Efficacy and safety of Carfilzomib in combination with Ibrutinib vs. Ibrutinib alone in Waldenström's Macroglobulinemia (CZAR-1)

A MULTICENTER, RANDOMIZED, OPEN LABEL PHASE II INTERNATIONAL TRIAL

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Substance identifier (IMP)	Carfilzomib, Ibrutinib
Therapeutic area	Hematology / Oncology
Sponsor	University Hospital Ulm, Albert-Einstein-Allee 29, 89081 Ulm, Germany; represented by the Chairman of the board
Coordinating Investigator	Prof. Dr. Christian Buske University Hospital Ulm Department of Internal Medicine III Albert-Einstein-Allee 23, 89081 Ulm, Germany

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1. KEY ROLES AND CONTACT INFORMATION

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Data management	University Medical Center Göttingen Clinical Trials Unit Von-Bar-Strasse 2/4, 37075 Göttingen, Germany
Funding	The study will be supported by Amgen GmbH and Janssen Pharmaceutica NV (see 19.10)

2. APPROVAL OF THE CLINICAL STUDY PROTOCOL

Sponsor representative:

0 1. APR. 2024 Date	Prof. Dr. Udo X. Kaisers Chief Medical Director
08. APR. 2024 Date	Hartmut Masanek Acting Chief Financial Director

Coordinating Investigator:
(LKP, according German law)

2.4.24 Date	Prof. Dr. Christian Buske Department Internal Medicine III University Hospital Ulm

Statistical analysis:

2.4.24 Date	Prof. Dr. Eva Hoster Institute for Medical Information Processing, Biometry, and Epidemiology, University of Munich

3. SIGNATURES OF NATIONAL COORDINATORS

National Coordinating investigator - Germany

I have thoroughly read and reviewed the study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to conduct the clinical study in compliance with the study protocol, the international good clinical practice principles and regulatory authority requirements for source document verification and auditing/inspection of the study. Furthermore, I agree to conduct the clinical trial in compliance with EU regulation 536/2014 as soon as the transition of the trial is approved by authorities.

…… ……

Date Prof. Dr. Christian Buske

University Hospital Ulm
Department of Internal Medicine III
Albert-Einstein-Allee 23
89081 Ulm, Germany

4. INVESTIGATOR STATEMENT

Study Site:

I confirm that I have read the clinical study 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 study 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 study at the disposal of my colleagues; in particular, I will promptly forward all information from the sponsor in relation to pharmaceutical safety (SUSARs, 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 study.

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

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

5. SYNOPSIS AND FLOWCHART

Name of sponsor	University Hospital Ulm, represented by the Chairman of the board
Investigational medicinal product	Carfilzomib, Ibrutinib
Title of study	Efficacy and safety of Carfilzomib in combination with Ibrutinib vs. Ibrutinib alone in Waldenström's Macroglobulinemia (CZAR-1)
Study design / phase	Phase II, randomized, open label, multicenter, international
Primary study objective	The primary objective of the study is to explore the efficacy of Carfilzomib in combination with Ibrutinib compared to Ibrutinib alone in patients with treatment naïve or relapsed WM. Primary study endpoint: Complete Remission (CR) or Very Good Partial Remission (VGPR) 12 months from randomization using the modified response criteria updated at the Sixth IWWM[1] (CR/VGPR). Secondary study endpoints: Response rate (CR, VGPR, PR, MR) and ORR (CR, VGPR, PR) 12 and 24 months after randomization, Best response, Time to best response, Time to first response, Time to treatment failure, Remission Duration, Progression free survival, Cause specific survival, Overall survival, Safety, Quality of life.
Background	In Waldenström's 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)[2]. However, also Ibrutinib fails to induce CRs and the VGPR rate is 16% in relapsed patients[2]. In addition, activity of Ibrutinib depends on the genotype: compared to patients with $MYD88^{mut}/CXCR4^{WT}$, single agent therapy with Ibrutinib 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)[2, 3]. 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[4]. 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 of 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 the following 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 (IWWM)[66]. Histopathology has to occur before randomization within the last 4 months. In addition, pathological specimens have to be sent to the pathological reference center prior to randomization for the determination of the mutational status of MYD88 and CXCR4 (if not already known).

	Immunophenotyping will be performed in each center and archived locally (for more details see protocol section 10.2 and 12.4.2.2). • De novo or 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 criteria from the Seventh IWWM[5]: o Recurrent fever, night sweats, weight loss, fatigue (at least one of them). 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 ≤ 2. • Left ventricular ejection fraction ≥ 40% as assessed by transthoracic echocardiogram (TTE). Other criteria: • Age ≥ 18 years (male and female). • Life expectancy > 3 months in the opinion of the investigator. • Baseline platelet count ≥ 50 x 10^9/L, absolute neutrophil count ≥ 0.75 x 10^9/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: ≤ 1.5 times the ULN. • Women of childbearing potential (WCBP), 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 Carfilzomib or Ibrutinib (for more details see section 11.4.4 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 their female partner to use a highly effective method (use of a condom) of birth control. Males must refrain from sperm donation for the duration of treatment and at least 6 months after the last dose of Carfilzomib or Ibrutinib.

	• Each patient must sign an informed consent form in a fluent language of the patient indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
Study Population - Exclusion criteria	The presence of the following criteria will exclude a patient from enrolment: • Previous treatments with following substances: o Prior exposure to Ibrutinib or other BTK inhibitors. o Prior exposure to Carfilzomib. Prior exposure to other proteasome inhibitors is allowed if the patients were not refractory, that is, had a remission (at least minor response) duration of ≥ 6 months. Prior plasmapheresis and short-term administration of corticosteroids ≤ 6 weeks administered at a dose equivalent to ≤ 20 mg/day of prednisone is also allowed. • Serious medical or psychiatric illness (especially undergoing treatment) likely to interfere with participation in this clinical study. • Active HIV, HBV or HCV infection (see protocol section 12.4.12.9). • 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 randomization, 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. o 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. o Cardiac amyloidosis. • Recent major surgery within 30 days prior to randomization. • Known cirrhosis (meeting child-pugh stage C). • Approved or investigational anticancer treatment 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. • Hypersensitivity to the active substances or to any of the excipients of the investigational medicinal products. • 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 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 according European Society of Hypertension/ European Society of Cardiology [ESH / ESC] 2013 guidelines) [57]. • History of stroke or intracranial hemorrhage within 6 months prior to randomization. • Known interstitial lung disease. • Infiltrative pulmonary disease, known pulmonary hypertension. • 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. • Autologous or allogeneic stem cell transplant less than 100 days prior to randomization. • Vaccination with live attenuated vaccines within 30 days prior to randomization. • Patients who require strong or moderate inducers or inhibitors for cytochrome P450, family 3 or subfamily A (CYP3A). • Patients who have an uncontrolled bleeding disorder or require an anticoagulant (e.g. warfarin or other vitamin K antagonists; novel oral anticoagulants (NOACs) are allowed) at time of screening. • 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 patient safety or interfere with the study evaluation, procedures or completion. • Patient is a woman who is pregnant or breastfeeding (and do not consent to discontinue breast-feeding) or planning to become pregnant while enrolled in this study or within 6 months after the last study treatment. • Vulnerable patients, e.g. patients who are incapable of giving informed consent (severe dementia or psychosis, patients kept in detention). • Participation in another interventional clinical study within 30 days before randomization in this study.
Study design	The phase II study will consist of an open labelled, stratified 1:1 randomization between Arm A and Arm B for de novo or relapsed / refractory WM patients in need of treatment. Stratification factors are MYD88 and CXCR4 status and number of prior lines (0 vs. ≥ 1 treatment lines) (details see chapter 12.5). A stratified central block randomization will be used. The primary goal of this study is to explore the efficacy of Carfilzomib plus Ibrutinib vs. 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 (max. 7 years after first patient in (FPI)). 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 by the patient.
Carfilzomib	*Cycle 1 (day 1-28)** 20mg/m^2 i.v. day 1 70 mg/m^2 i.v. day 8, 15 of a 28 days cycle *Cycle 2-12 (28-day cycles)** 70mg/m^2 i.v. day 1, 8, 15 of a 28 days cycle *Cycle 13-24 (28-day cycles)** 70mg/m^2 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 (max 7 years after FPI).

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

Follow-up Phase
All patients 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 (until end of study, 7 years after FPI).

Survival Follow-up Phase
All patients who experience a disease progression will be followed for survival every 6 months until the end of the study (7 years after FPI) or death. The same applies to patients who receive a new anti-lymphoma therapy without disease progression.

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 eCRF. Adverse events that occur between the first application / intake of study drug until end of treatment visit (30 days after last intake of study drug) will be collected.
Additionally, there will be a closer 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.

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 study. The data of all patients will

	be reviewed by the independent DSMC at the time point when the 6th 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 at the latest after 18 months of treatment, whichever comes earlier. The DSMC will give a benefit / risk assessment for the study and recommendations for continuation / discontinuation of the study according the safety data of the patients. (for more information see section 15 of the protocol).
Planned number of patients:	approximately 99 patients
Number of study centers	approximately 30 sites in the European Union
Investigational product	Carfilzomib, Ibrutinib
Statistical Methods	The primary goal of this study is to explore 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 at 12 months from randomization) 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 94 patients in total (i.e. 47 patients per group) to reach a power of 80% at a one-sided type one error of 0.10. It is expected that the rate of withdrawal in the study is smaller than 5%. In addition to the drop-out rate of 5%, patients who were randomized but withdrew consent before the start of therapy may be replaced until the end of the recruitment period. According to this, the study will enroll approximately 99 patients 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 following the intention to treat principle. 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 10% significance level (one-sided) in the core analysis population. The corresponding set of null and alternative hypothesis is: H0: RRA ≤ RRB HA: RRA > RRB where RRA is the CR/VGPR rate in arm A (Carfilzomib / Ibrutinib) and RRB is the CR / VGPR rate in arm B (Ibrutinib). If the obtained one-sided p-value is less than or equal to 0.10 and the point estimate for the CR / VGPR rate of arm A is larger than that of arm B, it will be concluded that the Carfilzomib / Ibrutinib combination statistically significantly increases CR / VGPR rate compared to single agent Ibrutinib. Additionally, the two-sided 95% confidence interval (CI) of the rate difference (RRA-RRB) 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 number of prior lines). A CMH 95% stratified CI of the rate difference (RRA-RRB) with each rate weighted by the number of patients 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	Q2 2024
Duration of the study for individual patient	Until disease progression or toxicity not tolerated by the patient plus follow-up or survival follow-up (max. 7 years after FPI)
Duration of the entire study	maximum 7 years after FPI (First Patient In 18.02.2021)

Table 1 Flowchart Screening / treatment phase arm A (Carfilzomib / Ibrutinib)

All assessments 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	*up to 45 days*			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*									
VISITS		**Screening**			**Cycle 1**		**Cycle 2 – 12**		**Cycle 13**		**Cycle 14 -24**		**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1-4** D1 *(±4 days)*	**Week 1-4** D8 / D15 *(±4 days)*	**Week 5-48** D1 *(±4 days)*	**Week 5-48** D8 / D15 *(±4 days)*	**Week 49-52** D1 *(±4 days)*	**Week 49-52** D15 *(±4 days)*	**Week 53-96** D1 *(±4 days)*	**Week 53-96** D15 *(±4 days)*	**Week 97+** D1 every 3 months *(±4 days)*[1]	30 days after last dose of study drug *(±7 days)*
Administrative procedure														
Obtain informed consent	18.1	x[2]												
Evaluation inclusion / exclusion criteria[3]	10.2, 10.3	x	x	x										
Registration		x[4]												
Molecular analysis: MYD88 and CXCR4 Mutational Status[5]	12.4.1	x												
Randomization	12.5			x[6]										
Clinical assessments														
Demographic data	12.4.4		x[7]											
Medical history	12.4.5		x[8]											
Complete physical examination[9]	12.4.7			x										x
Targeted physical examination[10]	12.4.7				x		x		x		x		x	
WHO / ECOG Performance status	12.4.7			x	x		x		x		x		x	x
Vital signs[11]	12.4.8			x	x	x	x	x	x	x	x	x	x	x
12-lead ECG[12]	12.4.9		x		(x) [11a]	x[11b]	x	x[11b]	x		x		x°	x
TTE[13]	12.4.9		x				x		x		x		x[13]	
Pulmonary function tests[14]	12.4.10		x		if clinically indicated									
Fundoscopy[15]	12.4.11		x											

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**									
	Duration	*up to 45 days*			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*									
VISITS		**Screening**			**Cycle 1**		**Cycle 2 – 12**		**Cycle 13**		**Cycle 14 -24**		**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1-4** D1 *(± 4 days)*	**Week 1-4** D8 / D15 *(± 4 days)*	**Week 5-48** D1 *(± 4 days)*	**Week 5-48** D8 / D15 *(± 4 days)*	**Week 49-52** D1 *(± 4 days)*	**Week 49-52** D15 *(± 4 days)*	**Week 53-96** D1 *(± 4 days)*	**Week 53-96** D15 *(± 4 days)*	**Week 97+** D1 every 3 months *(± 4 days)*[1]	30 days after last dose of study drug *(± 7 days)*
Laboratory assessments *(local laboratory)*[16]														
Pregnancy test (WCBP)	12.4.12.1			x[17]	x		x		x		x		X[17]	x
Hematology with diff[18]	12.4.12.2			x	x	x	x	x	x		x		x	x
Serum chemistry and electrophoresis[19]	12.4.12.3			x	x	x	x	x	x		x		x[19]	x
β2-microglobulin[20]	12.4.12.3			x			x		x		x		x[20]	
Coagulation[21]	12.4.12.4			x	x		x		x		x		x	x
Urine analysis[22]	12.4.12.5			x					x		x		x[22]	
Quantitative immunoglobulins	12.4.12.6			x	x		x		x		x		x	x
Free light chain	12.4.12.7			x					x					x
Cold agglutinin test, direct Coombs test[23]	12.4.12.8		x				x		x		x		x[23]	x
Anti-HIV, HBV, HCV[24]	12.4.12.9		x											
Staging and efficacy assessment														
CT neck / thorax / abdomen[25]	12.4.13		x				x (cycle 7, prior to D1)		x (cycle 13, prior to D1)		x (cycle 19, prior to D1)		x°	x
Bone marrow aspiration and -biopsy with flow cytometry[26]		x							x (cycle 13, prior to D1)[26]		x (cycle 19, prior to D1)[26]		x[26]	x
FACS Analysis peripheral blood			x						x		x (cycle 19, prior to D1)		x°	x
Further assessments														
FACT-Lym questionnaire	12.4.14		x						x				x°	x
Patient diary[27]	11.5.6				x	x	x	x	x	x	x	x	x	
Concomitant medication[28]	12.4.15		x		continuously									
Adverse events[29]	13				continuously									

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**									
	Duration	*up to 45 days*			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*									
VISITS		**Screening**			**Cycle 1**		**Cycle 2 – 12**		**Cycle 13**		**Cycle 14 -24**		**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1-4** D1 *(± 4 days)*	**Week 1-4** D8 / D15 *(± 4 days)*	**Week 5-48** D1 *(± 4 days)*	**Week 5-48** D8 / D15 *(± 4 days)*	**Week 49-52** D1 *(± 4 days)*	**Week 49-52** D15 *(± 4 days)*	**Week 53-96** D1 *(± 4 days)*	**Week 53-96** D15 *(± 4 days)*	**Week 97+** D1 every 3 months *(± 4 days)*[1]	30 days after last dose of study drug *(± 7 days)*
Study drug administration														
Carfilzomib	11.3.1				20 mg/m²	70 mg/m²	70 mg/m²	70 mg/m²	70 mg/m²	70 mg/m²	70 mg/m²	70 mg/m²		
Ibrutinib	11.3.3				420 mg p.o. daily until disease progression or unacceptable toxicity									
Biosampling[30]														
Cheek swap	12.4.16, 21.3		x											
30ml peripheral blood (Streck tube)			x						x		cycle 19		cycle 25	
15ml bone marrow[31]			x						x		cycle 19[30]		cycle 25[30]	
10ml serum			x						x		cycle 19		cycle 25	
10ml EDTA peripheral blood			x						x		cycle 19		cycle 25	

° Every 6 months

[1] In case of cytopenia the frequency of blood samples would be increased from the 25th cycle to once a month.
[2] Written informed consent form must be signed by the patient prior to any study-specific procedure are performed.
[3] Within 45 days prior to randomization a first check of inclusion / exclusion criteria must be done. If the mutational status is available all other screening assessments have to be done prior to randomization.
[4] Patients have to register at the screening visit via fax form (see ISF).
[5] Pathological specimens have to be sent to the pathological reference center for the confirmation of diagnosis and determination of mutational status (MYD88 / CXCR4 if the mutational status hasn´t been determined before).
[6] Randomization will be done in the eCRF. Stratification factors are MYD88 and CXCR4 status and number of prior therapy lines.
[7] Demographic data include year of birth, gender and childbearing potential.
[8] Relevant medical history not pertaining to the study indication started before signing informed consent over the last 5 years and assessments of any current medical conditions. Previous therapies for WM will also be documented.
[9] Thorough physical/medical examination includes, but is not limited to B-symptoms, cardiovascular, gastrointestinal, hepatobiliary, respiratory, skin, musculoskeletal, genitourinary/renal and other organ systems.
[10] A targeted physical examination to focus on areas involved by AEs or areas involved by WM (e.g. splenomegaly, lymphadenopathy) and for B-symptoms
[11] Vital signs include heart rate, blood pressure and temperature. Vital signs will be done on day 1, day 8 and day 15 during the first 6 cycles for the first 10 patients. For all other patients only on day 1 and day 15 vital signs measurement is necessary.
[12] A 12-lead ECG (including PR-, QT- and QTc interval) will be performed at every mentioned time point
a) On day 1, cycle 1 optional in the discretion of the investigator (depending on local standards and the timeframe between screening ECG and day 1)
b) The first 10 patients in the study in arm A will be monitored more closely during the first 6 cycles. ECG will be done on day 1 and day 15 during the first 6 cycles for the first 10 patients.

[13] Transthoracic echocardiography will be performed at screening and after that every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) or if clinically indicated.
[14] A pulmonary function test will be performed at screening and thereafter only if clinically indicated.
[15] If hyperviscosity syndrome is suspected a fundoscopy has to be performed.
[16] The laboratory values will be performed only locally, a detailed laboratory flow chart can be found in the appendix of the protocol.
[17] Pregnancy test must be repeated after two weeks during screening, after that monthly pregnancy test are mandatory (pregnancy test strips will be supplied by the sponsor for the 3-monthly treatment phase)
[18] CBC with diff will be done on day 1, day 8 and day 15 during the first 6 cycles for the first 10 patients. For all other patients only on day 1 and day 15 CBC with diff is necessary. Screening values can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and the timeframe between screening laboratory and day 1).
[19] Serum chemistry (sodium, potassium, calcium, creatinine, total bilirubin, SGOT, SGPT, LDH, magnesium, phosphate, glucose, urea or BUN, CRP, total protein, albumin) will be done on day 1, day 8 and day 15 during the first 6 cycles for the first 10 patients. For all other patients only on day 1 and day 15 during cycle 1 to 12 serum chemistry is necessary. Screening values can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and e.g. the timeframe between screening laboratory and day 1). Serum electrophoresis will be done only every 6 months.
[20] B2-microglobulin will be done every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.).
[21] INR and partial thromboplastin time (activated or not). Screening values can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and e.g. the timeframe between screening laboratory and day 1).
[22] Urine analysis will be performed from cycle 13 every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) until end of treatment.
[23] If cryoglobulinemia is suspected cold agglutinin test and direct Coombs test will be done at screening and after that every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) if initially positive.
[24] 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 HB-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 study.
[25] All tumor lesions at screening will be followed as target or non-target lesions. For screening evaluation a routine CT (or MRI) within 3 months prior to informed consent can be used for this study. Further assessments during treatment if clinically indicated or in case of initial lymph node / splenomegaly.
[26] Bone marrow aspirate and biopsy will be performed from cycle 13 every 6 months (cycle 19, cycle 25 etc.) until end of treatment (only if CR or delayed response is expected).
[27] A patient diary will be provided to each patient to record Ibrutinib intake each day. Missed doses should be explained by the patient. Also signs and symptoms between visits at the study site should be documented in the diary. The diary should be returned to the study personnel for review.
[28] Only current concomitant medication and supportive care will be recorded at Screening. In the following cycles ongoing and new medication will be documented
[29] Investigator should ask for any signs and symptoms (incl. known side effects) as part of the routine adverse event monitoring for each patient visit
[30] The patient consent and signature on the informed consent for biosampling is prerequisite for biological sampling. Cheek swap is only necessary at screening. Details are described in the laboratory manual.
[31] Bone marrow has to be collected during screening (only during routine assessment). After that bone marrow has only been collected to confirm CR or delayed response.

