TRIANGLE

autologous **T**ransplantation after a **R**ituximab/**Ibrutinib**/**A**ra-c containing i**N**duction
in **G**eneralized mantle cell **L**ymphoma –
a randomized **E**uropean mcl network trial

EudraCT-Number:	2014-001363-12
Protocol Code:	TRIANGLE
Protocol Version and Date:	Version 1.6_19.November 2019
Protocol Amendment:	4
Sponsor:	Klinikum der Universität München, Germany

Table of Contents

1 General information

1.1 Key roles and contact information

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1.2 Signatures

1.2.1 Protocol Signature Page Sponsor Level

Prof. Dr. med. Martin Dreyling
Sponsor Delegated Person and Coordinating Principal Investigator Germany

Munich, Date	Signature

1.2.2 Protocol Signature Page Country Level

Country to be added: _____

Printed Name of Coordinating Investigator: _____

_____ _____

City, Date Signature

1.2.3 Protocol Signature Page Center Level

[Signatures of local investigators will be obtained before study start in the respective participating sites.]

Local Site Name and Address:
(Printed Letters or Stamp)

Signature of Local Investigator	Date
Printed Name of Local Investigator	

By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.
I confirm that I was informed by a scientist, responsible for the pharmacological-toxicological test, about the findings of the test and the foreseeable risks involved in the clinical trial.

1.3 Study Synopsis

Title	**TRIANGLE**: autologous **T**ransplantation after a **R**ituximab/**Ibrutinib**/**A**ra-c containing i**N**duction in **G**eneralized mantle cell **L**ymphoma – a randomized **E**uropean MCL Network trial
Short title	**TRIANGLE**
EudraCT-no.	**2014-001363-12**
Trial design	Randomized, three-arm, parallel-group, open label, international phase III trial comparing six alternating courses of R-CHOP/R-DHAP (one cycle every 21 days) followed by ASCT versus the combination with ibrutinib in induction and maintenance (2 years) or the experimental arm without ASCT **Study Overview (Figure 1 and 2)**
Number of subjects	Up to 870 patients
Number of sites	Up to 250 sites internationally
Target population	Untreated patients (≥ 18 and ≤ 65 years) with mantle-cell lymphoma (MCL)
Study Duration	The maximal trial duration will be up to 10 years with up to 5 years recruitment. The trial may stop earlier based on the result of pre-planned interim analyses.
Trial participation duration for individual patient	The maximal trial participation duration per patient will be up to 10 years (18 weeks induction therapy, 6 weeks ASCT, 2 years Ibrutinib-Maintenance, observation until progression, and follow-up until the end of the trial)
Investigational medicinal product (IMP)	Trade Name: Imbruvica Substance: Ibrutinib Manufacturer: Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC.
Inclusion criteria	All patients must meet the following criteria: • Histologically confirmed diagnosis of MCL according to WHO classification • suitable for high-dose treatment including high-dose Ara-C • Stage II-IV (Ann Arbor) • Age ≥ 18 years and ≤ 65 years • Previously untreated MCL • At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations. • ECOG/WHO performance status ≤ 2 • The following laboratory values at screening (unless related to MCL): – Absolute neutrophil count (ANC) ≥1000 cells/μL

	– Platelets ≥100,000 cells/μL – Transaminases (AST and ALT) ≤3 x upper limit of normal (ULN) – Total bilirubin ≤2 x ULN unless due to known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome]) – Creatinine ≤2 mg/dL or calculated creatinine clearance ≥ 50 mL/min • Written informed consent form according to ICH/EU GCP and national regulations • Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods (combined oral contraceptives using two hormones, contraceptive implants, injectables, intrauterine devices, sterilized partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive caps) while on study; this should be maintained for 90 days after the last dose of study drug and 12 months after the last dose of rituximab
Exclusion criteria	Any potential subject who meets any of the following criteria will be excluded from participating in the study. • Major surgery within 4 weeks prior to randomization. • Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon). • History of stroke or intracranial hemorrhage within 6 months prior to randomization. • Requires treatment with strong CYP3A4/5 inhibitors. • Any life-threatening illness, medical condition, or organ system dysfunction, which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk. • Vaccinated with live, attenuated vaccines within 4 weeks prior to randomization. • Known CNS involvement of MCL • Clinically significant hypersensitivity (e.g., anaphylactic or anaphylactoid reactions to the compound of ibrutinib itself or to the excipients in its formulation) • Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies • Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy according to trial protocol • Serious concomitant disease interfering with a regular therapy according to the study protocol: – Cardiac (Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)

	– Pulmonary (e.g. chronic lung disease with hypoxemia) – Endocrinological (e.g. severe, not sufficiently controlled diabetes mellitus) – Renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min) – Impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2,0 mg/dl unless due to Morbus Meulengracht (Gilbert-Meulengracht-Syndrome) • Positive test results for chronic HBV infection (defined as positive HBsAg serology) (mandatory testing) • Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBSAb) after vaccination are eligible. • Positive test results for hepatitis C (mandatory hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA • Patients with known HIV positive infection (mandatory test) • Prior organ, bone marrow or peripheral blood stem cell transplantation • Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or in situ uterine cervix cancer • Pregnancy or lactation • Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule • Subjects not able to give consent • Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial • Participation in another clinical trial within 30 days before randomization in this study.
Scientific rationale	According to current European guidelines (Dreyling, Ann Oncol 2014), the standard of care in younger patients with mantle cell lymphoma (MCL) is a dose-intensified approach with a cytarabine containing immunochemotherapy induction followed by autologous transplantation (ASCT; Hermine, ICML 2013). Ibrutinib has recently shown impressive efficacy data in relapsed MCL while tolerability was rather favorable (Wang, NEJM 2013). Based on these prerequisites, our study proposal challenges the current standard of care and questions, whether the addition of ibrutinib (arm A+I) to the standard (control arm A) results in a superior clinical outcome. In addition, we investigate whether ASCT which sometimes is hampered by short and long term toxicity is still superior to a (hopefully much better tolerated) conventional treatment without ASCT

	and with the addition of ibrutinib in induction and maintenance (duration 2 years, arm I). As so far, combination data are only available with the R-CHOP regimen, ibrutinib is only applied in combination with R-CHOP. There will be an initial safety run-in phase of 50 patients which will be closely monitored for the observed toxicities during induction. Analysis of minimal residual disease (MRD) will play a critical role in identifying specific patient subpopulations which may be especially prone to one of the three therapeutical strategies. According to the recently completely recruited LyMa trial rituximab maintenance may be added to all 3 study arms depending on national guidelines.
Objectives and Endpoints	***Primary Objective:*** To establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP+ibrutinib /R-DHAP followed by ASCT and ibrutinib maintenance (experimental arm A+I), and R-CHOP+ibrutinib /R-DHAP followed by ibrutinib maintenance (experimental arm I) as future standard based on the comparison of the investigator-assessed failure-free survival (FFS). ***Primary Endpoint:*** FFS defined as time from randomization to stable disease at end of immuno-chemotherapy, progressive disease, or death from any cause. ***Secondary Objectives:*** • To compare the efficacy of the three treatment arms in terms of secondary efficacy endpoints • To determine the safety and tolerability of ibrutinib during induction immuno-chemotherapy and during maintenance and to compare the safety profile of the three treatment arms in terms of secondary toxicity endpoints ***Secondary Efficacy Endpoints:*** • Overall survival (OS) • Progression-free survival (PFS) from randomization, from end of induction immuno-chemotherapy in patients with CR or PR at end of induction immuno-chemotherapy, and from the staging 6 weeks after end of induction assessment (at month 6) • Overall response and complete remission rates at midterm, at end of induction, 3 months after end of induction immuno-chemotherapy (at month 6) • PR to CR conversion rate during follow-up after end of induction immuno-chemotherapy ***Secondary Toxicity Endpoints:***

- Rates of AEs, SAEs, and SUSARs by CTC grade (Version 4.03) during induction immuno-chemotherapy and during periods of follow-up after response to immune-chemotherapy
- Cumulative incidence rates of SPMs

Exploratory Objectives:

- To compare feasibility of ASCT in arm A+I vs. arm A
- To compare minimal residual disease status between the three treatment groups
- To determine the impact of ibrutinib during induction immuno-chemotherapy and during maintenance therapy on the minimal residual disease status
- To determine the prognostic value of minimal residual disease status
- To determine the prognostic value of positron emission tomography with fluorine 18-fluorodeoxyglucose
- To determine clinical and biological prognostic and predictive factors
- To determine the role of total body irradiation (TBI) in ASCT conditioning

Exploratory Endpoints:

- Rate of successful stem cell mobilisations (success: separation of at least $2x2x10^6$ CD34-positive cells, including a back-up)
- Rate of molecular remissions (MRD-negative patients) at midterm, at end of induction immuno-chemotherapy, and at staging time-points during follow-up in patients with remission after end of induction immuno-chemotherapy
- Time to molecular remission from start of therapy
- Time to molecular relapse for patients in clinical and molecular remission after end of induction immuno-chemotherapy
- RD (remission duration) in FDG-PET negative or positive patients after induction and ASCT

Exploratory objectives may be evaluated only in a subset of patients according to local standards and resources.

Regimen, Frequency, Dose and Route of Administration

ARM A: Standard of Care
Alternating 3 cycles R-CHOP / 3 cycles R-DHAP induction followed by ASCT (THAM or BEAM)

Induction: Alternating 3 x R-CHOP / 3 x R-DHAP, every 21 days,

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or 1 I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/m^2	D 1 I.V. 24 h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin 130 mg/m^2	D 1 I.V.)
		G-CSF 5µg/kg	D6 daily SC*

* G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l
Alternatively pegfilgrastim may be applied once at D6

Stem cell apheresis after the last cycle R-DHAP

ASCT conditioning (within 2 weeks after end of induction visit):
THAM or BEAM, stratified per site before trial activation at site

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m^2 q12h	D –4, –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5mg/kg twice a day D-7) may be considered based on a retrospective EBMT comparison[1]

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

Experimental Arm A+I
Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by ASCT (THAM or BEAM) and 2 years Ibrutinib-Maintenance

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cycles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or 1I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/ m^2	D 1 I.V. 24 h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin130mg/m^2	D1 I.V.)
Ibrutinib 560mg	D 1-19 oral	G-CSF 5µg / kg	D 6 daily SC*

*** G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l Alternatively pegfilgrastim may be applied once at D6**

Stem cell apheresis after the last cycle R-DHAP

ASCT conditioning (within 2 weeks after end of induction visit):
THAM or BEAM, stratified per site before trial activation at site

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m^2 q12h	D –4, –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5mg/kg twice a day D-7) may be considered based on a retrospective EBMT comparison[1]

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), for 2 years, see above

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

Experimental Arm I
Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by 2 years Ibrutinib-Maintenance

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cycles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/m^2	D 1 I.V. 24 h
Predniso(lo)ne 100 mg	D 1-5oral	(alternatively Oxaliplatin 130mg/m^2	D 1 I.V.)
Ibrutinib 560mg	D 1-19oral	G-CSF 5µg / kg	D6 daily SC*

* G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l
Alternatively pegfilgrastim may be applied once at D6

Since no ASCT is applied in this arm, stem cell apheresis is not planned but may be performed due to local standards.

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), 2 years

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

Data management

All data will be included in an e-CRF via a safe internet access. The data will be entered by the local study team.

Assessments of :

- **Efficacy**

Response assessment at midterm (after 4 cycles), at end of induction, 6 weeks after end of induction response assessment, and thereafter half-yearly for 2 years and thereafter yearly until progression

- **Safety**

During a safety run-in phase, 50 patients will be fully monitored. If no unexpected toxicity has been observed, subsequent patients will be monitored only for patient informed consent, grade III/IV toxicities and SAEs as well as remission status.

Statistical methods

– **Statistical tests**

Three pairwise one-sided statistical hypothesis tests will be performed using the log-rank statistic for FFS. The evaluation will be performed based on the intention to treat. The hypotheses are as follows:

FFS comparison	Null Hypothesis	Alternative Hypothesis
A vs. I	A not superior to I	A superior to I
A+I vs. A	A+I not superior to A	A+I superior to A
A+I vs. I	A+I not superior to I	A+I superior to I

For each pairwise test, the local significance level will be 0.05/3, such that a global significance level of 5% is maintained (Bonferroni-correction for multiple testing).
The trial is planned to be powered to detect a superiority of A compared to I of 16% in FFS at 5 years (64.8% vs. 48.5%, hazard ratio 0.60) with a probability of 95%. These differences are based on the clinical assumption that only a major benefit (>15% difference of FFS at 5 years) justifies the application of a myeloablative consolidation with potential late toxicities. It is also planned to detect a superiority of A+I vs. A and of A+I vs. I of 12% at 5 years (77.1% vs. 64.8% failure free, hazard ratio 0.60) with a probability of 90% each.

– **Interim analyses and early stopping rules**

Regular pre-planned interim analyses will be performed for each pairwise comparison half-yearly. The multiple testing correction for interim analyses will be performed using truncated sequential probability ratio tests (Whitehead, 1985). If the statistical monitoring decides for superiority of A compared to I, allocation to arm I will be closed prematurely, and the comparison of A+I vs. A will be continued until its decision. If the true hazard ratio of A vs. I is 0.60, 0.53, or 0.46, the median duration until the decision for superiority of A vs. I will be 5, 4, or 3.25 years, respectively. If the statistical monitoring for A vs. I decides for the null hypothesis, allocation to arm A will be closed prematurely, and the comparison of A+I vs. I will be continued until its decision. If the true hazard ratio of A vs. I is 1.0, 1.29, or 1.67, the median time until a decision for of A vs. I will be 4.75, 3.75, or 3.5 years, respectively. If the true hazard ratios are 1.0 for A vs. I and 0.6 for A+I vs. A, the median trial duration will be 6.5

years. The maximal trial duration will be 10 years (5 years of recruitment and 5 years additional follow-up).

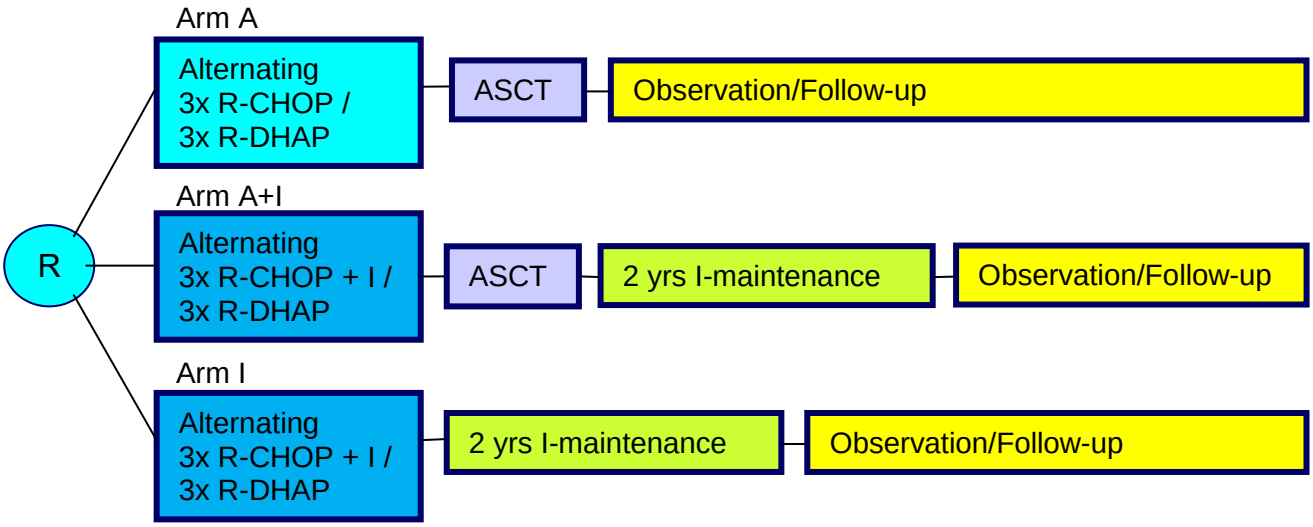
– **Decision for new standard**

Based on the results for the three pairwise statistical tests, the formal decision for the new standard will be taken according to the following procedure:

Test FFS A vs. I	**Test FFS A+I vs. A**	**Test FFS A+I vs. I**	**Future Standard**
A not significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A+I**
A not significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**

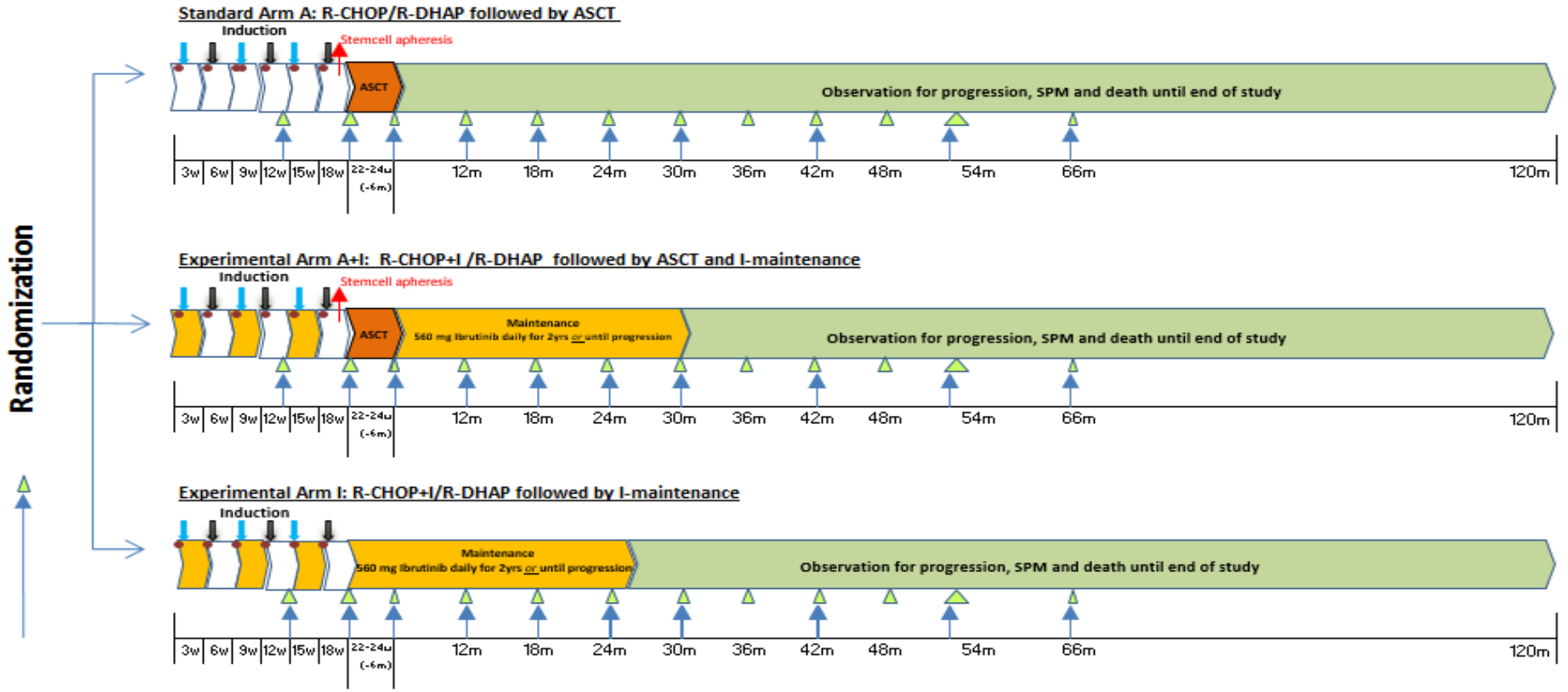
The final decision for a new standard will be based on this formal strategy taking into account all available clinical information at that time point.

Figure 1: Trial Design



According to the recently completely recruited LyMa trial rituximab maintenance may be added to all 3 study arms depending on national guidelines.

Figure 2: Study flow chart



Rituximab
CHOP
DHAP
ASCT THAM or BEAM
Ibrutinib
Stemcell apheresis
MRD
CT mandatory (optional PET)

Response Evaluation: CT (mandatory) // MRD // optional PET

Initial	CT and MRD	Before randomization
Midterm	CT and MRD	After completing cycle 4; before starting cycle 5 // appr. week 11
End of Induction	CT and MRD	After completing 6 cycles induction treatment // appr. week 18
pASCT	CT and MRD	Arm A and A+I: 3-5 weeks after ASCT // Arm I: 4-6 weeks after completing cycles
Maintenance / Observation	CT	Every 6 months for 2 years after "p-ASCT"-Evaluation, then yearly observation until 5 years. Thereafter according to clinical routine **and** on suspicion of **SPM or progression** until the end of the study.
	MRD	Every 6 months for 4 years and once 5 years after "pASCT"-Evaluation time point.

