Efficacy of Carfilzomib in combination with Ibrutinib in Waldenström's Macroglobulinemia (CZAR-1)

A MULTICENTER OPEN LABEL PHASE III INTERNATIONAL STUDY

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Protocol Number	V-0.7
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Clinicaltrials.gov No.:	NCT04263480
Substance Identifier (IMP)	Carfilzomib, Ibrutinib
Therapeutic Area	Hematology/Oncology
Sponsor	University Hospital Ulm, Germany; represented by the Chairman of the board
Coordinating Investigator, *Leiter der klinischen Prüfung acc. to German law*	Prof. Dr. Christian Buske University Hospital Ulm Department of Internal Medicine III Albert-Einstein-Allee 23 D-89081 Ulm

5. INVESTIGATOR STATEMENT

Trial Site: [Please enter particulars of the Trial Site]

I confirm that I have read the clinical trial protocol and hereby commit to adhering to all actions and terms as specified in the relevant sections of the clinical, ethical and general paragraphs.

I confirm that I and my colleagues will comply with the local legislation. I further confirm that the clinical trial will be carried out in compliance with the Declaration of Helsinki and ICH-GCP guidelines.

I acknowledge that all confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

Under my supervision I put copies of this protocol and possible updates as well as access to all information regarding the carrying out of this clinical trial at the disposal of my colleagues; in particular I will promptly forward all information from the sponsor in relation to pharmaceutical safety (SUSARs, SmPC and IB updates, if applicable) to my colleagues.

I confirm that I and my colleagues were informed by a responsible scientist about the results and expected risks of the pharmacological and toxicological examination associated with the clinical trial.

I will discuss this protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the trial.

I confirm that I will be responsible for supervising any individual or party to whom I delegate study tasks conducted at the trial site.

Furthermore I commit myself not to commence patient enrolment prior to approval of the competent authorities (CA) and acceptance by the responsible Ethics Committee (EC).

Date	Name (in CAPITALS)	Signature of Investigator

Date	Name (in CAPITALS)	Signature of Deputy Investigator

6. SYNOPSIS AND FLOWCHART

Sponsor	University Hospital Ulm (Germany), represented by the Chairman of the board
Investigational medicinal product	Carfilzomib, Ibrutinib
Protocol title	Efficacy of Carfilzomib in combination with Ibrutinib in Waldenström's Macroglobulinemia (CZAR-1)
Study design	Phase III, randomized, open label
Primary study objective	Complete Remission (CR) or Very Good Partial Remission (VGPR) 12 months after initiation of treatment using the response criteria updated at the Sixth IWWM (Owen et al. 2013) (CR/VGPR).
Background	In Waldenström macroglobulinemia (WM) chemotherapy induces only low CR/VGPR rates and responses of short duration compared to other indolent lymphomas. Thus, innovative approaches are needed which combine excellent activity and tolerability in WM. Chemotherapy-free approaches are highly attractive for this patient group. Based on its high activity in WM and its low toxicity, Ibrutinib was approved for the treatment of WM by the European Medicines Agency (EMA)[1]. However, also Ibrutinib fails to induce CRs and the VGPR rate is 16% in relapsed patients[1]. In addition, activity of Ibrutinib depends on the genotype: compared to $MYD88^{mut}/CXCR4^{WT}$ patients Ibrutinib single agent therapy induces substantially lower response rates in patients with the $MYD88^{mut}/CXCR4^{mut}$ or the $MYD88^{WT}/CXCR4^{WT}$ genotype (major response (at least PR) in 91.7 % compared to 61.9 and 0 %, respectively)[1,2]. Phase II data have indicated that the proteasome inhibitor Carfilzomib is able to overcome the inferior prognosis of Ibrutinib in $MYD88^{mut}/CXCR4^{mut}$ and $MYD88^{WT}/CXCR4^{WT}$ patients, as response rates were high for all genotypes in a phase II study combining Carfilzomib with Rituximab and Dexamethasone[3]. Based on this we hypothesize that addition of Carfilzomib to Ibrutinib will increase the VGPR/CR rate compared to Ibrutinib alone in patients with WM, in particular in patients carrying the CXCR4 mutation. In addition, we hypothesize, that the combination Carfilzomib and Ibrutinib will be also highly active in MYD88 wildtype patients and that this combination will be at least as efficient in treatment naïve patients as in relapsed/refractory patients.
Study Population - Inclusion criteria	Each patient must meet <u>all of the following</u> inclusion criteria to be enrolled in this study: • Proven clinicopathological diagnosis of WM as defined by consensus panel one of the Second International Workshop on WM[4]. Histopathology has to occur before randomization within the last 4 months. In addition, pathological specimens have to be sent to the national pathological reference center prior to randomization for the determination of the mutational status of MYD88 and CYCR4. Immunophenotyping will be performed in each center and saved locally (for more details see protocol section 11.2 and 13.3.2). • De novo and relapsed/refractory WM independent of the genotype • Patients must have <u>at least one</u> of the following criteria to start study treatment as partly defined by "Consensus Panel Two"