Table 2 Flowchart Screening / treatment phase arm B (Ibrutinib)

All assessments 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	*up to 45 days*			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*					
VISITS		**Screening**			**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 16, 19, 22**	**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1 - 4** D1 *(± 4 days)*	**Week 5 - 48** D1 *(± 4 days)*	**Week 49 - 52** D1 *(± 4 days)*	**Week 61 - 96** D1 every 3 months *(± 4 days)*[1]	**Week 97+** D1 every 3 months *(± 4 days)*	30 days after last dose of study drug *(± 7 days)*
Administrative procedure										
Obtain informed consent	18.1	x[2]								
Evaluation inclusion / exclusion criteria[3]	10.2, 10.3	x	x	x						
Registration		x[4]								
Molecular analysis: MYD88 and CXCR4 Mutational Status[5]	12.4.1	x								
Randomization	12.5			x[6]						
Clinical assessment										
Demographic data	12.4.1		x[7]							
Medical history	12.4.5		x[8]							
Complete physical examination[9]	12.4.7			x						x
Targeted physical examination[10]	12.4.7				x	x	x	x	x	
WHO / ECOG Performance status	12.4.7			x	x	x	x	x	x	x
Vital signs[11]	12.4.8			x	x	x	x	x	x	x
12-lead ECG[12]	12.4.9		x		(x)	x	x	x	x°	x
TTE[13]	12.4.9		x			x	x	x	x[13]	
Pulmonary Function Tests[14]	12.4.10		x		if clinically indicated					
Fundoscopy[15]	12.4.11		x							

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**					
	Duration	*up to 45 days*			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*					
VISITS		**Screening**			**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 16, 19, 22**	**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1 - 4** D1 *(± 4 days)*	**Week 5 - 48** D1 *(± 4 days)*	**Week 49 - 52** D1 *(± 4 days)*	**Week 61 - 96** D1 every 3 months *(± 4 days)*[1]	**Week 97+** D1 every 3 months *(± 4 days)*	30 days after last dose of study drug *(± 7 days)*
Laboratory assessments *(local laboratory)*[16]										
Pregnancy test (WCBP)	12.4.12.1			x[17]	x	x	x	x	x[17]	x
Hematology with diff	12.4.12.2			x	x	x	x	x	x	x
Serum chemistry and electrophoresis[18]	12.4.12.3			x	x	x	x	x	x[18]	x
β2-microglobulin[19]	12.4.12.3			x		x	x	x	x[19]	x
Coagulation[20]	12.4.12.4			x	x	x	x	x	x	x
Urine analysis[21]	12.4.12.5			x			x	x	x[21]	
Quantitative immunoglobulins	12.4.12.6			x	x	x	x	x	x	x
Free light chain	12.4.12.7			x			x			x
Cold agglutinin test, direct Coombs test[22]	12.4.12.8		x			x	x	x	x[22]	x
Anti-HIV, HBV, HCV[23]	12.4.12.9		x							
Staging and efficacy assessment										
CT neck / thorax / abdomen[24]	12.4.13		x			x (cycle 7, prior to D1)	x (cycle 13, prior to D1)	x (cycle 19, prior to D1)	x°	x[10]
Bone marrow aspiration and - biopsy with flow cytometry[25]		x					x (cycle 13, prior to D1)[25]	x (cycle 19, prior to D1)[25]	x[25]	x
FACS analysis peripheral blood			x				x (cycle 13, prior to D1)	x (cycle 19, prior to D1)	x°	x
Further assessments										
FACT-Lym questionnaire	12.4.14		x				x		x°	x
Patient diary[26]	11.5.6				x	x	x	x	x	
Concomitant medication[27]	12.4.15		x		continuously					
Adverse events[28]	13				continuously					

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**					
	Duration	*up to 45 days*			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*					
VISITS		**Screening**			**Cycle 1**	**Cycle 2 – 12**	**Cycle 13**	**Cycle 16, 19, 22**	**Cycle 25+**	**EOT Visit**
	Time / **Section**	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	**Week 1 - 4** D1 *(± 4 days)*	**Week 5 - 48** D1 *(± 4 days)*	**Week 49 - 52** D1 *(± 4 days)*	**Week 61 - 96** D1 every 3 months *(± 4 days)*[1]	**Week 97+** D1 every 3 months *(± 4 days)*	30 days after last dose of study drug *(± 7 days)*
Study drug administration										
Ibrutinib	11.3.3				420 mg p.o. daily until disease progression or unacceptable toxicity					
Biosampling[29]										
Cheek swap	12.4.16, 21.3		x							
30ml peripheral blood (Streck tube)			x				x	Cycle 19	Cycle 25	
15ml bone marrow[30]			x				x	Cycle 19[29]	Cycle 25[29]	
10ml serum			x				x	Cycle 19	Cycle 25	
10ml EDTA peripheral blood			x				x	Cycle 19	Cycle 25	

° Every 6 months

[1] In case of cytopenia the frequency of blood samples would be increased from the 14th cycle to once a month.
[2] Written informed consent form must be signed by the patient prior to any study-specific procedure are performed.
[3] Within 45 days prior to randomization a first check of inclusion / exclusion criteria must be done. If the mutational status is available all other screening assessments have to be done prior to randomization.
[4] Patients have to register at the screening visit via fax form (see ISF).
[5] Pathological specimens have to be sent to the pathological reference center prior to randomization for the confirmation of diagnosis and determination of mutational status (MYD88 / CXCR4 if the mutational status hasn´t been determined before).
[6] Randomization will be done in the eCRF. Stratification factors are MYD88 and CXCR4 status and number of prior therapy lines.
[7] Demographic data include year of birth, gender and childbearing potential.
[8] Relevant medical history not pertaining to the study indication started before signing informed consent over the last 5 years and assessments of any current medical conditions. Previous therapies for WM will also be documented.
[9] Thorough physical/medical examination includes, but is not limited to B-symptoms, cardiovascular, gastrointestinal, hepatobiliary, respiratory, skin, musculoskeletal, genitourinary/renal and other organ systems.
[10] A targeted physical examination to focus on areas involved by AEs or areas involved by WM (e.g. splenomegaly, lymphadenopathy) and for B-symptoms.
[11] Vital signs include heart rate, blood pressure and temperature.
[12] A 12-lead ECG (including PR-, QT- and QTc interval) will be performed at every mentioned time point. On day 1, cycle 1 optional in the discretion of the investigator (depending on local standards and the timeframe between screening ECG and day 1)
[13] Transthoracic echocardiography will be performed at screening and after that every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) or if clinically indicated.

[14] A pulmonary function test will be performed at screening and thereafter only if clinically indicated.
[15] If hyperviscosity syndrome is suspected a fundoscopy has to be performed.
[16] The laboratory values will be performed only locally, a detailed laboratory flow chart can be found in the appendix of the protocol.
[17] Pregnancy test must be repeated after two weeks during screening, after that monthly pregnancy test are mandatory (pregnancy test strips will be supplied by the sponsor for the 3-monthly treatment phase)
[18] Serum chemistry (sodium, potassium, calcium, creatinine, total bilirubin, SGOT, SGPT, LDH, magnesium, phosphate, glucose, urea or BUN, CRP, total protein, albumin) will be done on day 1 of each cycle. Screening values can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and e.g. the timeframe between screening laboratory and day 1). Serum electrophoresis will be done only every 6 months.
[19] B2-microglobulin will be done every 6 months.
[20] INR and partial thromboplastin time (activated or not). Screening values can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and e.g. the timeframe between screening laboratory and day 1).
[21] Urine analysis will be performed from cycle 13 every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) until end of treatment.
[22] If cryoglobulinemia is suspected cold agglutinin test and direct Coombs test will be done at screening and after that every 6 months (screening, cycle 7, cycle 13, cycle 19, cycle 25 etc.) if initially positive.
[23] 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 study.
[24] All tumor lesions at screening will be followed as target or non-target lesions. For screening evaluation, a routine CT (or MRI) within 3 months prior to informed consent can be used for this study. Further assessments during treatment if clinically indicated or in case of initial lymph node / splenomegaly.
[25] Bone marrow aspirate and biopsy will be performed from cycle 13 every 6 months (cycle 19, cycle 25, etc.) until end of treatment (only if CR or delayed response is expected).
[26] A patient diary will be provided to each patient to record Ibrutinib intake each day. Missed doses should be explained by the patient. Also signs and symptoms between visits at the study site should be documented in the diary. The diary should be returned to the study personnel for review.
[27] Only current concomitant medication and supportive care will be recorded at Screening. In the following cycles ongoing and new medication will be documented.
[28] Investigator should ask for any signs and symptoms (incl. known side effects) as part of the routine adverse event monitoring for each patient visit.
[29] The patient consent and signature on the informed consent for biosampling is prerequisite for biological sampling. Cheek swap is only necessary at screening. Details are described in the laboratory manual.
[30] Bone marrow has to be collected during screening (only during routine assessment). After that bone marrow has only been collected to confirm CR or delayed response.

Table 3 Flowchart follow up phase arm A and arm B

Follow Up will be done in the first two years every 3 months, after that every 6 months for three years. At time of progressive disease at any time during the study the assessments below has to be performed. After progression of disease or start of new anti-lymphoma therapy patients will be followed up for survival only. Within the study the follow up period is maximum 7 years after first patient in. All assessments listed in Table 3 are performed within routine on standard WM follow up.

PERIODS	**Name**		*Every 3 months 1st 2 years, after that every 6 months for 3 years (± 14 days)*	*Every 6 months (± 14 days)*
	Duration			
VISITS		**Progress**	**FU Visit(s)[1]**	**S- FU[#]**
	Time / **Section**	anytime	After end of treatment visit	After pro-gression or start of new WM therapy
Administrative procedure				
Molecular analysis: MYD88 and CXCR4 Mutational Status[1]	12.4.1	as clinically indicated		
Clinical assessments				
Targeted physical examination[2]	12.4.7	x	x	
WHO / ECOG Performance status	12.4.7	x	x	
Laboratory assessments (local laboratory)				
Pregnancy test (only WCBP)	12.4.12.1		x[3]	
Hematology with diff	12.4.12.2	x	x	
Serum chemistry and electrophoresis[4]	12.4.12.3	x	x[4]	
β2-microglobulin[5]	12.4.12.3	x	x[5]	
Coagulation[6]	12.4.12.4	x		
Quantitative immunoglobulins	12.4.12.6	x	x	
Free light chain	12.4.12.7	x		
Staging and efficacy assessments				
CT neck / thorax / abdomen[7]	12.4.13	x	x°	
Bone marrow aspiration and - biopsy with flow cytometry and FACS peripheral blood		x		
Further assessments				
FACT-Lym questionnaire	12.4.14	x	x°	
Concomitant medication	12.4.15	x		
Adverse events	13	x		
New anti-lymphoma treatment and survival		x	x	x

° Every 6 months

[1] Assessment of mutational status only as clinically indicated.
[2] A targeted physical examination to focus on areas involved by AEs or areas involved by WM (e.g. splenomegaly, lymphadenopathy) and for B-symptoms.
[3] Monthly for the first 6 months after end of treatment (will be provided by the Sponsor).
[4] Serum chemistry (sodium, potassium, calcium, creatinine, total bilirubin, SGOT, SGPT, LDH, magnesium, phosphate, glucose, urea / BUN, CRP, total protein, albumin). Serum electrophoresis will be done only every 6 months.
[5] β2-microglobulin will be done every 6 months.
[6] INR, prothrombin time and partial thromboplastin time (activated or not).
[7] Radiological assessments during follow up if clinically indicated or in case of initial lymph node / splenomegaly.
[#] Survival follow up can be done by phone or on site, regarding site policy.

6. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

AE	Adverse event	ECWM	European Consortium for Waldenström´s Macroglobulinemia
ALAT (SGPT)	Alanine Transaminase (Serum Glutamic Pyruvic Transaminase)	EMA	European Medicine Agency
ANC	Absolute Neutrophil Count	EOT	End of treatment
ASAT (SGOT)	Aspartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)	ESC	European Society of Cardiology
ASCO	American Society of clinical Oncology	ESH	European Society of Hypertension
AUC	Area under the curve	FACT	Functional Assessment of Cancer Therapy
BCR	B-cell receptor	FCR	Fludarabine / Cyclophosphamide / Rituximab
BDR	Bortezomib / Dexamethasone / Rituximab	FDA	Food and Drug Administration
BSA	Body Surface Area	FEV	Forced expiratory volume
BTK	Bruton‘s tyrosine kinase	FISH	fluorescence in situ hybridization
BUN	Blood urea nitrogen	FSH	Follicle stimulating hormone
BW	Body Weight	FU	Follow Up
CARD	Carfilzomib / Rituximab / Dexamethasone	GCP	Good Clinical Practice
CBC	Complete blood count	GI	Gastrointestinal
CCR	Cladribine / Cyclophosphamide / Rituximab	GLP	Good Laboratory Practice
CD20	antigen expressed on the surface of normal and malignant B lymphocytes	Hb	Hemoglobin
CI	Confidence interval	HBV	Hepatitis-B-Virus
CLL	Chronic lymphocytic leukemia	HCV	Hepatitis-C-Virus
CMH	Cochran-Mantel-Haenszel	HE	Hematoxylin eosin
CNS	central nervous system	HIV	Human immunodeficiency virus
COPD	Chronic obstructive pulmonary disease	HRT	Hormonal replacement therapy
CR	Complete Remission/Response	IB	Investigators Brochure
CrCL	Creatinine Clearance	ICH	International Conference on Harmonization
CRC	Central registration center	Ig	Immunoglobulin
CRO	Contract research organization	IL6	Interleukin 6
CRP	C reactive protein	IMP	Investigational Medicinal Product
CRF	Case Report Form	IND	Investigational New Drug
CSS	Cause specific survival	IPSSWM	International Prognostic Scoring System Waldenström’s Macroglobulinemia
CT	Computed Tomography	IR	Ibrutinib / Rituximab
CTCAE	Common Toxicity Criteria for Adverse Events	IRC	Independent Review Committee
CTFG	Clinical Trials Facilitation and Coordination Group	IRR	Infusion-Related Reaction
DFS	Disease-free survival time	ISF	Investigator site file
DLT	Dose-limiting toxicity	ITT	Intention to treat
DNA	Deoxyribonucleic acid	IUD	Intrauterine device
DRC	Dexamethasone/Rituximab/Cyclophosphamide	IUS	Intrauterine hormone-releasing system
DSMC	Data Safety Monitoring Committee	i.v.	intravenous
EC	Ethics Committee	IWWM	International Workshop on Waldenstrom's Macroglobulinemia
ECG	Electrocardiogram	LDH	Lactic DeHydrogenase
ECHO	Transthoracic echocardiography	LLN	Lower limits of normal
ECOG	Eastern Cooperative Oncology Group	LPL	lymphoplasmocytic lymphoma

LVEF	Left ventricle ejection function		
MedDRA	Medical Dictionary for Regulatory Activities		
MCL	Mantle Cell Lymphoma		
MM	Multiple Myeloma		
MR	Minor response		
MRI	Magnet Resonance Imaging		
MTD	maximal tolerated dose		
NCI	National Cancer Institute		
NEJM	New England Journal of Medicine		
NFkB	NFkappaB		
NHL	Non-Hodgkin's Lymphoma		
NOACs	New oral antocoagulants		
NYHA	New York Heart Association		
OR	Overall response		
OS	Overall Survival		
ORR	Overall response rate		
PCR	Pentostatin / Cyclophosphamide / Rituximab or Polymerase Chain Reaction		
PD	Progressive Disease		
PFS	Progression Free Survival		
P-gp	P-glycoprotein		
PHI	Protected health information		
PJP	Pneumocystis jirovecii-Pneumonia		
Plt	Platelets		
PK	Pharmacokinetic		
p.o.	per os		
PQC	Product quality complaint		
PR	Partial Remission		
PRES	Posterior reversible encephalopathy syndrome		
PS	Performance Status		
RCT	Randomized controlled trial		
RD	Remission duration		
RNA	Ribonucleic acid		
RSI	Reference Safety Information		
SAE	Serious Adverse Event		
SD	Stable Disease		
SDV	Source Data Verification		
SmPC	Summary of Product Characteristics		
SUSAR	Suspected Unexpected Serious Adverse Reaction		
TLS	Tumor Lysis Syndrome		
TMA	Thrombotic microangiopathy		
TTE	Transthoracic echocardiogram		
TTF	Time to treatment failure		
TTP	Time to progression		
ULN	Upper Limit of Normal		
US	United States		
VGPR	Very Good Partial Response		
WBC	White blood cells		
WCBP	Women of Childbearing Potential		
WHO	World Health Organization		
WM	Waldenström's Macroglobulinemia		

7. BACKGROUND INFORMATION AND STUDY RATIONALE

7.1 Waldenström‘s macroglobulinemia

Waldenström’s macroglobulinemia (WM) is defined by a bone marrow infiltration by lymphoplasmacytic cells and the presence of a monoclonal immunoglobulin (Ig) M gammopathy in the peripheral blood[6]. The clinical understanding of the disease has been greatly improved by the identification of internationally recognized criteria for initiating therapy[7], the description of an international prognostic index for patients requiring a first-line therapy[8] and the definition of response criteria. These criteria are mainly based on the evolution of serum IgM concentration[1]. However, delayed IgM monoclonal protein responses may cause important difficulties in response assessment[1]. In addition, discrepancies between the kinetics of serum M protein reduction and the clearance of monoclonal B-cells from the bone marrow have been reported[9].

Despite continuing advances in the therapy of WM, the disease remains incurable with a median survival of 5 to 8 years from the time of diagnosis, thereby necessitating the development and evaluation of novel treatment approaches.

7.2 Biology of Waldenström’s Macroglobulinemia

During the last 10 years, many biological studies demonstrated a large heterogeneity among WM patients[10]. More recently, whole genome sequencing study of 30 samples of WM patients confirmed the high frequency of losses in chromosome 6q (43%) and gains in chromosome 4 (23%). The most frequent somatic variant occurred in the myeloid differentiation primary response (MYD88) gene, resulting in a non-synonymous change at amino acid position 265 from leucine to proline (L265P) in 87% of patients. Of these, 15% had a variant effectively homozygous. Additional somatic variants occurred in transporter 2, ATP-binding cassette, sub-family B (TAP2) gene and in chemokine (C-X-C motif) receptor 4 (CXCR4) gene. Phosphorylation of the MYD88 downstream signaling proteins IRAK1, IκBα, NFκβ-p65 and STAT3 was greater in MYD88 L265P expressing cell lines and primary WM patient LPC, versus MYD88 wild type expressing healthy donor $CD19^+$ B-cells. Disruption of MYD88 Pathway Signaling induced Apoptosis of Cells Expressing the MYD88 L265P Mutation in WM[11-13].

Despite the large amount of biological understanding acquired recently and improvement of treatment results, few studies aimed to identify correlations between therapeutic results and biological findings.

7.3 Treatment results in Waldenström’s macroglobulinemia

Improvements of therapeutic results have been attempted by evaluating numerous combinations of the currently available agents. Nevertheless, it is especially important to take

the side effects of these regimens into account, because of the age at onset of the disease (median 65 years). Such regimens should be avoided in patients who will more likely experience damage than benefit due to their frailty, either related to a poor performance status or a significant number of comorbidities as assessed by the use of currently available comorbidity scores.

Single agent regimen based on alkylating agent, purine analogs, and Bortezomib demonstrated significant activity in symptomatic patients. Response rates from 48 to 92%[14-18] of 38%[18] and from 26 to 45%[19, 20] have been reported respectively as first line therapy.

The first European WM study, comparing chlorambucil vs. fludarabine, demonstrated that the median progression-free survival time (PFS), disease-free survival time (DFS) and time to progression (TTP) were significantly longer in the fludarabine arm: PFS 36.3 vs. 27.1 months (p=0.01), DFS 38.3 months vs. 19.9 months (p= 0.0005) and TTP 50.1 vs 34.6 months (p=0.01). The overall survival rate at 5 years was 62% with chlorambucil and 69% with fludarabine (p=0.05)[14].

The use of Rituximab as single agent regimen is associated with response rates between 27 to 48%[21-26].The delivery of this regimen can be associated with a flare syndrome defined by an unexpected rise of the level of the monoclonal component within the 4 to 8 weeks following treatment initiation[27]. In patients treated with Rituximab, the expression of L/H or L/R at Fcγ receptors (FcγR) 3A-48 and the expression of at least one valine (V/-) at FcγR3A-158 were associated with improved categorical responses, particularly attainment of CR/VGPR[28].

The response rates can reach 70% (see Table 4) with combination regimens including Rituximab and other chemotherapy agents[29-34]. The efficacy of the combination of Rituximab, Dexamethasone and Cyclophosphamide (DRC) appears similar to that of other combinations with a limited short term and long-term toxicity[35].

Faced with many effective regimens and few comparative studies, a consensus panel of experts recommended combination therapies such as Rituximab with nucleoside analogues with or without alkylating agents or with cyclophosphamide-based therapies (e.g. Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone or Cyclophosphamide and Dexamethasone) or combinations of Rituximab with Thalidomide. However, the guidelines did not recommend a specific first-line regimen. Because of the long natural history of WM, the choice of initial treatment is critical so that agents are not used that limit future treatment options. The prior use of purine nucleoside analogues has been associated with difficulty in mobilizing stem cells and should therefore be avoided in patients who may be eligible for autologous transplant. Furthermore, a recent report has indicated that nucleoside analogue-based combinations may be associated with an increased risk of transformation or myelodysplasia[36]. Alkylating agent–based regimens in combination with Rituximab may be preferable as initial therapy for WM.

Although there are no data from randomized clinical studies showing that the DRC regimen is superior to combinations containing purine nucleoside analogues, anthracyclines, or proteasome inhibitors, this effective regimen is associated with a modest toxicity profile and a low likelihood of limiting future stem cell collections. Therefore, the opinion of many groups is that this regimen is the combination of choice as initial treatment of patients with symptomatic or bulky disease, hematologic compromise, or hyperviscosity. This approach has been described in guidelines of the Mayo clinic[37].

