Combined therapy with ibrutinib and bortezomib followed by ibrutinib maintenance in relapsed or refractory mantle cell lymphoma and high-risk features: a phase 1/2 trial of the European MCL network (SAKK 36/13)

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Protocol SAKK 36/13

Combination of ibrutinib and bortezomib followed by ibrutinib maintenance to treat patients with relapsed and refractory mantle cell lymphoma; a multicenter Phase I/II trial

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The trial is supported by the European MCL network	

CONFIDENTIALITY

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PROTOCOL SIGN-OFF PAGE

SAKK 36/13 - Combination of ibrutinib and bortezomib followed by ibrutinib maintenance to treat patients with relapsed and refractory mantle cell lymphoma; a multicenter Phase I/II trial

The protocol SAKK 36/13 was accepted by the SAKK Board on 15.05.2014 and has passed the recommended review process for SAKK trials.

The final protocol (version 2.0) is dated 04.05.2015. Version 6.0 including Amendment 1, 2, 3 and 4 is dated 11.03.2019.

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PROTOCOL SIGN-OFF PAGE PROTOCOL VERSION 6.0 FOR THE PRINCIPAL INVESTIGATOR

SAKK 36/13 - Combination of ibrutinib and bortezomib followed by ibrutinib maintenance to treat patients with relapsed and refractory mantle cell lymphoma; a multicenter Phase I/II trial

Principal Investigator in: _____

Having read and understood protocol version 6.0 of 11.03.2019, including amendment 1,2,3 and 4, I agree to conduct the trial as specified in the protocol. Version 6.0 may only be implemented after the concerned regulatory authorities have accepted this amendment.

Name: _____ Title: _____

Date: _____ Signature: _____

ABBREVIATIONS

ADL	Activities of daily life
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	activated partial thromboplastin time
ASR	Annual safety report
AST	Aspartate aminotransferase
ATM	Ataxia Telangiectasia Mutated
BAG	Bundesamt für Gesundheit
BCR	B-cell antigen receptor
BIRC3	Baculoviral IAP repeat-containing 3
BMB	Bone marrow biopsy
BR	Bendamustine and rituximab
BSA	Body surface area
BTK	Bruton's tyrosine kinase
CARD11	Caspase recruitment domain-containing protein 11
CC	Coordinating Center
CD19	Cluster of differentiation 19 (B-lymphocyte antigen CD19)
CD20	Cluster of differentiation 20 (B-lymphocyte antigen CD20)
CD5	Cluster of differentiation 5
CD69	Cluster of differentiation 69
CI	Coordinating investigator
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPM	Clinical project manager
Cr	Creatinine clearance
CR	Complete Response
CRA	Clinical research assistant
CRF	Case report form
CRu	Complete response unconfirmed
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CV	Curriculum vitae
CYP2D6	Cytochrome P450 family 2, subfamily D, 6
CYP3A	Cytochrome P450 family 3, subfamily A
DL	Dose level
DLT	Dose limiting toxicity
DOR	Duration of response
DSUR	Development safety update report
EC	Ethics Committee
ECG	Electrocardiography
eCRF	electronic CRF
EDC	Electronic data capture

EMA	European medicines agency
ER	Endoplasmatic reticulum
ERK	Extracellular signal regulated kinase
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug administration
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GI	Growth inhibition
GTD	Greatest transverse diameter
Hb	Hemoglobin
HFV	Humanforschungsverordnung,
HID	Head of Innovation and Development
HRA	Human research act
i.v.	Intravenous
IB	Investigator`s Brochure
IC50	half minimal (50%) inhibitory concentration (IC)
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INR	International normalized ratio
IRC	Independent response committee
KlinV	Verordnung über klinische Versuche in der Humanforschung
KOFAM	Koordinationsstelle Forschung am Menschen
MCL	Mantle Cell Lymphoma
MLL2	Mixed-lineage leukemia protein 2
MM	Multiple Myeloma
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
NFκB	Nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NHL	Non-Hodgkin Lymphoma
NOTCH1	Neurogenic locus notch homolog 1
NOTCH2	Neurogenic locus notch homolog 2
NOXA	Phorbol-12-myristate-13-acetate-induced protein 1
NTL	Non target lesion
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l’être humain
OR	Overall response
ORR	Overall response rate
OS	Overall Survival
p.o.	per os

PAX5	Paired box protein 5
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal investigator
PI3K	Phosphoinositide 3-kinase
PLCγ	Phospholipase-Cγ
PNP	Peripheral polyneuropathy
PQC	Product quality complaint
PR	Partial Response
PT	Prothrombin time
R-CHOP	Chemotherapy regimen: **R**ituximab-**C**yclophosphamid, **H**ydroxydaunorubicin (Doxorubicin), Vincristin (Oncovin®), Predniso(lo)n
R-FC	Rituximab - fludarabine, cyclophosphamide
RP2D	recommended phase II dose
s.c.	subcutaneous
SAR	Serious adverse reaction
SAE	Serious adverse event
SAKK CC	SAKK Coordinating Center
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SAP	Statistical analysis plan
SCI	Supporting coordinating investigator
SD	Stable Disease
SDV	Source data verification
SLL	Small lymphocytic lymphoma
SmPC	Summary of product characteristics
SNCTP	Swiss National Clinical Trials Portal
SOC	System organ class
SOP	Standard operating procedure
SOX11	Sry-related HMG box 11
SPD	Sum of product diameters
SUSAR	Suspected unexpected serious adverse reaction
SUVA	Schweizerische Unfallversicherungsanstalt
TL	Target lesions
TP53	Tumor protein p53
TRAF2	TNF Receptor-Associated Factor 2
TRAF3	TNF Receptor-Associated Factor 3
TSA	Trial-specific agreement
TTF	Time to treatment failure
ULN	Upper limit of normal
UPN	Unique patient number
UPR	Unfolded protein response
US	United States
WHO	World Health Organization
WHSC1	Wolf-Hirschhorn Syndrome Candidate 1

β-hCG	Beta-human chorionic gonadotropin

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1 TRIAL OVERVIEW SAKK 36/13

SAKK 36/13 - Combination of ibrutinib and bortezomib followed by ibrutinib maintenance to treat patients with relapsed and refractory mantle cell lymphoma; a multicenter Phase I/II trial

Sponsor:	Swiss Group for Clinical Cancer Research (SAKK)
Trial registry No.:	SNCTP No. SNCTP000001235
	EudraCT No. 2014-003893-17
	ClinicalTrials.gov No. NCT02356458
Coordinating investigator:	PD Dr. med. Urban Novak, Inselspital Bern

TRIAL TYPE AND CATEGORISATION

Ibrutinib and bortezomib are medications with marketing authorization for relapsed and refractory mantle cell lymphoma. Bortezomib will be applied according to marketing authorization. Ibrutinib will be used in a way different from the authorized form (dose). According to the Swiss Human Research Act (HRA) [1] this trial is classified as category B in accordance with the new legal ordinance on clinical trials with an investigational medicinal product (KlinV/OClin).

TRIAL PHASE

The trial is a multicenter, prospective, single-arm, phase I/II trial.

The **phase I** was open for accrual from 11.08.2015 until 18.11.2016.

The **phase II** was opened for accrual on 18.11.2016 with the determined RP2D of 560mg Ibrutinib per day.

OBJECTIVE(S)

Trial objective(s):

Phase I	**Phase II**
The primary objective of the trial is to establish the recommended phase II dose (RP2D) of ibrutinib in combination with bortezomib in patients with relapsed or refractory MCL. The secondary objectives are • to determine the safety and tolerability of ibrutinib in combination with bortezomib and • to assess the **preliminary** antitumor activity of ibrutinib in combination with bortezomib	The main objective of the trial is to define the efficacy of ibrutinib in combination with bortezomib in patients with relapsed or refractory MCL. The secondary objectives are • to determine the safety and tolerability of the RP2D and • to assess the efficacy of ibrutinib in combination with bortezomib in patients with relapsed MCL followed by an ibrutinib maintenance therapy.

Additional research question:

The objective of the translational research project is to assess the role of genetic lesions influencing the BCR/NFκB signaling pathway in the response to ibrutinib combined with bortezomib following an ibrutinib maintenance therapy. The results will allow a better selection of patients to be treated with the regimen.

ENDPOINTS

Primary endpoint:

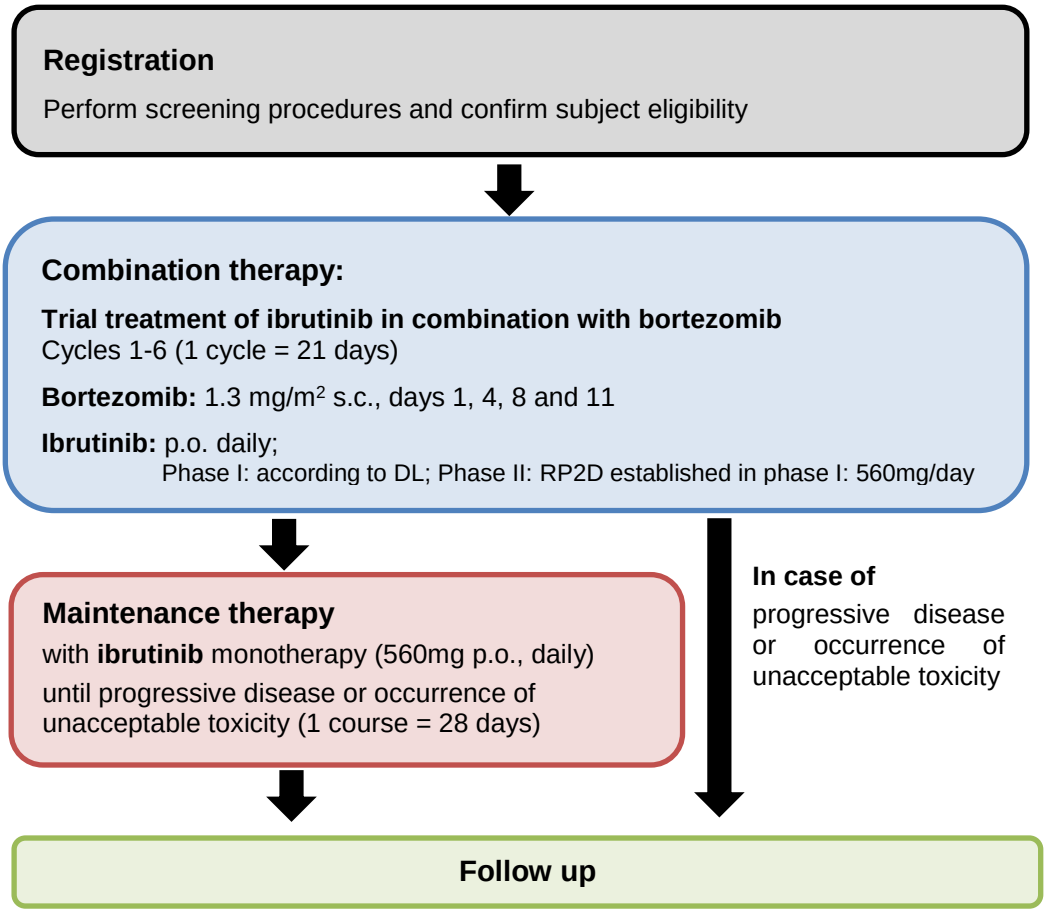
Phase I	Phase II
Dose limiting toxicity (DLT) observed during the first cycle of trial treatment	Overall response (OR) (combination therapy)

Secondary endpoints:

Phase I	Phase II
• Adverse events (AE) until 30 days after end of trial therapy • OR (combination therapy) • OR based on best response observed during treatment (combination and maintenance therapy)	• Adverse events (AE) until 30 days after end of trial therapy • OR based on best response observed during treatment (combination and maintenance therapy) • Progression-free survival (PFS) • Time to treatment failure (TTF) • Duration of objective response

TRIAL DESIGN

International multicenter, single-arm phase I/II trial



SELECTION OF PATIENTS

- Histologically confirmed mantle cell lymphoma with either overexpression of cyclin D1 protein or evidence of t(11;14)(q13;q32)
- Refractory or relapsed mantle cell lymphoma in need of systemic therapy after pretreatment of non-bortezomib-containing chemotherapy (including high-dose therapy plus autologous stem cell support as one line of treatment)
- At least one measurable lesion ≥11 mm in its greatest transverse diameter (see Appendix 1.2) measured with CT scan (contrast enhanced) or MRI (in case the disease cannot be adequately imaged using CT and if contrast is not appropriate for patients according to the treating physician) (see also Appendix 1)
- Adequate hematological, hepatic and renal function
- Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at baseline. Women who are pregnant or breastfeeding are ineligible for this trial
- No prior therapy with ibrutinib or bortezomib
- No neuropathy grade ≥2 (according to CTCAE criteria) as adverse event of prior therapy at registration
- No treatment with strong or moderate CYP3A inhibitors during trial treatment
- No presence or history of CNS disease
- No history of stroke or intracranial hemorrhage within 6 months prior to trial registration
- No requirement of anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon)

TRIAL DURATION

Duration of accrual: 3.5 years

Duration of trial therapy (per patient): *Combination therapy*: ca. 4.5 month, *maintenance therapy* until progressive disease or occurrence of unacceptable toxicity (1 course repeats every 28 days)

Duration of the follow-up: 2 years

Duration of study (in total): approximately 8 years

Accrual may be stopped early based on the results of an interim safety analysis or if new scientific data become available which change assessment of risk/benefit.

TRIAL SCHEDULE

Trial activation: (effective): 11.08.2015

First patient in: (effective): 31.08.2015

Phase I closed for accrual (effective): 18.11.2016

Phase II open for accrual (effective): 18.11.2016

Last patient in: (planned): Q4 2019

Last patient last treatment (planned): Q1 2021

Last patient, last visit: (planned): Q1 2023

TRIAL PRODUCTS

Ibrutinib (Imbruvica®) is licensed in Switzerland and the EMA region for the treatment of relapsed and refractory MCL In the maintenance therapy ibrutinib is given according to the approved dose and in the combination therapy it is given according to dose level (phase I) or the RP2D (phase II).

Bortezomib (Velcade®) is licensed for relapsed and refractory MCL. It will be given in its regulatory approved dose in combination with ibrutinib.

TRIAL TREATMENT

Combination therapy (ibrutinib with bortezomib)

Treatment consists of 6 cycles of **21 days each** of ibrutinib in combination with bortezomib, followed by a maintenance therapy

Ibrutinib is taken orally once per day, continuously. The dose for cycle 1-6 depends on the DL (phase I) and the RP2D.
Please note: The determined RP2D is 560mg/day.

Bortezomib is injected s.c. with a dose of 1.3 mg/m^2 on day 1, 4, 8, 11

Maintenance therapy (ibrutinib monotherapy)

In the maintenance therapy courses of ibrutinib (taken orally once per day, continuously) **are repeated every 28-days** in the absence of disease progression or unacceptable toxicity. The administered dose is 560mg/day.

Treatment duration

Please refer to chapter 9.8 (treatment duration) for reasons to stop the trial treatment (combination and maintenance therapy).

MEASUREMENTS AND PROCEDURES

Investigations before trial treatment:

Physical examination; blood analysis and control of lab values; imaging investigations (e.g. CT or MRI; electrocardiogram; cardiac ultrasound; pregnancy test (if applicable); bone marrow biopsy (if applicable); medical history.

Investigations during trial treatment:

Physical examination; blood analysis and control of lab values; imaging investigations (e.g. CT or MRI); bone marrow biopsy (only if involved at baseline); assessment of adverse events.

Investigations after trial treatment

Physical examination; blood analysis and control of lab values; imaging investigations (e.g. CT or MRI (if applicable); bone marrow biopsy (only if applicable); assessments of adverse events.

Follow-up

Physical examination; imaging investigations (e.g. CT or MRI), only in case of no progressive disease yet; disease status, survival status; further MCL treatments; assessment of late adverse events related to trial therapy .

Translational research (if patient has given consent only, Swiss sites, only):

5 sampling time-points (within the routine blood analysis) at the following time-points: at the beginning of the trial, after end of the combination therapy, after 12 weeks in maintenance therapy and at the end of treatment visit and in case of relapse.

STATISTICAL CONSIDERATIONS

For Phase I, a standard 3+3 dose escalation design is applied. A minimum of 4 (in case of two DLTs in the first two patients at dose level 1 and two DLTs in the first two patients at dose level -1) and a maximum of 18 (in case of six patients at each dose level) evaluable patients will be included in the dose escalation procedure. As soon as the RP2D is established in 6 patients, this dose will be brought forward to Phase II.

For Phase II, a Simon's two-stage minimax design is applied. An OR rate of 65% or less is considered uninteresting and 80% or higher is promising. With a significance level of 5% and a power of 80%, a total of 55 evaluable patients are required. The patients from Phase I who are treated at the RP2D will contribute to the number of patients for Phase II.

GCP STATEMENT

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as national legal and regulatory requirements.

2 INTRODUCTION AND BACKGROUND

2.1 Disease background

Mantle cell lymphoma (MCL) is a distinct subtype of B-cell lymphoma. It represents ~5% of all lymphomas and typically is present in advanced stages, a median age of 60-65 years and a dismal prognosis with a median survival of ~3 years. The clinical course of MCL is highly variable ranging from an indolent disease to a rapidly progressive malignancy. Currently, it remains incurable, as the patients will relapse after first line treatment and require subsequent therapy. The disease-free survival is progressively shorter with each subsequent relapse. MCL is predominantly a disease of the elderly who are not suitable for aggressive chemotherapy.

2.2 Therapy background

Currently, there is no standard therapy for relapsed MCL patients. Allogeneic transplants are preferred in young and fit patients, whereas (preferably single agent) chemotherapy is used to treat older patients. Therapeutic options include rituximab, bortezomib, lenalidomide, thalidomide, gemcitabine, fludarabine, chlorambucil, bendamustine, cladribine, furthermore mTOR inhibitors as single agents or in various combinations (such as rituximab - fludarabine, cyclophosphamide (R-FC), or gemcitabine, dexamethasone and cisplatinum), but usually with short duration of responses. Recently, the therapeutic armamentarium has been expanded with the availability of novel agents targeting crucial and deregulated pathways in MCL. These include idelalisib, by blocking the delta isoform of the enzyme phosphoinositide 3-kinase (PI3K), and the Bruton's Kinase (BTK) inhibitor ibrutinib both with excellent single agent activities.

Recently, a synergistic increase in the proteasomal inhibition of ibrutinib in both bortezomib-sensitive and refractory MCL cells was shown [2].

2.3 Investigational medicinal products

2.3.1 Ibrutinib

Ibrutinib is an oral, selective and irreversible BTK inhibitor. B-cell antigen receptor (BCR) signaling is implicated in the pathogenesis of various B-cell lymphomas, and essential for normal B-cell development. BTK is a signaling kinase upstream in the BCR cascade and a potential target for selective B-cell inhibition. Components of the B-cell receptor signaling pathway are constitutively active in MCL and contribute to proliferation and survival ([3-6]. By blocking BTK, ibrutinib inhibits proliferation, induces apoptosis, and blocks external signals, e.g. from the microenvironment [7].

Ibrutinib has recently been approved (November 2013) by the United States Food and Drug Agency (US FDA), in Switzerland (November 2014) and the European Medicines Agencies (EMA) region (October 2014) for the treatment of relapsed/refractory MCL. The recommended dose of ibrutinib for MCL as single agent is 560 mg (four 140 mg capsules) orally once daily.