Follow-Up after treatment stop without progression – with or without treatment outside the protocol.

Treatment stop (e.g. dute to toxicity) without further treatment outside the protocol and without progression of the disease: **MRD and CT for Response as in normal follow-up.**
Discontinuation of therapy and with further treatment outside the protocol without progression of the disease patients are observed in normal follow-up (as after completion of maintenance therapy): **CT for Response as in normal follow-up.** MRD under the decretion of the site, but has not to be performed necessarily.

SD or PD: No study specific treatment, only follow-up for survival

1.4 Schedule of treatment and assessments

Treatment Arm A

		Induction Therapy																							Observation period											
Schedule of Treatment and Assessments ARM A: Altering 3xR-CHOP/3xR-DHAP followed by ASCT and observation	Baseline D -28 till D 0	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 6	Cycle 2 Day 8	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 4 Day 6	Cycle 4 Day 8	**Cycle 4 Day 15 Midterm Evaluation**	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 6 Day 6	Cycle 6 Day 8	Cycle 6 Day 10 - Apheresis	**Cycle 6 Day 21 End of Induction Evaluation**	THAM or BEAM D -7	THAM or BEAM D 0	THAM or BEAM D 8	THAM or BEAM D 15	THAM or BEAM D 21 *10	**3 to 5 weeks after ASCT p ASCT Evaluation**	Months 12	Months 18	Months 24	Months 30	Months 36	Months 42	Months 48	Months 54	Months 66	**Months 78; every 12 months thereafter until end of trial**	For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until END of TRIANGLE trial. For details see chapter 11.9.	Patients in Follow-Up after treatment stop without progression: (For details see chapter 11.8.) -without further treatment outside protocol: MRD and CT for Response as for normal follow-Up -with treatment outside protocol: CT for Response as in normal follow-up. MRD under descretion of site, but has not to be performed necessarily.
Day	D -28 - D 0	D 1	D 8	D 15	D 22	D 27	D 29	D 36	D 43	D 64	D 69	D 71	D 78	D 85	D 106	D 111	D 113	D115 - D120	D 126	D 129	D 136	D 144	D 151	D 157	D 157 - D 171	D 365	D 547	D 730	D 912	D 1095	D 1277	D 1460	D 1642	D 2007	D2372		
appr. Week (W)	≤W - 4	W 0	W 1	W 2	W 3	W 3	W 4	W 5	W 6	W 9	W 9	W 10	W 11	W 12	W 15	W 16	W 16	W 16	W 18	W 18	W 19	W 21	W 22	W 22	W22 - W 24	W 52	W 78	W 104	W 130	W 156	W 182	W 208	W 234	W 286	W 338		
appr. Month (M)	M -1	M 0	M 1	M 1	M 1	M 1	M 1	M 2	M 2	M 3	M 3	M 3	M 3	M 3	M 4	M 4	M4	M 4	M 5	M 5	M 5	M 5	M 5	M 5	M 6	M 12	M 18	M 24	M 30	M 36	M 42	M 48	M 54	M 66	M 78		
Rituximab		X*1			X*1				X*1	X*1				X*1	X*1																						
CHOP		X							X					X																							
DHAP					X					X					X																						
Check availibility of stem cells																				X																	
G-CSF						X*2					X*2					X*3					X*4																
Stem cell apheresis																		X																			
THAM or BEAM																				X																	
PBSCT																					X																
Histological diagnosis of MCL including Ki-67 index	X																																				
Informed Consent	X																																				
Demographic data	X																																				
Inclusion / exclusion criteria	X																																				
Medical History	X																																				
Physical examination complete = C, targeted = T ; refer to protocol 11.1.1	C	T		T	T			T	T	T			C	T	T				C	T					C	T	C	T	C	T	C	T	C	C	C		
Imaging: **- CT scan mandatory:** (Neck, Thorax, abdomen, pelvis) *- PET optional*	X												X						X						X	X	X	X	X		X		X	X	X*11		
Assessment of tumor lesions	X												X						X						X	X	X	X	X		X		X	X			
Bone marrow biopsy	X												X*5						X*5						X*5		X*5		X*5		X*5		X* 5				
MRD Diagnostics (bone marrow, blood)	X												X*6						X						X*6	X*6	X	X*6	X	X*6	X	X*6	X	X*6			
Presence of B-symptoms	X	X	X	X	X		X	X	X	X		X	X	X	X		X		X	X					X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X		X	X	X	X		X	X	X	X		X		X	X					X	X	X	X	X	X	X	X	X	X	X		
New / Changed Drugs -> Crosscheck with drug prohibitions		X	X	X	X		X	X	X	X		X	X	X	X		X		X	X					X	X	X	X	X	X	X	X	X	X	X		
Recording of concomitant medication	X																																				
Cardiac function evaluation (ECG and US Echocardiography)	X												X*7						X						X*7												
Hepatitis / HIV Serology	X																																				
Hematology (RBC, WBC, Platelets, Differential BC)	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH) *8	X	X*9	X*9		X		X		X				X	X	X			X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Hepatology (yGT, ALT, AST, Bilirubin, AP)	X	X*9	X*9						X					X	X				X			X		X	X												
Coagulation (Quick and/or INR, aPTT)	X	X*9	X*9						X					X	X				X			X		X		X											
Pregnancy test (f)	X																																				
Consideration of sperm cryo-preservation and suppression of ovulation	X																																				
Recording of AEs / SAEs	X	X*12																																			
Assessments of AE of Special Interest	X	X																																			
Reference Pathology	X																																				

* 1 Rituximab: D 0 <u>or</u> D 1

* 2 G-CSF mandatory in R-DHAP from D6 daily 5µg/kgKG until recovery of WBC > 2.5 G/l. Alternatively pegfilgastrim may be applied once at D6

* 3 For the regeneration of granulopoiesis and mobilisation of peripheral stem cells G-CSF will be started on day 6 of the third DHAP cycle at a dose of 5-10 µg/kg body weight and will be continued until the completion of stem cell harvest.

* 4 The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 10^9/l is recommended, but not mandatory.

* 5 BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.

* 6 only peripheral blood; for detailed information see Appendix 5.

* 7 ECG or Echocadiography: If clinically indicated.

* 8 ß2-microgluboline mandatory at baseline. TSH mandotory at baseline and at days with planned CT.

* 9 Only in safety Run-In

* 10 D21 after ASCT and further according to clinical routine. Can be perfomed in an outpatient setting.

* 11 According to clinical routine and on suspicion of SPM or progression until the end of the study.

* 12 (S)AE assessment: From the time of randomization up to 30 days after last visit with the last individual trial specific medication of the subject.

Any patient presenting progressive disease during initial chemotherapy therapy should not receive further study-specific therapy. After complete documentation of progression, these patients need to be followed for survival.

Treatment Arm A+I

Schedule of Treatment and Assessments ARM A+I: Altering 3xR-CHOP+I/3xR-DHAP followed by ASCT, 2yrs Ibrutinib maintenance and observation		Induction Therapy																		Maintenance period												Observation period								
	Baseline D -28 till D 0	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 6	Cycle 2 Day 8	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 4 Day 6	Cycle 4 Day 8	**Cycle 4 Day 15 Midterm Evaluation**	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 6 Day 6	Cycle 6 Day 8	Cycle 6 Day 10 - Apheresis	**Cycle 6 Day 21 End of Induction Evaluation**	THAM or BEAM D -7	THAM or BEAM D 0	THAM or BEAM D 8	THAM or BEAM D 15	THAM or BEAM D 21 *10	**3 to 5 weeks after ASCT p ASCT Evaluation**	Months 06	Months 09	Months 12	Months 15	Months 18	Months 21	Months 24	Months 27	**Months 30 End of Maintenance**	Months 36	Months 42	Months 48	Months 54	Months 66	**Months 78; every 12 months thereafter until end of trial**		
Day	D -28 - D 0	D 1	D 8	D 15	D 22	D 27	D 29	D 36	D 43	D 64	D 69	D 71	D 78	D 85	D 106	D 111	D 113	D115 - D120	D 126	D 129	D 136	D 144	D 151	D 157	D 157- D 171	D 158 - D 172	D 273	D 365	D 455	D 547	D 637	D 730	D 820	D 912	D 1095	D 1277	D 1460	D 1642	D 2007	D2372		
appr. Week (W)	≤ W - 4	W 0	W 1	W 2	W 3	W 3	W 4	W 5	W 6	W 9	W 9	W 10	W 11	W 12	W 15	W 16	W 16	W 16- W17	W 18	W 18	W 19	W 21	W 22	W 22	W22 - W 24	W22- W25	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 156	W 182	W 208	W 234	W 286	W 338		
appr. Month (M)	M -1	M 0	M 1	M 1	M 1	M 1	M 1	M 2	M 2	M 3	M 3	M 3	M 3	M 3	M 4	M 4	M4	M 4	M 5	M 5	M 5	M 5	M 5	M 5	M 6	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 36	M 42	M 48	M 54	M 66	M 78		
Ibrutinib		X*0[a]							X*0[a]					X*0[a]							X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]								
Rituximab		X*1			X*1				X*1	X*1				X*1	X*1																										
CHOP		X							X					X																										
DHAP					X					X					X																										
Check availibility of stem cells																				X																				
G-CSF						X*2					X*2					X *3					X*4																				
Stem cell apheresis																		X																						
THAM or BEAM																				X																				
PBSCT																					X																				
Histological diagnosis of MCL including Ki-67 index	X																																								
Informed Consent	X																																								
Demographic data	X																																								
Inclusion / exclusion criteria	X																																								
Medical History	X																																								
Physical examination complete = C, targeted = T ; refer to protocol 11.1.1	C	T		T	T			T	T	T			C	T	T				C	T					C	T	T	C	T	C	T	C	T	C	T	C	C	C			
Imaging: **- CT scan mandatory:** (Neck, Thorax, abdomen, pelvis) *- PET optional*	X												X						X						X			X		X		X		X		X		X*11			
Assessment of tumor lesions	X												X						X						X			X		X		X		X		X	X				
Bone marrow biopsy	X												X*5						X*5						X*5					X*5				X*5		X*5					
MRD Diagnostics (bone marrow, blood)	X												X * 6						X						X * 6			X * 6		X		X * 6		X	X * 6	X	X * 6	X	X * 6			
Presence of B-symptoms	X	X	X	X	X		X	X	X	X		X	X	X	X		X		X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG performance status	X	X	X	X	X		X	X	X	X		X	X	X	X		X		X	X					X	X	X	X		X		X		X	X	X	X	X	X			
New / Changed Drugs -> Crosscheck with drug prohibitions		X	X	X	X		X	X	X	X		X	X	X	X		X		X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Recording of concomittant medication	X																																								
Cardiac function evaluation (ECG and US Echocardiography)	X												X*7						X						X*7																
Hepatitis / HIV Serology	X																																								
Hematology (RBC, WBC, Platelets, Differential BC)	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X			X	X	X	X			X		X		X		X	X	X	X	X	X			
Serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH) *8	X	X*9	X*9		X		X		X				X	X	X			X	X			X	X	X	X			X		X		X		X	X	X	X	X	X			
Hepatology (yGT, ALT, AST, Bilirubin, AP)	X	X*9	X*9						X					X	X				X			X		X	X																
Coagulation (Quick and/or INR, aPTT)	X	X*9	X*9						X					X	X				X			X		X				X													
Pregnancy test (f) *13	X																																								
Consideration of sperm cryo-preservation and suppression of ovulation	X																																								
Recording of AEs / SAEs	X	X*12																																								
Assessments of AE of Special Interest	X	X																																								
Reference Pathology	X																																								

For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until END of TRIANGLE trial. For details see chapter 11.9.

Patients in Follow-Up after treatment stop without progression: (For details see chapter 11.8.)
-without further treatment outside protocol: MRD and CT for Response as for normal follow-Up
-with treatment outside protocol: CT for Response as in normal follow-up, MRD under descretion of site, but has not to be performed necessarily.

* 0[a] Ibrutinib will be applied oral with 560 mg (4x 140mg capsules) daily in cycles 1, 3, 5 on days 1-19. Due to lack of published data for the combination of Ibrutinib/R-DHAP, Ibrutinib should NOT be applied in cycles 2,4,6. For details see chapter 7.1.2.

* 0[b] Patients randomized in the experimental arm A+I will receive additional oral ibrutinib 560 mg (4x 140mg capsules) daily maintenance for two additional years in case of CR or PR at ASCT-assessment. Ibrutinib Maintenance will start after regeneration of peripheral blood count after the end of ASCT (earliest maintenance start at week 22).

Requirements for start of Maintenance: ANC ≥ 1,000 cells/mm³ (1.0 X 10^9/L); Platelets ≥ 50,000 cells/mm³ (50 X 10^9/L); Rituximab or ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity.
Any other AE related to induction treatment or ASCT not requiring discontinuation has resolved to Grade ≤ 2 severity.

* 1 Rituximab: D 0 or D 1

* 2 G-CSF mandatory in R-DHAP from D6 daily 5µg/kgKG until recovery of WBC > 2.5 G/l. Alternatively pegfilgastrim may be applied once at D6.

* 3 For the regeneration of granulopoiesis and mobilisation of peripheral stem cells G-CSF will be started on day 6 of the third DHAP cycle at a dose of 5-10 µg/kg body weight and will be continued until the completion of stem cell harvest.

* 4 The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 10^9/l is recommended, but not mandatory.

* 5 BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.

*** 6 only peripheral blood; for detailed information see Appendix 5.**

* 7 ECG or Echocadiography: If clinically indicated.

* 8 ß2-microgluboline mandatory at baseline. TSH mandotory at baseline and at days with planned CT.

* 9 Only in safety Run-In

*10 D21 after ASCT and further according to clinical routine. Can be perfomed in an outpatient setting.

*11 According to clinical routine and on suspicion of SPM or progression until the end of the study.

*12 (S)AE assessment: From the time of randomization up to 30 days after last visit with the last individual trial specific medication of the subject.

*13 In Norway monthly pregnancy testing is required by competent authorities in women with childbearing potential during ibrutinib treatment

Any patient presenting progressive disease during initial chemotherapy therapy should not receive further study-specific therapy. After complete documentation of progression, these patients need to be followed for survival.

Treatment Arm I

		Induction Therapy																		Maintenance period										Observation period							
Schedule of Treatment and Assessments **Treatment ARM I: Altering 3xR-CHOP+I/3xR-DHAP followed by 2yrs Ibrutinib maintenance and observation**	Baseline D -28 till D 0	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 6	Cycle 2 Day 8	Cycle 2 Day 15	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 4 Day 6	Cycle 4 Day 8	**Cycle 4 Day 15 Midterm Evaluation**	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 6 Day 6	Cycle 6 Day 8	Cycle 6 Day 15	**Cycle 6 Day 21 End of Induction Evaluation (EOI)**	Months 05	**4-6 weeks after EOI pASCT Evaluation**	Months 09	Months 12	Months 15	Months 18	Months 21	Months 24	Months 27	**Months 30 End of Maintenance**	Months 36	Months 42	Months 48	Months 54	Months 66	**Months 78; every 12 months thereafter until end of trial**	For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until END of TRIANGLE trial. For details see chapter 11.9.	Patients in Follow-Up after treatment stop without progression: (For details see chapter 11.8.) -without further treatment outside protocol: MRD and CT for Response as for normal follow-Up -with treatment outside protocol: CT for Response as in normal follow-up. MRD under descretion of site, but has not to be performed necessarily.
Day	D -28 - D 0	D 1	D 8	D 15	D 22	D 27	D 29	D 36	D 43	D 64	D 69	D 71	D 78	D 85	D 106	D 111	D 113	D 120	D 126	D 127	D 157 - D 171	D 273	D 365	D 455	D 547	D 637	D 730	D 820	D 912	D 1095	D 1277	D 1460	D 1642	D 2007	D2372		
appr. Week (W)	≤W -4	W 0	W 1	W 2	W 3	W 3	W 4	W 5	W 6	W 9	W 9	W 10	W 11	W 12	W 15	W 16	W 16	W 17	W 18	W18	W22 - W 24	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 156	W 182	W 208	W 234	W 286	W 338		
appr. Month (M)	M -1	M 0	M 1	M 1	M 1	M 1	M 1	M 2	M 2	M 3	M 3	M 3	M 3	M 3	M 4	M 4	M 4	M 4	M 5	M 5	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 36	M 42	M 48	M 54	M 66	M 78		
Ibrutinib		X*0[a]							X*0[a]					X*0[a]						X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]	X* 0[b]									
Rituximab		X*1			X*1				X*1	X*1				X*1	X*1																						
CHOP		X							X					X																							
DHAP					X					X					X																						
Check availibility of stem cells																				X																	
G-CSF						X*2					X*2					X*2																					
Histological diagnosis of MCL including Ki-67 index	X																																				
Informed Consent	X																																				
Demographic data	X																																				
Inclusion / exclusion criteria	X																																				
Medical History	X																																				
Physical examination complete = C, targeted = T ; refer to protocol 11.1.1	C	T		T	T			T	T	T			C	T	T			T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	C	C		
Imaging: **- CT scan mandatory:** (Neck, Thorax, abdomen, pelvis) *- PET optional*	X												X						X		X		X		X		X		X		X		X	X	X*8		
Assessment of tumor lesions	X												X						X		X		X		X		X		X		X		X	X			
Bone marrow biopsy	X												X*3						X*3		X*3				X*3				X*3		X*3		X*3				
MRD Diagnostics (bone marrow, blood)	X												X*4						X		X*4		X*4		X		X*4		X	X*4	X	X*4	X	X*4			
Presence of B-symptoms	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
ECOG performance status	X	X	X	X	X		X	X	X	X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
New / Changed Drugs -> Crosscheck with drug prohibitions		X	X	X	X		X	X	X	X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Recording of concomitant medication	X																																				
Cardiac function evaluation (ECG and US Echocardiography)	X												X*5						X		X*5																
Hepatitis / HIV Serology	X																																				
Hematology (RBC, WBC, Platelets, Differential BC)	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X		X		X		X		X		X	X	X	X	X	X	X		
Serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH) *6	X	X*7	X*7		X		X		X				X	X	X				X		X		X		X		X		X	X	X	X	X	X	X		
Hepatology (yGT, ALT, AST, Bilirubin, AP)	X	X*7	X*7						X					X	X				X		X																
Coagulation (Quick and/or INR, aPTT)	X	X*7	X*7						X					X	X				X				X														
Pregnancy test (f) *10	X																																				
Consideration of sperm cryo-preservation and suppression of ovulation	X																																				
Recording of AEs / SAEs	X																		X*9																		
Assessments of AE of Special Interest	X																				X																
Reference Pathology	X																																				

* 0[a] Ibrutinib will be applied oral with 560 mg (4x 140mg capsules) daily in cycles 1, 3, 5 on days 1-19. Due to lack of published data for the combination of Ibrutinib/R-DHAP, Ibrutinib should NOT be applied in cycles 2,4,6! For details see chapter 7.1.3.

* 0[b] Patients randomized in the experimental I will receive additional oral ibrutinib 560 mg (4x 140mg capsules) daily maintenance for two additional years in case of CR or PR at EoI-assessment.

Requirements for start of Maintenance:

ANC ≥ 1,000 cells/mm³ (1.0 X 10^9/L); Platelets ≥ 50,000 cells/mm³ (50 X 10^9/L); Rituximab or ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity.
Any other AE related to induction treatment or ASCT not requiring discontinuation has resolved to Grade ≤ 2 severity.

- * 1 Rituximab: D 0 or D 1
- * 2 G-CSF mandatory in R-DHAP from D6 daily 5µg/kgKG until recovery of WBC > 2.5 G/l. Alternatively pegfilgastrim may be applied once at D6.
- * 3 BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.
- * 4 only peripheral blood; for detailed information see Appendix 5.
- * 5 ECG or Echocadiography: If clinically indicated.
- * 6 ß2-microgluboline mandatory at baseline. TSH mandotory at baseline and at days with planned CT.
- * 7 Only in safety Run-In
- * 8 According to clinical routine and on suspicion of SPM or progression until the end of the study.
- * 9 (S)AE assessment: From the time of randomization up to 30 days after last visit with the last individual trial specific medication of the subject.
- *10 In Norway monthly pregnancy testing is required by competent authorities in women with childbearing potential during ibrutinib treatment

Any patient presenting progressive disease during initial chemotherapy therapy should not receive further study-specific therapy. After complete documentation of progression, these patients need to be followed for survival.