Table 4 Results of immunochemotherapy in WM

Author	N patients	Treatment	ORR, %	Response duration (months)
Treon 2009[29]	43 (75% 1st line)	FR	86	51.2+
Tam 2005[30]	5	FCR	80	30+
Weber 2003[31, 38]	17	CCR	94	21+
Hensel 2005[32]	17	PCR	90	12+
Vargaftig 2006[39]	21 (19% 1st line)	FCR	78	18+
Tedeschi 2012[33]	43 (65% 1st line)	FCR	79% (12% CR)	88% à 24 m
Laszlo 2010[34]	29 (55% 1st line)	2-CdA/Rituximab (4 cycles)	89% (22% CR)	4 relapses, med Fup: 43m
Dimopoulos 2009[35]	72	DRC	83%	67% at 2 years
Buske 2009*[40]	72	CHOP/Rituximab (vs CHOP)	94%	48+
Treon 2009[41]	23	BDR	96%	
Dimopoulos, 2010[42]	61	BDR	78%	
Ghobrial[20]	37 (relapsed)	BR	81	19.5
Ghobrial[43]	26 (untreated)	BR	100	12 +

* lymphoplasmacytic lymphoma were also included
Abbreviations: med Fup: median follow-up; 2-CdA = 2-chloro-2`-deoxyadenosine; CHOP = Cyclophosphamide / Hydroxdaunorubicin / Vincristin / Prednisolon; DRC = Dexamethasone/ Rituximab / Cyclophosphamide; B(D)R = Bortezomib (Dexamethasone) Rituximab; FCR = Fludarabine / (cyclophosphamide) / Rituximab; CCR = Cladribine/ Cyclophosphamide / Rituximab; PCR = Pentostatin / Cyclophosphamide / Rituximab

7.4 Ibrutinib in Waldenström's Macroglobulinemia

Ibrutinib is an orally administered small molecule inhibitor of Bruton`s tyrosine kinase (BTK) which has demonstrated a remarkable single-agent activity in several B-cell lymphoma subtypes. Ibrutinib was tested in several prospective clinical studies. In Europe the EMA approved Ibrutinib for the indications mentioned in section 11.5 of this protocol.

Study NCT00849654

Pharmacyclics, Inc. sponsored a Phase 1 dose escalation study (Study PCYC-04753) that enrolled patients with a variety of B-cell malignancies[44]. Ibrutinib was well tolerated at doses that led to > 90% occupancy of the BTK active site. In this study, the ORR in 54 evaluable patients was 57%, including a complete response rate of 16%. The study enrolled 4 male

patients with relapsed/refractory WM who received a median of 3 prior systemic regimens and were treated at 2 different dose levels (560 mg/day and 12.5 mg/kg/day). IgM values at baseline varied between 4.4-5.5 g/dL. All 4 patients experienced at least 1 AE, and SAEs were reported in 3 patients. The majority of AEs were grade 1 and unrelated to Ibrutinib, with the exception of 3 grade 2 AEs (hypertension, atrial fibrillation [also an SAE], and pyrexia; all unrelated to Ibrutinib), and 1 grade 4 AE of neutropenia (unrelated to Ibrutinib). The 5 reported SAEs were all unrelated to Ibrutinib (2 patients each with grade 1 febrile neutropenia and 1 patient with grade 2 atrial fibrillation, grade 1 pneumonia, and grade 1 pneumonitis). No patients required a dose reduction or discontinued due to an AE. The majority of AEs did not require treatment; the remainder was readily managed with concomitant medications. One out of the 4 patients achieved disease stabilization according to the treating physician but ultimately discontinued Ibrutinib due to progressive disease after 8 months. Three out of the 4 patients achieved a PR (IgM reduction of at least 50% from baseline). The induced responses were durable, and all 3 patients rolled over onto the extension Study PCYC-1103-CA and continue to receive treatment with Ibrutinib for more than 3 years. In addition to the clinically significant IgM decrease in the 3 responders, all 4 patients had an increase in their hemoglobin and hematocrit over treatment time. Preliminary safety data from the ongoing PCYC-1103-CA study have indicated that all 4 patients experienced at least 1 AE grade 3 or higher, but no SAEs have been reported to date on the long-term extension.

Study NCT01614821

Approval in WM is based on a pivotal phase II multicenter study by Treon and colleagues, an investigator-sponsored study conducted under IND 113,935 at Dana Farber Cancer Institute, Memorial Sloan-Kettering Cancer Center, and Stanford University and led by Dr. Steven Treon at the Dana Farber Cancer Institute, was initiated in May 2012 in patients who received at least 1 prior therapy for WM and in need of treatment. In this phase II study, Ibrutinib was administered orally 420 mg once daily and continued for 2 years or until progressive disease or intolerability. Enrollment of 63 patients was completed in June 2013 (43 patients at Dana Farber Cancer Institute, 10 patients at Stanford University, and 10 patients at Memorial Sloan-Kettering Cancer Center) and represents one of the largest single-arm studies conducted specifically in patients with WM. Most treatment related side effects were mild and well tolerated and included neutropenia (22%) as well as thrombocytopenia (14%). No unexpected bleeding events were observed, there were no clinically relevant atrial fibrillations observed. Patients responded quickly within a median of 4 weeks with an overall response rate of 90.5%, including 73% major response rates. Responses were depending on the mutational status with highest response rates in patients with the mutation status $MYD88^{mut}/CXCR4^{WT}$, counting for the majority of patients (overall response rate of 100% and 91.2% „Major Response")[2, 11].

In another large prospective randomized phase III study 150 patients with treatment naïve or relapsed WM in need of treatment were randomized between Ibrutinib / Rituximab (IR) Rituximab / Placebo (R)[45]. Median age was 69 years. High IPSSWM was reported in 38% of patients; 45% of patients were treatment naïve. With prolonged follow-up and a median duration of treatment of 29.5 months with IR and 15.5 months with R. Investigator-assessed major response rates (≥ PR) were 77% with IR vs 33% with R (P<0.0001); ORRs (≥ MR) were 95% vs 48% (P<0.0001), respectively. With continued IR treatment, 27% of patients achieved a VGPR compared to only 3% in the R arm. Major responses with IR stayed robust independent of MYD88/CXCR genotype. Overall time to major response was 2.0 months with IR vs 5.6 months with R ($MYD88^{L265P}$/$CXCR4^{WT}$: 1.8 vs 5.2; $MYD88^{L265P}$/$CXCR4^{WHIM}$: 2.9 vs 10.8; $MYD88^{WT}$/$CXCR4^{WT}$: 5.7 vs 5.7). Median investigator-assessed PFS was not reached with IR vs 20.3 months (95% CI: 11.6–31.3) with R (HR=0.219 [0.122–0.393]; P<0.0001); estimated 30-mo PFS was 79% vs 41%. Among patients receiving IR, 30-months PFS estimates did not show any major differences among the different genotypes. The 30-months OS estimate was 93% with IR vs 90% with R; 31 patients on R crossed over to IR after IRC-confirmed PD. The AE profile in the IR arm was consistent with previous reports. Overall, grade ≥ 3 AEs occurred in 61% of patients in both arms. Incidence of grade ≥ 3 AEs was 53% during the first 12 months of treatment in the IR arm and increased 8% with longer follow up. SAEs occurred in 43% of IR patients vs. 33% of R patients. Similarly, incidence of SAEs was 39% during the first 12 months of treatment with IR and increased 4% with longer follow up.

These data and the approval of Ibrutinib have changed the therapeutic landscape in WM in shortest time and have fostered spread of chemotherapy-free approaches in the management of WM.

7.5 Carfilzomib in Waldenström´s macroglobulinemia

Another class of highly active drugs in WM are so called proteasome inhibitors. The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N terminal threonine protease activities: a chymotrypsin like activity, a trypsin like activity, and a caspase like activity[46]. The most known proteasome inhibitor for the treatment of WM is Bortezomib. Response rate from 26 to 45% and from 78 to 96% have been reported in WM patients who received first line therapy with Bortezomib alone or in combination with Rituximab and Dexamethasone, respectively[19, 41, 47]. The combination of Bortezomib with Rituximab was analyzed in a phase II study: 37 patients with relapsed or refractory WM were treated with Bortezomib 1.6 mg/m^2 day 1, 8, 15 in a 28 days cycle for 6 cycles combined with Rituximab 375

mg/m^2 day 1, 8, 15, 22 cycles 1 and 4. The median numbers of cycles was three and 78% of the patients completed the treatment. This combination induced an OR of 81% with 5% CR and 46% PR. Grade 3 or 4 toxicity was acceptable with 16% leukocytopenia, 11% anemia and 5% neuropathy. One patient died of pneumonia, emphasizing that severe infectious complications might occur in this patient population[20]. One of the major limitations of Bortezomib is its inherent neurotoxicity. This side effect limits treatment in particular in WM, as the disease causes neuropathy at diagnosis in up to every fourth patients, by this excluding any use of neurotoxic drugs in a large fraction of patients[48]. Of note, neuropathy is one of the toxicities, which compromises life quality most, so it is particular difficult to justify application of neurotoxic drugs in an indolent disease such as WM often associated with neuropathy by itself.

Another proteasome inhibitor is Carfilzomib, which has the key advantage that it lacks neurotoxicity to a large extent. Based on this characteristic, it is a highly attractive drug particularly for WM. Carfilzomib is a tetrapeptide epoxyketone based inhibitor of the 20S proteasome. Carfilzomib, showed less off target activity when measured against a broad panel of proteases including metallo-, aspartyl-, and serine proteases compared to Bortezomib. Bortezomib showed off target inhibitory activity in the nanomolar range against several serine proteases. This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in studies comparing Carfilzomib with Bortezomib[49]. Incubation of hematologic tumor cell lines with Carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death[50]. Carfilzomib entered clinical studies in September 2005. On 20 July 2012, “Kyprolis" was approved under the United States Food and Drug Administration's (US FDA) accelerated approval program for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including Bortezomib and an immunomodulatory drug, and have demonstrated disease progression on or within 60 days of completion of the last therapy. The initial accelerated approval was based on the results of the phase 2 X-171-003-A1 study in the United States. Subsequent full approval in the United States and globally were based on two phase 3 studies: PX 171-009 ASPIRE and 2011-003 ENDEAVOR[51, 52]. The EMA has approved Carfilzomib in combination with either Lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As of 19 July 2016, an estimated 3373 patients (2711 patient-years) have been exposed to Carfilzomib in company-sponsored clinical studies since the beginning of the development program.

The EMA has summarized the clinical efficacy and safety of Carfilzomib as follows[53]: the pivotal efficacy study was PX-171-009 (ASPIRE), a randomized, multicenter, phase III study to compare the efficacy and safety of CRd versus Rd in patients with relapsed MM[51]. Eligibility criteria included symptomatic and measurable MM; at least one prior treatment but no more than

three protocol-defined MM regimens, with documented relapsed or PD on or after any regimen (patients' refractory to the most recent line of therapy were eligible); achieved a response to at least one prior regimen; ECOG performance status 0-2. Carfilzomib was administered at an initial dose of 20 mg/m^2, which was increased to 27 mg/m^2 on cycle 1, day 8, twice weekly for 3 out of 4 weeks as a 10-minute infusion for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and Dexamethasone administration could continue until progression or unacceptable toxicity. The primary endpoint was PFS assessed by an IRC, defined as the duration in months from the date of randomization to the date of confirmed PD or death due to any cause, whichever was earlier, according to the International Myeloma Working Group Uniform Response Criteria. A total of 792 patients were randomly assigned (1:1 ratio) to receive either CRd or Rd and they were stratified by β2 microglobulin levels (< 2.5 mg/L vs. ≥ 2.5 mg/L), prior Bortezomib (yes vs. no), and prior Lenalidomide (yes vs. no). In the PFS analysis, which was carried out with 82% of the planned events, the median PFS in the CRd group was 26.3 months compared with 17.6 months for the Rd group (HR = 0.69; 95% CI, 0.57–0.83; one-sided log-rank *p* value < .0001).

Eleven completed clinical studies with 2123 patients formed the primary basis for evaluation of Carfilzomib safety. In study PX-171-009, the median relative dose intensity was 96% (CRd group) for Carfilzomib, 91% and 92% for Lenalidomide (CRd and Rd group, respectively), and 95% and 95% for dexamethasone. The most common adverse reactions (occurring in > 20% of patients) observed in patients receiving Carfilzomib were anemia, fatigue, diarrhea, thrombocytopenia, nausea, pyrexia, dyspnea, respiratory tract infection, cough, and peripheral edema. In study PX-171-009, 59.9% and 54.0% of patients experienced at least one SAE in the CRd and Rd arms, respectively, with pneumonia, respiratory tract infection, pyrexia, pulmonary embolism, deep vein thrombosis, anemia, bronchitis, and febrile neutropenia being the most frequently observed. The incidence of treatment-related grade ≥ 3 AEs was 67.1% in the CRd group and 60.2% in the Rd group. There were no grade ≥ 3 treatment-related AEs with a ≥ 5% difference between study arms. Grade ≥ 3 AEs with a ≥ 2% to <5% difference between study arms included neutropenia, thrombocytopenia, pneumonia, and hypophosphatemia. Thirty (7.7%) patients in the CRd arm and 33 (8.5%) patients in the Rd arm died on study (within 30 days after their last dose of any study treatment: Carfilzomib, Lenalidomide, or Dexamethasone) with AEs of infection being the most common cause of on-study deaths. No deaths were considered to be related specifically to Carfilzomib alone. Two of the deaths in the CRd arm were considered to be related to both Carfilzomib and Lenalidomide. In clinical studies, cardiac failure (reported in approximately 7% of patients), myocardial infarction (reported in approximately 2% of patients), and myocardial ischemia (reported in approximately 1% of patients) typically occurred early in the course of Carfilzomib therapy (< 5 cycles). Approximately 65% of cardiac failure events, 75% of myocardial infarction events, and 83% of myocardial

ischemia events were grade ≥3 events. In pivotal study PX-171-009, there were more cardiac failure events (6.4% vs. 4.1%), grade ≥ 3 cardiac failure (3.8% vs. 1.8%), ischemic heart disease (5.9% vs. 4.6%), grade ≥ 3 ischemic heart disease (3.3% vs. 2.1%), cardiac arrhythmias (16.6% vs. 15.2%), and cardiomyopathy (1.0% vs. 0.3%) in the CRd arm than in the Rd group. In addition, cardiotoxicity was reported as primary cause of death in 10 patients in CRd group vs. 7 patients in the Rd arm. Other important identified risks included pulmonary toxicities, pulmonary hypertension, dyspnea, hypertension, acute renal failure, tumor lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, thrombotic microangiopathy, posterior reversible encephalopathy syndrome, and febrile neutropenia. Recent data have proven, that a once weekly dosing of Carfilzomib with 70mg/m^2 per week significantly prolonged progression-free survival versus the twice weekly schedule with an overall safety that was comparable between the groups[54].

Carfilzomib was evaluated in combination with Rituximab and Dexamethasone (CaRD) in WM patients that were naive to both Bortezomib and Rituximab[4]. CaRD therapy consisted of i.v. Carfilzomib given at 20 mg/m^2 (on cycle 1), and on 36 mg/m^2 thereafter (cycles 2-6), on days 1, 2 and 8, 9 with Dexamethasone 20 mg on days 1, 2, 8, 9 and Rituximab 375 mg/m^2 on days 2, 9 every 21 days. Maintenance therapy followed 8 weeks after cycle 6 with i.v. Carfilzomib 36 mg/m^2 and Dexamethasone 20 mg on days 1, 2 and Rituximab 375 mg/m^2 on day 2 every 8 weeks for 8 cycles. The ORR in this study was 87%, and 68% of the patients achieved a major response. In this study, MYD88 and CXCR4 tumor mutational status were examined and did not appear to impact response attainment, although the numbers are small. With a median follow-up of 15.4 months, 20 patients remained progression-free at the time of reporting. Grade 2 polyneuropathy occurred in only 1 patient with underlying disease-related polyneuropathy, and no grade 3 or higher treatment-related neuropathy events were recorded. Other grade > 2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), and cardiomyopathy in one patient (3.2%) with multiple risk factors. Declines in serum levels of IgA and IgG were common and contributed to recurring sinobronchial infections and i.v. immunoglobulin use in a few patients. In a case series report, Vesole and colleagues reported a single-center experience of Carfilzomib treatment in relapsed WM treated in a phase 1b/ phase 2 program. Patients received Carfilzomib at 56 or 70 mg/m^2 after 20 mg/m^2 on the first 2 doses (day 1 and 2 of the first cycle), whereas Dexamethasone 8 mg was administered on each day of Carfilzomib therapy during the first cycle and was optional for subsequent cycles. If patients achieved less than a PR after 4 cycles, then Rituximab 375 mg/m^2 was added on day 16 of each cycle, and the Carfilzomib dose was decreased to 27 mg/m^2. Patients were treated to maximal response plus 2 additional cycles (for a maximum of 12 cycles). Seven patients received Carfilzomib, and no patient received Rituximab. Among the 7 patients, 4 received Carfilzomib at 70 mg/m^2 and 3 received Carfilzomib at 56 mg/m^2. No dose-limiting toxicities occurred, although

6 patients reported at least 1 grade > 3 adverse event and one patient discontinued treatment due to an adverse event. Two patients had neuropathy events (grade 3), whose relationship to study drug was considered probable. Six patients had a prior exposure to Bortezomib, and 2 were refractory. All patients achieved a minor response (MR) or better, including 1 stringent complete response (sCR) (overall 1 sCR, 3 PRs, 2 VGPRs, and 1 MR). The 2 patients that were Bortezomib refractory achieved a PR. In this small series of patients, 6/7 patients did not have a PD at a follow-up time of 13 to 27 months.

7.6 Rationale for the study design

7.6.1 Overall rationale

In WM conventional chemotherapy induces only low CR rates and responses of short duration compared to other indolent lymphomas. Thus, innovative approaches are needed which combine excellent activity and tolerability in patients with WM, who are mostly of advanced age. Today, chemotherapy in combination with the anti-CD20 antibody Rituximab is still the backbone of treatment in patients with WM and is recommended as first line in national and international treatment guidelines[55]. With the approval of Ibrutinib by the EMA 2015 for patients with relapsed WM or for patients not eligible for chemotherapy with treatment naïve WM treatment landscape has changed in this lymphoma subtype and there is an urgent need to evaluate to which extent chemotherapy-free approaches add clinical benefit to the patient[56]. Based on its high activity in WM and its low toxicity, Ibrutinib was approved for the treatment of WM by the EMA[2]. However, also Ibrutinib fails to induce CRs and the VGPR rate is 16% in relapsed patients[2]. In addition, activity of Ibrutinib depends on the genotype with inferior response rates in $MYD88^{mut}/CXCR4^{mut}$ patients and in patients with unmutated MYD88 and CXCR4 compared to $MYD88^{mut}/CXCR4^{WT}$ patients (major response [at least PR] in 91.7% compared to 61.9% and 0%, respectively)[2, 3]. 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[4]. 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.

7.6.2 Rationale for Ibrutinib monotherapy arm

In the international consensus manuscript, published in the “Lancet Haematology” Ibrutinib is among the preferred treatment options for symptomatic treatment naïve patients with WM[57].

This also illustrates that there is not one standard treatment for WM, but fortunately a variety of highly effective and well tolerated treatment options for this disease first line, among them Ibrutinib single agent. The EMA approved Ibrutinib in combination with Rituximab also for the first line treatment of WM, which again demonstrates that Ibrutinib is accepted as an important cornerstone of therapy in treatment naïve patients. This approval was based on the iNNOVATE trial, which compared Ibrutinib / Rituximab versus Placebo / Rituximab in treatment naïve and relapsed WM in a phase III study. We agreed with all authors that the trial does not prove that Ibrutinib / Rituximab is superior to Ibrutinib alone, reflected also in the aforementioned consensus manuscript[45, 57]. Thus, we believe that single Ibrutinib is comparable to the approved combination Ibrutinib / Rituximab in patients with WM in the first line setting. If we compare Ibrutinib single agent to classical Rituximab / chemotherapy, the efficacy of Ibrutinib is at least as good as for the polychemotherapies DRC or R-Bendamustine: in a recent update the 5-year PFS for Ibrutinib single agent in mostly relapsed / refractory patients was 54% compared to a reported 5-year PFS for R-Bendamustine (limited patient number of n=22) and compared to DRC with a median PFS of 35 months with disease progression at three years of 45%[58-60]. To the end, the trial offers the patients one of the standard treatments in WM with Ibrutinib single agent, not depriving them of one of the current standards of care.

7.6.3 Rationale for the proposed dosing regime

In previous studies in patients with multiple myeloma 840 mg Ibrutinib was tested with 36 mg/m^2 Carfilzomib. Carfilzomib was administered intravenously on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle from cycle 1 through cycle 12 and thereafter on days 1, 2, 15, and 16. The Carfilzomib starting dose was 20 mg/m^2 on days 1 and 2 of cycle 1, and if tolerated, the dose was increased to 36 mg/m^2 on day 8 of cycle 1 and stayed at that level for subsequent cycles. In preceding phase 1 trial, no dose limiting toxicity had been observed with this dosing regimen[61, 62]. In second phase 1 trial in patients with mantle cell lymphoma Ibrutinib was administered orally daily at 560 mg on days 1 - 28 of each 28-day cycle. Carfilzomib was given intravenously in escalating dose cohorts of 27, 36, 45 or 56 mg/m^2 on days 1, 2, 8, 9, 15 and 16 of each 28-day cycle for cycles 1 - 12 and on days 1, 2, 15 and 16 (with the omission of days 8 and 9) for cycles ≥ 13 with no dose limiting toxicity up to dose level 3 (45 mg/m^2 Carfilzomib; the level 4 dose level could not be tested because of slow patient recruitment and stop of the study)[63]. Taking together, in both trials a higher dose of Ibrutinib was administered than planned in our study, which will limit the dose of Ibrutinib to 420 mg/d.

