk of false positive results.

LDRT alone of the involved lymph nodes regions results in responses shown in Table 2. However, LDRT alone leads less often to a CR than a full dose radiation therapy in these patients (see Table 1 and 2 and the FORT trial).

Since a negative FDG-PET is an independent predictive factor regarding PFS [7, 51], the decision for or against salvage radiation will be done based on a restaging FDG-PET/CT (FDG-PET positive: salvage RT of additional 18 x 2 Gy; FDG-PET negative: no salvage RT).

Since only patients with initially PET positive lymph nodes are valuable for the evaluation of the primary endpoint (metabolic CR rate after LDRT and anti-CD20 antibody), the FDG-PET in week 18 can be omitted in case of FDG-PET negativity at the initial staging (e.g. all macroscopic pathological lymph nodes were surgically removed).

Obitunuzumab (Gazyvaro)

The additional use of Rituximab in the radiation treatment of the early stages of nodular follicular lymphomas has been successfully proven in the MIR trial. However, Rituximab is a chimeric antibody and known to induce allergic reactions. One patient in the MIR trial could not complete the treatment due to an allergic reaction to Rituximab. It will, therefore, be useful to use a third generation humanized antibody instead.

Obinutuzumab is a humanized anti-CD20 antibody, which has already been approved for the treatment of CLL: Obinutuzumab showed superior results compared to Rituximab in an interim analysis of a prospective randomized trial [53, 54].

In follicular lymphoma, Obinutuzumab showed improved response rates in phase II trials if compared to Rituximab [55, 56]. A prospective randomized trial comparing Rituximab and Obinutuzumab in combination with a chemotherapy has completed recruitment. Just recently, primary results of the GADOLIN trial for Rituximab in refractory or fast recurrent follicular lymphoma resulted in the EMA registration of Gazyvaro in combination with Bendamustin chemotherapy. The combination of Bendamustin with Gazyvaro resulted in a 52% risk reduction for recurrence or death compared to Bendamustin alone [8, 57].

Based on these results, it can be assumed that the use of Obinutuzumab may induce a higher CR rate compared to the Rituximab data of the MIR trial. It might be, therefore, an ideal partner for LDRT and should reduce the portion of patients who need salvage RT. Additionally, QLQ data and MRD data can be used for historical comparison with the use of Rituximab in the MIR trial.

1.3 Benefit-/ Risk-Assessment

The standard treatment for the early stages of follicular lymphoma is under permanent discussion. Treatment recommendations range from watch & wait (with deferement of treatment until progression) to large field irradiations. The combination of *involved-field* irradiation and use of MabThera becomes more and more popular after the successful completion of the MIR trial. This includes an off-label use of MabThera, which is only accredited in the combination with chemotherapy for the treatment of follicular lymphoma.

The actual trial offers the chance of a substantial reduction of the radiation time (2 instead of 20 fractions in the best case) and the radiation dose (10% of the radiation dose in the best case). In any case, no patient will receive a higher radiation treatment dose compared to the dose of the MIR trial.

In addition to and in comparison with the MIR trial, the patients are treated with a humanized CD20 antibody with less allergic potential, receive only 7 instead of 8 administrations, and a potentially more efficent antibody as shown in CLL.

The use of LDRT has a higher risk of recurrence compared to a higher radiation dose according to the FORT trial. This risk will be minimized by additional salvage radiation up to the ”full dose” in case of a failure to reach a complete remission. The use of FDG-PET/CT strengthens the initial staging and the evaluation of the response. The remaining risk of a late *in-field* recurrence after Obinutuzumab and LDRT has to be balanced against the substantially reduced radiation dose to the patent. In addition, “full dose” radiation therapy is still possible in case of a late recurrence.

1.4 Additional Scientific Project

The members of the pathology panel of the GLSG will conduct the pathological scientific add-on project. Genetic and molecular examinations of the already excised lymphoma specimen will be tested for different subgroups, which might result in the generation of new hypothesis [58, 59]. The genetic and molecular research strictly limited to all aspects of the lymphoma disease. The detection of certain genetic profiles, which might predict the response to LDRT is one of the goals of these studies.

1.5 Committees

The following committees were initiated to control certain aspects during the course of the trial:

1.5.1 Data Monitoring Committee (DMC)

The DMC consists of independent experts in the treatment of malignant lymphomas. The DMC should evaluate the conduct of the trial, the safety, and the achievements of the major endpoints. The duty of the DMC is to secure the ethically correct conduct of the trial and to protect the interests of safety for the patients.
The DMC will meet on a regular basis (GLSG annual meetings). The DMC will give recommendations to the LKP regarding modifications, stopping or continuation of the clinical trial. Those recommendations should be send to the LKP in written form within 2 months after the meeting. The DMC will get the annual DSURs.
The members of the DMC are listed in the protocol.

1.5.2 Steering Committee (SC)

The steering committee is comprised of the coordinating investigator and his supporting co-investigators, clinical experts not directly involved in the clinical trial, and the responsible biometrician. The steering committee is responsible for the scientific integrity of the study protocol, the quality of the study conduct as well as for the quality of the final study report. The Steering committee will decide on the recommendations made by the DMC. Members of the steering committee are listed in the protocol.

2. OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The rate of metabolic CR after low-dose radiotherapy in combination with Gazyvaro (Obinutuzumab) for early stage nodal follicular lymphoma will be assessed. In addition, the feasibility of a response adapted approach using FDG-PET/CT regarding success (PFS, rates of remission, analysis of recurrences) and safety in combination with Gazyvaro will be assessed.

The results will be historically compared to the results of the MIR trial regarding morphologic response in week 7 and the quality of life (secondary endpoints). Additional secondary endpoints are PFS, the site of recurrences in the three subgroups (1. PET negative after initial staging; 2. PET negative in week 18; 3. PET positive in week 18).

2.2 Primary Endpoint

- Metabolic complete response (CR) in week 18 in patients with initially remaining lymphoma judged by FDG-PET/CT

2.3 Secondary Endpoints

- Morphologic CR, PR, SD, PD in week 7, week 18 and month 6 in patients with initially remaining lymphoma judged by CT/MRI
- Historical comparison of the morphologic response with MIR data (using MabThera); The comparison of the CR rate in week 7 will allow for a comparison of the two different CD20 antibodies. Due to the restricted patient numbers no matched pair analysis will be possible
- Progression free survival (PFS) of all treated patients (2 years after individual treatment start)
- Toxicity (NCI-CTC criteria, version 4.03) of all patients
- Relapse rate and pattern of recurrence of all treated patients at all follow-up visits.
- Overall survival (OS) of all treated patients (2 years)
- Quality of life according EORTC QLQ C30 and FACT-Lym questionnaires at inclusion and in week 18, month 12, and 24 (all treated patients)
- MRD response in peripheral blood: initially, week 18, months 6, 12, 18 and 24 (all treated patients). MRD is evaluated by the laboratory of C. Pott (Kiel) using at least the markers: t(14:18) PCR for MBR, 3'mbr, 5'mcr and MCR; clonal IGH rearrangements (FR1-3); clonal IGL rearrangements (IGK and Kappa-KDE)

2.4 Additional Scientific Program

- Genetic and molecular profiling of responders and non-responders (coordinated by W. Klapper, Kiel)

2.5 Extended Follow-up Phase (Register Phase)

The GAZAI trial ends 30 months after the first Gazyvaro infusion for each individual patient. Further follow-up will be performed according to the standards of each participating center. The patients will

be asked to allow the transfer of this follow-up data to the trial center in Heidelberg to enable the collection and evaluation of long-time follow-up (PFS, OS, etc.) of this patient group.

3. TRIAL CONCEPT/ DESIGN

GAZAI is a prospective, open, nationally multi-center phase II trial for evaluation of LDRT in combination with Gazyvaro (Obinutuzumab) in patients with early stage nodal follicular lymphoma grade 1/2. Patients will get a completion of the "full" radiation dose in case of not reaching a sufficient response (metabolic CR *AND* morphologic PR/CR) after LDRT.

4. DURATION OF THE TRIAL AND EARLY STOPPING

4.1 Duration and Time Line

The individual duration for each participant is 30 months. Patients may enter in a succeeding register phase without trial specific appointments or examinations.

Initial therapy phase: 3 months

Week 1-4 and week 8: 1 x weekly Gazyvaro (1000mg flat dose)

Week 9: Radiation therapy: 2x2 Gy *involved-site*

Week 12, 16: 1x weekly Gazyvaro (1000mg flat dose)

Week 18: Re-Staging (if applicable)

Week 20-23: Radiation therapy 18 x 2 Gy *involved-site* (if applicable)

Follow-up Phase: Month 6 – month 30 months (every 6 months)

The trial (FPI – LPO) will last approximately 5.5 years. The duration of patient recruitment is estimated with 3.5 years and starts in Q4 2017.

Length of the clinical phase:	5.5 years (66 months)
Start of trial preparation:	Q1 2015
FPI (First Patient In):	Q4 2017
LPI (Last Patient In):	Q1 2021
LPO (Last Patient Out):	Q3 2023
DBL (Data Base Lock):	Q1 2024
Completion of the statistical analysis:	Q2 2024
Completion of the trial report:	Q3 2024

4.2 Early Stopping of the Trial or Early Stopping of a Trial Site

The trial can be stopped by the LKP if the DMC detects an unexpected accumulation of side effects (each grade 5, 2 succeeding grade 4 or 3 succeeding grade 3 CTC side effects), has new information about the effect-risk ratio of the investigated therapy or the used methods of examination. The trial can also be stopped by the LKP if recruitment is below the expectations and cannot be improved.

