POLE-1

Pembrolizumab in MarginalzoneLymphoma

A MULTICENTER OPEN LABEL SINGLE-ARM PHASE II STUDY

Project Code:	POLE-1
Protocol Number	V-3.0
Date	12 April 2021
EUDRACT Number:	2018-000187-28
Included in clinicaltrials.gov database	Yes ☒ No ☐ NCT-No: NCT04268277
Substance Identifier (IMP)	Pembrolizumab (Keytruda®) Rituximab (Truxima®)
Therapeutic Area	Hematology/Oncology
Sponsor	University Hospital Ulm, Ulm, Germany; represented by the Chairman of the board
Coordinating Investigator, ***Leiter der klinischen Prüfung*** **acc. to German law**	Prof. Dr. Christian Buske University Hospital of Ulm Department of Internal Medicine III Albert-Einstein-Allee 23 D-89081 Ulm [redacted]

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Funding	The study will be funded by an unconditional grant of MSD SHARP & DOHME GMBH.

1.2 Coordinating Investigator (Austria)

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1.3 Statistics

I have thoroughly read and reviewed the study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to perform the clinical study according to the international good clinical practice principles and regulatory authority requirements for source document verification and auditing/inspection of the study.

I agree to use the study material, including medication, only as specified in the protocol.

[redacted]

Date

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2. Synopsis

STUDY	
Project Code	POLE-1
Project Title	**P**embr**o**lizumab in Margina**l** Zon**e** Lymphoma
Date	12 April 2021
Protocol Version	3.0
EUDRACT - Number:	2018-000187-28
Included in clinicaltrials.gov database	Yes ☒ No ☐ NCT-No: NCT04268277
Substance Identifier (IMP)	Pembrolizumab (Keytruda®), Rituximab (Truxima®)
Sponsor	University Hospital Ulm
Trial Design	Phase II, single arm, multicentric, open label
Scientific Rationale	For marginal zone lymphoma (MZL) Rituximab in combination with conventional chemotherapy is widely used for those patients who fail local therapy or do not qualify for such. Depending on the MZL subtype Rituximab/chemotherapy is able to induce in part long remissions, but does not prevent relapse later on. In addition, chemotherapy associated toxicity is often problematic in MZL patients, who are mostly of advanced age. Thus, chemotherapy–free approaches are highly attractive for this patient group. **Rituximab single agent is a widely used chemotherapy – free approach in MZL, but was significantly inferior compared to Rituximab/chlorambucil in a large randomized prospective clinical trial in treatment naïve MZL with a CR rate of 55,8% vs. 78,8%, respectively (P < 0.001)[1].** Thus, it is the major aim to develop chemotherapy–free approaches for MZL, which approach or surpass efficacy of Rituximab/chemotherapy combinations, but avoid chemotherapy associated toxicities. Checkpoint inhibitors such as **Pembrolizumab** have revolutionized cancer treatment and have also shown first encouraging results in Non-Hodgkin lymphomas [2-4]. Based on these observations it is the aim of this study to test the toxicity and efficacy of **Pembrolizumab** in combination with the anti-CD20 antibody Rituximab in patients with newly diagnosed or relapsed MZL in need of treatment, who are not eligible or failed local therapy, following the assumption that this novel chemotherapy – free combination is significantly more effective than Rituximab single agent therapy and at least as efficient as Rituximab/chemotherapy, but avoids chemotherapy–related toxicity.

Objectives	The objective of this trial is to test the efficacy and toxicity of the treatment of Pembrolizumab/Rituximab in patients with MZL in need of treatment, who have failed or are not eligible for local therapy or relapsed after local or systemic therapy. For efficacy the rate of complete remissions (according to the GELA criteria for gastric MALT or to the Cheson 2007 criteria for non-gastric extranodal, nodal and splenic MZL) after therapy will be primarily analysed[5-7]. For toxicity assessment treatment associated adverse events, quality of life and cumulative incidence of secondary malignancies will be documented.
Endpoints	Primary Endpoint: • CR rate (CRR) after end of treatment (18 cycles) Secondary Endpoint(s): • Response rate (CR, PR, CR or PR) • Best response • Time to best response • Time to first response • Progression free survival (PFS) • Time to treatment failure (TTF) • Duration of Response (DR) • Cause specific survival (CSS) • Overall survival (OS) • Quality of life during therapy Safety Variables: Safety variables will include AEs, SAEs, laboratory parameters, ECG and vital signs. The severity of AEs will be graded using the NCI-CTCAE version 5.0 dictionary. An AE is defined as any event arising or worsening from the time a signed and dated ICF is obtained until 110 days after the last study drug intake. Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. All AEs, drug related AEs, serious AEs will be summarized by MedDRA classification and worst CTCAE grade.
Projected Study Design	European phase II trial, multicenter, single arm, open label
Projected Number of Subjects	maximum of 56 subjects
Projected Number of Sites	Approximately: 15 trial sites in **Germany**, 3 trial sites in **Austria**
Participating Countries	Germany, Austria
Estimated First Patient in – first visit date	Q3 2020
Anticipated Last Patient - last visit date	Q1 2028
Estimated Duration of Enrollment	12-18 months

Estimated individual Duration of Treatment	54 weeks
Study Duration	approximately 7.5 years starting with first patient in (FPI)
Eligibility Criteria	Inclusion Criteria: Patients must have a proven pathological diagnosis of MZL, diagnosed by a reference pathology center. Patients must meet the following inclusion criteria to be eligible for participation in this study: – Confirmed CD20 positive de novo or relapsed **MALT Lymphoma** in need of treatment following or being not eligible for **local** therapy (including surgery, radiotherapy and antibiotics e.g. for H. pylori-positive gastric lymphoma arisen at any extranodal site) OR – Confirmed CD20 positive de novo or relapsed **splenic MZL** in need of treatment following or not being eligible for local therapy (including surgery and antiviral therapy for Hepatitis C Virus) OR – Confirmed CD20 positive de novo or relapsed **nodal MZL** in need of treatment following or not being eligible for local therapy (radiotherapy). The need of treatment is applicable in the case of B symptoms, deterioration of peripheral blood counts due to lymphoma infiltration of the bone marrow, rapid enlargement of lymph nodes or compression of vital organs by bulky disease. **For nodal MZL and extragastric MALT lymphoma:** – At least one bi-dimensionally measurable lesion (≥ 1.5 cm in its largest dimension by CT/ PET-CT scan or MRI). Please refer to Appendix D. **For splenic MZL (SMZL)** In patients with splenic MZL, an enlarged spleen on CT scan and lymphoma cell infiltration has to be seen in bone marrow and/or peripheral blood. Please refer also to Appendix F. **At least one of the following criteria must be fulfilled:** – Bulky progressive or painful splenomegaly – one of the following symptomatic/progressive cytopenias: Hb < 10 g/dL, or Platelet count < 80.000 /µL, or neutropenia < 1000 /µL, whatever the reason (autoimmune or hypersplenism or bone marrow infiltration) – splenectomised patients with rapidly raising lymphocyte counts, development of lymphadenopathy or involvement of extranodal sites if not being eligible for local therapy – SMZL with concomitant hepatitis C infection which has not responded to or has relapsed after Interferon and/or Ribavirin and/or direct antiviral agents (patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA) **For gastric MALT Lymphoma:**

	– For gastric MALT lymhoma, the clinical evidence of the MZL as seen by gastroendoscopy is sufficient. There is no need to show a measurable lesion by CT scan or MRI. Please refer to Appendix E. Inclusion is possible for patients with: – H. pylori-negative disease de novo or following or being not eligible for local therapy (i.e., surgery, radiotherapy or antibiotics) or after systemic therapy – H. pylori-positive disease that has remained stable, progressed, or relapsed following antibiotic therapy
Eligibility Criteria	**Others:** • Age ≥ 18 years • Life expectancy >3 months. • Meet the following pretreatment laboratory criteria at the Screening visit conducted within 28 days of study enrollment (unless due to underlying lymphoma): – Baseline platelet count ≥ 75 $\times 10^9$/L (if not due to BM infiltration by the lymphoma), absolute neutrophil count ≥ 1.5 $\times 10^9$/L – Hemoglobin ≥ 9.0 g/dL or ≥ 5.6 mmol/L (Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks) – International Normalized Ratio (INR) or Prothrombin Time (PT): ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants – Activated Partial Thromboplastin Time (aPTT): ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants – ASAT (SGOT): ≤ 2,5 times the upper limit of institutional laboratory normal value or ≤ 5 times the upper limit of institutional laboratory normal value in subjects with lymphoma in the liver – ALAT (SGPT): ≤ 2,5 times the upper limit of institutional laboratory normal value or ≤ 5 times the upper limit of institutional laboratory normal value in subjects with lymphoma in the liver – Serum total bilirubin: ≤ 1.5 × ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN (unless clearly related to the disease) – Serum creatinine ≤1.5 × ULN OR ≥60 mL/min GFR or CrCl for subjects with creatinine levels > 1.5 × institutional ULN – Negative HIV antibody – 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 HBSAb after vaccination or prior but cured hepatitis B are eligible* – Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA – For women of child-bearing potential only: Serum or urine β-HCG must be negative during screening and at study enrolment visit. • Premenopausal fertile females must agree to use a highly effective method of birth control for the duration of the therapy up to 12 months after the last dose of Rituximab and through 4 months after the last dose of pembrolizumab. A

	highly effective method of birth control is defined as those which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner or sexual abstinence. Contraception and pregnancy testing are required according the CTFG recommendations • Men must agree not to father a child for the duration of therapy and 6 months after and must agree to advice a female partner to use a highly effective method of birth control. According to CTFG recommendations, men must use condoms. • Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions • Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation
	<u>Exclusion Criteria:</u> The presence of any of the following will exclude a subject from enrolment: • ECOG performance status ≥ 2 • History of a malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for ≥1 year prior to study enrolment visit, other malignancy treated with a curative intent and currently in complete remission, for ≥3 years • Central nervous system lymphoma, leptomeningeal lymphoma, or histologic evidence of transformation to a high-grade or diffuse large B-cell lymphoma • Has had prior chemotherapy (systemic anti-cancer therapy), targeted small molecule therapy, within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or baseline value) from AEs due to a previously administered agent – Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study – Note: If a subject received major surgery, they must have recovered adequately from complications from the intervention prior to starting therapy • Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of study enrolment visit • Ongoing drug-induced liver injury, chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cholangitis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension

	• Treatment with any other investigational agent or participating in another clinical trial with an investigational product within 4 weeks prior to entering this study or within 5 x the half-life (t1/2) of the investigational product, whichever is longer • Breastfeeding or Pregnancy • Congestive heart failure > New York Heart Association (NYHA) class 2 • Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months) • Myocardial infarction less than 6 months before start of study medication • Uncontrolled arterial hypertension despite optimal medical management • Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results • Vaccination with a live vaccine within 30 days prior to start of therapy • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication. • Non-healing wound, ulcer, or bone fracture • History or concurrent interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator) • Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) • Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease • Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment • Has a history of non-infectious pneumonitis that required steroids, or current pneumonitis • History of anaphylaxis in association with previous administration of monoclonal antibodies or severe hypersensitivity (≥Grade 3) to the investigational medicinal products and/or any of its excipients • Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment • Has a known history of active TB (Bacillus Tuberculosis) • Medical history of allogeneic stem cell transplant

	• Ongoing alcohol or drug addiction or known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial • Diagnosis of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
Treatment	**Cycle 1 (21 days cycle)**: Rituximab: 375 mg/m^2 IV day 1, 8, 15 Pembrolizumab: 200 mg IV fixed dose day 2 **Cycle 2-18 (21 days cycle) or until progression or non-tolerable toxicity:** Rituximab: 375 mg/m^2 IV day 1 every second cycle Pembrolizumab: 200 mg IV fixed dose day 1 **Rationale for dosing schedule of rituximab after cycle 1:** Rituximab single agent is one of the widely used chemotherapy free approaches in MZL and has clear anti-lymphoma activity in MZL. This is why we aim at continuing Rituximab applications beyond cycle 1 to exploit this activity. In addition, conceptually Pembrolizumab as a PD1 inhibitor should increase the activity of Rituximab by “re-freshing” ADCC, which is important for Rituximab activity. Thus, we anticipate that Rituximab beyond its known activity as a single agent, shows increased activity when combined with Pembrolizumab until cycle 18 in a de-escalated application scheme with one infusion every 8 weeks. **Follow-up Phase:** All subjects who enter the trial will continue to be followed every 3 months for disease progression, subsequent treatment, and survival for two years after completion/ discontinuation of the treatment. Subsequently, patients will be monitored every 6 months for three additional years. The follow-up phase will be shorter than 5 years if End of Study is reached before this time period.
Safety	**There will be a close safety monitoring of the first 6 included patients. For these 6 patients safety evaluations will be performed on day 1, 8 and 15 for cycle 1 and on day 1 and 15 for cycles 2-6.** Safety evaluations include: adverse event monitoring, physical examinations, evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, serum chemistry, serum immunoglobulin [IgG, IgM, IgA], CRP). The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Serious adverse events will be reported according to applicable legislation. The DSMC will review data regarding safety as planned according to the DSMC Charter latest 4 weeks after the 6th patient has ended cycle 9. **Based on the review of the data of the first 6 patients the DSMC will give a risk assessment for the trial and recommendations for continuation/discontinuation of the study**.