When the absolute amount of Carfilzomib is calculated for the study in multiple myeloma, the patients have received 6 applications each 36mg/m^2 for 12 cycles (n= 72 applications) and thereafter 4 applications per cycle for subsequent cycles (until progression) with a median time on study of 24.1 months (median 12 cycles, n=48 applications)[61]. Thus, patients received a

total of 120 applications of 36 mg/m^2 each, summing up to 4320 mg/m^2 per patient. In the second trial patients received escalating doses up to 45 mg/m^2 6 applications for the first 12 cycles (n=72 applications) and later on 4 applications up to 45 mg/m^2, resulting in a higher cumulative dose per patient compared to the multiple myeloma trial[63]. Of note, both trials did not find a dose limiting toxicity as mentioned above. In our trial Carfilzomib will be given with a starting dose of 20 mg/m² on day 1 cycle 1, and if tolerated, the dose will be increased to 70 mg/m² for day 8 and 15 of cycle 1 (n = 3 applications). Carfilzomib will be administered thereafter on day 1, 8, 15 of cycle 2 to 12 (n = 33 applications) and on day 1 and 15 for cycle 13 to 24 (n = 24 applications). In summary the patients will receive 4150 mg/m² Carfilzomib in this trial. Thus, our trial will combine Ibrutinib at lower dose with a total amount of Carfilzomib comparable to the both studies described above. We do not use the twice weekly application of Carfilzomib at a dose of 56 mg/m^2, but the once weekly application of Carfilzomib at 70 mg/m^2. This not only reduces the total amount of Carfilzomib given per week, but there are in addition large data sets in patients with multiple myeloma, demonstrating convincingly that the toxicity of the once weekly application is not higher, but probably even lower than the twice weekly application with comparable efficacy. This was demonstrated in several large phase III trials and is summarized in the publication by Moreau et al[64]. In this pooled analysis the authors state that “In the side-by-side analysis of the subgroups, fewer grade ≥ 3 AEs were observed with Kd70 QW (67.6%) compared with Kd56 BIW (85.3%), despite similar median treatment exposure times (38.1 vs 40.3 weeks). The frequency of grade ≥ 3 AEs of interest also differed between Kd70 QW and Kd56 BIW, with lower rates of cardiac failure (1.4% vs 5.1%), acute renal failure (3.4% vs 6.0%), and hypertension (5.5% vs 15.7%) observed with Kd70 QW vs Kd56 BIW. In a safety analysis limited to the first 6 months from receiving treatment, a lower frequency of grade ≥ 3 AEs with Kd70 QW vs Kd56 BIW was also observed. These results support that Kd70 QW represents a convenient and well-tolerated dosing option for patients with RRMM.” Based on the data of the ENDEAVOUR trial Carfilzomib one weekly at 70 mg/m^2 was already approved earlier on by the FDA and EMA for multiple myeloma[52].

To the end we believe that the benefit / risk ratio justifies this treatment schedule proposed in our trial. Nevertheless, the safety of the Ibrutinib / Carfilzomib should be monitored carefully in this trial. Therefore, it will be a close monitoring for treatment related toxicity comprising the first 10 included patients into the study in arm A (see section 13.1). Safety evaluations will be performed on day 1, day 8 and day 15 for cycle 1-6 and include additionally laboratory assessments and further ECGs. Furthermore, we established an independent DSMC (see section 15).

7.7 Risk benefit assessment

The expected toxicity described above is countered by the potential benefits regarding increase of VGPR / CR rate, which correlates with progression free survival (see above). The precautionary safety measures, the regular monitoring of safety by the sponsor and the implementation of an independent DSMC enables early identification of safety signals in the study and minimizes the risk to enrolled patients. In conclusion, based on the known safety profile of Ibrutinib and Carfilzomib as well as the mechanism of action of the two products, it is considered that the benefit-risk ratio for this study is favorable.

COVID-19 risk benefit assessment

As the spread of COVID-19 varies between different locations and over time and vaccination coverage has generally increased, there is a greater need for flexibility when it comes to infection prevention. The measures need to be adapted to regional and local conditions and may, depending on the situation, need to be stepped up or down within the relevant region or activities. Precautionary measures commonly used are distance in waiting areas, between staff and patient, when possible, wearing face masks, use of disinfection and limitations in visitors to the hospital that are accompanying patients (if not medically warranted).

In overall, we assess that currently the benefit outweighs the risk as these patients have a high medical need to receive treatment for their disease.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective

The primary objective of the study is to explore the efficacy of Carfilzomib in combination with Ibrutinib compared to Ibrutinib alone in patients with treatment naïve or relapsed WM.

8.2 Secondary objective

Secondary objectives of the trial are to evaluate the anti-lymphoma activity of Carfilzomib / Ibrutinib compared to Ibrutinib alone in patients with treatment naïve or relapsed WM assessing response rates, time to treatment failure, remission duration, cause specific survival and overall survival and to assess the safety and quality of live.

8.3 Primary endpoint

The aim of this study is to investigate the rate of CR or VGPR 12 months from randomization using the modified response criteria updated at the Sixth IWWM[1] (CR/VGPR).

8.4 Secondary endpoints

Secondary endpoints are the following and will be described in more detail in section 14.1 of the protocol:

- Response rate (CR, VGPR, PR, MR) and ORR (CR, VGPR, PR) 12 and 24 months after randomization
- Best response
- Time to best response
- Time to first response
- Time to treatment failure
- Remission Duration
- Progression free survival
- Cause specific survival
- Overall survival
- Safety
- Quality of life

8.5 Safety endpoints

Safety variables will include AEs, SAEs, laboratory parameters, ECG and vital signs. The severity of AEs will be graded using the NCI-CTCAE version 5.0 dictionary. An AE is defined as any event arising or worsening after first application / intake of study drug until 30 days after the last study drug intake. Safety variables will be summarized by means of descriptive statistics and / or frequency tables as appropriate. All AEs, drug related AEs and serious AEs will be summarized by MedDRA classification and worst CTCAE grade.

9. STUDY DESIGN

The study is an international, phase II, multicenter, open label and randomized trial comparing Carfilzomib in combination with Ibrutinib (treatment arm A) versus Ibrutinib alone (treatment arm B) in male or female patients aged ≥ 18 years of de novo or relapsed / refractory WM in need of treatment.

The phase II study will consist of an open labeled, stratified 1:1 randomization between arm A and arm B. Stratification factors are MYD88 and CXCR4 status (mutated / not mutated) and number of prior lines (0 vs. ≥ 1 treatment lines) (details in chapter 12.5). A stratified central block randomization will be used. All patients will be followed up max. 7 years after FPI. The study flow is shown in Figure 1.

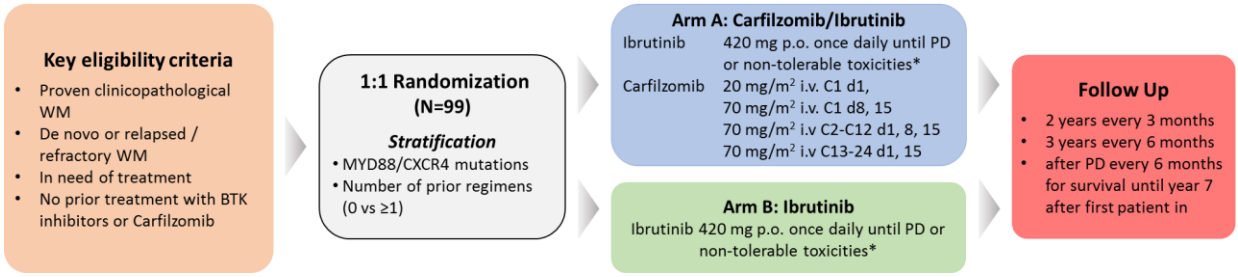

Figure 1 Study design

*Treatment with Ibrutinib and follow up for a maximum of 7 years after FPI within this trial.

9.1 Estimated study duration

Approximately 99 patients at approximately 30 study sites in Europe will be recruited. Patients will receive Ibrutinib in both treatment arms until progression, non-tolerated toxicity or until the study duration has reached its maximum of 7 years after the first patient was included into the study. Patients will be followed up after end of treatment. Follow-up (5 years or until disease progression for patients who discontinue treatment due to toxicity) or survival follow-up (for patients with disease progression) will be performed until the study duration has reached its maximum of 7 years after the first patient was included into the study.

1st patient included:	Q1 2021 (18.02.2021)
Last patient included:	Q2 2024
Maximal duration of study therapy/patient:	Until progression, non-tolerated toxicities or until the study duration has reached its maximum of 7 years after the first patient was included into the study.
Duration of follow-up / patient:	a) In the case that treatment is terminated because of non-tolerable toxicity follow up will be performed 5 years or until the study duration has reached its maximum of 7 years after the first patient was included into the study. b) In the case of progression or start of a new anti-lymphoma therapy every 6 months for survival until the end of the study.
End of study:	5 years after the last included patient has finished therapy or until the study duration has reached its maximum of 7 years after the first patient was included into the study.

Further treatment with Ibrutinib outside this protocol, for patients who continue to benefit from the Ibrutinib treatment 7 years after first patient in, will be at the investigator's discretion

according to local practice and local commercial availability of Ibrutinib. After finishing all study relevant procedures (therapy and follow-up period), the patient will be followed in terms of routine aftercare and treated if necessary by the primary responsible hematologic-oncologic center.

10. STUDY POPULATION

10.1 Gender distribution

No gender ratio has been stipulated in this study as the results of preclinical and / or clinical studies or medical literature did not indicate any difference in the effect of the study treatment in terms of efficacy and safety.

10.2 Inclusion criteria

Each patient must meet the following inclusion criteria to be enrolled in this study:

- Proven clinicopathological diagnosis of WM as defined by consensus panel one of the Second IWWM[66]. Histopathology has to occur before randomization within the last 4 months. In addition, pathological specimens have to be sent to the pathological reference center prior to randomization for the determination of the mutational status of MYD88 and CXCR4 (if not already known). Immunophenotyping will be performed in each center and archived locally. The positivity for CD20 can be assumed from any previous bone marrow immunohistochemistry or flow cytometry analysis performed up to 4 months prior to enrollment. Flow cytometry of bone marrow and blood cells will include at least one double staining and assess the disease specific expressions.
- De novo or relapsed / refractory WM independent of the genotype.
- Patients must have at least one of the following criteria to start study treatment as partly defined by consensus panel criteria from the Seventh IWWM[5]:
    - Recurrent fever, night sweats, weight loss, fatigue.
    - Hyperviscosity.
    - Lymphadenopathy which is either symptomatic or bulky (≥ 5 cm in maximum diameter).
    - Symptomatic hepatomegaly and / or splenomegaly.
    - Symptomatic organomegaly and / or organ or tissue infiltration.
    - Peripheral neuropathy due to WM.
    - Symptomatic cryoglobulinemia.
    - Cold agglutinin anemia.
    - IgM related immune hemolytic anemia and / or thrombocytopenia.
    - Nephropathy related to WM.

  - Amyloidosis related to WM.
  - Hemoglobin ≤ 10 g/dL (patients should not have received red blood cells transfusions for at least 7 days prior to obtaining the screening hemoglobin).
  - Platelet count < 100 x 10^9/L (caused by BM infiltration of the lymphoma).
  - Serum monoclonal protein > 5 g/dL, even with no overt clinical symptoms.
  - IgM serum concentration ≥ 5 g/dl.
  - and other WM associated relevant symptoms.
- World Health Organization (WHO) / ECOG performance status ≤ 2.
- Left ventricular ejection fraction ≥ 40% as assessed by transthoracic echocardiogram (TTE).
- Other criteria
  - Age ≥ 18 years (male and female).
  - Life expectancy > 3 months in the opinion of the investigator.
  - Baseline platelet count ≥ 50 x10^9/L, absolute neutrophil count ≥ 0.75 x 10^9/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:
    - ASAT (SGOT): < 3.0 times the ULN.
    - ALAT (SGPT): < 3.0 times the ULN.
    - Total Bilirubin: < 1.5 times the ULN, unless clearly related to the disease (except if due to Gilbert's syndrome).
    - Serum creatinine: ≤ 1.5 times the ULN.
- Women of childbearing potential (WCBP), 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 Carfilzomib or Ibrutinib. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner or sexual abstinence. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause (refer to chapter 11.4.4). Contraception and pregnancy testing are required according the CTFG recommendations.
- Men must agree not to father a child for the duration of therapy and 6 months after (use of a condom) 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.

- Each patient must sign an informed consent form in a fluent language of the patient indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

10.3 Exclusion criteria

The presence of the following criteria will exclude a patient from enrolment:

- Previous treatments with following substances:
  - Prior exposure to Ibrutinib or other BTK inhibitors.
  - Prior exposure to Carfilzomib. Prior exposure to other proteasome inhibitors is allowed if the patients were not refractory, that is, had a remission (at least minor response) duration of ≥ 6 months. Prior plasmapheresis and short-term administration of corticosteroids ≤ 6 weeks administered at a dose equivalent to ≤ 20 mg/day of prednisone is also allowed.
- Serious medical or psychiatric illness (especially undergoing treatment) likely to interfere with participation in this clinical study.
- Active HIV, HBV or HCV infection (see protocol section 12.4.12.9).
- 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 randomization, other Stage 1 or 2 cancer treated with a curative intent and currently in complete remission, for ≥ 3 years.
- Uncontrolled illness including, but not limited to:
  - Uncontrolled diabetes mellitus (as indicated by metabolic derangements and / or severe diabetes mellitus related uncontrolled organ complications).
  - Chronic symptomatic congestive heart failure (Class NYHA III or IV) or LVEF < 40%.
  - Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months prior to randomization.
  - Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
  - 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.
  - Cardiac amyloidosis.
- Recent major surgery within 30 days prior to randomization.
- Known cirrhosis (meeting child-pugh stage C).
- Approved or investigational anticancer treatment 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.
- Hypersensitivity to the active substances or to any of the excipients of the investigational medicinal products.
- 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 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 according European Society of Hypertension/European Society of Cardiology [ESH / ESC] 2013 guidelines[65].
- History of stroke or intracranial hemorrhage within 6 months prior to randomization.
- Known interstitial lung disease.
- Infiltrative pulmonary disease, known pulmonary hypertension.
- 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 (see also https://www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf), or currently has uncontrolled asthma of any classification or at time of screening has an FEV1 of < 50% of predicted normal.
- Autologous or allogeneic stem cell transplant less than 100 days prior to randomization.
- Vaccination with live attenuated vaccines within 30 days prior to randomization.
- Patients who require strong or moderate inducers or inhibitors for cytochrome P450, family 3 or subfamily A (CYP3A).

- Patients who have an uncontrolled bleeding disorder or require an anticoagulant (e.g. warfarin or other vitamin K antagonists; novel oral anticoagulants (NOACs) are allowed) at time of screening.
- 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 patient safely or interfere with the study evaluation, procedures or completion.
- Patient is a woman who is pregnant or breastfeeding (and do not consent to discontinue breast-feeding) or planning to become pregnant while enrolled in this study or within 6 months after the last study treatment.
- Vulnerable patients, e.g. patients who are incapable of giving informed consent (severe dementia or psychosis, patients kept in detention).
- Participation in another interventional clinical study within 30 days before randomization in this study.

11. TREATMENTS

Eligible patients will be registered at the first screening visit (after signing the informed consent) and will be randomized between the experimental treatment arm A (Carfilzomib and Ibrutinib) and treatment arm B (Ibrutinib) after mutational status is determined by reference pathology (if not already known) and all inclusion criteria and no exclusion criteria are fulfilled. In general, study treatment should occur on the scheduled day (± 4 days during treatment, for further time window see flowcharts), with the exception of delays resulting from toxicities.

11.1 Experimental arm (arm A)

Treatment with Ibrutinib will be given until evidence of progressive disease or if the patient didn´t tolerate the therapy anymore (maximum of 7 years' treatment within the study after first patient in). Additionally, all patients in arm A receive Carfilzomib for two years. Treatment courses are administered in 28-day cycles. If one drug has been discontinued due to toxicities, the other drug can be administered alone in arm A according the protocol.

Cycle 1		
Ibrutinib	420 mg p.o.	Daily, until evidence of progressive disease or no longer tolerated by the patient
Carfilzomib	20 mg/m^2 i.v. 70 mg/m^2 i.v.	Day 1 Day 8,15
Cycle 2-12		
Ibrutinib	420 mg p.o.	Daily, until evidence of progressive disease or no longer tolerated by the patient
Carfilzomib	70 mg/m^2 i.v.	Day 1,8,15
Cycle 13-24		
Ibrutinib	420 mg p.o.	Daily, until evidence of progressive disease or no longer tolerated by the patient
Carfilzomib	70 mg/m^2 i.v.	Day 1,15
From Cycle 25 until end of treatment		
Ibrutinib	420 mg p.o.	Daily, until evidence of progressive disease or no longer tolerated by the patient

11.2 Standard arm (arm B)

Treatment with Ibrutinib will be given until evidence of progressive disease or no longer tolerated by the patient (maximum of 7 years' treatment within the study after first patient in).

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

11.3 Study drugs

11.3.1 Carfilzomib

Carfilzomib is a proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. For the most comprehensive nonclinical and clinical information regarding Carfilzomib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of Carfilzomib, refer to the latest version of the Carfilzomib Investigator's Brochure.

11.3.1.1 Dosage, administration and schedule

Carfilzomib will be administered as an i.v. infusion. Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the 30-minute infusion duration can be reliably maintained. For patients with baseline chronic hepatic impairment (child-pugh stage B), a close monitoring of worsening of the hepatic impairment is recommended (special focus during clinical visits, laboratory assessments). Prophylactic Dexamethasone (4 mg) is obligatory before the first Carfilzomib infusion and for later Carfilzomib infusions as indicated.

Carfilzomib will be dosed as follows in the study in 28-day cycles:

Cycle 1	20 mg/m² i.v.	Day 1
	70 mg/m² i.v.	Day 8, 15
Cycle 2 - 12	70 mg/m² i.v.	Day 1, 8, 15
Cycle 13 - 24	70 mg/m² i.v.	Day 1, 15

Each patient's first dose of Carfilzomib will be calculated based upon baseline body surface area (BSA). In patients with BSA of greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each patient should not be revised unless the patient experiences a change in body weight of ~ 20% to the last visit in which case the BSA and dose should be recalculated. The dose can also be modified in response to toxicity following the dose modification guideline tables (chapter 11.3.2). Administration will be documented in the drug accountability form and the eCRF.

11.3.1.2 Intravenous prehydration

Infusion reactions, including life-threatening reactions, have been reported in patients who received Carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Carfilzomib. Patients in arm A will receive i.v. prehydration prior to each Carfilzomib infusion during cycle 1. Prehydration will consist of 250 mL normal saline or other appropriate i.v. fluid. Thereafter, Carfilzomib prehydration should only be administered if the patient's condition and / or risk factors require it.

11.3.2 Dose modifications for Carfilzomib

11.3.2.1 Dosage adjustments, delays, rules for withholding or restarting, permanent discontinuation

Carfilzomib will be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related adverse event that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in Table 5 and Table 6. The patient will be considered on protocol treatment while receiving either Carfilzomib and / or Ibrutinib (i.e. if either Carfilzomib or Ibrutinib are discontinued or interrupted, the patient is still considered on treatment if still taking the other investigational product). If day 1 of a cycle is delayed, day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. If Carfilzomib administration does not commence

within the allowable window of the scheduled administration date, then this dose will be considered a missed dose with continuation of the subsequent cycles. Administration may resume at the next planned dosing date. A missed dose will not be made up. Carfilzomib must be discontinued permanently if a delay of more than 6 weeks is required due to unresolved toxicity.

11.3.2.2 Dosage reduction levels

Dose reduction levels of Carfilzomib for toxicity and adverse event management of individual patients are provided in Table 5. In case of adverse events not described in the following sections, the treating physician may adjust the Carfilzomib treatment at his or her discretion, considering the dose modification guidelines described in the Table 6 and Table 7 and in the RSI. Patients that require a dose level reduction and tolerate the reduced dose for 1 full cycle, may at the discretion of the investigator increase the dose to the prior dose starting with the next cycle except when the dose reduction is due to: pulmonary hypertension or pulmonary adverse events grade 3 or worse cardiac failure, and drug-induced hepatotoxicity.

Table 5 Dose decrements for Carfilzomib

Dose[a] (mg/m^2)	First Dose Reduction Dose -1 (mg/m^2)	Second Dose Reduction Dose -2 (mg/m^2)	Third Dose Reduction Dose -3 (mg/m^2)	Fourth Dose Reduction Dose -4 (mg/m^2)
70	56	45	36	27

[a] If dose reduction of Carfilzomib is required, the investigator should contact the coordinating investigator to discuss the situation, before any additional doses of Carfilzomib are administered.

11.3.2.3 Guidelines for hematologic adverse events

Guidelines for Carfilzomib dose modification in the event of thrombocytopenia and neutropenia are summarized in Table 6.