2.3.1.1 Preclinical experience

Ibrutinib was designed as a selective and irreversible inhibitor of the BTK protein [8]. *In vitro* studies have shown that ibrutinib binds covalently and irreversible to a cysteine residue (Cys-481) in the active side of BTK, leading to potent and sustained inhibition of BTK enzymatic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position [8]. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase (ERK). Ibrutinib also inhibited the growth of a subset of B-cell lymphoma derived cell lines, with 50% growth inhibition (GI50) values ranging from 0.1 to 5.5 µM and inhibited tumor growth in vivo in xenograft models [9].

When added directly to human whole blood, ibrutinib inhibits signal transduction from the BCR and blocks activation of B cells (IC50 = 80 nM). Inhibition of B cell activation by ibrutinib in peripheral blood mononuclear cells is measured by quantifying the level of the cell surface marker CD69 following stimulation of the B cell receptor with anti-Ig antibodies.

Refer to the ibrutinib Investigator's Brochure (IB) [10] for more information on nonclinical pharmacology and toxicology studies.

2.3.1.2 Clinical experience

In a phase I trial with 56 patients, ibrutinib achieved an overall response rate (ORR) of 54 %. This trial included 9 patients with relapsed MCL of whom 7 responded [11, 12]. The safety and efficacy of ibrutinib in patients with MCL who have received at least one prior therapy were evaluated in an open-label phase II, multi-center, single-arm trial of 111 previously treated patients. This phase II trial reported an ORR of 68 % with a CR in 21%. Interestingly, the latter increased over time, e.g. with longer exposure to the drug, and was not lower when the patients were previously exposed to bortezomib. When the results were first reported in 2013 [13], the median progression-free survival (PFS) was 13.9 months, and the median overall survival (OS) was not reached. In the full prescribing information (US) from November 2013 the ORR is described as 66% (IRC review demonstrated an ORR of 69%) with CR of 17% with a duration of response (DOR) of 17.5 months [14]. In a recently published phase Ib trial, Ibrutinib in combination with R-CHOP achieved a complete response (CR) in 70 % of treatment-naive patients with CD20-positive B-NHL patients, with an ORR of 91 %. 5 (out of 32) of the patients in this trial were MCL patients [15].

A short list of trials with ibrutinib in MCL patients currently ongoing is listed here below:

- A phase III trial Combination in newly diagnosed MCL patients with bendamustine and rituximab (BR) (NCT01776840)
- A phase III trial older than 65 years is testing the combination of ibrutinib with bendamustine (NCT01886872),
- A phase III trial where single-agent ibrutinib is compared to temsirolimus (NCT01646021)
- The ongoing SPARK trial (Phase II) will independently assess the efficacy of ibrutinib that are previously exposed to bortezomib (NCT01599949).

The main observed toxicities of ibrutinib that have been seen in one of every 3-4 patients were diarrhea and fatigue, nausea and infection. Grade 4 adverse events (AEs) include neutropenia (10%), and less frequently thrombocytopenia, abdominal pain and hyperuricemia. Full information on AEs and safety matters are provided in the most recent IB or summary of product characteristics

2.3.2 Bortezomib

Bortezomib is a targeted therapy and belongs to the class of proteasome inhibitors. Bortezomib works by reversibly inhibiting the β5 subunit of the proteasome [16]. Bortezomib inhibits constitutive nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB) and cyclin D1 expression, and induces apoptosis via phorbol-12-myristate-13-acetate-induced protein 1 (NOXA) [17]. Despite the initial rationale to develop an NF-κB inhibitor, no evidence of an inhibition of constitutive NF-κB activity in MCL cells by Bortezomib was found [18] which indicated that inhibition of NF-κB may not be as important for its antitumor activity. Instead, inhibition of the proteasome profoundly disrupts protein homeostasis and leads to rapid accumulation of cytosolic poly-ubiquitinated proteins at the endoplasmic reticulum (ER) membrane [19]. This triggers an ER stress response also termed the unfolded protein response (UPR) [20]. In MCL cells, this leads to cell death through transcriptional activation of NOXA [21].

Bortezomib has been approved for MCL by the US FDA (2006) and in Switzerland (2009) for patients who received at least one prior therapy. In the EMA region bortezomib is not yet approved for MCL (status January 2015), but the marketing authorization application was filed in 2014. The recommended starting dose of bortezomib is 1.3 mg/m^2 (s.c. or i.v.). Bortezomib may be administered intravenously at a concentration of 1 mg/ml, or subcutaneously at a concentration of 2.5 mg/ml on days 1, 4, 8 and 11 of a 21-day cycle.

2.3.2.1 Preclinical experience

For information on nonclinical pharmacology and toxicology studies please refer to the IB of bortezomib [22].

2.3.2.2 Clinical experience

Bortezomib is the first proteasome inhibitor approved in the US and Switzerland for the treatment of multiple myeloma (MM) and in US and Switzerland for relapsed MCL especially in patients not eligible for high-dose chemotherapy.

The trials in MCL reported overall response rates up to 50%, with a PFS of 3.9 to 5.6 months in relapsed patients [23]. The limiting toxicity of the intravenous infusion is peripheral neuropathy (25%). Other toxicities include thrombocytopenia (25%), anemia (20%), diarrhea (50%), fever (20%), nausea (50%) and vomiting (30%). On the basis of pharmacokinetics, bortezomib is given twice weekly. Attempts to increase the tolerability of bortezomib have been conducted in MM and so far included once weekly (instead of bi-weekly) and subcutaneously (s.c., instead of an iv push) administrations. Weekly bortezomib has also been used in MCL [24]. Studies in MM have shown that once weekly vs. biweekly [25] and s.c. vs. iv administration [26, 27] are equally effective, but with significantly less frequent polyneuropathy. However, in MCL, weekly bortezomib monotherapy was shown to be inferior to the bi-weekly administration [28]. Recently, the s.c. administration has been approved in the EU and Switzerland.

Full information on AEs and safety matters are provided in the most recent IB [29] or summary of product characteristics.

2.4 Rationale for performing the trial

MCL remains an incurable disease with frequent relapses and no standard therapeutic options in case of relapse. Prolongation of remissions or induction of longer remissions are therefore crucial. Bortezomib is an approved agent to treat relapsed/refractory MCL with an ORR of 50 %. Ibrutinib is a highly selective and potent oral and irreversible inhibitor of BTK with very significant single agent activity in B-cell lymphomas including relapsed mantle cell lymphomas of 65 % [13]. Ibrutinib was approved recently by EMA and Swissmedic for MCL. Both compounds are well tolerated, and do not have overlapping toxicity profiles.

Recently, a synergistic increase in the proteasomal inhibition of ibrutinib in both bortezomib-sensitive and refractory MCL cells was shown [2]. These findings, along with the reported single agent activities and the non-overlapping toxicities, are the rationale to combine ibrutinib and bortezomib in MCL in this trial. Further data on the combination of bortezomib with ibrutinib are currently not available. Given the absence of a dose-limiting toxicity also when applied long-term, Ibrutinib is well suited in this patient population as a maintenance therapy.

The aim of this trial is to find a new therapeutic option in the relapsed MCL setting.

2.5 Trial population

This trial is targeting patients with diagnosis of refractory or relapsed MCL disease after pretreatment with any lines of non-bortezomib-containing chemotherapy. MCL is predominantly a disease of the elderly where aggressive chemotherapy is not suitable. Up to now there is no standard therapy available. Thus, new therapeutic options in this patient population are clearly needed. The proposed treatment of ibrutinib in combination with bortezomib might lead to an improvement of the therapy in the relapsed/refractory patient population.

2.6 Dose Selection

For bortezomib, the labeled and approved dose of 1.3 mg/m^2 d1, 4, 8, 11, q21 days for MCL (s.c. injection) is administered. The dose of ibrutinib in this combination treatment will be assessed in the phase I part of this SAKK trial (see chapter 9.2). In the ibrutinib maintenance therapy, the recommended and approved dose by EMA and Swissmedic for ibrutinib 560 mg p.o. daily is given to the patient.

2.7 Choice of design

The trial is a multicenter, prospective, single-arm, phase I/II trial. Given the rarity of the disease, the phase II is a single-stage design based on proportions to provide efficacy data on a drug combination that could further be compared with other combinations in subsequent phase II or III trials.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective

Phase I	Phase II
The primary objective of the phase I (dose escalation of ibrutinib) is to establish the recommended phase II dose (RP2D) of ibrutinib in combination with bortezomib in patients with relapsed or refractory MCL.	The primary objective of the phase II is to define the efficacy of ibrutinib in combination with bortezomib in patients with relapsed or refractory MCL.

3.1.2 Secondary objectives

Phase I	Phase II
The secondary objectives of the phase I are • to determine the safety and tolerability of ibrutinib in combination with bortezomib • to assess the **preliminary** antitumor activity of ibrutinib in combination with bortezomib	The secondary objectives of this trial are • to determine the safety and tolerability of the RP2D of ibrutinib in combination with bortezomib • to determine the efficacy of ibrutinib in combination with bortezomib in patients with relapsed MCL followed by an ibrutinib maintenance therapy.

3.2 Endpoints

For definition of endpoints see section 13.

3.2.1 Primary endpoint

Phase I	Phase II
Dose limiting toxicity (DLT) observed during the first cycle of trial treatment	Overall response (OR) (combination therapy)

3.2.2 Secondary endpoints

Phase I	Phase II
• Adverse events (AE) until 30 days after end of trial therapy • OR (combination therapy) • OR based on best response observed during treatment (combination and maintenance therapy)	• Adverse events (AE) until 30 days after end of trial therapy • OR based on best response observed during treatment (combination and maintenance therapy) • Progression-free survival (PFS) • Time to treatment failure (TTF) • Duration of objective response

3.3 Additional research questions

"The detection of genetic lesions predicting the response to ibrutinib plus bortezomib followed by ibrutinib maintenance therapy" will be investigated in a translational research project. Please refer to section 18.1 for details.

4 TRIAL DESIGN

International multicenter, single-arm phase I/II trial

The planned duration of treatment in the absence of disease progression or other cause for discontinuation (e.g. unacceptable toxicity) is 6 cycles. Thereafter, treatment can be continued with ibrutinib monotherapy as long as there is clinical benefit/until relapse.

4.1 Phase I and Phase II

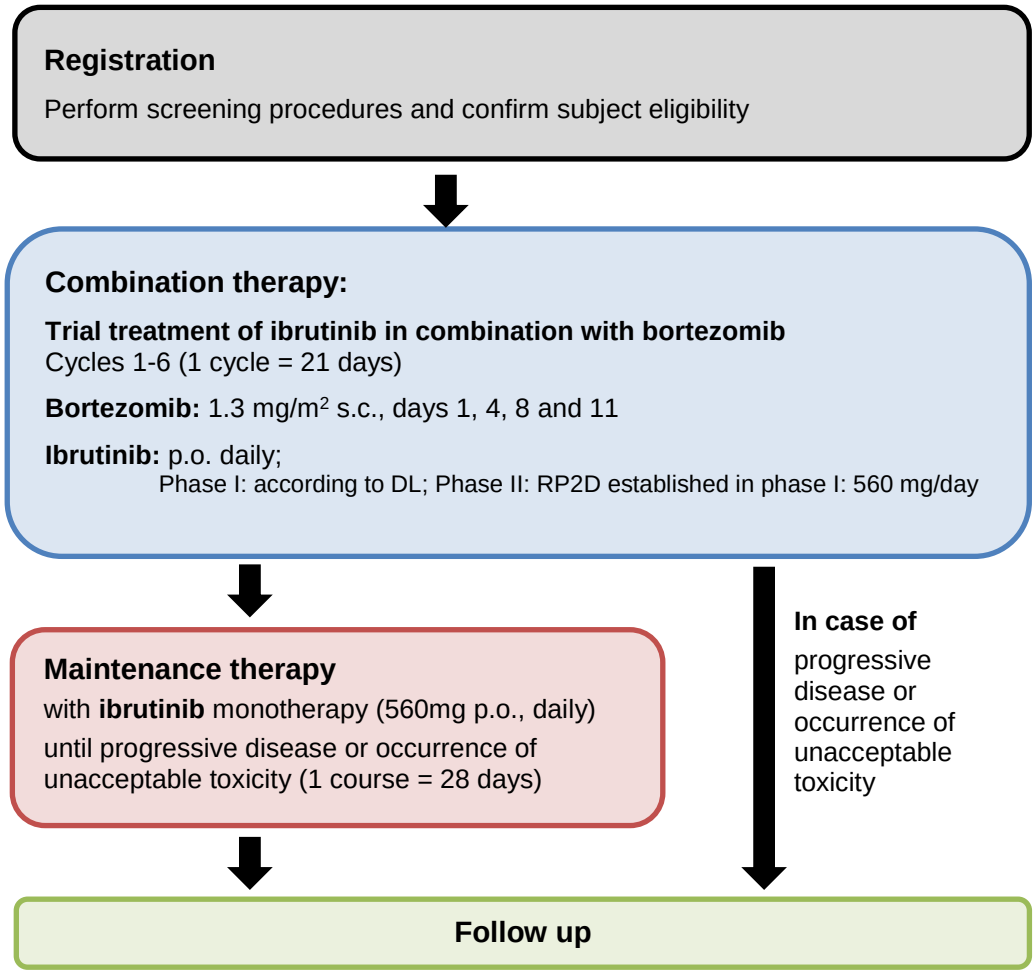


Figure 1: Trial design

Please note:

All the patients of phase I that are treated at the corresponding phase II dose level will be included for assessing the preliminary tumor activity (see secondary endpoint, phase I).

4.2 Methods of minimizing bias

This trial is a phase I and single-arm phase II trial. In order to minimize bias the following measures are taken

- Minimization of selections bias at inclusion: well defined criteria for inclusion, furthermore the screening list will permit to determine that all consecutive patients are included.
- Central pathology review: only MCL patients are included into the trial analysis, patients that do not fulfill these criteria will be replaced.
- The response criteria for the tumor assessment are clearly defined (see Appendix 1)

5 TRIAL DURATION AND TERMINATION

The inclusion of patients is planned to start in Q2-3 2015 (Phase I).

Number of patients planned to be included:

- Phase I: 4 to 18 patients (for details see section 9.2.1)
- Phase II: total of 55 evaluable patients (for details see section 15.3.1) including 6 patients of the phase I treated at the corresponding dose level

The Phase I was closed for accrual (18th November 2016) after the RP2D was established. The Phase II will stop after the inclusion of 55 evaluable patients (including the 6 patients treated on the corresponding dose level in phase I), which is expected in Q4 2019. End of trial treatment is expected for Q1 2021.

All patients will be followed up for 2 years. Trial termination (last patient last visit) is expected to be in 2023 or when the trial team decides to stop collecting further follow-up data.

The trial may be stopped early based on the results of an interim analysis (see section 15, Statistical Considerations) or if new scientific data become available which change assessment of risk/benefit.

6 SELECTION OF PATIENTS

6.1 Inclusion criteria

Please refer to chapter 12 for evaluations and their respective timelines before registration. Each potential patient must satisfy **all** of the following criteria:

6.1.1 Patient must give written informed consent before registration indicating that the patient understands the purpose of the procedures required for the trial and is willing to participate in the trial.

6.1.2 Histologically confirmed mantle cell lymphoma with either overexpression of cyclin D1 protein or evidence of t(11;14)(q13;q32) assessed by cytogenetics, by fluorescence, in situ hybridization (FISH) or by polymerase chain reaction (PCR).

6.1.3 Refractory or relapsed disease in need of systemic therapy after pretreatment with non-bortezomib-containing chemotherapy (including high-dose therapy plus autologous stem cell support; induction and consolidation with high-dose chemotherapy is considered one line of chemotherapy.)

6.1.4 At least one measurable lesion ≥11 mm in its greatest transverse diameter (see Appendix App 1.2) measured with CT scan (contrast enhanced) or MRI (in case of the disease cannot be adequately imaged using CT and if contrast is not appropriate for patients according to the treating physician) (see also Appendix 1).

6.1.5 WHO performance status 0-2 (see 0)

6.1.6 Age ≥ 18 years

6.1.7 Adequate hematological values:

- Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L independent of growth factor support
- Platelets ≥ 100 x 10^9/L or ≥ 50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation,
- Hb ≥ 80 g/L

6.1.8 Adequate hepatic function:

- Total bilirubin ≤1.5xupper limit of normal (ULN) unless bilirubin is due to Gilbert`s syndrome $\leq 5.0 \times$ ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3xULN

6.1.9 Adequate renal function: Body surface area (BSA) corrected creatinine clearance ≥40mL/min/1.73m^2 (calculated according to the corrected formula of Cockcroft-Gault, see 0)

6.1.10 Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the trial (see below) consistent with local regulations regarding the use of birth control methods for patients participating in clinical trials (see section 9.12). Men must agree to not donate sperm during and after the trial. These restrictions apply for

- Ibrutinib: 3 month after the last dose of trial drug for males and 1 month for females.
- Bortezomib: during trial treatment (for males and females): no restrictions of birth control after last dose of trial drug. Donation of sperm: 6 month after the last dose of trial drug.

6.1.11 Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at baseline. Women, who are pregnant or breastfeeding are ineligible for this trial.

6.2 Exclusion criteria

Any potential patient who meets any of the following criteria has to be excluded from trial participation:

6.2.1 Prior therapy with ibrutinib or bortezomib

6.2.2 Adverse event neuropathy of prior therapy grade ≥2 (according to CTCAE criteria Version 4.0) at registration

6.2.3 Previous malignancy within 5 years with the exception of adequately treated in situ cervical cancer or localized non-melanoma skin cancer.

6.2.4 Presence or history of CNS disease (either CNS lymphoma or lymphomatous meningeosis)

6.2.5 Evidence of ongoing systemic infections of all kind

6.2.6 Exclusion of the following prior treatments prior to trial registration

- major surgery within 4 weeks
- concurrent treatment with other experimental drugs or treatment in a clinical trial within 30 days.
- treatment with chemotherapy and radiotherapy within 3 weeks
- vaccinated with live, attenuated vaccines within 4 weeks

6.2.7 History of stroke or intracranial hemorrhage within 6 months prior to trial registration.

6.2.8 Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon)

6.2.9 Requires treatment with strong or moderate CYP3A inhibitors (see http://medicine.iupui.edu/clinpharm/ddis/main-table and also chapter 9.11.1.2)

6.2.10 Clinically significant cardiovascular disease such as congestive heart failure NYHA III or IV (as defined by the New York Heart Association Functional Classification, see Appendix 5), uncontrolled or symptomatic arrhythmias, significant QT-prolongation, unstable angina pectoris myocardial infarction within 6 months of prior to registration,

6.2.11 Known history of human immunodeficiency virus (HIV) or active Hepatitis C virus or active Hepatitis B virus infection or any uncontrolled active systemic infection requiring treatment.

6.2.12 Prior allogeneic bone marrow or solid organ transplantation

6.2.13 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion,

- could impair the ability of the patient to participate in the trial
- could compromise the patient's safety,
- could interfere with the absorption or metabolism of ibrutinib capsules, or
- could put the trial outcomes at undue risk
- could prevent compliance with trial treatment.