Statistical Methods	In MZL a variety of treatment modalities are used such as Rituximab single agent, chemotherapy or Rituximab in combination with chemotherapy. It is widely accepted that in this non-curative indolent B – cell lymphoma of the mostly elderly patient chemotherapy – related toxicity should be avoided and that chemotherapy-free approaches are highly attractive in this patient population. So far Rituximab single agent is the most frequent chemotherapy-free approach used in this entity. Thus, a novel chemotherapy – free treatment approach should be at least as efficient as Rituximab monotherapy. In a large randomized study Rituximab single agent therapy induced a CRR of 55.8 % compared to 78.8 % for the combination of Rituximab and chlorambucil in de novo MZL of the MALT type. CR rates in splenic MZL are comparable high at about 60%[8], whereas only 10% of patients with nodal MZL achieve a CRR of around 20%[9]: As the distribution of subtypes is about 70% MALT, 20% splenic, and 10% nodal MZL, a CRR which is better than 56% should at least be achieved by a new chemotherapy – free approach after end of treatment (18 cycles) for such a mixture of the population. The goal of this study is to test the efficacy of the **chemotherapy - free combination Pembrolizumab/Rituximab** in treatment – naïve and relapsed symptomatic MZL aiming at achieving comparable treatment results compared to immuno- chemotherapy. <u>Sample size/Power Calculation:</u> For sample size calculation the one-sided one sample exact binomial test was used. According to the above data, the CRR must be better than 56% after end of treatment (18 cycles). Based on a CRR for Pembrolizumab/Rituximab of about 75%, a significance level of 2.5% (because of one- sided test) and a power of 80%, 48 full evaluable patients will be necessary to show that the chemo-free combination will be a promising candidate for challenging immunochemotherapy (SAS PROC POWER, SAS 9.3; 48 patients is the first number of patients with a stable power of more than 80%). It is expected, that the rate of withdrawal in the study is smaller than 15%. According to these parameters, the study will enroll a maximum of 56 subjects. <u>Statistical analysis of primary and secondary endpoints:</u> The primary parameter CRR will be evaluated in an intention to treat way after end of treatment (18 cycles), which means that all eligible patients who received at least one cycle of treatment will be included in the analysis of the primary endpoint (Core Analysis Population). Only patients who withdraw will be excluded from this analysis population (about 15%). This analysis population consists of all eligible patients included in the study who received at least one cycle of treatment. Patients without staging at regular end of treatment will be defined as non-responder (i.e. CR='NO'). The one sample exact binomial test will be used for the analysis of the primary endpoint to test the CRR against the fixed value 56% at the 2.5% significance level (one-sided). Thus, the decision about the new concept will be based on a statistical test of the form: HA : { CRR > 56%} vs. H0: { CRR ≤ 56%} Thus, claim of success can be done if 36 (75% of 48 patients) or more complete responders (patients with CR) will be observed. Patients who withdraw will be included in a separate explorative analysis. Additionally, a one-sided 97.5% confidence interval for CRR will be calculated as an effect estimator. Exploratory use of univariate logistic regression models will be used to investigate the influence of putative risk factors associated with CRR. All secondary endpoints will be analyzed exploratory by respective descriptive analysis and 95%-confidence intervals.

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3. List of abbreviations and glossary of terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ADCC	Antibody Dependent Cell-mediated Cytotoxicity
ALAT (SGPT)	ALanine AminoTransferase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASAT (SGOT)	ASpartate AminoTransferase (Serum Glutamic Oxaloacetic Transaminase)
ASCT	autologous stem cell transplantation
AUC	Area Under the Curve
BSA	Body Surface Area
BM	Bone Marrow
BW	Body Weight
CBC	Complete Blood Count
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CIRS	Cumulative Illness Rating Scale
CNS	Central Nervous System
CR	Complete Remission/Response
CrCL	Creatinine Clearance
CRO	Contract research organization
CRP	C-reactive protein
CRR	Complete Remmision Rate
CSS	Cause Specific Survival
CT	Computed Tomography
CTO	Clinical Trials Office
CTCAE	Common Toxicity Criteria for Adverse Events
DFS	Disease-free survival time
DLT	Dose-limiting toxicity
DSMC	Data Safety Monitoring Committee
DR	Duration of Remission
DRESS	Drug Rash with Eosinophilia and Systemic Symptom
EC	Ethics Committee
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOT	End of Treatment
FISH	Fluorescence *In Situ* Hybridization
FL	Follicular Lymphoma
FPI	First patient in
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice

Hb	Hemoglobin
HBV	Hepatitis-B-Virus
HCV	Hepatitis-C-Virus
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IR	immune related
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ITT	Intention-To-Treat
IV	IntraVenous
LDH	Lactic DeHydrogenase
LLN	Lower Limits of Normal
LPL	Lymphoplasmocytic Lymphoma
MZL	Marginal Zone Lymphoma
MTD	Maximal Tolerated Dose
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NFkB	NFkappB
NHL	Non-Hodgkin’s Lymphoma
OS	Overall Survival
ORR	Overall response rate
PD	Progressive Disease
PFS	Progression Free Survival
Plt	Platelets
PK	Pharmacokinetic
PR	Partial Remission
PS	Performance Status
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SPD	Sum of the Product of the Diameters
SSE	Significant safety event
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type I Diabetes Mellitus
TEN	Toxic epidermal necrolysis
TLS	Tumor Lysis Syndrome
TTF	Time to treament failure

ULN	Upper Limit of Normal
WBC	White blood cells
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

4. BACKGROUND INFORMATION AND STUDY RATIONALE

4.1 Marginal Zone Lymphoma

MZL belongs to the group of indolent B – NHL and is characterized by an indolent clinical course. MZL is diagnosed in the local or advanced stage and is in this situation a non-curative disease. MZL comprises 3 histological entities: splenic (SMZL), nodal (NMZL), and extranodal MZL of mucosa-associated lymphoid tissue (MALT) type. The subtypes share a similar immunophenotype, but differ with regard to clinical characteristics and prognosis.

Splenic marginal zone lymphoma (SMZL) infiltrates the spleen, bone marrow and peripheral blood and usually occurs in the elderly. Marked splenomegaly as well as thrombocytopenia and anemia are the main features at presentation. In SMZL, peripheral lymph nodes and other mucosa-associated lymphoid tissue (MALT) are not usually infiltrated, except for the splenic hilar lymph nodes. Monoclonal IgM is observed in approximately 1/3 of cases. The diagnosis is based usually on spleen tissue samples whose lesions are characterized by a micronodular pattern, in which the lymph follicles (white pulps) have increased number and size. Characteristic histopathological features of infiltration also may occur in the bone marrow, peripheral blood and splenic hilar lymph nodes, which together with clinical findings, often help to diagnose the disease correctly [10-12].

Nodal marginal zone lymphoma (NMZL), whose diagnosis is made only after excluding other low-grade lymphomas, is characterized by the presence of a primary lesion in the lymph nodes and is a neoplastic counterpart of post-germinal center marginal zone cells. The histopathological findings of NMZL overlap with those of other MZLs, including MALT lymphoma and SMZL, as well as lymphoplasmacytic lymphoma (LPL), and can be difficult to distinguish from these lymphoma subtypes with secondary lymph node infiltration. Lymph node involvement of NMZL can be localized or systemic; infiltration into the bone marrow or peripheral blood is rare. Plasmacytoid differentiation is observed but generally without monoclonal IgM, differentiating it from Waldenström's Macroglobulinemia. The histopathological features of NMZL resemble those of MALT type and SMZL. Lymphoma cells proliferate in a marginal zone pattern in the lymph nodes [9, 13-15].

In Mucosa- Associated Lymphoid Tissue (MALT Lymphoma), infiltration occurs in a variety of extranodal organs, with digestive organs accounting for about half (of which about 85% of cases have gastric involvement). Virtually every organ can be affected by MALT lymphoma infiltration and can include the lung (14%), head and neck (14%), ocular adnexa (12%), skin (11%) and thyroid gland (4%). Monoclonal IgM paraproteinemia appears in 1/3 of cases. MALT

lymphoma presents a variety of histological findings which can make it difficult to distinguish MALT lymphoma with prominent colonization from FL [16].

Several prognostic factors have been identified for MZL: thus, the „Integruppo Italiano Linfomi“ carried out a study to assess the outcomes of SMZL to identify prognostic factors in 309 patients. Using three variables, hemoglobin level less than 12 g/dl, LDH level greater than normal and albumin level less than 3.5 g/dl, they grouped patients into three prognostic categories: low-risk group (41%) with no adverse factors, intermediate-risk group (34%) with one adverse factor and high-risk group (25%) with two or three adverse factors. The 5-year cause specific survival (CSS) rate was 88% for the low-risk group, 73% for the intermediate-risk group and 50% for the high-risk group [10]. Subsequently, an international study of 593 SMZL patients identified hemoglobin, platelet count, high lactate dehydrogenase level, and extrahilar lymphadenopathy as parameters independently associated with lymphoma-specific survival (LSS). Three risk groups were identified with significantly different 5-year LSS (94%, 78%, and 69%, respectively) [17]. In a subsequent study that aimed at optimizing prognostication clinically acceptable cut points were established: 9.5 g/dL for hemoglobin, and $80x10^9$/L for platelet count. The patients were allocated into 3 groups: low risk (36%) with 0 points, intermediate risk (56%) with 1 or 2 factors, and high risk (8%) with 3 or 4 factors. The 3 groups had a 5-year LSS of 95%, 87%, and 68%, respectively [18].

For extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) a prognostic index was built by Cox regression, using data from 401 patients enrolled in the international randomized International Extranodal Lymphoma Study Group 19 (IELSG-19) trial. A validation set, including 633 patients, was obtained by merging 3 independent cohorts of MALT lymphoma patients. The 3 individual features maintaining the greatest prognostic significance for event-free survival (EFS, the main endpoint of the IELSG-19 trial) were age > 70 years (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.26-2.33), Ann Arbor stage III or IV (HR, 1.79; 95% CI ,1.35-2.38), and an elevated lactate dehydrogenase level (HR, 1.87; 95% CI, 1.27-2.77). The prognostic index (MALT-IPI) constructed using these 3 parameters identified 3 groups: low, intermediate, and high risk (corresponding to the presence of 0, 1, or ≥ 2 of these factors, respectively). The 5-year EFS rates in the low-, intermediate-, and high-risk groups were 70%, 56%, and 29%, respectively. The MALT-lymphoma International Prognostic Index (MALT-IPI) also significantly discriminated between patients with different progression-free, overall, and cause-specific survival. The prognostic utility was retained in gastric and nongastric lymphomas, in each treatment arm (chlorambucil, Rituximab, and Rituximab plus chlorambucil), and was confirmed in the validation set [19].

4.2 Treatment in Marginal Zone Lymphoma

Treatment of MALT lymphoma

Local Treatments

Although surgical resection of tumors may be curative in many patients with MALT lymphoma, the use of this strategy is progressively decreasing. This is because postsurgical sequels and organ dysfunction are more injurious than the lymphoma itself. Therefore, surgery is mostly limited to diagnostic procedures for histopathologic diagnosis, management of therapeutic complications, or treatment of relapsing disease in patients who are not candidates for other treatments. Gastrectomy, for example, is currently being used as a salvage or palliative approach to bleeding or perforation, both of which are extremely rare in gastric MALT lymphoma. It is noteworthy that some cases of pulmonary MALT lymphoma are completely resected, because radiologic assessment initially suspected a diagnosis other than lymphoma (i.e., lung carcinoma). Complete excision can be performed in many conjunctival and lacrimal gland MALT lymphomas, especially in pseudoencapsulated lesions. However, additional efforts to completely resect lymphomatous lesions should be avoided considering that the extent of surgical resection does not influence survival. Radiotherapy is used as salvage therapy in patients with gastric MALT lymphoma who do not respond to or who relapse after HP eradication. The best disease control is attained in lymphomas arising in the thyroid gland, whereas up to 40% of patients with ocular adnexal MALT lymphoma experience contralateral or distant relapse. Most irradiated patients with stage I MALT lymphoma achieve an objective response that is slow and gradual. In-field relapses are uncommon. Patients with ocular adnexal MALT lymphoma often develop a cataract 2 to 5 years after treatment. Irradiated patients with gastric MALT lymphoma develop transient anorexia and malaise and occasional nausea or dyspepsia. Radiotherapy is associated with significant residual xerostomia in patients with Sjörgen Syndrome and MALT lymphoma of the salivary glands; this complication is often symptomatic and requires permanent dietary modifications. Radiation pneumonitis, presenting as permanent but nonprogressive fibrosis, occurs in patients with lung MALT lymphoma, even when low doses are used; this event is usually asymptomatic. Rare cases of in-field second cancers have been reported [16].

Systemic treatments

Patients with (mostly advanced) MALT lymphoma had been and still are included in trials mostly encompassing follicular lymphomas. The first paper to single out MALT lymphoma patients treated with the oral alkylating agents chlorambucil and cyclophosphamide was published in 1995, showing a 75% complete response rate (CRR) after a median duration of therapy of 12 months [20]. Since then, several mostly small, uncontrolled trials using various

agents and combinations in MALT lymphoma have been published, although few randomized data currently exist. Two randomized trials exist, including the International Extranodal Lymphoma Study Group (IELSG)-19 study on chlorambucil versus Rituximab plus chlorambucil [1, 21] and a randomized study on wait and see versus chlorambucil in patients with gastric MALT lymphoma after HP eradication [22]. Interestingly, the latter study, which randomized 110 patients, could not establish a benefit for chlorambucil monotherapy after HP eradication. The 5-year recurrence rate was 21% in the "wait-and-see" arm versus 11% in the chlorambucil arm (p = .15), and it is also interesting that no benefit was seen with chlorambucil in patients who had residual lymphoma after antibiotics. To date, the randomized, multicenter IELSG-19 trial is the largest prospectively randomized trial in MALT lymphoma, including a total of 231 patients, comparing chlorambucil versus Rituximab-chlorambucil. Chlorambucil was given orally at 6 mg/m^2 for 42 consecutive days (weeks 1-6), followed by chlorambucil for 2 weeks every 28 days up to 4 cycles. The response rate was 87% for the chlorambucil arm and 94% for the combination arm (*P* = .069), whereas both the CRR and the 5-year event-free survival rate were significantly higher with the combination (78% vs 65% [*P* = .025] and 68% vs 50%, respectively) in both gastric and extragastric MALT lymphoma. However, the long-term outcome was not significantly improved, questioning the need for combining chlorambucil and Rituximab in asymptomatic patients. As a consequence, the study was extended to include a Rituximab-monotherapy arm to allow for further comparison of activity between Rituximab and chlorambucil monotherapy. Rituximab single agent therapy was inferior to the combination with a CR rate of 55.8% and an EFS at 5 years of 50% (95% CI, 42 to 59), but with similar overall survival in all three arms[1].