All investigators have to be informed immediately about a stopping or a permanent ending of the trial. The participating sites must accept the decision.

All study material has to be returned to the LKP in case of early stopping of the trial.

A participating site can also be closed early by the LKP if the site does not act according to ICH-GCP or according to the trial protocol or the recruitment or the quality of the data is below the expectations.

If the DMC suggests an interruption or an ending of the trial due to SAE evaluations or other reasons, the ethical board and the authorities (BOB and sate authority) have to be informed. The Ethical Board and the authorities can also decide about an interruption or an ending of the trial.

5. PARTICIPANTS

5.1 Number of Participants

As described in the chapter Sample Size Calculation, a maximum of 93 patients will be included in the trial.

The recruitment will be stopped, if (whatever occurs first)

- 79 patients will have a FDG-PET/CT confirmed stage I/II follicular lymphoma and a trial specific therapy has been initiated or
- 55 patients had a second restaging FDG-PET/CT in week 18 or
- 93 patients were included

Recruitment and treatment of the participating patients will be performed in 15 locations/30 sites (each location consists of a radiation oncology site and a hemato-oncology site).

The sites should have experience in the treatment of early stage follicular lymphoma (min. 5 patients / year). The sites should have the infrastructure for execution and documentation of a clinical trial according the AMG, Röntgenverordnung and Strahlenschutzverordnung. There must be the possibility to conduct a FDG-PET/CT.

Each location should include 6-7 patients. All sites, which successfully recruited and completely documented the therapy and follow-up of at least 4 patients will be considered for authorship in the final publication.

5.2 Common Criteria for Patient Selection

Patients (≥18 yrs) with histologically proven and centrally histologically reviewed nodal follicular lymphoma grade 1 or grade 2 in the clinical stage I or II (Ann Arbor classification) should be included. The biopsy must be performed within the last 6 months and the complete staging must be within the last 4 months. A fine needle biopsy is not sufficient for a qualified diagnosis. The diagnosis must be centrally verified by one of the reference pathologists of the GLSG.

Gender

According to the MIR data, no gender specific effects regarding the efficacy or the safety are anticipated. It is expected that the distribution of gender in the trial mirrors the natural distribution of the disease.

5.3 Inclusion Criteria

- Centrally reviewed CD20-positive follicular lymphoma grade 1/2 based on WHO classification (2008)
- Untreated (radiation-, chemo- or immunotherapy) nodal lymphoma (including involvement of Waldeyer´s ring)
- Age: ≥18 years
- ECOG: 0-2

- Stage: clinical stage I or II (Ann Arbor classification)
- Risk profile: Largest diameter of the lymphoma ≤ 7 cm (sectional images)
- Written informed consent and willingness to cooperate during the course of the trial
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows: Hemoglobin ≥ 9.0 g/dL; absolute neutrophil count ≥ 1.5 × 10^9/L, Platelet count ≥ 75 × 10^9/L
- Adequate bone marrow capacity: ANC ≥ 1.5 x 10^3/ml, thrombocytes ≥ 100000 x 10^3/ml, hemoglobin ≥ 10 g/dL
- Capability to understand the intention and the consequences of the clinical trial
- Adequate contraception for men and women of child-bearing age during therapy and 18 months thereafter
- Patients with non-active hepatitis B infection (HBsAg neg/HBcAB pos/HBV DNA neg) under 1-year prophylactic anti-viral therapy (e.g. Entecavir®) possible (see also 5.6. Prior and Concomitant Disease)

5.4 Exclusion Criteria

- Extra nodal manifestation
- Secondary cancer in the patient's medical history (exclusion: basalioma, spinalioma, melanoma in situ, bladder cancer T1a, non-metastasized solid tumor in constant remission, which was diagnosed >3 years ago
- Concomitant diseases: congenital or acquired immune-deficiency syndromes, active infections including viral hepatitis (serology positive for HBsAg or HBcAb in combination positive HBV DNA), uncontrolled concomitant diseases including significant cardiovascular or pulmonary disease (see also 5.6. Prior and Concomitant Disease)
- Severe psychiatric disease
- Pregnancy / lactation
- Known hypersensitivity against Gazyvaro (Obinutuzumab) or drugs with similar chemical structure or any other additive of the pharmaceutical formula of the study drug
- Participation in another interventional trial or follow-up period of a competing trial which can influence the results of this current trial
- Creatinine > 1.5 times the upper limit of normal (ULN) (unless creatinine clearance normal), or calculated creatinine clearance < 40 mL/min
- AST or ALT > 2.5 × ULN
- Total bilirubin ≥ 1.5 × ULN
- INR > 1.5 × ULN
- PTT or aPTT > 1.5 × the ULN

No patient must be included more than once.

5.5 Criteria of Withdrawal

5.5.1 Withdrawal of patients from treatment

Any patient can withdraw from the treatment at any time without personal disadvantages and without having to give a reason. Patients who discontinue participation in the clinical study on their own or patients who are withdrawn by the investigator, for reasons other than disease progression (i.e. in case of AEs, protocol violations, …), will be defined as premature withdrawals. Premature withdrawals will not be replaced.

The investigator can also discontinue the study after considering the risk-to-benefit ratio, if he/she no longer considers the further treatment of the patient according to study protocol justifiable. The date of and the primary reason for the withdrawal, as well as the observations available at the time of withdrawal are to be documented on the CRF. Reasons leading to the withdrawal of a patient can include the following (**one primary reason must be determined**):

- **Lack of efficacy** of the study medication, e.g.
  - Progress of study disease compared to baseline
  - Need for a prohibited concomitant medication for the treatment of study disease
- **Intolerable adverse events**
- **Lack of patient's cooperation**, e.g.
  - Patient's request to withdraw
  - Lack of compliance, patient fails to attend the interim visits as agreed
  - Existing or intended pregnancy, lactation
- **Other reasons** (noting reason), e.g.
  - Other diagnosis than study disease
  - Did not meet major in-/exclusion criteria (coming to light after inclusion)

In all patients who finish the study prematurely, a withdrawal examination at least with respect to the primary endpoint should be carried out. The patient must be asked to consent to this last examination. The withdrawal examination must be documented in the CRF.

In case of a drop-out, all ongoing AEs or SAEs should be monitored until there are no more signs or symptoms or until the participant shows a stable condition.

5.5.2 Definition of drop-outs

Term	**Definition**
Drop-out, study	Participation terminated completely, including follow-up Possible reasons: • Patient withdraws consent: **Withdrawal** • Patient moved/cannot be contacted • Follow-up-interventions cannot be performed due to medical reasons • Non-compliance of patient Drop-out after completion of study intervention: **Lost to follow-up** FU-CRF-forms need to be marked as invalid. Final examination will be performed, if patient agrees. Study-Completion/ Withdrawal-form will be completed.
Drop-out, study intervention	Termination of study intervention, follow-up as per protocol.
Screening-failure	Exclusion criteria given prior to screening / enrolment: Patient will be recorded at screening list, but will not be provided with a patient number. (Depending on sponsor a screening CRF may have to be completed)
Protocol deviation	Drop-out to study and drop-out to study intervention are both protocol deviations. It needs to be predefined, how to manage each type of protocol deviation. Major deviations:

	If exclusion criteria become evident after enrolment, and safety of the participant is affected, or if the diagnosis does not any more relate to the indication listed in the protocol affecting the benefit/risk negatively, the participant has to be excluded from study intervention. FU-examinations may still be performed. Minor deviations: Other protocol deviations (errors in timing of visits/ missing samples/ missing examinations) do not result in exclusion

5.5.3 Replacement of participants

Drop-outs will not be replaced.

5.6 Prior and Concomitant Diseases

Relevant additional diseases present at the time of informed consent are regarded as concomitant diseases and will be documented on the appropriate pages of the case report form (CRF). Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities, which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.7 Prior and Concomitant Medication

The treatment of accompanying illnesses not subject to the exclusion criteria is permissible if this is not expected to have any effect on the outcome measures used in this study and to interfere with the trial medication.

If concomitant drugs are administered, these must be recorded in the patient file and in the CRF.

All patients must get a Hepatitis B testing before treatment with Gazyvaro. At least the HBsAg status and the HBcAb status should be assessed and can be added by other markers according to the local recommendations. In case of HBsAg negative/HBcAb positive status, also serology for HBV DNA has to be done. Patients suffering from an active Hepatitis B infection (all HBsAg positive and all HBcAb positive/HBV-DNA positive) must not be treated with Gazyvaro and have to be excluded.

Patients with HBcAb positive / HBV DNA negative status should be referred to a hepatologist or gastroenterologist before start of treatment and should be monitored and managed following local standards to prevent hepatitis reactivation. It is recommended to do a 1-year prophylaxis with antiretroviral medication (e.g. Entecavir®). If there is no chance of prophylaxis, the patient must be excluded.

6. STUDY MEDICATION

6.1 General Information

Roche Pharma AG will provide the quantity of trial medication required for the clinical trial. The medication provided must be used only in the context of this clinical trial. Careful records will be kept of the trial medication supplied to the centers and distributed to the patients. At the end of the study, all unused medication will be returned to manufacturer. If deficiencies of the trial medication are noticed, the monitor, the project manager and the LKP must be informed immediately.

The order and delivery of the mediation includes the local pharmacy of each site. The order fax for each patient will be faxed by the site to the study trial center.