1.5 List of abbreviations

AE	Adverse Event
AR	Adverse Drug Reaction
AMG	Arzneimittelgesetz (German Medicinal Products Act ; The Drug Law)
ANC	Absolute Neutrophil Count
ALAT	Alanin-Aminotransferase
ASAT	Aspartat-Aminotransferase
ASCT	Autologous stem cell transplantation
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BM	Bone Marrow
CA	Competent Authority
CBC	Complete Blood Count
CR	Complete Remission
CRO	Contract Research Organization / Clinical Research Organisation
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data Safety and Monitoring Committee
DDI	Drug-Drug-Interaction
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report form
EoI	End of Induction
ENT	Ear, Nose and Throat
FDG	Fluorodeoxyglucose
FFS	Failure Free Survival
FISH	Fluorescence In Situ Hybridization
FPPV	First Patient First Visit
FU	Follow up
GCP	Good Clinical Practice
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ISF	Investigator Site File
ITT	Intention to treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LPLV	Last Patient Last Visit
MCL	Mantle Cell Lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	Minimal residual disease
NaCL	Sodium Chloride
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PCR (RQ-PCR)	Real-Time Quantitative Polymerase Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography

PFS	Progression Free Survival
PR	Partial Remission
PS	Performance Status
QoL	Quality of Life
RD	Remission Duration
RNA	Ribo Nucleic Acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SDP	Sponsor Delegated Person
SDV	Source data verification
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
ToP	Time-of-Progression
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal
WHO	World Health Organization

2 Background information and study rationale

2.1 Background information

2.1.1 Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma (MCL) is a rare lymphoma subtype that accounts for 5-7% of non-Hodgkin lymphomas in adults. The diagnosis is based on histological, cytological and cytogenetic examinations. The histological description characterizes different subgroups: small cell, blastoid or pleomorphic types with a mantle zone pattern, a nodular pattern and a diffuse pattern. The classic MCL immunophenotype shows that lymphoma cells express CD19+, CD20+, CD22+, CD79a+ and the surface IgM and IgD B-cell mature markers but also CD5+ and CD43+. MCL cells are negative for CD10, CD23 and Bcl-6. Some cases may not express CD5 or may be CD23 positive. However, detection of the characteristic cyclin D1 overexpression either by immuno-histochemistry or FISH t(11;14) is generally mandatory to confirm the diagnosis of mantle cell lymphoma.

2.1.2 Current treatment of patients with MCL

Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab[2]. However, many other chemotherapeutic regimens have been evaluated. Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper CVAD or alternating R-CHOP and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by consolidation therapy with autologous stem cell transplant (SCT).

2.1.3 Non-clinical data on Ibrutinib

Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class, potent, orally-administered covalently-binding small molecule inhibitor of Bruton's tyrosine kinase co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC for the treatment of B-cell malignancies.

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways.

Signaling from the B-cell antigen receptor (BCR) regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival.[3,4] The BCR pathway is implicated in several B-cell malignancies, including follicular lymphoma.[5,6]
The covalent bond formed between ibrutinib and Cys-481 is highly stable, resulting in sustained inhibition of the target.[7] Ibrutinib, based on available clinical exposure data, is extensively metabolized. The contribution of metabolites to the overall activity is unknown.[8]. Ibrutinib inhibits BCR and chemokine-receptor signaling pathways in malignant B-cells. Ibrutinib is also expected to inhibit Blk, Bmx/Etk, FGR, CSK and Txk to a lesser extent. 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.

Ibrutinib disrupts integrin-dependent B-cell migration and adhesion in vitro. Further, it promotes egress of malignant B cells from tissues and prevents homing of these cells to tissues.

In summary because of the described mechanism of action, Ibrutinib breaks down the BCR- and chemokine-controlled retention of malignant B cells in their supportive microenvironments, which could lead to the disruption of the pathogenesis of several B-cell malignancies.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, including accurate and current information regarding adverse drug reactions (ADRs) and information on the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure and Addenda/supplements for ibrutinib.

Because ibrutinib is in clinical development, its safety profile is not yet fully understood. Further investigation is necessary to better understand the safety of ibrutinib. Therefore, unanticipated side effects that have not been previously observed may occur. A brief overview of the potential risks associated with the administration of ibrutinib based on the Investigator's Brochure is outlined below in section 2.1.6.

2.1.4 Pharmacokinetics

Ibrutinib is metabolized via cytochrome P450 (CYP)3A4/5 pathway.
Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and should be avoided. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (Cmax and AUC0-last) of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤2-fold in 37 subjects treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 subjects not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 subjects treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone and cobicistat) and moderate inhibitors (e.g., voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A inhibitor must be used, reduce ibrutinib treatment to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A.
Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (e.g.,

carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.
Guidance on concomitant use of ibrutinib with CYP3A4/5 inhibitors or inducers is provided in Section 9.

In a food effect study in 43 healthy subjects (PCI-32765CLL1001), administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure (AUClast) as compared to administration either 30 minutes before or 2 hours after a meal (the recommended dosing conditions). When ibrutinib was taken 30 minutes after a high fat breakfast (fed condition), the exposure (AUClast) was comparable to the recommended dosing conditions of either 30 minutes before or 2 hours after a meal.

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib treatment results in any clinically relevant DDIs with drugs that may be metabolized by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-gp, nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P--gp substrates. Ibrutinib is a mild inhibitor of P--gp and BCRP. Ibrutinib is not expected to have systemic DDIs with P--gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P--gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP mediated hepatic efflux, such as rosuvastatin.
Refer to the ibrutinib (PCI-32765) Investigator's Brochure for more information on nonclinical pharmacology and toxicology studies.

2.1.5 Clinical efficacy of ibrutinib in mantle cell lymphoma

Efficacy results from Study PCYC-04753 and Study PCYC-1104-CA demonstrate that ibrutinib has activity as a single-agent in treatment of subjects with relapsed or refractory MCL.

2.1.5.1 Study PCYC-04753

In this Phase 1, multicenter, multicohort, open-label, dose-escalation study, 56 subjects with relapsed or refractory NHL including CLL and Waldenström's macroglobulinemia were enrolled across 7 dose cohorts.1,2 Nine of 56 subjects had a diagnosis of MCL and were evaluable for response. Seven of them achieved an objective response by the Revised Response Criteria for Malignant Lymphoma6, including 3 CRs and 4 partial responses [PRs]; 1 subject had stable disease and 1 subject had progressive disease. All of the subjects responding to treatment achieved response at the time of the first postbaseline response assessment (after 2 cycles of treatment). Of the 3 subjects who achieved a CR, 2 subjects had CR on initial postbaseline assessment, and 1 subject achieved a PR initially and they had a CR after 8 cycles (28-days cycle duration) of therapy. Five subjects who entered a long-term follow-up study have durations of response ranging from 10.5 to 27.5 months.

2.1.5.2 Study PCYC-1104-CA

This was a multicenter Phase 2 study in 111 subjects with MCL who were relapsed or refractory to their previous treatment. Subjects were stratified based on their previous exposure to the chemotherapeutic agent bortezomib. The objectives included studying the efficacy of ibrutinib given as a continuous fixed dose of 560 mg/day. Overall response rate was the primary end point. 86% of the patients had intermediate- or high-risk mantle cell lymphoma. The overall response rate was 68%, complete response were achieved in 21%, partial response in 47% of the patients. Prior treatment with bortezomib had no impact on response. In some patients, treatment with ibrutinib was associated with a transient increase in peripheral lymphocyte count representing a compartmental shift of cells with the CD19+/CD5+ phenotype from nodal tissues to peripheral blood.

2.1.5.3 Study MCL2001

In Study MCL2001, a Phase 2 study of ibrutinib in subjects with MCL, the IRC-assessed ORR was 62.7% (20.9% CR+ 41.8% PR) for the response-evaluable population (n=110). With an estimated median time of efficacy follow-up of 14.5 months, the estimated median DOR was 14.9 months (95% CI: 12.4, not estimable). Median PFS by IRC assessment was 10.5 months, and median OS was not reached.

2.1.6 Clinical Safety of Ibrutinib

Safety data are presented for 2477 subjects in B-cell malignancy, chronic graft versus host disease and healthy volunteer studies:

- 2055 subjects treated with single-agent ibrutinib
- 1523 subjects with B-cell malignancies
- 42 subjects with cGVHD
- 460 healthy volunteers
- 30 subjects in a hepatic impairment study (healthy subjects and subjects with hepatic impairment)

- 422 subjects with B-cell malignancies treated with ibrutinib in combination with immunotherapy or chemoimmunotherapy

The most important findings are summarized below. For a detailed listing of the integrated Safety Data from these studies refer to the Ibrutinib Investigators Brochure.

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Initially subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Although causality has not been established,

cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Cytopenias
Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

Interstitial Lung Disease
Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines as needed.

Cardiac Arrhythmias

Atrial fibrillation, and atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia atrial fibrillation. Periodically monitor subjects clinically for cardiac arrhythmia atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment, and follow the dose modification guidelines.

Tumor Lysis Syndrome (TLS)
Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of TLS are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Treatment related Lymphocytosis
Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count > 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (approximately 69% to 75%) with CLL/SLL treated with single-agent ibrutinib. This effect has also been observed in some patients (33%) with MCL treated with single-agent ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (e.g., >400000/mcL) has been observed in some subjects. Lymphocytosis was not observed in subjects with WM treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemo-immunotherapy.

Diarrhea
Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea,

vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as Clostridium difficile or other infectious agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in the individual protocols.

Rash
Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study 1112. Most rashes were mild to moderate in severity.
Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens - -Johnson-Syndrome (SJS) have been reported in subjects with CLL. The subject received ibrutinib. (420 mg/day) and was also receiving various antibiotics and medication for gout (allopurinol) known to be associated with SJS. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, angioedema have been reported.

Hypertension
Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Secondary Primary Malignancies and Non-melanoma skin cancer
Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Non-melanoma skin cancers have occurred in subjects treated with Ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

2.1.7 Contraindications

Ibrutinib is contraindicated in subjects with clinically significant hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to the compound itself or to the excipients in its formulation.

2.1.8 The role of MRD

MRD detection by PCR-based amplification of clonal immune gene rearrangements is an established tool for disease monitoring in ALL. Moreover it proved to be an effective outcome predictor also in mature B-cell tumors and particularly in MCL. The achievement of PCR-negativity in increasing proportions of patients heralded the clinical successes observed in the treatment of this neoplasm following the introduction of Rituximab and high-dose Ara-C containing programs. More importantly, several studies have clearly demonstrated that achievement of PCR-negativity confers significant PFS advantages to MCL patients[9-11]. The results of these analyses are in line with the most recent study from the European Mantle Cell lymphoma Network reporting the largest MRD analysis so far conducted in MCL. This analysis included patients involved in two large trials of the European Mantle Cell Lymphoma Network including 259 patients[12]. The results from this large analysis clearly indicate that molecular remission achievement acts as a major independent predictor of superior outcome in MCL.

Based on the high predictive value of MRD, most current lymphoma trials now include PCR-analysis as additional outcome parameter.
MRD determination is usually performed using the immunoglobulin heavy chain rearrangement (IgH) rearrangement and the t(11;14) translocation. Both clonal events provide stable and reliable MRD markers. Based on the published experience it is possible to obtain a molecular marker using the t(11;14) in approximately 30% of patients while the rate of success with the IgH rearrangement is greater than 80%[12]. Based on the combined use of these two methods the vast majority of patients (approximately 90%) can currently obtain a molecular marker suitable for MRD determination. In recent years to validate the MRD approach in MCL, the Euro-MRD group (previously known as European Study Group for Minimal Residual Disease) has conducted a multi-laboratory standardization process that has involved 11 laboratories across Europe[13]. This effort had led to the development of common guidelines for the conduction of the experiments and the interpretation of results ensuring the achievement of excellent levels of reliability and reproducibility among the participating labs. Thus MRD detection in MCL performed by a trained laboratory in accordance to the Euro-MRD indications might be considered a validated and standardized highly reproducible tool, perfectly suitable for application in the context of large international Phase III trials.
The objectives of minimal residual disease (MRD) analysis are:

- to evaluate MRD level at diagnosis, at the end of induction, during maintenance and follow up;
- to evaluate the relative impact of the two induction and maintenance regimens on MRD kinetics assessed in terms of (a) rate of conversion to molecular response, (b) rate of molecular relapse, (c) quantitative increase of tumor burden in the bone marrow and peripheral blood.
- to assess the prognostic impact of molecular response, molecular relapse and disease kinetics assessed by real time PCR at various time points (both on peripheral blood and bone marrow) on PFS.

Investigation of potential predictive markers of prognosis as well as the biological effects of induction and maintenance treatment on minimal residual disease will be examined as described below. Patient participation in these exploratory correlative science sub-studies is strongly encouraged.

2.2 Study rationale

According to current European guidelines[2], the standard of care in younger patients with mantle cell lymphoma (MCL) is a dose-intensified approach with a cytarabine containing immunochemotherapy induction followed by autologous transplantation[14]. Ibrutinib has recently shown impressive efficacy data in relapsed MCL while tolerability was rather favorable[15].

Based on these prerequisites, our study proposal challenges the current standard of care and questions, whether the addition of ibrutinib (arm A+I) to the standard (control arm A) results in a superior clinical outcome. In addition, we investigate whether ASCT which sometimes is hampered by short and long term toxicity is still superior to a (hopefully much better tolerated) conventional treatment without ASCT and with the addition of ibrutinib in induction and maintenance (duration 2 years, arm I and A+I). As so far combination data are only available with the R-CHOP regimen but not for the alternating R-DHAP regimen.[16] Ibrutinib will be only given during the R-CHOP regimen, and during an initial safety run-in phase 50 patients randomized will be closely monitored for the observed toxicities during induction therapy (see 13.8 Safety Run-In Phase).

Analysis of minimal residual disease (MRD) will play a critical role in identifying specific patient subpopulations which may be especially prone to one of the three therapeutical strategies.

Finally, if the recently completely recruited LyMa trial proves a benefit of rituximab maintenance after an ASCT, rituximab maintenance will be added to all 3 study arms depending on national guidelines.

2.3 Risk benefit assessment

Mantle cell lymphoma have a considerable worse prognosis than indolent non hodgkin lymphoma. Median overall survival in advanced stages (II-IV) is about 3-5 years, a curative treatment approach is currently not known (with the exception of allogeneic transplantation, which has a high morbidity and mortality rate). Aim of a systemic therapy is an initial reduction of tumor load in order to achieve long lasting remissions so the time in which patients are without any need of therapy are as long as possible. In a former multicenter trial of the European MCL Network high dose cytarabin containing induction therapy showed a longer progression free survival compared with the anthracycline base regimen CHOP [17]. Additionally in several phase II and III trials consolidating autologous stem cell transplantation achieved significantly longer progression free survival and overall survival so that this kind of regimen can be considered as standard of care in younger MCL patients. Nevertheless high dose chemotherapy containing regimens have considerable acute and long term toxicities.

Ibrutinib is a well tolerated drug which has shown high response rates especially in relapsed MCL patients [15]. In an international randomized phase III trial Ibrutinib had shown response rates of about 70% with durable remissions (Dreyling, Lancet 2015). Tolerability was good with a low rate of infections and manageable bleeding complications (see above). On the other hand it is to assume that because of the lack of autologous high dose consolidation the tolerability of the experimental arm I will be markedly better compared with the standard high dose approach. This approach is used in arm A so this population will not be exposed to additional risk compared to the current standard.

For Arm A+I, there is a risk of a higher incidence of side effects with the combination of standard therapy with ibrutinib, most notably in terms of hematotoxicity, bleeding, and atrial fibrillation. Because of this, in an initial safety run-in phase of the first 50 randomized patients, these will be closely monitored for observed toxicities during induction therapy so early identification of currently unknown safety risks is ensured. These data will be discussed by an independent Data Safety Monitoring Committee to minimize the potential risk for all study participants.

The expected toxicity described above is countered by the potential benefits regarding longer progression free and treatment free intervals.

The precautionary safety measures, the safety run-in phase of 50 patients, regular monitoring of safety by an independent Data Safety Monitoring Committee (DSMC) and the Sponsor enables early identification of safety signals in the study and minimizes the risk to enrolled patients. In conclusion, it is considered that the benefit-risk ratio for this study is favorable.

3 Study design

This study is a randomized, three-arm, parallel-group, open label, international multicenter phase III trial comparing six alternating courses of R-CHOP/R-DHAP (one cycle every 21 days) followed by ASCT versus the combination with Ibrutinib in induction and maintenance (2 years) or the experimental arm without ASCT

4 Objectives and endpoints

4.1 Primary objective and primary endpoint

The primary objective of the trial is to establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP+ibrutinib /R-DHAP followed by ASCT and followed by ibrutinib maintenance (experimental arm A+I), and R-CHOP+ibrutinib /R-DHAP followed by ibrutinib maintenance (experimental arm I) as future standard based on the comparison of investigator-assessed failure-free survival (FFS).

The primary endpoint of the trial will be FFS and is defined as the time from randomization to stable disease at end of induction immuno-chemotherapy, progressive disease, or death from any cause, whichever comes first.

4.2 Secondary objectives and endpoints

Secondary objectives:

- To compare the efficacy of the three treatment arms in terms of secondary efficacy endpoints
- To determine the safety and tolerability of ibrutinib during induction immuno-chemotherapy and during maintenance and to compare the safety profile of the three treatment arms in terms of secondary toxicity endpoints

Secondary efficacy endpoints:

- Overall survival (OS)
- Progression-free survival (PFS) from randomization, from end of induction immuno-chemotherapy in patients with CR or PR at end of induction immuno-chemotherapy, and from the staging 6 weeks after end of induction assessment
- Overall response and complete remission rates at midterm, at end of induction, 3 months after end of induction immuno-chemotherapy
- PR to CR conversion rate during follow-up after end of induction immuno-chemotherapy

Secondary safety endpoints:

- Rates of AEs, SAEs, and SUSARs by CTC grade (Version 4.03) during induction immuno-chemotherapy and during periods of follow-up after response to immune-chemotherapy
- Cumulative incidence rates of secondary primary malignancies

4.3 Exploratory objectives and endpoints

Exploratory Objectives:

- To compare feasibility of ASCT in arm A+I vs. arm A
- To compare minimal residual disease status between the three treatment groups
- To determine the impact of ibrutinib during induction immuno-chemotherapy and during maintenance therapy on the minimal residual disease status
- To determine the prognostic value of minimal residual disease status
- To determine the prognostic value of positron emission tomography with fluorine 18-fluorodeoxyglucose
- To determine clinical and biological prognostic and predictive factors
- To determine the role of total body irradiation (TBI) in ASCT conditioning

Exploratory Endpoints:

- Rate of successful stem cell mobilisations (success: separation of at least $2x2x10^6$ CD34-positive cells, including a back-up)
- Rate of molecular remissions (MRD-negative patients) at midterm, at end of induction immuno-chemotherapy, and at staging time-points during follow-up in patients with remission after end of induction immuno-chemotherapy
- Time to molecular remission from start of therapy
- Time to molecular relapse for patients in clinical and molecular remission after end of induction immuno-chemotherapy
- MRD in FDG-PET negative or positive patients after induction and ASCT

Exploratory objectives may be evaluated only in a subset of patients according to local standards and resources.

5 Study duration

The maximal duration of the trial will be 10 years; up to 5 years recruitment and up to 5 years additional follow-up. The trial may stop earlier based on the result of pre-planned interim analyses.

5.1 Duration of study participation for individual patients

The maximal trial participation period per individual patient will be 10 years.

Study Arm A:
18 weeks induction therapy, 6 weeks ASCT, observation without therapy until progression, and follow-up until the end of the trial

Study Arm A+I:
18 weeks induction therapy, 6 weeks ASCT, 2 years ibrutinib-maintenance, observation without therapy until progression, and follow-up until the end of the trial

Study Arm I:
18 weeks induction therapy, 2 years ibrutinib-maintenance, observation without therapy until

progression, and follow-up until the end of the trial

6 Trial population and patient selection

6.1 Target Population

The current study is designed for previously untreated adult patients up to 65 years of age with advanced stage (II – IV) mantle cell lymphoma.