The Spanish Lymphoma/Autologous Marrow Transplant Study Group (GELTAMO) has included 60 patients with treatment-naïve MALT lymphoma in a trial of Rituximab 375 mg/m^2 intravenously on day 1 and Bendamustine 90 mg/m^2 (R-Benda) on days 1 and 2 [23]. The protocol was designed to expose patients to minimal necessary therapy; thus, patients in complete remission after 3 courses were given only 4 cycles, whereas other patients underwent 6 cycles. In this study, a 100% response rate was seen, with no relapses occurring after a median follow-up of 14 months. In addition, an Austrian retrospective series has also shown responses in heavily pretreated patients with extragastric MALT lymphoma, underlining the high potential of R-Benda [24]. In view of these findings, the combination of R-Benda appears to be attractive for use outside of clinical trials, if a chemotherapy is planned in these patients.

Treatment of nodal MZL

As of today, there are no standard recommended treatments for NMZL. Typically, the same strategy as that used for follicular lymphoma is applied in NMZL patients. Patients with strictly

localized disease may be considered for localized radiation therapy. In cases of low tumor burden, a watchful waiting strategy is usually employed, whereas in disseminated-stage disease, immunochemotherapy (Rituximab plus chemotherapy with or without an anthracycline) is considered an appropriate option. Current combinations include Rituximab/cyclophosphamide/vincristine/prednisone (R-CVP), Rituximab/fludarabine (FR), and fludarabine/cyclophosphamide/Rituximab (FCR), (although only a limited number of patients have been treated), with reported overall response rates (ORRs) >85% and 3-year PFS in the range of 60% to 90%. Of note, in the trial evaluating FR, excessive toxicity was reported and only 58% of these MZL patients completed the planned protocol [9, 12].

As the most common treatment of all lymphomas, anthracycline-containing chemotherapy (Rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone [R-CHOP]) is commonly used to treat NMZL patients; however, there are no convincing data justifying its recommendation in this patient population. Bendamustine-Rituximab (BR) was tested as first-line therapy in a multicenter, randomized, phase 3 study comparing the efficacy and safety of BR vs R-CHOP in 549 indolent lymphomas (including 67 MZL, 41 lymphoplasmacytic lymphoma, 21 small lymphocytic lymphoma) [25]. In the overall study population, after a median follow-up of 45 months, median PFS was longer in the BR group than with R-CHOP (69.5 vs 31.2 months; hazard ratio, 0.58; 95% confidence interval, 0.44-0.74; $P < .0001$). BR was less frequently associated with serious adverse events than R-CHOP (19% vs 29%), notably severe infectious complications with fatal outcomes. The very small proportion of MZL patients included limits unequivocal extrapolation of this data to NMZL patients.

Treatment of splenic MZL

Consensus guidelines recommend treating SMZL only in the presence of symptomatic splenomegaly, cytopenias, systemic symptoms, or progressive nodal disease. Autoimmune cytopenias should be specifically treated [26]. No randomized trials have been conducted in SMZL and, as consequence, there is no consensus on how to treat newly diagnosed and relapsed patients. The therapeutic options for SMZL have a wide range and include splenectomy, chemotherapy, and Rituximab alone or Rituximab with chemotherapy. In addition, antiviral treatment should be considered in patients with SMZL and concurrent chronic infection with HCV-related hepatitis who do not need immediate conventional treatment against the lymphoma.

Splenectomy

As a therapeutic approach, surgical removal of large spleens may eliminate a significant amount of disease by ameliorating abdominal discomfort and resolving cytopenias that result from splenic sequestration. After surgery, patients can remain free from treatment for many

years. Because cytopenias resulting from marrow failure do not resolve after splenectomy, a BM biopsy is advisable during the workup to define the burden of BM infiltration by the disease. One additional advantage of splenectomy is that it allows a definitive diagnosis of SMZL. Drawbacks of splenectomy are short-term (perioperative events) and long-term (immune suppression and infections) complications. Perioperative complications were registered in one quarter of a recent series of 41 splenectomized patients: pulmonary dysfunction in 8 (19.5%), deep vein thrombosis in 1 (2.4%), portal vein thrombosis in 1 (2.4%), and major bleeding in 9 (21.9%). Infections caused by encapsulated bacteria are the major risk associated with splenectomy, and vaccination against capsulated bacteria is mandatory at least 2 weeks before elective splenectomy. Splenectomy should be contraindicated in cases with disseminated lymphoma with nodal involvement outside the splenic hilum [8, 26, 27].

Rituximab-based treatment

Rituximab monotherapy yield results similar to those of splenectomy, avoid the toxicity of chemotherapy, and potentially eradicate the disease at the molecular level. Kalpadakis et al reported 58 patients treated with Rituximab once per week for 6 weeks, followed by a maintenance phase once every 2 months for 1 to 2 years. At the end of the induction phase, the CR rate was 45%, unconfirmed CR 26%, and partial response 24%; the 5-year overall survival and progression-free survival (PFS) were 92% and 73%, respectively. According to the European Society for Medical Oncology guidelines, Rituximab monotherapy is a reasonable first-line therapy and a less traumatic alternative to splenectomy. The combination of Rituximab with chemotherapy is considered standard therapy for symptomatic, indolent B-cell NHL. In SMZL, this approach is indicated for eligible patients with disseminated disease, constitutional symptoms, and/or signs of high-grade transformation. The combination of Rituximab with Bendamustine (BR) is effective in indolent NHL, although it has never been tested in a dedicated trial of SMZL. In the Bright study, the overall response rate to BR was 92% in 25 patients with MZL. In the StiL trial, the PFS for BR therapy was not longer than that for Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) among patients with MZL, but the study was not powered to find differences in the MZL subset [8, 15].

4.3 Rationale of the trial

As pointed out above there is no standard treatment for patients with MZL and systemic treatment approaches range from Rituximab single agent therapy to more intense immunochemotherapies such as Rituximab-Bendamustine or Rituximab-CHOP. With the latter approaches high remission rates and long responses are induced, but the dilemma here is, that data do not convincingly show that patients live longer with dose intense approaches

compared with less intensive treatments. Furthermore, it has taken into account that none of the dose intense approaches are curative and that the majority of patients suffering from MZL are elderly, quite often having non-lymphoma related co-morbidities. Thus, mild chemo-free approaches are highly attractive in this disease and the feasibility of this approach has been recently shown for the BTK – inhibitor Ibrutinib. The drug showed comparably low toxicity and anti-lymphoma activity in patients with relapsed MZL, leading to the approval of the drug by the FDA for patients with relapsed/refractory MZL, which have received a Rituximab containing regimen before. However, the disadvantage of this treatment approach is that the drug has to be given continuously and that overall response and the CR rates were moderate with 48% and 3%, respectively. Median progression-free survival was 14.2 months. Probably the most widely used chemofree approach is Rituximab single agent in patients with MZL. As described above Rituximab monotherapy is well tolerated, safe and has reasonable anti-lymphoma activity in all three subtypes of MZL. The largest randomised trial, the IELSG-19 trial, assigned patients towards Chlorambucil, Rituximab/Chlorambucil and Rituximab single agent in patients with treatment naïve MALT lymphoma [1]. In this trial ORR was 78.3% with 55.8% CR and 22.5% PR for Rituximab single agent compared to 94.7%, 78.8 and 15.9% for Rituximab/Chlorambucil. The event free survival at 5 years was 50% for Rituximab single agent treatment compared to 68% with the combination. These data show that Rituximab efficacy can be further augmented by adding chemotherapy such as Chlorambucil, but at the cost of chemotherapy associated toxicities such as haematological toxicity.

The hypothesis of this study is that adding Pembrolizumab to Rituximab is superior to Rituximab single agent and is approaching the efficacy of Rituximab/Chlorambucil without exposing the patient to chemotherapy associated toxicity. This hypothesis is based on recently reported data, which demonstrated high activity of Pembrolizumab in different types of B-cell lymphomas: Thus, safety and antitumor activity of Pembrolizumab was tested in relapsed and refractory peripheral mediastinal B-cell lymphoma as part of the KEYNOTE-013 multicohort phase 1b trial. At time of data cutoff, 18 patients (median age 30 years; median 3 prior lines of therapy) had been enrolled and treated, of whom 17 were included in the efficacy analyses. Eleven patients (61%) experienced drug-related adverse events (mostly grade 1-2); none discontinued treatment due to adverse events. ORR was 41% (7/17); 6 additional patients (35%) had stable disease. Of patients evaluable by imaging, 13 out of 16 (81%) had decreases in target lesions. With a median follow-up of 11.3 months, median duration of response was not reached. Two patients reached the maximum 2-year treatment duration and remain in remission. Median overall survival was not reached for treated patients overall; all responders were still alive at data cutoff. These results in heavily pretreated rrPMBCL patients demonstrated that PD-1 blockade with Pembrolizumab has a manageable safety profile and promising antitumor activity[28] . In a phase II study the efficacy and safety of Pembrolizumab

were tested at a dose of 200 mg every 3 weeks in transformed CLL. Twenty-five patients including 16 relapsed CLL and 9 RT (all proven diffuse large cell lymphoma) patients were enrolled, and 60% received prior ibrutinib. Objective responses were observed in 4 out of 9 RT patients (44%). All responses were observed in RT patients who had progression after prior therapy with ibrutinib. After a median follow-up time of 11 months, the median overall survival in the RT cohort was 10.7 months, but was not reached in RT patients who progressed after prior ibrutinib. Treatment-related grade 3 or above adverse events were reported in 15 (60%) patients and were manageable. Overall, Pembrolizumab exhibited selective efficacy in CLL patients with RT[29]. In relapsed or refractory classic Hodgkin lymphoma a single-arm phase II study of Pembrolizumab in three cohorts of patients with rrHL, defined on the basis of lymphoma progression after (1) autologous stem cell transplantation (ASCT) and subsequent brentuximab vedotin (BV); (2) salvage chemotherapy and BV, and thus, ineligible for ASCT because of chemoresistant disease; and (3) ASCT, but without BV after transplantation, were performed. Patients received Pembrolizumab 200 mg once every 3 weeks. Response was assessed every 12 weeks. The primary end points were ORR by central review and safety. A total of 210 patients were enrolled and treated (69 in cohort 1, 81 in cohort 2, and 60 in cohort 3). At the time of analysis, patients received a median of 13 treatment cycles. Per central review, the ORR was 69.0% (95% CI, 62.3% to 75.2%), and the complete response rate was 22.4% (95% CI, 16.9% to 28.6%). By cohort, ORRs were 73.9% for cohort 1, 64.2% for cohort 2, and 70.0% for cohort 3. Thirty-one patients had a response of 6 months. The safety profile was largely consistent with previous Pembrolizumab studies[4]. In a study for NK/T-cell lymphoma, seven male patients with NK/T-cell lymphoma, for whom a median of 2 (range, 1-5) regimens (including L-asparaginase regimens and allogeneic hematopoietic stem-cell transplantation in 2 cases) failed, were treated with Pembrolizumab. All patients responded, according to various clinical, radiologic (positron emission tomography), morphologic, and molecular (circulating Epstein-Barr virus [EBV] DNA) criteria. Two patients achieved complete response (CR) in all parameters. Three patients achieved clinical and radiologic CRs, with two having molecular remission. Two patients achieved partial response. After a median of 7 cycles of Pembrolizumab and a follow-up of a median of 6 months, all five CR patients were still in remission. The only adverse event was grade 2 skin graft-versus-host disease in one patient with previous allogeneic HSCT[30]. In a recent report at the annual Meeting of the American Society of Hematology the efficacy of Pembrolizumab in combination with Rituximab in relapsed/refractory follicular lymphoma was tested. Patients received Rituximab (375 mg/m^2 IV) on days 1, 8, 15, and 22 of cycle 1 and Pembrolizumab (200mg IV) every 3 weeks for up to 16 infusions starting on day 2 of cycle 1. 32 subjects were enrolled with a median follow-up of 13.8 months. Overall response rate was 67% with a high CR rate of 50%. The median duration of response was 14.1 months. There were three grade 3 or grade 4 immune related

adverse events [31]. Please refer to the current investigator brochure for all available Pembrolizumab data.

In summary, these data showed high anti-lymphoma activity in pretreated indolent B – NHL by Pembrolizumab, providing the rationale to test this drug in combination with Rituximab in this lymphoma subtype with the goal to increase efficacy of Rituximab single agent, but to avoid chemotherapy associated toxicities.

In this study, no comparator arm is included. The reason is that MZL is a rare disease and a comparator arm would require the inclusion of a large number of patients. Importantly, despite being a single arm study, this trial will give important information about the efficacy and toxicity of the Pembrolizumab/Rituximab combination, However, in case the results of this trial are encouraging and the risk-benefit ratio is justifiable a subesequent larger phase III trial with a comparator arm will be considered as an international trial.

5. Trial Objective and endpoints

5.1 Primary Objective

The objective of the trial is to test the efficacy of treatment with Pembrolizumab and Rituximab in patients with MZL in need of treatment, who have failed or are not eligible for local therapy or relapsed. For efficacy the rate of complete remissions (according to the GELA criteria for gastric MALT or to the Cheson 2007 criteria for nodal and splenic MZL) after end of treatment (18 cycles) will be primarily analyzed.

5.2 Primary Endpoint

Primary endpoint is the complete response (CR rate (CRR) determined after end of treatment (18 cycles). Patients who progress before EOT will be treated as CR='NO' and will be included in the calculation of the primary endpoint. No primary endpoint will be determined for patients who withdraw. These patients will be excluded from the confirmatory data analysis but will be analyzed in a separate exploratory sensitivity analysis of the primary endpoint.

For further information about the statistical analysis of the primary endpoint, see section 12.

5.3 Secondary Endpoints

The following parameters are the secondary endpoints:

- ***Response rate***

  The response rates (complete response (CR), partial response (PR)) and overall response rate (CR or PR) are evaluated 4 weeks after the end of treatment.