6.2 Characteristics of the Trial Medication

Obinutuzumab (also known as RO5072759, GA101, GAZYVA®, GAZYVARO™) is a humanized glycoengineered type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high-affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction.

Proprietary name:	GAZYVARO®
International Nonproprietary Name (INN):	Obinutuzumab
ATC code, if officially registered:	L01XC15
Manufacturer:	Roche Pharma AG
Pharmaceutical formulation:	Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and HPW.
Mode of administration:	iv infusion
Batch no.:	
Storage instructions:	Store in a refrigerator (2 °C-8 °C). Do not freeze. Keep the vial in the outer carton in order to protect from light. From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.3 Therapeutic Effects of Gazyvaro

(Cited from IB, September 2014)

Non-clinical in vitro studies show that Obinutuzumab mediates superior induction of direct cell death and effector cell-mediated ADCC and ADCP on a panel of NHL cell lines as compared to the type I CD20 antibodies rituximab and Ofatumumab. Its potency to mediate CDC is significantly reduced as compared to these two antibodies. In ex vivo autologous whole blood B-cell depletion studies with blood from healthy volunteers as well as CLL patients, Obinutuzumab mediated superior B-cell

depletion when compared with rituximab.

These properties of Obinutuzumab translated into superior anti-tumor efficacy in direct comparison to Rituximab against a number of aggressive subcutaneous (SC) and disseminated NHL xenograft models. The efficacious and optimal dose range of Obinutuzumab in xenograft models was in the range of 10-30 mg/kg, corresponding to trough levels of 300-600 µg/mL. Treatment with Obinutuzumab resulted in potent and superior depletion of B-cells in the peripheral blood and in lymphoid tissues of hCD20 transgenic mice and cynomolgus monkeys. Vaccination studies in cynomolgus monkeys and human CD20 transgenic mice showed that the enhanced efficacy in terms of B-cell depletion of Obinutuzumab translated into suppression of de novo antibody responses, but left the protective humoral memory responses intact.

The data generated to date imply that Obinutuzumab represents a novel therapeutic CD20 antibody with outstanding efficacy compared to classical Type I and non-ADCC enhanced CD20 antibodies, such as Rituximab and Ofatumumab.

6.4 Known Side Effects

(Cited from ANEX I. package leaflet amended by the GADOLIN data [8])

Important risks identified in clinical investigations with Obinutuzumab were: IRRs (infusion related reactions, TLS (tumor lysis syndrome), thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), prolonged B-cell depletion, infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions and GI perforation.

6.4.1 Infusion-related reactions (IRRs)

The incidence of IRRs was higher in the Gazyvaro plus chlorambucil arm compared to the Rituximab plus chlorambucil arm. The incidence of IRRs was 65% with the infusion of the first 1,000 mg of Gazyvaro (20% of patients experiencing a Grade 3-4 IRR, with no fatal events reported). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg dose and 1% thereafter. No Grade 3-5 IRRs were reported beyond the first 1,000 mg infusions of Cycle 1.

IRRs grade 3-5 occurred in 11% of the patients in the Bendamustin/Obinutuzumab arm compared to 6% in the Bendamustin only arm in the GADOLIN trial [8].

Most frequently reported symptoms associated with an IRR were nausea, chills, hypotension, pyrexia, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, and diarrhea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal edema and atrial fibrillation have also been reported.

6.4.2 Hypersensitivity reactions including anaphylaxis

Anaphylaxis has been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated.

6.4.3 Tumour lysis syndrome (TLS)

Tumour lysis syndrome (TLS) has been reported with Gazyvaro. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count [> 25 x 109/L] and/or renal impairment [CrCl <70 mL/min]) should receive prophylaxis. Prophylaxis should

consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidate (e.g. rasburicase) starting 12-24 hours prior to the infusion of Gazyvaro as per standard practice (see section 4.2). All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

6.4.4 Neutropenia and infections

The incidence of neutropenia was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte-colony stimulating factors. The incidence of infection was 38% in the Gazyvaro plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the Gazyvaro plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyvaro plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported.

Concerning treatment of follicular lymphoma in the GADOLIN trial, the grade 3-5 neutropenia reached 33% in the Bendamustin/Obinutuzumab arm compared to 26% in the Bendamustin only arm. Serious (grade 3-5) infections were reported in 18% or 17%, respectively [8]

6.4.5 Thrombocytopenia

The incidence of thrombocytopenia was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyvaro infusion). The overall incidence of hemorrhagic events was similar in the Gazyvaro treated arm and in the rituximab treated arm. The number of fatal hemorrhagic events was balanced between the treatment arms; however, all of the events in patients treated with Gazyvaro were reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established.

The reported thrombocytopenia (grade 3-5) in the GADOLIN trial was 11% in the arm with Obinutuzumab and 16% in the Bendamustin only arm [8]

6.4.6 Special populations

Elderly

In the pivotal study, 46% (156 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than those patients < 75 years of age.

Renal impairment

In the pivotal study, 27% (90 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those with CrCl ≥50 mL/min.

Additional safety information from clinical studies experience

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with

Gazyvaro. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham viral DNA). Therapy with Gazyvaro should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyvaro. Hepatitis B virus screening should be performed in all patients before initiation of treatment with Gazyvaro. At a minimum this should include hepatitis B surface antigen (HBsAg) status and hepatitis B core antibody (HBcAb) status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease (all HBsAg positive and all HBcAb positive/HBV DNA positive) must not be treated with Gazyvaro. Patients with HBcAb positive/HBV-DNA negative status should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation (e.g. Entecavir®).

Worsening of pre-existing cardiac conditions

Cases of arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro. These events may occur as part of an IRR and can be fatal.

Laboratory abnormalities

Transient elevation in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) has been observed shortly after the first infusion of Gazyvaro.

The most frequently observed identified risk in patients receiving Obinutuzumab was IRRs; these occurred predominantly during the first infusion/first cycle. In patients with CLL as observed in study BO21004, the incidence and severity of infusion related symptoms decreased substantially with subsequent infusions, with most patients having no IRRs during the second and subsequent administrations of Obinutuzumab. In patients with NHL as observed in study GAO4753g, the incidence of IRRs was highest during the first cycle (55.2%), and gradually decreased during subsequent cycles (24.3%, 21.8%, 13.7%, 14.8%, 10.3% during Cycles 2, 3, 4, 5, and 6, respectively). The commonly experienced IRRs are characterized by nausea, fatigue, chills, hypotension, fever, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, dizziness, diarrhea amongst other symptoms. Respiratory and cardiac symptoms, such as bronchospasm, larynx and throat irritation, wheezing, laryngeal edema and atrial fibrillation have also been reported. In the majority of patients, IRRs were mild or moderate and could be managed by the slowing or temporary halting the first infusion but severe IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumor burden (e.g. high peripheral lymphocyte count in CLL [$> 25 \times 10^9$/L]) may be at increased risk of severe IRR.

Risks associated with prolonged B-cell depletion

B-cell depletion by itself is not an adverse outcome in patients with B-cell malignancies. It reflects drug efficacy. However, B-cell depletion could increase the risk of infection, including serious infections, and/or reactivation of latent viral infections. Overall, although Obinutuzumab has a potent and prolonged effect on B-cell depletion; the AEs observed in trials did not suggest any clinically relevant effect. Potentially B-cell depletion can be associated with the risk of PML and Hepatitis B reactivation (which are analyzed and described separately). In addition, immunization with live or attenuated viral vaccines, following Obinutuzumab treatment has not been studied, therefore the vaccination with live vaccines is not recommended during treatment and until B-cell recovery. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Obinutuzumab during pregnancy until the infants' B-cell levels are within normal ranges.

6.5 Dosage and Dosage Schedule

6.5.1 Dosage

The recommended dose of Gazyvaro is 1,000 mg.

6.5.2 Instruction for dilution

Gazyvaro should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

Withdraw 40 mL of concentrate from the vial and dilute in polyvinyl chloride (PVC) or non-PVC polyolefin infusion bags containing 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

After dilution, chemical and physical stability have been demonstrated in sodium chloride 9 mg/mL (0.9%) solution for injection at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C followed by 48 hours (including infusion time) at ≤ 30°C.
From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use other diluents such as glucose (5%) solution.
The bag should be gently inverted to mix the solution in order to avoid excessive foaming. The diluted solution should not be shaken or frozen.
Parenteral medicinal products should be inspected visually for particulates and discoloration prior to administration.

6.5.3 Administration of Gazyvaro

Gazyvaro has to be administered as an intravenous infusion by experienced medical oncologists in a medical institution and with direct access to emergency facility, where emergency situations can be handled immediately. The administration can be done in an out-patient setting, if these preconditions are fulfilled.

After the end of administration patients should be monitored around ≥ 1 hours with remaining catheter to give the possibility for administration of drugs if required. If no reactions occur during this period of observation, the patients may be discharged. Patients with pre-existing cardiac or pulmonary disease

should be carefully monitored during the infusion and afterwards (as described in the Investigator Brochure).

6.5.4 Infusion rate

Standard infusion rate in the absence of infusion reactions/hypersensitivity

Cycle	**Day of treatment**	**Rate of infusion**
Cycle 1	Day 1 (1000 mg)	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
Cycles 2-7	Day 1 (1000 mg)	If there were no infusion related side effects during previous administrations, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below.

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.

- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see above). The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.

- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Table 3)..