6.2 Gender distribution

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

6.3 Inclusion and exclusion criteria

This trial can fulfil its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

Inclusion criteria

All patients must meet the following criteria:

- Histologically confirmed diagnosis of MCL according to WHO classification
- suitable for high-dose treatment including high-dose Ara-C
- Stage II-IV (Ann Arbor)
- Age ≥ 18 years and ≤ 65 years
- Previously untreated MCL
- At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations.
- ECOG/WHO performance status ≤ 2
- The following laboratory values at screening (unless related to MCL):
  - Absolute neutrophil count (ANC) ≥1000 cells/μL
  - Platelets ≥100,000 cells/μL
  - Transaminases (AST and ALT) ≤3 x upper limit of normal (ULN)
  - Total bilirubin ≤2 x ULN unless due to known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome])
  - Creatinine ≤2 mg/dL or calculated creatinine clearance ≥ 50 mL/min
- Written informed consent form according to ICH/EU GCP and national regulations
- Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods (combined oral contraceptives using two hormones, contraceptive implants, injectables, , intrauterine devices, sterilized partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive caps) while on study; this should be maintained for 90 days after the last dose of study drug and 12 months after the last dose of rituximab

Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

- Major surgery within 4 weeks prior to randomization.
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon).
- History of stroke or intracranial hemorrhage within 6 months prior to randomization.
- Requires treatment with strong CYP3A4/5 inhibitors.
- Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
- Vaccinated with live, attenuated vaccines within 4 weeks prior to randomization.
- Known CNS involvement of MCL
- Clinically significant hypersensitivity (e.g., anaphylactic or anaphylactoid reactions to the compound of ibrutinib itself or to the excipients in its formulation)
- Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies
- Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy outlined in this trial protocol
- Serious concomitant disease interfering with a regular therapy according to the study protocol:
  - Cardiac (Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)
  - Pulmonary (chronic lung disease with hypoxemia)
  - Endocrinological (severe, not sufficiently controlled diabetes mellitus)
  - Renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min)
  - Impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2,0 mg/dl unless due to Morbus Meulengracht (Gilbert-Meulengracht-Syndrome)
- Positive test results for chronic HBV infection (defined as positive HBsAg serology) (mandatory testing)
  Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBSAb) after vaccination are eligible.
- Positive test results for hepatitis C (mandatory hepatitis C virus [HCV] antibody serology testing). Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
- Patients with known HIV positive infection (mandatory test)
- Prior organ, bone marrow or peripheral blood stem cell transplantation
- Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or in situ uterine cervix cancer
- Pregnancy or lactation
- Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule
- Subjects not able to give consent
- Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial

- Participation in another clinical trial within 30 days before randomization in this study.

6.4 Prohibitions and restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. During the study, subjects receiving ibrutinib should avoid consuming food and beverages containing grapefruit or Seville oranges as these contain certain ingredients that inhibit CYP3A4/5 enzymes.

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

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

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

- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Prohibited medications and precautions with concomitant medications are detailed in Sections 9 respectively.

6.5 Screening, informed consent and recruitment

If a subject appears to be eligible for the trial, the investigator will inform the subject about the trial and ask the patient for his/her written consent.

It is a requirement that written consent is obtained prior to any trial-specific procedures. In addition, the informed consent for the collection of biological samples should be signed before sampling for minimal residual disease (MRD) analysis. The patient and the investigator will date and sign the informed consent form. The investigator shall provide a copy of the signed consent to the study patient; an original shall be maintained in the investigator's study file.

The informed consent process has to be recorded into the patients file by the investigator with date, time and signature. The investigator will then record the details of the eligible subjects on trial specific lists provided.

6.6 Stratification and Randomization

After verification of eligibility (registration checklist) patient registration and randomisation will be performed via EDC system. Registration is only accepted from authorised investigators and must be done before the start of the treatment.

Randomization will ensure equal probability for assignment to every treatment group. Thus, the allocation ratio will be 1:1:1 unless one treatment arm has been closed; allocation ratio will then be changed to 1:1. Randomization will be stratified according to study groups and MIPI risk groups at study entry.

Inclusion of the patient in the trial will be based on local pathological assessment.

In addition, diagnostic material from all study patients must be submitted for central pathologic review to one of the members of the pathology review panel as indicated below (refer to 12.1. Pathology Review and Appendix 4).

Please refer to Appendix 4 for detailed information on coordination of reference pathology.

7 Study Treatment

Study treatment will be administered only to eligible subjects according to inclusion and exclusion criteria after registration and randomization.

Standard treatment will be administered according to the standard preparation and infusion procedures of each investigational site. Refer to the specific package inserts for preparation, administration and storage guidelines.

Induction therapy in all study arms (A, A+I and I) is alternating standard 3xR-CHOP / 3xR-DHAP chemotherapy. Patients randomized to the experimental arms A+I and I will receive additional oral ibrutinib 560 mg (4x 140mg capsules) daily in cycles 1, 3, 5 days 1-19 and for two years in the Ibrutinib maintenance therapy in case of CR or PR at ASCT- or EoI-assessment. As so far combination data are only available with the R-CHOP regimen but not for the alternating R-DHAP regimen.[16] Thus ibrutinib is applied only in cycles 1,3,5 (R-CHOP) and not in combination with R-DHAP!

In case of progressive disease (proven by CT scan) study treatment has to be stopped but patient remains in study for survival follow-up. Any salvage therapy according to institutional standard can be used after stopping study treatment.

THAM or BEAM conditioning prior to ASCT will only be applied to patients randomized to arm A and A+I and in remission after induction immuno-chemotherapy. Participating sites have to determine the ASCT conditioning regimen to be used before trial activation at the site.

In patients who do not achieve a remission at end of induction immuno-chemotherapy (treatment failure), no study specific treatment has been defined; rather, the further treatment is upon the discretion of the treating physician. Patients remain in study for progression and survival follow-up.

7.1 Treatment Schedules

7.1.1 Treatment schedule in study arm A

ARM A: Standard of Care
Alternating 3 cycles R-CHOP / 3 cycles R-DHAP induction followed by ASCT (THAM or BEAM)

Induction: Alternating 3 x R-CHOP / 3 x R-DHAP, every 21 days,

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D0 or 1 I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/ m^2	D1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin 130mg/m^2	D1 I.V.)
		G-CSF 5µg / kg	D6 daily SC*

* G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l
Alternatively pegfilgrastim may be applied once at D6

Stem cell apheresis after the last cycle R-DHAP

ASCT conditioning (should follow the end of induction visit within 2 weeks):
THAM or BEAM, stratified per site before trial activation at site

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m^2 q12h	D –4, –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5 mg / kg twice a day D-7) may be considered based on a retrospective EBMT comparison[1]

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

7.1.2 Treatment schedule in study arm A+I

Experimental Arm A+I
Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by ASCT (THAM or BEAM) and 2 years Ibrutinib-Maintenance

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cycles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5):		R-DHAP (cycle 2,4,6):	
Rituximab 375 mg/m^2	D 0 or 1I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/ m^2	D 1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin 130mg/m^2	D 1 I.V.)
Ibrutinib 560mg	D 1-19 oral	G-CSF 5µg / kg	D6 daily SC*

*** G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l**
Alternatively pegfilgrastim may be applied once at D6

Stem cell apheresis after the last cycle R-DHAP

ASCT conditioning (should follow the end of induction visit within 2 weeks):
THAM or BEAM, stratified per site before trial activation at site

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m^2 q12h	D –4, –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

or

BEAM:

BCNU 300 mg/m^2	D –7,IV 1h
Etoposide 2x 100 mg/m^2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m^2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m^2	D –2 IV 1h

The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5 mg / kg twice a day D-7) may be considered based on a retrospective EBMT comparison[1]

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), for 2 years, see above

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

7.1.3 Treatment schedule in study arm I:

Experimental Arm I
Alternating 3 cycles R-CHOP+Ibrutinib / 3 cycles R-DHAP induction, followed by 2 years Ibrutinib-Maintenance

Induction: Alternating 3x R-CHOP / 3x R-DHAP, every 21 days plus oral Ibrutinib in cycles 1, 3, 5, days 1-19

Due to lack of published data Ibrutinib is applied only in cycles 1, 3, 5 (R-CHOP) and not in combination with R-DHAP.

R-CHOP (cycle 1,3,5),.:		R-DHAP (cycle 2,4,6), i.v.:	
Rituximab 375 mg/m^2	D 0 or 1I.V.	Dexamethasone 40 mg	D 1-4 oral or I.V.
Cyclophosphamide 750 mg/ m^2	D 1 I.V.	Rituximab 375 mg/m^2	D 0 or 1 I.V.
Doxorubicin 50 mg/ m^2	D 1 I.V.	Ara-C 2x 2 g/m^2 q12h	D 2 I.V. 3 h
Vincristine 1,4 mg/m^2(max 2mg)	D 1 I.V.	Cisplatin 100 mg/ m^2	D 1 I.V. 24h
Predniso(lo)ne 100 mg	D 1-5 oral	(alternatively Oxaliplatin 130 mg/ m^2	D1 I.V.)
Ibrutinib 560mg	D 1-19 oral	G-CSF 5µg / kg	D6 daily SC*

* G-CSF mandatory in R-DHAP from D6 daily 5µg/kg until recovery of WBC > 2.5 G/l
Alternatively pegfilgrastim may be applied once at D6

Since no ASCT is applied in this arm, stem cell apheresis is not planned but may be performed due to local standards.

Ibrutinib-Maintenance: Ibrutinib 560 mg (daily, oral), 2 years

Rituximab maintenance may be added to all 3 study arms depending on national guidelines. (Refer to 7.2.7 for details)

7.2 Pre-Phase, conventional treatment, ibrutinib treatment, Stem Cell Apheresis, ASCT, Maintenance

7.2.1 Cytoreductive Pre-Phase

Patients with relevant B-symptoms or disease progression but incomplete diagnostic reports may receive a pre-phase therapy of one single dose of vincristine (1.4 mg/m^2, max. 2 mg) and 100 mg prednisone or another steroid in equivalent doses per day for 1 to 5 days before registration in the study or cycle 1 of study treatment. After prephase treatment the first cycle of study treatment should follow without further delay. The pre-phase therapy should be only started after all necessary biopsies were performed. In patients receiving vincristine as a pre-phase treatment, vincristine dose in the first cycle of R-CHOP should be omitted.

7.2.2 Conventional treatment R-CHOP/R-DHAP

R-CHOP / R-DHAP will be applied according to institutional guidelines.

Refer to specific product information and package inserts for premedication, preparation,

administration and storage guidelines.

Rituximab will be given at a dose of 375 mg/m^2 on the first day of CHOP or DHAP (day 21) or delayed until the circulating number of lymphoma cells is < 100 x 10^9/L, to avoid a cytokine release syndrome more frequently observed in leukemic lymphoma. That criterion has to be reconsidered before each consecutive course.

Prednisone, according to the CHOP dose will be given 1 hour prior to Rituximab. Rituximab may be given the day before CHOP or DHAP according to institutional guidelines.

The first rituximab infusion may be applied in an inpatient setting. If no adverse events have occurred the following infusions may be given in an outpatient ward. A peripheral (IV) line will be established. Vital signs (blood pressure, pulse, respiration, and temperature) should be monitored every 15 minutes during the first hour or until stable and then hourly until the infusion is discontinued and vital signs are stable. Premedication with paracetamol and/or antihistaminics (e.g. Tavegil or diphenhydramine) is strongly advised. For patients receiving CHOP, the oral prednisone dose should be taken at least one hour before the rituximab infusion, or given intravenously. The initial infusion rate of rituximab should be 50 mg/hr for the first hour. If no adverse event is seen, the dose may be escalated in 30 minutes intervals with increment steps of 50 mg/hr, to a maximum of 400 mg/hr. Patients may experience transient fever and shivering during infusion of chimeric anti-CD20 antibody. When any of the following events is noted, antibody infusion should be temporarily discontinued, the patient should be observed and the severity of the adverse events should be evaluated:

- fever > 38.5° C
- mild/moderate shivering
- mild/moderate mucosal congestion or edema
- drop in systolic blood pressure > 30 mm Hg

The patient should be treated according to the best available local practice. Following observation, if the patients symptoms improve, the infusion should be continued at 1/2 the previous rate. If there are no complications, the IV line may be discontinued after one hour of observation following the antibody infusion. If complications occur during infusion, the patient should be observed for two hours after the completion of the infusion. If no adverse event is seen with the previous infusion, the initial infusion rate of following infusions can be increased to 100 mg/hr and if no further adverse event is observed the infusion rate can be increased in 30 minutes intervals by 50 mg/h to a maximum of 400 mg/h.

Cisplatinum will be given as a continuous infusion over a 24 hour period. Alternatively Oxaliplatin 130 mg/ m^2 can be applied as an infusion over 2 hours. The infusion duration of cytarabine should be 3 hours. For safety reasons, it must not exceed the time of 3 hours.

7.2.3 Investigational Therapy R-CHOP+ Ibrutinib / R-DHAP

R-CHOP / R-DHAP will be applied according to institutional guidelines. Please refer to 7.1.2 for details. Cisplatinum will be given as a continuous infusion over a 24 hour period. Alternatively Oxaliplatin 130 mg/ m2 can be applied as an infusion over 2 hours. The infusion duration of cytarabine should be 3 hours. For safety reasons, it must not exceed the time of 3 hours.

Ibrutinib will be applied oral with 560 mg (4x 140mg capsules) daily in cycles 1, 3, 5 on days 1-19. Due to lack of published data for the combination of Ibrutinib/R-DHAP, Ibrutinib should **NOT** be applied in cycles 2, 4, 6!

Temporarily discontinue ibrutinib in patients who develop signs or symptoms of ventricular tachyarrhythmia, including, but not limited to, palpitations, chest pain, dyspnoea, dizziness, or fainting. Perform a complete clinical benefit-risk assessment before possibly restarting therapy.

Ibrutinib (4 capsules of 140mg for a dose of 560 mg) should be administered orally once daily at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. Avoid grapefruit and Seville oranges with ibrutinib treatment.

If the patient misses a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

At each study visit, sufficient study drug required for treatment until the next visit should be dispensed to the patient. Patient should bring all study drug bottles to their study visits - empty bottles and bottles with remaining capsules – together with patient diary.

Patient's drug accountability will be updated based on patient diary records. Only plausibility check to be done by site staff. Site should ask patient in case of discrepancies.

Returned capsules – in case of treatment stop by any reason or expiring study drug - cannot be re-used in this study or outside study. Study staff will instruct patients how to store study drug for at-home use as indicated for this protocol.

7.2.4 Stem Cell Mobilization and Harvest

For the regeneration of granulopoiesis and mobilization of peripheral stem cells G-CSF will be started on day 6 of the third DHAP cycle at a dose of 5-10 µg/kg body weight and will be continued until the completion of stem cell harvest.

Stem cell separation will be performed after achievement of a WBC count > 1 x 10^9/l following the WBC nadir (minimal 2 - 4x 10^6/kg body weight CD34+ cells for transplantation and "back-up"). Separation and asservation will be done according to the accepted local practice at the participating institution.

No enrichment of stem cell subpopulations or in vitro purging should be performed. However, material should be frozen for molecular studies.

Patients with insufficient cell mobilization after the first standard mobilization with G-CSF can undergo a second mobilization with plerixafor (Mozobil®) according to EMA indication and prescription schedule- For this second mobilization cyclophosphamide 2-4g/m² as conditioning is allowed. All subsequent time points for trial specific assessments will shifted accordingly.

Since no ASCT is applied in experimental arm I, stem cell apheresis is not planned in arm I but may be performed due to local standards.

7.2.5 ASCT conditioning

Each site has to decide before trial activation which ASCT conditioning – THAM or BEAM will be chosen for all patients. If clinically indicated centers may switch to the alternative conditioning regimen.

7.2.5.1 THAM:

The myeloablative radioimmunochemotherapy and peripheral stem cell transplantation should follow the end of induction visit within 2 weeks.
This procedure depends on the following requirements:
- continuous complete or partial remission
- number of stored CD34+ cells > 2 - 4x 10^6/kg body weight for transplantation and "back-up"
- no medical contraindications to myeloablative radioimmunochemotherapy

The myeloablative treatment consists of a combined radiochemotherapy with fractionated total body irradiation with a total of 10 Gray (d-7 d-6, d-5), Ara-C 1,5 g/m^2, q12h (d-4 and d–3), and Melphalan 140 mg/m^2 (d-2). The total body irradiation (TBI) will be applied according to local institutional guidelines.
The peripheral stem cells will be retransfused on day 0 (2 days after Melphalan) and should contain at least 2,0 x 10^6/kg body weight CD34+ positive cells. The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 10^9/l is recommended, but not mandatory.

7.2.5.2 BEAM:

The myeloablative chemotherapy and peripheral stem cell transplantation should follow the end of induction visit within 2 weeks. This procedure depends on the following requirements:
- continuous complete or partial remission
- number of stored CD34+ cells > 2 - 4x 10^6/kg body weight for transplantation and "back-up"
- no medical contraindications to myeloablative chemotherapy

The myeloablative treatment consists of a combined chemotherapy with Carmustine 300 mg/m^2 (d-7), Cytarabine 200 mg/m^2, q12h (d-6 to d–3), Etoposide 100mg/m^2, q12h (d-6 to d-3) and Melphalan 140 mg/m^2 (d-2).
The peripheral stem cells will be retransfused on day 0 (2 days after Melphalan) and should contain at least 2,0 x 10^6/kg body weight CD34+ positive cells. The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 10^9/l is recommended, but not mandatory.
The availability of BCNU may be challenging in some centers. Instead, TEAM (Thiotepa 5 mg / kg twice a day D-7) may be considered based on a retrospective EBMT comparison[1]

7.2.6 Maintenance (Ibrutinib)

Patients randomized to the experimental arms A+I and I will receive additional oral ibrutinib 560 mg (4x 140mg capsules) daily maintenance for two additional years in case of CR or PR at ASCT- or EoI-assessment.
For details of Ibrutinib application refer to 7.1.3. and 7.2.3.
Ibrutinib maintenance will start after regeneration of peripheral blood count after the end of the last cycle of induction therapy (earliest maintenance start at week 18) or ASCT (earliest maintenance start at week 22).

If tolerated, for maintenance therapy ibrutinib can be resumed at full dose even if it had to be reduced in induction therapy because of hematologic toxicity.

Requirements for start of Maintenance:

ANC ≥ 1,000 cells/mm^3 (1.0 X 10^9/L);

Platelets ≥ 50,000 cells/mm^3 (50 X 10^9/L);

Rituximab or ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity

Any other AE related to induction treatment or ASCT not requiring discontinuation has resolved to Grade ≤ 2 severity.

7.2.7 Rituximab Maintenance

Rituximab maintenance is not under investigation in this trial but is allowed after Induction or ASCT in case of CR or PR at ASCT or EoI-assessment according to national guidelines. The decision on additional rituximab maintenance must be identical for all 3 study arms to avoid treatment related bias.

Participating sites should contact their national study group to clarify about the additional application of rituximab maintenance. Application and management of rituximab maintenance will follow the standards of the participating study groups.

7.3 Dose adjustment

7.3.1 R-CHOP/R-DHAP (with or without Ibrutinib)

No dose modification will be made in the first course.

Requirements for therapy resumption:

- ANC ≥ 1000 cells/mm³ (1.0 X 10^9/L);
- Platelets ≥ 75,000 cells/mm³ (75 X 10^9/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related to induction treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.

- If ANC < 1.0 x 10^9/l or thrombocytes < 75 x 10^9/l at the day of the next course (d22 or d21 if rituximab is applied at d0) it is strongly recommended to postpone treatment (including Ibrutinib) for 1 week.
- If an insufficient hematologic recovery after one week delay (d29) remains, it is strongly recommended to postpone treatment until the requirements for therapy resumption outlined above are fulfilled. Then a two-step-approach of dose modifications is recommended:
  - In a first step reduce the next R-DHAP regimen according to the rules outlined in 7.3.1.1 (depending on d29 blood levels)
  - In a second step, dose modifications of the next R-CHOP (depending on d29 blood levels) are recommended according to the rules outlined in 7.3.1.2.
- In the event of insufficient blood level recovery or persistent AEs grade > 2 severity contact trial office or medical advisor to discuss permanently stop of study treatment
- In the event of severe treatment associated toxicity (CTC grade IV) in the last cycle but with complete recovery at d29 the investigator may reduce the next dosing of chemotherapy to 75% of Cyclophosphamide and Doxorubicin in case of CHOP or 75% of Cytarabine and Cisplatinum/Oxaliplatinum in case of DHAP.

Dose reduction strategy

Postpone treatment until ANC > 1000 cells/mm^3 (1.0 x10^9/L) and platelets > 75.000 cells/mm^3 (75.0 x10^9/L), than follow dose reduction recommendations

Insufficient recovery at/after d29	**Dose reduction according to blood levels on d29**
First occurrence	Reduce next R-DHAP
Second occurrence	Reduce next R-CHOP and keep reduced dose level of R-DHAP
Third occurrence	Further reduce next R-DHAP and keep reduced dose level of R-CHOP
Fourth occurrence	Further reduce next CHOP and keep reduced dose level of DHAP

7.3.1.1 Dose modifications of DHAP

In case of severe neurotoxicity: (peripheral neuropathy, severe constipation/paralytic ileus, ototoxicity): 50% reduction or stop cisplatinum/oxaliplatin according to the discretion of the treating physician.

Nephrotoxicity: If >50% decrease of creatinine clearance cisplatinum will be stopped and oxaliplatin will be applied alternatively.