- ***Best response***

Best response is determined in the time interval from the start of therapy to end of follow-up

- ***Time to best response***
  Time to best response is defined as the time from the start of therapy to best response the patient achieves (CR, PR)
- ***Time to first response***
  Time to first response is defined as the time from the start of therapy to first response (CR, PR).
- ***Progression free survival (PFS)***
  Progression free survival (PFS) is defined as the time from registration to the first occurrence of progression or relapse as assessed by the investigator, or death from any cause. PFS for patients without disease progression, relapse, or death will be censored at the time of the last tumor assessment.
- ***Time to treatment failure (TTF)***
  Time to treatment failure (TTF) is defined as the time of registration to discontinuation of therapy for any reason including death from any cause, progression, toxicity or add-on of new anti-cancer therapy. Patients alive without treatment failure are censored at the latest tumor assessment date.
- ***Duration of Response (DR)***
  Duration of Response will be calculated in patients with response (CR, PR) to therapy from diagnosis of response to the date of progression, relapse or death from any cause. Patients alive without progression and relapse will be censored at the latest tumor assessment date or the stopping date.
- ***Cause specific survival (CSS)***
  Cause specific survival is defined as the period from the study registration to death from lymphoma or lymphoma related cause; death unrelated to MZL is considered as a competing event.
- ***Overall survival (OS)***
  Overall survival is defined as the period from the induction registration to death from any cause. Patients who have not died until the time of the analysis will be censored at their last contact date.
- ***Quality of life during trial***
  Quality of life will be measured by the FACT Lym (see Appendix I) before start of treatment and during trial participation.

5.4 Safety Variables

Safety variables will include AEs, SAEs, laboratory parameters, ECG and vital signs. The severity of AEs will be graded using the NCI-CTCAE version 5.0 dictionary. An AE is defined as any event arising or worsening after start of study drug administration until 110 days (based on five times the terminal elimination half-life of Rituximab and Pembrolizumab) after the last study drug intake. Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. All AEs, drug related AEs, serious AEs will be summarized by MedDRA classification and worst CTCAE grade.

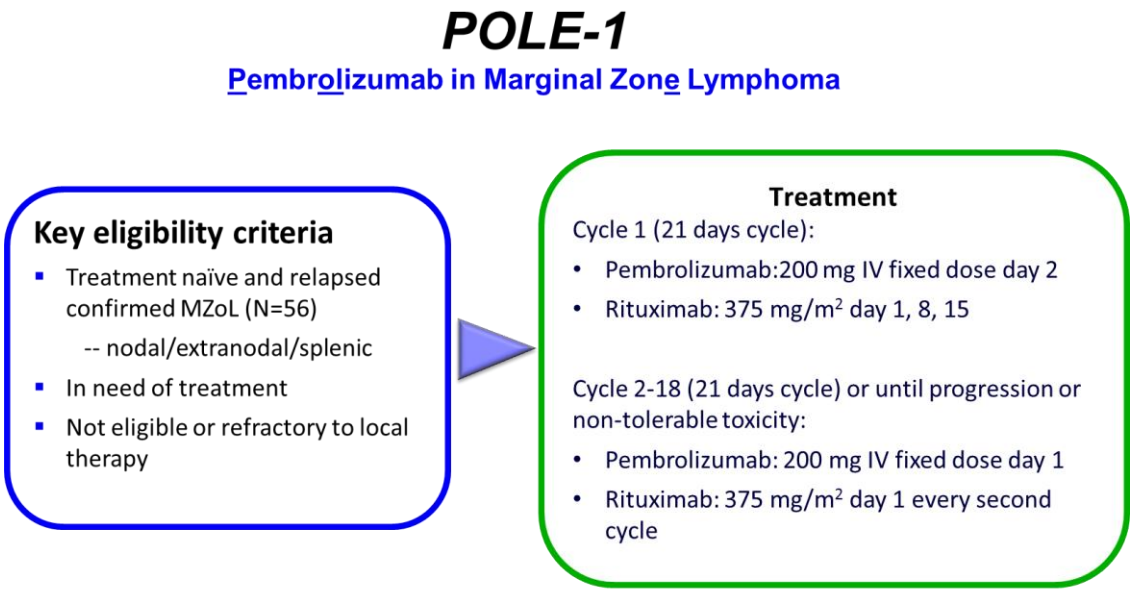
6. Study Design

This study is a European multicenter, single-arm, open-label, phase II trial of 18 cycles of Pembrolizumab and Rituximab in patients aged ≥ 18 years with previously untreated or relapsed MZL in need of treatment.

The study flow will be as follows:

- Previously untreated or relapsed patients will be screened for eligibility for the trial. If the patient is eligible for the study, the patient will be registered before the first cycle of treatment.
- Patients who progress at any time point during treatment are considered as treatment failure. They will be followed up for overall survival until end of follow up period or death.
- Patients, who achieve at least a SD after treatment will be followed up for response until progression/relapse and for overall survival until death.

Fig.1: Study Design



A multicenter open-label single-arm phase II study

6.1 Estimated Study Duration

It is expected that a total of 56 patients at approximately 15 investigator trial sites in Germany and 3 trial sites in Austria will be registered. Every patient will receive treatment over a time period of 18 cycles (each cycle lasts 3 weeks). Subsequently, patients will be monitored every 3 months for 2 additional years, subsequently every 6 months for three additional years.

Patients will be recruited over a period of 12-18 months.

1st patient registered (estimated):	Q3 2020
Last patient registered (estimated):	Q1 2022
Maximal duration of study therapy/patient: (18 cycles with 21 days = 378 days resp. 54 weeks)	18 cycles
Duration of follow-up/patient:	up to 5 years (until End of Study is reached)

End of study: LPLV 7.5 years (=90 months) after the first patient is included in the study

Considering a recruitment period of 12 – 18 months and a treatment period of 54 weeks, after 7.5 years all patients will either be in Follow-Up or will already have completed Follow-up. In the 90th month after FPI Follow-up Visits that were scheduled for this month can still take place. Sites will be notified in advance about EOS so that they can plan the Follow-up visits accordingly.

After finishing all study relevant procedures, therapy and follow-up period, the patient will be followed in terms of routine aftercare and treated if necessary by the primary responsible hematologic-oncologic center.

7. Study Population

Patients must have a proven pathological diagnosis of MZL, diagnosed by a reference pathology center.

7.1 Inclusion criteria for Registration

Patients must have a proven pathological diagnosis of MZL, diagnosed by a reference pathology center.

Patients must meet the following inclusion criteria to be eligible for participation in this study:

- Confirmed CD20 positive de novo or relapsed **MALT Lymphoma** in need of treatment following or being not eligible for local therapy (including surgery, radiotherapy and antibiotics e.g. for H. pylori-positive gastric lymphoma arisen at any extranodal site)

  OR

- Confirmed CD20 positive de novo or relapsed **splenic MZL** in need of treatment following or not being eligible for local therapy (including surgery and antiviral therapy for Hepatitis C Virus)

  OR

- Confirmed CD20 positive de novo or relapsed nodal MZL in need of treatment following or not being eligible for local therapy (radiotherapy). The need of treatment is applicable in the case of B symptoms, deterioration of peripheral blood counts due to lymphoma infiltration of the bone marrow, rapid enlargement of lymph nodes or compression of vital organs by bulky disease.

For nodal MZL and extragastric MALT lymphoma:

At least one bi-dimensionally measurable lesion (≥ 1.5 cm in its largest dimension by CT/ PET-CT scan or MRI). Please refer to Appendix D.

For splenic MZL (SMZL):

In patients with splenic MZL, an enlarged spleen on CT scan and lymphoma cell infiltration has to be seen in bone marrow and/or peripheral blood. Please refer also to Appendix F.

At least one of the following criteria must be fulfilled:

- Bulky progressive or painful splenomegaly
- one of the following symptomatic/progressive cytopenias: Hb < 10 g/dL, or Platelet count < 80.000 /µL, or neutropenia < 1000 /µL, whatever the reason (autoimmune or hypersplenism or bone marrow infiltration)
- splenectomised patients with rapidly raising lymphocyte counts, development of lymphadenopathy or involvement of extranodal sites if not being eligible for local therapy
- SMZL with concomitant hepatitis C infection which has not responded to or has relapsed after Interferon and/or Ribavirin and/or direct antiviral agents (patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA)

For gastric MALT Lymphoma:

For gastric MALT lymphoma, the clinical evidence of the MZL as seen by gastroendoscopy is sufficient. There is no need to show a measurable lesion by CT scan or MRI. Please refer to Appendix E.

Inclusion is possible for patients with:

- H. pylori-negative disease de novo or following or being not eligible for local therapy (i.e., surgery, radiotherapy or antibiotics) or after systemic therapy.
- H. pylori-positive disease that has remained stable, progressed, or relapsed following antibiotic therapy

Others:

- Age ≥ 18 years
- Life expectancy > 3 months
- Meet the following pretreatment laboratory criteria at the Screening visit conducted within 28 days of study enrollment (unless due to underlying lymphoma):

- Baseline platelet count ≥ 75 $\times 10^9$/L (if not due to BM infiltration by the lymphoma), absolute neutrophil count ≥ 1.5 $\times 10^9$/L.
- Hemoglobin ≥ 9.0 g/dL or ≥ 5.6 mmol/L (Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks)
- International Normalized Ratio (INR) or Prothrombin Time (PT): ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

- Activated Partial Thromboplastin Time (aPTT): ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
- ASAT (SGOT): ≤ 2,5 times the upper limit of institutional laboratory normal value or ≤ 5 times the upper limit of institutional laboratory normal value in subjects with lymphoma in the liver
- ALAT (SGPT): ≤ 2,5 times the upper limit of institutional laboratory normal value or ≤ 5 times the upper limit of institutional laboratory normal value in subjects with lymphoma in the liver
- Serum total bilirubin: ≤ 1.5 × ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN (unless clearly related to the disease)
- Serum creatinine ≤ 1.5 × ULN OR ≥ 60 mL/min GFR or CrCl for subjects with creatinine levels > 1.5 × institutional ULN
- Negative HIV antibody
- 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 HBSAb after vaccination or prior but cured hepatitis B are eligible.
- Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- *For women of child-bearing potential only: Pregnancy β-HCG negative. Serum or urine β-HCG must be negative during screening and at study enrolment visit.*

- Premenopausal fertile females must agree to use a highly effective method of birth control for the duration of the therapy up to 12 months after the last dose of Rituximab and through 4 months after the last dose of Pembrolizumab. A highly effective method of birth control is defined as those which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner or sexual abstinence. Contraception and pregnancy testing are required according the CTFG recommendations (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf)

- Men must agree not to father a child for the duration of therapy and 6 months after and must agree to advice a female partner to use a highly effective method of birth control. According to CTFG recommendations, men must use condoms.
- Willingness and ability to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions
- Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

7.2 Exclusion Criteria for Registration

The presence of any of the following will exclude a subject from enrolment:

- ECOG performance status ≥ 2
- History of a malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for ≥ 1 year prior to study enrolment visit, other malignancy treated with a curative intent and currently in complete remission, for ≥ 3 years
- Central nervous system lymphoma, leptomeningeal lymphoma, or histologic evidence of transformation to a high-grade or diffuse large B-cell lymphoma
- Has had prior chemotherapy (systemic anti-cancer therapy), targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or baseline value) from AEs due to a previously administered agent
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study
    - Note: If a subject received major surgery, they must have recovered adequately from complications from the intervention prior to starting therapy
- Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of study enrolment visit

- Ongoing drug-induced liver injury, chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cholangitis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension
- Treatment with any other investigational agent or participating in another clinical trial with an investigational product within 4 weeks prior to entering this study or within 5 x the half-life (t1/2) of the investigational product, whichever is longer
- Breastfeeding or Pregnancy
- Congestive heart failure > New York Heart Association (NYHA) class 2
- Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months)
- Myocardial infarction less than 6 months before start of study medication
- Uncontrolled arterial hypertension despite optimal medical management
- Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or impair the assessment of study results
- Vaccination with a live vaccine within 30 days prior to start of therapy
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication
- Non-healing wound, ulcer, or bone fracture
- History or concurrent interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator)
- Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137)
- Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease
- Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are

radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment

- Has a history of non-infectious pneumonitis that required steroids, or current pneumonitis
- History of anaphylaxis in association with previous administration of monoclonal antibodies or severe hypersensitivity (≥Grade 3) to the investigational medicinal products and/or any of its excipients
- Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
- Has a known history of active TB (Bacillus Tuberculosis)
- Medical history of allogeneic stem cell transplant
- Ongoing alcohol or drug addiction or known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial
- Diagnosis of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

8. Treatments

8.1 Study drug (IMP)

8.1.1.1 *Packaging and labeling*

MSD will supply Pembrolizumab and Celltrion Healthcare Co., LTD will supply Rituximab.

All study drugs will be labeled according to the requirements of local law and legislation. The label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request. For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file. An approved representative

at the site will ensure that all received study drugs are stored in a secured area on site, under recommended storage conditions and in accordance with applicable regulatory requirements.

8.1.1.2 *Responsibilities*

Supplies have to be obtained by sending a drug order form.
All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.
The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All IMPs must be stored in accordance with labeling and shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained. Any quality issue noticed with the receipt or use of an IMP (deficient IMP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the Investigator supply the IMP to a third party, allows the IMP to be used other than as directed by this Clinical Trial Protocol, or dispose of the IMP in any other manner.

8.1.1.3 *Storage and Handling Requirements*

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.1.1.4 *Returns and Reconciliation*

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the IMP. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient. Used vials can be destroyed directly after preparation of the infusion for safety reasons. The study monitor will periodically check the supplies of IMP held by the investigator or pharmacist to verify accountability of all IMP used. All unused treatments will also be verified by the Sponsor/Monitor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team. The Investigator will not destroy the unused IMP unless the Sponsor/monitor provides written authorization. The investigator is

responsible for keeping accurate records of the clinical supplies received, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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

8.1.2 Pembrolizumab

8.1.2.1 *Structure and Mechanismen of Action of Pembrolizumab*

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, Pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (Pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

8.1.2.2 *Pharmaceutical and Therapeutic Background*

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in Marginal zone lymphoma.