6.2.14 Psychiatric disorder precluding understanding of trial information, giving informed consent, or interfering with compliance for oral drug intake.

6.2.15 Known hypersensitivity to trial drug(s) or hypersensitivity to any other component of the trial drugs.

6.2.16 Any concomitant drugs contraindicated for use with the trial drugs according to the approved product information.

6.2.17 Any psychological, familial, sociological or geographical condition potentially hampering compliance with the trial protocol and follow-up.

7 REGISTRATION

7.1 Pre-registration procedure

Prior to registration, the following steps have to be performed:

- Fill in the patient screening and enrollment list
- Check the eligibility criteria
- Obtain written informed consent from the patient prior to any protocol-specific procedure

7.2 Registration procedure

Registration is done via Internet using the following web address **www.sakk.ch/edc**

If this is not possible investigators can **fax** the completed, dated and signed form E to the SAKK CC (Opening hours: Monday to Friday 8:00 a.m. to 5:00 p.m.) to **+41 31 508 41 42.**

In order to receive authorization for online registration and data entry, sites must send a copy of the completed staff list (available on the SAKK website) to the SAKK CC. Login details for the EDC system will be sent to authorized persons within 2 working days.

The SAKK CC will be closed on the following days:

1st January	1st August (National holiday)*
2nd January	4th Monday of November, from 3:00 pm
Good Friday (Friday before Easter)*	24th December (from 12:00 noon)
Easter Monday	25th December
Ascension Thursday*	26th December
Whit Monday (Pentecost)	31st December (from 12:00 noon)

* The SAKK CC will close at 4:00 pm on weekdays before these holidays.

7.2.1 For the phase I part of the trial

The statistical design, dose escalation rule and trial stopping rule are described in section 9.2 statistical considerations.

Enrollment will be suspended after each cohort in order to allow evaluation.

Therefore, a slot reservation procedure will be implemented: Before informing a patient, the site should contact the SAKK CC to ask whether the patient can still be registered at the current dose level. The responsible clinical project manager or the substitute will reserve a slot and create the patient in the web based EDC system.

7.2.2 For the translational research project/biobanking

If a patient agrees to take part in the translational research and/or biobank project (E Form), the responsible scientist (see section 18) will be informed by an automatically generated email via the EDC system.

7.2.3 Pathology review

The review pathologist Prof. Dirnhofer (for details see section 17) will be informed about every new registered patient by an automatically generated email via the EDC system. Samples at initial diagnosis or at baseline (if available) need to be sent together with a copy of the coded pathology report and an accompany letter (www.sakk.ch →Members → Trials →Lymphoma →SAKK 36/13 – useful tools → accompanying letter of local pathology) to the Institute of Pathology, Prof. Dirnhofer, University Hospital of Basel immediately after inclusion of the patient into the trial (for details please refer to chapter 17.2).

7.3 After registration

Report the baseline, clinical and laboratory information, baseline symptoms, and baseline tumor assessment and all other required information according to the visit plan of the trial in the CRFs.

Trial therapy should be started within *7* days from registration.

Update the screening and enrollment list and fill in the patient identification list.

7.3.1 Signed eligibility form

7.3.1.1 Phase I

The signed Eligibility Form (printout of eCRF form ER) has to be sent to the SAKK CC by email or fax within one day after randomization/registration. The original is kept in the investigator's file

7.3.1.2 Phase II

The signed Eligibility Form (printout of eCRF form ER) has to be sent to the SAKK CC by email or fax within one month after randomization/registration. The original is kept in the investigator's file.

8 DRUG SUPPLY AND HANDLING

8.1 Drugs in protocol

8.1.1 Investigational medicinal product (IMP)

Ibrutinib is approved in the EMA region (October 2014) and Switzerland (November 2014) for MCL and marketed under the name Imbruvica®. The approved dose for monotherapy is 560 mg p.o. daily.

Bortezomib (Velcade®) will be given in combination with ibrutinib. It will be given according to its Swissmedic-approved indication, the applicable safety precautions and the Swiss law.

8.2 Drug supply and handling of ibrutinib

8.2.1 Drug supply

Ibrutinib will be provided free of charge by Janssen. The distribution will be managed by an authorized pre-wholesaler.

Ibrutinib will be supplied as 140 mg capsules for oral intake in bottles (with labels bearing the appropriate label text as required by competent regulatory authorities) with total 120 capsules.

After site activation, an initial stock of trial medication will be dispatched by the authorized pre-wholesaler to the site. Re-ordering of new trial medication will be done by the sites directly with pre-wholesaler. The SAKK CC will also receive all the completed drug order forms in order to be informed about the drug supply status of all opened sites. The site has to expect approx. 5 days between order and delivery.

Instructions on ordering, packaging and shipment are given in a separate document which can be downloaded from www.sakk.ch, members section, trials (www.sakk.ch → Members → Trials → Lymphoma → SAKK 36/13) in the subsection drug supply and handling of IMP.

8.2.2 Handling and safety of ibrutinib

Ibrutinib must be stored in their original packaging according to labeled conditions, in a dry, non humid place outside the reach of children and other non-authorized persons. Ibrutinib capsules must not be used after the expiration date.

For additional information regarding handling and safety refer to the current country specific product information (which can be downloaded for Switzerland from http://compendium.ch/home/de) or the respective Investigator's Brochure [10, 30].

Storage area temperature conditions must be monitored and recorded daily. A temperature log is available on the SAKK website (www.sakk.ch →Members →Trials →Lymphoma →SAKK 36/13).
The following events have to be immediately reported to SAKK CC:

- all temperature excursions above 30°C

Please refer to the most current approved product information for detailed information on handling and safety of ibrutinib.

8.2.3 Labeling of ibrutinib

Each bottle will be labelled in German, French, and Italian.

Ibrutinib will be labeled as follows:

- SAKK protocol number, EudraCT number
- Pharmaceutical dosage form, route of administration and quantity of dosage units
- Medication description and directions for use
- Storage conditions
- Please return empty packaging and unused products
- The regulatory caution statements ('for clinical trials use only' and 'keep out of reach of children')
- Blank spaces are provided for the name of the treating investigator, the patient identification UPN, and the date of dispensing

- Lot number and medication number
- Expiry date
- Name, address and telephone number of the sponsor

8.2.4 Dispensing and accountability of ibrutinib

The drug supply must be kept in an appropriate, limited-access, secure place until it is dispensed to trial participants.

At day 1 of each cycle, the trial drug will be dispensed to the patient in the open label bottle [medication for one treatment cycle plus 9 day overage in the combination therapy of ibrutinib with bortezomib (1 cycle= 21 days) and usually plus 2 day overage in the maintenance therapy (1 course = 28 days)] with the label clearly visible. **Blank spaces need to be filled in on each bottle before the medication is dispensed to the patient.** The patient has to return empty or the partly used bottle at the beginning of the next cycle. Returned trial drug must not be dispensed again, even to the same subject. Trial drug may not be relabeled or reassigned for use by other subjects.

In order to facilitate drug accountability and drug administration reporting, the patient has to keep a diary on the intake of ibrutinib and bring it along to day 1 of each cycle. Patients must be instructed to note the date and time of drug intake in this diary. The patient diary is available on the SAKK website (www.sakk.ch → Members → Trials → Lymphoma → SAKK 36/13). Unused trial drug and trial drug returned by the patient must be available for verification by the sponsor's site monitor during on-site monitoring visits.

The site must maintain 100% accountability for all trial medication received and dispensed during the entire participation in the trial. Proper drug accountability includes:

- Continuously monitoring of expiration dates
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the drug accountability log and the drug dispensing log are completed accurately and legibly
- Continuously monitoring of patients' use records (patient diary)

The drug dispensing log should include all required information as a separate entry for **each** UPN to whom trial medication is dispensed. The use of the dispensing log and drug accountability log for ibrutinib (available on the SAKK website) has to be ensured. This log must be kept up-to-date and identify the receipt, dispensing and destruction of the drug (including date, amount, batch number UPN). If sites already have their own accounting system, it may be used instead of the SAKK drug inventory log only after inspection and approval by the monitor.

If any dispensing errors or discrepancies are discovered, SAKK CC must be notified immediately.

Copies of the diaries, the drug accountability logs and the drug dispensing logs will be collected by the monitor.

Drug order forms and logs are available from the SAKK website www.sakk.ch → Members → Trials → Lymphoma → SAKK 36/13.

8.2.5 Unused ibrutinib

All unused or expired trial medication must be destroyed. Partly unused or expired medication can only be destroyed at the site after a check of the monitor. The destruction should be documented using the drug dispensing log and the drug accountability log (available on the SAKK website).

In case trial drug is lost or damaged, its disposition should be documented in the source documents.

8.3 Drug supply and handling of bortezomib

8.3.1 Drug supply

Bortezomib is applied within its Swissmedic approved indication. It will be provided free of charge by Janssen. The distribution will be managed by an authorized pre-wholesaler.

Bortezomib is delivered in vials (3.5 mg) as powder for solution for injection.

Instructions on ordering, packaging and shipment are given in a separate document which can be downloaded from www.sakk.ch, members section, trials (www.sakk.ch → Members → Trials → Lymphoma → SAKK 36/13) in the subsection drug supply and handling of IMP.

8.3.2 Handling and safety of bortezomib

For handling refer to the current country specific product information (which can be downloaded for Switzerland from www.swissmedicinfo.ch or http://compendium.ch/prod/velcade-trockensub-3-5-mg/de) or the up to date respective Investigator's Brochure [22]. Bortezomib will we administered and prepared according to instructions in the drug brochure by health care professional experienced in the use of cytotoxic medicines. National guidelines on handling of cytostatic drugs [31] have also to be considered.

Storage area temperature conditions must be monitored and recorded daily. A temperature log is available on the SAKK website (www.sakk.ch →Members →Trials →Lymphoma →SAKK 36/13). The following events have to be reported to SAKK CC: All temperature excursions above 30°C

8.3.3 Labeling of bortezomib

For Bortezomib supplies, a multilingual label Velcade® booklet is available (provided by Janssen) on the box and vial with the following information:

Box

- Pharmaceutical dosage form, route of administration and quantity of dosage units
- Medication description and directions for use
- Storage conditions
- The regulatory caution statements ('for clinical trials use only' and 'keep out of reach of children')
- Blank spaces are provided for the name of the treating investigator and the patient identification (= subject number)
- Ref number (= Lot number) and medication number
- Expiry date

Vial

- Ref number (= Lot number) and medication number
- Pharmaceutical dosage form and route of administration
- Medication description and directions for use
- The regulatory caution statements ('for clinical trials use only')
- Blank spaces are provided for protocol and sponsor

Trial specific label (Box and Blister)

In addition, an extra trial specific-label will be fixed on blister and box.

- Box
    - SAKK protocol number, EudraCT number
    - Name, address and telephone number of the sponsor
- Blister
    - SAKK protocol number, EudraCT number
    - Blank spaces are provided for the patient identification UPN (subject number)
    - Name, address and telephone number of the sponsor

8.3.4 Dispensing and accountability of bortezomib

Please ensure the use of the drug accountability log for bortezomib (available on the SAKK website), which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, UPN). If sites already have their own accounting system, it may be used instead of the SAKK drug inventory log only after inspection and approval by the monitor.
Drug order forms and inventory logs are available from the SAKK website (www.sakk.ch → Members → Trials → Lymphoma → SAKK 36/13).

8.4 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. 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 agencies worldwide.

8.4.1 Procedures

In case site staff identifies a potential product complaint situation, SAKK CC must be contacted immediately. In case a patient identifies a potential product complaint situation, the investigator must be contacted immediately, as outlined in the patient information and informed consent form. All initial PQCs must be forwarded within 24 hours to the SAKK CC. The SAKK CC will report all product complaint situations to Janssen within 24 hours after being made aware of the event.

Product complaints in and of themselves are not AEs. If the defect is combined with a serious adverse event, the investigational staff must report the PQC to SAKK CC according to the serious adverse event reporting timelines (see chapter 11.5). A sample of the suspected product should be maintained in accordance with the label instructions for further investigation if requested by SAKK CC or Janssen.

9 TRIAL TREATMENT

9.1 Treatment overview

Treatment consists of 6 cycles of 21 days each of ibrutinib in combination with bortezomib, followed by a maintenance therapy with ibrutinib monotherapy. In the maintenance, therapy courses repeat every 28-days in the absence of disease progression or unacceptable toxicity.

Ibrutinib is taken orally once per day, continuously. The dose for cycle 1-6 depends on the DL (phase I) and the RP2D. In the maintenance therapy, the patient receives the dose approved by the EMA and Swissmedic.

Bortezomib is injected s.c. with a dose of 1.3 mg/m^2 on day 1, 4, 8, 11.

Phase I and Phase II																					
	Combination therapy																				**Maintenance therapy**
Cycle / Course	cycle 1 to 6 (1 cycle =21 days)																				until progression or unacceptable toxicities (1 course will be repeated every 28 days)
Week	**1**							**2**							**3**						**1-4**
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	daily
Ibrutinib 280mg-560mg p.o. depending on DL (phase I) or RP2D (phase II)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	**Ibrutinib** 560mg p.o.
Bortezomib 1.3mg/m^2, s.c.	●			●				●			●											

9.2 Phase I

The aim of phase I is to determine the RP2D of ibrutinib in combination with bortezomib. A fixed dose of bortezomib will be used with two different DLs of ibrutinib starting from 420 mg daily for 21 days.

The use of hematopoietic growth factors (e.g. colony stimulating factor (G-CSF)) during cycle 1 is only allowed after the patient experienced a DLT. Otherwise, the administration of prophylactic hematopoietic growth factors during cycle 1 is considered as a protocol violation. In this case, the patient is not evaluable for the primary endpoint and will be replaced. From cycle 2 on, hematopoietic growth factors administration is allowed according to the physician's discretion.

9.2.1 Dose finding

Dose finding is done according to the following dose escalation table:

Dose level	**Bortezomib**	**Ibrutinib**
-1	*1.3 mg/m^2 d 1, 4, 8,11*	*280 mg/day p.o.*
1	*1.3 mg/m^2, d 1, 4, 8, 11*	*420 mg/day p.o.*
2	*1.3 mg/m^2 d 1, 4, 8, 11*	*560 mg/day p.o.*

There will be two dose levels, 1 and 2, with each level consisting initially of a cohort containing 3 patients. One additional dose level, dose level -1 shall be allowed in the event that dose level 1 is considered too toxic.

In each new cohort, 3 patients can be enrolled simultaneously. After enrolling a cohort of 3 patients at a given dose level, the patients will be evaluated for DLT, before a new cohort will be opened.

Every DLT will be reviewed by the coordinating investigator (CI) and/or supporting coordinating investigator (SCI), clinical project manager (CPM) and statistician together with the Head of Innovation and Development (HID) and the Medical Advisor. The decision to escalate to the next DL will be taken based on the number of the reported DLTs observed in the first cycle of trial therapy and according to the table below. In addition, all available safety data are considered before escalating to the next dose level.

The tentative RP2D is defined as the dose level just below the one containing 2 or more DLTs.

There will be no further dose escalation after DL 2. If at this highest DL the number of DLTs is 1 or less out of 6 patients, this will be declared the tentative RP2D for phase II.

The RP2D will be determined by the CI and SCI, CPM and statistician together with the HID and the Medical Advisor. Persistent and late adverse events and significant dose reductions (occurring after the DLT-defining period) will be also considered for determination of RP2D, if available.

Table 1: Summary of dose finding procedure

Dose level	Cohort	Number of patients per cohort	Number of patients who experienced a DLT by cumulative cohort per DL	Action
1	A	3	0/3	Proceed to DL 2 cohort A
			1/3	Proceed to DL 1 cohort B
			≥ 2/3	DL 1 is considered too toxic. Proceed to DL -1 cohort A
	B	3	0/6	Stop and declare DL1 as tentative RP2D
			1/6	If DL 2 cohort A complete: stop and declare DL 1 as tentative RP2D Else proceed to DL 2 cohort A
			≥ 2/6	DL 1 is considered too toxic. Proceed to DL -1 cohort A
2	A	3	0/3	Proceed to DL 2 cohort B
			1/3	Proceed to DL 2 cohort B
			≥ 2/3	If DL 1 cohort B complete: stop and declare DL 1 as tentative RP2D. Else proceed to DL 1 cohort B
	B	3	0/6	Declare DL 2 as tentative RP2D
			1/6	Declare DL 2 as tentative RP2D
			≥ 2/6	If DL 1 cohort B complete: stop and declare DL 1 as tentative RP2D Else proceed to DL 1 cohort B
-1	A	3	0/3	Proceed to DL -1 cohort B
			1/3	Proceed to DL -1 cohort B
			≥ 2/3	Stop, trial therapy is too toxic
	B	3	0/6	Declare DL -1 as tentative RP2D
			1/6	Declare DL -1 as tentative RP2D
			≥ 2/6	Stop, trial therapy is too toxic

9.2.2 Definition of DLT

DLTs are defined based on adverse events observed in cycle 1 that are possibly, probably or definitively related to ibrutinib and/or bortezomib. All AEs shall be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0[1].

DLT is defined as one of the following events occurring within the first cycle only (d1-d21):

- Trial therapy related death
- ≥ 7 missed consecutive therapy days of ibrutinib due to trial drug--related toxicity
- ≥ 2 missed consecutive doses of bortezomib due to trial drug related toxicity
- Delay of >2 weeks of cycle 2 due to trial drug-related toxicity

Hematologic DLTs (without evidence of malignant bone marrow infiltration)

- Absolute neutrophils count (ANC) < 0.5 x 10^9/L for 7 or more consecutive days
- Febrile neutropenia (ANC < 1.0 x 10^9/L, fever $\geq$ 38.5°C)
- Platelets < 25 x 10^9/L or thrombocytopenic bleeding (platelets < 50 x 10^9/L and associated with clinically significant bleeding)

Non-hematologic DLTs

- Any Grade 3 or higher non-hematologic toxicity possibly, probably, definitely related to trial treatment.
  Exception: Clinically irrelevant non-haematological laboratory findings (e.g. transient grade 3 hypokalaemia that can be effectively substituted) according to trial team together with the Head of CPM and the Medical Advisor.

As soon as the patient experiences a DLT, the patient will be transferred to the follow-up phase.

9.3 Phase II

In phase II patients will be treated for maximum treatment duration of 6 cycles.

- with bortezomib in its labeled dose (1.3 mg/m^2 s.c. d1, 4, 8, 11, q 21 d, s.c.)
- in combination with oral ibrutinib (daily) at the RP2D established in the phase I part, which is 560mg/day

Please note: Patients can continue on the combination therapy without bortezomib, provided that at least 4 cycles of combination therapy (ibrutinib and bortezomib) were completed. For details please refer to chapter 9.8.

This combination therapy is followed by ibrutinib maintenance until progression.

Please refer to chapter 9.8 (treatment duration) for reasons for stopping trial treatment.

9.4 Maintenance therapy (Phase I and Phase II)

The combination therapy is followed by ibrutinib maintenance (28 days courses) with the labeled dose 560 mg p.o., daily until disease progression. Please refer to section 9.8 (treatment duration) for additional reasons to stop the trial therapy.

9.5 Pre-phase

Steroid pre-phase for lymphocytosis is not required, but up to the discretion of the treating physician.

