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 $\times$ 10^9/L, Platelet count ≥ 75 $\times$ 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

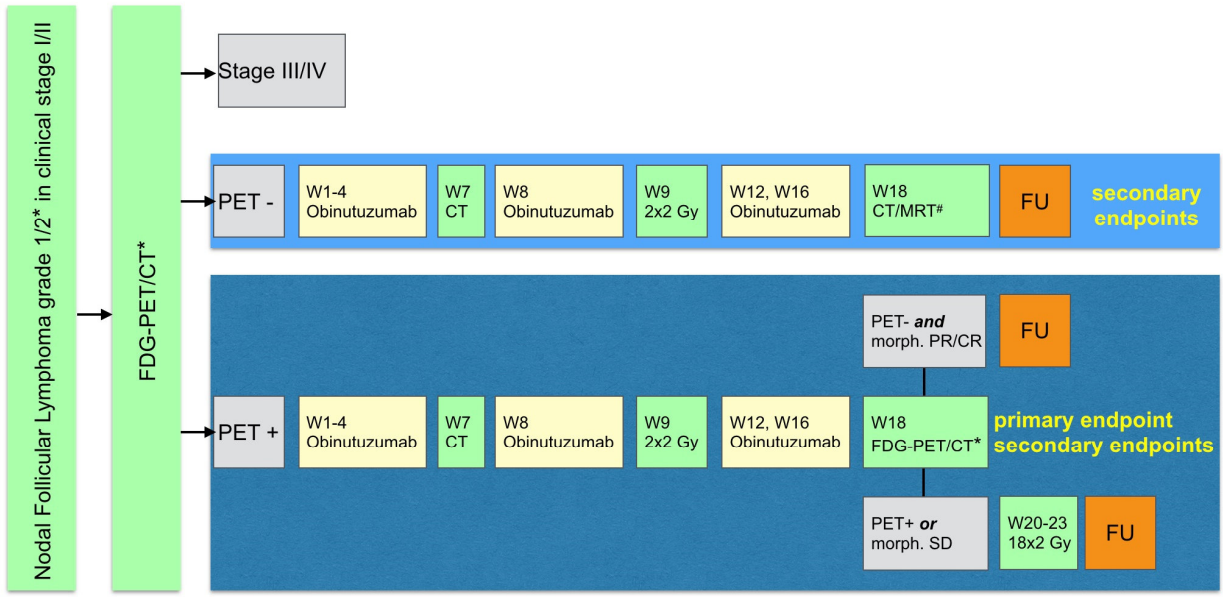
Length of the clinical phase:	5.5 years (66 months)
Start of trial preparation:	Q1 2015
FPI (First Patient In):	Q2 2018
LPI (Last Patient In):	Q4 2021
LPO (Last Patient Out):	Q2 2024
DBL (Data Base Lock):	Q4 2024
Completion of the statistical analysis:	Q1 2025
Completion of the trial report:	Q2 2025

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)



= only in case of initially enlarged PET negative lymph nodes

* = centrally reviewed

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	4d		4d	4d	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]						X[22]	X[22]	X[22]	X[22]	
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[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
INR, PTT or aPTT[23]	R	X																			
Total protein, Albumin, protein electrophoresis[15]; ß2-Microglobulin	R	X																			X

	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	4d		4d	4d	1w	1w				2w	2w	2w	2w	2w
FDG-PET/CT	S	X[13]										X[14]									
CT/MRI[16]	R	X					CT[17]					X[19]					X[24]	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 not 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 cervica l/ supraclavicular 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) with minimum time gap of 5 weeks to a surgical intervention (e.g. lymph node extirpation): 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.
[23] Coagulation parameters (INR; PTT or aPTT): baseline value must not be older than 3 months
[24] Can be droppped if patient showed a metabolic and morphologic CR in week 18