8.1.2.3 *Preclinical and Clinical Trial Data*

Please refer to the Investigator's Brochure for all Preclinical and Clinical data. In hematological neoplasms Pembrolizumab was tested in different lymphomas and multiple myeloma. Pembrolizumab in combination with Pomalidomide and Dexamethasone were given in the KN183 trial in subjects with refractory or relapsed and refractory multiple myeloma in comparison to the control arm with Pomalidomide and Dexamethasone alone. In the KN185 trial Subjects with newly diagnosed and treatment naive multiple myeloma were treated with Pembrolizumab in combination with Lenalidomide and Dexamethasone in comparison to the control arm with Lenalidomide and Dexamethasone. A full safety analysis based on June 2, 2017 data cutoff date was conducted for both studies. 249 randomized participants were included in the KN183 study. The median follow-up was 8.1 months. Objective response rate was 34% in the investigational arm compared to 40% in the control arm. In the safety analysis, there was an increase of Grade 3-5 events (83% vs. 65%, investigational vs. control arm). The

incidence of serious adverse events was 63% vs. 46%, respectively. At the cutoff date 301 randomized participants were included in the KN185 study. The median follow-up was 6.6 months. Objective response rate was 64% in the investigational arm compared to 62% in the control arm. In the safety analysis, there was an increase of Grade 3-5 events (72% vs. 50%, investigational vs. control arm). The incidence of serious adverse events was 54% vs. 39 %, respectively. These data demonstrated that the combination of Pembrolizumab with so called immunomodulatory agents such as pomalidomide and lenalidomide induce considerable toxicity and should be avoided.

8.1.2.4 *Pembrolizumab Materials*

Please refer to IB for Pembrolizumab for more details regarding drug properties and formulation.

Pembrolizumab will be provided by MSD as summarized here:

Pembrolizumab 100 mg/ 4mL solution for infusion

Pembrolizumab solution for infusion 100 mg/vial is a liquid Drug Product (DP) (manufactured using the fully formulated Drug Substance (DS) with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier and Water for Injection as Solvent).

The solution is stored under refrigerated conditions (2°C to 8°C). The liquid is intended for IV administration.

It is a clear to opalescent solutions, essentially free of visible particles and is intended for IV administration. The color of the solution is colorless to slightly yellow. At the point of use, Pembrolizumab DP is diluted with 0.9% sodium chloride injection, USP (normal saline) or 5% dextrose injection, USP (5% dextrose) to 1 to 10 mg/mL before IV administration through an infusion filter. Liquid DP is compatible with the IV bag and infusion-line materials. Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. Do not freeze the diluted solution. If the diluted Pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24-hour total hold time may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or IV bags must be allowed to come to room temperature before use.

8.1.2.5 *Timing of Dose Administration*

Pembrolizumab 200 mg will be administered as a 30 minutes IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the Pembrolizumab infusion fluid and administration of infusion solution.

Shelf life of reconstituted vials

Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. If the diluted Pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24-hour total hold time from reconstitution may include up to 6 hours at room temperature (at or below 25°C). Any additional hold time must be at 2°C to 8°C. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

Premedication

Premedication with antipyretic and antihistamine may be considered.

8.1.3 Rituximab

Rituximab (Truxima®) will be applied IV and will be supplied by Celltrion Healthcare Co., LTD.

8.1.3.1 *Formulation Packaging and Labeling*

Formulation, Packaging and Labeling

Truxima 100 mg concentrate for solution for infusion.

Truxima 500 mg concentrate for solution for infusion.

Qualitative and quantitative composition

Each vial contains 100 mg or 500 mg of Rituximab. Each mL of concentrate contains 10 mg of Rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

Excipient with known effect:

This medicinal product contains up to 23.06 mmol (or 530.1 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Incompatibilities

No incompatibilities between Truxima and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

Shelf life

Unopened vial

For unopened vials 3 years.

Diluted solution

The prepared infusion solution of Truxima is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature (≤25°C).

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2°C – 8°C). Keep the container in the outer carton in order to protect from light. For storage conditions after dilution of the medicinal product, see above.

Nature and contents of container

10 mL vial: Clear Type I glass vials with butyl rubber stopper containing 100 mg of Rituximab in 10 ml.
50 mL vial: Clear Type I glass vials with butyl rubber stopper containing 500 mg of Rituximab in 50 ml.

8.1.3.2 *Preparation and Administration of Rituximab IV Formulation*

Special precautions for disposal and other handling

Truxima is provided in sterile, preservative-free, non-pyrogenic, single use vials. Aseptically withdraw the necessary amount of Truxima, and dilute to a calculated concentration of 1 to 4 mg/mL Rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/mL (0.9%) solution for injection or 5% D-Glucose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Administration

Truxima should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an analgesic/ anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of Truxima. In patients with non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (CLL), premedication with glucocorticoids should be considered if Truxima is not given in combination with glucocorticoid-containing chemotherapy. In patients with rheumatoid arthritis, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to Truxima infusions to decrease the incidence and severity of infusion related reactions (IRRs). In patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, methylprednisolone given intravenously for 1 to 3 days at a dose of 1,000 mg per day is recommended prior to the first infusion of Truxima (the last dose of methylprednisolone may be given on the same day as the first infusion of Truxima). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after Truxima treatment.

Method of administration

Truxima is for intravenous use. The prepared Truxima solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumor lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions (IRR) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

First infusion

The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Subsequent infusions

Subsequent doses of Truxima can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Please refer to the IB for further formulation, storage and handling instructions for Rituximab IV.

8.1.3.3 *Known serious adverse reactions of Rituximab*

Contraindications

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia: Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients. Active, severe infections. Patients in a severely immunocompromised state.

Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis: Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients. Active, severe infections. Patients in a severely immunocompromised state. Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease.

Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the tradename of the administered product should be clearly recorded in the patient file.

Progressive multifocal leukoencephalopathy

All patients treated with Truxima for rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis must be given the patient alert card with each infusion. The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML). Very rare cases of fatal PML have been reported following use of Rituximab. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated. If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of Truxima must be permanently discontinued. Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of Rituximab therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Infusion related reactions

Rituximab is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use of the Rituximab intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first Rituximab intravenous infusion. They were characterized by pulmonary events and in some cases included rapid tumor lysis and features of tumor lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumor lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest X-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumor lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Patients with a high tumor burden or with a high number (≥ 25 x 109/L) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 109/L.

Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with Rituximab (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10% of patients). These symptoms are usually reversible with interruption of Rituximab infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions. Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of Rituximab. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Since hypotension may occur during Rituximab administration, consideration should be given to withholding antihypertensive medicinal product 12 hours prior to the Truxima infusion.

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with Rituximab. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Haematological toxicities

Although Rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/L and/or platelet counts < 75 x 10^9/L as clinical experience in this population is limited. Rituximab has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity. Regular full blood counts, including neutrophil and platelet counts, should be performed during Truxima therapy.

Infections

Serious infections, including fatalities, can occur during therapy with Rituximab. Truxima should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections).

Physicians should exercise caution when considering the use of Truxima in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.

Cases of hepatitis B reactivation have been reported in subjects receiving Rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. Limited information from one study in relapsed/refractory CLL patients suggests that Rituximab treatment may also worsen the outcome of primary hepatitis B infections. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Truxima. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Truxima. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of Rituximab in NHL and CLL. The majority of patients had received Rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunisations

The safety of immunisation with live viral vaccines, following Rituximab therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with Truxima may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received Rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for > 2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials. Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with Rituximab.

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported. In case of such an event, with a suspected relationship to Rituximab, treatment should be permanently discontinued.

Sodium

This medicinal product contains up to 23.06 mmol (or 530.1 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

8.1.3.4 *Undesirable effects*

Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Summary of the safety profile

The overall safety profile of Rituximab in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with Rituximab monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving Rituximab were IRRs which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of Rituximab.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55% of patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions (ADRs) were:

• IRRs (including cytokine-release syndrome, tumor-lysis syndrome)

• Infections

• Cardiovascular events

Other serious ADRs reported include hepatitis B reactivation and PML.

8.2 Treatment schedule and design

Cycle 1 (21 days cycle):

Rituximab:

375 mg/m^2 IV day 1, 8, 15

Pembrolizumab:

200 mg IV fixed dose day 2

Cycle 2-18 (21 days cycle) or until progression or non-tolerable toxicity:

Rituximab:

375 mg/m^2 IV day 1 every second cycle

Pembrolizumab:

200 mg IV fixed dose day 1

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Appendix A).

All trial treatments will be administered on an outpatient basis.

Sequence of treatment:

On days when both Pembrolizumab and Rituximab are administered, Pembrolizumab will be administered first IV, subsequently Rituximab will be applied IV. There should be at least a 30 min break between the infusions. Pre-medication for Rituximab will be applied before the start of Pembrolizumab as described in section 8.1.3 and according to the center's standard procedures. The administration will take place under the close supervision of an experienced healthcare professional and patients will be closely monitored for adverse reactions like cytokine release syndrome.

Rationale for dosing schedule of rituximab after cycle 1:

Rituximab single agent is one of the widely used chemotherapy free approaches in MZL and has clear anti-lymphoma activity in MZL. This is why we aim at continuing Rituximab applications beyond cycle 1 to exploit this activity. In addition, conceptually Pembrolizumab as a PD1 inhibitor should increase the activity of Rituximab by "re-freshing" ADCC, which is important for Rituximab activity. Thus, we anticipate that Rituximab beyond its known activity as a single agent, shows increased activity when combined with Pembrolizumab until cycle 18 in a de-escalated application scheme with one infusion every 8 weeks.

Follow-up Phase

All subjects who enter the trial will continue to be followed every 3 months for disease progression, subsequent treatment, and survival for two years after completion/discontinuation

of the treatment. Subsequently, patients will be monitored every 6 months for three additional years. The follow-up phase will be shorter than 5 years if End of Study is reached before this time period.

Patients with disease progression at any time will be followed every 6 months (after early completion visit) until the end of the study (app of 7.5 years starting with first patient in) for the following:

- New anti-lymphoma therapy
- Survival

8.3 Dose adjustments

In general, the following rules should be adhered to:

- In case of several toxicities, the most severe reaction is to be taken for dose reductions.
- Patients must have at least a hemoglobin value ≥7.5 g/dL, an ANC ≥0.5 × 10^9/L, **and** a platelet count ≥30 × 10^9/L before continuing treatment.
- Delays of cycles will be done by regimen and not by individual compound.
- Dose reductions will be done by individual compounds as described below.
- If there is the necessity to stop application of single compounds, treatment can be continued omitting the individual drug with the other compounds of the regimen.
- If there is a delay in treatment of > 3 weeks, contact the 'Clinical trials office (Ulm)'.

8.3.1 Pembrolizumab i.v.

8.3.1.1 *Dose Modification and toxicity management for irAEs associated with Pembrolizumab and combination therapy*

AEs associated with Pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of Pembrolizumab/ combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of Pembrolizumab/ combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue Pembrolizumab and administer corticosteroids.

Dose modification and toxicity management guidelines for irAEs associated with Pembrolizumab/ combination treatment are provided in Table 1.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to rituximab alone or to pembrolizumab alone, for adverse events listed in Table 1, both interventions must be held according to the criteria in Table 1.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 1.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 1, the combination of rituximab and pembrolizumab may be restarted at the discretion of the investigator

8.3.1.2 *Dose modification and toxicity management of infusion-reactions related to Pembrolizumab*

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on Pembrolizumab associated infusion reaction are provided in Table 2.

Table 1: Dose modification and toxicity management guidelines for immune-related AEs associated with Pembrolizumab monotherapy and immuno-oncology combinations

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where study intervention has been withheld, study intervention can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Study intervention should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
4. For signs or symptoms of SJS or TEN, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue pembrolizumab.

Immune-related AEs	Toxicity grade (CTCAEv5.0)	Action With Pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

Increased bilirubin	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: Grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. [e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

Table 2: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) at http://ctep.cancer.gov		

8.3.1.3 *Other dose interruption allowed for Pembrolizumab*

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.3.2 Rituximab i.v.

If any NCI CTCAE (v 5.0) grade 1 or 2 infusion-related reaction (IRR) occurs during an infusion, infusion should be slowed or interrupted (at the discretion of the investigator) and supportive treatment instituted. The infusion rate can be increased or restarted on resolution of the symptoms.

If any NCI CTCAE (v 5.0) grade 3 or 4 IRR occurs during an infusion, infusion will be discontinued immediately and not restarted until resolution of the symptoms. Treatment can be reinitiated (at half the original infusion rate) at the discretion of the investigator, but if the same adverse event appears again with the same severity, treatment must be permanently discontinued.

If bronchospasm or dyspnea occurs in the patient during the infusion, the infusion should be stopped immediately. Medication such as anti-histamines or steroids should be given for symptomatic relief. The infusion should not be re-started until symptoms have resolved completely and should be given at half the original infusion rate. Neutropenia and thrombocytopenia could be due to the course of the disease and it may be necessary to delay the dose of Rituximab until they are resolved, up to a maximum of 2 weeks.

Please also consider section “8.1.3.3 Serious adverse reactions”.

8.4 Permitted Medications and Supportive Therapies

- Standard therapies for concurrent medical conditions
- Treatment with non-conventional therapies (for example acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Bisphosphonates
- Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT is stable. Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should

be repeated weekly until it is stable.

- Antiemetics: Prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to Pembrolizumab administration will be not allowed.
- Palliative and supportive care for the other disease-related symptoms (with the exception of radiotherapy) and for toxicity associated with treatment will be offered to all patients in this trial.
- Patients may receive palliative and supportive care for any underlying illness (with the exception of radiotherapy).
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin are permitted.
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine and digoxin.

The following medications and supportive therapies are examples of support therapies that may be used if needed during this study:

- Platelet, and packed red blood cell transfusions are permitted, as necessary;
- Granulocyte-Colony Stimulating Factor, Erythropoietin;
- Medications to prevent and treat Rituximab related infusion reactions (i.e. Acetaminophen, Diphenhydramine, glucocorticoids, Ranitidine or Cimetidine).