[1] http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

9.6 Therapy with ibrutinib

Please refer to the most recent investigator's drug brochure [10] for detailed information on handling and safety.

9.6.1 Schedule

Combination therapy - Phase I

Ibrutinib will be administered daily d1-d21 (cycle = 21 days) for a maximum of 6 cycles. In the dose escalation phase of the trial the starting dose will be 420 mg/d p.o. Dose increments will apply based on DLTs as described in section 9.2.1.

Combination therapy - Phase II:

Ibrutinib dose according to RP2D will be administered daily d1-d21 (cycle = 21 days) for a maximum of 6 cycles. The established dose for phase II is 560mg/day.

Maintenance therapy (Phase I and Phase II)

To allow a fluid transition from the combination therapy to the maintenance therapy without stopping the ibrutinib therapy, patients can be transferred after the combination therapy directly into maintenance therapy upon discretion of the treating physician. The tumor assessment has to be performed at latest 14 days after end of the combination therapy. Upon the result of this tumor assessment, the patient continues on maintenance therapy (if the disease did not progress) with ibrutinib monotherapy 560 mg p.o. daily until disease progression or patient is transferred into follow-up phase.

9.6.2 Dose administration

All protocol-specific criteria for administration of trial drug must be met and documented prior to drug administration.

Trial drug will be administered continuously throughout each treatment cycle of the trial, except for dose modifications (see section 10.5-0).

Each capsule contains 140 mg of ibrutinib. Patients will be instructed to take the amount of capsules depending on the dose level (phase I) or RP2D (phase II).

Each dose of ibrutinib capsules must be taken orally once daily with a glass of water at approximately the same time every day. For further details, please refer to the current country specific approved prescribing information for the intake of ibrutinib. All capsules should be taken and swallowed intact. Patients must not attempt to open capsules or dissolve them in water. If a dose of Ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib must not be taken to make up for the missed dose.

Please note: Patients must avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the trial due to cytochrome (CYP) 3A4/5 inhibition.

During the first 1-6 cycles, trial drug will be dispensed at the beginning of each 21-day cycle. Patients will be provided with 9 days overage[2] each time trial drug is dispensed to allow for delayed return visits. After the 6 cycles (combination therapy), the trial drug is given in a 28-day cycle. Patients will be provided with 2 days overage each time trial drug is dispensed to allow for delayed return visits. After 15 months of treatment, site visits may be conducted every 56 days. Sufficient drug supply until next visit will be dispensed.

9.6.3 Warnings and precautions

Please refer to the chapter 9.11.1

[2] These nine days are calculated if 560mg ibrutinib (highest dose possible) is given daily and a bottle with 120 capsules is dispensed to the patient.

9.6.4 Assessment of compliance

Patients will be given a diary to record trial drug intake. If a dose is missed entirely, the missed dose will be recorded as “not taken”.

Compliance is checked by reviewing the diary which the patient is asked to complete daily and which must include the date of dosing, start and stop times, dose administered, and any dose interruptions or reductions. The completed diary is checked by the site personnel while the patient is still present. If necessary, the patient should be asked to fill in any missing information.

Trial drug compliance will be calculated for each patient by taking into account whether a patient has taken the trial drug as instructed. Patients will be instructed to bring any unused ibrutinib capsules, dispensed during previous visits, to each visit for reconciliation. The number of capsules taken will be calculated by subtracting the number of capsules returned from the number of capsules dispensed.

9.7 Therapy with bortezomib

Bortezomib is approved for treatment of relapsed MCL. Please refer to the up-to-date investigator’s drug brochure (e.g. [22]) and the current summary of product information for detailed information on drug handling and safety.

9.7.1 Schedule

Bortezomib will be administered according to Swissmedic approved indication s.c. on day 1, 4, 8, 11, q21 days (see chapter 9.1 for details) for a maximum of 6 cycles (phase I and II).

Bortezomib is not part of the maintenance therapy.

9.7.2 Dose calculation and administration

Bortezomib dose will be calculated according to the body surface area (see Appendix 4).

Bortezomib will be administered as subcutaneous injection. Bortezomib will we administered and prepared according to instructions in the drug brochure by health care professional experienced in the use of cytotoxic medicines; the treatment can only be initiated and conducted by a qualified investigator experienced in the use of cytotoxic medicines.

9.7.3 Warnings and precautions

Please refer to the chapter 9.11.2

9.7.4 Assessment of compliance

The principle investigator or designee has to ensure the use of the drug inventory log for bortezomib, which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, UPN). If sites already have their own accounting system, it may be used instead of the SAKK drug inventory log only after inspection and approval by the monitor.

9.8 Treatment duration

Patients will be transferred to the **follow-up phase** as soon as one of the following events occurs:

- progressive disease (PD)
- DLT
- symptomatic deterioration
- unacceptable toxicity
- withdrawal by patient (see 22.4 Premature withdrawal)
- withdrawal by the treating physician (see 22.4 Premature withdrawal)
- protocol treatment has to be delayed for more than *2* weeks (also for vacation) Please note: **Patients can continue on combination therapy without bortezomib**, if they had to stop of bortezomib administration due to unacceptable toxicity, **provided that at least 4**

cycles (minimum one injection in cycle 4) **of combination therapy (ibrutinib and bortezomib) were completed**.

- patient becomes pregnant

See section 12.4 for evaluations after treatment termination.

All patients will be followed up for up to *2* years after end of treatment. No trial-specific assessments will be performed after progression.

9.9 Permitted medication during trial treatment

Standard supportive care therapies other than anticancer treatment (e.g., antiemetics, loperamide), needed for the management of symptoms, are permitted as clinically indicated.

The **administration of dexamethasone** (but not more than 8 mg per application) as a facultative supplementary medication before the injection of bortezomib is permitted at the discretion of the treating investigator in order to attenuate local and systemic inflammatory reaction

9.10 Prohibited medications during trial treatment

The following treatments are not permitted during the trial treatment phase:

Phase I - cycle 1 - only:

- use of hematopoietic growth factors

Phase I and II

- any chemotherapy
- other anticancer treatments
- other experimental therapy
- radiotherapy
- Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent unless reviewed and approved by the coordinating investigator and/or supporting coordinating investigator (see 9.9 for more details) .
- Concomitant administration of warfarin and vitamin K antagonists

Patients must be instructed not to take any medications, including all over-the-counter products such as vitamins, minerals, and other dietary supplements, without consulting the investigator first. In addition, patients must be instructed not to eat grapefruits or Seville orange and not to drink grapefruit juice.

The responsible CPM at SAKK CC must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9.11 Warnings and precautions

9.11.1 Ibrutinib

Please note, for complete information on precautions refer to the Investigator Brochure [10] and the current summary of product information (SmPC).

9.11.1.1 Perioperative period

Please refer to chapter dose modifications 10.6.4 or the guidance that should be applied during the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib during trial treatment.

9.11.1.2 Precautions with concomitant medication

Guideline for use of CYP inhibiting/inducing drugs

Ibrutinib is metabolized primarily by CYP3A4/5 (Cytochrome P450 family 3, subfamily A4, Cytochrome P450 family 3, subfamily A5), and to a lesser extent by CYP2D6 (Cytochrome P450 family 2, subfamily D6). Co-administration of ibrutinib with strong CYP3A4/5 or CYP2D6 inhibitors

may increase ibrutinib plasma concentrations. Thus, concomitant use of strong CYP3A4/5 inhibitors (such as clarithromycin, ketoconazole, itraconazole, nefazodone, and ritonavir) and strong CYP2D6 inhibitors (such as bupropion, fluoxetine, paroxetine, and quinidine) must be avoided, if possible. Co-administration of ibrutinib with strong CYP3A4/5 inducers may decrease ibrutinib plasma concentrations. Thus, concomitant use of strong CYP3A4/5 inducers (such as carbamazepine and rifampin) must be avoided, if possible.

If no alternative treatment is available, the coordinating investigator should be consulted, and strong CYP3A4/5 inhibitors, CYP2D6 inhibitors and CYP3A4/5 inducers should be used with caution: patients should be closely monitored for potential toxicities with temporary interruption of ibrutinib as appropriate.

The patients co-medication has to be cross-checked with the list of CYP2D6 **and CYP3A4/5 inhibitors and substrates** that is provided at **http://medicine.iupui.edu/clinpharm/ddis/main-table.** This website is continually revised and should be checked frequently for updates (please scroll down the list to get the complete information).

QT prolonging agents

During the course of trial drug treatment, medications with a risk of causing *Torsades des Pointe* should be avoided. If no alternative treatment is available, the sponsor's medical advisor and/or coordinating investigator must be consulted. Any medications known to cause QT prolongation may be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered. **A list of drugs causing Torsades des Pointe may be found at** https://www.crediblemeds.org/index.php/login/dlcheck **.** (Please note: you have to register (for free) to view the complete drug list.)

Antiplatelet agents and anticoagulants

No concomitant administration of ibrutinib and warfarin or vitamin K antagonists is allowed. Antiplatelet agents and other anticoagulants such as heparin, low molecular weight heparins, and antithrombotics should be used with caution. Coagulation parameters (international normalized ratio [INR]/prothrombin time [PT], and activated partial thromboplastin time [aPTT]) should be monitored closely according to institutional guidelines and patients should closely be observed for any signs or symptoms of bleeding. **The risks and benefits must be considered carefully before restarting ibrutinib treatment**. Dose modifications are discussed in section 10.5-0.

9.11.2 Bortezomib

Bortezomib might cause tiredness, dizziness, fainting, or blurred vision. Patient should be instructed not to drive or operate tools or machines if they experience such side effects; even if they do not, they should still be cautious.

For precautions with concomitant medication please refer the latest investigator's drug brochure [22] and the current summary of product information.

9.12 Contraception, pregnancy and breastfeeding

The effects of ibrutinib and bortezomib on a developing unborn baby are unknown. Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman; therefore, women who are pregnant or nursing are excluded from this trial. Some drugs cause women to prematurely (early) deliver or to have babies with birth defects.

The following precautions are valid for all **women** taking part in this clinical trial:

Women with child-bearing potential must use highly effective contraception during the trial (combination and maintenance therapy) and 1 month thereafter. **Women using *mechanical contraceptives* must combine two methods of mechanical contraception** (like condom, coil, diaphragm or another device). **Women using *hormonal contraceptives*** e.g. contraceptive pill, injections, or implants **must use one additional method of mechanical contraception**.

The following precautions are valid for all **men** taking part in this clinical trial:

Men with potential to father a child must use a condom to avoid procreation during the trial and after the trial. Men must agree to not donate sperm during and after the trial. These restrictions apply for 6 month after the last dose of bortezomib and 3 months after the last dose of ibrutinib.

9.13 Subsequent Therapies

Administration of subsequent anti-MCL therapy should not be initiated until progressive disease (or relapse after CR) is established according to the criteria described in [32]. If clinically appropriate, the subsequent therapy should be withheld until confirmation of progressive disease by the investigator. After progressive disease is established, subsequent therapy is permitted at the investigator's discretion.

10 ADVERSE EVENT REPORTING, DOSE MODIFICATIONS AND SUPPORTIVE TREATMENT

10.1 Definition of adverse event (AE)

An adverse event is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event may therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH] [33].

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF.

10.2 Reporting of AEs

Patients will be instructed by the investigator to report the occurrence of any AE.

10.2.1 Procedures

Phase I and II

All AEs (grade 1-5) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the patient`s last trial-related procedure (which may include contact for follow-up of safety).

Exception: patients with relevant weight loss due to the relapse of the MCL: Weight gain back to normal baseline in context of response to therapy should not be classified as AE. This should be noted in the source data.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of trial drug, must be reported.

All events that meet the definition of a serious adverse event (SAE, see chapter 11.1) will be reported as serious adverse events, regardless of whether they are protocol-specific assessments (see chapter 11 for detailed safety reporting of SAEs).

All adverse events, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded using medical terminology in the source document and the CRF. 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 in the CRF their opinion concerning the relationship of the adverse event to trial therapy. All measures required for adverse event management must be recorded in the source document.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the Janssen all serious adverse events that are unlisted / unexpected and associated with the use of the trial drug(s) (for details see chapter11.4, SUSAR). The sponsor must report these events to the appropriate IEC that approved the trial protocol unless otherwise required and documented by the IEC (for details see chapter11.6).

Severity criteria

AEs are coded with the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0, and assigned a grade (from 1 = mild to 5 = death related to AE) as well as a relationship to trial treatment. The NCI CTCAE v4.0 (as pdf) as well as instructions on how to use the criteria can be found on http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The investigator should use clinical judgment in assessing severity of events not directly experienced by the patient (e.g. laboratory abnormalities).

Note:

- Report the start and end date of the event and any changes in grading observed within the reporting period.
- Baseline symptoms will be recorded on the case report form (CRF) and will continue to be followed up during treatment.
- AEs are documented by the codes according to CTCAE v4.0. If none of the codes are applicable, it exists for each of the 26 system organ classes (SOCs) the term 'others' to describe the AE. If the term 'others' is applicable, briefly describe the AE in a comprehensive and understandable manner.
- Laboratory values will be documented as absolute values on the CRFs.
    - For phase I and II: All out of range laboratory values occurring outside of predefined assessment times or any laboratory values not specifically asked to be assessed by the protocol need to be documented as AEs (grade 1-5) except the ones already documented as absolute values on the CRFs.

10.2.2 Definitions of AEs

Relationship of AEs to treatment is assessed using the following scale:

1 **Unrelated** An adverse event that is not related to the use of the drug. The AE is completely independent of trial treatment and/or evidence exists that the event is definitely related to another etiology.

2 **Unlikely** An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

3 **Possible** An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

4 **Probable** An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

5 **Definite** An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by de-challenge and re-challenge).

10.2.3 Special Reporting Situations

Safety events of interest of trial treatment that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of ibrutinib and/or bortezomib
- Suspected abuse/misuse of ibrutinib and/or bortezomib
- Inadvertent or accidental exposure to ibrutinib and/or bortezomib
- Medication error involving ibrutinib and/or bortezomib (with or without patient exposure to ibrutinib and/or bortezomib, e.g., name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE form (see chapter 11 for details).

10.2.4 Adverse events of special interest (AESI)

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities. These events will be reported to Janssen within 24 hours of awareness irrespective of seriousness (i.e., serious and non-serious adverse events) following the procedure described for serious adverse events (see section 11.5) and will require enhanced data collection.

10.3 Drug-related adverse events

Ibrutinib and bortezomib are generally well tolerated. The most common side effects for ibrutinib (seen in one of every 5-10 patients) are diarrhea, nausea, fatigue and infections. The frequencies of most common and very common AEs suspected to be related to the treatment are listed in the tables below. Common side effects are described in chapter 10.3.3.

Please be aware: Full information on AEs and safety matters are provided in the **most recent** IB.

Please note: The data in the following tables is based on the most recent IB.

10.3.1 Most common side effects (>20%)

System Organ Class	Ibrutinib	Bortezomib
Blood and lymphatic system disorders	Neutropenia	Thrombocytopenia, Anemia Neutropenia
Gastrointestinal	Diarrhea, Nausea	Constipation, Diarrhea Vomiting, Nausea
General disorders and administration site conditions		Pyrexia, Fatigue, Asthenia
Injury, poisoning and procedural complications	Bruises	
Metabolism and nutrition disorders		Decreased appetite
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Skeletal muscle pain
Nervous system disorder		Neuropathy, Peripheral sensory Neuropathy, Neuralgia, Dysesthesia
Skin and subcutaneous tissue disorders	Rash	

10.3.2 Very common side effects (>10%)

Most of these side effects have been mild to moderate in severity; however, severe side effects have occurred. Some side effects have been severe enough to lead to hospitalization, disability and sometimes death.

System Organ Class	Ibrutinib	Bortezomib
Blood and lymphatic system disorders	Thrombocytopenia;	Leukopenia, Lymphopenia
Ear and labyrinth disorders		Vestibular disorder
Eye Disorders		Conjunctivitis, swelling of the eyes, blurred vision
Gastrointestinal	Constipation, vomiting, oral Mucositis (Stomatitis)	GI bleeding, Dyspepsia, Stomatitis, abdominal distension, Oropharyngeal pain, abdominal pain, Flatulence
General disorders and administration site conditions	Fever, Peripheral edema	Edema, pain, indisposition, chills
Hepato-biliary disorders		abnormal liver enzyme values
Infections and infestations	Pneumonia, Sinusitis, , infection of upper respiratory tract, skin infection	Herpes zoster, pneumonia, herpes simplex, fungal infections, infection of upper and lower respiratory tract
Investigations		Anorexia
Metabolism and nutrition disorders		Dehydration, Hypokalemia, Hypernatremia, abnormal blood sugar values, Hypercalcemia, Enzyme anomaly
Musculoskeletal and connective tissue disorders	Arthralgia, muscle spasm	Muscle spasms, muscle weakness, pain in extremity

Nervous system disorder	Headache	Peripheral motor neuropathy¨, loss of consciousness (including syncope), Dizziness, Dysgeusia, headache, lethargy
Psychiatric disorders		Anxiety, depression, Insomnia
Renal and urinary disorders		Dysfunction of renal function
Respiratory, thoracic and mediastinal disorders		Dyspnea, cough, Epistaxis,
Skin and subcutaneous tissue disorders		Rash, Pruritus, Erythema, dry skin
Vascular disorder	Hypertension	Hypotension, orthostatic Hypotension, Hypertension

10.3.3 **Common side effects (1-10 %)**

Side effects (for ibrutinib) that have been seen in at least 1 in 100 patients:

• Dizziness	• Atrial fibrillation	• Hyperuricemia
• Urinary tract infection	• Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	• Lymphocytosis and/or leukocytosis
• Epistaxis	• Onychoclasis	• Erythema
• Petechiae	• Blurry vision	• Sepsis
• Interstitial lung disease	• Febrile neutropenia	

10.3.4 **Uncommon side effects (0.1-1%)**

Uncommon side effects (0.1-1%) include the following events: Tumor Lysis Syndrome, Urticaria, subdural hematoma, angioedema, leukostasis syndrome, Stevens - Johnson syndrome, ventricular tachyarrhythmia and hepatic failure. For more detailed information and information of rare side effects of ibrutinib please refer to the most recent IB.

For the uncommon/rare AEs of bortezomib please refer to the most recent IB and SmPC.

10.3.5 **Notes for ibrutinib**

Treatment related Lymphocytosis and Leukostasis

In patients treated with ibrutinib, a rapid reduction of lymphadenopathy has been seen that continues over the course of treatment and is accompanied by a transient phase of lymphocytosis. This is seen particularly in CLL/SLL but in MCL patients as well. Peripheral lymphocyte counts may increase dramatically, with a peak typically occurring during the initial 2 months of ibrutinib therapy. In patients remaining on therapy, lymphocyte counts gradually fall to baseline or below. A similar pattern of response has been reported with other BCR inhibitors [34, 35]. Isolated lymphocytosis should not lead to a diagnosis of disease progression in ibrutinib-treated patients. Lymphocytosis is not considered to represent an adverse event per se but reflects the pharmacodynamics of ibrutinib.

Bleeding effects

Bruising or bleeding during treatment with ibrutinib might be experienced. Rarely, serious internal bleeding, such as bleeding in the stomach, intestine, or brain, may occur. If the patient takes other medicines or supplements that increase your risk of bleeding, or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib.