	recommendations from the Second International Workshop on Waldenström macroglobulinemia[4]: o Recurrent fever, night sweats, weight loss, fatigue. o Hyperviscosity. o Lymphadenopathy which is either symptomatic or bulky (≥ 5 cm in maximum diameter). o Symptomatic hepatomegaly and/or splenomegaly. o Symptomatic organomegaly and/or organ or tissue infiltration. o Peripheral neuropathy due to WM. o Symptomatic cryoglobulinemia. o Cold agglutinin anemia. o IgM related immune hemolytic anemia and/or thrombocytopenia. o Nephropathy related to WM. o Amyloidosis related to WM. o Hemoglobin ≤ 10 g/dL (patients should not have received red blood cells transfusions for at least 7 days prior to obtaining the screening hemoglobin). o Platelet count < 100 x 10^9/L (caused by BM infiltration of the lymphoma). o Serum monoclonal protein > 5 g/dL, even with no overt clinical symptoms. o IgM serum concentration ≥ 5 g/dL. o and other WM associated relevant symptoms. • World Health Organization (WHO)/ECOG performance status 0 to 2. • Left ventricular ejection fraction ≥ 40% as assessed by transthoracic echocardiogram (TTE). Other criteria: • Age ≥ than 18 years (male and female). • Life expectancy > 3 months. • Baseline platelet count > 50x10^9/L, absolute neutrophil count > 0.75x10^9/L (if not due to BM infiltration by the lymphoma). • Meet the following pre-treatment laboratory criteria at the screening visit conducted within 30 days prior to randomization: o ASAT (SGOT): < 3.0 times the ULN. o ALAT (SGPT): < 3.0 times the ULN. o Total Bilirubin: < 1.5 times the ULN, unless clearly related to the disease (except if due to Gilbert's syndrome). o Serum creatinine: ≤ 2 mg/dl. • Women of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal must agree to use a highly effective method of birth control for the duration of the therapy up to 6 months after end of therapy with Ibrutinib or Carfilzomib (for more details see section 12.6.5 of the protocol). • Men must agree not to father a child for the duration of therapy and 6 months after and must agree to advice a female partner to use a highly effective method of birth control. Males must refrain from sperm donation for at least 6 months after the last dose of Carfilzomib or Ibrutinib. • Voluntary written informed consent in the native language of the patient before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

Study Population - Exclusion criteria	The presence of <u>any of the following</u> will exclude a subject from enrolment: • Previous treatments with following substances are not allowed including into the trial: o Prior exposure to Ibrutinib or BTK inhibitors. o Prior exposure to Carfilzomib. Prior exposure to other proteasome inhibitors are allowed if the patients were not refractory, that is had a remission duration of ≥ 6 months. Prior Plasmapheresis and short - term administration of corticosteroids ≤ 6 weeks administered at a dose equivalent to ≦ 20 mg/day prednisone is also allowed. • Serious medical or psychiatric illness (especially undergoing treatment) likely to interfere with participation in this clinical study. • Uncontrolled bacterial, viral or fungal infection. • Active HIV, HBV or HCV infection. • Known interstitial lung disease. • Central Nervous System involvement by lymphoma. • History of a non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for ≥ 1 year prior to study enrolment visit, other Stage 1 or 2 cancer treated with a curative intent and currently in complete remission, for ≥ 3 years. • Uncontrolled illnesses including, but not limited to: o Uncontrolled diabetes mellitus (as indicated by metabolic derangements and/or severe diabetes mellitus related uncontrolled organ complications). o Chronic symptomatic congestive heart failure (Class NYHA III or IV) or LVEF < 40%. o Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months prior to randomization. o Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia. o Known pericardial disease. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Primary amyloidosis. • Acute diffuse infiltrative pulmonary and pericardial disease. • Recent major surgery (within 30 days prior to randomization). • Chemotherapy with approved or investigational anticancer therapeutic within 21 days prior to randomization. • Glucocorticoid therapy within 14 days prior to randomization that exceeds a cumulative dose of 160 mg of dexamethasone or equivalent dose of other corticosteroids. • Focal radiation therapy within 7 days prior to randomization. Radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to randomization (i.e. prior radiation must have been to less than 30% of the bone marrow).

	• Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs. • Infiltrative pulmonary disease, known pulmonary hypertension. • Active infection within 14 days prior to randomization requiring systemic antibiotics, antiviral (except antiviral therapy directed at hepatitis B) or antifungal agents. Such infection must be fully resolved prior to initiating study treatment. • Pleural effusions requiring thoracentesis within 14 days prior to randomization. • Ascites requiring paracentesis within 14 days prior to randomization • Uncontrolled hypertension, defined as an average systolic blood pressure > 159 mmHg or diastolic > 99 mmHg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology [ESH/ESC] 2013 guidelines). • History of stroke or intracranial haemorrhage within 6 months prior to randomization. • Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal. • Known severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification or at time of screening has an FEV1 of < 50% of predicted normal. • Known cirrhosis. • Autologous stem cell transplant less than 90 days prior to randomization. • Allogeneic stem cell transplant less than 100 days prior to randomization. • Vaccination with live attenuated vaccines within 30 days prior to randomization. • History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or sponsor, if consulted, would pose a risk to subject safely or interfere with the study evaluation, procedures or completion. • Women who are pregnant as well as women who are breast-feeding and do not consent to discontinue breast-feeding. • Participation in another interventional clinical trial within 30 days before randomization in this study.
Study design	The phase III study will consist of an open labeled, stratified 1:1 randomization between Arm A and Arm B for de novo and relapsed / refractory WM patients in need of treatment. Stratification factors are MYD88 and CXCR4 status (positive vs. negative) and number of prior lines (0 vs. ≥ 1 treatment lines). A stratified central block randomization will be used. The primary goal of this study is to show the efficacy of Carfilzomib plus Ibrutinib versus Ibrutinib alone in the treatment of de novo and relapsed / refractory patients (Arm A vs. Arm B). In detail the study design will be as follows: <u>Arm A (Carfilzomib / Ibrutinib):</u> Patients will be treated with Ibrutinib until evidence of progressive disease or no longer tolerated. Patients will receive in addition Carfilzomib for two years.

Ibrutinib	*Continuous treatment* 420 mg p.o. daily, until evidence of progressive disease or no longer tolerated.
Carfilzomib	*Cycle 1 (day 1-28)** 20mg/m² i.v. day 1 70 mg/m² i.v. day 8, 15 of a 28 days cycle *Cycle 2-12 (28 day cycles)** 70mg/m² i.v. day 1, 8, 15 of a 28 days cycle *Cycle 13-24 (28 day cycles)** 70mg/m² i.v. day 1,15 of a 28 days cycle

*Prophylaxis for HZV reactivation is obligatory for all patients treated with Carfilzomib during the treatment phase. Acceptable antiviral therapy includes acyclovir (e.g. 400mg p.o. 3 times-a-day), famcyclovir (e.g. 125mg p.o. twice-a-day) or valacyclovir (e.g. 500mg p.o. twice-a-day). Prophylactic Dexamethasone (4 mg) is obligatory before the first Carfilzomib infusion and for later Carfilzomib infusions as indicated.

Arm B (Ibrutinib alone):
Patients will be treated with Ibrutinib until evidence of progressive disease or no longer tolerated.

Ibrutinib	*Continuous treatment* 420 mg p.o. daily, until evidence of progressive disease or no longer tolerated by the subject.

Follow-up Phase
All subjects who stop therapy due to non-tolerable toxicity will go into the follow up. During the first two years every 3 months and the following three years every 6 months or until disease progression.