Table 6 Dose modification guidelines for thrombocytopenia and neutropenia

Hematologic adverse events		**Recommended Action**
Thrombocytopenia		
When platelets fall to < 30 x 10^9/L and for each subsequent drop to < 30 x 10^9/L	If platelets ≥ 10 to ≤ 30 x 10^9/L without evidence of bleeding	• Hold • Restart at previous dose when platelets > 30 x 10^9/L
	If evidence of bleeding or platelets < 10 x 10^9/L	• Hold • Restart at 1 dose decrement when platelets > 30 x 10^9/L
Neutropenia		
When ANC falls to < 0.75 x 10^9/L and for each subsequent drop to < 0.75 x 10^9/L	If ANC ≥ 0.5 to < 0.75 x 10^9/L	• Continue at full dose

	If ANC < 0.5 x 10^9/L	• Hold dose • Resume at 1 dose decrement when ANC ≥ 0.5 x 10^9/L

11.3.2.4 Guidelines for non-hematologic adverse events

Guidelines for dose modification in the event of non-hematologic adverse events are summarized in Table 7. Furthermore, adverse event management is in the discretion of the investigators according routine medical care.

Table 7 Dose modification guidelines for non-hematologic adverse events

Symptom/Sign/Investigation	Recommended Action
Renal Dysfunction[a]	
CrCL ≥ 15 and < 50 ml/min	• Full dose
CrCL < 15 ml/min (NCI-CTCAE grade 4)	• Hold dose until CrCL returns to ≥ 15 ml/min then resume same dose. • If dialysis required use the maximal dose of 20 mg/m^2 and administer Carfilzomib after dialysis.
Chronic dialysis stable for ≥ 30 days	• Dose may be re-escalated up to full dose as clinically tolerated
Hepatic Dysfunction and Related Investigations	
Mild to moderate liver dysfunction: Defined as 2 consecutive values, at least 28 days apart, of: (1) Total bilirubin (> 33% direct) > 1x ULN to < 3x ULN *OR* (2) An elevation of AST and / or ALT with normal bilirubin	• Reduction to dose -1 (see Table 5). • Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.
Grade 3 elevation in ALT and / or AST (> 5x ULN)	• Hold Carfilzomib until resolution to baseline
Grade 3 elevation in total bilirubin	• Hold Carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly. • Upon resolution of total bilirubin to normal, resume Carfilzomib dosing with a reduction of -1 dose (see Table 5) if drug-induced hepatotoxicity is excluded.
Drug-induced hepatotoxicity (attributable to Carfilzomib)	• Discontinue Carfilzomib

Other Non-hematologic adverse events	
Tumor lysis syndrome: 3 or more of the following: • Increase in creatinine of ≥ 50% • Increase in uric acid, of ≥ 50% • Increase in phosphate ≥ 50% • Increase in potassium of ≥ 30% • Decrease in calcium OR • Increase in LDH of ≥ 2-fold from baseline	• Hold Carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.
Congestive heart failure	• Any patient with congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline. • Appropriate medical management should be initiated. • Once congestive heart failure resolves or returns to baseline, treatment may continue at one dose level reduction. • If no resolution after 4 weeks, the patient will be withdrawn from all study treatment.
Cardiac adverse events (grade 3 or 4)	• Hold Carfilzomib. • Once cardiac adverse events resolve or returns to baseline, treatment may continue at one dose level reduction.
Infection (grade 3 or 4)	• Hold Carfilzomib. • Once infection is controlled and the patient is without infection-related symptoms, and if ANC ≥ 1.0 x 10^9/L, resume at full dose. • If ANC < 1.0 x 10^9/L, follow hematologic toxicities dose reduction guidelines.
Neuropathy (grade 2 with emergent pain, or grade 3)	• Hold Carfilzomib until resolved to ≤ grade 2 without pain; then resume at 1 dose decrement.
Neuropathy (grade 4)	• Permanently discontinue Carfilzomib.
Dyspnea (grade ≥ 2)	• Hold Carfilzomib until resolution to grade 1 or baseline, then resume at 1 dose decrement. • Investigate cause and record findings. • If caused by another adverse event listed in this table below recommendations for that adverse event.
Hypertension (SBP > 140 and / or DBP > 90) < grade 3	• Continue at same dose if initiation of appropriate treatment controls hypertension
Hypertension (SBP > 140 and / or DBP > 90) ≥ grade 3	• Hold Carfilzomib until resolution to normal or baseline. • Initiate appropriate anti-hypertensive therapy prior to resuming Carfilzomib at 1 dose decrement.
Pulmonary adverse events: Non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥ grade 3)	• Hold Carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.

Pulmonary hypertension (≥ grade 3)	• Hold Carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.
Posterior reversible encephalopathy syndrome (PRES): Headaches, altered mental status, seizures, visual loss, and hypertension	• If PRES is suspected, hold Carfilzomib. • Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. • If PRES is confirmed, permanently discontinue Carfilzomib. • If the diagnosis of PRES is excluded, Carfilzomib administration may resume at same dose, if clinically appropriate.
Thrombotic microangiopathy (TMA): Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	• If the diagnosis is suspected, hold Carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. • If TMA is confirmed, permanently discontinue Carfilzomib. • If the diagnosis is excluded, Carfilzomib can be restarted.
Venous thrombosis (≥ grade 3)	• Hold Carfilzomib and adjust anticoagulation regimen; resume at full dose one anticoagulation has been optimized per treating investigator's discretion.
Progressive Multifocal Leukoencephalopathy (PML)	• Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. • If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue Carfilzomib if PML diagnosis is confirmed.
Hepatitis B reactivation	• Carriers of HBV who require treatment with Carfilzomib should be closely monitored for signs and symptoms of active HBV infection throughout treatment. • Any subject who becomes HBV DNA positive or develops reactivation of HBV should have Carfilzomib treatment interrupted and receive appropriate anti-viral treatment.
Any other drug-related non-hematologic adverse event ≥ grade 3[b]	• For Carfilzomib attribution, hold dose. • Resume at 1 dose decrement when toxicity has resolved to grade 1 or less or to baseline grade.

[a] For a rapid fall from baseline in CrCL or an absolute fall of ≥ 60 mL/min, contact the coordinating investigator.

[b] In the event of a possible drug-related non-hematologic adverse event, the investigator should, to the best of his/ her ability, assess its relationship to Carfilzomib or Ibrutinib, or the combination of both to the extent possible. If both Carfilzomib and Ibrutinib are considered likely to be involved, then recommended actions for both should be instituted

11.3.3 Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of BTK. Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, Ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

Data from Study PCYC-04753 demonstrate that although Ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with Ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours' post-dose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration. For the most comprehensive nonclinical and clinical information regarding Ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of Ibrutinib, refer to the latest version of the Ibrutinib Investigator´s Brochure.

11.3.3.1 Ibrutinib administration and dosage schedule

Patients will be instructed to take 3 capsules of Ibrutinib (for a dose of 420 mg) orally once daily. The capsules are to be taken around the same time each day with approximately 240 ml of water (i.e. 8 ounces). The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water.

If a dose is missed, then it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, then the dose should be skipped and the patient should continue treatment at the scheduled time the next day.

At any visit at the study site, sufficient study medication required for treatment until the next visit should be dispensed. Unused study medication dispensed during previous visits must be returned and drug accountability records will be updated. Returned capsules cannot be re-used in this study or outside the study. Study staff will instruct patients on how to store medication for at-home use as indicated for this protocol.

11.3.3.2 Dose modifications for Ibrutinib

Ibrutinib therapy will be withheld for any new onset or worsening grade 2 cardiac failure, Grade 3 cardiac arrhythmias, grade ≥ 3 non-hematological adverse events, grade 3 or greater neutropenia with infection or fever, or grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), resume Ibrutinib therapy at the recommended dose as per the tables below.

Table 8 Study drug (Ibrutinib) dose modifications

Cardiac adverse events		
Symptom/Sign/Investigation	**Toxicity occurrence**	**Recommended Action**
Grade 2 cardiac failure	First	• Restart at 280 mg daily
	Second	• Restart at 140 mg daily
	Third	• Discontinue Ibrutinib
Grade 3 cardiac arrhythmias	First	• Restart at 280 mg daily[1]
	Second	• Discontinue Ibrutinib

[1] Evaluate the benefit-risk before resuming treatment.

Non-cardiac adverse events, for more details see also description below the table		
Symptom/Sign/Investigation	**Toxicity occurrence**	**Recommended Action**
Grade 3 or 4 non-hematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First[2]	• Restart at 420 mg daily
	Second	• Restart at 280 mg daily
	Third	• Restart at 140 mg daily
	Fourth	• Discontinue Ibrutinib

[2] When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the adverse event reoccurs, reduce daily dose by 140 mg.

The dose of Ibrutinib should be modified according to the dose modification guidelines above if any of the following adverse events occur:

- Grade 4 ANC (< 500/µL) for more than 7 days. The use of neutrophil growth factors is permitted per American Society of Clinical Oncology (ASCO) guidelines and must be recorded in the eCRF. Refer to section 11.3.4 for instruction regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets < 50,000/µL) in the presence of grade ≥ 2 bleeding events.
- Grade 4 thrombocytopenia (platelets < 25,000/µL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and / or anti-diarrheal therapy.
- HBV reactivation: HBV DNA by PCR, if the value is between 20 IU/mL and 100 IU/mL then the HBV-DNA level should be rechecked within 2 weeks. Ibrutinib should be held and anti-viral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV-DNA by PCR is 100 IU/mL or higher then Ibrutinib should be stopped and anti-viral therapy initiated.

- Any other grade 4 or 3 or unmanageable adverse event attributed to study drug.

Progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with Ibrutinib. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated. In case of adverse events not described in the section above, the treating physician may adjust the Ibrutinib treatment at his or her discretion, considering the dose modification guidelines described below and in the RSI.

11.3.4 Concomitant Medications

Permitted concomitant medications for both treatment arms

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of granulocyte colony-stimulating factors or erythropoietin growth factors is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006), but according the SmPC of Carfilzomib should be used with caution due to the potential risk of thrombosis. Transfusions may be given in accordance with institutional policy. Cotrim as PJP prophylaxis under Carfilzomib treatment is highly recommended. Short courses (≤ 14 days) of steroid treatment for non-WM related medical reasons (e.g. joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Carfilzomib. Thromboprophylaxis should be considered based on an individual benefit / risk assessment. The use of these medications / transfusions must be recorded in the eCRF.

Medications to be used with caution:

CYP3A inhibitors / inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy patients increased dose normalized exposure, C_{max} and AUC0-last, of Ibrutinib by 29- and 24-fold, respectively. The maximal observed Ibrutinib exposure AUC was ≤ 2-fold in 37 patients treated with mild and / or moderate CYP3A inhibitors when compared with the Ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (e.g. ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong

CYP3A inhibitor must be used, consider reducing the Ibrutinib to 140 mg or withhold treatment temporarily. Patients should be monitored for signs of Ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor patient for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during Ibrutinib treatment, as these contain moderate inhibitors of CYP3A (patients will be introduced about this). Co-administration of Ibrutinib with strong CYP3A inducers decrease Ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g. carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

The in vitro and in vivo results indicate a low potential for Carfilzomib to inhibit or induce the metabolism of CYP3A4/5 substrates and other CYP substrates in human patients. Therefore, no special recommendations are necessary.

Drugs that may have their plasma concentrations altered by Carfilzomib or Ibrutinib

In vitro studies indicated that Ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC50 of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that Ibrutinib could inhibit intestinal P-gp after a therapeutic dose. Currently, no clinical data is available; therefore, co-administration of narrow therapeutic index P-gp substrates (e.g. digoxin) with Ibrutinib may increase the substrate's blood concentration and should be used with caution and patients should be monitored closely for toxicity.

Carfilzomib is a substrate of efflux transporter P-glycoprotein (P-gp), but it showed only a marginal inhibitory effect to P-gp at concentrations as high as 3 µM and is not a BCRP substrate. Given that Carfilzomib is administered i.v. and is extensively metabolized, the pharmacokinetic profile of Carfilzomib is unlikely to be affected by P-gp or BCRP inhibitors or inducers.

Concomitant use of QT prolonging agents

Any medications known to cause QT prolongation should be used with caution and in the direction of the investigators; further periodic ECG and electrolyte monitoring should be considered.

Concomitant use of antiplatelet agents and anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with Ibrutinib. NOACs are allowed. Supplements such as fish oil and vitamin E preparations should be avoided (patients will be introduced about this in the patient information). Use Ibrutinib with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients with

congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. Patients requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with Ibrutinib held and Ibrutinib should not be restarted until the patient is clinically stable. Patients should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

Prohibited concomitant medications

Concurrent therapy with a marketed or investigational anticancer therapeutic or radiation to large marrow reserves for either a palliative or therapeutic intent is excluded. Short-term corticosteroids for non-malignant conditions (e.g. asthma, inflammatory bowel disease) equivalent to a Dexamethasone dose > 4.0 mg/day or Prednisone 100 mg per day are not permitted. Higher steroid doses given short term for exacerbations of nonmalignant conditions (e.g. asthma flare) are permitted with the approval of the coordinating investigator. Investigational agents are not to be used during the study.

Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) Ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the patient is on Ibrutinib, it is not necessary to hold study drug for these procedures.

Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.

Emergency Procedures

For emergency procedures, study drug should be held after the procedure for at least 7 days after the urgent surgical procedure.

11.4 Other Protocol-required Therapies

All other protocol-required therapies listed below are commercially available and will not be provided or reimbursed by the sponsor. The investigator will be responsible for obtaining supplies of these treatment-required therapies.

11.4.1 Antiviral prophylaxis

An antiviral concomitant medication is required for the duration of treatment with Carfilzomib. Acyclovir (e.g. 400 mg p.o. 3 times a day, or 800 mg p.o. 2 times a day or per institutional standards), Famcyclovir (e.g. 125 mg p.o. given 3 days, twice a day or per institutional standards), or Valacylovir (e.g. 500 mg p.o., twice a day or per institutional standards). Dose adjustments for renal function where appropriate (see section 11.3.2.1), initiated within 1 week of the first dose, should continue for the duration of treatment with Carfilzomib.

Hepatitis B prophylaxis has to be initiated in patients which are positive for either HBsAg and / or anti-HBc and HBV-DNA negative. Prophylaxis treatment is in the discretion of the treating investigator and could be include Entecavir, Tenofir or other substances preventing HBV reactivation. HBV-DNA needs to be re-evaluated in regular intervals (for more details see section 12.4.12.9).

11.4.2 Thromboprophylaxis

An anticoagulant (e.g. enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low molecular weight heparin, or warfarin) is a suggested concomitant medication and should be used with caution in patients on Ibrutinib. Application in patients should be based on an individual benefit risk assessment at the discretion of the investigators.

11.4.3 Tumor Lysis Syndrome Prophylaxis

An approved uric acid-lowering agent (e.g. allopurinol) in patients at high risk for tumor lysis syndrome (TLS) due to high tumor burden may be prescribed at the investigator's discretion and according to the IBs.

11.4.4 Contraceptive requirements

Women of childbearing potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered of child bearing potential:

1. Premenopausal woman with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

        Note: Site personnel documentation from the following sources is acceptable:

- review of patient medical records
- patient medical examination, or
- patient medical history interview.

2. Postmenopausal woman:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Women on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Female patients

Contraception and pregnancy testing are required according the CTFG recommendations:

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

WCBP should be advised to avoid becoming pregnant while being treated with Carfilzomib or Ibrutinib. WCBP and / or their male partners should use highly effective contraception methods or abstain from sexual activity during treatment and for 6 months after treatment with Carfilzomib or Ibrutinib. Female patients of childbearing potential must agree to use 1 highly effective method of contraception (as described below). It cannot be excluded that the efficacy of oral contraceptives may be reduced during Carfilzomib or Ibrutinib treatment. In addition, due to an increased risk of venous thromboembolic events associated with Carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with Carfilzomib. Female patients of childbearing potential who are using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis should switch to an alternative hormonal method (without risk of thrombosis) or non-hormonal method of highly effective contraception.

The following contraceptive methods are considered highly effective for female patients:

Failure rate of < 1 % *per year when used consistently and correctly*

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral intravaginal [vaginal ring], or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)

- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation / occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female patient of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence: Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

If a female patient is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

Lactation

It is not known if Carfilzomib or Ibrutinib are transferred into breast milk. If the patient is breastfeeding and wishes to be in this study, they will be required to discontinue nursing during study treatment and for additional 6 months after stopping Carfilzomib or Ibrutinib.

Male patients

If the male's sole sexual partner is of non-childbearing potential or has had a bilateral tubal ligation / occlusion, he is nevertheless required to use a condom during treatment and for 6 months after end of treatment. The definition of non-childbearing potential is provided in the chapter before. Male patients with a partner of childbearing potential must agree to not father a child during treatment of Carfilzomib or Ibrutinib and for additional 6 months after the last dose of Carfilzomib or Ibrutinib.

Contraceptive options for male patients include:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies). The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient, or
- Use of a condom during treatment of Carfilzomib / Ibrutinib and for additional 6 months after the last dose of Carfilzomib or Ibrutinib. Male patients with a pregnant partner must practice sexual abstinence or wear a condom to prevent exposure of the unborn child to Carfilzomib / Ibrutinib through semen.

Unacceptable methods of birth control for male and female patients

Birth control methods that are considered unacceptable in clinical studies include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhea method.

Male and female patients of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant or father a child or donate sperm during treatment of Carfilzomib and / or Ibrutinib and for 6 months after the last dose of Carfilzomib and / or Ibrutinib.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female patients to use highly effective methods of contraception and for an increased length of time. In addition, male patients may also be required alter the duration and / or methods of contraception. The investigator must discuss these topics with the patients.

11.5 Drugs description, storage and handling

11.5.1 Description

In this study, Ibrutinib p.o. and Carfilzomib i.v. are considered as investigational medicinal products (IMP). Ibrutinib will be provided by Janssen, Carfilzomib by Amgen Inc.

Proprietary name:	Imbruvica
Name of substance:	Ibrutinib
Manufacturer:	Janssen
Approved indications:	• for the treatment of adult patients with MCL who have received at least 1 prior therapy, • CLL/SLL, CLL/SLL with the presence of 17p deletion, • WM, MZL who require systemic therapy and have received at least 1 prior anti-CD20-based therapy, • and cGvHD after failure of 1 or more lines of systemic therapy. • Ibrutinib continues in late-stage development for patients with B-cell malignancies, cGvHD, and solid tumors.
Dosage form:	Capsules
Strength:	140 mg
Total daily dose:	420 mg

Proprietary name:	Kyprolis
Name of substance:	Carfilzomib
Manufacturer:	Amgen
Approved indications:	Approved in combination with either Lenalidomide and Dexamethasone or Dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
Dosage form:	Infusion

Strength:	60 mg
Total daily dose:	20 mg/m² or 70 mg/m²

11.5.2 Storage and handling

Ibrutinib

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of Ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the Ibrutinib IB for a list of excipients. The Ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging and will be stored by room temperature. Refer to the site investigational product manual for additional guidance on study drug storage, preparation and handling. Patients receive a handling instruction in their patient diary.

Carfilzomib

Carfilzomib is supplied as a sterile, lyophilized, white to off-white powder, ready for reconstitution. It is supplied for single use in 50 mL type 1 glass vials containing 60 mg of Carfilzomib drug product with an elastomeric stopper and flip-off lid. Upon reconstitution with 29 mL of preservative-free sterile water for injection, the reconstituted solution contains 2 mg/mL Carfilzomib, 100 mg/mL sulfobutylether beta-cyclodextrin sodium, and 1.9 mg/mL citrate buffer, at pH 3.0 to 4.0.

Carfilzomib is supplied in labelled cartons containing 4 single use vials per carton. Carfilzomib must be stored between 2°C to 8°C and remain protected from light. Further information will be found in the site investigational product manual.

11.5.3 Packaging and labelling

Medication labels will be in the local language and comply with GMP Annex 13 and legal requirements of each country.

11.5.4 Supply and ordering

Supplies have to be obtained by sending an order form (located in the ISF) directly to the vendor for Ibrutinib or Carfilzomib. There are no starter supplies. The initial order will be done by the Sponsor after the first patient is in screening at the site. For more information, see the pharmacy manual.

11.5.5 Receipt and storage

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.

The investigator, the hospital pharmacist or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical study are securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements. All IMPs must be stored in accordance with labeling and shall be dispensed in accordance with the investigator's prescription. It is the investigator's responsibility to ensure that an accurate record of IMP used and returned is maintained. Any quality issue noticed with the receipt or use of an IMP (deficient IMP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the sponsor, who will initiate a complaint procedure. Under no circumstances will the investigator supply the IMP to a third party, allows the IMP to be used other than as directed by this protocol, or dispose of the IMP in any other manner.

11.5.6 Accountability and Compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the IMP. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient. The study monitor will periodically check the drug accountability held by the investigator or pharmacist to verify accountability of all used and unused IMP. The sponsor will verify that a final report of drug accountability is prepared and maintained in the investigator study file and trial master file. Administration of the study treatment will be supervised by the investigator or authorized representative.

The dispensing of study drug to the patients and the return of study drug from the patients must be documented on the drug accountability form. Patients must be instructed to return all original containers of Ibrutinib, whether empty or containing study drug. Site staff must not combine contents of the study drug containers. All patients receive a patient diary to document their Ibrutinib intake, any signs and symptoms between site visits and also concomitant medication. Personnel from the study site will review the patient diary during the visit at the site.

11.5.7 Destruction of Study Drug

Study drugs such as used and unused study drugs should be destroyed on site. On-site destruction is allowed provided the accountability and disposal records are complete, up-to-date, and after release of the sponsor. Used vials can be destroyed after preparation according to local regulations.

A potential defect in the quality of the IMP may be initiate a recall procedure by the manufacturer. In this case, the investigator will be responsible for promptly addressing any request made by the manufacturer, in order to recall the IMP and eliminate potential hazards.