Cardiac events

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia (including some

fatal events), have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, increased blood pressure, acute infections, or any previous history of cardiac arrhythmia. Periodically monitor patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms (e.g. palpitations, light headedness, syncope, chest discomfort) or new onset of dyspnea should be evaluated clinically and if indicated have an ECG performed. For cardiac arrhythmia which

persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.

There is no evidence of QT prolongation with increasing plasma concentrations of ibrutinib. Any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered and if needed, the medical monitor may be contacted.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in patients treated with Ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Although causality has not been established, cases of progressive multifocal leukoencephalopathy have occurred in patients treated with Ibrutinib. Patients should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

Second primary malignancies

Non melanoma skin cancers have been reported with more frequency. In addition, other cancers have been reported such as solid tumors and blood cancers. The relationship to the use of ibrutinib is unknown. Monitor patients for the appearance of second primary malignancies.

Tumor Lysis Syndrome

Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures.

Drug interruption for any surgical procedures

Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be held at least 3 to 7 days before and after surgery depending upon the type of surgery and the risk of bleeding. For emergency surgical procedures, ibrutinib should be discontinued (stopped) after the procedure until the surgical site is reasonably healed (without signs of potential infection). For details refer to section 10.6.4.

Liver Failure

Rare cases of liver failure have been reported in patients treated with ibrutinib.

Interstitial lung disease

Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (e.g. bacteria, fungi and viruses) and has been reported in patients treated with ibrutinib. If patients develop cough, any sign of new or worsening respiratory symptoms (shortness of breath or difficulty of breathing) should be evaluated clinically.

10.3.6 **Notes for Bortezomib**

Peripheral polyneuropathy (PNP) might occur under bortezomib treatment or might worsen under bortezomib treatment if pre-existing. Bortezomib induced PNP can improve if dose modification is considered before severe damage (CTCAE grade ≥ 2) has developed.

10.4 Safety parameters

Renal function:	Serum creatinine or BSA corrected creatinine clearance (according to the formula of Cockcroft-Gault, see 0)
Liver function:	Bilirubin, AP, AST/ALT
Hematological function:	Hemoglobin, leucocytes incl. neutrophils/lymphocytes platelets

10.5 General remarks on dose modifications

On Day 1 of each treatment cycle (Phase I and Phase II), the patient will be evaluated for possible drug toxicities related to trial treatment and trial drug. All previously established or new toxicities observed at any time are to be managed as described below. The coordinating investigator or supporting coordinating investigator should be contacted in case the investigator has any questions regarding doubts about treatment delays and/or dose reductions.

In case of conflicting recommendations, use the most restrictive treatment adjustment.

***Please note for phase I and phase II (except cycle 1 Phase I)**:* If an adverse event could be related to both agents, reduce first bortezomib and if the adverse event is not improving thereafter the dose of ibrutinib.

Doses omitted for adverse events are not replaced.

Interrupt therapy for the following reasons	
Ibrutinib	**Bortezomib**
• any Grade 3 or greater non-hematological toxicity, • Grade 3 or greater neutropenia with infection or fever, • Grade 4 hematological toxicities.	• Grade 3 non-hematological or • Grade 4 hematological toxicities
Special dose modifications: For dose modifications due to - **the use of CYP3A inhibitors** please refer to section 10.6.2 - the use of antiplatelet agents and anticoagulants please refer to section 0 - **surgical procedures** please refer to section 10.6.4	**Special dose modifications:** For dose modifications due to due to - **peripheral neuropathy** please refer to section 10.6.1
Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery)	
Ibrutinib	**Bortezomib**
• ibrutinib therapy may be reinitiated at the starting dose[3]. • if the toxicity reoccurs, reduce dose by one capsule (140 mg per day). • a second reduction of dose by 140 mg may be considered as needed. • if these toxicities persist or recur following **two** dose reductions, **discontinue** ibrutinib.	bortezomib therapy may be reinitiated • at a 25% reduced dose (1.3 mg/m²/dose reduced to 1 mg/m²/dose; 1 mg/m²/dose reduced to 0.7 mg/m²/dose).

[3] except for phase I, cycle 1: a patient that experienced a DLT

Examples		
	Ibrutinib	**Bortezomib**
Toxicity occurrence	**Dose modification after recovery** ***Example chosen:*** *Starting Dose 560 mg*	**Dose modification after recovery** Starting Dose 1.3 mg/m^2 per dose
First	Restart at 560 mg daily	Reduction to 1.0 mg/m^2 per dose
Second	Restart at 420 mg daily	Reduction to 0.7 mg/m^2 per dose
Third	Restart at 280 mg daily	Discontinue bortezomib
Fourth	Discontinue ibrutinib	

Additional notes	
Ibrutinib	**Bortezomib**
• Ibrutinib may be held for a maximum of 14 consecutive days. Ibrutinib should be permanently discontinued if the treatment cannot be resumed within 14 days. • Once the ibrutinib dose is reduced it cannot be re-escalated. No dose escalation of ibrutinib (above 560 mg) is allowed in this trial. • If ibrutinib treatment has to be delayed and no such delay is specified for bortezomib, bortezomib treatment shall be continued.	• Once the dose for bortezomib has been reduced for any type of adverse event, it should never be increased at a later date. If bortezomib treatment has to be delayed and no such delay is specified for ibrutinib, ibrutinib treatment shall be continued.

Supportive therapy may be performed according to local clinical standards and at the discretion of the investigator. Local routine standards and precautions for the application of ibrutinib have to be followed.

10.6 Special Dose modifications

In the following chapter, special dose modifications for peripheral neuropathy, use of CYP3A inhibitors, use of antiplatelet agents and anticoagulants and surgical procedure are listed.

10.6.1 Peripheral neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	**Ibrutinib**	**Bortezomib**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function)	No action	No action
Grade 1 with pain or Grade 2 moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**	No action	Reduce to 1 mg/m²
Grade 2 with pain or Grade 3 severe symptoms; limiting self-care ADL ***	Follow dose modification in section 10.5	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m² once per week.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Interrupt/delay treatment (see section (10.50))	Discontinue treatment

*Grading based on NCI Common Terminology Criteria CTCAE v4.0
**Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.;
***Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

10.6.2 Use with CYP3A inhibitors

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. **Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.** (A list of strong and moderate CYP3A inhibitors can be found here http://medicine.iupui.edu/clinpharm/ddis/main-table)

Concomitant use of <u>strong</u> CYP3A inhibitors*	**Ibrutinib**	**Bortezomib**
Chronically	Exclusion criteria for trial. Not recommended during therapy	No action
Short term use (7 days or less) **	Interrupt until CYP3A inhibitor is no longer needed	No action

Concomitant use of <u>moderate</u> CYP3A inhibitors***	**Ibrutinib**	**Bortezomib**
Chronically	Exclusion criteria for trial	No action
During trial treatment	Reduce ibrutinib dose to 140 mg until CYP3A inhibitor is no longer needed	No action

***** ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone

** e.g., antifungals and antibiotics

**fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin

10.6.3 Antiplatelet agents and anticoagulants

Antiplatelet agents and other anticoagulants such as heparin, low molecular weight heparins, and antithrombotics should be used with caution. **No concomitant administration with warfarin and vitamin K antagonists is allowed.** Please refer to the approved prescribing information for details of permitted concomitant medication with anticoagulants.

Concomitant use of antiplatelet agents and anticoagulants (except for warfarin and vitamin K antagonists)	**Ibrutinib**	**Bortezomib**
Before trial entry	Not recommended during therapy	No action
During trial treatment	Interrupt until a stable dose of antiplatelet agents/anticoagulants has been established. Please note: Coagulation parameters ([INR]/[PT], and [aPTT]) should be monitored closely according to institutional guidelines and patients should be observed for any signs or symptoms of bleeding. **The risks and benefits should be considered carefully before restarting ibrutinib treatment**.	No action

10.6.4 Ibrutinib dose modifications for surgical procedures

Type of procedure	any surgery or invasive procedure requiring sutures or staples for closure	minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis)	For emergency procedures
Duration of interruption	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.	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.	Ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Note: For bone marrow biopsies that are performed while the patient is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

11 SAFETY REPORTING

11.1 Definition of serious adverse event (SAE)

11.1.1 SAEs during trial treatment

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human use is any untoward medical occurrence that at any dose is listed in the table below and occurring between registration and up to 30 days after end of trial treatment.

	Comments
Fatal	All events resulting in death
Life-threatening	The patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.
Requires inpatient hospitalization (> 24 hours)	Events not considered to be SAE are hospitalizations > 24 hours and occurring under the following circumstances: - elective surgery (planned before entry into the trial) - part of the normal treatment or monitoring of the trial treatment - hospitalization for social reasons (e.g. in rehabilitation home)
Prolongs hospitalization	Prolongation of an existing hospitalization
Disabling	Includes persistent or significant disability/incapacity
Secondary malignancy	Any new malignancy other than a relapse of the current tumor
Congenital anomaly Abnormal pregnancy outcomes	Birth defect in neonate/enfant, spontaneous abortion, stillbirth, and congenital anomaly
Suspected transmission of infectious agent	A suspected transmission of any infectious agent via a medicinal product
Other medically significant condition	Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Exceptions:

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a patient's participation in a trial must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the trial (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

- A standard procedure for protocol therapy administration will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event
- A procedure planned before entry into the trial (must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the trial drug remains a reportable serious adverse event.

Unresolved SAEs

All serious adverse events that have not resolved by the end of the trial, or that have not resolved upon discontinuation of the patient`s participation in the trial, 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 trial drug or to factors unrelated to trial 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)

11.1.2 SAEs after end of trial treatment

During the follow-up phase (starting 30 days after end of trial treatment), the following events have to be reported as SAE:

- fatal and life-threatening events possibly, probably or definitely related to late effects of trial treatment
- other medically significant events possibly, probably or definitely related to late effects of trial treatment
- disabling events possibly, probably or definitely related to late effects of trial treatment
- secondary malignancy
- congenital anomaly

11.1.3 Pregnancy

In the case of pregnancy occurring during the trial treatment or during the follow up phase of this trial (2 years), the investigator must report the event to the SAKK by completing the SAKK pregnancy reporting form. This form is available on the SAKK website: member's section → Lymphoma → SAKK 36/13 → pregnancy report form. All initials reports of pregnancy must be reported to the SAKK CC within 24h of their knowledge of the event. The investigator shall ensure that the case is followed up to the end of the pregnancy and supply a final report on the outcome to the SAKK CC. In case of pregnancy, additional detailed pregnancy report forms from Janssen are provided by SAKK to the site and have to be completed in a timely manner. In addition, the investigator has to report any fetal anomaly, stillbirth or any other medicinal significant event concerning the pregnancy as SAE (see above 11.1.1). Any patient who becomes pregnant during the trial must discontinue further trial treatment.

In case the female partner of a male patient becomes pregnant while the patient is on trial treatment or in the follow up period of this trial the patient should, with his partner's consent, notify the investigator. Pregnancies will be reported by the study site personnel within 24 hours of their knowledge of the event. It is recommended that the investigator shall ensure that the case is followed up until the end of the pregnancy and supply a final report on the outcome to the SAKK CC.

11.1.4 Other malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of the trial treatment and during any protocol specified follow up periods including post-progression follow up.

11.1.5 Reporting of quality complaint handling

For the definition and process of quality complaint handling reporting please refer to chapter 8.4.

11.2 Definition of adverse events of special interest (AESI)

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities. These events will be reported to Janssen irrespective of seriousness (i.e., serious and non-serious adverse events) following the procedure described below in section 11.5 and will require enhanced data collection.

11.2.1 Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

11.2.2 Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

11.3 Definition of serious adverse reaction (SAR)

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, very likely or definite by the definitions listed in chapter 10.2.2 .

11.4 Definition of suspected unexpected serious adverse reaction (SUSAR)

An adverse event is considered unexpected (unlisted) if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib /bortezomib, the expectedness of an adverse event will be determined by whether or not it is listed in the respective up to date Investigator's Brochure.

11.5 Reporting of individual SAEs and AESI by the investigator

Any **SAE** and any **AESI** (for definition see 11.2) must be reported by submitting the completed initial report section of the trial specific SAE/AESI form within 24 hours of becoming aware of the event. This form can be downloaded from SAKK website (member's section→Lymphoma→SAKK 36/13)

Submission is done by sending the SAE form by fax to:

SAKK Coordinating Center
Fax: +41 31 508 41 42

The SAE outcome must be reported within 2 weeks after initial report by submitting the **follow-up** report (e.g. initial SAE form, updated with follow-up information) to the SAKK CC as above. In case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome.

The originals of the SAE forms (both initial and follow-up reports) are kept at the sites in the Investigator's file. The SAKK CC will forward each individual SAE and any AESI (see section 11.2) within one working day of knowledge (please be aware of our office hours, see chapter 7.2) to the coordinating investigator, the supporting investigator and to Janssen.

Foreign sites only: The local investigator at a foreign site is requested to report local SAEs to the local EC according to the EU Clinical Directive2001/20/EC (if applicable) and/or national law for foreign sites.

11.6 Reporting of individual SAEs and SURARs by the sponsor

The SAKK CC ensures that all reporting requirements and timelines for reporting, as defined in the applicable national and international laws are followed:

The SAKK CC

- will forward any SAE which is fatal and occurred at a Swiss site to the concerned local and lead EC according to the Swiss Human Research Act (HRA) and its applicable Ordinances.
- will report every SUSAR to all principal investigators, to the involved ECs, to Swissmedic and to Janssen and to the competent authorities of foreign countries, unless specified otherwise in the contract with a foreign site as specified in the Swiss HRA and the EU Clinical Directive2001/20/EC .

In case of international trials conducted by the SAKK: SUSARs occurring within Switzerland and the EU will be entered into the EudraVigilance database by SAKK Safety Office within the required timeframe.

11.7 Reporting of safety signals

The investigator must report external safety reports/letters associated with ibrutinib and bortezomib to the SAKK within 7 days. The SAKK CC will forward these reports/letters to all investigators and to the local and lead ECs if applicable.

11.8 Periodic reporting on safety by the sponsor

The SAKK CC ensures that the reporting requirements and timelines for reporting, as defined in the respective applicable laws, are followed.

An annual safety summary (ASR) or in case the trial will also be conducted in the EU, a yearly Data Safety Update Report (DSUR) will be provided to the local investigators for filing into the investigator's file. The SAKK CC will submit all annual safety reports to the concerned regulatory authorities, to the required regulatory authorities of foreign countries and to Janssen.

12 EVALUATIONS AND INVESTIGATIONS BEFORE, DURING AND AFTER TRIAL TREATMENT

A schedule of assessments, treatments and CRF completion is provided in Appendix 6 (phase I) and Appendix 7 (phase II). An adaptable scheduler (MS Excel file) can be downloaded from the SAKK website.

Definition:

Vital signs include the measurement of body temperature, heart rate, and blood pressure

12.1 Pretreatment evaluations and procedures

- Diagnosis / tumor histology by local pathologist (see section 17.1) of MCL with either overexpression of cyclin D1 protein or evidence of t(11;14)(q13;q32) (biopsy of MCL diagnosis must not be repeated for screening)
- Informed consent must be obtained before registration and prior to any trial-specific procedures.

12.1.1 The following investigations have to be performed within 30 days <u>before registration</u> for phase I and II

- Tumor Assessment
  - Bone marrow assessment [4]
  - Assessment of disease-related symptoms
  - Radiological assessments
    - of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1)
- Medical history, including baseline symptoms, previous therapies, location of tumor sites
- Physical examination including assessment of WHO performance status, weight and height
- Vital signs
- Cardiovascular function: echocardiography (or MUGA scan) and ECG
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Hepatic function: AP, AST, ALT, bilirubin, albumin
- IgA, IgG, IgM
- Coagulation parameters: INR & Quick
- Beta-2 microglobulin
- Renal function: BSA corrected creatinine clearance (according to the corrected formula of Cockcroft-Gault, see 0)
- Women of childbearing potential must have a negative serum β-hCG (minimum sensitivity of 25 U/ml) or urine pregnancy test at screening.
- LDH measurement
- Serology of hepatitis B and C and HIV
- Tumor re-biopsy (if needed according to protocol see chapter 17)

12.2 Evaluations within 7 days <u>before treatment start</u> (Phase I and Phase II)

[4] Patients who have a bone marrow biopsy result since completion of their last therapy for MCL may use those bone marrow results in lieu of the baseline bone marrow aspirate/biopsy required for this study provided, that the biopsy/aspirate was done within 60 days of the first dose of study drug.

These evaluations can be skipped if the below specified assessments have been done at baseline (section 12.1.1) within 7 days before treatment start.

- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Pregnancy test for women of child-bearing potential: serum β-hCG (minimum sensitivity of 25 U/ml) or urine pregnancy test.
- Blood sampling for translational research (if patient has given consent only, Swiss sites, only)

12.3 Evaluations during trial treatment

12.3.1 Phase I (combination therapy)

On day 1 of each cycle (For cycle 1: the measurements below can be skipped if baseline assessment -2 days)

- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Hepatic function: AP, ALT, AST, bilirubin, albumin
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Renal function: BSA corrected creatinine clearance according to the corrected formula of Cockcroft-Gault (see 0)
- Verify patient's compliance of ibrutinib and bortezomib, collect patient diaries and count ibrutinib pills (except of cycle 1) and complete the drug accountability log accordingly

During cycle 1

On day 1, 8, 15 or in case of grade 3 hematologic toxicity of neutrophils or platelets more frequently (at the discretion of the investigator):

For cycle 1, Day 1: assessment (see below) can be skipped if baseline assessment within 2 days

- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Vital signs

On day 1 of cycle 3 and 6

- Serum IgG, IgM, IgA and beta2-microglobulin

During cycle 2 to 6: on day 8:

- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets

After cycle 3 or upon clinical indication:

- Tumor assessment:
    - Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (+2/- 1 week(s))
    - Bone marrow assessment - not mandatory, only necessary upon clinical indication
    - Assessment of disease-related symptoms

During each cycle:

- Adverse events

12.3.1.1 After end of the combination therapy and after start of maintenance therapy

The following investigations and the associated analysis (e.g. tumor assessment) incl. evaluations have to be performed at the **latest after 14 days**:

- Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (only, in case the assessment was not done after cycle 3 and 6)
- Bone marrow assessment (only if bone marrow involvement at baseline and to confirm CR according to tumor assessment (latest 14 days after radiological assessment))
- Bone marrow biopsy Assessment of disease-related symptoms

12.3.1.2 Examinations to be performed at the end-of-trial-treatment visit (after premature end of combination therapy, maintenance therapy and/or after transfer to follow up)

The following investigations have to be performed prior to start of next therapy (in case of relapse) or transfer to follow-up for other reasons **at the latest after 14 days after last dose of trial medication** (whatever is first)

- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Tumor assessment
    - Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (in case of relapse only, if not done before)
    - Bone marrow assessment (only if bone marrow involvement at baseline and only to confirm CR according to tumor assessment (latest 14 days after radiological assessment)
        - Bone marrow biopsy

      <u>Please note:</u> Bone marrow assessment during and after maintenance therapy is not mandatory (only upon clinical indication).
    - Assessment of disease-related symptoms
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Serum IgG, IgM, IgA and beta2-microglobulin
- Adverse events
- Blood sampling for translational research (if patient has given consent only, Swiss sites, only)

12.3.2 Phase II (combination therapy)

On day 1 of each cycle: (For cycle 1: The measurements below can be skipped if baseline assessment within -2 days)

- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Hepatic function: AP, ALT, AST, bilirubin, albumin
- Renal function: BSA corrected creatinine clearance according the corrected formula of Cockcroft-Gault (see 0)
- Verify patient's compliance of ibrutinib and bortezomib, collect patient diaries and count ibrutinib pills (except of cycle 1) and complete the drug accountability log.