Survival Follow-up Phase
All subjects who experience a disease progression will be followed for survival every 6 months until the end of the study (10 years after first patient in) or death.

Safety
Generally, safety evaluations include: adverse events, vital signs, physical examinations and clinical laboratory parameters. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 and will be documented in the CRF. Adverse events that occur between the signing of the informed consent until end of treatment visit will be collected. Additionally, there will be a close monitoring for treatment related toxicity comprising the first 10 patients included into Arm A. For these 10 patients safety evaluations will be performed at least every two weeks for cycle 1-6 and include the assessments mentioned above. The data of these first 10 patients in Arm A will be reviewed by the independent DSMC at the time point when 10th patient has completed 6 cycles of treatment in Arm A. The second analyses will be reviewed when the 30th patient in Arm A completed 6 cycles or latest after 18 months of treatment. The DSMC will give a benefit / risk assessment for the trial and recommendations for continuation/discontinuation of the study according the safety data of the patients.

Data and Safety Monitoring Committee (DSMC)

	A DSMC will be installed and composed of 3 members, including a statistician, who are not involved in the execution of the trial. The DSMC will review data described above and as described in the DSMC Charter (for more information see section 16 of the protocol). Pathological Reference Archival lymph node or bone marrow biopsy specimen obtained at the time of initial diagnosis with representative stained slides, must be submitted to the national pathology of the participating study group for confirmation of WM and mutational status. The investigative site must submit a bone marrow biopsy as well as aspirate slides and tumor/lymph node biopsy slides (if available) as part of the baseline screening (preferentially whole tumor blocks, and both unstained and HE stained slides).
Patient recruitment	184 patients
Number of study centers	60
Involved study groups	ECWM
Investigational product	Carfilzomib, Ibrutinib
Statistical Methods	The primary goal of this study is to show the efficacy of Carfilzomib in combination with Ibrutinib compared to Ibrutinib alone in the treatment of WM. Sample size estimation: RCT - Arms A and B: The sample size calculation is based on the comparison of the primary endpoint (CR/VGPR rate) between the arms A and B using the one-sided chi-square test. According to Treon et al. (NEJM 2015) the CR/VGPR rate in WM patients treated with Ibrutinib is about 16%. Assuming a CR/VGPR rate of 35% in patients treated with Carfilzomib/Ibrutinib, this scenario requires a number of 164 patients in total (i.e. 82 patients per group) to reach a power of 80% at a one-sided type one error of 0.025. It is expected that the rate of withdrawal in the study is smaller than 10%. According to this, the study will enroll a maximum of 184 subjects in the arms A and B in total. Statistical analysis of primary and secondary endpoints in the RCT: The primary study endpoint CR/VGPR rate will be evaluated in a full intention to treat way, so that only withdrawal of informed consent will make observations not evaluable for the primary study endpoint. The chi square test will be used for the analysis of the primary endpoint to test the CR/VGPR rate in the arms A and B at the 2.5% significance level (one-sided) in the ITT population. The corresponding set of null and alternative hypothesis is: H0: RRB ≤ RRA HA: RRB > RRA where RRB is the CR/VGPR rate in Arm A (Carfilzomib/Ibrutinib) and RRA is the CR/VGPR rate in Arm B (Ibrutinib). If the obtained one-sided p-value is less than or equal to 0.025, it will be concluded that the Carfilzomib/Ibrutinib combination statistically significantly increases CR/VGPR rate compared to single agent Ibrutinib. Additionally, the one-sided 97.5% confidence interval (CI) of the rate difference (RRB-RRA) will be calculated as effect estimator. Further exploratory analyses of the primary study endpoint encompass the Cochran-Mantel-Haenszel (CMH) test of rate difference adjusting for stratification factors (MYD88 and