Patients must not receive further Gazyvaro infusions if they experience:

- acute life-threatening respiratory symptoms,

- a Grade 4 (i.e. life threatening) IRR or,

- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion). Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

6.5.5 Overdosage

No experience with overdose is available from human clinical studies. In clinical studies with Gazyvaro, doses ranging from 50 mg up to and including 2,000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell depleted.

6.5.6 Time Window for the Gazyvaro Administration

Therapy starts after inclusion of the patient and reconfirmation of stage I/II disease by the initial FDG-PET/CT. Gazyvaro should be administered weekly (every 7 days) for the first 4 weeks (week 1 – week 4). A deviation of +/- 2 days is defined as conform to the protocol. Additional infusions are scheduled for week 8, 12 and 16 (every 28 days). A deviation of +/- 4 days is defined as conform to the protocol.

The LDRT (2x2 Gy) is scheduled for week 9 (after the 5. Gazyvaro infusion in week 8)

6.6 Premedication before Gazyvaro infusion

Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1..	All patients	Intravenous corticosteroid (recommended) [1]	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
Cycle 2-7 ..	All patients without IRR during previous administrations	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
	Patients with IRR grade 1 or 2 during previous administrations	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
	Patients with IRR 3 during previous administrations ***OR*** Patients with lymphocytes > 25 x 10^9 before next administration	Intravenous corticosteroid [1]	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	

[1] *100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be*

used as it has not been effective in reducing rates of IRR.

[2] e.g. *1,000 mg acetaminophen/paracetamol*

[3] e.g. *50 mg diphenhydramine*

6.7 Subject Number

Trial medication must only be used for participants of the clinical trial.

All patients who might be suitable for inclusion and are under screening get a screening number. If the patient fits into the study in respect of the inclusion and exclusion criteria and if the patient agrees to participate in the trial (signed informed consent), the patient receives a running patient number. Patients who were excluded from the trial keep their screening and patient number. New participants always receive a new identification code (ID code).

The ID code will be locally assigned (by the site, which includes the patients (hemato-oncology or radiation oncology) and is composed of the site number and the running patient number with the prefix GAZ (e.g. GAZ-01-03). Each recruiting site keeps their own identification list. The same ID will be used by the treating hemato-oncology site and radiation oncology site.

6.8 Packing and Labeling

The trial medication will be packed by Roche Pharma AG.

One vial of 40 mL concentrate contains 1,000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

The trial medication will be provided free of charge by Roche Pharma AG (Roche Pharma AG, Postfach 1270, D-79630 Grenzach-Wyhlen) and will be delivered to the trial site or the pharmacy of the trial site.

The trial medication will be labeled by Roche Pharma AG according to § 5 of GCP-V.

6.9 Delivery and Drug Accountability

The investigator will confirm correct receipt of the trial medication in writing and ensure that the medication is stored safely and correctly. The trial medication must be carefully stored in accordance with manufacturer's instructions at 2-8 °C and dry at the study sites in a locked area with restricted access, separately from other drugs, and kept out of the reach and sight of children. The investigator will document the distribution and return of the trial medication to the patient with the date, recording the quantity distributed and used on the forms provided for this purpose. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be completely returned to Roche Pharma AG. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

The medication must not be used after the expiry date, which is stated on the carton after EXP. The expiry date refers to the last day of that month.

6.10 Ordering of Gazyvaro

Each new patient will be reported to the trial center in Heidelberg by using the inclusion fax form send together with the order form for study medication. The inclusion fax will be send forward to the trial monitor at the KKS and the data manager at the IMBI.

The information on the inclusion form also includes the anticipated date of the FDG-PET/CT.

- After the FDG-PET/CT, following items should be send by mail to the trial center in Heidelberg:
- Imaging of the staging (CT/MRI) on a CD in DICOM format
- Data of the FDG-PET/CT in DICOM format
- Gazyvaro order form including the patients trial ID and the delivery address

Studiensekretariat
Radioonkologie & Strahlentherapie
z.Hd. Frau Renate Haselmann
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Fax: 06221/56 1979
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All images will be centrally reviewed by the LKP, an experienced radiologist (CT/MRI) and specialist for nuclear medicine (PET).
If the central review confirms an early stage, the order fax will be send forward to Roche Pharma AG and the trial site will be informed. The delivery of all vials necessary for the patient will be carried out directly to the address of the site, which is noted on the order form. The delivery usually lasts 3 days.
The trial center will inform the monitor about the order.

Gazyvaro is labeled as trial medication and must not be given to patients other than within the trial. An early notification and good internal communication within the trial site (pharmacist, physician and investigator) is mandatory for a smooth order.

7 IRRADIATION

The CT for 3D treatment planning is scheduled for week 7 and should be done using appropriate positioning devices (e.g. thermoplastic masks etc.). The response to the first 4 Gazyvaro administrations is also assessed using this CT. The irradiation occurs in week 9 after der fifth Gazyvaro administration (week 8).

7.1 Target volume

A 3D treatment planning is mandatory. The target volume should be assigned as involved site according to the guidelines of the International Lymphoma Radiation Group (ILROG) [60]:

The clinical target volume (CTV) encompasses the original GTV (at study inclusion). Normal structures such as lungs, kidneys, and muscles that were clearly uninvolved, though previously displaced by the GTV, should be excluded from the CTV according to clinical judgment. Potential subclinical involvement should also be considered. Therefore, the CTV should also include at least adjacent lymph nodes in that site and a generous margin dictated by the clinical situation. If there are questions about the delineation of the target volume the trial center in Heidelberg should be contacted.

Although a LDRT with 2x2 Gy will be carried out initially, the treatment plan should be prepared for a dose of 40 Gy in 20 fractions and the usual normal tissue constraints should be accepted for this dose. If a salvage irradiation is necessary after the FDG-PET/CT in week 18, the same irradiation plan should be used.

7.2 LDRT (week 9)

The irradiation in week 9 is a LDRT using 2x2 Gy on two succeeding days (no start on a Friday or before a holiday). The dose delivery should be according ICRU50. The irradiation delivery may include photons, electrons and protons.

7.3 Salvage irradiation (week 20-23)

All patients with PET positive lymphoma before the first Gazyvaro administration (initial FDG-PET/CT), will get an additional FDG-PET/CT in week 18 which should be sent to the trial center in Heidelberg. All of those patients who do not show a morphologic CR/PR or do not have a metabolic CR will get a salvage irradiation starting in week 20.

The target volume is identical to the initial LDRT irradiation in week 9. The dose is 18 x 2 Gy (ICRU 50). The same positioning devices, the same planning CT and the same treatment plan as for the LDRT should be used (see above).

8. METHODS OF DATA COLLECTION / STUDY VISITS

8.1 Initial Staging

The extent of the lymphoma manifestation will be assessed according the Ann-Arbor classification system and using 3D imaging and bone marrow aspiration. A pathological staging is not necessary.

8.1.1 Procedures

Medical history (incl. of B-symptoms)
Current medication
Clinical examination (including palpation of lymph node regions)
Shipping of the biopsy tissue to a reference pathologist of the GLSG
Laboratory testing:
- Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
- Clinical chemistry (sodium, potassium, AST/ALT, total bilirubin, alkaline phosphatase, creatinine)
- LDH
- albumin, immunoglobulins, immunefixation
- $ß_2$ microglobuline
- Peripheral blood (10 ml EDTA) for MRD analysis and STRECK tube (10 ml) for cell-free DNA collection
- Hepatitis- und HIV – serology (not applicable if there are values < 3 months)
- Pregnancy test (serum) for all women with childbearing potential (including tubal ligation)
CT or MRI (</= 4 months), **if necessary:** additional ultrasound
- head&neck*
- thorax*
- abdomen*
- pelvis including inguinal region*

*These regions must be screened using 3D sectional imaging and should also be scanned during the follow-up examinations from months 6 on. Ultrasound can be used additionally, but it cannot replace a CT or MRI since the morphological remission criteria are based on 3D sectional imaging. A FDG-PET/CT of these regions can be used instead of CT or MRI.

Site-specific examinations:

Thyroid testing in case of cervical or supraclavicular lymphoma (TSH, fT3/fT4)
Consultation of a head&neck in case of supra-diaphragmal lymphoma

8.1.2 Risk profile and FLIPI

A risk profile according to the "Follicular lymphoma International Prognostic Index (FLIPI)" [61] and additional potential risk factors should be recorded.

General condition ECOG 0, 1 or 2
Age ≤ 40, 41 - 60, > 60 years
Largest lymphoma < 3 cm or ≥ 3 cm in max. diameter (sectional imaging)
Morphologically macroscopic tumor remaining after surgical intervention for proof of histology
stage I or II
Serum-LDH normal or elevated
Serum-$ß_2$ microglobulin ($ß_2$m) normal or elevated
Hemoglobin ≥ or < 12 g/dl

The actual concomitant medication should be checked at each visit and should be documented in the patient chart and the CRF.