12. STUDY ASSESSMENTS

A detailed flowchart is provided in Table 1, Table 2 and Table 3 in the synopsis. The schedule of assessment lists all of the assessments and indicates with an "x" when they have to be performed. All data obtained from these assessments must be available in the patient's source documentation. During the course of the study, visits and test procedures should occur on schedule whenever possible; visits that occur ± 4 days (during treatment, further time window sees flowchart) from the scheduled date will not constitute any protocol deviation.

12.1 Screening phase

The signed informed consent form must be obtained before any study specific procedures are performed. The informed consent for the biosampling should be signed before sampling. The patient and the investigator will date and sign the informed consent form. The investigator shall provide a copy of the signed consent to the study patient; the original shall be maintained in the ISF. If a patient signed the informed consent the registration form (available in the ISF) has to be filled and sent to the sponsor via fax or e-mail.

Screening evaluations have to be performed within 45, 30 or 7 days prior to randomization respectively. However, determination of the mutational status of MYD88 and CXCR4 and bone marrow aspirate performed up to 4 months and CT or MRI performed up to 3 months prior to randomization as routine standard of care for the patient´s disease can be used. Patients considered eligible by the investigator once all screening procedures are complete and will be randomized to the study on day 0 (see section 12.5).

12.2 Active treatment phase

Details of the procedures performed during the treatment phase are described in the flowcharts and in the sections below. All patients will be closely monitored for adverse events, laboratory abnormalities, ECG abnormalities and response. Clinical evaluations and laboratory assessments may be repeated more frequently, if clinically indicated.

Additionally, for the first 10 patients in treatment arm A (Carfilzomib and Ibrutinib) laboratory assessments will be performed on day 8 and 15 of the first 6 cycles. Also, an ECG will be performed on day 15 during the first 6 cycles.

If a patient completes the active treatment phase, an end of treatment visit 30 calendar days after last dose of study treatment has to be performed.

If progression occurs at any time point of the study (i.e. during therapy or during follow up) the assessments described in the flowchart have to be performed (could be combined with another visit of the flow chart, e.g. end of treatment or follow up, depending on what applies). Relapse / progression will be determined by the modified response criteria as published[1] (appendix 21.1). A pathological confirmation by biopsy of the bone marrow or lesion if present should be done if possible.

IgM levels obtained more than 35 days after plasmapheresis can be used in response determination. If disease progression is suspected solely based on the results of a single examination or a single laboratory parameter, this finding should be confirmed by a subsequent evaluation at least within 4 weeks from the first finding. Additional hematologic parameters, radiographic evaluation and bone marrow biopsy should be performed at the discretion of the investigator to confirm progressive disease if indicated.

12.3 Follow up phase

As soon as the treatment is stopped because of non-tolerated toxicity, patients will enter follow-up and will be clinically evaluated every 3 months after the last treatment for 2 years and then every 6 months for 3 additional years or until progression of disease (until end of study).

Patients with progression or starting of new anti-lymphoma therapy will be followed up only for survival data and data with regard to further treatment of WM every 6 months until end of study.

12.4 Specification of assessments

12.4.1 MYD88 and CXCR4 mutational status

It is **obligatory** for the study to determine the mutational status of the following genes within 4 months prior to randomization into the study:

- **MYD88 (L265P) Mutation**
- **CXCR4 Mutation**

Known MYD88 mutation and CXCR4 mutation are mandatory for randomization into the study. Detection of MYD88 and CXCR4 mutations can be performed from peripheral blood or bone marrow. If mutations are not detected in the peripheral blood, a confirmation of the negative result is necessary by performing a mutational analysis from bone marrow cells (exclusion of false negative results).

12.4.2 Histopathology

12.4.2.1 Histological material

The local histological examination of bone marrow biopsy must be performed within 4 months prior to randomization. Additionally, a pathological assessment will be performed by a designated reference pathologist (list in the ISF).

12.4.2.2 Pathological diagnosis

Inclusion of the patient in the study will be based on the pathological assessment and mutational status and the histopathological diagnosis of lymphoplasmacytic lymphoma (LPL), which is the underlying histology of WM.

Beside the local pathological assessment, a central pathological review will be organized for all patients included in the study at screening. The pathological review will be done nationally in each of the participating countries (if available) or in Germany.

The pathological review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of LPL. This pathological diagnosis is the basis of the diagnosis of WM, which is defined as LPL with bone marrow infiltration and an IgM monoclonal gammopathy of any concentration and requires therefore morphology, immunophenotyping from the bone marrow and IgM characterization.

For the diagnostics of LPL as the underlying histopathology of WM it is recommended that the following material is sent to the reference pathology:

- Bone marrow trephine (≥ 1 cm) fixed in formalin (no other fixative)
- 4 bone marrow smears (air dried, unstained)
- 4 blood smears (air dried, unstained)

It is important to have a minimum of smears sent to pathology independent of whether the smears are also analyzed elsewhere to allow the hematopathologist to generate a report based on all morphological features including cytology on smears. Optionally the following material should be sent to the pathology:

- Any other biopsy specimen including lymph nodes

Furthermore, information about:

- year of birth, gender
- Monoclonal IgM gammopathy (yes / no)
- Previous hematological diseases
- Known MYD88 mutation yes / no
- Known CXCR4 mutation yes / no

should be sent to the pathology by using the appropriate form in the ISF. The mandatory diagnostic staining panel of the reference pathology will include:

- CD20, CD5, CD23, cyclin D1, Kappa, Lambda, IgM

with optional staining panels according to differential diagnosis in each individual case.

12.4.3 Imaging

CT scans of neck, thorax and abdomen routinely performed within 3 months prior to randomization will be accepted for study inclusion. If there are contraindications against performing CT scans, MRI imaging is also accepted. All further imaging will be done as outlined in the flowcharts according standard of care every 6 months and only if initially positive.

12.4.4 Patient demographics

Patient's demographics comprise year of birth, gender and childbearing potential.

12.4.5 Medical history

At screening relevant medical history not pertaining to the study indication started within 5 years before signing informed consent and assessments of any current medical conditions that are considered relevant for the patient's study eligibility have to be documented in the eCRF.

12.4.6 Previous therapies

At screening previous therapies for WM will be documented in the eCRF. This includes name of therapies, number of cycles and start / stop date.

12.4.7 Physical examination

Thorough physical examination includes, but is not limited to B-symptoms, cardiovascular, gastrointestinal, hepatobiliary, respiratory, skin, musculoskeletal, genitourinary / renal and neurological system. Physical examinations will be performed according to the flowcharts; relevant findings concerning these examinations will be documented in the eCRF at screening as medical history. A targeted physical examination to focus on areas involved by AEs or areas involved by WM (e.g. splenomegaly, lymphadenopathy) and for B-symptoms will be performed during further visits according to the flowcharts.

Height (cm) will only be measured at screening. Weight (kg) must be taken at screening and on day 1 of every cycle and results must be present on the patient's chart and recorded correspondingly into the eCRF.

The performance status will be done according to WHO / ECOG criteria (see appendix 21.2) during screening and thereafter on day 1 of every cycle.

12.4.8 Vital signs

Vital signs include heart rate, blood pressure and temperature.

12.4.9 Electrocardiogram (ECG) / transthoracic echocardiography (TTE)

A 12-lead ECG (including PR-, QT- and QTc interval) will be performed at screening and at visits according to the flowcharts. Each ECG tracing will be kept in the source documents at the investigational site.

Transthoracic echocardiography will be performed at screening and after that every 6 months (cycle 7, cycle 13, cycle 19, cycle 25 etc.) and if clinically indicated. Clinically significant abnormalities of ECG or TTE should be reported as medical history during screening or after that as AEs in the eCRF.

12.4.10 Pulmonary function test

A pulmonary function test will be performed at screening and thereafter only if clinically indicated. Only clinically significant abnormalities should be reported as medical history during screening and thereafter as AEs in the eCRF.

12.4.11 Fundoscopy (Ophthalmoscopy)

A fundoscopy will only be performed if hyperviscosity is suspected during screening visit. Clinically significant abnormalities should be documented in the medical history in the eCRF.

12.4.12 Laboratory tests (local laboratory at the site)

Blood tests and urinalysis include the routine parameter listed below and will be scheduled according to the laboratory flowcharts (see appendix 21.4 and 21.5) and in addition as clinically indicated. In case of cytopenia the frequency of blood samples would be increased from the 25th cycle (Arm A) and 14th cycle (Arm B) to once a month. Test results from the screening visit can be used for Cycle 1, day 1 in the discretion of the investigator (depending on local standards and e.g. the timeframe between screening laboratory and day 1).

12.4.12.1 Pregnancy test

All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at screening, which has to be repeated 2 weeks after the first test to confirm results. After that monthly pregnancy tests are mandatory until 6 months after end of treatment. For patients who continue treatment after cycle 24 pregnancy test strips will be supplied by the sponsor.

12.4.12.2 Haematology

Complete blood count (CBC) including leucocytes, platelets, hemoglobin, erythrocytes, hematocrit and differentiation (absolute lymphocytes, monocytes, neutrophils, eosinophils, basophiles).

12.4.12.3 Serum chemistry and electrophoresis

Chemistry panel include sodium, potassium, calcium, creatinine, total bilirubin, SGOT, SGPT, LDH, magnesium, phosphate, glucose, urea / BUN, total protein, albumin, CRP.

ß2-microglobulin will be assessed at screening and after that every 6 months. Serum electrophoresis includes the M-protein and will be assesses at screening and after that every 6 months. A serum immunofixation must be performed at screening, cycle 13 and after that every 6 months.

12.4.12.4 Coagulation

Coagulation tests include INR and partial thromboplastin time (activated or not).

12.4.12.5 Urine analysis

Urine status analysis include total protein and the Bence Jones protein.

12.4.12.6 Quantitative immunoglobulins

Quantitative immunoglobulins include IgM, IgG and IgA.

12.4.12.7 Free light chain

Free light chain panel include free kappa, free lambda and kappa / lambda ratio.

12.4.12.8 Cryoglobulins

If cryoglobulinemia is suspected the following test will be done: cold agglutinin, direct Coombs test. Repeated assessments are only necessary if initially positive.

12.4.12.9 Virology

Hepatitis B / C serologic markers and / or viral load and HIV will be tested at screening. 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. It is also necessary to know if the patient was HBV-DNA positive in the past due to the risk of Hepatitis B reactivation (in this case

prophylaxis of HBV reactivation has to be initiated, see also section 11.4.1). Patients who are currently HBV-DNA positive at screening may not be included into the trial.

12.4.13 Staging and efficacy assessments

Response to treatment will be evaluated as indicated in Table 1 and Table 2 of the flowcharts. In case of response or stable disease, the next cycle will be delivered. Progression will be considered as treatment failure. In this case the patients will discontinue treatment and will enter survival follow-up. Modified response criteria as defined[1] will be used for evaluating responses, identifying stable or progressive disease (appendix 21.1). After the first 12 months of treatment the response will be assessed prior to day 1 or at day 1 of cycle 13. CT scan in case of initial lymph node enlargement or splenomegaly, FACS analysis peripheral blood (B-NHL panel), bone marrow trephine biopsy, bone marrow smear and aspirate will be repeated at that time (bone marrow evaluation only for confirmation of complete response or documentation of delayed response). Best response within the time period between the beginning of treatment and end of follow-up should be documented for every patient. Therefore:

1. Changes in the serum concentration of monoclonal immunoglobulin will be monitored with serum protein densitometry tracing (electrophoresis) (in particular if IgM monoclonal protein exceeds 5 g/dL) or by nephelometry. Sequential analyses of serum IgM should be performed using the same methodology in the same laboratory.
2. During the subsequent follow-up bone marrow trephine biopsy and bone marrow smears and aspirate is only mandatory to confirm complete response and CT scan (if contraindications MRI) only in case of abnormalities related to WM before initiation of therapy.
3. Serum protein electrophoresis, nephelometry or densitometry (whichever is used for an individual patient) and immunofixation have to be repeated at least 6 weeks later in case of complete response to confirm CR.

12.4.14 Assessments of Quality of life

The quality of life of the patients will be evaluated using the FACT-Lym questionnaire (see ISF). Questionnaires and all related subscales, translations, and adaptations are owned and copyrighted by David Cella, Ph.D. This questionnaire is a validated and well-established scoring instrument to measure the management of chronic illness in lymphoma patients.

12.4.15 Concomitant medication

Only current concomitant medication and supportive care including hematopoietic stimulating factors at screening will be recorded into the eCRF. In the following cycles ongoing and new medication will be documented.

12.4.16 Biological sampling

The patient consent and signature on the informed consent for biosampling (if applicable in the participating country) is prerequisite for biological sampling. The procedures for the management of biological samples will be explained in appendix 21.3 and in the laboratory manual. If any patients will withdraw his / her consent to further biological sampling and storage during study participation, no further collection of biological samples will take place and already stored samples will be destroyed if possible and wished by the patient. This does not affect the patient's participation in the clinical study in any other respect.

12.5 Randomization Procedure

A stratified central block randomization will be used to allocate the patients 1:1 to the 2 arms. Stratification factors are MYD88 and CXCR4 status with the following groups: $MYD88^{mut}/CXCR4^{non\text{-}mut}$; $MYD88^{mut}/CXCR4^{mut}$; $MYD88^{non\text{-}mut}/CXCR4^{non\text{-}mut}$ ($MYD88^{non\text{-}mut}/CXCR4^{mut}$ not applicable) and number of prior lines (0 vs. ≥ 1 treatment lines). A stratification by site is not feasibly due to the rare disease status and the high number of sites (approximately 30 sites).

In this study an electronic randomization will be used. For electronic randomization each site will log on to the eCRF (only authorized personal). The questions for stratification factors and questions on inclusion / exclusion criteria have to be answered prior to randomization. The treatment arm assigned to the patient will be shown immediately and sent by e-mail to site personnel and sponsor in addition. A user manual describing the randomization and documentation process will be distributed to each site.

12.6 Patient study participation card

All participating patients will receive a study participation card, on which the study title and study drug are indicated. Furthermore, the address and telephone number of the local investigator is listed in case of emergency. The patients should always carry this card with them.

12.7 Criteria for premature discontinuation of the study

12.7.1 Early study termination for an individual patient

Patients can withdraw their informed consent to this study at any time and this does not interfere with their right of treatment by the local investigator. In case of cessation of the study-treatment a final statement concerning the treatment effect and the causes of premature study-termination have to be given by the investigator.

In case it becomes evident ex-post that a patient did not qualify for the study (e. g. did not fulfill all inclusion criteria or had an exclusion criterion at the time of randomization) the patient will

not be excluded from the study because the analysis of the study will be performed according to the intention-to-treat principle. In case that the patient has not completed the therapy according to the protocol of this study it is up to the local investigator to decide whether the patient should continue with the per-protocol therapy or not. However, the documentation of patients with ex-post non-qualification must continue as planned in the protocol.

The per-protocol treatment of the patient must be stopped for the following reasons:

- disease progression at any time;
- intercurrent illness that would, in the judgment of the investigator, affect assessment of clinical status to a significant degree;
- repeated clinically relevant violation of the protocol;
- non-compliance by the patient with protocol requirements;
- pregnancy;
- excessive and unexpected toxicity of the treatment;
- patient's decision to stop her / his treatment or participation in the study;
- decision by the local investigator for medical reasons;
- discontinuation of the study at the request of sponsor;
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact (at least 3 attempts have to be documented in the source data). In any circumstance, every effort should be made to document patient outcome, if possible.

The reason for the early termination of the per-protocol treatment must be documented on the respective eCRF page. Patients who stop per-protocol therapy early must be documented and followed-up according to protocol. Early termination should be avoided. In case of an early termination of therapy, reasons / circumstances and if applicable the final disease status of the patient have to be documented. If the patient does not withdraw the consent for further follow-up, he or she should be followed-up as planned.

12.7.2 Early closing of a study site

The closing of a study site will be considered if:

- it does not meet the technical requirements of the protocol;
- the recruitment rate is not sufficient;
- inaccurate, incomplete or insufficient data collection and quality after repeated requests of the sponsor (GCP non-compliance);
- detected fraud;
- the conduct of the study is repeatedly not compliant with the protocol.

The early closing of a site will be decided by the coordinating investigator / sponsor and national co-coordinator. If an investigator of a site decides not to take part in the study any longer they have to inform the coordinating investigator immediately. The decision should be well-founded. Details on further treatment and follow-up of patients already on study are in the discretion of the investigator of the site.

12.7.3 Early termination of the study

Early termination of the entire study may be necessary for the following reasons:

- the occurrence of serious unexpected side effects of treatment;
- excessive treatment-related mortality;
- relevant pertaining new information from other studies or publications;
- inadequate recruitment rate in the whole study;
- excessive number of deviations from the study protocol in the whole study;
- any other fact which would change the risk-benefit analysis of this study.

Any premature discontinuation will be appropriately documented according to local requirements (e.g. EC, regulatory authorities, etc.).

The DSMC will monitor the study conduct and the safety aspects of the study as described in section 15 and will give recommendations to the coordinating investigator / sponsor of the study whether to stop the study or to change the study protocol. The coordinating investigator / sponsor will then decide on the actions to be taken. The decision on an early termination of the study is a complex action which has to consider in addition to statistical also medical and ethical as well as organizational and financial aspects. Finally, according to the national drug laws, the study may be suspended or early terminated by decision of the respective competent authorities. All CAs and the ECs in charge will be notified about the early termination of the study.

13. ASSESSMENT OF SAFETY

13.1 Closer monitoring of the first 10 patients in arm A

Both study medications are not approved in the study indication in this combination. Therefore, it will be a close monitoring for treatment related toxicity comprising the first 10 included patients into the study in arm A. Safety evaluations will be performed on day 1, day 8 and day 15 for cycle 1-6 (more details about the assessments will be found in section 12.2).

13.2 Monitoring, recording and reporting of adverse events

All patients will be monitored for AEs during the study. Assessments may include monitoring of the following parameters: the patient’s clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings or other appropriate tests and procedures.

All adverse events, serious adverse events and special reporting situations, whether serious or non-serious, will be recorded from the time of first application / intake of IMPs until the patient's end of treatment visit (30 days after last intake of study drug). Additionally, all kinds of secondary malignancies have to be reported until end of study.

13.3 Adverse event

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of the study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patients' health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e. any clinically significant adverse change in the frequency or intensity of a pre-existing condition (documented as medical history)) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the adverse event to study treatment in the eCRF. All measures required for AE management must be recorded in the source data.

13.4 Evaluation of adverse events

A qualified and for this task delegated investigator at the site will evaluate all AEs according the following topics.

13.4.1 Seriousness

A serious adverse event (SAE) is any AE that results in any of the following outcomes or actions:

- Results in death;
- Is life-threatening (i.e. in the opinion of the investigator, the patient is at immediate risk of death from the AE). The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability / incapacity (a substantial disruption of the patients' ability to conduct normal life functions);
- Is a congenital anomaly / birth defect;
- Is considered an important medical AE by the investigator based on medical judgment
  Important medical adverse events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

NOTE:

Events excluded from reporting as SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol / disease-related investigations (e.g. surgery, scans, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- A procedure or hospitalization for progression / relapse investigations (e.g. surgery, scans, sampling for laboratory tests, bone marrow sampling).
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned prior to signing informed consent; must be documented in the source document.
- Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- Sign, symptoms and physical findings indicative of progression of WM are not to be reported as SAE.

If an AE is considered serious, both the AE page of the eCRF and the SAE report form must be completed.

For each SAE, the investigator will provide at least information on severity, start and stop dates, outcome, relationship to IMP and action taken regarding IMP.

13.4.2 Severity

For both AEs and SAEs, the investigator must assess the severity of the event.

The severity of AEs will be graded based upon the patients' symptoms according to the current version of NCI-CTCAE, Version 5.0:

AEs that are not defined in the current NCI CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention / therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention / therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention / therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention / therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (i.e. as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on patient / event outcome or action criteria associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

13.4.3 Causality

The investigator must determine the relationship between the administration of the IMPs and the occurrence of an AE / SAE as not related or related as defined below:

Not related: A causal relationship is unlikely or remote between the AE and study drug administration. Other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: A causal relationship is possible between the AE and study drug administration. Other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

13.4.4 Expectedness / Reference safety information (RSI)

A SAE that is not included in the adverse reaction section of the relevant Reference Safety Information (RSI) by its specificity, severity or outcome is considered an unexpected adverse event. The RSI for this study is the relevant section in the valid IB of Carfilzomib and the relevant section in the valid SmPC of Ibrutinib.

13.4.5 Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

13.4.6 Action Taken

The investigator will record the action taken with IMP as a result of an AE or SAE, as applicable (e.g. discontinuation or reduction of IMP, as appropriate) and report it in the eCRF or SAE form if concomitant and / or additional treatments were given for the event.

13.4.7 Outcome

The investigator will record the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the patient´s participation in the study must be followed until recovered / resolved, recovered / resolved with sequelae, not recovered / not resolved (death due to another cause) or fatal (due to the SAE).

13.4.8 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality is clinically significant in the discretion of the investigator at the site (e.g. results in discontinuation from the study; requires treatment, modification / interruption of IMP dose, or any other therapeutic intervention; or is judged to be of significant clinical importance).

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented and reported as a SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the eCRF. If the abnormality laboratory value was not a part of a diagnosis or syndrome, then the abnormal laboratory value should be recorded as an AE.