	CXCR4 status and status for number of prior lines). A CMH 97.5% stratified CI of the rate difference (RRB-RRA) with each rate weighted by the number of subjects in each stratification factor combination will be calculated as an effect estimator. Additionally, logistic regression models will be used to investigate the influence of putative risk factors on the CR/VGPR rate. All secondary endpoints will be analyzed exploratory. Group comparisons in binary endpoints will be performed two-sided using the chi square test or Fisher's exact test as appropriate. Additionally, 95% CIs will be calculated for group differences. Survival times will be analyzed using the Kaplan-Meier estimator incl. 95% CI. Furthermore, the Cox Proportional Hazard model will be used to investigate the influence of putative risk factors on survival time. Group comparison in quality of life (ordinal endpoint) will be performed using the Wilcoxon rank-sum test. Additionally, the 95% CI will be calculated for the difference of the medians. For safety analysis of the RCT, all adverse events will be listed and the frequencies of the most frequent will be calculated. Group comparisons (A vs. B) of frequencies of AEs and SAEs will be performed using the chi square test or Fishers exact test as appropriate.
Duration of recruitment	Approximately 24-36 months
Duration of the study for individual patient	Until progression or toxicity not tolerated by the patient plus follow-up or survival follow-up (maximum of 10 years after first patient in)
Duration of the entire study	Maximum of 10 years after inclusion of the first patient

Table 1 Flow Chart Arm A (Carfilzomib / Ibrutinib)

All assessments and treatments listed in Table 1 excepting the administration of the study medications Carfilzomib i.v. and Ibrutinib p.o. and the biosampling are performed within therapy and diagnostic routine on standard WM therapy. During routine bone marrow aspiration and routine peripheral blood collection additional material will be collected for study purposes (additional characterization of the disease) in the case of the patient's consent.

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1#**	**Cycle 2 – 12#**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 / D8 / D15 *(±4 days)*	**Week 5 - 48** D1 / D8 / D15 *(±4 days)*	**Week 49 – 52** D1 *(±4 days)*	**Week 53 - 96** D1 / D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
Administrative procedure													
Obtain informed consent	18.1	x											
Evaluation inclusion / exclusion criteria	11	x	x										
Registration		x											
Molecular analysis: MYD88 and CXCR4 Mutational Status	**Fehler! Verweisquelle konnte nicht gefunden werden.**	x									x		
Randomisation	13.5			x									
Clinical assessments													
Demographic data	13.7.1		x										

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1#**	**Cycle 2 – 12#**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 / D8 / D15 *(±4 days)*	**Week 5 - 48** D1 / D8 / D15 *(±4 days)*	**Week 49 – 52** D1 *(±4 days)*	**Week 53 - 96** D1 / D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
Medical history	13.7.2		x										
Physical examination	13.7.3		x		x	x	x	x	x	x	x	x	
Vital signs	13.7.4		x		x	x	x	x	x	x	x	x	
WHO / ECOG Performance status	13.7.3		x		x	x	x	x	x	x	x	x	
12-lead ECG with QTc interval	13.7.5		x		(x)[2]	x (D1)	x (D1)	x (D1)	x (D1)	x			
ECHO	13.7.5		x		(x)[2]	if clinically indicated							
Pulmonary Function Tests	13.7.6		x		(x)[2]	if clinically indicated							
Fundoscopy[3]	13.7.7		x										
Laboratory assessment *(local laboratory)[4]*													
Pregnancy test (WCBP)	13.7.8		x[5]		x	x	x	x	x		x		
Serum protein electrophoresis, CBC with diff, coagulation, chemistry			x		x	x	x	x	x	x	x	x	
Serumimmunofixation, quantitative immunoglobulins (IgM, IgG, IgA)			x		x	x	x	x	x	x	x	x	

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
	Duration	*45 to 30 days*			*Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity*								
VISITS		**Screening**		**Rando-mization**	**Cycle 1#**	**Cycle 2 – 12#**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 / D8 / D15 *(±4 days)*	**Week 5 - 48** D1 / D8 / D15 *(±4 days)*	**Week 49 – 52** D1 *(±4 days)*	**Week 53 - 96** D1 / D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
β2-microglobulin, LDH, CRP			x			x[6]	x[6]	x[6]	x[6]		x[6]	x[6]	
Urine analysis: Bence Jones proteinuria and other proteinuria assays			x				x[6]	x[6]	x[6]				
Direct antiglobulin test, cryoglobulinemia, cold agglutinin test, Coombs test			x			x[6, 7]	x	x[6, 7]	x[6, 7]	x[6, 7]		x[6, 7]	
Anti-HIV, HBV, HCV			x[8]										
Free light chain			x				x			x	x		
Staging and efficacy assessment													
CT chest / abdomen / pelvis	13.7.9		x[9]			x[10] (cycle 7, prior to D1)	x[10] (cycle 13, prior to D1)	x[10] (cycle 19, prior to D1)	x[6, 10]	x[10]	x	x[6, 10]	
Bone marrow aspiration and - biopsy with flow cytometry			x				x	x[6]	x[6]	x	x	x[6]	
Further assessments													
FACT-Lym questionaire	13.7.10		x				x		x	x	x	x	
Concomitant medication	13.7.11		x		continuously						x		
Adverse events	14.3		x		continuously						x		