For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

ANC/µl on d29	Thrombocytes/µl on d29	Cis-platinum	Ara-C	Dexa-methason	Rituximab
>1.000/µl	>75.000/µl	100%	100%	100%	100%
500 – .1000/µl	50.000-75.000/µl	75%	75%	100%	100%
< 500/µl	< 50.000/µl	50%	50%	100%	100%

Dose reduction of DHAP - All dose reductions are calculated on the blood values after 1 week of treatment delay (d29)

Dose reduction will be calculated according to the doses of R-DHAP given in the previous cycle. This reduction of dose should be omitted if the severe myelosuppression can be assumed to be the result of an initial bone marrow involvement of the lymphoma.

Based on the potential toxicity, a sufficient hydration (2-3 l/ day) and regular ENT examinations during the course of Cisplatinum containing induction therapy is mandatory.

7.3.1.2 Dose modifications of CHOP (with our without ibrutinib)

For Ibrutinib dose modifications refer to 7.3.2.

In case of severe neurotoxicity (peripheral neuropathy, severe obstipation/paralytic ileus): adapt vincristine according to the discretion of the treating physician. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

ANC/µl on d29	thrombocytes /µl on d29	Cyclophos - phamide	Doxo-rubicin	Vin-cristine	Pred-nison e	Ritu-ximab	Ibrutinib
>1.000/µl	>75.000/µl	100%	100%	100%	100%	100%	Refer to 7.3.2
.500–1.000/µl	50.000-75.000/µl	75%	75%	100%	100%	100%	Refer to 7.3.2
< 500/µl	< 50.000/µl	50%	50%	100%	100%	100%	Refer to 7.3.2

Dose reduction of CHOP - All dose reductions are calculated on the blood values after 1 week of treatment delay (d29)

Dose reduction will be calculated according to the doses of CHOP given in the previous cycle. This reduction of dose should be omitted if the severe myelosuppression can be assumed to be the result of an initial significant bone marrow involvement of the lymphoma.

7.3.2 Ibrutinib

On Day 1 of each treatment cycle, the subject will be evaluated for possible drug toxicities. All previously established or new toxicities observed at any time are to be managed as described below.

Ibrutinib-treatment should be interrupted for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Study drug may be interrupted for a maximum of 28 consecutive days for drug-related toxicity. Study drug should be discontinued permanently in the event of a drug-related toxicity Grade ≥ 3 is lasting more than 28 days. No dose escalation of study drug (more than 4 capsules/day [i.e., above 560 mg]) is allowed in this study. Changes must be recorded in the Dosage Administration page of the eCRF.

For Grade ≥ 3 hematologic toxicities (defined as neutropenia, anemia or thrombocytopenia), treatment will be delayed for a maximum of 4 weeks until resolution to Grade ≤ 2. In case of recurring Grade 3 hematological toxicity or Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity or any Grade 3 toxicity that is not resolving with medical management, dosing of ibrutinib should be modified as outlined below:

Occurrence	**Action**
First	Hold ibrutinib until recovery to Grade ≤1 (≤2 for hematologic toxicity) or baseline; may restart at original dose level
Second	Hold ibrutinib until recovery to Grade ≤1 (≤2 for hematologic toxicity) or baseline; restart at 1 dose level lower (3 capsules [i.e., 420 mg daily])
Third	Hold ibrutinib until recovery to Grade ≤1 (≤2 for hematologic toxicity) or baseline; restart at 1 dose level lower (2 capsules [i.e., 280 mg daily])
Fourth	Discontinue study drug

Doses that were missed, due to toxicity or any other reasons, will not be rescheduled. If a dose is reduced, re-escalation is not permitted.

There will be no dose reductions of rituximab. In case of cycle delay due to ibrutinib induced toxicity, immunochemotherapy of the next cycle will also be postponed until AE has resolved and recycling is allowed.

Resumption of Ibrutinib-dosing may begin if:

The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);

The platelet count is ≥ 50,000 cells/mm³ (50 X 10^9/L);

Rituximab or ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity

Any other AE related treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.

In induction therapy if R-CHOP is postponed due to toxicity ibrutinib has to be also postponed.

If tolerated, for maintenance therapy ibrutinib can be resumed at full dose even if it had to be reduced in induction therapy because of hematologic toxicity.

8 Compliance

Upon termination of the study, the remaining IMP will be destroyed at the site as agreed upon by both the sponsor and the site.

Ibrutinib is to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. Records should be kept on the study drug accountability form provided by the sponsor or its designee. Dispensing of the study drug (ibrutinib) must be recorded in the subject's source documents. The ibrutinib may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Investigator or the site pharmacist will maintain a log of all ibrutinib dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects will be provided with a diary card to record intake at home. Site personnel are to instruct the subject to bring the diary card and any unused ibrutinib including empty bottles to the site at the beginning of each treatment cycle to check ibrutinib dosing compliance.

Instructions for proper self-administration and ibrutinib storage conditions will be provided. Precautions associated with the use of ibrutinib and prohibited concomitant medications will be reviewed. Site staff will provide additional instruction to reeducate any subject who is not compliant with the ibrutinib schedule.

9 Concomitant Therapy

9.1 Permitted Concomitant Medications and Procedures

Therapies considered necessary for the subject's well-being may be administered at the discretion of the Investigator. All medications (prescription and non-prescription), growth factors, transfusions, treatments and therapies taken from 14 days prior to start of induction through the last dose of maintenance therapy, must be recorded on the appropriate page of the eCRF.

The use of rasburicase for the treatment of tumor lysis syndrome and the prevention of hyperuricemia is allowed according to institutional guidelines.

The use of antibiotic and/or anti-viral prophylaxis according to institutional guidelines is also allowed.

Primary prophylaxis with granulocyte colony stimulating factors (G-CSFs) is obligatory during the R-DHAP cycles of induction and recommended after autologous stem cell transplantation.

Patients who experience Rituximab infusion-related temperature elevations of > 38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (≥ 500 mg) and/or H1- and H2-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β2 agonists/epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice.

9.2 Prohibited concomitant Medications

The following medications are prohibited during the study: any chemotherapy, anticancer immunotherapy, experimental therapy, and radiotherapy. Corticosteroids are allowed when as premedication or manage rituximab infusion-related reactions or contrast allergies, as well as short courses (<14 days) of corticosteroid treatment for non-cancer related medical reasons (i.e.; treatment for autoimmune cytopenias) at doses not to exceed 100 mg/day of prednisone or equivalent, otherwise systemic use of corticosteroids (i.e., any systemic corticosteroids ≥20 mg/day prednisone or its equivalent per day for more than 10 days) is prohibited unless reviewed and approved by the sponsor's medical monitor. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Use of the following therapies is prohibited during the study:

-
- Radiotherapy
- Immunotherapy (other than rituximab)
- Hormone therapy (other than contraceptives, hormone-replacement therapy, ormegestrol acetate)
  Hormonal therapy (e.g., GmRH-agonists) for egg cell harvest/fertility preservation is allowed in women of childbearing age
- Any therapies intended for the treatment of NHL, whether approved or experimental (outside of this study)

9.3 Concomitant Medication to be used with Caution

CYP3A4/5 Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4/5 (Section 2.1.3). Co-administration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) can decrease ibrutinib plasma concentrations and should be avoided. Since no exposure data are available in patients treated concomitantly with strong inhibitors of CYP3A4/5 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone), these inhibitors should be avoided. If ibrutinib must be administered with a strong inhibitor the national coordinating investigator should be consulted before use, and a dose reduction of ibrutinib to 140 mg daily or a temporary hold of ibrutinib should be considered. Patients should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, monitor patient for toxicity and follow dose modification guidance as needed.

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A4/5.

Examples of inhibitors, inducers, and substrates can be found in Appendix

QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

Other Drug Interactions

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

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

9.4 Special precautions to minimize bleeding risk

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. Refer to 6.4 for guidance during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements, such as fish oil and vitamin E preparation should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied.
Subjects requiring the initiation of therapeutic anticoagulation therapy (other than Vitamin K antagonist) during the course of the study should have treatment with ibrutinib held, the sponsor's medical monitor should be contacted, and ibrutinib should not be restarted until the subject is clinically stable and the re-initiation of ibrutinib is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

10 Investigational Medicinal Product(s) (IMP)

In this trial **ibrutinib** is considered as investigational medicinal product (IMP). The other drugs are standard of care.

The investigator or the site pharmacist will maintain a log of all ibrutinib dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects will be provided with a diary card to record intake at home. Site personnel are to instruct the subject to bring any unused ibrutinib to the site at the beginning of each treatment cycle to check ibrutinib dosing compliance.

Instructions for proper self-administration and ibrutinib storage conditions will be provided. Precautions associated with the use of ibrutinib and prohibited concomitant medications will be reviewed. Site staff will provide additional instruction to reeducate any subject who is not compliant with the ibrutinib schedule.

10.1 Physical description of IMP, Packaging and Labelling

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib.

All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients. The ibrutinib capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles and will utilize child resistant packaging (caps will be child resistant).

Each bottle contains 120 capsules of ibrutinib.

Bottles will contain study specific label to meet Good Manufacturing Practice guidelines and the local requirements. The investigational product will be labelled and handled as open-label material.

10.2 Storage and handling

The recommended storage condition for ibrutinib capsules is controlled room temperature (15° to 25°C) with excursions permitted up to 30°C. Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions.

Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol.

10.3 Study drug supply, drug accountability, study drug return and destruction

The Sponsor will arrange the supply of IMP to investigational sites in a timely manner.

No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of ibrutinib to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. The subject must be instructed to return all original containers, whether empty or containing ibrutinib. All study drugs will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject (if applicable), must be available for verification by the sponsor's site monitor during on-site monitoring visits.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drugs (ibrutinib) from, nor store it at, any site other than the study sites agreed upon with the sponsor.

The destruction of unused study drug must be documented on the drug destruction form. Used returned study drug bottles will be documented.

11 Schedule of Treatment and Assessments

For the schedule of treatment and assessments see flow chart figure 1.4.

All scheduled assessments and treatments can be performed within a timeframe of +/- 4 days unless otherwise noted. Nevertheless the period between the last intake of ibrutinib and the first day of the following R-DHAP should be at least 3 days to ensure an adequate drug washout.

The following sections will give an overview and adequate explanations to the examinations and procedures to be performed in this trial.

Source documents, including radiological imaging, must be stored and be available for subsequent review. The respective printouts will be stored in the subject's medical file.

11.1 Methods of Assessments

11.1.1 Physical Examination

A complete physical examination should include an evaluation of head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

A targeted physical examination should be limited to systems of primary relevance that is, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

11.1.2 Tumor and Response Assessments

Response assessments will be performed by the investigator, based on physical examinations, CT scans, laboratory results and bone marrow examinations through use of the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

Response evaluation by the investigator should be done without the optional FDG-PET results. FDG-PET remains optional upon investigator's discretion.

Bone marrow examinations should include a biopsy for morphology, an aspirate for local hematology (optional, if part of standard of care at site), and an aspirate for MRD determination. Bone marrow examinations are required at screening for staging purposes and for determination of MRD baseline levels in all patients.

If there was bone marrow infiltration at screening, then subsequent bone marrow biopsies at the response assessment time points are mandatory for clinical response evaluation. In patients with PR due to continued bone marrow involvement, subsequent bone marrow examinations should be performed to confirm CR at a later time point.

If the bone marrow changed from involved to not involved further bone marrow biopsies are optional. Bone marrow aspirations for MRD should be performed even in cases which are negative in conventional cytomorphological examination (see below)."

An additional bone marrow aspirate may be done if that is standard of care at the site.

If bone marrow involvement was diagnosed by morphology at screening, a subsequent bone marrow aspirate for MRD is required at the induction completion/end-of-treatment visit and at the maintenance completion / end of maintenance visit for all patients who achieve a CR or PR (all responders). If bone marrow was free of lymphoma by morphology at screening, subsequent bone marrow aspirates for MRD is not mandatory, but strongly recommended for MRD assessment. This recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology.

Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

Response evaluation with CT scans using contrast media are the preferred radiology method at the following time points:

- Midterm Evaluation: After completion of 4 cycles of chemotherapy (approx. 11 weeks after the first dose date (should match with MRD assessment time point)),
- End of Induction (EOI) Evaluation: 3 weeks after completion of the last cycle of chemotherapy (approx. 18 weeks (ca 5 months) after the first dose date),
- Post ASCT (pASCT) Evaluation: within 4-6 weeks after EOI evaluation (ca 6 months after the first dose date)
- 6 months after "pASCT Evaluation" (ca 12 months after the first dose date),
- 12 months after "pASCT Evaluation" (ca 18 months after the first dose date)
- 18 months after "pASCT Evaluation" (ca 24 months after the first dose date),
- 24 months after "pASCT Evaluation" (ca 30 months after the first dose date),
- 36 months after "pASCT Evaluation" (ca 42 months after the first dose date),
- 48 months after "pASCT Evaluation" (ca 54 months after the first dose date),
- 60 months after "pASCT Evaluation" (ca 66 months after first dose date and then according to local clinical routine.

Complete physical examination (including ECOG/WHO Performance Status and B symptoms) should be performed during each response assessment by CT scans.

11.1.3 Laboratory Examinations / Biological Specimens

Samples for the laboratory assessments will be analyzed at the study site's local laboratory.

Tumor tissue samples will be sent for central pathology review (for details refer to 12.1)
MRD peripheral blood and bone marrow samples will be sent to central MRD laboratories (for details refer to12.2 and Appendix 5).
Protection of patient confidentiality will extend to any data generated from the analysis of these samples.
All clinically significant findings will be documented in the source data and in the eCRF as adverse events. Clinically significant findings at baseline visit will be documented as concomitant disease under medical history.

11.2 Baseline Examination

The patients will be required to give written informed consent to participate in this study before any non-routine baseline evaluations are conducted.

The histological examination of representative diagnostic material (lymph node, other involved soft tissue or bone marrow only if lymph node material is not available) must be performed prior to start of therapy.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent within a time period of 14 days (for CT scan and bone marrow 28 days) prior to study entry may be used; such tests do not need to be repeated for baseline.
The subject's eligibility has to be evaluated during the baseline period prior to randomization and administration of the first cycle of chemotherapy. The baseline period of 28 days is the time frame from obtaining informed consent to start of study therapy.

Please see the schedule of activities and assessments provided in chapter 1.4 for baseline assessments and for MRD samples see 12.2.

11.3 Assessment during induction treatment

Assessments scheduled on the day of study drug administration should be performed prior to immunochemotherapy infusion, unless otherwise noted.
Please see chapter 1.4 for schedule of activities and assessments to be performed during induction treatment.

However, if Baseline or standard of care labs are drawn within 1 week before receipt of study drug on cycle 1 day 1, they do not need to be repeated on cycle 1 Day 1.

Any patient presenting progressive disease during initial chemotherapy should not receive further study-specific therapy. After complete documentation of progression, these patients need to be followed for survival.

During Safety Run In Phase blood counts will be done twice a week from day 7 until complete recovery of hematopoiesis (for criteria of full recovery refer to “Requirements for therapy resumption” in section 7.3.1)
(Safety Run In Phase is completed.)

11.4 Midterm Evaluation

To avoid unnecessary continuation of therapy after 4 cycles treatment response of the patient should be evaluated by the following examinations provided in chapter 1.4. .

For response assessment at midterm please see chapter 11.1.2 Tumor and Response evaluation and for MRD Samples see 12.2.

11.5 End of induction treatment (EOI) evaluation

The end of induction treatment evaluation has to be performed after completing the induction chemotherapy treatment, before patients proceed to intensified consolidation and ASCT (Arm A + Arm A+I) or to ibrutinib maintenance (Arm I) or at time point of clinically indicated progressive disease.
For assessments at end of induction treatment please see chapter 1.4 for schedules of assessments to be performed during induction treatment and for MRD samples please see chapter 12.2.

11.6 Post ASCT (pASCT) Evaluation

Patients in Arm A and Arm A+I, undergoing ASCT will have an evaluation after 3-5 weeks after transplantation before proceeding to maintenance phase.

Patients in Arm I will have the same assessments at the same time points, this is approx.4-6 weeks after End of induction treatment assessment (ca. 6 months after start of therapy). The term pASCT will be used for this visit even if patient has not received ASCT because of randomization or due to medical reasons. This is important for the comparability of efficacy of the three study arms.

Please see the chapter 1.4 for schedules of assessments to be performed during induction treatment and for MRD samples please see 12.2.

11.7 Assessments during maintenance – period

During maintenance treatment period all visits must occur within ± 1 week from the scheduled date, unless otherwise noted. Assessments scheduled should be performed prior to study drug dispension, unless otherwise noted.

Please see the study flowcharts provided in chapter 1.4 for schedules of assessments to be performed during maintenance.

For response assessments during maintenance see 11.1.2 (Tumor and Response evaluations).

11.8 Assessments during observation without therapy

During observation (patients in CR and PR) all visits must occur within ± 4 weeks from the scheduled date, unless otherwise noted.

Please see chapter 1.4 for schedules of assessments to be performed during follow-up. For response assessments during follow up see 11.1.2 (tumor and response evaluations) and for MRD samples see chapter 12.2.

In case of treatment stop (e.g. due to toxicity) without further treatment outside the protocol and without progression of the disease patient should be followed up as in normal follow–up: every 6 months for MRD and Response (CT) until month 30 and thereafter for MRD every 6 months until month 54 and last MRD at month 66. For CT every 12 months until month 66 and also corresponding laboratory tests should be performed.

In case of discontinuation of therapy and further treatment outside the protocol without progression of the disease, patients are observed in normal follow-up for response (as after completion of maintenance therapy). So a CT every 6 months until month 30 and thereafter every 12 months until month 66 for Response evaluation and also corresponding laboratory tests should be performed.

For this case sending of material for MRD examinations is under discretion of the site but has not to be performed necessarily.

11.9 Assessments at time of progression and during survival follow-up

If patient has progressive disease during the study treatment medication will be stopped and a “Time-of-Progression-visit” (ToP) will be performed.

For the ToP visit all assessments of the End-of-Induction (EoI)-visit should be performed as outlined in chapter 1.4.

However, all results of routine tests performed at the time of suspected progression may be used for ToP visit and do not need to be repeated.

After the EOI/ToP visit patient enters survival follow up phase where disease and performance status and information about salvage therapy should be provided all 6 months until the end of study. The patients will be followed until the end of the trial for survival status, treatment status, lymphoma status and SPM.

12 Reference assessments

12.1 Pathology Review

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis.

A mandatory central pathological review will be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to classify precisely the malignancy according to the WHO classification 2008. The pathological review will be centralized nationally in each participating countries in their national reference laboratory

The review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of mantle cell lymphoma (both by morphology and immunophenotyping including CD5, CD10, CD20, CD23, BCL2 and Cyclin D1), and recording of the morphological variants including prognostic factors such as Ki67 expression[18].

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, will be sent to the designated national pathology platform according to the process described in Appendix 4.

In absence of tumor samples, when bone marrow samples of good quality are available, patient can be included and bone marrow fixed sample can be sent for pathological review.

At reception, routinely stained sections will be assessed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized, and a consensus diagnosis will be established. When the diagnosis has been revised the clinician and the initial pathologist will be informed.

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction; both will be used to study the expression of markers which may influence the prognosis of mantle cell lymphoma

At the end of the inclusion, frozen tumor tissue will be requested and organized by the designated national pathological platform. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of mantle cell lymphoma patients.

12.2 Minimal Residual Disease (MRD) assessment

MRD detection in MCL has been evaluated in several publications for both staging and follow-up[11,12,19,20]. The EU MCL network is developing guidelines for standardization both the technology and the reporting of MRD in MCL and other hematological diseases.

In this trial, we will use the expertise of the EU MCL network to assess MRD status using allele-specific quantitative PCR (RQ-PCR) to determine each individual patient's MRD status. Allele-specific quantitative PCR is currently the most sensitive, specific and standardized method for MRD assessment in MCL and has been successfully used in multicenter clinical trials for the treatment of MCL.

For RQ-PCR, it will be necessary to determine an individual clonal marker by DNA sequencing of the individual lymphoma clone from each patient. This will be possible from diagnostic peripheral blood and bone marrow analysis prior to any treatment. A prerequisite for establishment of an individual MRD assay is the determination of lymphoma cell infiltration in the diagnostic peripheral blood or bone marrow samples based on flow-cytometry. Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

In all induction arms, peripheral blood and bone marrow will be collected at the timepoints specified in Appendix 5: .

For each time point, peripheral blood and bone marrow samples (see Appendix 5: for description of the samples required for each time point) will be sent to the national reference biology laboratories listed in section 1 of the protocol. MRD analysis will be performed in the each national reference laboratory and reported centrally to the Sponsor.

13 Safety Parameters

13.1 Definitions (AE, SAE, AR, SUSAR, Toxicity)

The following definitions are used for throughout the trial. For special reporting conventions and exceptions see chapter 13.4.