8.1.3 Examinations after inclusion and before start of therapy

FDG-PET/CT incl. central review (not applicable if already done for initial staging (see above))
EORTC QLQ-C30 and FACT-Lym questionnaires

8.1.4 Examinations during therapy (up to week 18)

– **before each Gazyvaro administration:**

Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
Assessment of AEs
Pregnancy test (serum or urine) in premenopausal female patients before Gazyvaro administration in week 1, week 4, week 8, week 12 and week 16. In case of a positive urine pregnancy test, dosing will be delayed, until patient's status is determined by a serum pregnancy test

– **week 7:**

CT imaging of the involved lymphoma region for radiation planning and response assessment
Palpation of the lymphatic region
Laboratory testing:
- Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
- clinical chemistry (sodium, potassium, AST/ALT, total bilirubin, alkaline phosphatase, creatinine)

- LDH
Assessment of AEs

– **week 18**

Medical history
Clinical examination (including palpation of lymph node regions, skin reaction in the radiation area)
ECOG-Performance status
Laboratory testing:
- Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
- clinical chemistry (sodium, potassium, AST/ALT, total bilirubin, alkaline phosphatase, creatinine)
- LDH
EORTC QLQ-C30, FACT-Lym questionnaires
In dependence of the initial FDG-PET/CT before the first Gazyvaro administration: • **FDG-PET/CT** of the initially involved region for response evaluation (central review) for patients with initially PET positive remaining lymphoma • **Contrast enhanced CT/MRI** for patients with initially PET negative remaining lymphoma • **No imaging** for patients without initially remaining macroscopic lymphoma after surgical intervention for proof of histology
Peripheral blood (10 ml EDTA) for MRD analysis and STRECK tube (10 ml) for cell-free DNA collection
Assessment of AEs

8.1.5 Follow-up examinations month 6, 12, 18, 24

Medical history (incl. assessment of B-symptoms)
Clinical examination (including palpation of lymph node regions, skin reaction in the radiation area)
ECOG-Performance status
Laboratory testing:
- Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
- Clinical chemistry (sodium, potassium, calcium, AST/ALT, total bilirubin, alkaline phosphatase, creatinine)
- LDH
- Total protein, protein-electrophoresis
CT or MRI (</= 4 months), **if necessary:** additional ultrasound
- head&neck
- thorax
- abdomen
- pelvis including inguinal region
Peripheral blood (10 ml EDTA) for MRD analysis and STRECK tube (10 ml) for cell-free DNA collection
EORTC QLQ-C30 und FACT –Lym questionnaires **(only month 12, 24)**
Assessment of AEs

Independent of the follow-up examinations: Pregnancy test (serum or urine) in all women with childbearing potential (including tubal ligation) if menstruation is overdue more than 2 weeks up to month 24

8.1.6 Final examination (month 30)

Medical history (incl. assessment of B-symptoms)
Clinical examination (including palpation of lymph node regions, skin reaction in the radiation area)
ECOG-Performance status
Laboratory testing:
- Differential blood cell count (hemoglobin, leucocytes, thrombocytes, neutrophils, lymphocytes)
- Clinical chemistry (sodium, potassium, calcium, AST/ALT, total bilirubin, alkaline phosphatase, creatinine)
- LDH
- Total protein, protein-electrophoresis
- ß2 microglobuline
CT or MRI (</= 4 months), **if necessary:** additional ultrasound
- head&neck
- thorax
- abdomen
- pelvis including inguinal region
Site specific examinations: Thyroid testing in case of cervical or supraclavicular lymphoma (TSH, fT3/fT4)
Assessment of AEs

8.1.7 MRD analysis

10 ml EDTA-blood and 10 ml STRECK tube for cell-free DNA collection (STRECK tubes will be provided by the Laboratory of Prof. Pott in Kiel).

Time points:

- Before the first administration of Gazyvaro
- Week 18
- Month 6 /12 / 18 / 24

All samples will be pseudonymized using the patient ID code and send to the analyzing laboratory in Kiel. The shipment can be performed any time using the regular mail.

Hämatologie Labor Kiel

Medizinischen Klinik II

Universitätsklinikum Schleswig-Holstein, Campus Kiel

Langer Segen 8-10

24105 Kiel

phone: 0431/ 500-24981

Sekretariat: 0431/ 500-24970

Fax: 0431/ 500-24974

8.1.8 Genetic and molecular testing of the initial lymph node biopsy (additional scientific program)

Genetic and molecular investigations (e.g. p53 mutations, bcl2 transformation, genetic profiling testing for mutations on several sites) in relation to lymphoma disease are planned on the initial biopsy specimen as additional scientific program. These investigations are planned and coordinated by the pathology panel of the GLSG. All investigations should serve the increase of knowledge about origin, expansion and therapy of malignant lymphomas. There might be new scientific questions/methods concerning the aim of the study, which cannot be addressed today (e.g. knowledge of a new genetic mutation in follicular lymphomas, new measurement tools, which allow a more sensitive evaluation of MRD,…). For this reason, blood and tissue samples should be stored for an unlimited time or until the draw back of the patients consent.

8.2 FDG-PET/CT

The FDG-PET/CT within the trial should be performed according to the recommendations of Juweid et al.[49]

- There should be at least 5 weeks interval after a surgical intervention (e.g. lymph node extirpation)
- No use of „non attenuation PET scans“
- FDG dosage 3.5 – 8 MBq/kg body weight with a minimal dose of 185 MBq
- 4 hours fasting before FDG injection
- Glucose level < 200 mg/dL at the time of injection
- Primary staging FDG-PET/CT: Whole body scanning 60 +/- 10 minutes after FDG injection; Week 18: Whole body PET scanning, CT scanning of the initially involved regions
- contrast enhancing agents are not mandatory for the CT imaging
- Oral contrast agent might be used for better differentiation of bowel and other structures

The interpretation of the initial staging PET should be done using visual assessment, with PET/CT images scaled to fixed SUV display and color table [50]

8.3 Efficacy Parameters

8.3.1 Criteria of Remission of the FDG-PET (metabolic remission)

The metabolic remission criteria of the PET scan is according to the revised Cheson criteria of 2014 under the use of the 5-PS score [50, 62].

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

- Score 1: No uptake
- Score 2: Uptake ≤ mediastinum
- Score 3: Uptake ≥ mediastinum but ≤ liver
- Score 4: Uptake moderately higher than liver
- Score 5: Uptake markedly higher than liver and/or new lesions
- Score X: New areas of uptake unlikely to be related to lymphoma

Complete Metabolic Response (CMR)

Score 1 and score 2.

Partial Metabolic Response (PMR)

Score 3, 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size

Metabolic Treatment Failure / Metabolic Progressive Disease (MPD)
An increase in FDG uptake to a score of 5, score 5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma

8.3.2 Criteria of Remission of CT/MRI

The morphologic remission is according to the NCI criteria [63].

Complete Response (CR)

All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes ≥ 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

Complete Response/unconfirmed (CRu)

A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

Partial Response (PR)

≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Stable Disease (SD)

Stable disease is defined as less than a PR but is not progressive disease

Progressive Disease (PD)

- ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
- Appearance of any new lesion during or at the end of therapy.

8.4 Parameters of safety

Clinical examination and medical history, blood values at the above mentioned visits. The classification of side effects is according to the NCI-CTC criteria version 4.03

8.5 Additional Parameters

The quality of life is assessed on a longitudinal time line using the EORTC QLQ-C30 questionnaire and the FACT-Lym questionnaire.

9. FOLLOW-UP AND POSSIBLE TREATMENTS AFTER END OF TRIAL

Follow-up procedures and possible further treatments after the trial (early ending or after month 30) should be performed according to local standard procedures at each site. The results of this extended follow-up should be collected with the consent of the patient as in a register. It is the goal to analyze these long time follow-up data retrospectively in the future.

In case of a recurrence at the primary involved site after 2x2 Gy, it should be respected, that a "full dose" up to the target dose of the MIR trial (40 Gy) should still be possible.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions

- New diagnosis

- Changes of laboratory parameters

The criteria that should be considered when determining whether an abnormal test finding should be reported as adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result require diagnostic testing or medical/surgical intervention, and/or
- Test result lead to a change in trial dosing outside the protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered clinically relevant at the discretion of the investigator or sponsor

- Intercurrent diseases and accidents

- Worsening of medical conditions/ diseases existing before clinical trial start

- Recurrence of disease

- Increase of frequency or intensity of episodic diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial. In the latter case the condition should be reported as medical history.

AEs are classified as "non-serious" or "serious".

10.1.2 Serious Adverse Event, SAE

A serious adverse event (SAE) is an AE that regardless of the dosage of the IMP (GAZYVARO) or by irradiation:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires hospitalisation or prolongation of existing hospitalisation*
- Results in persistent or significant disability/ incapacity**
- Is a congenital anomaly/ birth defect or
- Is otherwise medically relevant

* Hospitalisation for performing protocol-required procedures or administration of study treatment is not classified as an SAE. Hospitalisations for disease-related procedures (surgery, imaging, laboratory tests) or any procedures planned before entry into the study are not considered SAEs. Hospitalisations for social reasons in the absence of an adverse event are not classified as SAEs either.

** Persistent or significant disability or incapacity means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g. paresis, diabetes, cardiac arrhythmia) fulfils this criterion.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations - such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse).

Progression of the malignancy under treatment needs not to be reported as an adverse event.

10.1.3 Serious Adverse Reaction, SAR

SAEs that potentially may be attributed to the investigational medicinal product (IMP; Gazyvaro) are to be classified as Serious Adverse Reactions (SARs). This terminology is also used in the context of side effects due to irradiation.

10.1.4 Expectedness

An ‘unexpected’ adverse reaction is one the nature or severity of which is not consistent with the applicable product information, the Investigator’s Brochure (IB). Furthermore, reports, which add significant information on specificity or severity of a known adverse reaction constitute ‘unexpected’ events.