During cycle 1 to 6: on day 8:

- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets

On day 1 of cycle 3 and 6

- Serum IgG, IgM, IgA and beta2-microglobulin

After cycle 3 or upon clinical indication:

- Tumor assessment

- Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (- 1/ +2 week(s))
- Bone marrow assessment - not mandatory, only necessary upon clinical indication
- Assessment of disease-related symptoms

During each cycle:

- Adverse events

12.3.2.1 After end of the combination therapy and after start of maintenance therapy

The following investigations and the associated analysis (e.g. tumor assessment (including evaluations) has to be performed at the **latest after 14 days**

- Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (only in case an assessment was not done after cycle 3 and 6)
- Bone marrow assessment (only if bone marrow involvement at baseline and only to confirm CR according to tumor assessment (latest 14 days after radiological assessment)).
  - Bone marrow biopsy
- Assessment of disease-related symptoms

12.3.2.2 Examinations to be performed at the end-of- trial-treatment visit (after premature end of combination therapy, maintenance therapy and/or after transfer to follow up)

- The following investigations have to be performed prior to start of next therapy (in case of relapse) or transfer to follow-up for other reasons at the **latest after 14 days** after last dose of trial medication (whatever occurs first)
- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Tumor assessment
  - Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1) (in case of relapse – only, if not done before)
  - Bone marrow assessment (only in case of bone marrow involvement at baseline and to confirm CR according to tumor assessment (latest 14 days after radiological assessment)
    - Bone marrow biopsy

    <u>Please note:</u> Bone marrow assessment during and after maintenance therapy is not mandatory (only upon clinical indication).
  - Assessment of disease-related symptoms
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Serum IgG, IgM, IgA and beta2-microglobulin
- Adverse events
- Blood sampling for translational research (if patient has given consent only, Swiss sites, only)

12.3.3 Maintenance therapy with ibrutinib (Phase I and Phase II)

On day 1 of every cycle

- Physical examination including assessment of WHO performance status and weight
- Vital signs
- Hematological values: hemoglobin, leucocytes including neutrophils and lymphocytes, platelets
- Hepatic function: AP, ALT, AST, bilirubin
- Renal function: BSA corrected creatinine clearance according the corrected formula of Cockcroft-Gault (see 0)
- Adverse events

Every 12 ± 1 week

- Tumor assessment
    - Radiological assessment of measurable disease: CT or MRI according to the International Working group criteria for NHL [32] (see Appendix 1)
    - Bone marrow assessment (only upon clinical indication)
    - Assessment of disease-related symptoms
- Serum IgG, IgM, IgA and beta2-microglobulin

At day 1 of first maintenance cycle and after 12 weeks ± 1 week

Blood sampling for translational research (if patient has given consent only, Swiss sites, only)

12.3.4 End of trial treatment visit

For the end-of-trial-treatment visit please refer to section 12.3.1.2 (Phase I) and 12.3.2.2 (Phase II)

12.4 Evaluations in the follow-up phase (Phase I and Phase II)

All patients will be followed up for 2 years after end of treatment.

For all patients every 12 ± 3 weeks

- Survival status, further MCL treatments, disease status
- Physical examination including assessment of WHO performance status and weight
- Fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment
- **For patients without progressive disease**: Tumor assessment according to Cheson criteria (see Appendix 1) until progression (including radiological assessment (CT or MRI), bone marrow assessment (only upon clinical indication) and disease-related symptoms).

13 CRITERIA OF EVALUATION AND DEFINITION OF ENDPOINTS

13.1 Criteria of evaluation

Phase I

Patients will be considered non-evaluable for the phase I, cycle 1 part of the trial if

- They fail to satisfy major eligibility criteria or
- They miss ≥ 7 consecutive therapy days of ibrutinib or ≥ 2 consecutive doses of bortezomib in the first cycle, except if the treatment is stopped due to DLT

All other patients will be considered evaluable. Non-evaluable patients will be replaced.

The populations used for the phase I analysis will include the following:

- Phase I Full Analysis Set: the phase I full analysis set is defined as all evaluable patients for phase I.
- Phase I Safety Analysis Set: the phase I safety analysis set is defined as all patients who received any dose of trial treatment in phase I.

Phase II

Patients will be considered non-evaluable for the phase II part of the trial if

- They fail to satisfy major eligibility criteria or
- They fail to receive at least one dose of both ibrutinib AND bortezomib

All other patients will be considered evaluable. Non-evaluable patients will be replaced.

The populations used for the phase II analysis will include the following:

- Phase II Full Analysis Set: the phase II full analysis set is defined as all evaluable patients for phase II.
- Phase II Safety Analysis Set: the phase II safety analysis set is defined as all patients who received any dose of trial treatment in phase II.

13.2 Definition of Endpoints

13.2.1 Primary endpoints of phase I

Dose limiting toxicities (DLT) during first cycle

For the definition of a DLT refer to section 9.2.2.

13.2.2 Primary endpoint of phase II

Overall response (OR) (combination therapy)

ORR is defined as the proportion of patients whose best overall response, is either complete response (CR), complete response unconfirmed (CRu) or partial response (PR) according to the International Working group criteria for NHL [30] (see Appendix 1). The primary endpoint of phase II is OR observed during the combination therapy.

13.2.3 Secondary endpoints of phase I

Adverse events (AE)

All AEs will be assessed according to NCI CTCAE v4.0 (see section 10.1). Management and dose modifications associated with the above AEs are outlined in section 0.

Overall response (OR)

OR observed during the combination therapy and OR observed during trial treatment (OR as defined for the primary endpoint of phase II).

13.2.4 Secondary endpoints of phase II

Adverse events (AE)

All AEs will be assessed according to NCI CTCAE v4.0 (see section 10.1). Management and dose modifications associated with the above AEs are outlined in section 10.6.

Overall response (OR) during trial treatment

OR, as defined for the primary endpoint of phase II, observed during trial treatment.

Progression-free survival (PFS)

Time from registration until progression of disease or death as a result of any cause.

Patients not experiencing an event, including patients receiving a subsequent anti-MCL therapy without documented progressive disease (or relapse after CR), will be censored at the last time they were known to be without progression (i.e. last date of tumor assessment without progression under trial treatment).

Time to treatment failure (TTF)

Time from registration until treatment failure (due to unacceptable toxicity, progression, patient refusal, death, start of subsequent anti-MCL therapy or any other event that determines the termination of the trial treatment will be considered as treatment failure).

Patients not experiencing an event will be censored at the last time they were known to be under trial treatment.

Duration of objective response

Time from first observation of CR, CRu or PR until documentation of progression, or relapse thereafter.

Only patients with CR, CRu or a PR will be included in this analysis.

Patients without any documentation of progression, or relapse thereafter will be censored at the last time they were known to be without progression (i.e. last date of tumor assessment without progression under trial treatment).

14 DOCUMENTATION

14.1 CRFs and reports

CRFs specifically created for this trial are used for documentation. It is very important to adhere to the schedule of visits prescribed in the protocol for all patients. All CRFs needed for the corresponding visit will be displayed automatically in the web-based electronic data capture (EDC) system for the SAKK trial 36/13.

Sites must use a patient identification list in order to allow identification of a patient. This list must be kept at the site in the investigator's file.

The CRF data have to be completed online (www.sakk.ch/edc) in a timely manner at the specified time points.

14.1.1 Phase I

The reporting of DLT must be done on the day of toxicity assessment, as specified in chapter 12.

All baseline assessments and all assessments for cycle 1 day 1 should be entered in the system in due time (latest at the first DLT assessment on cycle 1 day 8)

In addition, all CRFs related to the DLT assessment (cycle 1 day 8 and 15 as well as cycle 2 day 1) have to be completed on the day of the DLT assessment (max. +1day).

- AE form
- DLT form
- Trial Drug Exposure form (EX) (updated as much as possible)
- Hematology form, hepatic and renal function form (form HE and HR)
- Physical examination (PE)

For all other visits (from cycle 2, day 8 on), the data should be entered into the CRFs within 14 days from the visit or medical examination.

14.1.2 Phase II

In general, the data should be entered into the CRFs within 14 days from the visit or medical examination.

14.2 Notes for special handling of CRFs

Eligibility CRF:

- The completed form ER in the web based EDC system has to be printed and signed by the investigator. A copy of **the signed form has to be sent to SAKK CC by mail or fax within one month after registration.** The original signed form is kept at the site in the investigator`s file
- If it is not possible to enter the eligibility form online, complete a paper CRF and fax the CRF before registration to the SAKK CC (see also Section 7).

SAE and pregnancy report forms:

- Trial-specific SAE/AESI report forms and trial-specific pregnancy report forms have to be submitted **by fax** to SAKK CC within 24 hours of becoming aware of the SAE/AESI or pregnancy (see also Section 11 for SAE reporting and pregnancy reporting). Originals of SAE and pregnancy reports are kept at the site in the investigator`s file.

Tumor assessment CRF

The tumor assessment CRFs have to be completed at the latest 14 days after tumor assessment.

14.3 Source data

Additionally to other source data, the following data entered directly onto trial documents are considered to be source data:

- patient screening and enrollment list
- patient identification list
- drug inventory logs
- diaries

15 STATISTICAL CONSIDERATIONS (HYPOTHESIS)

15.1 Introduction

The sample size estimations are based on the primary endpoints of the trial.

15.2 Phase I trial design

15.2.1 Dose finding procedure

For Phase I, a standard 3+3 dose escalation design is applied. The dose levels considered are listed in section 9.2.1. The dose finding procedure is described in detail in section 9.2.1.

15.2.2 Sample size estimation

A minimum of 4 (in case of two DLTs in the first two patients at dose level 1 and two DLTs in the first two patients at dose level -1) and a maximum of 18 (in case of six patients at each dose level) evaluable patients will be included in the dose escalation procedure. As soon as the RP2D is established in 6 patients, this dose will be brought forward to Phase II.

15.2.3 Statistical analyses

For the dose finding, the evaluation will be performed using all evaluable patients for Phase I as defined in section 13.1. The RP2D will be chosen according to the dose finding procedure described in section 9.2.1.

DLTs, AEs and SAEs will be fully listed. Laboratory values will be expressed as raw values (continuous variables) and as grading (ordinal categorical variables) according to NCI CTCAE v4.0.

Before proceeding to Phase II, a report including the dose finding evaluation will be written and provided to the competent authority and Lead EC.

15.3 Phase II

15.3.1 Sample size estimation

- Software package: PASS 11.0.10
- Number of treatment arms: 1 arm
- Type of design: Simon's two-stage minimax design [36]
- Trial intention: to determine whether the trial treatment has sufficient antitumor activity to warrant further investigation
- Null hypothesis: OR ≤ 65%; this assumption is based on the results observed in a trial that investigated ibrutinib in 111 patients with relapsed or refractory MCL [14]. An overall response rate of 65.8% (95% CI 56.2, 74.5) was reached in this trial.
- Alternative hypothesis: OR ≥ 80%
- Type I error: 5%
- Power: 80%
- Number of interim analyses for the primary endpoint: 1
- Timing of interim analyses: 31 evaluable patients (in Phase II) have completed the combination therapy
- Maximum sample size: 55 patients (including 6 patients from Phase I treated at the corresponding dose level)

A total of 55 evaluable patients will be included in the primary endpoint analysis of Phase II. If 42 or more patients reach a complete or partial response the null hypothesis will be rejected and the trial treatment will be considered active and promising for further investigation.

15.3.2 Interim safety analyses

An interim safety analysis after 10 patients (phase II) will assess whether this new combination harbors any unexpected side effects. The accrual will not be suspended while waiting for the interim analysis results. The results of the interim safety analysis will be presented to selected SAKK board members.

15.3.3 Interim efficacy analyses

An interim analysis will be performed once the first 31 patients in Phase II (including 6 patients from Phase I treated at the corresponding dose level) have completed the combination therapy. Note that the interim analysis will take place after 34 patients have been accrued in the trial, as the first 3 patients in Phase I have been treated at a different dose level and will not be included in the analysis. The accrual will not be suspended while waiting for the interim analysis results. If less than 21 of the 31 patients reach a complete or partial response, the trial will be discontinued and the therapy will be considered *unworthy of further investigation*, otherwise the trial will continue until the planned total sample size is achieved. The results of the interim efficacy analysis will be presented to selected SAKK board members.

15.3.4 Statistical analyses

All efficacy endpoints will be analyzed based on the Phase II full analysis set. All safety endpoints will be analyzed based on the phase II safety analysis set.

The primary analysis will be performed after all patients in the Phase II full analysis set have completed the combination therapy. The final analysis will be performed after trial termination (last patient last visit).

In general, the summary statistics presented for quantitative variables will be the median, minimum and maximum values. The summary statistics presented for categorical data will be the count and percentage of patients in each category.

For the primary endpoint, the point estimate and two-sided 95% confidence interval (CI) will be presented.

For secondary efficacy endpoints expressed as a rate, the point estimate of the rate and the associated 95% CI will be calculated. All time-to-event endpoints shall have the median value estimated using the Kaplan-Meier method, along with a 95% CI. The types of events of each endpoint shall be presented descriptively by frequency and percentage.

AEs will be presented by type and grade using frequency and percentage of the within-patient worst grades. In addition, grade ≥ 3 AEs and AEs related to trial treatment (relation to trial treatment is either “possible” or “probable” or “definite”) will be summarized separately.

SAEs will be fully listed. In addition, SAEs will be summarized showing the SAE description, relationship to trial treatment and outcome.

Laboratory values will be expressed as raw values (continuous variables) and as grading (ordinal categorical variables) according to NCI CTCAE v4.0.

Full analysis details will be outlined in the statistical analysis plan (SAP).

15.4 Handling of missing data and drop-outs

No imputation of missing data will be performed. A row denoted “Missing” will be included in count tabulations if necessary to account for drop-outs and missing values. As mentioned in Section 13.1, non-evaluable patients will be replaced. Evaluable patients without any response assessment will be regarded as a failure for OR.

16 QUALITY OF LIFE

Not applicable

17 PATHOLOGY

17.1 Local pathology

17.1.1 Tasks for the local investigator

The local investigator has to inform the local pathologist of each site participating in the trial about the protocol, the trial specific investigations and the sample handling for the pathology review process and the shipping of histology material. If a patient was registered into the trial, the local pathologist has to be informed by the local investigator.

Biopsy and all other required material (e.g. paraffin embedded tissue and slides (if applicable)) will be ordered by the local investigator from the local pathologist for sending to the centralized review pathologist.

17.1.2 Task for the local pathologist

Examinations of the pre-treatment biopsies are to be performed according to the protocol of the College of American Pathologists [37].

Notably the following items must be documented by the local pathologist:

For the biopsy at initial diagnosis:

- Preparation of formalin fixed, paraffin embedded tumor biopsy (if applicable)
- Histological confirmation of MCL and morphology
- Expression of cyclin D1 protein in association with one B-cell marker including CD19, CD20, PAX5 and co-expression of CD5 or evidence of t(11;14) as assessed by cytogenetics, FISH, or PCR[5]. FISH testing is recommended in cases where analysis by PCR does not reveal the presence of the t(11;14) translocation

Please note: The information above can be also retrieved from the original pathology report of the initial diagnosis (if done by the concerned local pathologist and applicable)

For the optional biopsy at baseline (only if clinically needed):

A re-biopsy is recommended if paraffin embedded and/or fresh frozen tumor tissue is not available in sufficient quantity or quality from biopsy of initial diagnosis. In order to retrieve this biopsy it should only be performed, if possible and clinically needed.

- Preparation of formalin fixed, paraffin embedded tumor biopsy

For the biopsy at relapse, if available:

- Histology of tumor including assessment of transformation and histological subtyping of MCL
- Preparation of formalin fixed, paraffin embedded tumor biopsy

17.1.3 Required material for review

The following material is required for pathological review.

Biopsies at initial diagnosis or optional biopsy at baseline:

- Paraffin block(s); slides can be sent only in the exceptional case that blocks are not available
- A copy of the local pathology report (coded)
- The accompanying letter of local pathology (www.sakk.ch →Members → Trials →Lymphoma →SAKK 36/13 – useful tools)
- If the report from the local laboratory is not available, slides or block(s) must be sent to the central laboratory for confirmation of MCL diagnosis before inclusion of the patient.

[5] MCL cells generally over-express cyclin D1 due to a t(11;14)(q13;q32t) chromosomal translocation in the DNA.

All material has to be clearly labeled (SAKK 36/13), UPN and local unique number, site, biopsy or re-biopsy, date of biopsy and sent by Swiss post to

Prof. Dr. Stephan Dirnhofer
Institute for Pathology
University of Basel
Schönbeinstrasse 40
CH-4031 Basel

Local pathologists will be compensated by the SAKK for sending the paraffin blocks or in exceptional cases slides.

17.2 Pathology review

In order to uniformly confirm the diagnosis of MCL at baseline, a central histo-pathological review will be performed by Prof. Dr. Stephan Dirnhofer (Institute of Pathology, University Basel). Biopsies need to be sent together with a copy of the coded pathology report and the accompanying letter of local pathology to Prof. S. Dirnhofer for review (Institute of Pathology University Hospital of Basel) immediately after inclusion of the patient into the study.

Notably the following items must be documented by the review pathologist:

- Histological confirmation of MCL and morphology
- Expression of **cyclin D1** and **SOX11** protein in association with one B-cell marker including CD19, CD20, PAX5 and CD5 or evidence of t(11;14) as assessed by cytogenetics, FISH, or PCR. FISH testing is recommended in cases where analysis by PCR does not reveal the presence of the t(11;14) translocation

After the central pathology review has been performed, the central pathology report (including the local pathology report) of each patient will be sent to the SAKK CC.

The resulting data of the central pathology report for diagnosis and morphology of MCL will be entered in the web based EDC system by SAKK CC. Results of the review will be provided to the local investigator for scientific purposes only.

Please note:

- The central pathologist cuts slices from the biopsies and sends them to the responsible person for the translations research project for extracting DNA. For details of the translational research project please refer to section 18.1.
- The paraffin blocks will be returned to the primary pathology institute after completion of the review analysis, remaining sections will be stored at the Institute of Pathology in Basel (if patient has given consent, only).

18 TRANSLATIONAL RESEARCH

The patient's refusal to participate in the subproject of SAKK 36/13 will not be an exclusion criterion for the clinical trial. Any research question not included in the protocol has to be formulated in an amendment. This amendment has to consider the funding of the research and must be submitted to the SAKK Board and to all concerned regulatory authorities for approval.

18.1 Detection of genetic lesions predicting the response to ibrutinib plus bortezomib followed by ibrutinib maintenance therapy.

Samples (Phase I and II) will be collected from patients of Swiss sites only. Only if patient has given consent.