13.5 Pregnancy / Lactation exposure

Any pregnancy / lactation exposure in a female patient or in a female partner of a male patient diagnosed during the treatment period or within 6 months after last study treatment administration must be reported without undue delay but not later than within 24 hours of obtaining knowledge of the events by anyone of the study team members at the site using the study specific pregnancy reporting form to the sponsor / ZKS Ulm. In female study patients IMP must be discontinued in the case of pregnancy / lactation exposure during study treatment. Follow-up information on the patients and her pregnancy / lactation exposure outcome should be communicated by the investigator / site to the sponsor / ZKS Ulm as soon as available.

The investigator / site will follow-up all female patients or female partners of men participating in the study who become pregnant until end of pregnancy. The investigator / site must notify the sponsor of the outcome of the pregnancy / lactation exposure as specified below (follow up report to the initial report). Pregnancy / lactation exposure should be reported on the pregnancy/ lactation exposure report form. If the outcome of the pregnancy / lactation exposure meets the criteria for immediate classification as a SAE (i.e. spontaneous or therapeutic abortion, any congenital anomaly [including that in an aborted fetus], stillbirth, neonatal death, elective abortion due to developmental anomalies), the investigator / site should follow the procedures for reporting SAEs in addition to providing the pregnancy / lactation exposure report form. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days of birth that the investigator suspects as related to the in-utero exposure to the study drug should also be reported as SAE.

The investigator should counsel the patient or the partner of the patient, discuss the risks of continuing the pregnancy / lactation, and possible effects on the fetus or new born. Monitoring of the patient should continue until conclusion of the pregnancy / end of lactation.

Since IMPs may cause fetal harm, female partners of men participating in the study who become pregnant will be asked to sign an ICF and will be monitored for the outcome of the pregnancy as described above.

13.6 Special Situations

Uses of the IMPs outside what is foreseen in the protocol and defined below as „special situations“ are subject to the same obligation to report as SAEs. All special reporting situations, even in absence of an AE, that occur during the defined study period must be recorded on the source documentation, in the eCRF and reported to the sponsor using the SAE report form without undue delay but not later than within 24 hours after awareness by anyone of the study team members at the site.

Pregnancy / Breast feeding / Lactation exposure

For more details refer to see section 13.5.

Overdose

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported on the SAE form / event of special reporting situations form. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

Abuse

Intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, abuse potential refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Desired psychological effects can include euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood.

Misuse

Any intentional therapeutic use of a drug product in an inappropriate way. Inappropriate use should be considered in the context of the clinical study protocol.

Transmission of infectious agents

Suspected transmission of an infectious agent by a medicinal product will be reported on the SAE report form.

Medication Error

An unintended failure in the drug treatment process. Examples include administration of a drug product in the wrong dose, by an incorrect route, or to the wrong person; administration of a drug product resulting in a drug interaction due to drugs or foods that are known to interact; administration of the wrong drug product; or inadvertently consuming a greater than prescribed dose of a drug product (e.g. double dose) due to memory lapse. Therapeutic errors may be made by the patient, physician, pharmacist, clinical study staff etc.

Inadvertent or accidental exposure

Exposure to an IMP, as a result of one´s professional or non-professional occupation.

Unexpected therapeutic benefit or clinical benefit

To explore potential new indications for the study drug, any unexpected therapeutic benefits not associated with WM (e.g. unexpected hair growth is stimulated by one of the study drugs).

13.7 Reporting of Serious Adverse Events

All events that meet one or more criteria of seriousness that occurred from the time of patient's first application / intake of IMPs up to 30 days after the last study drug intake, regardless the relationship to the study drugs require the completion of a SAE report form in addition to being recorded on the AE page of the eCRF.

A SAE that occurs after this time, if considered related to the study drugs, will be reported regardless of the time between the last drug administration and the event onset.

The investigator shall report serious adverse events to the sponsor / ZKS Ulm without undue delay but not later than within 24 hours of obtaining knowledge by e-mail, using the SAE report form. Where relevant, the investigator shall send a follow-up report to the sponsor (with the same time requirements) to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial.

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drugs) that occur during reporting period, and those made known to the investigator at any time thereafter that are considered being related to study drugs.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient´s participation in the study, must be followed until any of the following occurs:

- the event resolves;
- the event stabilizes;
- the event returns to baseline, if a baseline value / status is available;
- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct;
- it becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

13.7.1 Obligations of the investigator

In case of SAE, special situation or pregnancy, the investigator shall report them to the sponsor / ZKS Ulm without undue delay but not later than within 24 hours of obtaining knowledge by e-mail to:

pv.lymphom@uniklinik-ulm.de

All SAE forms must be dated and signed by the responsible investigator or one of his / her authorized medical staff members.

- The SAE report should provide a detailed description of the SAE specifying the date of onset, severity, duration, relevant concomitant medication, relevant medical history, relevant lab data, action taken regarding study medication, corrective therapy given, outcome of all serious adverse events and the investigator´s opinion as to whether the serious adverse event can be related to the study drugs. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.
- All information for detailed description of the SAE may not be available at the time of the initial report. Nevertheless, initial reports should be submitted as long as at least the following minimum criteria are met:
  - an identifiable patient;
  - a suspected medicinal product;
  - an identifiable reporting source;
  - an event that can be identified as serious;
  - a causality assessment (if investigator causality assessment is not provided, the worst case scenario is assumed and the event will be considered related).
- Information about results of any examinations carried out including laboratory tests that are important for the diagnosis, assessment, or treatment of a SAE and the dates on which these examinations were performed should be given within the SAE form. For laboratory tests the units and the respective normal reference range should be provided as well.
- Additional information to any SAE should be actively sought and reported by the investigator / site on a subsequent SAE report follow up form and sent by e-mail to the sponsor / ZKS Ulm as soon as they become available. Missing information to any SAE that is fatal or life threatening should be provided as soon as possible, but not later than within 3 further calendar days. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent as soon as these become available. A translation of the autopsy report and death certificate into English language has to be provided, if written in a language other than English or German.
- Where required by local legislation, the investigator is responsible for informing the EC of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator / site must keep copies of all SAE information on file including correspondence with the sponsor / ZKS Ulm and the EC.

13.7.2 Safety Queries

Queries pertaining to SAEs will be communicated from the sponsor / ZKS Ulm to the site by e-mail. The response time is expected to be no more than 24 hours for urgent queries (e.g. fatal or life-threatening SAEs, missing causality assessment) and for all other queries 5 calendar days.

13.7.3 Obligations of the sponsor

The expectedness of an adverse reaction will be determined by the sponsor according to the RSI of the IMPs.

Expedited reporting (SUSAR, New Safety Issues), and submission of Development safety update reports to the relevant CA and to the EC, as appropriate, in accordance with current legislation will be performed by the sponsor / ZKS Ulm.

During the course of the study, the sponsor will report in a pseudonymized, expedited manner all SAEs that are both unexpected and suspected to be related to study drugs, by either the investigator or the sponsor, to the EudraVigilance database, concerned EC and to the investigators in each country / site in accordance with international and local regulations:

- within 7 calendar days of first knowledge by the sponsor for fatal or life-threatening events. Relevant missing information for fatal- or life-threatening cases will be subsequently submitted within an additional 8 calendar days.
- within 15 calendar days of first knowledge by the sponsor for all other serious adverse events.
- All FU reports will be submitted within 15 calendar days of knowledge by the sponsor.

Once the trial is transitioned to CTIS SUSARs will only be reported to the EudraVigilance database in compliance with regulatory timelines; the investigators will be informed by periodic SUSAR Line Listing twice per year together with a summary analysis of safety profile and updated benefit risk for the ongoing clinical trial. Single SUSAR CIOMS I reports will only be distributed to the investigators if the safety of the participants is adversely affected. In addition after the transition the annual safety report will be uploaded to CTIS.

13.8 Product quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity (e.g. damaged or broken product, packaging issues, issues with product appearance, missing component / product). A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory authorities worldwide.

All initial PQCs of an IMP must be reported to sponsor and supporting companies by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined

with a SAE, the investigational staff must report the PQC to sponsor / ZKS Ulm according to the SAE reporting timelines. A sample of the suspected product if possible should be maintained for further investigation.

13.9 Protocol Deviations and Serious Breach

13.9.1 Protocol Deviations

Protocol deviations are documented by the site staff for each center in a special area in the eCRF. The CRA supports the center if necessary and escalates to the sponsor if necessary. The sponsor assessment takes place at regular intervals. The sponsor takes appropriate measures to ensure patient safety and data quality.

13.9.2 Serious Breach

The following section will become applicable only after this protocol has been approved by authorities after transition to the EU regulation 536/2014. The study centers will be adequately informed by the sponsor.
A serious breach is any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety of a trial participant and/or the rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.
Suspected serious breaches, as well as any communication related to the suspected serious breach have to be reported to the sponsor / ZKS Ulm and CTO by e-mail using the following email-address: **seriousbreach.IET@uniklinik-ulm.de** within 24h of knowledge. The sponsor provides a “Serious Breach Report Form” to support the completeness of the documentation.
Queries pertaining to suspected serious breaches will be communicated from the sponsor / ZKS Ulm or CTO to the reporter by e-mail (urgent query is indicated in the subject header of the email). The response time for any query is expected to be no more than 24 hours.

The sponsor will assess each suspected serious breach to decide whether it should be reported as a serious breach.

CTO will notify (upload of the final document in the EU portal) any serious breach according to the EU Regulation 536/2014 without undue delay and at the latest within 7 calendar days of the sponsor becoming aware of a serious breach. Participating centers, including participating pharmacists, as well as clinical research associates (CRAs) and other designees of the sponsor, will support the sponsor by promptly reporting suspected serious breaches.

14. STATISTICAL CONSIDERATIONS

The primary goal of this study is to explore the efficacy of Carfilzomib in combination with Ibrutinib compared to Ibrutinib alone in the treatment of WM.

14.1 Endpoints

Following endpoints will be considered in this study:

14.1.1 Primary Endpoint

The primary endpoint is the rate of CR / VGPR 12 months after randomization.

14.1.2 Secondary Endpoints

The following secondary efficacy endpoints will be evaluated:

Response rate

The response rates (CR, VGPR, PR, MR) and ORR (CR, VGPR, PR) are evaluated 12 and 24 months after randomization.

Best response

Best response (at least achieving a MR) is determined in the time interval from randomization to end of follow-up.

Time to best response

Time to best response is defined as the time from randomization to best response the patient achieves (CR, VGPR, PR, MR).

Time to first response

Time to first response is defined as the time from randomization to first response (MR, PR, VGPR or CR).

Time to treatment failure (TTF)

TTF is defined as the time from date of randomization to discontinuation of therapy for any reason including death from any cause, progression, non-tolerable toxicity or add-on of new anti-cancer therapy. Patients alive without progression and relapse or other treatment failure will be censored at the latest tumor assessment date.

Response duration (RD)

Response duration will be calculated in patients with response (CR, VGPR, PR, MR) from the date of response to the date of progression, relapse or death from any cause. Patients alive without progression and relapse will be censored at the latest tumor assessment date.

Progression Free Survival (PFS)

PFS will be calculated from the date of randomization to the following events: the date of progression (as defined in appendix 21.1) and the date of death if it occurred earlier. Patients alive without progression and relapse will be censored at the latest tumor assessment date.

Cause specific survival (CSS)

Cause specific survival is defined as the period from the randomization to death from lymphoma or lymphoma related cause (e.g. infections, bleeding, amyloid caused organ failure); death unrelated to WM is considered as a competing event.

Overall survival (OS)

Overall survival is defined as the period from the randomization to death from any cause. Patients who have not died until the time of the analysis will be censored at their last contact date.

Safety

Safety including adverse events, SAEs, laboratory parameters, ECG and vital signs.

Quality of Life

Quality of Life will be assessed by the FACT-Lym questionnaire as indicated in Table 1, Table 2 and Table 3.

14.2 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%. We see an increase from 16% to 35% CR / VGPR as a clinically relevant increase, which corresponds to a more than doubling of deep remissions. Deep remissions correlate with PFS and the disease-free interval, thus we assume that the risk-benefit ratio justifies the addition of Carfilzomib when we achieve this improvement. Assuming a CR / VGPR rate of 35% in patients treated with Carfilzomib and Ibrutinib, this scenario requires a number of 94 patients (i.e. 47 patients per group) to reach a power of 80% at a one-sided type one error of 0.10. It is expected that the rate of withdrawal in the study is smaller than 5%. In addition to the drop-out rate of 5%, patients who were randomized but withdrew consent before the start of therapy may be replaced until the end of the recruitment period. According to this, the study will enroll approximately 99 patients in the arms A and B in total.

14.3 Statistical analysis

The primary study endpoint CR / VGPR rate will be evaluated following the intention to treat principle. 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 10% significance level (one-sided) in the core analysis population. The corresponding set of null and alternative hypothesis is:

H0: RRA ≤ RRB

HA: RRA > RRB

where RRA is the CR / VGPR rate in arm A (Carfilzomib / Ibrutinib) and RRB is the CR / VGPR rate in arm B (Ibrutinib). If the obtained one-sided p-value is less than or equal to 0.1 and the point estimate for the CR / VGPR rate of arm A is larger than that of arm B, it will be concluded that the Carfilzomib / Ibrutinib combination statistically significantly increases CR / VGPR rate compared to single agent Ibrutinib. Additionally, the two-sided 95% confidence interval (CI) of the rate difference (RRA-RRB) 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 number of prior lines). A CMH 95% stratified confidence interval (CI) of the rate difference (RRA-RRB) with each rate weighted by the number of patients 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.

14.4 Feasibility:

All sites of the participating study groups may include patients in this study. The expected rates for inclusion per year were estimated by the numbers of patients that were submitted to the former European WM study. In addition, prior to site selection a feasibility has to be performed. The number of study sites will be around 30. The following inclusion rates will be attainable in the study:

Involved study groups	Patients accrual
GLA (C. Buske/Germany)	15 / year
Greek Myeloma Study Group (M. Dimopoulos, Greece)	20 / year
Austria (A. Staber)	5 / year

14.5 Analysis populations

14.5.1 Core Analysis Population

The core analysis population consists of all patients randomized in the study evaluated in the group they were randomized to. Patients with missing or unevaluable response assessment12 months after randomization (primary endpoint) will be excluded from analysis of the primary outcome. Patients who progressed or died within 12 months from randomization are not in CR/VGPR at this time point and are thus classified as non-responders (i.e. CR/VGPR=”no”). We do not impute missing or unevaluable response assessment because we expect those missing values as missing at random since regular follow-up for lymphoma progression is foreseen also in case of early treatment discontinuation. We will make sure by communication and monitoring that the follow-up schedule will be maintained in case of early treatment discontinuation irrespective of the treatment group. As a sensitivity analysis for the primary outcome, we will perform a conservative imputation of the CR/VGPR rate at 12 months from randomization by defining patients alive without progression and with missing or unevaluable response assessment at this time point as non-responders (i.e. CR/VGPR=”no”). The group comparisons of secondary efficacy outcomes represent further sensitivity analyses with different approaches to missing or unevaluable response assessment at 12 months from randomization (e.g. last observation carried forward in best response, counting treatment discontinuation as event in TTF, and censoring at last staging in PFS).

14.5.2 Safety population

The safety population includes patients who started the respective treatment (Ibrutinib without or with Carfilzomib) and groups patients according to the treatment given, irrespective of the randomization result.

15. INDEPENDENT DATA SAFETY MONITORING COMMITTEE

An independent DSMC will review ongoing safety data throughout the study. The DSMC includes at least three independent members (2 experts in WM and one independent statistician). Review of the safety data by the DSMC will take place based on the safety analyses, which will be performed for all patients after the first 6 patients in arm A have completed the first 6 cycles of treatment with ongoing recruitment. Additionally, a second DSMC will take place after 30 patients in arm A completed 6 cycles or at the latest after 18 months of

treatment whichever comes earlier. All data presented at the meeting will be considered confidential. Following each meeting the DSMC will prepare a report and may recommend changes in the conduct of the study. Details on the work of the DSMC will be described in a specific DSMC charter, to be jointly agreed upon the DSMC members and the sponsor.

16. DATA HANDLING AND DATA MANAGEMENT

16.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient informed consent form informing the patient of the following:

- what protected health information (PHI) will be collected from patients in this study;
- who will have access to that information and why;
- who will use or disclose that information;
- the rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes his / her consent to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least survival status (i.e. that the patient is alive) at the end of their scheduled study phase.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

16.2 Use and completion of the electronic case report forms (eCRF)

An electronic case report form will be completed for each study patient. It is the responsibility of the investigator to ensure the accuracy, completeness, legibility and timeliness of the data reported in the patient's eCRF which have been designed by the sponsor to record all observations and other pertinent data to the clinical investigation.

Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events and patient status.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably within 5 to 7 business days after an

examination, treatment, or any other study procedure but not later than prior to the next visit. Any outstanding entries must be completed immediately after the final examination.

16.3 Data management

The data management will be performed with SecuTrial®, a proprietary remote data entry system, which is maintained by the Clinical Trials Unit at the University Medical Center Göttingen. Details on data management (procedures, responsibilities, etc.) will be described in a data management plan prior to the study start. During the study, the performance of data management and any deviations from the data management plan will be documented in a data management report. The technical specifications of the database and the e-forms (variable names, attributes and data entry checks) will be described in a corresponding data base plan. Before any data entry is performed, the study database and edit checks of the e-forms will be validated. Data entry personnel will not be given access to the study data base until they have been trained and signed an access form. An audit trail provides a data history which data were entered, changed or deleted, by whom and when.

SAS software will be used to review the data for completeness, consistency and plausibility. The checks to be programmed will be specified beforehand in a data validation plan. After running the check programs, the resulting queries will be sent via the system to the investigator / site personnel for correction or verification of the documented data. Data corrections will be entered directly into SecuTrial® by the responsible investigator or designated person.

17. STUDY MONITORING

17.1 Investigators responsibilities

Investigator responsibilities are set out in the ICH-GCP and in the local regulations. The sponsor staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately GCP trained and informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient’s source documents.

The investigator, or a designated member of the investigator’s staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (e.g.

medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of eCRFs, queries and SAE-reports.

17.2 Sponsor responsibilities

The sponsor (University Hospital Ulm) or an authorized representative of this study has responsibilities towards the national legislature to take all reasonable steps to ensure the proper conduct of the study as regards patient safety, ethics, study adherence, integrity and validity of the data recorded in the eCRF. Thus, the main duty of the coordinating investigator and of his clinical research support team is to help the investigators maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

17.3 Source document requirements

According to the ICH-GCP, the study monitor has to check the CRF entries against the source documents. The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (study monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

17.4 Monitoring visits

Risk-based monitoring will be done according to ICH-GCP E6 and standard operating procedures to verify that patients' rights and wellbeing are protected, reported study data are accurate, complete and verifiable from source documents and that the study is conducted in compliance with the currently approved protocol / amendment, with ICH-GCP and with the applicable regulatory requirements to ensure patient safety and integrity of clinical study data.

At regular intervals during the study, the study sites will be contacted, through site visits (on-site visits) or telephone calls (remote visits), by a representative of the monitoring team or sponsor to review study progress, investigator and patient adherence to study requirements and any emergent problems. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries (source data verification, SDV). During monitoring visits, the following points will be scrutinized with the investigator: patient informed consent, inclusion and exclusion criteria, patient recruitment and follow-up, patient compliance to the study treatment, study drug accountability, concomitant therapy use, evaluations of response, serious / non-serious adverse event documentation and reporting, and quality of data. The number of contacts will depend on the characteristics of the respective study site, e.g. the number of recruited patients. All study specific monitoring procedures (on-site /

remote), monitoring visit frequency and extent of SDV will be predefined in a study specific monitoring manual.

18. ETHICAL AND REGULATORY STANDARDS

This clinical study was designed, shall be implemented and reported in accordance with the ICH-GCP, with applicable national and international regulations and with the ethical principles laid down in the Declaration of Helsinki.

Before initiating the clinical study, the sponsor should submit the protocol and any required application(s) to the appropriate CA for review, acceptance, and / or permission, as required by the applicable regulatory requirements.

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted EC before study start. A signed and dated statement that the protocol and informed consent have been approved by the EC must be available prior to initiation of the study.

The sponsor must submit this study to country EC and to CA and forward a copy of written approvals / advices signed to the investigators (in the ISF).

18.1 Informed consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each patient prior to any study related procedures or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining patient´s informed consent must be reviewed and approved by the EC. The documents must be available in a fluent language of the patient to include the patient into the study.

The investigator must explain in a fluent language of the patient (e.g. using official translators and informed consent forms in a fluent language of the patient) the aims, methods, reasonable anticipated benefits and potential hazards of the study and any discomfort it may entail. Patients will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal or withdrawal will not prejudice future treatment.

If the withdrawal is caused by any adverse drug event, the patient should inform the investigator about this fact. All data collected before the time point of withdrawal remain within the study database. Consent will be sought from the patient, in order to be allowed to:

- report further major outcome information (e.g. efficacy data)
- guarantee the safety of a patient
- comply with requirements to submit complete documents for authorization

Documentation that informed consent occurred prior to the study patient´s entry into the study and of the informed consent process should be recorded in the study patient´s source documents including the date.

The original informed consent document signed and dated by the study patient and by the person having informed and obtained consent from the study patient prior to the study patient´s entry into the study, must be maintained in the ISF and a copy given to the study patient. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study patients undergoing treatment when the revised patient information is implemented must be re-informed and should re-consent with the revised version of the informed consent document. Patients within follow up must only re-consent if essential or safety relevant information were changed in the patient information form (in consultation with the responsible EC and sponsor). The revised informed consent document signed and dated by the study patient and by the person having informed and obtained consent form the study patient must be maintained in the ISF and a copy given to the study patient. No compensation will be paid to the patients by the sponsor.