Adverse Event (AE)
An Adverse Event/Experience (AE) is any untoward medical occurrence in a subject or in a clinical investigation subject who has administered a medicinal or pharmaceutical product or is participating in a clinical trial, and which does not necessarily have a causal relationship with this treatment.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies,
- Preexisting medical conditions (other than MCL), judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

Toxicity
The historical use of the term “toxicity”, while not clearly defined by regulatory organizations, has been described as an AE that has a causal relationship to investigational treatment.

Adverse (Drug) Reaction (AR)
This is defined as any unintended (harmful or unwanted) response to a medicinal product that is used for prophylaxis, diagnosis or therapy of diseases, or for modification of physiological function, and is suspected to be related to the drug. A suspected AR is fulfilled, if the causality is judged as possibly or probably related by the investigator.

Unexpected Adverse (Drug) Reaction (UAR)
This is defined to be an adverse drug reaction which nature and severity is not consistent with the applicable product information (Investigator’s Brochure IMBRUVICA® (Ibrutinib), JNJ-54179060), or an event which has not previously been observed or documented and which is thus not on the basis of what might be anticipated from the pharmacological properties of the product.

Serious Adverse Event (SAE)
A Serious Adverse Event is any untoward medical occurrence or effect at any dose, any undesirable or unintentional effect that:

- results in death (regardless of cause)
- is life threatening
  - places the subject, in the view of the investigator, at immediate risk of death at the time of event
  - It does not refer to an event that, which hypothetically might have caused death if it were more severe

- results in subjects hospitalization (overnight stay) or prolongation of existing subjects’ hospitalization, unless hospitalization is for:
  - Hospitalization that does not necessitate an overnight stay.
  - routine scheduled treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - planned prior to subject entering in the trial
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication treated in the trial and which has not worsened since the start of treatment with the investigational medicinal product

- results in persistent or significant disability or incapacity of the subject
  - disability is a substantial disruption of a person's ability to conduct normal life functions
- is associated with a congenital anomaly or birth defect
- is qualified as "other" important medically significant event or condition e.g. the event may jeopardize the subject or may require intervention to prevent one of the outcome listed above (e.g. intensive treatment in an emergency room or at home).

Serious Adverse (Drug) Reaction (SAR)
This is defined as an adverse drug reaction that is serious and at least possible related to IMP (see SAE criteria above). The events that are excluded from the definition of an SAE are also excluded from the definition of an SAR.

Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)
A SUSAR is an adverse reaction, which is both serious and unexpected because the nature or severity of this event is not consistent with the applicable product information (Investigator's Brochure IMBRUVICA® (Ibrutinib), JNJ-54179060).

Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Drug Interaction
- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion)
- Suspected transmission of an infectious agent

Special reporting situations should be recorded in the eCRF and also with a short notice via fax to GLSG Pharmacovigilance Department (Fax: +49 89-4400-77900/01). Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

13.2 Criteria to be evaluated by investigator (1st assessment)

Assessment of seriousness, causality, severity and of medical interest
For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of severity, seriousness and causality.
The terms severe and serious are not synonymous. "Severe" refers to the intensity of an AE; the event itself may be of relatively minor medical significance. "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness serves as the guide for defining regulatory reporting obligations.

Assessment of Severity
The intensity (severity) of adverse events will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). Adverse events not explicitly included in the NCI Common Toxicity Criteria list should be described in detail and graded according to the five points system below:

Grade 1	Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade 2	Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
Grade 4	Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable (Please note: grade 4 does **not always** imply, that the event is serious)
Grade 5	Death - the event results in death (Please note: grade 5 does **always** imply, that the event is serious and should be reported immediately)

Assessment of Seriousness
See definition of Serious Adverse Event above (13.1). As mentioned above, the criterion "serious" serves as guide for expedited reporting obligations.

A Serious Adverse Event should be immediately reported (within 24 hours) to the sponsor after becoming aware of the event.

Assessment of Causality
Relationship of the adverse events to the investigational products should be assessed as follows:

Related	The temporal relationship between the event and study drug administration makes **causal** relationship **possible, probably or definitely**, AND other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Not Related	The temporal relationship between the event and study drug administration makes **causal** relationship **unlikely or impossible (not related)** OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

When the final causality assessment is unknown and it is uncertain whether or not the investigational product caused the event, then the event should be handled as related to the investigational product for reporting purposes.

13.3 Criteria to be evaluated by the sponsor (2nd assessment)
To ensure subject safety and data quality a first evaluation is performed by the investigator and a second evaluation with respect to expectedness and risk-benefit assessment is

performed by the Sponsor Delegated Person/LKP to process safety evaluation according to a four-eye principle.

Assessment of seriousness and relatedness: please refer to previous definitions

Assessment of Expectedness

Expected AEs that have been previously observed with the use of the study agent(s) and are listed in the in the following basic reference document:

- Investigator's Brochure IMBRUVICA® (Ibrutinib), JNJ-54179060

Unexpected AEs

- AEs whose nature or severity (intensity) is not consistent with the applicable basic reference document (see above)

Risk-Benefit Evaluation

The second evaluation by the sponsor must additionally include a risk-benefit evaluation and describe which actions should be taken regarding:

- safety issues that might alter the current benefit-risk assessment

the protection of study participants against direct hazards that affect the conduction of the clinical trial

13.4 Reporting of Serious Adverse Events

All events that meet one or more criteria of seriousness (see Section Definition for SAE Section 13.1) that occurred from the time of randomization up to 30 days after last visit with the last individual trial specific medication of the subject**,** regardless the relationship to the study treatment must be carefully documented in the source documents and reported to the GLSG Pharmacovigilance Department.

The last individual trial specific medication in Arm A is the ASCT, in Arm A+I and Arm I it is the last dose of Ibrutinib-Maintenance.

If the study therapy has to be stopped during induction phase the last application of induction therapy is the last individual trial specific medication.

The Investigator shall inform the sponsor immediately of the occurrence of a serious adverse event (SAE) and Adverse Event of Special Interest (AESI) with the exception of events which need not to be reported immediately according to the protocol or investigator's brochure. Personal data must be pseudonymised before being transmitted by using the Patient Identification Code of the trial patient.

For initial SAE reports, site should enter all data that can be gathered immediately at the latest within 24 hours after becoming aware of occurrence of the SAE in the specified Serious Adverse Event Report Electronic Form and send to the sponsor.

Relevant follow-up information should be entered immediately at the latest within 24 hours after awareness in the specified Serious Adverse Event Report Electronic Form.

Further information on reporting and documentation details are described in the study specific Safety Management Plan.

Minimum Criteria for Adverse Event Reporting

- Duration of an AE (start date and stop date)

- Grade of AE (according to CTC criteria, version 4.03 , available in eCRF)
- Drug relationship of the AE to the investigational product (Causality assessment)
- Outcome of the AE
- Assessment of seriousness of the event

Due to the expected toxicity of the study treatments, only the following events must be recorded in the appropriate eCRF Adverse-Event-Form (from time of randomization up to 30 days after last visit with the last individual trial specific medication of the subject):

- All adverse events of any grade which are serious or of special interest must be recorded by the site on an eCRF AE-Form and marked as "serious" or of "special interest" within 24 hours after the site becomes aware of the event; only in the case that the eCRF is not accessible for technical problems, the event should be reported on the paper-based SAE-form by fax to the sponsor; the data will be entered into the eCRF by the Sponsor. As soon as the eCRF becomes accessible at the site again, the site has to check and confirm the correctness and completeness of the SAE documentation in the eCRF folder “paper SAE report”.

- All non-hematological events of CTCAE grade 3 or 4
- All infections of CTCAE grade 2, 3 or 4
- All events with anemia, neutropenia or thrombocytopenia of CTCAE grade 2, 3 or 4
- All events of any grade, if found to be medical significant by the investigator

Clinical symptoms of progression may be reported as AE if the symptom cannot be determined as exclusively due to the progression of the underlying cancer. In case of uncertainty whether an AE is only due to the disease under study, it should be reported as an AE or SAE.

The following events should **not** be reported as AE or SAE.

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Hospitalizations due to stem cell apheresis
- Hospitalization for a maximum of 4 weeks following the stem cell transplantation for patient monitoring in cytopenia, not associated with any deterioration in condition besides the expected cytopenia
- Treatment in a health resort facility for physical regeneration after induction or high dose chemotherapy
- Progression of lymphoma including its clinical symptoms should <u>not</u> be reported as AE or SAE if it is clearly consistent with the suspected progression of the underlying lymphoma
- Hospitalization due solely to the progression of underlying MCL should not be reported as SAE; 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
- Hospitalization because of a diagnostic or elective surgical procedure for a pre-existing (= already documented in the patient’s medical history!) medical condition that has not deteriorated does not require reporting as a SAE. 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.

Exclusion of Treatment related SAEs from immediate reporting:

The following events are well known side effects and are excluded from immediate reporting (within 24 hours) if they occur during and within 30 days after complete therapy (induction, high dose chemotherapy consolidation and maintenance therapy):

- nausea and emesis
- mucositis
- hematologic toxicity
- infectious complications

Nevertheless, these events should be reported on the SAE eCRF, as they are part of the annual safety report.

13.5 Pregnancy

Women of childbearing potential are required to have a serum β-hCG pregnancy test to exclude a pregnancy before to be enrolled in the clinical trial.

Pregnancy testing will be conducted within 28 days prior to the first dose of trial drug and during treatment if clinically indicated.

There are no adequate and well-controlled studies of ibrutinib in pregnant women. Based on findings in animal trials, ibrutinib is teratogenic and may cause fetal harm such as post--implantation loss, increased visceral malformations, increased skeletal malformations or decreased fetal weights. No teratogenicity events have been reported from the available clinical trials. Ibrutinib should not be used during pregnancy. Women of child--bearing potential must use highly effective contraceptive measures while taking ibrutinib. Those using hormonal methods of birth control must add a second barrier method. The time period following treatment with ibrutinib where it is safe to become pregnant is unknown. Women should avoid becoming pregnant while taking ibrutinib and for up to 3 months after ending treatment with Ibrutinib or 12 months after the last administration of Rituximab (whichever is the longest period of time).

If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

In some countries competent authorities require pregnancy tests during the exposition to ibrutinib on a regular basis. Please refer to the schedule of treatment and assessments for details.

It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from ibrutinib in nursing infants, breast-feeding should be discontinued during ibrutinib treatment.

Action to be taken in case of pregnancy

If a female subject becomes pregnant or suspect to be pregnant (including a positive pregnancy test regardless of age or disease state) while participating in this trial and being on study drug, or within 6 months of the last dose of the study drug, the investigator has to be informed immediately about this event in order to decide the further proceedings and consequences for the female subject.

The pregnant subject has to discontinue permanently the treatment with the IMP, has to be excluded from the trial, and has to be instructed to return any unused portion of the study drug to the investigator, if applicable.

Likewise, if the partner of a male trial subject becomes pregnant or suspects to be pregnant while the subject participates in this trial, the investigator has to be informed immediately by

the male subject about this suspected or confirmed pregnancy. The investigator will then provide this information to the sponsor/sponsor delegated person for follow-up as necessary.

To ensure the safety of female subjects or female partners of male subjects, each pregnancy that becomes known to the investigator during the trial, must be reported as an event.

Therefore the investigator will record and report pregnancy information on the appropriate pregnancy report form as an initial report contact immediately (latest within 24 hours) to the sponsor/ the sponsor delegated person.

The pregnancy itself is not considered to be an AE or SAE, but the pregnancy must be followed through delivery for SAEs. Any pregnancy complication or elective termination of a pregnancy for medical reasons has to be recorded as an AE or a SAE, if applicable (see section 13.1) and will be followed up as described above.

Therefore the pregnancy should be followed up until completion or until pregnancy termination and the outcome of pregnancy should be notified to the sponsor/ the sponsor delegated person to determine the outcome of the pregnancy regarding maternal or newborn complications. The investigator will seek and provide this follow-up information after the planned date of delivery. This information will be forwarded to the sponsor/ sponsor delegated person. For this purpose the pregnancy report form will be used as follow-up report. The timeframe to follow up the details of birth will be no longer than 28 days following the delivery date.

The investigator should report the outcome of the pregnancy as SAE if it includes

- Spontaneous, therapeutic abortion or voluntary termination,
- stillbirth,
- neonatal death,
- presence of birth defects, or
- congenital anomaly (including that in an aborted fetus, stillbirth or neonatal death),

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs.

In addition, any infant death after 28 days that the investigator suspect is related to the in utero exposure to the study drug should be reported.

Furthermore, any SAE occurring as a result of a post-trial pregnancy and considered reasonably related to the investigational medicinal product by the investigator, will be reported as described above. The investigator is not obliged to actively seek this information in former trial participants, but has to meet the reporting obligations as soon the investigator will be aware of this event through spontaneous reporting by the person concerned.

13.6 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 subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information.

Procedures

All initial PQCs must be reported by the study site personnel within 24 hours after being made aware of the event to the national coordinator / project manager, who will inform the sponsor.

Detailed contact information will be handed over to the study sites at study initiation visit.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section13.4 Reporting of Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.7 Events of special interest

Second primary malignancies, major and intracranial hemorrhage will be monitored as events of special interest.

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

Major hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is grade 3 or greater in severity or that result 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.

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.

Any event of hemorrhage which meets the above mentioned criteria for a event of special interest has to be reported up to 30 days after last dose of study specific treatment of the trial patient.

Second primary malignancies (SPM)

All SPMs occurring from the time of signing the ICF until end of study must be considered as an “Important Medical Event” and reported as serious adverse events regardless of causal relationship to study treatment. Information about the diagnosis of the SPM must be provided with the SAE report.t (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

<u>Reporting to the Competent Authority and Ethics Committee by the Sponsor</u>

The GLSG Pharmacovigilance Department should report all suspected unexpected serious adverse reactions (SUSARs) to the responsible national ethics committees (IEC) the EMA and the competent authorities of the participating countries depending on each CA’s national legislation in the defined time frame:

- within 7 days after knowledge of such a case for fatal or life-threatening events. Relevant follow-up information for these cases will be subsequently submitted within an additional eight days and

- within 15 days of first knowledge by the investigator for other serious adverse events.

Yearly, a Development Safety Update Report (DSUR) will be submitted to the responsible ethics committees (IEC) and the competent authorities of the participating countries depending on the national legislation. Further national reporting obligations regarding pharmacovigilance (e.g. biannual reporting obligations) will be done by the responsible national study group as agreed by contract.

Independent Data Safety Monitoring Committee

For clinical trials that run for a longer period of time, it is advisable to establish an independent data safety monitoring committee (DSMC) with pertinent expertise that will monitor the progress of the trial and will review accumulating data on a regular basis.

The DSMC advises the sponsor regarding the continuity safety of trial participants and should make recommendations on the discontinuation, modification or continuation of the trial. The independent Data Monitoring Committee will only review safety data since efficacy is controlled by the monitoring of PFS in this trial.

Frequency and contents of the DSMC meetings are detailed in the SOP AE1-A07 “Analysis of the Overall Safety Data of Trial by the DSMC for the DSUR.

Following each meeting the DSMC will prepare a report and may recommend changes in the conduct of the trial.

13.8 Safety Run In Phase (already completed)

So far combination data with Ibrutinib are only available with the R-CHOP regimen and not for alternating R-DHAP regimen. Thus there will be an initial safety run-in phase of 50 patients randomized which will be closely monitored for the observed toxicities during induction therapy with special observation to hematotoxicity. After completion of induction of the first 50 patients randomized or if a relevant safety signal is observed during the induction treatment of the first 50 randomized patients, the Data and Safety Monitoring Committee (DSMC) will advise the sponsor delegated person / principal coordinating investigator and the international coordinating investigators about the continuation of the study.

During Safety Run In Phase blood counts will be done twice a week from day 7 till complete recovery of hematopoiesis (for criteria of full recovery refer to “Requirements for therapy resumption” in section 7.3.1)

The following events qualify as severe toxicity in the safety run in phase (Safety Events in Run-In) and should be monitored:

- grade ≥ 3 non-hematologic toxicity
- grade 4 neutropenia lasting ≥ 7 days (unless due to bone marrow infiltration of the lymphoma, and despite the use of G-CSF)
- grade 4 febrile neutropenia
- grade 4 thrombocytopenia (unless due to bone marrow infiltration of the lymphoma)
- death whatever the cause, except death due to lymphoma

with the following restrictions:

1. Infusion related reactions attributed to Rituximab are not considered as safety event
2. Alopecia of any grade is no safety event
3. Laboratory abnormalities grade 3 are only considered if they persist for > 2 weeks or if they do not return to ≤ grade 1

4. For nausea, vomiting, or diarrhea, subjects must have a grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered as safety event.
5. Any infection/fever requiring iv antibiotics is not considered to be safety event, only grade 4 infections are considered
6. If an event is attributed to progressive disease, it will not be counted as safety event.

The following variables will be evaluated to investigate a potential safety signal during the safety run in period:

- Rate of occurrence of at least one safety event per patient as defined above stratified by treatment arm (arm A vs. combined arms A+I and I)
- Number of occurrences of safety events as defined above stratified by treatment arm (arm A vs. combined arms A+I and I)
- Rate of substantial induction treatment delays (defined as mean induction cycle duration of more than 28 days) stratified by treatment arm (arm A vs. combined arms A+I and I). A rate of 5% is considered as expected, and a rate of 35% or more is a reason for not considering the combination of R-CHOP/R-DHAP and Ibrutinib as safe. An explorative statistical test (Chi-square test to detect with significance level 5% one-sided) on 33 experimental patients vs. 17 control patients would have a power 80% to detect of a rate of substantial treatment delays of 35% vs. 5%.

The rules of stopping the trial due to safety concerns will be outlined in a separate DSMC charter.

14 Termination of the Study

The sponsor may decide to terminate the study prematurely based on the following criteria:

- One of the stopping rules has been reached (see section15.1.3);
- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.
- The DSMC recommends to end the trial based on viable arguments other than described above

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

Early Termination by the Subject

Patients can abandon the study at any time for any reason if they wish to do so without any consequences.

If a patient withdraws consent please consult GLSG Studienzentrale, for contacts see section 1.1 Data Management.

Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

14.1 Specific criteria for withdrawal of Individual Subjects

The investigator can decide to withdraw a patient from the study treatment for urgent medical reasons.

Specific criteria for withdrawal are:

- Excessive toxicity
- No compliance of the patient
- Refusal to continue protocol treatment
- Progression/relapse during protocol treatment

14.2 Follow-up of Patients Withdrawn from Treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in Section 11.8 for follow up.
SAE information will be collected as described in13.4. No further information will be collected for patients who have withdrawn their consent.

14.3 Early Termination of the Trial Sites

In addition, the Investigator or the sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14.4 Definition of End of Study

The regular end of trial is defined as **Last Subject Last Visit** in the entire trial.

15 Statistical Methods

15.1 Statistical Analysis of Primary Objective

15.1.1 Primary Objective and Primary Endpoint

The primary objective of the trial is to establish on of the three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), R-CHOP+ibrutinib/R-DHAP followed by ASCT and ibrutinib maintenance (experimental arm A+I), and R-CHOP+ibrutinib/R-DHAP followed by ibrutinib maintenance (experimental arm I) as future standard based on the comparison of investigator-assessed failure-free survival (FFS). The primary endpoint, FFS, is defined as the time from randomization to stable disease at end of induction immuno-chemotherapy, progressive disease, or death from any cause, whichever comes first.

We use FFS as primary endpoint, and not PFS, because FFS is more suitable for assessment of treatment efficacy in MCL than PFS. According to current treatment guidelines for MCL, in this trial, stable disease at end of induction immuno-chemotherapy is an indication for salvage treatment not part of the study treatment upon the discretion of the treating physician. Therefore, to assess the efficacy of the study treatments, the achievement of stable disease at end of induction immuno-chemotherapy especially in MCL should be considered as treatment failure and therefore an event for the primary efficacy endpoint. In contrast, PFS should be censored at the time of initiation of a new lymphoma treatment without progression. (Cheson 2007) Furthermore, censoring PFS at time points based on decision of the treating physician is in contrast to the principle of non-informative censoring required in analyses of time-to-event endpoints. In the preceding MCL Younger trial of the European MCL Network (Hermine et al., ASH 2012), only 3% of the patients in the experimental R-CHOP/R-DHAP treatment arm were in stable disease at end of induction immuno-chemotherapy. Therefore FFS is more adequate as primary endpoint than PFS, but only minimally different.