8.5 Prohibited concomitant therapy

- Any treatment responsible for lymphocyte depletion and live-attenuated vaccines are not permitted
- Antineoplastic systemic chemotherapy or biological therapy
- This list is not comprehensive and is only meant to be used as a guide:
  - Herbal medications/preparations (except for vitamins). Herbal medications include, but not limited to: St. John’s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, mistletoe and ginseng. Patients should stop using all herbal medications at least 7 days prior to first dose of study treatment.
  - Other investigational and antineoplastic therapies
  - Anti-arrhythmic therapy other than beta blockers or digoxin
  - Systemic corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent. Previous corticosteroid therapy must be stopped or reduced to the allowed

dose at least 7 days prior to the screening CT/MRI). If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids. Short-term systemic corticosteroids above 15 mg prednisolone or equivalent will be allowed. The use of corticosteroids as antiemetics prior to Pembrolizumab administration will not be allowed

- Ongoing immunosuppressive therapy
- Concomitant radiotherapy (it is assumed that radiation would be indicated only in case of progression, when the patient would come off study medication anyway)
- Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during therapy.

The therapies listed above are not prohibited anymore 110 days after last study drug administration (based on five times the terminal elimination half-life of Rituximab and Pembrolizumab). In case of disease progression the patient can receive a new anti-lymhoma treatment before this time period, the decision is at the discretion of the treating physician.

8.6 Vaccinations

- Immunizations status of eligible patients must be checked at the inclusion. National recommendations for adult immunization policy must be fulfilled before Rituximab delivery.
- Pneumococal and hemophilus B vaccines are recommended in the absence of contraindications before Rituximab therapy. The interval of time between any immunization and the first Rituximab delivery should be at least of 28 days.

9. Schedule of assessments

9.1 Definition of (staging) examinations

9.1.1 Pathological diagnostic

Tissue diagnostic procedures must be performed within 12 months prior to study entry and have to include diagnostics by a reference pathology center. Biopsy material from an excisional or core biopsy must be submitted for retrospective central confirmation. Tissue samples dated > 12 months prior to informed consent can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient.
A local pathological diagnosis of MZL is obligatory before registration into the clinical trial. In addition, a reference pathological confirmation of the diagnosis MZL has to be available at the

end of the screening period and before initiation of treatment. The pathological review will be centralized nationally in each participating country in their national reference laboratories. The review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of MZL including specification of the MZL sub-type. Preferably, all the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis) will be sent to one of the Pathology Reference Centers named in Appendix J. If this is not possible at least 10 unstained slides should be sent. As part of the central pathological review also the MYD88 mutation will be assessed. Furthermore, PD-L1 expression of lymphoma cells will be assessed by a validated method. The block remains at the central reference pathologist if patient gave his informed consent for that. The central reference pathologist will send the reference pathology report to the study site and the local pathologist that submitted the case for 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.

9.1.2 Tumor and Response Evaluation

All measurable disease must be documented at baseline and re-assessed according to assessment schedule provided in Appendix A.
Initial CT/MRI scans used for screening evaluation should not be older than 6 weeks before start of treatment.
Response assessments will be performed by the investigator, based on physical examinations, CT/MRI scans, hematology, laboratory results, and bone marrow examinations, through use of Response Criteria for nodal, extranodal and splenic MZL (see Appendix D-F). CT scans (with contrast) should include chest, abdomen, and pelvis scans; CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease on physical examination) and must be followed throughout the trial if there is disease involvement at baseline. MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If MRI is used at screening, then MRI should be used throughout the study (**same method during the entire study).** In addition, the CT portion of a combined FDG-PET/CT scan may be used and collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Use of FDG-PET/CT when clinically indicated and must be conducted always beforehand Pembrolizumab administration. Any time the investigator suspects disease progression, a full tumor

assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities).
In case of several lesions, the 6 largest ones should be measured and used as baseline value (if possible, the lesions should be from disparate regions of the body and should include mediastinal and retroperitoneal areas of disease whenever these sites are involved). If only a splenomegaly has been diagnosed, the spleen should also be measured by ultrasound so that the spleen can be monitored by ultrasound only to avoid unnecessary radiation.

In patients with gastric extranodal MZL, the initial staging should include a gastroduodenal endoscopy with multiple biopsies from the stomach, duodenum, gastroesophageal junction, and any site that seems abnormal and must not be older than 12 weeks before start of treatment. If any disease sites are identified in this manner at screening, a subsequent gastroduodenal endoscopy and biopsy are required to confirm a CR. In addition, if other sites are involved at baseline, they should be appropriately staged at baseline and re-evaluated during follow-up. For response evaluation endoscopy should be performed at C10D1 and at the end of treatment. H. pylori status must be evaluated. Endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration should be performed.

In patients with non-gastric extranodal MZL, the initial staging should be adapted to the affected site as follows and according to local practice:

- Small intestine (immunoproliferative small intestinal disease, IPSID): Campylobacter Jejuni search in the tumor biopsy by polymerase chain recation (PCR), immunohistochemistry or in situ hybridization may be carried out.
- Large intestine: colonoscopy.
- Lung: Bronchoscopy + bronchoalveolar lavage.
- Salivary glands: Ear/nose/throat examination and ultrasound. To eliminate association with Sjögren syndrome anti-SSA or anti-SSB antibodies should be investigated.
- Thyroid: echography ± computer tomography (CT) scan of the neck and thyroid function tests.
- Ocular adnexa: MRI (or CT scan) and ophthalmologic examination. Chlamydia psittaci in the tumor biopsy and blood mononuclear cells by PCR may be considered.
- Breast: mammography and MRI (or CT scan).
- Skin: Borrelia Burgdorferi in the tumor biopsy by PCR (in endemic areas) may be considered.

For all patients with extranodal MZL the MALT-IPI should be determined. It is the decision of the investigator to conduct a FDG-PET-CT. Investigations must not be older than 12 weeks before start of treatment. If any disease sites are identified in this manner at screening, a subsequent investigation is required to confirm a CR. For response evaluation investigations should be performed at C10D1 and at the end of treatment.

9.1.3 Bone marrow examinations

Bone marrow examinations should include a biopsy for morphology and an aspirate for local hematology (optional, if part of standard of care at site). Bone marrow examinations are required at screening for staging purposes in all patients (CR definition requires clearing of a previously infiltrated bone marrow) and must not be older than 12 weeks before start of treatment. If there was bone marrow infiltration at screening, then a subsequent bone marrow biopsy at the completion of cycle 9 is required for clinical response evaluation for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later time point. An additional bone marrow aspirate may be done if that is standard of care at the site.

9.1.4 Demographic and medical history

Demographic data will include year of birth, gender and ethnic origin.
The investigator or designee will collect a complete medical and surgical history from 5 years before the screening through to the time of informed consent. Medical history will include information on the subject's concurrent medical conditions.
Relevant medical history, including previous chemotherapy/immunotherapy or radiotherapy, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (only ongoing events) will be collected. Lymphoma history must date back to the initial diagnosis and any response duration must be recorded. Additionally the Ann Arbor Stage (Appendix G) will be determined.

9.1.5 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. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. At screening a complete physical examination will be performed. At the other timepoints physical examination should only include systems of most clinical relevance.

9.1.6 B Symptoms

At least the following B Symptoms have to be assessed: fever, night sweats and weight loss (unintentional loss of weight; e.g. more than 10% of body weight within the last 6 months).

9.1.7 Vital Signs

The assessment of vital signs must include height (only screening), weight, blood pressure, pulse and temperature.

9.1.8 ECOG

The ECOG Performance Status is one of two widely used methods to assess the functional status of a patient. The scale for evaluation is shown in appendix H.

9.1.9 Electrocardiograms

A 12-lead ECG and an echocardiography is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine whenever possible, echocardiogram to measure LVEF

9.1.10 Laboratory Assessments

During treatment laboratory tests prior to each infusion may be performed either the day before or on the planned day of infusion. For dosing criteria, see Section 8.3.

Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell count, and percent or absolute differential count [total neutrophils, segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes (e.g., villous lymphocytes in splenic MZL), other cells])
- Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, magnesium, total bilirubin, total protein, albumin, CRP, LDH, ALT, AST, GGT, alkaline phosphatase, uric acid, glucose, BUN/creatinine ratio, lipase, amylase and β2 microglobulin (β2 microglobulin required only at screening). Phosphate, total cholesterol, LDL and triglycerides will be determined at Screening, on Day 1 of every 2nd cycle (2, 4, 6 etc.) and at the EOT visit. On these days patients must be fasting prior to sampling according to local standards. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
- Quantitative immunoglobulins (IgG, IgA, and IgM)

- Serum electrophoresis (albumin, alpha 1, alpha 2, beta, gamma), relative and absolute determination of M protein if present. If M protein is present, immunofixation for detection of Ig subtype (IgG, IgA, IgM, IgD, light-chain kappa or lambda)
- Thyroid hormones: T3, T4, TSH
- Urine analysis: In a fresh sample of midstream urine, a dipstick testing for proteinuria is required (and microscopy including protein, specific gravity, glucose and blood).
- Urine Protein to Creatinine Ratio (UPCR) measurement.
- GFR calculation according to MDRD abbreviated formula
- Leukocyte immunophenotyping (FACS) PB and Bone Marrow Aspirate; Mandatory CD5, CD10, CD19, CD20, CD23, CD27, CD43, FMC7, kappa/lambda light chains.
- Coagulation (PTT or aPTT, prothrombin time, INR)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a pregnancy test at screening. WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities and may be performed more frequently if required by local legislation. If a urine pregnancy test is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.
- Viral serology and detection: Hepatitis B (HBsAg and total HBcAb and HBSAb) HBV DNA should be monitored every 4 weeks by real-time PCR with a limit of quantification of at least 29 IU/mL until at least 1 year after the last treatment cycle in patients who are HBsAg negative and HBcAb positive. If a patient is HBsAg negative and HBcAb positive during screening, additional serology for hepatitis B surface antibody (HBsAb) is required prior to Day 1 of Cycle 1. HCV antibody (also HCV RNA by PCR in a local laboratory if the patient is HCV antibody positive).

9.1.11 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

To address health-related quality-of-life (HRQL) issues for Non-Hodgkin's lymphoma (NHL) patients. Patient completes the questionnaire at the start of treatment (Cycle 1 Day 1) and afterwards at Day 1 of every third cycle, before contact with the investigator or other investigative site personnel.

9.1.12 Collection of Biological Material for Biobank

Only German study sites will participate in the biological sampling project.

The patient's consent and signature at the "Transfer of Ownership Agreement" is prerequisite for biological sampling. The required materials, amounts and procedures for the management of biological samples will be explained in Appendix B.

If any patients will withdraw his/her consent to further biological sampling and storage during study participation, no further collection of biological samples will take place and already stored samples will be destroyed if possible and wished by the patient. This does not affect the patient's participation in the clinical study in any other respect.

9.2 Screening procedures

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site. Screening tests and evaluations will be performed within 28 days prior to Day 1 of Cycle 1 (defined as the day of the first dose of Rituximab). Results of standard-of-care tests or examinations performed within 14 days prior obtaining informed consent may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before initiation of study treatment. Please see the Study Flowcharts provided in Appendix A for schedules of screening and pretreatment assessments.

At the end of the screening period a reference pathology report has to be available before start of treatment.

After the patient signs the study informed consent, any new finding discovered not present in the patient's medical history or a worsening of a prior medical history finding must be recorded as an adverse event. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue, CT (or MRI) scans, endoscopy with biopsies, bone marrow sample, echocardiogram and hepatitis testing which may be used provided they fall into the protocol specified window (see section 9.1). However, these historical results can only be used after the patient gives informed consent to use them.

The following procedures will be conducted at the Screening visit (after obtaining informed consent):

- Discussion of fertility issues and sperm banking should be performed in patients at childbearing age
- Demographic, Medical History and Ann Arbor Stage
- Complete physical examination, vital signs and ECOG performance status
- Initial staging procedures: iter alia imaging and bone marrow examinations (for details see section 9.1)

- Presence of B–symptoms (fever, weight loss, night sweat)
- 12-lead ECG and Echocardiography
- Laboratory:
  - Hematology
  - Serum chemistry
  - electrophoresis
  - If M protein is present: Serum protein immunofixation
  - Coagulation
  - Thyroid hormones
  - Urine analysis
  - Urine Protein to Creatinine Ratio (UPCR) measurement
  - GFR calculation according to MDRD abbreviated formula
  - Quantitative immunoglobulins (IgG, IgA, and IgM)
  - Leukocyte immunophenotyping (FACS) PB and Bone Marrow Aspirate
  - Viral serology and detection
- Concomitant medication
- All women of childbearing potential will have a pregnancy test at screening

Once screening studies are complete and patient eligibility for this study is established, the provided inclusion checklist form will be completed for registration of the patient.

9.3 Assessments during Treatment

Local laboratory assessments may be performed within 4 days prior to study drug administration on Day 1 of each cycle. Results must be reviewed and the review documented prior to study drug administration. During treatment, all visits must occur within ± 4 days from the scheduled date, unless otherwise noted. Assessments scheduled on the day of study drug administration should be performed prior to study drug infusion, unless otherwise noted. Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed during treatment.

Treatment – Cycle 1

Cycle 1, Day 1

The following assessments should be performed on Cycle 1 Day 1 before receiving study drug unless otherwise specified in the protocol.

- Complete physical examination, including vital signs
- ECOG Performance Status
- Laboratory tests

  - Hematology
  - Serum Chemistry (excluding phosphate, total cholesterol, LDL and triglycerides) and electrophoresis
  - Women of childbearing potential: negative urine pregnancy test
- Safety assessment (see Section 8.3 and 11). AE reporting period starts with informed consent signature
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Quality of life questionnaire (FACT-Lym)

Cycle 1, Day 2

- Vital signs
- Safety assessment
- Concomitant medication review

Cycle 1 Day 8

The following assessments should be performed on Cycle 1 Day 8 before receiving study drug unless otherwise specified in the protocol.

- Vital signs
- Laboratory:
  - Hematology
  - Serum Chemistry (excluding phosphate, total cholesterol, LDL and triglycerides) and electrophoresis
  - Urine Protein to Creatinine Ratio (UPCR) measurement when clinically indicated
- Safety assessment (see Section 8.3 and 11).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).

Cycle 1, Day 15

The following assessments should be performed on Cycle 1 Day 15 before receiving study drug unless otherwise specified in the protocol.

- Vital signs
- Laboratory:
  - Hematology

  - Serum Chemistry (excluding phosphate, total cholesterol, LDL and triglycerides) and electrophoresis
  - Urine Protein to Creatinine Ratio (UPCR) measurement when clinically indicated
- Safety assessment (see Section 8.3 and 11).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).