19. ADMINISTRATIVE PROCEDURES

19.1 Secrecy agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf) and the patient case report forms are the exclusive property of the sponsor.

They may not be given or disclosed by the investigator or by any person within his team either in part or in totality to any unauthorized person without the prior written formal consent of the sponsor.

It is specified that the submission of this study and other necessary documentation to the EC or a like body is expressly permitted, the EC members having the same obligation of confidentiality.

The investigator shall consider all information as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the study, other than that information to be disclosed by law.

19.2 Record retention in study sites

The investigator must maintain all study records including the investigator site file, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be considered, the longest time having to be considered.

The investigator is required to arrange for the retention of the patient identification codes in accordance with applicable law. If longer storage periods are needed, the sponsor will inform the site prior to the end of the archival time. The sponsor is responsible for archiving the trial master file in accordance with applicable law.

19.3 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the CA and EC of any country (final clinical study report).

19.4 Publication

The final publication of the study results will be written by the coordinating investigator and the national co-coordinating investigators on the basis of the statistical analysis. A draft manuscript will be submitted to all co-authors for review. After revision by the co-authors, the manuscript will be sent to a peer reviewed scientific journal. Authors of the manuscript will include the coordinating investigator and the national co-coordinating investigators, investigators who have included more than 3% of the evaluable patients in the study (by order of inclusion), the statisticians, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses. Any publication, abstract or presentation based on patients included in this study must be approved by the coordinating investigator. This is applicable to any individual patient registered in the study, or any subgroup of the study patients. Such a publication cannot include an analysis of any of the study end-points unless the final results of the study have already been published.

Prior to submission for publication of any manuscript, poster, presentation, abstract, or other written or oral material describing the results of this study, the sponsor shall provide supporting companies 30 calendar days to review the manuscript and 15 calendar days to review any poster, presentation, abstract, or other written or oral material derived from the study.

19.5 Insurance compensation

If required according to the national regulations for each participating country, the sponsor of the study will obtain insurance coverage for eventually occurring damage caused by the treatment or any actions taken according to the treatment plan. A certificate of insurance will be provided to the investigator in countries in which this document is required. The investigator, or

an individual who is designated by the investigator, will inform the patient of the existence of the insurance, including the obligations arising from it. The study patients must be given access to the insurance documents and, on request, a copy of the general conditions of insurance.

19.6 Audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory guidelines it may be necessary to conduct a site audit or an inspection.

By participating in this study and signing the study contract, the investigator agrees to allow the sponsor and its representative, and competent authorities to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits or inspections involve review of source documents supporting the adequacy and accuracy of data gathered in eCRF, review of documentation required to be maintained, and checks on drug accountability.

The investigator needs to inform the sponsor immediately of an inspection requested by a CA. The investigator is responsible for providing / giving access to source data / documents to auditors / inspectors. The sponsor will in all cases help the investigator prepare for an inspection.

19.7 Clinical study report

The sponsor will inform the CA and EC about the end of the study within 90 days following the end of study. A study report will be prepared under the responsibility of the sponsor less than one year after the end of the study and forwarded to the EudraCT database, CA, EC and the supporting companies.

19.8 Study Amendments

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the coordinating investigator, Amgen, Janssen and the sponsor.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the coordinating investigators, by the sponsor and study statistician, who is responsible for study planning.

Approval / advice of amendments by EC and CA are required prior to their implementation, unless there are overriding safety reasons.

19.9 Contract of Investigation

The participating institutions are selected by the coordinating investigator, based on the proven qualification in the framework of previous studies in the cooperative groups. The clinical study sites will document their appropriate qualification and capacities for taking part in the study, in order to allow for a qualified decision of the EC on their participation.

The investigator of every participating study site has to sign the contract before start of the study. With this contract the investigator agrees to treat all patients who have been admitted to the participating study site during active study-recruitment fulfilling the inclusion criteria and not the exclusion criteria after giving an informed consent and registration at the study office within the present study. Additionally, he agrees to document all required study relevant data into the specific eCRFs.

19.10 Financing

The coordinating investigator and the sponsor will take care of the financing / funding of the study. The study will be funded in part by Amgen and by Janssen. The study drug, “Ibrutinib” will be provided by Janssen free of charge, the study drug “Carfilzomib” by Amgen free of charge.

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21. APPENDICES

21.1 Appendix A: Modified Response Criteria according to Owen et al[1]

Response category	Definition
Complete response (CR)	• Absence of serum monoclonal IgM protein by immunofixation[3] • Normal serum IgM level • Complete resolution of lymphadenopathy[2] and splenomegaly if present at baseline[5] • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response (VGPR)	• Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline • Decreased lymphadenopathy[2] / splenomegaly if present at baseline[5] • No new signs or symptoms of active disease
Partial response (PR)	• Monoclonal IgM protein is detectable • > 50% but < 90% reduction in serum IgM level from baseline[5] • Decreased lymphadenopathy[2] / splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor response (MR)	• Monoclonal IgM protein is detectable • > 25% but < 50% reduction in serum IgM level from baseline[5] • No new signs or symptoms of active disease
Stable disease (SD)	• Monoclonal IgM protein is detectable • < 25% reduction and < 25% increase in serum IgM level from baseline[5] • No progression in lymphadenopathy[2] / splenomegaly • No new signs or symptoms of active disease
Progressive disease (PD)[6]	• ≥ 25% increase in serum IgM level from lowest nadir[1] (with confirmation[4]) and / or • progression in clinical features attributable the disease. An absolute increase of at least 5 g/l is required to define progression when the IgM level is the only applicable criterion.

1. Nadir for serum IgM is defined as the lowest serum IgM value obtained at any time from baseline onwards with the exception that serum IgM levels post-plasmapheresis will not be considered for up to 35 days.
2. Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node
3. Serum protein electrophoresis, nephelometry or densitometry (whichever is used for an individual patient) and immunofixation have to be repeated at least 6 weeks later in case of complete response to confirm CR.
4. Progression should be confirmed by a second measurement after 7 to 14 days.
5. Baseline is the IgM value at C1D1.
6. When interrupting ibrutinib, some patients may experience an IgM rebound, which must be carefully differentiated from progression.

21.2 Appendix B: Performance Status

ECOG Performance Status Scale	
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

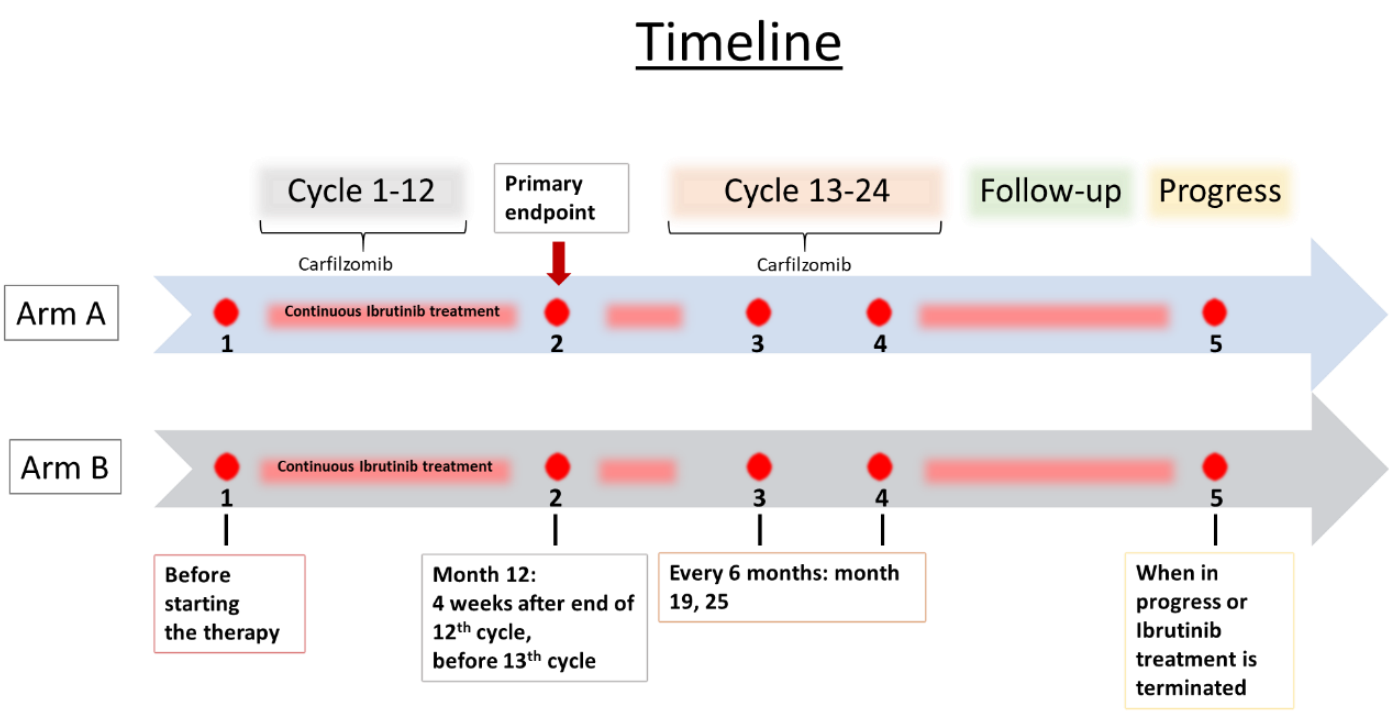
21.3 Appendix C: Biological samples for further ancillary studies

In the case of patient's consent, the following biological samples will be obtained:

a) Bone marrow cells
   - before start of treatment
   - during therapy only in those patients in whom bone marrow aspiration is performed to confirm CR or to document delayed response (see Table 1, Table 2 and Table 3).

b) Cheek swap
   - once before start of treatment

c) Peripheral blood and serum
   - at different time points as indicated below and in case of progression at any time of the study.



Time points

Five eligible time points are described for bio-sampling:

1) Prior to treatment
2) Primary endpoint: month 12, before start of cycle 13
3) At Cycle 19
4) At Cycle 25
5) At progress and / or 30 days after termination of Ibrutinib treatment

Sample	Usage	Delivery
30 ml of peripheral blood in CELL-FREE DNA blood collection tubes (BCT®) (Streck)	• Storage of plasma for cell free DNA (cfDNA),	• Peripheral Blood should be collected on site in CELL-FREE DNA blood collection tubes (BCT®) (Streck), which will be provided by the sponsor. Tubes will be sent to the national reference laboratory at ambient temperature by regular delivery service
15 ml of bone marrow	• Storage of freshly isolated cells • Storage of DNA and RNA from sorted bone marrow B cells	• EDTA tube at ambient temperature should be sent to the national reference laboratory with overnight carrier for next day delivery
10 ml of serum	• Storage of serum proteins	• Serum tubes at ambient temperature with overnight carrier for next day delivery
10 ml of EDTA peripheral blood	• Storage of DNA for MRD measurements	
Cheek swap (once before start of treatment)	• Storage of DNA of non-hematopoietic cells (FTA cards)	• DNA of non-hematological cells will be collected by cheek swabs and the Whatman® FTA® card technology (Sigma-Aldrich). The kit will be provided by the sponsor. Genomic DNA stored on FTA Cards at room temperature is stable for years. FTA cards will be sent to the national reference laboratory by regular delivery service.

All the collected biological samples are common property and are open for scientific projects performed by the participants of this study. Transport costs will be covered by the sponsor of the study.

21.4 Appendix D: Laboratory Flow Chart Arm A

PERIODS	**SCREENING**			**TREATMENT (28 days cycles)**																
	up to 45 days			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*																
VISITS	**Screening**			**Cycle 1 to 6**			**Cycle 7**		**Cycle 8 to 12**		**Cycle 13**		**Cycle 14 to18**		**Cycle 19**		**Cycle 20 to 24**		**Cycle 25+** (every 3 months)	**EOT Visit**
	Day -45 to 0	**Day -30 to 0**	**Day -7 to 0**	D1	D8*	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	
Haematology																				
Leucocytes			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Haemoglobin			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Haematocrit			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Platelets			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Erythrocytes			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Lymphocytes			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Monocytes[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Neutrophils			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Eosinophils[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Basophils[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Serum chemistry																				
Sodium[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Potassium[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Calcium[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Phosphate[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Creatinine			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
GFR (CKD-EPI)			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Urea or BUN[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Glucose[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Total bilirubin			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
ASAT			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
ALAT			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
LDH			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x

PERIODS	**SCREENING**			**TREATMENT (28 days cycles)**																
	up to 45 days			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*																
VISITS	**Screening**			**Cycle 1 to 6**			**Cycle 7**		**Cycle 8 to 12**		**Cycle 13**		**Cycle 14 to18**		**Cycle 19**		**Cycle 20 to 24**		**Cycle 25+** (every 3 months)	**EOT Visit**
	Day -45 to 0	**Day -30 to 0**	**Day -7 to 0**	D1	D8*	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	
Albumin			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Magnesium[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
Total protein			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
CRP[#]			x	x	x	x	x	x	x	x	x	x	x		x		x		x	x
ß2-microglobulin			x				x				x				x				x[°]	
Serum protein electrophoresis																				
M-protein			x				x				x				x				x[°]	
Serum immunofixation																				
Assessment for IgM, IgA, IgG and Kappa / lambda			x								x				x				x[°]	
Immunglobuline																				
IgM			x	x			x		x		x		x		x		x		x	x
IgA			x	x			x		x		x		x		x		x		x[°]	x
IgG			x	x			x		x		x		x		x		x		x[°]	x
Serum free light chain																				
Free kappa			x								x									x
Free lambda			x								x									x
Kappa / lambda ratio			x								x									x
FACS analysis peripheral blood																				
FACS	x										x				x				x[°]	x

* only for the first 10 patients in Arm A

[#] Values must be done and must be documented in the source data / patient file. Values will not be entered in the eCRF. If a value is clinically significant it has to be documented as adverse event

° Every 6 months

PERIODS	**SCREENING**			**TREATMENT (28 days cycles)**																
	up to 45 days			***Arm A:*** *Carfilzomib for 24 cycles, Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*																
VISITS	**Screening**			**Cycle 1 to 6**			**Cycle 7**		**Cycle 8 to 12**		**Cycle 13**		**Cycle 14 to18**		**Cycle 19**		**Cycle 20 to 24**		**Cycle 25+** (every 3 months)	**EOT Visit**
	Day -45 to 0	**Day -30 to 0**	**Day -7 to 0**	D1	D8*	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	
Coagulation																				
INR			x	x			x		x		x		x		x		x		x	x
(activated) partial thromboplastin time			x	x			x		x		x		x		x		x		x	x
Urine immunofixation																				
Total protein			x								x				x				x°	
Bence Jones protein			x								x				x				x°	
Cryoglobuline																				
Cold agglutinin test			x				x*				x*				x*				x*	
Direct Coombs test			x				x*				x*				x*				x*	
Virology																				
HIV		x																		
Hepatitis B (HbsAg, anti-Hbc)		x																		
Hepatitis C		x																		
Biosampling (only if patient has signed the additional informed consent and only during routine assessments)																				
Cheek swap	x																			
30ml peripheral blood (Streck tube)	x										x				x				Cycle 25	
15ml bone marrow	x										x				x				*Cycle 25*	
10ml serum	x										x				x				*Cycle 25*	
10ml EDTA peripheral blood	x										x				x				*Cycle 25*	

* If cryoglobulinemia is suspected cold agglutinin test and direct Coombs test will be done at screening and after that every 6 months if initially positive
° every 6 months
! only in case BM biopsy is done (to confirm CR, to investigate progression, other medical indication)

21.5 Appendix E: Laboratory Flow Chart Arm B

PERIODS	**SCREENING**			**TREATMENT (28 days cycles)**								
	up to 45 days			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*								
VISITS	**Screening**			**Cycle 1 to 6** *(every 28 days)*	**Cycle 7**	**Cycle 8 to 12** *(every 28 days)*	**Cycle 13**	**Cycle 14 to 18** *(every 3 months)*	**Cycle 19**	**Cycle 20 to 24** *(every 3 months)*	**Cycle 25+** *(every 3 months)*	**EOT Visit**
	Day -45 to 0	**Day -30 to 0**	**Day -7 to 0**	D1	D1	D1	D1	D1	D1	D1	D1	
Haematology												
Leucocytes			x	x	x	x	x	x	x	x	x	x
Haemoglobin			x	x	x	x	x	x	x	x	x	x
Haematocrit			x	x	x	x	x	x	x	x	x	x
Platelets			x	x	x	x	x	x	x	x	x	x
Erythrocytes			x	x	x	x	x	x	x	x	x	x
Lymphocytes			x	x	x	x	x	x	x	x	x	x
Monocytes[#]			x	x	x	x	x	x	x	x	x	x
Neutrophils			x	x	x	x	x	x	x	x	x	x
Eosinophils[#]			x	x	x	x	x	x	x	x	x	x
Basophils[#]			x	x	x	x	x	x	x	x	x	x
Serum chemistry												
Sodium[#]			x	x	x	x	x	x	x	x	x	x
Potassium[#]			x	x	x	x	x	x	x	x	x	x
Calcium[#]			x	x	x	x	x	x	x	x	x	x
Phosphate[#]			x	x	x	x	x	x	x	x	x	x
Creatinine			x	x	x	x	x	x	x	x	x	x
GFR (CKD-EPI)			x	x	x	x	x	x	x	x	x	x
Urea or BUN[#]			x	x	x	x	x	x	x	x	x	x
Glucose[#]			x	x	x	x	x	x	x	x	x	x
Total bilirubin			x	x	x	x	x	x	x	x	x	x
ASAT			x	x	x	x	x	x	x	x	x	x
ALAT			x	x	x	x	x	x	x	x	x	x
LDH			x	x	x	x	x	x	x	x	x	x
Albumin			x	x	x	x	x	x	x	x	x	x

PERIODS	**SCREENING**			**TREATMENT (28 days cycles)**								
	up to 45 days			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*								
VISITS	**Screening**			**Cycle 1 to 6** *(every 28 days)*	**Cycle 7**	**Cycle 8 to 12** *(every 28 days)*	**Cycle 13**	**Cycle 14 to 18** *(every 3 months)*	**Cycle 19**	**Cycle 20 to 24** *(every 3 months)*	**Cycle 25+** *(every 3 months)*	**EOT Visit**
	Day -45 to 0	**Day -30 to 0**	**Day -7 to 0**	D1	D1	D1	D1	D1	D1	D1	D1	
Magnesium[#]			x	x	x	x	x	x	x	x	x	x
Total protein			x	x	x	x	x	x	x	x	x	x
CRP[#]			x	x	x	x	x	x	x	x	x	x
ß2-microglobulin°			x		x		x		x		x°	
Serum protein electrophoresis												
M-protein			x		x		x		x		x°	
Serum immunofixation												
Assessment for IgM, IgA, IgG and Kappa / lambda			x				x		x		x°	
Immunglobuline												
IgM			x	x	x	x	x	x	x	x	x	x
IgA			x	x	x	x	x	x	x	x	x°	x
IgG			x	x	x	x	x	x	x	x	x°	x
Serum free light chain												
Free kappa			x				x					x
Free lambda			x				x					x
Kappa / lambda ratio			x				x					x
FACS analysis peripheral blood												
FACS	**x**						x		x		x°	x
Coagulation												
INR			x	x	x	x	x	x	x	x	x	x
(activated) partial thromboplastin time			x	x	x	x	x	x	x	x	x	x

[#] Values must be done and must be documented in the source data / patient file. Values will not be entered in the eCRF. If a value is clinically significant it has to be documented as adverse event

° Every 6 months

PERIODS	**Name**	**SCREENING**			**TREATMENT (28 days cycles)**								
	Duration	*up to 45 days*			***Arm B:*** *Ibrutinib until disease progression or non-tolerable toxicity (max. 7 years after FPI)*								
VISITS		**Screening**			**Cycle 1 to 6** *(every 28 days)*	**Cycle 7**	**Cycle 8 to 12** *(every 28 days)*	**Cycle 13**	**Cycle 14 to18** *(every 3 months)*	**Cycle 19**	**Cycle 20 to 24** *(every 3 months)*	**Cycle 25+** (every 3 months)	**EOT Visit**
	Time / Section	**Day -45 to 0**	**Day -30 to 0**	**Day -7 to 0**	D1	D1	D1	D1	D1	D1	D1	D1	
Urine immunofixation													
Total protein				x				x		x		x°	
Bence Jones protein				x				x		x		x°	
Cryoglobuline													
Cold agglutinin test				x		X*		X*		X*		X*	
Direct Coombs test				x		X*		X*		X*		X*	
Virology													
HIV		x											
Hepatitis B (HbsAg, anti-Hbc)		x											
Hepatitis C		x											
Biosampling (only if patient has signed the additional informed consent and only during routine assessments)													
Cheek swap	x												
30ml peripheral blood (Streck tube)	x							x		x		Cycle 25	
15ml bone marrow[!]	x							x		x		Cycle 25	
10ml serum	x							x		x		Cycle 25	
10ml EDTA peripheral blood	x							x		x		Cycle 25	

- If cryoglobulinemia is suspected, cold agglutinin test and direct Coombs test will be done at screening and after that every 6 months if initially positive

° Every 6 months

! only in case BM biopsy is done (to confirm CR, to investigate progression, other medical indication)