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1#**	**Cycle 2 – 12#**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 / D8 / D15 *(±4 days)*	**Week 5 - 48** D1 / D8 / D15 *(±4 days)*	**Week 49 – 52** D1 *(±4 days)*	**Week 53 - 96** D1 / D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
New anti-lymphoma treatment and survival													x
Study drug administration													
Ibrutinib	12.3.2				420mg p.o daily until disease progression or unacceptable toxicity								
Carfilzomib	12.3.1				20mg/m² D1 70mg/m²	70mg/m²	70mg/m²	70mg/m²					
Biosampling													
Bone marrow cells storage, DNA and RNA	13.7.12, 21.4		x				x	Month 19	Month 25				
Blood cells, serum plasma storage			x				x	Month 19	Month 25				

The first 10 randomized patients in the trial in arm A will be monitored closely during the first 6 cycles. During the first 6 cycles every two weeks the following assessments will be done: adverse event assessment, vital signs, physical examination, safety laboratory assessment

1 in the first two years every 3 months, after that every 6 months until end of study

2 optional

3 if hyperviscosity syndrome is suspected

4 The following laboratory values will be performed: serum protein electrophoresis, serum immunofixation, IgM, IgG, IgA, CBC with differential, PT, PTT, sodium, potassium, calcium, total bilirubin, SGOT, SGPT, LDH, urea, creatinine, total protein, albumin, β-microglobulin, cryoglobulinemia, free light chain.

5 must be repeated after two weeks during screening, after that monthly pregnancy test are mandatory (pregnancy test kits will be supplied by the sponsor)

6 every 6 months, CRP only if clinically indicated

7 if initially positive

8 Testing for HbsAg and anti-Hbc is obligatory for the Hepatitis B serology. In case the patient is positive for either HbsAg and/or anti-Hbc, patients can be only included if HBV - DNA is negative. In this case Hepatitis B prophylaxis has to be initiated and HBV DNA in these patients needs to be re-evaluated in regular intervals according to local guidelines. HBV DNA positive patients may not be included into the trial.

9 All tumour lesions at screening, follow target lesions accordingly. For screening also a CT (if contraindicated MRI is accepted) within 3 months prior to informed consent can be used for this trial.

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1#**	**Cycle 2 – 12#**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 / D8 / D15 *(±4 days)*	**Week 5 - 48** D1 / D8 / D15 *(±4 days)*	**Week 49 – 52** D1 *(±4 days)*	**Week 53 - 96** D1 / D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*	30 days after last dose of study drug	anytime	After end of treatment	After progression

[10] If clinically indicated or in case of initial lymph node / splenomegaly

Table 2 Flow Chart Arm B (Ibrutinib)

All assessments and treatments listed in Table 2 excepting the administration of the study medication Ibrutinib p.o. and the biosampling are performed within therapy and diagnostic routine on standard WM therapy. During routine bone marrow aspiration and routine peripheral blood collection additional material will be collected for study purposes (additional characterization of the disease) in the case of the patient's consent.