Cycle 2 and higher, Day 1

The following assessments should be performed on Cycle 2 and higher, Day 1 before receiving study drug unless otherwise specified in the protocol.

- Physical examination, including vital signs
- ECOG Performance Status
- Laboratory:
  - Hematology
  - Serum Chemistry and electrophoresis. Phosphate, total cholesterol, LDL and triglycerides will be determined at Screening, on Day 1 of every 2nd cycle (2, 4, 6 etc.) and at the EOT visit. On these days patients must be fasting prior to sampling according to local standards. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
  - GFR
  - Coagulation panel
  - Urinalysis (dipstick). Microscopy as clinically indicated
  - Urine Protein to Creatinine Ratio (UPCR) measurement when clinically indicated
  - HBV DNA PCR in patients who are HBsAg negative and HBcAb positive
- Safety assessment (see Section 8.3 and 11).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- B-Symptoms on Day 1 of each third cycle (i.e. on Day 1 of Cycles 1, 3, 6, 9 etc. and Cycle 10)
- QoL questionnaire (FACT-Lym) on Day 1 of each third cycle (i.e. on Day 1 of Cycles 1, 3, 6, 9 etc.)

Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed during Treatment phases.

Safety monitoring of the first 6 included patients

There will be a close safety monitoring of the first 6 included patients. For these 6 patients safety evaluations will be performed on:

- Cycle 1 day 1, day 8 and day 15
- Cycles 2 to 6 day 1 and day 15

All included patients will have study visits as described above. For these 6 first patients additionally the visits C2D15, C3D15, C4D15, C5D15 and C6D15 have to be scheduled.

The following assessments should be performed:

- physical examinations
- Laboratory:
  - Hematology
  - Serum Chemistry and electrophoresis
  - CRP
  - serum immunoglobulin [IgG, IgM, IgA]
- adverse event monitoring
- concomitant medications

End of Cycle 9 (Cycle 10 Day 1) or Early Termination Visit

Patients who complete Cycle 9 will be asked to return to the clinic within 4−6 weeks after Cycle 9 Day 1 for C10D1 visit. Patients who discontinued treatment early will be asked to return to the clinic for Early Termination Visit. An early termination visit should occur within 4−8 weeks after last dose (in case of early termination due to adverse event) or within 2−8 weeks after last dose (in case of early termination due to clinical disease progression). Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed at the induction completion/early termination visit.

The following assessments should be performed on Cycle 10 Day 1 before receiving study drug or on Early Termination Visit unless otherwise specified in the protocol:

- In patients with gastric extranodal MZL: Gastroduodenal endoscopy
- Tumor Assessment: by CT/PET-CT/MRI and/or Bone Marrow aspirate and biopsy and/or Immunophenotyping PB and BM
- Complete physical examination, including vital signs
- ECOG Performance Status
- Laboratory:
  - Quantitative Immunglobulins (IgA, IgG, IgM)
  - Serum Protein Immunofixation if initially positive for monoclonal Ig

  - Leukocyte immunophenotyping (FACS) PB (and Bone Marrow Aspirate);
  - Hematology
  - Serum Chemistry and electrophoresis
  - Coagulation
  - HBV DNA PCR in patients who are HBsAg negative and HBcAb positive
  - Urinalysis (dipstick). Microscopy as clinically indicated
  - Urine Protein to Creatinine Ratio (UPCR) measurement when clinically indicated
  - GFR
  - Women of childbearing potential: negative urine pregnancy test
- 12-lead ECG and an echocardiography when clinically indicated
- Safety assessment (see Section 8.3 and 11).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- In case of Early Termination Visit: new anti-lymphoma treatment

Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed during Treatment phases.

Patients with at least SD will continue study treatment as specified above until end of cycle 18 or until PD is determined.

9.4 Therapy Completion (EOT)

Patients who complete the treatment period will be asked to return to the clinic *4 weeks* after *Cycle 18 Day 1* for an EOT visit. The visit at which a response assessment showed disease progression may be used as the early termination visit (see above).
The following assessments should be performed at the End of Treatment (EOT):

- In patients with gastric extranodal MZL: gastroduodenal endoscopy
- Tumor Assessment: by CT/PET-CT/MRI and/or Bone Marrow aspirate and biopsy and/or Immunophenotyping PB and BM
- Complete physical examination, including vital signs
- ECOG Performance Status
- Laboratory:
  - Quantitative Immunglobulins (IgA, IgG, IgM)
  - Serum Protein Immunofixation if initially positive for monoclonal Ig
  - Leukocyte immunophenotyping (FACS) PB (and Bone Marrow Aspirate);
  - Hematology
  - Serum Chemistry and electrophoresis

  - HBV DNA PCR in patients who are HBsAg negative and HBcAb positive
  - Urinalysis (dipstick). Microscopy as clinically indicated
  - Urine Protein to Creatinine Ratio (UPCR) measurement when clinically indicated
  - GFR
  - Women of childbearing potential: negative urine pregnancy test
- 12-lead ECG and an echocardiography when clinically indicated
- Safety assessment (see Section 8.3 and 11).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- New anti-lymphoma treatment
- B-Symptoms
- QoL questionnaire (FACT-Lym)

9.5 Follow-Up Assessments

Neither in the case of CR/SD nor in the case of PD is it necessary to provide the study medication beyond the end of the study. In the case of PD, treatment is continued with a different treatment regimen.

a. Patients with response or stable disease

For patients who have at least SD at the EOT visit, disease assessments will continue every 3 months ± *14 days* for 2 years (with CT/PET-CT/MRI if initially positive or indicated every 6 months) and then every 6 months ± *14 days* for 3 years (with CT/PET-CT/MRI if initially positive or indicated every year) until the end of the study or until disease progression, whichever occurs first. This assessment is consistent with both NCCN and ESMO guidelines. Patients will then be followed twice per year until the end of the study for the following:

- New anti-lymphoma therapy
- Survival

Patients who start a new anti-lymphoma therapy or discontinue study drug in the absence of disease progression should be followed according to the above schedule.

b. Patients with disease progression

Patients with disease progression at any time will be followed every 6 months (after early completion visit) until the end of the study (approximately 7.5 years after inclusion of first patient) for the following:

- New anti-lymphoma therapy
- Survival

10. Study procedures

10.1 Informed consent

All subjects must sign and date the most current IRB/IEC approved informed consent form. It is the responsibility of the investigator or a designated physician who is part of the study team to obtain informed consent in compliance with national requirements from each subject prior to any study related procedures or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by the sponsor prior to IRB/IEC submission.

The investigator must explain to a potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be

informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal or withdrawal will not prejudice future treatment.

Confirmation that the informed consent form has been signed should occur before any study-specific procedures are performed and before patient registration. All subjects who receive protocol-specified therapy or specified treatment should be re-informed and should re-consent with at least every safety relevant updated version of the IRB/IEC approved informed consent form during study participation as applicable and per institutional guidelines.

Withdrawal in case the patients experiences an adverse event which indicates to the investigator that continued participation is not in the best interest of the patient is performed by the investigator. All data collected before the time point of withdrawal remain within the study database (according to AMG §40 (2a) 3) Consent will be sought from the patient, in order to be allowed to

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

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

The original informed consent document signed and dated by the study subject and by the person having informed and obtained consent from the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy will be given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised.

No compensation will be paid to the patients.

10.2 Registration Procedure

The Informed Consent has to be signed by all parties before starting of any trial related procedures.

Patients have to be registered in a web-based system when informed consent signature is obtained and as soon as Eligibility Criteria are fulfilled to generate the unique trial identification number. Registration must occur prior to initiation of treatment.

Following data must be provided in the web-based system:

- Name of pathological reference investigator

- Patient's birth date (month/year)
- Eligibility criteria
- Electronic signature of the responsible investigator for confirmation of inclusion and exclusion criteria

10.3 Patient Study Participation card

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

10.4 Criteria for premature discontinuation of the study

10.4.1 Early Treatment discontinuation for an individual patient

Per-protocol treatment of the patient must be discontinued for the following reasons:

- pregnancy
- disease progression at any time
- intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree
- recurrent Grade 2 pneumonitis
- repeated clinically relevant violation of the protocol
- non-compliance by the patient with protocol requirements
- excessive and unexpected toxicity of the treatment
- patient’s decision to stop her/his participation in the trial or study treatment
- decision by the treating physician for medical reasons
- discontinuation of the whole study at the request of sponsor
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.

In summary, a patient should be withdrawn from the trial treatment if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the patient.

The reason for the early termination of the per-protocol treatment must be documented and the ’Coordinating Investigator’ must be informed in written form e.g. on the respective eCRF. Patients who stop per-protocol therapy early must be documented and followed-up according to protocol. Early termination should be avoided. In case of an early termination of therapy, reasons / circumstances and if applicable the final disease status of the patient have to be

documented. **If the patient does not withdraw the consent for further follow-up, he or she should be followed-up as planned.**

10.4.2 Early study termination for an individual patient

The only reason for the exclusion of a patient from the study is his or her withdrawal of consent. Patients can withdraw their informed consent to this study at any time and this does not interfere with their right of treatment by the local investigator (physician). In case of cessation of the study-treatment a final statement concerning the treatment effect and the causes of premature study-termination have to be given by the local investigator.

In case it becomes evident *ex post* that a patient did not qualify for the study (e. g. did not fulfill all inclusion criteria nor had an exclusion criterion at the time of registration) the physician treating the patient with *ex-post* non-qualification will be informed by the Clinical Trial Office Ulm on the ex post non-qualification of a patient. A thorough benefit risk assessment has to be performed by the investigator together with the sponsor to decide if the patient with *ex-post* non-qualification should continue study treatment and the result has to be documented. The patient with *ex post* non-qualification is only allowed to continue study treatment if it is concluded that in this case for the patient benefits will outweigh risks. The documentation and follow up of patients with *ex post* non-qualification must continue as planned in the protocol, because the documentation of such patients is not different from the documentation of qualified patients.

10.4.3 Early closing of a trial site

The closing of a given trial site will be considered if:

- it does not meet the technical requirements of the protocol,
- the recruitment rate is not sufficient,
- inaccurate or incomplete data collection
- detected fraud,
- GCP noncompliance,
- the conduct of the study is not compliant with the protocol, or
- the data quality is not sufficient.

The early closing of a site will be decided by the Coordinating Investigator after consultation with the responsible Data Safety Monitoring Committee. Investigators and trial sites deciding not to take part in the trial any longer have to inform the Coordinating Investigator immediately. The decision should be well-founded. Details on further treatment and follow-up of patients already on study have to be discussed with the Principal Investigator.

10.4.4 Early termination of the study

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

- the occurrence of serious unexpected side effects of treatment
- excessive treatment-related mortality
- insufficient efficacy of study treatment
- relevant pertaining new information from other studies or publications
- inadequate recruitment rate
- excessive number of deviations from the study protocol
- logistic and / or financial reasons
- any other fact which would change the risk-benefit analysis of this trial

The *Data Safety Monitoring Committee* (see Appendix K) will monitor the study conduct and the safety aspects of the trial on a regular basis, and will give recommendations to the Coordinating Investigator of the trial whether to stop the trial or to change the trial protocol. The *Coordinating Investigator* will then decide on the actions to be taken. Basis for his decision are the Development Safety Update Reports and the recommendations of the Data Safety Monitoring Committee. These recommendations take into consideration the time course of the recruitment, characteristics of the study population, execution of the therapy *per protocol*, adherence to protocol and frequency of adverse and serious adverse events. The decision on an early termination of the study is a complex action which has to consider in addition to statistical also medical and ethical as well as organizational and financial aspects. Finally, according to the National drug laws, the trial may be suspended or early terminated by decision of the respective National Authorities. All Federal Authorities and the ethics committee in charge will be notified about the early termination of the trial.

11. Assessment of Safety

11.1 Monitoring, Recording and Reporting of Adverse Events

11.1.1 Adverse Event

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

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be recorded as an AE. If an overdose is associated with an AE, the overdose and adverse event should be recorded as separate terms.

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

All AEs and special situations will be recorded by the Investigator from the time a signed and dated ICF is obtained until 110 days after the last dose of study drug.

All adverse events and special situations, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology (CTCAE, Version 5.0) in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document.

All SAEs must be reported to the Sponsor/ZKS, within 24 hours of the Investigator's knowledge of the event by email to [redacted] using the SAE Report Form.

11.1.2 Adverse Event of Special Interest

AESIs (serious or non-serious) are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the IMP or to the Sponsor's product or research, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., MAH, Regulatory Authorities) may also be warranted.

Adverse events of special interest (AESI) (synonym: Events of Clinical Interest (ECI)) either serious or non-serious, are required to be reported by the investigator to the Sponsor/ZKS in the SAE form immediately (i.e., no more than 24 hours after learning of the event) and will be recorded on the AE page of the eCRF additionally. Adverse events of special interest for this study include the following:

Table 3: Adverse Event of Special Interest

Adverse Events of Special Interest
An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

AESIs (ECI) must be reported within 1 working day after becoming aware by the Sponsor to MSD Pharmacovigilance Germany [redacted]

For the time period beginning when the consent form is signed until treatment allocation, any AESI (ECI), or follow up to an AESI (ECI), that occurs to any participant must be reported within 1 working day after becoming aware by the Sponsor to MSD Pharmacovigilance Germany if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 110 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any AESI (ECI), or follow up to an AESI (ECI), whether or not related to MSD product, must be reported within 1 working day after becoming aware by the Sponsor to MSD Pharmacovigilance Germany

11.1.3 Adverse Drug Reaction

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An ADR should be recorded on the AE page of the eCRF.

11.1.4 Special Situations

Uses of the IMP outside what is foreseen in the protocol and defined below as „special situations“ are subject to the same obligation to report as adverse reactions. All special

situations, even in absence of an AE, that occur during the defined study period must be recorded on the source documentation, transcribed into the eCRF and in addition reported to the Sponsor/ZKS on the „Report form for SAEs, AESIs and Special Situations“.

Note: All instances of incorrect medication not in accordance with the study protocol should be additionally categorized as deviation in the eCRF.