18.1.1 Background, aim and rationale

18.1.1.1 Scientific Background and rationale

Initial clinical studies with the BTK-inhibitor ibrutinib have reported responses in MCL. A number of molecular mechanisms driving B-cell tumor resistance to ibrutinib circumventing the inhibition of BTK have now been reported. Here, we aim to assess the role of genetic lesions affecting the BCR/NFκB signaling in affecting the response to ibrutinib combined with bortezomib following an ibrutinib maintenance therapy. The results will allow a better selection of patients to be treated with the regimen.

18.1.1.2 Current status of research in the field

MCL clinical and biological features are more heterogeneous than initially recognized [38-41]. The primary oncogenic driver is the t(11;14)(q13;q32) translocation, which virtually occurs in all cases and causes cyclin D1 overexpression [38-42]. This event usually pairs with additional lesions that recurrently (≥5% of cases) target genes regulating DNA damage response (*TP53* and *ATM*), non-canonical NFκB signaling (*BIRC3*, *TRAF2* and *TRAF3*), NOTCH signaling (*NOTCH1* and *NOTCH2*), and chromatin modifiers (*MLL2* and *WHSC1*) [43-45]. Initial clinical studies with ibrutinib [46] have yielded substantial responses in MCL [11, 47]. However, ~30% of MCL cases might be primary resistant to ibrutinib and, at 1 year, ~50% of MCL patients are destined to fail ibrutinib [47]. In an optimized management algorithm of MCL, the early identification of ibrutinib-resistant patients, ideally prior to treatment, is a pre-requisite for designing strategies tailored at overcoming therapy resistance.

A number of molecular mechanisms driving B-cell tumor resistance to ibrutinib are emerging at both pre-clinical and clinical levels [45, 48, 49]. All these mechanisms have been selected to circumvent the inhibition of BTK. Pre-clinical evidence indicate that BTK-independent activation of NFκB through mutations affecting the *TRAF2*, *TRAF3* and *BIRC3* non-canonical pathway genes confers resistant to ibrutinib in MCL [45]. In diffuse large B-cell lymphoma, mutations of CARD11, which constitutively activate the B-cell-receptor signaling by acting downstream and independently of BTK, have been associated with in vitro resistance and absence of clinical responses to ibrutinib [48]. Finally, mutations that block the binding of ibrutinib to BTK or that activate in a BTK-independent fashion its downstream targets (i.e. PLCG2) have described in chronic lymphocytic leukemia patients who are resistant to ibrutinib [49].

18.1.1.3 Aims and objectives

The project aims to characterize the impact of recurrent mutations affecting the treatment outcome in MCL patients treated with a scheme combining ibrutinib with bortezomib followed by an ibrutinib maintenance therapy. The expected results will possibly allow to:

I. address the molecular basis of ibrutinib-refractoriness in MCL;
II. provide novel biomarkers for the early identification, ideally before treatment, of ibrutinib resistant patients; and
III. ultimately, propose a personalized algorithm of treatment for MCL based on the genetic signature.

18.1.2 Organization of the project

18.1.2.1 Experimental procedure.

1. Mutation screening will be performed by next generation sequencing of shot gun libraries. Design and production of an optimized custom sequence capture system (target region ~250kb) will be done targeting the coding exons of genes that have been identified as recurrently implicated in mature B-cell tumors, including MCL. Targeted sequence capture, with pre-capture ligation-mediated PCR, hybridization, washing, elution and quantitative PCR to assess capture success, will be performed according to the manufacturer's instructions. Captured DNA-sequencing libraries will be loaded on an Illumina MiSeq next generation sequencer. Sequence reads will be aligned to the reference genome for variant calling. All variants will be validated by Sanger sequencing of tumor DNA and their somatic origin will be confirmed by Sanger sequencing of the paired normal DNA, whenever available. We will analyze samples also at relapse whenever possible. All mutations that have clonally emerged at this time will be investigated by an ultra-deep next generation sequencing approach in the paired tumor sample collected at time of enrollment into the trial and that showed to be negative for the mutation. Tagged amplicons covering the mutated sequence will be obtained from genomic DNA. Purified amplicons will be quantified, diluted, pooled and loaded on the MiSeq next generation sequencer. To identify subclonal variants, the BackTracker algorithm will be employed, as previously performed.

   The needed DNA for this project will be extracted at the Institute of Oncology Research (IOR) in Bellinzona.
2. Diagnostic sections will be immune-stained with anti-NFκB1 (p105/p50) and anti-NFκB2 (p100/p52) antibodies to identify cases with canonical and/or non-canonical NFκB activation.

18.1.2.2 Start of analysis

Analysis will be performed at the end of the clinical trial (phase I and II). The data will then be available in six months.

18.1.2.3 Access to clinical data

It is needed to show the association between genetic lesions and response to treatment, therefore the access to clinical data is required.

18.1.3 Procedure (to be performed by the sites)

18.1.3.1 Required biological material

- Peripheral blood
- Tumor biopsies
  (Please note: baseline samples will be sent to the IOR in the context of the central pathology review (Prof, Stephan Dirnhofer, Institute for Pathology, University of Basel), sites only need to send tumor biopsy samples to the IOR at the time point of relapse (if applicable)
- Bone marrow biopsy samples

18.1.3.2 Scheduling of sampling

There will be a maximum of 5 time points for translational research sampling. An overview is given in the figure below.

1. Baseline
   - Peripheral blood (7 days before start of treatment) and bone marrow samples
   - Tumor diagnostic biopsies (baseline samples will be sent to the IOR by the responsible person of central pathology review (Prof. Stephan Dirnhofer, Institute for Pathology, University of Basel).
2. End of ibrutinib/bortezomib treatment
   - Peripheral blood
   - Tumor diagnostic biopsies (if available)
   - Bone marrow samples (only, if clinically indicated and if available).
3. Maintenance therapy (after 12 weeks)

- Peripheral blood

4. End of treatment
   - Peripheral blood
5. Relapse/progression
   - Peripheral blood
   - Tumor diagnostic biopsies (sections of paraffin embedded tissue, if available)
   - bone marrow samples (only, if clinically indicated and available).

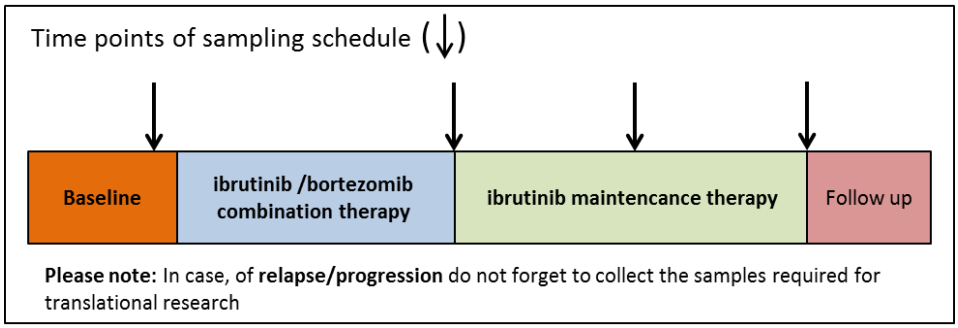


Figure 2: Scheduling of sampling

18.1.3.3 Sample preparation

Peripheral blood and bone marrow samples have to be drawn using normal EDTA and heparin tubes, respectively.

18.1.3.4 Sample storage before shipping

Peripheral blood and bone marrow samples have to be shipped on the same day or on the following day. Samples have to be stored at 4ºC.

18.1.3.5 Labelling and shipment

Labeling

All material (biopsies, peripheral blood and bone marrow) has to be clearly labeled SAKK 36/13,

- Type of material (peripheral blood / bone marrow / paraffin embedded tissue sections)
- UPN,
- Site
- Baseline, or end of combination therapy, or maintenance therapy, or follow up, or relapse
- date sampling
- Storage condition: 4°C (in case of peripheral blood and bone marrow samples), RT (in case of paraffin embedded tissue sections).

Labels are provided by the SAKK CC.

No tube material will be provided by the SAKK CC.

Shipment

No shipping material will be provided by the SAKK CC. Shipment will be paid by SAKK CC.

Samples can be shipped with cold packs using normal mail services.

Samples have to be sent with an accompanying letter to

SAKK 36/13
Dr. Francesco Bertoni, MD
Lymphoma and Genomics Research Program,
Institute of Oncology Research (IOR)
Via Vela 6, 6500, CH-Bellinzona
Phone +41918200367
Fax +41918200305
email: francesco.bertoni@ior.iosi.ch

The accompanying letter is available on the SAKK website (www.sakk.ch →Members → Trials →Lymphoma →SAKK 36/13). The parcels must not arrive on a weekend.

The accompanying letter must also be sent to the SAKK CC by fax (Fax: +41 31 508 41 42) or email (trials@sakk.ch) and to Dr. Bertoni by fax (Fax: +41 91 820 03 05) or email (frbertoni@mac.com or francesco.bertoni@ior.iosi.ch) on the day of shipment. Costs for shipment will be covered by SAKK.

18.2 Sample banking

Only if patient has given consent

Translational research

Samples/data of the research project described in section 18.1 will be banked and kept for a maximum of 20 years at the Institute for Oncology (IOR), Bellinzona (Switzerland) for future analysis in regard to Lymphoma according to the SAKK banking regulation which is based on the HRA [1].

The patient retains the right to have the sample material/data irreversibly anonymized at any time by contacting the PI according to the HRA and the applicable ordinances [1]. However, this anonymized material/data can be used for intended analysis.

The SAKK will be responsible for the anonymization of the sample(s)/data at the request of the patient through the PI. The SAKK will be responsible for the destruction of the sample(s) at the end of the storage period.

Any new analysis on these samples/data not planned in this protocol has to be approved by the SAKK board and by the relevant IEC.

Pathology

Remaining sections/data of the central pathology review (see section 17.2) will be stored at the Institute of Pathology in Basel (Switzerland) for indefinite period of time for future analysis according to the banking regulation of the pathology institute Basel which is based on the HRA [1].

The patient retains the right to have the sample material/ data irreversibly anonymized at any time by contacting the PI according to the HRA and the applicable ordinances [1]. However, this anonymized material/data can be used for analysis.

The SAKK will be responsible for the anonymization of the sample(s)/data at the request of the patient through the PI. The SAKK will be responsible for the destruction of the sample(s) at the end of the storage period.

Any analysis on these samples/data has to be approved by the SAKK board and by the relevant IEC.

19 DIAGNOSTIC SUBSTUDY

Not applicable

20 ECONOMIC EVALUATION

Not applicable

21 INDEPENDENT RESPONSE REVIEW

Not applicable

22 ETHICAL CONSIDERATIONS

The trial will be carried out in accordance with the principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the applicable Swiss HRA and its associated Ordinances and the requirements from the Swiss and European regulatory authorities [33, 50-53].

The protocol, the patient information and consent form, as well as all other trial-related documents shall be submitted to all involved IECs and competent authorities in agreement with local legal requirements for formal authorization. Any amendment to the protocol or patient information and informed consent will be submitted for authorization to these institutions. The decision of the regulatory authorities and competent authorities regarding the conduct of the trial will be made in written to the Sponsor prior trial initiation. Any substantial amendment to the protocol (except for safety reasons) can only be implemented at site after obtaining written authorization by the corresponding regulatory authorities.

The clinical trial can only begin once approval from all required authorities has been received by the sponsor. Patient recruitment at local sites can only take place after the site has officially been opened for accrual by the SAKK CC.

Sites in Switzerland have to adhere to the Swiss HRA and all applicable local regulatory guideline.

Please note, according the HRA and its applicable ordinances [1]: The regular end of the trial has to be reported in Switzerland to the IECs within 90 days upon trial termination. The premature end or interruption of the trial including the motives has to be reported to the IECs within 15 days upon permanent suspension of the trial. The final clinical study report has to be provided to the IECs and competent authority within one year after termination of the trial.

Sites in foreign countries have to adhere to local applicable national law, locally applicable regulatory guideline.

22.1 Risks/benefits

MCL remains an incurable disease with frequent relapses and no standard therapeutic options in case of relapse. Ibrutinib has a very significant single agent activity in B-cell lymphomas including relapsed mantle cell lymphomas. The compound is generally well tolerated and given the absence of a dose-limiting toxicity also when applied long-term, is well suited in this patient population. The non-overlapping toxicity offers the herein proposed combination with bortezomib, an established drug to treat relapsed MCL. The safety and tolerability of the combination treatment will be established in the phase I part of the trial.

The trial population is defined as patients with relapsed or refractory MCL who have received previous therapy lines of non-bortezomib-containing chemotherapy. The treatment offered in this trial may provide a significant clinical benefit. The potential benefit of treatment might be a prolonged remission and/or induction of longer remissions and/or a longer PFS.

The main identified adverse events associated with ibrutinib treatment include, nausea, diarrhea, low white blood cell count, bruises and rash. Rare and more severe side effects could be bleedings, liver- and heart problems. Bortezomib is also usually well tolerated. The main identified risks associated with bortezomib include asthenia, fatigue, peripheral neuropathy, low platelet count, temporary skin alterations at the injection site. Very rare are severe side effects at the heart, in form of allergic reactions, at the liver and lung. Some can be anticipated so that a mitigation of the risks can be performed.

In view of the documented risks, and in view of the overall potential benefit for patients suffering from MCL, the benefit-risk-balance for this trial is considered to be acceptable.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the trial.

22.2 Trial categorization

Clinical trial with IMP

The IMP is a medication with marketing authorization in EU and Switzerland. According to the Swiss HRA and its current Ordinance on clinical trials with an investigation medicinal product, this trial is classified as category B.

22.3 Patient information and informed consent

The informed consent procedure must conform to the guidelines on GCP issued by ICH and the applicable national or international law.

All patients will be informed of the aims and procedures of the trial, the possible AEs, how to react in case an AE occurs, and possible hazards to which he/she will be exposed. They will be informed as to the strict confidentiality of their patient data, but they need to know that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The investigator must provide the patient with sufficient opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence. The information provided shall be in a language intelligible to the patient and may not include any content that appears to waive any of the patient's legal rights, or appears to release the investigator, the sponsor, or the institution from liability for negligence.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the trial whenever he/she wants. This will not prejudice the patient's subsequent care.

Only, in case the patient agrees (informed consent form), the family doctor may be informed about the participation in the trial and/or may be contacted by the treating investigator to retrieve information about follow up.

Informed consent will be obtained once: before registration and prior to any protocol-specific procedures.

Informed consent shall be obtained on a written form approved by the local EC and signed and personally dated by the patient and the investigator. The patient information as well as a copy or original of the signed and dated informed consent will be handed to the patient. No inclusion of legally incompetent patients is permitted in this trial.

In case new results become available that shift the risk/benefit ratio, the patient should re-consent.

Patients refusing to accept non-mandatory translational projects can nevertheless participate in the trial.

22.4 Premature withdrawal

Patients have the right to refuse further treatment for any reason and at any time and they retain the right to have any sample material/ data irreversibly anonymized by contacting the PI. Patients who decide to withdraw from the trial will be informed that all data/samples collected until the time point of their withdrawal will be used. After analysis of the data/samples, the data/samples will anonymized according to the HRA and the applicable ordinances [1]. The anonymization according to HRA [1] can only be omitted, if an irreversible anonymization is not possible (already known at the beginning of the trial) and the patient at the time point of withdrawal explicitly renounces the right for anonymization.

For the patient's security, a last examination should be performed.

Patients may be withdrawn at any time from trial treatment at the discretion of the investigator due to a SAE, or based on any other relevant medical condition. The patient will then be transferred to the follow-up phase.

23 ADMINISTRATIVE CONSIDERATIONS

23.1 Insurance

The SAKK will indemnify patients for damages they have suffered as participants in the trial. For this purpose, SAKK has taken out a special insurance for clinical trials according to the categorization of the trial (category B) with Chubb Insurance Company of Europe SE, branch office Zollikerstrasse 141, 8034 Zürich, Switzerland.

23.2 Monitoring and auditing

All source data must be accessible for auditing and monitoring. Monitors and auditors will maintain patient confidentiality.

23.2.1 Monitoring strategy

This trial will be monitored. The SAKK is performing risk-adapted monitoring according to the concept developed by the ADAMON group [54]. Based on the risk analysis, for phase I an intermediate risk monitoring strategy has been chosen and low risk monitoring strategy for phase II. The different monitoring activities as well as the frequency of the visit are described in a trial-specific monitoring plan.

23.2.2 Auditing/inspecting

Authorities have the right to perform inspections, and the SAKK has the right to perform on-site auditing during working hours upon reasonable prior notice.

23.3 Quality control and quality assurance

Several procedures ensure the quality of the trial in compliance with applicable regulatory requirements, GCP and the protocol:

- Written standard operating procedures are implemented
- Personnel involved in conducting the trial is qualified by education, training and experience
- An updated staff list must be kept at the site (template available on the SAKK website)
- Validation of database and statistical analysis
- Quality control principles are implemented
- On-site monitoring (SDV, verification of informed consent etc.) by personnel designated by the SAKK
- Data captured online will be validated in real-time, yielding errors (for inacceptable data) and warnings (for possibly inconsistent data - these warnings may be overruled by the user).
- Audit trail of changes
- Medical data review by the coordinating investigator or a delegated person (all CRFs will be reviewed and checked on medical content)
- Pathology review
- Safety monitoring
- Accountability of ibrutinib and bortezomib
- Internal audit procedures

23.4 Trial activation procedure

Prior to activation, sites have to submit the following documents to the SAKK CC:

23.4.1 Swiss sites

- The signed and dated trial-specific agreement (TSA), indicating that they will fully comply with the protocol, including an estimation of their annual accrual and additional items
- Signed and dated up-to-date CV (including proof of GCP training) of the principal investigator
- Signed and dated protocol sign-off page for the principal investigator
- A copy of the signed and dated staff list
- A signed and dated "Basisformular / Formulaire de base" by the PI (the completed document will be provided by the SAKK CC to the site of the Lead-EC, only.)

Once all documents of a site are submitted to the SAKK CC, they will be forwarded to the involved ECs and Swissmedic**.**

The investigator will only be allowed to register patients into the trial after the ECs and Swissmedic have authorized the trial at the site and the SAKK CC has opened the site for accrual.

23.4.2 Foreign sites

Prior to activation, sites have at least to submit the following documents to the SAKK CC:

- The signed and dated TSA, indicating that they will fully comply with the protocol, including an estimation of their annual accrual and additional items
- Signed and dated up-to-date CV (including proof of GCP training) of the principal investigator
- Locally requested approval(s) of ethical committee(s) and competent authority
- Approved patient information and informed consent adapted for the site

The SAKK CC will ensure that all required documents will be submitted to the relevant EC and competent authorities, in agreement with the specificities defined in the contract with each foreign site.
Additional country specific documents (if applicable) that the sites have to provide to the SAKK CC prior to activation will be detailed described in the country specific Appendix respectively.

The investigator will only be allowed to register patients into the trial after the relevant ECs and competent authority have authorized the trial at the site and the SAKK CC has opened the site for accrual.

23.5 Local trial records

23.5.1 Investigator`s File

All trial-related correspondence should be filed in the Investigator's file. A suggested table of contents (according to ICH E6, chapter 8) is provided on the SAKK website (→ Members → Trials → Lymphoma → SAKK 36/13).

23.5.2 Useful tools

CRFs, drug order forms and accountability logs, documents required for EC approval, schedules of assessments etc. can be downloaded from the SAKK website (→ Members → Trials → Lymphoma → SAKK 36/13).