10.1.5 Suspected Unexpected Serious Adverse Reaction, SUSAR

SAEs that are both ‘suspected’, i.e., possibly related to the study drug (investigational medicinal product (IMP)) and ‘unexpected’, i.e., the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor, classifies the SAE as 'suspected' and the SAE is unexpected it will be categorised as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent authority and to all participating investigators

10.1.6 AEs of special interest

The following AEs of special interest (AESI) will be reported as AE and SAE, considered an "Important Medical Event" even if no other criteria for seriousness apply, on the appropriate pages of the CRF and in the source documents:

- Non-drug specific Drug induced liver injury (DILI)

  The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the upper limits of normal (ULN) of ALT or AST than the (nonhepatotoxic) control agent or placebo. Among subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3 x ULN, some subjects also show elevation of serum total bilirubin (TBL) to ≥ 2 x ULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity < 2 x ULN). No other reason can be found to explain the combination of increased AT and serum TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.)

- Progressive multifocal leucoencephalophathy (PML)

  PML is a disease that is always serious, and that is fatal or severely debilitatingin the large majority of patients. There is a potential risk that B-cell depletion may have an impact on the incidence and severity of infections. Rituximab has been associated with serious viral infections including PML. As obinutuzumab is more potent in terms of B-cell depletion than rituximab, there may be an increased risk of infections with obinutuzumab compared to rituximab. PML occurs almost exclusively in immunocompromised patients with deficits in the humoral or cellular immune response or both. PML has been observed most frequently in subjects with hematological malignancies (e.g. NHL and CLL) as well as subjects with liver transplants and autoimmune disease (e.g. SLE) [66].

- Suspected transmission of an infectious agent (STIAMP)

The definition of STIAMP is any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. As in the case of suspected adverse reactions and adverse reactions, the terms suspected transmission and transmission are considered synonymous. Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent.

- Tumour-lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a well-known constellation of metabolic abnormalities resulting from spontaneous or treatment-related tumor necrosis or fulminant apoptosis. The metabolic abnormalities include: hyperkalemia, hyperuricemia and hyperphosphatemia with secondary hypocalcaemia with risk of renal failure. TLS has been reported in patients receiving anti-CD20 antibody therapy plus chemotherapy.

The presence of known risk factors such as bulky disease, preexisting (moderate) renal insufficiency, high ALC and high uric acid levels (> 8 mg/dL) prior to therapy are known to increase the likelihood of TLS. Early identification of patients at risk and the prevention of TLS development with the initiation of preventive measures, as well as the careful monitoring for early signs of laboratory TLS and the prompt initiation of supportive care are critical to prevent potentially life-threatening metabolic derangements [64].

All AESIs will be entered into the pharmacovigilance database. However, if none of the 'seriousness' criteria applies, the AESIs are not to be handled as serious adverse events. Hence, even if they are 'unexpected' and potentially related to the IMP, they will not undergo expedited reporting.

10.1.7 Grading of AEs

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale defined in the CTCAE v4.03:

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life threatening or causing disablement
Grade 5: Death

The grading of all AEs listed in the CTCAE v4.03 will be based on the information contained therein. The grading of all other AEs, i.e., those, which are not listed in the CTCAE v4.03 will be performed by a responsible investigator, based on definitions given above.

Clarification of the difference in meaning between "serious" and "severe":

The terms "serious" and "severe" are not synonymous. The term 'severe' should be used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as "serious", which is based on the existence of one of the above mentioned seriousness criteria.

If the intensity of AEs worsened or if there are different CTC-grades during the course of trial, the highest intensity should be documented generally. If applicable, dependent on the AE, one AE for each intensity level should be recorded.

In case of lab parameters of CTC-grade 4 but without any clinical symptoms, it should be reconsidered whether the event is classified as serious. If so, the SAE reporting to the KKS Heidelberg is additionally necessary (see section 9.3). Anyway, if one of the seriousness criteria, e.g. hospitalisation required or life-threatening condition, applies, the SAE reporting is essential.

10.1.8 Relationship and outcome of AEs

The investigator and second assessor will evaluate each AE that occurred after administration of Gazyvaro regarding the **relationship** with the administration of Gazyvaro and in this clinical trial also to the radiation therapy:

Definitely related:	There is a reasonable possibility that the event may have been caused by the IMP/radiation therapy. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.
Probable:	An AE that has a reasonable possibility that the event is likely to have been caused by the IMP/radiation therapy. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.
Possible:	An AE that has a reasonable possibility that the event may have been caused by the IMP/radiation therapy. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
Unlikely:	Only a remote connection exists between the IMP/radiation therapy and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
Not related:	An AE that does not follow a reasonable temporal sequence related to the IMP/radiation therapy and is likely to have been produced by the subject's clinical state, other modes of therapy or other known aetiology.
Not assessable:	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

All subjects who have reportable AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the **outcome**. The clinical course of the AE will be followed up until resolution or normalisation of changed laboratory parameters or until it has changed to a stable condition. This also holds for on-going AEs/SAEs of withdrawn subjects.

The outcome of an AE at the time of the last observation will be classified as:

Recovered / resolved:	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.
Recovering / resolving:	The intensity of signs and symptoms has been diminishing and / or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/not resolved:	Signs and symptoms of an AE are mostly unchanged or worsened at the time of the last interrogation.
Recovered / resolved with sequel:	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE.
Fatal:	Resulting in death. If there is more than one adverse event only the adverse event leading to death (possibly related) will be characterised as 'fatal'.

Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

The action taken with the IMP/radiation therapy will be assigned to one of the following categories:

Dose not changed:	No change in the dose of the IMP/radiation therapy.
Dose reduced:	Reduction in the dose of the IMP/radiation therapy.
Dose increased:	Increase in the dose of the IMP/radiation therapy.
Drug withdrawn:	Discontinuation of the IMP/radiation therapy.
Unknown:	The information is unknown or implausible and it cannot be supplemented or verified
Not applicable:	The question is implausible (e.g. the subject is dead).

The term “countermeasures” refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. Following categories will be used to categorise the countermeasures to adverse events:

None:	No action taken.
Drug treatment:	Newly prescribed medication or change in dose of a medication.
Others:	Other countermeasures, e.g. an operative procedure.

10.2 Period of Observation and Documentation

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the Gazyvaro (before the first administration of the Gazyvaro: medical history) and ends with the last study visit, i.e. 30 month after the last take of study medication. AEs will be documented in the patient file and in the CRF. All subjects who present AEs, whether considered associated with the use of the trial medication/radiation therapy or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals too.

The end date of the SAE is defined typically the same as for AEs. The end date of the SAE must not be later than the end date of the corresponding AE.

AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

All SAEs and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report. All SAEs will be documented in the "Serious Adverse Event" form.

10.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the responsible Safety Officer at the KKS Heidelberg **within 24 hours** after the SAE becomes known using the "Serious Adverse Event" form. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication/radiation therapy.

The reporting will be performed by faxing a completed ‘SAE Form’ to the KKS Heidelberg, fax number: **06221-56-33725**

The investigator must also inform the site monitor in all cases.

10.4 Expedited Reporting

SUSARs are to be reported to the responsible ethics committee, the competent authority (PEI) and to all participating investigators within defined timelines, i.e. they are subject to an expedited reporting.

All SAEs will be subject to a second assessment by a designated person, who will be independent from the reporting investigator. The designated person for the present trial, referred to as the second assessor is the LKP:

Prof. Dr. K. Herfarth, Radiation Oncology, University Hospital Heidelberg, INF 400, 69120 Heidelberg

Dr. J. Schmier, Internal Medicine V, University Hospital Heidelberg, INF 410, 69120 Heidelberg

The second assessor will fill out a 'Second Assessment Form' for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours, fax-number:

06221 – 56 – 33725

The 'Second Assessment Form' will contain the following information:

I) Assessment of relationship between SAE and IMP/radiation therapy (causality)
II) Assessment of expectedness of SAE (derived from IB)
III) Statement if the benefit/ risk assessment for the trial did change as a result of SAE.

The expedited reporting (to competent authority, responsible ethics committee and investigators) will be carried out by a responsible Safety Officer at KKS Heidelberg. Only SUSARs occurring after administration of Gazyvaro will undergo expedited reporting.

Details concerning the reporting of SUSARs will be described in a separate document "Safety Manual".

10.5 Emergency Treatment

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AE including clinically significant laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

11. STATISTICAL PROCEDURES

11.1 Number of Patients

Due to the descriptive character of the trial, no assessment of any formal statistical hypotheses is performed. The calculation of the number of patients is primarily based on the aspects of practicability and precision of the results. The following calculations are based on the intention-to-treat (ITT) population. Since the strength of the results for the primary endpoint may be weakened due to early drop-outs (as described later), the number of patients needed should be high enough to compensate for potential drop-outs. Primary endpoint is the rate of metabolic CR in week 18 in patients with initially remaining lymphoma judged by FDG-PET/CT. Based on the morphologic CR rate of 37-84% after 2 x 2 Gy in the literature (see Table 2) and in face of a lack of data for metabolic CR after 2x2 Gy, a CR rate of 60% (about the median of CR in Table 2 and approximately the CR rate in week 18 in the MIR

trial (62%)) is assumed. If fifty patients enter the FDG-PET/CT and the observed metabolic CR rate amounts to 60%, the half width of the asymptotic two-sided 95% confidence interval amounts to about ± 13.5%.
Based on the experience of the MIR trial, a general drop-out rate of 10% is assumed, and about 30% of the included patients are expected to have no remaining lymphoma after initial surgery to prove the histology. In addition, we expect an additional drop-out rate of about 15% after the initial FDG-PET due to stage-shifting in a stage III disease based on the Barrington paper about PET staging [45].
These considerations lead to the following calculation:
If 93 patients are being recruited, about 15% will drop out due to a stage-shift to higher stages after FDG-PET (79 patients remaining). Of these 79 patients, about 30% will have no remaining PET-positive lymphoma after initial surgery (according to the experiences in the MIR trial). Therefore, 55 patients would start therapy with the goal of reaching the primary endpoint assessment. Assuming a drop-out rate of 10%, 50 patients will be available for final assessment of the primary endpoint.
The number of n=93 is at the upper limit of the patients to be included. This number of definitively included patients might drop during the trial (e.g. if less patients show a stage-shift or more patients show remaining lymphoma).