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 *(±4 days)*	**Week 5 - 48** D1 *(±4 d)*	**Week 49 – 52** D1 *(±4 d)*	**Week 53 - 96** D1 every 3 months *(±4 d)*	**Week 97+** D1 every 3 months *(±4 d)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
Administrative procedure													
Obtain informed consent	18.1	x											

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**									
	Duration	*45 to 30 days*			*Ibrutinib until disease progression or non-tolerable toxicity*								*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**	
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 *(±4 days)*	**Week 5 - 48** D1 *(±4 d)*	**Week 49 – 52** D1 *(±4 d)*	**Week 53 - 96** D1 every 3 months *(±4 d)*	**Week 97+** D1 every 3 months *(±4 d)*	30 days after last dose of study drug	anytime	After end of treatment	After progression	
Evaluation inclusion / exclusion criteria	11	x	x											
Registration		x												
Molecular analysis: MYD88 and CXCR4 Mutational Status	**Fehler! Verweisquelle konnte nicht gefunden werden.**	x									x			
Randomisation	13.5			x										
Clinical assessments														
Demographic data	13.7.1		x											
Medical history	13.7.2		x											
Physical examination	13.7.3		x		x	x	x	x	x	x	x	x		
Vital signs	13.7.4		x		x	x	x	x	x	x	x	x		
WHO / ECOG Performance status	13.7.3		x		x	x	x	x	x	x	x	x		
12-lead ECG with QTc interval	13.7.5		x		(x)[2]	x (D1)	x (D1)	x (D1)	x (D1)	x				
ECHO	13.7.5		x		(x)[2]	if clinically indicated								

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 *(±4 days)*	**Week 5 - 48** D1 *(±4 d)*	**Week 49 – 52** D1 *(±4 d)*	**Week 53 - 96** D1 every 3 months *(±4 d)*	**Week 97+** D1 every 3 months *(±4 d)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
Pulmonary Function Tests	13.7.6		x		(x)[2]	if clinically indicated							
Fundoscopy[3]	13.7.7		x										
Laboratory assessment *(local laboratory)*[4]													
Pregnancy test (WCBP)	13.7.8		x[5]		x	x	x	x	x		x		
Serum protein electrophoresis, CBC with diff, coagulation, chemistry			x		x	x	x	x	x	x	x	x	
Serumimmunofixation, quantitative immunoglobulins (IgM, IgG, IgA)			x		x	x	x	x	x	x	x	x	
β2-microglobulin, LDH, CRP			x			x[6]	x[6]	x[6]	x[6]		x[6]	x[6]	
Urine analysis: Bence Jones proteinuria and other proteinuria assays			x				x[7]	x[7]	x[7]				
Direct antiglobulin test, cryoglobulinemia, cold agglutinin test, Coombs test			x			x[6, 7]	x	x[6, 7]	x[6, 7]	x[6, 7]		x[6, 7]	

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*45 to 30 days*			*Ibrutinib until disease progression or non-tolerable toxicity*							*Every 3 months 1st 2 years, after that every 6 months*	*Every 6 months*
VISITS		**Screening**		**Rando-mization**	**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 14 -24**	**Cycle 25+**	**EOT Visit**	**At progression**	**FU Visit(s)[1]**	**Survival FU**
	Time / **Section**	**Day -45 to -1**	**Day -30 to -1**	**Day 0**	**Week 1 - 4** D1 *(±4 days)*	**Week 5 - 48** D1 *(±4 d)*	**Week 49 – 52** D1 *(±4 d)*	**Week 53 - 96** D1 every 3 months *(±4 d)*	**Week 97+** D1 every 3 months *(±4 d)*	30 days after last dose of study drug	anytime	After end of treatment	After progression
Anti-HIV, HBV, HCV			x[8]										
Free light chain			x				x			x	x		
Staging and efficacy assessment													
CT chest / abdomen / pelvis	13.7.9		x[8, 9]			x[10] (cycle 7, prior to D1)	x[10] (cycle 13, prior to D1)	x[10] (cycle 19, prior to D1)	x[6, 10]	x[10]	x	x[6, 10]	
Bone marrow aspiration and - biopsy with flow cytometry			x				x	x[6]	x[6]	x	x	x[6]	
Further assessments													
FACT-Lym questionaire	13.7.10		x				x		x	x	x	x	
Concomitant medication	13.7.11		x		continuously						x		
Adverse events	14.3		x		continuously						x		
New anti-lymphoma treatment and survival													x
Study drug administration													
Ibrutinib	12.3.2				420mg p.o daily until disease progression or unacceptable toxicity								
Biosampling													
Bone marrow cells storage, DNA and RNA	13.7.12, 21.4		x				x	Month 19	Month 25				
Blood cells, serum plasma storage			x				x	Month 19	Month 25				