23.5.3 Record retention

The site will retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, drug inventory and destruction logs, and all other information collected during the trial. These documents were stored until at least 10 years after the termination of the trial. The end of this retention period will be communicated to the sites by the SAKK CC**.** For the patient trial records,

which are entered into the EDC system, the sponsor guarantees the access and availability of the data at any time at least 10 years after the termination of the trial.

Longer retention may be required for foreign sites according to local applicable law.

In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer will be given to the SAKK CC. The SAKK will notify the concerned regulatory authorities.

23.6 Trial registration

The SAKK will register the trial at www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at www.kofam.ch. With the participation of sites in the EU it will also be registered with the EudraCT database (https://eudract.emea.europa.eu) of clinical trials.

23.7 Participation of local and foreign sites

A list of sites and investigators that have agreed to participate in the trial are given in a separate document which can be downloaded from www.sakk.ch (→ Members section → Trials → Lymphoma → SAKK 36/13.

Separate trial-specific agreements will be issued for participating sites outside of Switzerland.

23.8 Modifications of the protocol

23.8.1 Substantial amendment

Any amendments which may have an impact on the conduct of the trial, the potential benefit of the trial, or may affect patient safety, including changes of trial objectives, trial design, patient population, sample sizes, trial procedures, or significant administrative aspects. Such an amendment must be accepted by the SAKK Board and must receive the authorization of the concerned IEC and competent authority prior to implementation.

23.8.2 Safety amendment

A safety amendment is a special kind of substantial amendment which is released when it is necessary to eliminate immediate hazards to trial participants. A safety amendment requires immediate implementation at local sites and is submitted in parallel for authorization to the IECs and competent authority.

23.8.3 Non substantial amendment

Non-substantial amendments such as minor corrections and/or clarifications that have no effect on the way the trial is conducted have to be submitted to the IECs for approval once a year, along the yearly submission of the safety report. Non-substantial amendments which affect the evaluation of the competent authority have to be submitted as soon as possible to the competent authority.

24 PUBLICATION

The results of the trial will be published according to the current version of the SAKK publication guidelines (available on the SAKK website). The SAKK publication guideline guarantees the freedom of reporting of the participating physicians independent of the current version.

25 CONFIDENTIALITY

25.1 Copyright

The information contained in this protocol is copyright protected by the SAKK (Swiss Group for Clinical Cancer Research). This information is given for the needs of the trial and must not be disclosed to persons outside of the SAKK without prior written consent of the SAKK CC.

25.2 Confidentiality

Trial-related data of the patient will be provided in a coded manner to the SAKK CC. The names of the patients will not be disclosed to the SAKK CC. A unique patient number (UPN) will be attributed to each patient randomized/registered into the trial.

Identification of patients must be guaranteed at the site. For this purpose, sites are requested to use the patient screening and enrollment and the patient identification lists specifically produced for the trial (available on the SAKK website). In order to avoid identification errors, the year of birth and the UPN have to be provided on the CRFs. Patient confidentiality will be maintained according to applicable legislation. Patients must be informed of, and agree to, data and material transfer and handling, in accordance with Swiss data protection law.

All information concerning the IMPs supplied by Janssen in connection with this trial and not previously published is considered confidential and proprietary information.

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27 APPENDICES

Appendix 1 Criteria for Evaluation of Response in Non-Hodgkin's Lymphoma

Refer to the applicable literature, Cheson, et al 1999 [32, 55] for CT/MRI measurements.

App 1.1 Methods of assessment

For this trial, a CT scan (with contrast unless contraindicated) is required for tumor assessment. Additional PET is allowed. Magnetic resonance imaging (MRI) may be used to evaluate sites of disease that cannot be adequately imaged using CT and if contrast is not appropriate for patients according the treating physician.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline, end of ibrutinib/bortezomib treatment, in ibrutinib maintenance therapy and during follow-up.

App 1.1.1 CT scan

Contrast enhanced CT scans with IV contrast agent and oral (if clinically needed) area required for tumor assessments. CT scans should be performed of the chest, abdomen, and pelvis and any other disease sites (e.g., neck).

App 1.1.2 MRI

Magnetic resonance imaging (MRI) may be used to evaluate sites of disease that cannot be adequately imaged using CT, or if preferred by local health care regulations. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations. For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

App 1.1.3 PET

Tumor assessment: PET scans are allowed, but do not substitute for CT and MRI imaging. Therefore the Deauville Score for PET positivity are not defined for this protocol as the PET scans are only allowed and not mandatory.

App 1.2 Definition of measurability

Measurable lesions are defined as ≥ 11 mm in the greatest transverse diameter (GTD) and clearly measurable in two dimensions. For an example of the measurement of GTD please see figure 3 below.

All other lesions (including nodal, extranodal and assessable disease) should be followed as non-measured disease (e.g. cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions or ascites).

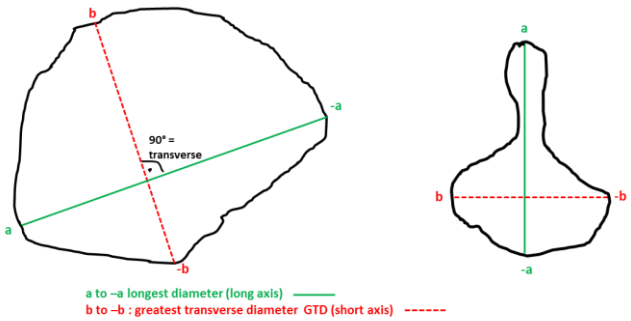

Figure 3: The larger of these two axes, which corresponds to the largest distance between antipodal points on the drawing, is called the long axis or longest diameter (a to –a). The greatest transverse diameter (GTD) corresponds to the short axis (b to –b), which has to be perpendicular to the long axis.

App 1.3 Selection of lesions

App 1.3.1 Selection of measurable lesions

Up to a maximum of 6 Target lesions (TL) representative of all involved regions, should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of product of diameters (SPD) for all target lesions will be calculated and reported at baseline. This sum will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

These nodes or target lesion should be selected according to the following features:

a) they should be clearly measurable in at least two perpendicular dimensions,
b) they should be from as disparate regions of the body as possible, and
c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

App 1.3.2 Selection of non-measurable lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the CRF (e.g. "multiple liver metastases").

App 1.4 Evaluation of lesions

App 1.4.1 Evaluation of measurable lesions

All target lesions will be measured at each tumor assessment, and the sum of product of their diameters will be compared to previous assessments in order to assign the response status.

App 1.4.2 Evaluation of non-measurable lesion

All non-target lesions will be assessed at each tumor assessment and categorized as absent or regressed to normal size respectively.

App 1.4.3 Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumor. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan.

Lesions found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

App 1.5 Determination of response

App 1.5.1 Complete Response (CR)

A complete response requires the following:

a) Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities definitely assignable to NHL
b) All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
c) The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
d) Bone marrow, if positive at baseline, must be histologically negative for lymphoma.

App 1.5.2 Complete Response, unconfirmed (CRu)

CRu includes those patients who fulfill criteria a and c above, but with the following feature:

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

App 1.5.3 Partial Response (PR)

A partial response requires the following:

a) ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
    a. When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value
    b. When a lesion is no longer visible assign 0 mm x 0 mm
    c. for a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
b) No increase in the size of the other nodes, liver, or spleen
c) Splenic and hepatic nodules must regress by at least 50% in the SPD.
d) With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
e) No new sites of disease

App 1.5.4 Stable Disease (SD)

Stable disease is defined as less than a PR (as described above) but not PD (see below).

App 1.5.5 Relapsed disease (after CR, CRu)

A relapsed disease requires the following:

a) Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.
b) ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

App 1.5.6 Progressive disease (after PR or SD)

Progressive Disease is defined as follows:

a) ≥50% increase from nadir in the SPD of any previously identified abnormal node
b) Appearance of any new lesion during or at the end of therapy

App 1.5.7 Summary - Criteria for Evaluation of Response in Non-Hodgkin's Lymphoma

Response Category	Organ enlargement	Lymph nodes	Lymph Node Masses	Bone Marrow	New lesions
CR	Normal or Spleen regressed in size and not palpable (if enlarged before therapy) Liver and kidneys decreased in size (if enlarged before therapy)	Regressed to normal size, i.e. for **nodes > 1.5 cm** before therapy: ≤ 1.5 cm in their greatest transverse diameter (GTD) for **nodes between 1.1 to 1.5 cm** GTD: decreased to ≤ 1 cm or by more than 75% in the sum of the products of the greatest diameters (SPD)	Regressed to normal size, i.e. for **masses > 1.5 cm** before therapy: ≤ 1.5 cm in their greatest transverse diameter (GTD) for **masses between 1.1 to 1.5 cm** GTD: decreased to ≤ 1 cm or by more than 75% in the sum of the products of the greatest diameters (SPD)	Normal	No
CRu	See under CR	See under CR	A residual **lymph node mass > 1.5 cm** in GTD before therapy has regressed > 75% in the SPD. Individual lymph node that were previously confluent must have		No

Response Category	Organ enlargement	Lymph nodes	Lymph Node Masses	Bone Marrow	New lesions
			regressed by more than 75% in their SPD		
PR	No increase in size of spleen decrease in intensity for PET (if done)	- 50 % decrease in SPD of the selected nodes No increase in the size of the other nodes • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When a lesion is no longer visible assign 0 mm x 0 mm • For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation Splenic and hepatic nodules must regress by at least 50% in the SPD (if involved)	50% decrease in SPD of the selected nodal masses	Irrelevant	No
SD			Stable disease is defined as less than a PR (as described above) but not progressive disease (see below).		
Relapse (after CR or CRu)	Enlarging spleen or increase in intensity for PET (if done)	≥50% increase in the size (GTD) of previously involved sites or ≥50% increase in greatest diameter of any previously identified node greater than 1.1 cm in its short axis	≥50% increase in the size (GTD) of previously involved sites or ≥50% increase in the SPD of more than one previously identified node.	Reappearance	Yes
PD (after PR or SD)	Enlarging spleen or increase in intensity for PET (if done)	≥50% increase from nadir in the SPD of any previously identified abnormal node	≥50% increase from nadir in the SPD of any previously identified abnormal site	Reappearance	Yes

Appendix 2 Calculation of BSA corrected creatinine clearance

The creatinine clearance rate (Cr) should be calculated according to the formula of Cockcroft-Gault [56] and corrected with the constant 1.73 and the body surface area (BSA) of the patient.

Cockcroft-Gault formula:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times \text{constant}}{\text{serum creatinine (in µmol/L)}}$$

Creatinine clearance $_{\text{Cr-corrected}}$ (ml/min/1.73m^2) = (C_{CR} x 1.73) / BSA

Constant is 1.04 for females and 1.23 for males

Appendix 3 WHO performance status

Performance status should be calculated according to the ECOG/WHO definition [57].

0 Fully active, able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

2 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 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 Dead.

Appendix 4 - Calculation of body surface area (BSA)

The DuBois & DuBois Formula:

$$BSA_{\text{Du Bois}}\ (m^2) = 0.20247 \times \text{Height(m)}^{0.725} \times \text{Weight(kg)}^{0.425}$$

Appendix 5 New York Heart Association (NYHA) classification [58]

Class I	Patients have cardiac disease but without significant limitations of physical activity. Ordinary activity does not cause undue fatigue, palpitations, dyspnea (shortness of breath), or anginal pain.
Class II	Patients have slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class III	Patients have marked limitations of physical activity. They are comfortable at rest, however less than ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class IV	Patients are unable to carry out any physical activity without symptoms referred to above. Some Class IV patients may have symptoms at rest.

Source: The Criteria Committee of the New York Heart Association [58]

Appendix 6 Schedule of assessments, treatments and documentation (Phase I)

An adaptable scheduler is available on the SAKK website (www.sakk.ch, members). Phase I was closed for accrual on 18th November 2016.

	Screening phase		Combination treatment (phase I) (1 cycle= 21 days)																		After end of the combination therapy and after start of maintenance therapy[g,e]	Maintenance therapy[e] 1 course = 28 days				End of trial treatment visit (latest 14 days after last dose of trial medication or prior to start of next therapy (whatever is first)	Follow up Phase
Cycle or course			**1**			**2**			**3**			**4**			**5**			**6**				7	8	9	etc		Every 12±3 weeks
Week		-1 to 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		19	23	27	31		
Day	-30 to 0	-7 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15		127	155	183	211		
Ibrutinib (according to dose level)			oral intake once daily																			orally intake once daily					
Bortezomib			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11								
Informed consent	X[l]																										
Diagnosis /Tumor histology (by local pathologist)	X[l]																										
Medical history (including baseline baseline symptoms, previous therapies, location of tumor sites)	X																										
Vital signs (measurement of body temperature, heart rate, and blood pressure)		X	X[f]	X	X	X	X		X	X		X	X		X	X		X	X			X	X	X	X	X	
Physical examination (incl. WHO PS[1], height[2], weight[3])	X[1,2,3]	X[1,3]	X[f,1,3]			X[1,3]			X[1,3]			X[1,3]			X[1,3]			X[1,3]				X[1,3]	X[1,3]	X[1,3]	X[1,3]	X	X
Radiological assessment (CT/MRI) and assessment of disease related symptoms	X										X										X				X[c]	X	X[m]
Bone marrow biopsy; if applicable: material of bone marrow biopsy for translational research (if patient has given consent only, Swiss sites only)	X																				X[d]					X[d]	
Inclusion/exclusion criteria	X																										
Echocardiography (or MUGA) and ECG	X																										
Hematological values (hemoglobin, leucocytes including neutrophils and lymphocytes, platelets)	X	X	X[f,a]	X[a]	X[a]	X[a]	X		X	X		X	X		X	X		X	X			X	X	X	X	X	
Hepatic function (AP, ALT, AST, bilirubin, albumin) and LDH (only at baseline)	X		X[f]			X			X			X			X			X				X	X	X	X		
Renal function (calc. creatine clearance)	X		X[f]			X			X			X			X			X				X	X	X	X		
Coagulation parameters INR/Quick	X																										
IgA, IgG, IgM and Beta-2 microglobulin	X								X									X							X[c]	X	
HIV test, Serology of Hepatitis B and C	X																										
Pregnancy test (if necessary)[b]	X	X																									
Tumor re-biopsy (not mandatory)	X																										
Dispensing of ibrutinib			X			X			X			X			X			X				X	X	X	X		
Check patient diary						X			X			X			X			X				X	X	X	X	X	
Survival status																											X
Disease status																											X
Further MCL treatments																											X
Blood sampling for translational research (if patient has given consent only; Swiss Sites only)		X																				X			X	X	
Adverse events (AE)	**Record throughout trial phase (until 30 days after treatment end)**																										Fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment

a: cycle 1 weekly (incl. Day 1 of cycle 2) or in case of G3 hematologic toxicity of neutrophils or platelets more frequently
b: for women of child-bearing potential: serum β-human chorionic gonadotropin (β-hCG) or urine pregnancy test
c: every 12 +/- 1 weeks after starting the trial treatment or upon clinical indication
d: only if involved at baseline and in case of CR
e: in case no maintenance therapy is given, please proceed immedeatly to "End of Treatment" and "Follow Up" procedures
f: for day 1, cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 2 days of the first dose of trial medication.
g: after end of ibrutinib/bortezomib treatment, patients can directly receive ibrutinib maintenance therapy if there is the **no** clinical impression of progressive disease
h: only if no bone marrow biopsy is performed and in case of CR and only at the end of combination therapy
l: these procedures can be done also before 30 days
m: only for patients without documented progressive disease

Appendix 7 Schedule of assessments, treatments and documentation (Phase II)

An adaptable scheduler is available on the SAKK website (www.sakk.ch, members). Phase II was opened for accrual on 18th November 2016.

	Screening phase		Combination treatment (phase I) (1 cycle= 21 days)																		After end of the combination therapy and after start of maintenance therapy[g,e]	Maintenance therapy[e] 1 course = 28 days				End of trial treatment visit (latest 14 days after last dose of trial medication or prior to start of next therapy (whatever is first)	Follow up Phase
Cycle or course			**1**			**2**			**3**			**4**			**5**			**6**				**7**	**8**	**9**	**etc**		
Week		-1 to 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		19	23	27	31		**Every 12±3 weeks**
Day	-30 to 0	-7 to 0	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15		127	155	183	211		
Ibrutinib (according to dose level)			oral intake once daily																			**orally intake once daily**					
Bortezomib			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11			s.c injection on d1, d4, d8 and d11								
Informed consent	X[l]																										
Diagnosis /Tumor histology (by local pathologist)	X[l]																										
Medical history (including baseline baseline symptoms, previous therapies, location of tumor sites)	X																										
Vital signs (measurement of body temperature, heart rate, and blood pressure)		X	X[f]			X			X			X			X			X				X	X	X	X	X	
Physical examination (incl. WHO PS[1], height[2], weight[3])	X[1,2,3]	X[1,3]	X[f,1,3]			X[1,3]			X[1,3]			X[1,3]			X[1,3]			X[1,3]				X[1,3]	X[1,3]	X[1,3]	X[1,3]	X	X
Radiological assessment (CT/MRI) and assessment of disease related symptoms	X										X										X				X[c]	X	X[m]
Bone marrow biopsy; if available: material of bone marrow biopsy for translational research (if patient has given consent, Swiss sites only)	X																				X[d]					X[d]	
Inclusion/exclusion criteria	X																										
Echocardiography (or MUGA) and ECG	X																										
Hematological values (hemoglobin, leucocytes including neutrophils and lymphocytes, platelets)	X	X	X[f]	X		X	X		X	X		X	X		X	X		X	X			X	X	X	X	X	
Hepatic function (AP, ALT, AST, bilirubin, albumin) and LDH	X		X[f]			X			X			X			X			X				X	X	X	X		
Renal function (calc. creatine clearance)	X		X[f]			X			X			X			X			X				X	X	X	X		
Coagulation parameters INR/Quick	X																										
IgA, IgG, IgM and Beta-2 microglobulin	X								X									X							X[c]	X	
HIV test, Serology of Hepatitis B and C	X																										
Pregnancy test (if necessary)[b]	X	X																									
Tumor re-biopsy (not mandatory)	X																										
Dispensing of ibrutinib			X			X			X			X			X			X				X	X	X	X		
Check patient diary						X			X			X			X			X				X	X	X	X	X	
Survival status																											X
Disease status																											X
Further MCL treatments																											X
Blood sampling for translational research (**if patient has given consent only; Swiss Sites only)**		X																				X			X	X	
Adverse Events	**Record throughout trial phase (until 30 days after treatment end)**																										Fatal, life-threatening and other medically significant events possibly, probably or definitely related to late effects of trial treatment

b: for women of child-bearing potential: serum β-human chorionic gonadotropin (β-hCG) or urine pregnancy test
c: every 12 +/- 1 weeks after starting the trial treatment or upon clinical indication
d: only if involved at baseline and in case of CR
e: in case no maintenance therapy is given, please proceed immedeatly to "End of Treatment" and "Follow Up" procedures
f: for day 1, cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 2 days of the first dose of trial medication.
g: after end of ibrutinib/bortezomib treatment, patients can directly receive ibrutinib maintenance therapy if there is the **no** clinical impression of progressive disease
l: these procedures can be done also before the 30 days
m: only for patients without documented progressive disease