15.1.2 Hypothesis and Confirmatory Statistical Test

According to the three possible pairwise comparisons of the three treatment groups (A vs. I, A+I vs. A, and A+I vs. I), three pairwise one-sided statistical hypothesis tests will be performed using the log-rank statistic for FFS. The hypotheses of these three log-rank tests are as follows:

FFS Comparison	Null Hypothesis	Alternative Hypothesis
A vs. I	A not superior to I	A superior to I
A+I vs. A	A+I not superior to A	A+I superior to A
A+I vs. I	A+I not superior to I	A+I superior to I

For each pairwise test, the local one-sided significance level will be 0.05/3 such that a global significance level of 5% is maintained (Bonferroni-correction for multiple testing). Based on the results for the three pairwise statistical tests, the formal decision for the new standard will be taken according to the following procedure:

Test FFS A vs. I	Test FFS A+I vs. A	Test FFS A+I vs. I	Future Standard
A not significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**I**
A not significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A+I**
A not significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I not significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I not significantly superior to I	**A+I**
A significantly superior to I	A+I not significantly superior to A	A+I significantly superior to I	**A**
A significantly superior to I	A+I significantly superior to A	A+I significantly superior to I	**A+I**

The final decision for a new standard based will be based on this formal strategy taking into account all available clinical information at that time point.

All three pairwise statistical tests will be performed one-sided, because only differences observed in the direction indicated by the respective alternative hypothesis will result in consequences for the decision in favour of a treatment arm. In the statistical test of A vs. I, only the superiority of A compared with I justifies the further standard application of myeloablative treatment, taking the higher toxicity of this regimen into account. The ability to detect the potential inferiority of A vs. I does not ethically justify the higher sample size needed for a two-sided test, because this detection would not result in different consequences compared to the one-sided test. Similarly, only the superiority of A+I vs. A or of A+I vs. I would result in

consequences with respect to the decision for a new standard, because for these two questions the addition of a treatment element is tested that might introduce a higher toxicity. In the same way, a higher sample size to detect the potential inferiority of A+I vs. A or A+I vs. I by a two-sided test is ethically not justified, because this detection would have no different consequences compared to the one-sided test.

15.1.3 Interim Analyses

General Strategy

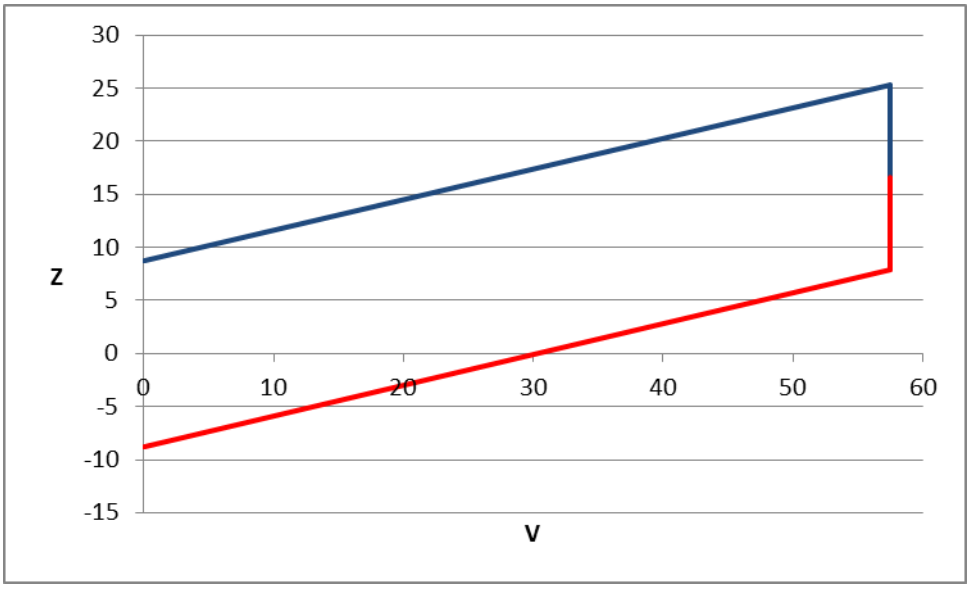
Regular pre-planned interim analyses will be performed for each pairwise comparison to allow early stopping for efficacy or futility. The multiple testing correction for interim analyses will be performed using truncated sequential probability ratio tests (Whitehead, 1985). For the truncated sequential probability ratio test, the number of interim analyses has not to be specified in advance. We will perform regular interim analyses in approximately half-yearly schedule triggered by the regular meetings of the European MCL Network that take place twice a year. Before each interim analysis, the efficacy data of all randomized patients will be medically reviewed by the sponsor. The Christmas tree adjustment is used to adjust for the discrete nature of interim analyses.

At each interim analysis, for each pairwise comparison, the observed values Z_i and V_i of the log-rank statistic Z and V, Fisher's information about the true log-hazard ratio contained in Z (for low event rates approximately proportional to the number of events) are calculated. Using e_C, the number of observed events in the control group, o_j, the number of events observed at each of k observation time t_j with at least one event, r_{jC}, r_{jE} and r_j (>1) the number of patients under observation immediately before t_j in the control arm, the experimental arm, and in both arms, respectively, $Z_i = e_C - \sum_{j=1}^{k} \frac{o_j r_{jC}}{r_j}$, and $V_i = \sum_{j=1}^{k} \frac{o_j(r_j - o_j) r_{jC} r_{jE}}{(r_j - 1) r_j^2}$.

Comparison of A vs. I

Figure 3 shows the design of the truncated sequential probability ratio test for the comparison of treatment arms A vs. I. The continuation region is bounded by the upper line defined by $Z = 8.736 + 0.2887 \times V$, the vertical line $V = 57.5$ and the lower line defined by $Z = -8.736 + 0.2887 \times V$. As long as the maximal V has not been reached (i.e. $V_i < 57.5$), the null hypothesis will be rejected (early stopping for efficacy) if $Z_i \geq 8.736 + 0.2887 \times V_i - 0.583\sqrt{V_i - V_{i-1}}$ and the null hypothesis will be accepted (early stopping for futility) if $Z_i \leq -8.736 + 0.2887 \times V_i + 0.583\sqrt{V_i - V_{i-1}}$. Otherwise, the statistical monitoring continues until the next interim analysis. If the maximal V has been reached ($V_i = 57.5$), then the null hypothesis will be rejected if $Z_i \geq 16.6035$, and the null hypothesis will be accepted if $Z_i < 16.6035$. This truncated sequential probability ratio test decides at latest with $V_{max} = 57.5$, corresponding to a maximal number of events of 230. The corresponding fixed-sample test (without interim analyses) would require 218.3 events ($V_{fix} = 54.58$).

Figure 3: Design of the truncated sequential probability ratio test for statistical monitoring of the log-rank test for FFS of A vs. I. Z is the log-rank statistic; V is Fisher's information about the true log-hazard ratio contained in Z and for low event rates approximately proportional to the observed number of events.

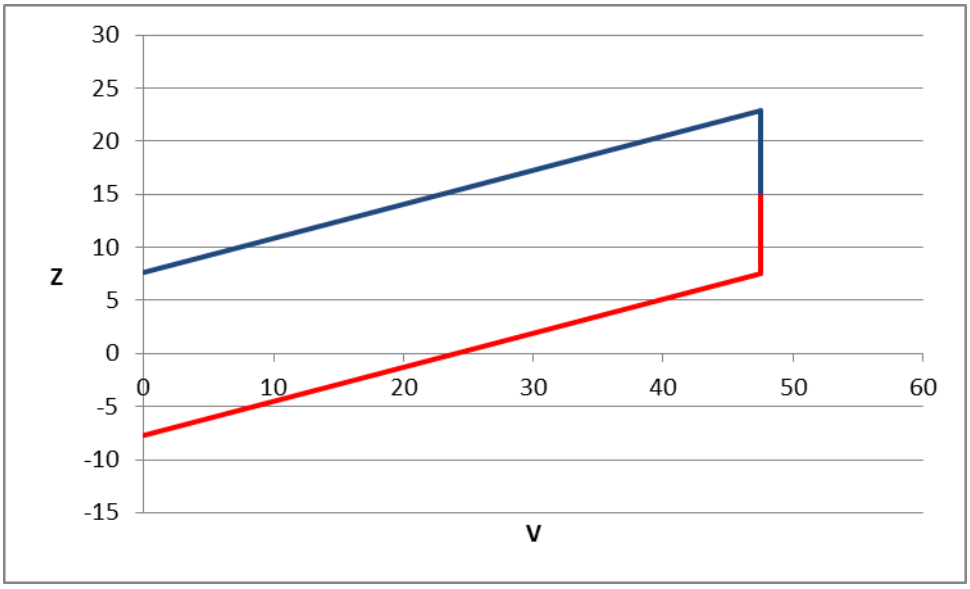


Comparison of A+I vs. A and A+I vs. I

Figure 4 shows the design of the truncated sequential probability ratio test identical for the comparisons of arms A+I vs. A and A+I vs. I. The continuation region is bounded by the upper line defined by $Z = 7.693 + 0.3199 \times V$, the vertical line $V = 47.5$ and the lower line defined by $Z = -7.693 + 0.3199 \times V$. As long as the maximal V has not been reached (i.e. $V_i < 47.5$), the null hypothesis will be rejected (early stopping for efficacy) if $Z_i \geq 7.693 + 0.3199 \times V_i - 0.583\sqrt{V_i - V_{i-1}}$ and the null hypothesis will be accepted (early stopping for futility) if $Z_i \leq -7.693 + 0.3199 \times V_i + 0.583\sqrt{V_i - V_{i-1}}$. Otherwise, the statistical monitoring continues until the next interim analysis. If the maximal V has been reached ($V_i = 47.5$), then the null hypothesis will be rejected if $Z_i \geq 15.1965$, and the null hypothesis will be accepted if $Z_i < 15.1965$.This truncated sequential probability ratio test decides at latest with $V_{max} = 47.5$, corresponding to a maximal number of events of 190. The corresponding fixed-sample test (without interim analyses) would require 178.3 events ($V_{fix} = 44.57$).

Figure 4: Design of the truncated sequential probability ratio test for statistical monitoring of the log-rank test for FFS of A+I vs. A and A+I vs. I. Z is the log-rank statistic, V is Fisher's information about the true

log-hazard ratio contained in Z and for low event rates approximately proportional to the observed number of events.



15.1.4 Sample Size and Trial Duration

The following assumptions were used to estimate the sample size and the trial duration:

- Randomization period up to 5 years
- Additional follow-up period up to 5 years
- Randomization rate 174 per year
- Allocation ratio 1:1:1
- Drop-out rate 5% of randomized patients
- Three pairwise log-rank tests for FFS with local one-sided significance level 0.05/3; overall significance level 5%
- FFS curve for control arm A as estimated from the experimental arm of the preceding MCL Younger trial of the European MCL Network (clinical cut-off date April 7, 2013, Figure 5)
- Power 95% to detect a FFS superiority of A vs. I (hazard ratio 0.60, 5-year FFS: 64.8% vs. 48.5%)
- Power 90% to detect a FFS superiority of A+I vs. A and of A+I vs. I (hazard ratio 0.60, 5-year FFS: 77.1% vs. 64.8%)
- Regular interim analyses to allow early stopping for efficacy or futility by truncated sequential probability ratio tests truncated at 230 events for A vs. I and at 190 events for A+I vs. A and A+I vs. I

Under these assumptions, if the true hazard ratio of A vs. I is 0.60, 0.53, or 0.46, the median duration until the decision for inferiority of I vs. A will be 5, 4, or 3.25 years, respectively (Table 1). If the true hazard ratio of A vs. I is 1.0, 1.29, or 1.67, the median time until a decision for of I vs. A will be 4.75, 3.75, or 3.5 years, respectively (Table 1).

Similarly, if the if the true hazard ratio of A+I vs. A or A+I vs. I is 0.60, 0.53, or 0.46, the median duration until the decision for superiority of A+I vs. A or I will be 6.5, 5.25, or 4.5 years, respectively (Table 2). If the true hazard ratio of A+I vs. A or A+I vs. I is 1.0, 1.29, or

1.67, the median time until a decision for of A+I vs. A/I will be 4.25, 3, or 2.5 years, respectively (Table 2).

If the statistical monitoring decides for superiority of A compared to I, allocation to arm I will be closed prematurely, and the comparison of A+I vs. A will be continued until its decision. If the statistical monitoring for A vs. I decides for the null hypothesis, allocation to arm A will be closed prematurely, and the comparison of A+I vs. I will be continued until its decision. Taken together, if the true hazard ratios are 1.0 for A vs. I and 0.6 for A+I vs. A and A+I vs. I, the median trial duration will be 6.5 years.

Figure 5: FFS of experimental treatment arm R-CHOP/R-DHAP followed by ASCT vs. control treatment arm R-CHOP followed by ASCT in preceding MCL Younger trial of the European MCL Network (primary analysis, clinical cut-off date April 7, 2013)

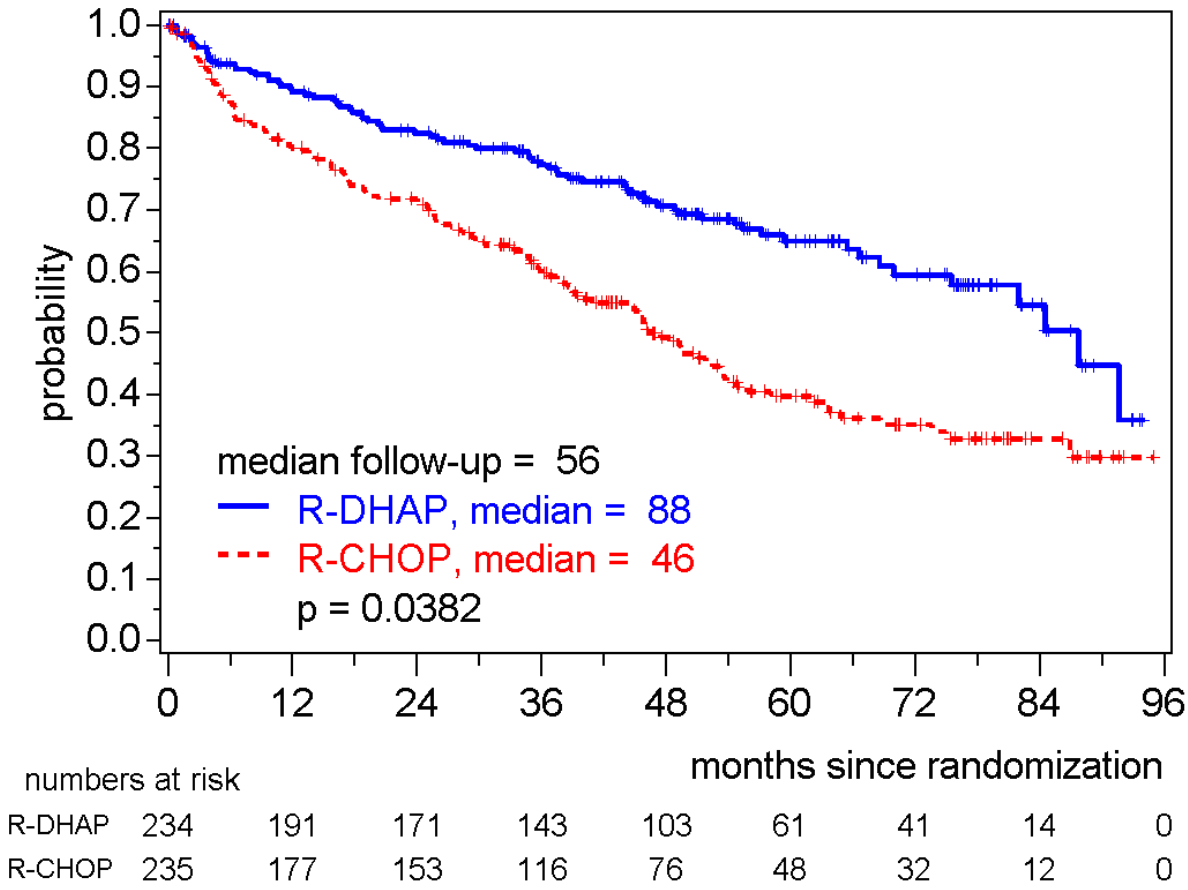


Table 1: Probability to reject the null hypothesis, median and maximal number of events, and median and maximal trial duration needed for a decision of the truncated sequential probability ratio test for the comparison of arms A vs. I depending on the true hazard ratio

			Events Needed		Duration (years)	
Hazard Ratio A vs. I	Difference 5-yr FFS	Probability to reject the null hypothesis	Median	Maximum	Median	Maximum
1.67	-12%	0.0%	40.8	230	3.5	10.5
1.29	-7%	0.0%	58.2	230	3.75	9.5
1.00	0%	1.7%	101.0	230	4.75	9
0.77	8%	40.2%	230.0	230	8.25	8.25
0.68	12%	75.9%	210.5	230	7.25	7.75
0.60	16%	95.0%	130.9	230	5	7.5

0.53	21%	99.5%	89.4	230	4	7.25
0.46	25%	100.0%	67.4	230	3.25	6.75

Table 2: Probability to reject the null hypothesis, median and maximal number of events, and median and maximal trial duration needed for a decision of the truncated sequential probability ratio test for the comparison of arms A+I vs. A and A+I vs. I depending on the true hazard ratios

			Events Needed		Duration (years)	
Hazard Ratio A+I vs. A/I	Difference 5-yr FFS	Probability to reject the null hypothesis	Median	Maximum	Median	Maximum
1.67	-16%	0.0%	34.4	190	2.5	6.25
1.29	-8%	0.0%	48.1	190	3	7
1.00	0%	1.7%	79.9	190	4.25	7.5
0.77	7%	33.2%	177.7	190	7.75	8.25
0.68	10%	66.5%	188.9	190	8.5	8.5
0.60	12%	90.0%	126.8	190	6.5	8.75
0.53	15%	98.3%	85.4	190	5.25	9
0.46	17%	99.8%	63.3	190	4.5	9.5

15.1.5 Analysis cohort

The analysis of the primary objective will be performed according to the intention to treat. Thus, all randomized patients will be included in the primary analysis irrespective of eligibility and evaluated according to the treatment arms they were randomly allocated to. No exclusion or censoring will be done in case of protocol violations.

15.1.6 Statistical Analysis Methods

The primary endpoint, FFS will be calculated from randomization to stable disease at end of induction immuno-chemotherapy, progressive disease, or death from any cause, whichever comes first. The date of stable disease at end of induction will be the end of induction lymphoma restaging date. Patients alive without failure at latest contact will be censored at the latest tumor assessment date. Patients without any lymphoma restaging during or at end of induction will be censored at the date of randomization.

The sample size calculation and the evaluation of the primary objective are done using the PEST software (The Medical and Pharmaceutical Statistics Research Unit, Department of Mathematics and Statistics, Fylde College; Lancaster University) to adjust for the sequential statistical design. Until the decision of each confirmatory statistical test, results of interim analyses will remain with the trial statisticians and will not be disclosed to any other person, with the exception of the DSMC. For the primary analysis, p-values and hazard ratios for the treatment effects will be calculated correcting for the sequential design.

15.2 Statistical Analysis of Secondary Objectives

After the decision of the confirmatory statistical test, secondary efficacy endpoints will be compared between the three treatment groups. As secondary sensitivity analysis for the primary analyses of FFS, a modified intention-to-treat cohort will be used including randomized patients with confirmed MCL who started induction immuno-chemotherapy according to the randomly allocated treatment arm. As further sensitivity analysis, cumulative incidence rates for stable disease after end of induction immuno-chemotherapy, progressive disease, and death without failure will be estimated and compared between groups.

Remission rates after induction will be compared between the combined A+I/I treatment group and A.

OS is the time to death from any cause, and will be censored at the latest follow-up date in patients alive. OS will be calculated from randomization and from end of induction immuno-chemotherapy in patients with CR or PR at end of induction immuno-chemotherapy.

PFS is the time to progression or death from any cause. Patients alive without progression at latest follow-up will be censored at the latest tumour assessment date. PFS will be calculated from randomization, from end of induction immuno-chemotherapy in patients with CR or PR at end of induction immuno-chemotherapy, and from the staging 3-months after end of induction staging.

Secondary efficacy analyses will be performed according to the intention-to-treat in treatment groups as randomly allocated and without exclusion or censoring for protocol violations. Patients without restaging during or at end of induction immuno-chemotherapy will be excluded from the analysis of response rates. Analyses of safety will be performed according to the treatment started.

Time-to-event endpoints will be described using Kaplan-Meier estimates and compared between groups using log-rank tests. Categorical endpoints will be described by absolute and relative frequencies and compared between groups by Fisher's exact tests. Toxicity during induction will be compared between the combined A+I/I treatment groups and A.

For efficacy endpoints we will perform multivariable regression models to adjust treatment effects for potential confounders, such as MIPI, Ki-67 index, and remission status. We will perform subgroup analyses according to MIPI, Ki-67 index, remission status (CR vs. PR) at end of induction immuno-chemotherapy, and remission status 3 months after end of induction immuno-chemotherapy. For subgroup analyses, statistical tests will be done in multivariable regression models on the interaction term of treatment group and the subgroup indicator including the main effects treatment group and subgroup indicator.