11.2 Variables of analysis

Primary endpoint is the metabolic complete response (CR) in week 18 in patients with initially remaining lymphoma judged by FDG-PET/CT.

Secondary endpoints are:

- Morphologic CR, PR, SD, PD in week 7, week 18 and month 6 in patients with initially remaining lymphoma judged by CT/MRI
- Historical comparison of the morphologic response with MIR data (using MabThera); the comparison of the CR rate in week 7 would be a comparison of the two different CD20 antibodies. Based on the patient numbers no matched pair analysis will be possible
- Progression-free survival (PFS) of all treated patients (2 years after individual treatment start)
- Toxicity (NCI-CTC criteria, version 4.03) of all patients
- Relapse rate and pattern of recurrence of all treated patients at all follow-up visits.
- Overall survival (OS) of all treated patients (2 years)
- Quality of life according EORTC QLQ C30 and FACT-Lym questionnaires at inclusion and in week 18, month 12, 24 and 30 (all treated patients)
- MRD response: initially, week 18, months 12 and month 24 (all treated patients). MRD is evaluated by the laboratory of C. Pott (Kiel) using at least the markers: t(14:18) PCR for MBR, 3'mbr, 5'mcr and MCR; clonal IGH rearrangements (FR1-3); clonal IGL rearrangements (IGK and Kappa-KDE)

11.3 Definition of the Trial Populations

All patients, who received at least parts of the treatment defined in this protocol, will be analyzed in the intention-to-treat (ITT) population as well as in the safety population. All patients, who deviated less than 20% from the protocol-defined dose and fulfill all inclusion and exclusion criteria, will be analyzed in the per-protocol (PP) population. Efficacy will be evaluated in the ITT- as well as in the PP population. Toxicity data will be analyzed in safety population.

11.4 Statistical Methods

There will be a descriptive analysis of the data. The rate of metabolic CR in week 18 will be calculated as relative frequency. The related 95% confidence interval will be calculated using the "score method" by Wilson [65]. This method showed excellent performance characteristics as compared to alternative

approaches of constructing confidence intervals for rates [64]. In addition, the rate of metabolic CR will be estimated using the Kaplan-Meier method and the 95% Greenwood confidence interval to take into account a potential influence of censored values. (ITT and PP population)
PFS and OS at 2 years after initiation of the therapy of each patient will be analyzed using the Kaplan-Meier method and the two-sided 95% confidence intervals according to Greenwood. (ITT and PP population).
Remission- and recurrence rates will be calculated as relative frequencies and reported together with the 95% confidence intervals according to Wilson. (ITT and PP population)
Quality of life will be evaluated according to the evaluation guide of the two questionnaires. (ITT and PP population)
Toxicity will be evaluated for frequency and intensity (safety population). Adverse events will be coded by MedDRA (actual version at the time of data base lock). The counts of the events and the counts of patients will be listed in a table. All patients under observation will be taken into account for the calculations of the frequency of recurrences at the respective time.
All statistical procedures will be defined in a statistical analysis plan (SAP), which will be finalized before data base lock. The responsible statistician and the LKP will authorize the SAP.

11.5 Interim Analysis
No interim analysis is planned.

11.6 Definition of Target Variables
Progression-free survival:

a) Calculated from start of therapy up to the time of progression (morphologic or metabolic) or death

b) Calculated from start of therapy up to the time of progression (morphologic or metabolic) or death in patients with initially remaining lymphoma (morphologic or metabolic)

Overall survival:

Calculated from start of therapy up to the time of death

12. DATA MANAGEMENT

12.1 Data Collection
All entries in the CRF must be verifiable by source documents. In advance, exceptions to this rule can be defined by the sponsor. A detailed list will be provided in the Investigator Site File. Regardless, there must be a minimum documentation, which provides information on study participation and includes all medical information necessary for appropriate medical care outside of the clinical trial in the patient record.

In addition, source documents must mention that the patient has been included in an investigational study. Finally, there must be no data that are inconsistent between CRF and source documents.

The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. Any errors should have a single line drawn through them so that the original entry remains legible and the correct data should be entered at the side with the investigator's signature, date and reason for change. Self-explanatory corrections need not to be justified.

The correctness of entries in CRF will be confirmed by dated signature of the responsible investigator. The original CRF will be transferred to the data management in the Institute of Medical Biometry and Informatics (IMBI) Heidelberg; one copy will be remained by the investigator.

12.2 Data Handling

All data will be entered in a database as recorded in the CRF by trained staff of the IMBI. To ensure data quality, a double data entry will be done. The data management will check completeness, validity, and plausibility of data by validation programs, which will generate queries.

All missing data or inconsistencies will be reported back to the centre(s) and have to be clarified by the responsible investigator prior to database lock. If no further corrections are to be made in the database it will be declared locked and used for statistical analysis.

All data management activities will be done according to the current SOPs of the IMBI.

Original files of the CRF will be transferred to the LKP after analysis and completion of the trial report.

12.3 Archiving of Essential Documents

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including subject identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

The sponsor or other owner like investigators of the data shall retain all other documentation pertaining to the trial for at least 10 years according to the §13 of the German GCP-Ordinance. These procedures shall include:

- The protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product used.
- Standard operating procedures
- All written opinions on the protocol and procedures,
- Final report,
- Case report forms (not RDE),
- Audit certificate(s), if available.
- All other relevant documents of the trial master file, according to the ICH-GCP guideline

Any change of data ownership shall be documented. All data shall be made available if requested by relevant authorities.

According to the §28c of the German X-Ray Directive and to the §87 of the German Radiation Protection Directive the informed consent forms including subjects' consent for trial participation, application of x-rays, application of radioactive materials or irradiation and data transmission to the competent authority will be archived for at least 30 years after the trial termination.

The LKP is responsible for archiving of the trial master file (TMF). It will be archived according the SOP for archiving of the University Hospital of Heidelberg.

The investigator will archive all study documents including patient identification list and relevant correspondence in the Investigator Site File (ISF). The ISF, all source documents as well as all other in section 8 of the ‚ICH Consolidated Guideline on GCP' listed documents are to be stored and archived after the regular or early ending of the trial according to the legal regulations.

13. ETHICAL AND LEGAL ASPECTS

13.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by ICH harmonised tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

The regulations of the AMG and GCP regulations as well as the Bundesdatenschutzgesetz (BDSG) will be respected.

13.2 Legal Bases

The study has to be conducted in compliance with the protocol, ICH-GCP and the applicable regulatory requirements

13.2.1 Declaration of Helsinki

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by ICH harmonised tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

13.2.2 Other legal bases

The other legal bases of this clinical trial are as follows:

- ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997
- Directive 2001/20/EC (April 4, 2001)
- Commission Directive 2005/28/EC (April 8, 2005)
- National regulatory requirements/guidelines of the participating countries concerning Clinical Trials [e.g. federal drug law (AMG), GCP ordinance (GCP-Verordnung)]
- Valid version of the Radiation Protection Ordinance / Röntgenverordnung
- General national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG)

The Coordinating Investigator and all investigators will be given an up-to-date investigator's brochure containing full details of the status of the pre-clinical and clinical knowledge of the study medication. As soon as new information is obtained, an updated version will be supplied or an amendment added to the existing investigator's brochure.

13.2.3 Approval and trial protocol amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent authority (PEI).

A written favourable vote of the EC and an (implicit) approval by the competent authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the

decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

The investigator and the KKS Heidelberg will keep a record of all communication with the EC and the regulatory authorities.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met.

All planned substantial changes (see §10, (1) of German GCP-Regulation) will be submitted to EC and the competent authority in writing as protocol amendments. They have to be signed by the sponsor and biometrician and approved by the EC and the competent authority.

An approval by Federal Office for Radiation Protection (Bundesamt für Strahlenschutz) for the investigational use of FDG-PET/CT in this trial is prerequisite for the initiation of the trial.

The use of radiation therapy in this trial has been reviewed by an radiation safety committee of experts of the DEGRO. The radiation treatment is considered as a treatment under the circumstances of "Heilkunde" and not as scientific research as defined by the German Radiation Protection Directive.

13.2.4 Notification of regulatory authorities

In addition to the approval by the competent authority, the clinical trial must also be notified to the competent authority before recruitment of the first patient (according to AMG §67).

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority whereas the notification of the competent authority is the responsibility of the sponsor. Both responsibilities have been delegated to the KKS.

Substantial Amendments, interruption or premature end of the trial need to be reported, too.

13.3 Subject Information and Informed Consent

Before being admitted to the clinical trial, the patient must consent to participate after being fully informed by the investigator or a designated member of the investigating team about the nature, importance, risks and individual consequences of the clinical trial and their right, to terminate the participation at any time.