All secondary objectives will be analysed in a descriptive way without correction for multiple testing.

15.3 Statistical Analysis of Exploratory Objectives

Time-to-event endpoints will be described using Kaplan-Meier estimates and compared between groups using log-rank tests. Categorical endpoints will be described by absolute and relative frequencies and compared between groups by Fisher's exact tests. Multivariable regression models will be performed to identify clinical and biological prognostic or predictive factors. All exploratory objectives will be analysed in a descriptive way without correction for multiple testing.

15.4 Statistical Reports

During the conduct of the trial, regular reports on trial performance, baseline comparability, efficacy in the whole patient groups pooled from all treatment groups, and safety will be prepared twice a year. Baseline comparability and safety may be reported according to treatment groups, whereas efficacy results according to treatment groups will not be

disclosed to any other person than the trial statisticians or the DSMC before the decision of the confirmatory statistical test.

16 Data Management

Data Management will be performed at the GLSG Studienzentrale at Klinikum der Universität München. Details on data management (responsibilities, data collection, handling, audit trial, record keeping, etc.) will be described in a Data Management Plan prior to the trial. During the trial, the performance of data management and any deviations from the data management plan will be documented in a data management report. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented.

16.1 Electronic Case Report Form (eCRF)

The investigator has ultimate responsibility for accuracy, authenticity, timely collection and reporting of all clinical, safety and laboratory data entered on the CRFs. All these data may only be entered into the CRF by authorized qualified trial personnel as promptly as possible. In this clinical trial, the electronic CRF-system “MARVIN” licensed by X-Clinical will be used. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented. The study sites should provide the sponsor with a list of persons to whom data entry has been assigned. The sponsor will make sure that these persons receive an adequate training and are provided with written data entry and processing guidelines. The study sites will be made aware to contact the GLSG study center for assistance.

The data collected on the CRFs must match with the data in the source documents. Any corrections to entries made in the CRFs and source documents must be dated, signed and explained (if necessary). In some cases, the eCRF, or parts of the eCRF, may also serve as source documents. In these cases, a document at the investigator’s site should be available and clearly identify those data. If a screen shot of the eCRF will be used as source data the printed screen shot has to be dated and signed by an investigator and filed. Inconsistencies will be queried and discussed with the investigator. After data clearance the database will be locked and data will be used for statistical analysis.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably within two weeks after a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data. Entry and corrections on e-CRF pages are automatically documented via “audit trail” created by MARVIN.

Data will be collected on eCRF to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints.

The monitor is responsible to verify the eCRF at regular intervals throughout the trial to verify the adherence to the protocol, completeness, accuracy, and consistency of the data. Therefore the monitor should have access to subject medical records and other trial-related records needed to verify the entries on the eCRF.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRF are resolved.

The investigator has to sign the Investigator Verification Form for this EDC trial.

A separate eCRF-Manual is available to support the data entry.

16.2 Investigator Site File

The Trial site will be provided with a trial site file (ISF) containing all sponsor-specific essential and trial specific documents. The monitor will regularly check the trial site file for accuracy and completeness. The trial site file has to be stored locked and secure. After end of trial or early termination of the trial the trial site file should be retained for 15 years at the site.

The ISF includes the subject identification list, where the investigator has to record the trial participation of each subject. This list allows identification of each subject and contains the subject number, the name, telephone number (if applicable), birth date and the date of inclusion of the subject into the trial, and will be reviewed by the monitor for completeness. After end of the trial the subject identification list remains with the subject site. In addition, trial participation of the subject should be recorded in the subject chart (trial drug, screening/randomization number, start and end date of the trial).

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. This list will be provided with the ISF, too.

Furthermore, trial personnel responsible for documentation in the eCRFs should be identifiable. Therefore a signature log with the name, signature, initials/abbreviation and trial responsibilities of all persons who are allowed to make entries into the eCRF will be filed in the investigator's site file.

The trial documents provided by the sponsor are confidential and may not be made accessible to third parties not involved in the trial by the investigator or other staff members. All trial data are collected pseudonymously.

17 Quality Control and Quality Assurance

During the clinical trial quality control and quality assurance will be endured through monitoring and auditing.

17.1 Monitoring

According to the guidelines on Good Clinical Practice, the investigator's sites and trial procedures will be monitored by a representative of the sponsor (study monitor) to ensure accurate, complete, consistent and reliable data. The study monitor has to check the eCRF entries against the source documents. The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

The monitor will visit the site:

- to evaluate the progress and recruitment of the trial,
- to review the source documents and eCRFs for protocol compliance, -accuracy and validation,
- to review all other documents needed for the proper conduct of the trial (e.g. ISF)
- to check for protocol compliance,

- to assure the AE/SAE reporting,
- to verify proper handling and dispensing of the IMP and other factors.

17.1.1 Monitoring Plan

Frequency and scope of the monitoring visits will be defined in the **Monitoring Plan** for this trial which also includes the extent of source data verification that is required.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, and therefore ensures the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial.

17.2 Audits and Inspections

In accordance with the applicable laws and ICH GCP this trial may be selected for audit by representatives of the sponsor or for inspection by site responsible representatives of the regulatory authorities.

The investigator agrees to give the auditor or inspector access to all relevant documents for review and to support the sponsor to solve possible audit or inspector findings concerning the trial conduct at the respective site.

After every audit the auditee(s) will receive an audit confirmation and an audit report by the auditor. Only the confirmation document has to be filed together with the trial documentation and has to be made available also to the authorities in case of an inspection.

18 Ethical Considerations

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements and laws in which the trial is performed, as well as any applicable guidelines.

18.1 Compliance with Laws and Regulations

The clinical trial must be approved and conducted according to the applicable laws by the responsible competent authority and by the responsible ethics committee. It is the sponsor’s responsibility to ensure, that all required regulatory and administrative documents are provided to the investigational sites before shipment of study drug and before enrollment of the first patient.

This will always include Ethics Committee approval for the investigational site. Each investigational site will be notified when all requirements are met and enrolment can start. The local Investigator is responsible for the proper conduct of the study at the study site.

18.2 Subject Information and Consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of subject personal data.

The investigator will follow the applicable laws, regulations and guidance (e.g. ICH-GCP, DoH) in informing the patient and obtaining consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.

The content of the patient information letter, informed consent form and any other written information to be provided to the patients will be in compliance with the applicable laws, regulations and guidance and will be approved by the Ethics Committee in advance of use.

The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

18.3 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH-GCP

In the event of any prohibition or restriction imposed (i.e. clinical hold) by a responsible competent authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the sponsor should be informed immediately.

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH-GCP that the investigator becomes aware of.

18.4 Data Protection and Subject Confidentiality

The pertinent provisions of the country-specific legislation on data protection must be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to local applicable laws (Data Protection Act). Prior to trial participation, each subject must be informed by the investigator about the purpose and extent of the collection and use of personal data, particularly medical data and must give written informed consent.

The subjects must be informed that:

a. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial – subject number-, year of birth) and will only be transmitted to

- the coordinating investigator/sponsor/sponsor delegated person/data monitoring safety board for scientific and adverse event evaluation

- the responsible regulatory authorities and local authorities, the ECs of the trial sites and the European Data Base (EudraCT data base) for verifying the proper conduct of the trial and for assessment of trial results and adverse events

b. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the local regulatory authority(ies) must have direct access to personal data. In this case, the investigator is released from confidential medical communication.

18.5 Financing

The study will be conducted as “Investigator-Initiated Trial”. Klinikum der Universität München is sponsor of the TRIANGLE trial. The trial is financially sponsored by Janssen Pharmaceuticals. Patients will not receive any payments for their participation in the study.

18.6 Insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. The sponsor will provide an insurance policy or delegate this responsibility to a national co-sponsor. Proof of insurance will be submitted to the Ethics Committee.

In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial.

19 Administrative aspects and publications

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

19.1 Archiving of essential documents, record retention

Archiving of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies) The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

Record retention

The following retention periods will apply after completion or stop of the clinical trial:

- Maximum possible period permitted by the hospital, the institution or the private practice for medical records, patient files and other source documents

- National regulations should be taken into account. The longest time has to be considered.
- the subject identification list for at least 15 years,
- All essential documents and trial related data must be retained securely for at least 15 years, according to applicable law.
- Any center will notify the sponsor before destroying any data or records.

The investigator will be responsible for the storage at the site. The investigator/institution should take arrangements to prevent accidental or premature destruction and illegitimate access to these documents.

It is the responsibility of the sponsor to inform the investigator / institution when these documents are no longer needed to be retained. The investigator/institution will notify the sponsor before destroying any data or records.

19.2 Protocol Amendment(s)

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical / administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change

- the safety of the persons concerned,
- the interpretation of the scientific trial documents or the scientific informational value of the trial results,
- the nature of management or conduct of the clinical subject (e.g. change of principal coordinating investigator, sponsor delegated person etc.),
- the pharmaceutical quality or safety of the investigational medicinal products,
- the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical subjects with drugs consisting of or containing genetically modified organisms

require a new authorization of the Competent Authority and a new favorable opinion by the Ethics Committee.

The clinical trial may only be continued when a favorable opinion has been obtained from the competent ethics committee and if the competent authority has not raised any objections accompanied by reasons.

If applicable, an updated Informed Consent Form has to be signed by all subjects enrolled in the trial who are affected by the amendment.

Amendments which only have to be approved by the EC (e.g. changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial) also will be notified to the CA with the comment “For information only”. Similarly, the EC will be informed of any substantial amendments for which only the CA is responsible (e.g. quality data), unless national legal regulations require a different approach.

If administrative protocol changes (e.g. change of monitoring, telephone numbers) are necessary, the EC and CA will be notified only.

19.3 Study Reports

Annual progress report
The sponsor will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

End of study report
The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority.

19.4 Appendices

Appendix 1: Categories of Staging according to Ann Arbor

Stage I: -I = Involvement of a single lymph node region.

-IE = Localized involvement of a single extralymphatic organ or site.

Stage II: -II = Involvement of 2 or lymph node regions on the same side of the diaphragm.

-IIE = Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm.

Stage III: -III = Involvement of lymph node regions on both sides of the diaphragm.

-IIIE = Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site.

-IIIS = Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen*****.

-IIIS+E = Both IIIS+IIIE *****.
*(*****Of note, in FLIPI, spleen involvement is categorized as stage IV)*

Stage IV: -IV = Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement.

-IVE = Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Appendix 2: ECOG/WHO Performance Status Criteria

GRADE	PERFORMANCE STATUS – WHO CLASSIFICATION
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more 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 out any self-care; totally confined to bed and chair.

Appendix 3: Mantle Cell Lymphoma International Prognostic Index (MIPI)

MIPI Score =
0.03535 X age (years)

+ 0.6978 (if ECOG > 1, otherwise 0)

+ 1.367 X $\log_{10}$(LDH/ULN)

+ 0.9393 X $\log_{10}$(WBC count per 10^{-6} L)

ECOG: ECOG performance status (see Appendix 2), LDH: lactate dehydrogenase, $\log_{10}$: logarithm with respect to base 10, MIPI: Mantle Cell Lymphoma International Prognostic Index, ULN: upper limit of the normal range, LDH/ULN: LDH divided by ULN, WBC: white blood cell.

All parameters are evaluated at baseline, i.e. after diagnosis and before randomization for induction.

Risk groups are defined by:

MIPI risk group	MIPI score
Low risk	< 5.7
Intermediate risk	≥ 5.7 and < 6.2
High risk	≥ 6.2

Appendix 4: Review of Pathological Samples

General principles and organization of the pathological review:
The TRIANGLE study requires a histological review of all cases included in the trial at diagnosis. Histological criteria of inclusion and exclusion have been detailed in the current protocol. Histological review requires both morphology and immuno-histochemistry. In addition, a tissue collection will be organized to allow production of tissue-arrays and to optimize collection and conservation of frozen tissue.
The review process will be by the national reference pathology institute. Each center should send the material (paraffin blocks and/ or slides) of their cases directly to the national reference pathology institute(s).

Practical aspects of the pathology review:

 Sample request
At reception of the pathological report and inclusion form, the designated pathological coordinator will contact the initial pathologist and send:
 a copy of the pathological form or the histo-pathological report

 an explanatory letter describing the importance of the ancillary genomic and tissue micro-arrays projects and requesting:

- the paraffin block from the formalin fixed tumor sample that was used to set the diagnosis. In cases where the block no longer contains tumor material, 10 unstained Superfrost+ slides or stained slides could be sent to the Institute (stained slides will be returned as soon as the review is completed.)

- a copy of the pathological report if it was not obtained before

- a copy of the bone marrow pathological report.

- to notify the Institute of the presence of frozen tissue from this tumor.

All these requirements (excluding frozen tissue) will be sent to the national reference pathology institutes

Tissue microarray (TMA) construction:
For tissue microarray construction, a slide stained with hematoxylin and eosin will be prepared from each formalin-fixed paraffin donor block, and two or three tissue cylinders representative of tumor regions will be punched and transferred into a recipient paraffin block following a defined design. Reactive lymphoid tissues will be also included in the TMA blocks, as controls.

Review:
For the review process, routinely stained sections will be obtained and an appropriate panel of antibodies according to morphological aspects will be applied. A review of all the national cases will be organized by the national reference pathologist or a designated substitute. Diagnosis will be assigned to each case according to the WHO-classification from 2008. In addition a joint review by all national reference pathologists will be performed on a yearly basis. The following cases will be included in the joint review:

- Diagnosis other than MCL according to national reference pathologists review.
- Uncertain diagnosis for any reason according to national reference pathologists review.
- Rare variants of MCL (e.g. Sox11 negative MCL, cyclin D1 negative MCL) according to national reference pathologists review.

Reporting and sample storage:
The review pathologists for TRIANGLE Study will send the reference pathology report to the study site clinician and the initial pathologist that submitted the case for review its review conclusions.
In addition, results of all the national reference reviews will be sent to the study pathologist coordinator and to the sponsor on a yearly basis in tabular format. The results of the yearly joint meeting will also be reported to the sponsor and – if deviating from the national pathologist results also to study site pathologist and pathology center that submitted the case for review.
The block will be returned to the pathologist upon request by the site pathologist and/or according to national law. In any other case, the block remains at the national reference pathologist, the initial pathologist may ask at any time for the block to be returned.

Appendix 5: MRD Diagnostics

The sample collection will be centralized and organized by the defined national reference lab.

For all patients bone marrow and peripheral samples will be obtained at diagnosis and at 12 subsequent time points in order to verify the impact of different therapeutic options on MRD clearance. No samples will be sent after disease progression.

All patients will be screened for both IgH rearrangement and the t(11;14) according to published methods[19,21] in order to identify a patient-specific clonal marker by DNA sequencing of the individual lymphoma clone. Patient-specific primers and probes will be subsequently generated for RQ-PCR-based MRD determination using diagnostic peripheral blood and bone marrow prior to any treatment. If both markers will be obtained they will be both monitored. In this trial, the MRD status will be assessed using allele-specific quantitative PCR (RQ-PCR) according to the Euro-MRD Guidelines[13]. A prerequisite for establishment of an individual MRD assay is the flow-cytometric determination of lymphoma cell infiltration in the diagnostic peripheral blood or bone marrow samples or alternatively the availability of CD19 purified tumor cells at diagnosis. Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

Time points for sample collection for MRD analysis are:

	TIME POINTS	SAMPLES
INDUCTION PHASE	Prior treatment: for all patients before any treatment	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5 ml EDTA Bone marrow
	Midterm evaluation: after 4 cycle of induction (ca. 11 weeks after start of study treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
	End of induction evaluation (ca. 18 weeks after start of study treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow
Post ASCT	3-5 weeks after ASCT (Arm A und Arm A+I) (ca. 22-24 weeks after start of study treatment) 4-6 weeks after end of induction (Arm I) (ca. 6 months after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
MAINTENANCE PHASE	6 months of maintenance treatment (ca. 12 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
	12 months of maintenance treatment (ca. 18 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow (optional)
	18 months of maintenance treatment (ca. 24 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
	24 months / End of maintenance treatment (ca. 30 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow (optional)

FOLLOW-UP PHASE	6 months of follow-up (ca. 36 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
	12 months of follow-up (ca. 42 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow (optional)
	18 months of follow-up (ca. 48 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
	24 months of follow-up (ca. 54 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow (optional)
	36 months of follow-up (ca. 66 month after start of treatment)	10 ml EDTA Blood, 20 ml STRECK tube Blood

Appendix 6: Response Criteria according to Cheson et al, JCO 2007[22]

Selection of Target Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions at baseline
  All nodal lesions must measure:
  - 1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement, or
  - If the GTD measures between 1.1-1.5 cm, the short axis must measure > 1.0 cm.
- All extranodal lesions must measure ≥ 1.0 cm in the GTD.
- If possible, the lesions should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

Selection of Nontarget Lesions

Nontarget lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions. Examples of nontarget lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites with cytological evidence of malignancy

Reporting Conventions

Lesion not assessable

This category is reserved for target and non-target lesions that are deemed “not assessable” because:

- One or more target/nontarget cannot be assessed (e.g., inadequate scan coverage, contrast, artifacts, or other factors).
- One or more target/non-target lesions were excised or irradiated and have not reappeared or increased.

Examples of lesions not assessable are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples, the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller.

Effects of Lesions not Assessable on Response Assessment

If a target lesion is classified as not assessable after baseline, the sum of the product of the diameters (SPD)/area (whichever applies) of the target lesions cannot accurately be determined for that time point. In this case the clinical judgment of the investigator together with the measurements of all other assessable lesions is necessary to record the timepoint response.

PD can be determined without evaluation of all sites of disease on the basis of the GTD, area or SPD for target lesions, evaluation of unequivocal progression in nontarget lesions, or observation of a new lesion within the available radiographic or clinical assessments.

Response Criteria

Complete Response (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.
2. Variably FDG-avid lymphomas/FDG avidity unknown: In patients without a pretreatment PET scan, or if a pretreatment PET scan was negative: all lymph nodes and nodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and >1.0 cm in their short axis prior to treatment must have decreased to < 1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable as a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes rather than lymphoma.

4. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immuno-histochemistry. A sample that is negative by immuno-histochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Response (PR)

1. >50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of other nodes, liver or spleen
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually evaluable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small neoplastic B cells. Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. In cases where the bone marrow was involved prior to therapy that resulted in a clinical CR, but with no bone marrow assessment following treatment, patients should be considered as partial responders.
6. No new sites of disease
7. Variably FDG-avid lymphomas/FDG-avidity unknown; for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, standard CT criteria should be used.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).
2. Variably FDG-avid lymphomas/FDG-avidity unknown

For patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post treatment CT scan.

Progressive Disease (PD)

Lymph nodes should be considered abnormal if the long axis is >1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1-1.5 cm it should only be considered abnormal if its

short axis is >1.0. Lymph nodes < 1.0 cm x <1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearances of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if others are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histological confirmation.
2. >50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
3. 50% increase in the longest diameter of any single previously identified node >1 cm in its short axis.
4. Lesions should be PET-positive if a typical FDG-avid lymphoma or one that was PET-positive prior to therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Please note, that PET is not part of the regular tumor assessment in this trial and that PET should only be done if medically indicated; so in regular cases judgement about response has to be done without PET information.

Matrix for Time point Response Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Time point Response
CR	CR	No	CR
CR	SD	No	PR
PR	CR	No	PR
PR	SD	No	PR
SD	CR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD

Appendix 7: List of CYP3A4/5 Inhibitors and Inducer

Examples of inhibitors and inducers of CYP3A4/5 can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Strong inhibitors:
INDINAVIR
NELFINAVIR
RITONAVIR
CLARITHROMYCIN
ITRACONAZOLE
KETOCONAZOLE
NEFAZODONE
SAQUINAVIR
TELITHROMYCIN

Moderate inhibitors:
aprepitant
erythromycin
diltiazem
fluconazole
grapefruit juice
Seville orange juice
verapamil
Weak inhibitors:
cimetidine

All other inhibitors:
amiodarone
NOT azithromycin
chloramphenicol
boceprevir
ciprofloxacin
delaviridine
diethyl-dithiocarbamate
fluoxetine-metabolite norfluoxetine
fluvoxamine
gestodene
norfluoxetine
imatinib
mibefradil
mifepristone
norfloxacin
star fruit
voriconazole
telaprevir
troleandomycin

Azithromycin is unique in that it does not inhibit CYP3A4.

Inducers of CYP3A4/5

efavirenz
nevirapine
barbiturates
carbamazepine
glucocorticoids
modafinil
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's wort
troglitazone

Appendix 8: References

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