The patient should also have the opportunity to consult the investigator, or a physician member of the investigating team about the details of the clinical trial. The informed consent to participate in the clinical trial may be withdrawn by the patient verbally in the presence of, or in written form directed to, the investigator or a physician member of the investigating team at any time during the trial. The patient must not entail any disadvantage therefor or be coerced or unduly influenced to continue to participate. Furthermore, the patient is not obligated to disclose reasons for the withdrawal of the consent.

If the patient has a primary physician, the investigator should inform him or her about the patient's participation in the trial, provided the patient agrees hereto.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed by the personally dated signature of the patient and by the personally dated signature of the physician conducting the informed consent discussion.

If the patient is unable to write, oral presentation and explanation of the content of the informed consent form and of the data protection information must take place in the presence of an impartial witness. The witness and the physician conducting the informed consent discussions must also sign and personally date the consent document. The witness must not be in any way dependent on the sponsor of the trial, the trial site or any member of the investigating team (e. g. an employee at the trial site.).

A copy of the signed informed consent document must be given to the subject; the original will be filed by the investigator. The documents must be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

The informed consent for genetic profiling and the extended follow-up according to a patient register will be independent of the consent of participation in the trial.

Informed consent for irradiation and PET

All patients will receive a separate information about the radiation procedure and will give their informed consent to irradiation. This information will specify the risks of the procedure according to the treatment site. The informed consent for the irradiation will be documented on the site specific forms and archived along with the radiation plan and radiation protocol.

The informed consent for the FDG-PET/CT will also be on the site specific forms and should be archived with the patient's documents.

13.4 Data Protection

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law (Bundesdatenschutzgesetz, BDSG).

During the clinical trial, subjects will be identified solely by means of their individual identification code. Trial data stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. Distribution of these data to unauthorised persons has to be prevented strictly. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorised persons (inspectors, clinical monitors, auditors). Authorised persons (inspectors, clinical monitors, auditors) may inspect the subject-related data collected during the trial ensuring the data protection law.

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. Subjects who did not consent to circulate their pseudonymised data will not be included into the trial.

This protocol, the CRFs and other trial-related documents and material must be handled with strict confidentiality and not be disclosed to third parties except with the express prior consent of Sponsor. In particular, it must be ensured that the study medication is kept out of reach of third parties. Staffs of the investigators involved in this study are also bound by this agreement.

13.5 Continuous Information to the Ethics Committee and the Competent Authority

Pursuant to the German Drug Law (AMG) and the GCP Ordinance, the responsible EC, the competent authority and all participating investigators will be informed of all suspected unexpected serious adverse reactions (SUSARs) occurring during the trial. Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on the subjects safety will be submitted once a year – Development Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPO).

13.6 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The insurance was taken out at

HDI Global SE (insurance number: 57 010310 03018)

Any impairment of health, which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

The insurance company has to be informed about all amendments that could affect subjects' safety.

Additional Insurance for irradiation and PET/CT:

Since the radiation therapy is not considered as scientific research (see above), an additional insurance for the radiation is not necessary.

According to §91 of the radiation protection legislation, an insurance for FDG-PET/CT as accompanying diagnostic tool is not necessary, since this is already covered by the insurance for trials under the law of AMG.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor, the investigators, and all involved study personnel agree to conduct this clinical trial in accordance with the ICH Guideline for Good Clinical Practice

14.1 Direct Access to Source Documents According to ICH GCP

According to ICH-GCP the investigator(s)/institution(s) must provide direct access to source data/documents for trial related monitoring, audits and regulatory inspection. Each subject has consented - via written informed consent - to direct access to his/her original medical records for trial-related monitoring, audit and regulatory inspection. Any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data must be clearly identified (see 11.1).

In the absence of either an audit-trail or limited access for the monitor the electronic record of data must be printed out (certified copy). In case of changes a new print-out has to be made.

14.2 Monitoring

Monitoring will be done by on-site visits by a clinical monitor according to SOPs of the KKS. The monitor will review the entries into the CRFs on the basis of source documents. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the

monitor. The monitor will document the visit in a report for the sponsor. The site will be provided with a follow-up letter of the findings and the necessary actions to be taken.

By frequent communications (letters, telephone, fax, e-mail), the site monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

Frequency and details of monitoring will be defined in the monitoring manual.

If there are major findings during monitoring or an audit, the investigational site might be closed by the LKP.

Central quality assurance of imaging

The initial FDG-PET/CT will be sent together with the initial staging imaging in DICOM format (mandatory for PET images, optional for staging images) to the trial center in Heidelberg. Specialists for nuclear medicine, diagnostic and radiation oncology will review it. In patients with PET positive remaining lymphoma, there is a second FDG-PET/CT of the involved region planned in week 18. The DICOM data of this should also be sent to the trial center in Heidelberg and will be reviewed by specialists of nuclear medicine and radiation oncology. It is planned to establish a direct electronic transfer of the data. In case of the necessity of clarification of staging and/or response evaluation, the CT and/or MR images and radiation plans, which were recorded during the treatment phase and the follow-up phase, might also be sent for central review to the trial center in Heidelberg.

14.3 Inspections and Audits

Regulatory authorities and/ or auditors authorised by the sponsor may request access to all source documents, CRFs, and other trial documentation. The investigator who must provide support at all times for these activities must guarantee direct access to these documents.

The investigator will inform the sponsor immediately about a planned inspection.

14.4 Responsibilities of the Investigator

The investigator ensures that all team members are informed adequately about the protocol, all amendments to the protocol, the study procedures und study specific duties and tasks.

The investigator will maintain a list to delegate tasks to the team members.

15. ADMINISTRATIVE AGREEMENTS

15.1 Financing of the Trial

The trial will be co-financed by Roche Pharma AG and the Department of Radiation Oncology of the University of Heidelberg.

15.2 Financial Disclosure

Before the start of the trial, the investigator will disclose any proprietary or financial interests he or she might hold in a funding company, in the investigational product(s) or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

15.3 Reports

Within one year of the completion of the trial, the competent federal authority and the ethics committee will be supplied with a summary of the final report on the clinical trial containing the principle results according to §42 AMG.

15.4 Registration of the Trial

Prior to the beginning of the clinical phase (FPI) the LKP will register the trial at http://www.clinicaltrials.gov. Thus the trial will be given a unique ISRCTN, which is a prerequisite for a publication in a peer-review paper.

15.5 Publication

All information concerning the trial is confidential before publication. The data will be published independent of their results. The LKP will determine the list of authors at the end of data analysis. Each site, which included at least 4 completely documented patients (receiving the protocol defined therapy) will be considered for the list of authors. The order of appearance on the list of authors depends on the count of included and fully documented patients. KKS and IMBI staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors. The LKP will be first or senior author.

Study data published or disclosed to third parties must not contain data that allow the identification of a subject.

A copy of all publications will be sent to the KKS.

16 SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the guidelines of ICH Good Clinical Practices and the applicable legal and regulatory requirements.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

It will be ensured that the first subject is enrolled only after all ethical and regulatory requirements are fulfilled. Written consent from all subjects is received after detailed oral and written information and according to the requirements of local law (AMG). According to GCP-V §7, Section 2 No 15, it will be confirmed that all study participants will be informed on the type of encoding their personal data (pseudo-anonymisation) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the trial. In this context it will be assured (according to GCP-V §7, Section 3 No 15) that all investigational sites comply with the local regulatory requirements for data protection.

According to GCP-V §7, Section 3 No 4 the Sponsor/ Sponsor representative states that it is not planned to include subjects in a relationship of any dependence to the investigator or sponsor.

Via current versions of the clinical trial protocol and the investigator's brochure (IB), it will be ensured that all principal investigators are informed about the pharmacological-toxicologial assessments and results regarding the benefits and risks of the clinical trial.

Date: _____ Signature: _____

Prof. Klaus Herfarth

Function: LKP according §40 AMG and authorized representative of the Sponsors

Signature:

Date: _____ _____

Prof. Meinhard Kieser

Function: Statistician

Datum: _____ Unterschrift: _____

Dr. Sabine Gack

Function: Project manager

17. DECLARATION OF INVESTIGATOR

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enrol the first subject only after all ethical and regulatory requirements are fulfilled. I will obtain written consent for trial participation from all subjects after detailed oral and written information and according to the requirements of local law (AMG). According to GCP-V §7, Section 2 No 15 I declare that all study participants will be informed on the type of encoding their personal data (pseudo-anonymisation) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the trial. In this context I confirm (according to GCP-V §7, Section 3 No 15) that my investigational site complies with all local regulatory requirements for data protection.

Furthermore I declare (according to GCP-V §7, Section 3 No 4 that to the best of my knowledge no subjects in a relationship of any dependence to the investigator or sponsor will be included.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I declare that I am informed about the pharmacological-toxicological assessments and results regarding the benefits and risks of the clinical trial by reading the description in the clinical trial protocol and in the current version of the investigator's brochure (IB). I ensure that all investigators/ relevant staff at my site will be informed of this results and possibly new risks that are forwarded by the sponsor later on (e.g. via new version of the investigator's brochure).

I confirm that every staff will be adequately trained to guaranty compliance to the trial protocol incl. subsequent amendments.

I will retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV and Financial Disclosure (FD) may be submitted to the responsible EC.

As the clinical trial and the results have to be published in a clinical trial register and forwarded to the EC and competent authorities I agree that my name and clinic address will be part of this final trial (summary) report/ public register and are disclosed pursuant to §42b AMG.

Date: _____ Signature: _____

Name (block letters): _____

Function: Investigator

Investigational Site (address): _____

_____

_____

Date: _____ Signature: _____

Name (block letters): _____

Function: Deputy of the Investigator

18. LITERATURE

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