- **Pregnancy/Breast feeding**
  see section 11.5
- **Overdose***
  Any administration of a quantity of a medicinal product given per administration or cumulatively that results in drug exposure exceeding that which is defined in the protocol.
- **Abuse**
  Intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, abuse potential refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Desired psychological effects can include euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood.
- **Misuse**
  Any intentional therapeutic use of a drug product in an inappropriate way. Inappropriate use should be considered in the context of the clinical trial protocol.
- **Medication Error**
  An unintended failure in the drug treatment process.
  Examples include administration of a drug product in the wrong dose, by an incorrect route, or to the wrong person; administration of a drug product resulting in a drug interaction due to drugs or foods that are known to interact; administration of the wrong drug product; or inadvertently consuming a greater than prescribed dose of a drug product (e.g. double dose) due to memory lapse. Therapeutic errors may be made by the patient, physician, pharmacist, clinical study staff etc.
- **Occupational exposure**
  Exposure to an IMP, as a result of one´s professional or non-professional occupation.
- ***Lack of therapeutic efficacy***
  Although MZL is a serious and life-threatening disease, patients will receive approved therapies while participating in this study. Efficacy of Rituximab/Pembrolizumab combination treatment has yet to be demonstrated in the MZL population. Therefore, lack of therapeutic efficacy is not the scope of this study.

*an overdose of MSD product, as defined in Section 11.3.

11.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1 Seriousness

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

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE); it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Any other event that the Investigator judges to be an important medical event
- adverse event associated with an overdose of IMP

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious. Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

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

Events excluded from SAE reporting are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to signing informed consent); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- Sign, symptoms and physical findings indicative of progression of lymphoma are not to be reported as “Serious Adverse Event”.
- “Alopecia” toxicity (any grade) will never be reported as “Serious Adverse Event”.
- Serious adverse events will not be recorded 30 days after the start of a new chemotherapy treatment, with the exception of second primary malignancies or if it is related to the study drug as assessed by the investigator.

11.2.2 Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject’s symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0):

AEs that are not defined in the NCI CTCAE (v 5.0) should be evaluated for severity / intensity according to the following scale:

- *Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required*
- *Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required*

- *Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible*
- *Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable*
- *Grade 5 = Death - the event results in death*

Specific NCI Working Group or other criteria pertinent to the indication may also be used as applicable.

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3 Causality

The Investigator must determine the relationship between the administration of the IMPs and the occurrence of an AE/SAE as Not Related or Related as defined below:

Not related:	**A** causal relationship is **unlikely or remote** between the adverse event and study drug administration and other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Related:	A causal relationship is **possible** between the adverse event and study drug administration and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event

11.2.4 Expectedness

A serious adverse event that is not included in the Adverse Reaction Section of the relevant Reference Safety Information (RSI) by its specificity, severity or outcome is considered an unexpected adverse event. The reference safety information for this study are the respective sections of the IB of Pembrolizumab and of the SmPC of Rituximab. For the purpose of SUSAR reporting, the version of the IB in force at the time of occurrence of the SUSAR applies.

11.2.5 Duration

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

11.2.6 Action Taken

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

11.2.7 Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

11.2.8 Abnormal Laboratory Values

Abnormal laboratory values in laboratory tests that are performed for safety surveillance and are not needed for assessment of any efficacy variables will be captured as adverse events, rather than capturing the raw laboratory values.

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IMP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

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

11.3 Definition of an Overdose of Pembrolizumab for this Protocol and Reporting of Overdose

For purposes of this study, an overdose of Pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the

treatment of overdose of Pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with the overdose of a MSD product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of MSD's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as Special Reporting Situation, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 1 working day after becoming aware by the Sponsor to MSD Pharmacovigilance Germany [redacted]

11.4 Other malignancies

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

11.5 Pregnancy

Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 12 months after last study treatment (Rituximab and Pembrolizumab) administration must be reported **immediately** to the Sponsor/ZKS. Follow-up information on the subject and her pregnancy outcome should be communicated by the investigator to the Sponsor as soon as available.

If a participant inadvertently becomes pregnant while on treatment, the participant will be immediately discontinued from study treatment. The investigator should counsel the subject or the partner of the subject, discuss the risks of continuing the pregnancy, and possible effects on the foetus. Monitoring of the patient should continue until up to 8 weeks of age of the newborn. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated.

Pregnancy should be reported on the **Pregnancy Report Form**. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion, any congenital anomaly [including that in an aborted fetus], stillbirth,

neonatal death), the investigator should follow the procedures for reporting SAEs. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects as related to the *in utero* exposure to the study drug should also be reported as SAE.

Such events must be reported within 24 hours to the Sponsor and within 1 working day after becoming aware by the Sponsor to MSD Pharmacovigilance Germany ([redacted]).

If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Sponsor within 24 hours. The pregnant female partner should be advised to call their healthcare provider immediately.

11.6 Reporting of Serious Adverse Events

11.6.1 Reporting period

All events that meet one or more criteria of seriousness that occurred **from the time the patient's signed informed consent up to 110 days after the last study drug administration,** regardless the relationship to the study treatment requires the completion of an SAE Report Form in addition to being recorded on the AE page of the eCRF.

A Serious Adverse Event that occurs after this time, including during the follow-up period, **if considered related to the study medication**, will be reported regardless of the time between the last drug administration and the event onset.

11.6.2 Obligations of the Investigator

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drugs) that occur during the study (from the time the patient signs informed consent to 110 days after the last dose of study drug(s)), and those made known to the Investigator at any time thereafter that are considered to be related study drugs.

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to MSD product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately according to SAE reporting requirements mentioned above. Events concerning secondary malignancy need to be reported during follow-up period regardless of causality.

All participants with serious adverse events must be followed up for outcome.

In case of serious adverse events, AESI and special situations **the Investigator must immediately report by sending the scanned and signed the SAE form to:**

[redacted]

Recipients: ZKS and CTO (Ulm)

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

- The SAE report should provide a detailed description of the SAE specifying the date of onset, severity, action taken regarding trial medication, corrective therapy given, outcome of all serious adverse events and his opinion as to whether the serious adverse event can be related to the study drugs. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.
- Information about results of any examinations carried out including laboratory tests that are important for the diagnosis, assessment, or treatment of a SAE and the dates on which these examinations were performed should be given within the SAE form. For laboratory tests the respective normal reference range should be provided as well.
- Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an identifiable patient; a suspect medicinal product; an identifiable reporting source (the identity of the Investigator: name, address, site number and email/telephone number); an event or outcome assessed as reportable;

investigator causality assessment (in case the investigator causality is missing, the causality will be considered related and the case may qualify as a SUSAR). Follow-up information should be actively sought and submitted as it becomes available.

- Additional information to any SAE should be provided by the investigator on a subsequent SAE-Report Follow up form and sent by e-mail to Sponsor/ZKS as soon as they become available, but not later than 3 days. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent as soon as these become available. A translation of the autopsy report and death certificate into English language has to be provided, if written in a language other than English or German.
- For the time period beginning at treatment allocation through 110 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the MSD product, must be reported within 24 hours to the Sponsor and by the Sponsor within 1 working day to MSD Pharmacovigilance Germany [redacted]

Where required by local regulation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the Sponsor/ZKS and the IRB/EC.

11.6.3 Safety Queries

Queries pertaining to SAEs will be communicated from the Sponsor/ZKS to the site via facsimile or electronic mail. The response time is expected to be no more than 1 calendar day (urgent queries) or three (3) business days (non-urgent queries). Urgent queries (e.g., missing causality assessment) may be handled by phone.

11.6.4 Obligations of the sponsor

SAE reports and any other relevant safety information must be reported from the Sponsor to MSD Pharmacovigilance Germany [redacted] within 1 working day after becoming aware by the Sponsor if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. It has to be reported by facsimile, or other appropriate

method, using the SAE Report Form. This instruction pertains to initial SAE reports as well as any follow-up reports.

During the course of the study, the Sponsor will report in a pseudonymized, expedited manner all SAEs that are both unexpected and suspected to be related to study drugs, to the Competent Authorities, concerned Ethic Committees in each country in accordance with international and local regulations, and to the Investigators:

- within 7 days of first knowledge by the sponsor of such a case for fatal or life-threatening events. Relevant missing information for fatal or life-threatening cases will be subsequently submitted within an additional eight days
- and within 15 days of first knowledge by the sponsor for other serious adverse events.

The expectedness of an adverse reaction will be determined by the Sponsor according to the reference safety information (e.g. Investigator's Brochure or SmPC) of the trial medication.

Expedited reporting (SUSAR, New Safety Issues) and submission of Development Safety Update Reports to the relevant Competent Authorities and to the Ethics Committees according to local regulation will be performed by ZKS Ulm and CTO.

11.7 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. All initial PQCs of an IMP must be reported to Sponsor/ZKS by the study-site personnel within 24 hours after being made aware of the event. The sponsor is responsible to report the PQC to either MSD Pharmacovigilance Germany or Pharmacovigilance Mundipharma [redacted] (depending on the IMP concerned). If the defect is combined with a serious adverse event, the investigational staff must report the PQC to Sponsor/ZKS according to the serious adverse event reporting timelines. A sample of the suspected product if possible should be maintained for further investigation.

11.8 Benefit/Risk assessment of treatment program

MZL is a subtype of cancer with a normally indolent clinical course. Despite this the disease is life threatening and leads to continuous deterioration of the patient's clinical situation without

adequate treatment. In this trial only patients will be included who are in need of treatment for whom local therapy is not feasible, for whom local therapy did not result in disease control or who relapsed after systemic treatment. In this situation the treatment program with Pembrolizumab/Rituximab represents a chemo-free approach, which promises high efficacy without major toxicity. The assumption of high efficacy is based on the experience with Pembrolizumab single agent in partly heavily pretreated relapsed/refractory B-Non-Hodgkin's lymphoma and on experience with Pembrolizumab in combination with Rituximab in relapsed follicular lymphoma, demonstrating high efficacy and clinically manageable toxicity. In addition, there is a large body of evidence, that Rituximab single agent is well tolerated and has anti-lymphoma activity in patients with MZL. Adequate pre-medication is obligatory in this trial and there will be close monitoring for toxicity of the first 6 patients included. Taken together, the risk for the patients to experience unexpected serious toxicity will be low and has to be balanced with the high likelihood to receive a chemo-free treatment, which will allow disease control for a longer time period, thereby delaying the need for the patient to accept more dose intense chemotherapy. Thus, the benefit of the treatment program is expected to be superior to the potential short and long term toxicities.

12. Statistical Considerations

12.1 Expected Improvement

In MZL a variety of treatment modalities are used such as Rituximab single agent, chemotherapy or Rituximab in combination with chemotherapy. It is widely accepted that in this non-curative indolent B – cell lymphoma of the mostly elderly patient chemotherapy – related toxicity should be avoided and that chemotherapy-free approaches are highly attractive in this patient population. So far Rituximab single agent is the most frequent chemotherapy-free approach used in this entity. Thus, a novel chemotherapy – free treatment approach should be at least as efficient as Rituximab monotherapy. In a large randomized study Rituximab single agent therapy induced a CRR of 55.8% compared to 78.8% for the combination of Rituximab and chlorambucil in de novo MZL of the MALT type [1]. CR rates in splenic MZL are comparable high at about 60% [8, 11], whereas patients with nodal MZL achieve a CRR of around 20%[9]. As the distribution of subtypes is about 70% MALT, 20% splenic, and 10% nodal MZL, a CRR which is better than 56% for the total population with MZL should at least be achieved by a new chemotherapy – free approach after end of treatment (18 cycles after start of therapy) for such a mixture of the population.

The goal of this study is to test the efficacy of the chemotherapy - free combination Pembrolizumab/Rituximab in treatment – naïve and relapsed symptomatic MZL aiming at achieving comparable treatment results compared to immuno- chemotherapy.

12.2 Sample Size

For sample size calculation the one-sided one sample exact binomial test was used. According to the above data, the CRR for the total group of the different subtypes of MZL must be better than 56% after end of treatment (18 cycles). Anticipating a CRR for Pembrolizumab/Rituximab of about 75%, a significance level of 2.5% (because of one- sided test) and a power of 80%, 48 full evaluable patients will be necessary to show that the combination will be a promising candidate for challenging immuno- chemotherapy (PROC POWER, SAS 9.3; 48 patients is the first number of patients with a stable power of more than 80%). It is expected, that the rate of withdrawal in the study is smaller than 15%. According to these parameters, the study will enrol 56 subjects. The distribution between the sexes is not relevant, because neither incidence of MZL is differed between sexes nor clinically outcome measures such as response, progression free and overall survival has been shown to be related to sexes.

12.3 Analysis of the Primary Endpoint

The primary endpoint (CRR) will be evaluated after end of treatment (18 cycles) after the last recruited patient has started her/his treatment. The primary parameter CRR will be evaluated in a modified intention to treat way, which means that all patients for whom the primary endpoint CRR is measured after end of treatment will be included in the analysis of the primary endpoint (Core Analysis Population, see subsection 12.6). Only patients who withdraw will be excluded (about 15% are expected). The one sample exact binomial test will be used for the analysis of the primary endpoint to test the CRR against the fixed value 56% at the 2.5% significance level (one-sided). Thus, the decision about the new concept will be based on a statistical test of the form:

HA: {CRR > 56%} vs. H0: {CRR ≤ 56%}

Thus, claim of success can be done if 36 (75% of 48 patients) or more responders (patients with CR) will be observed. Patients who withdraw will be included in a separate explorative analysis. Additionally, a one-sided 97.5% confidence interval for CRR will be calculated as an effect estimator. Exploratory use of univariate logistic regression models will be used to investigate the influence of putative risk factors associated with CRR.

Subgroup analyses in the subtype (MALT lymphoma, splenic MZL, nodal MZL) will be performed as further exploratory analyses.

12.4 Analysis of the Secondary Endpoints

Details of the secondary endpoints are described in section 5.3. All secondary endpoints will be analyzed exploratory by respective descriptive analysis and 95%- confidence intervals.

12.5 Safety Analyses

Safety evaluations include: adverse event monitoring, physical examinations, evaluation of changes to concomitant medications, and clinical laboratory parameters (hematology, serum chemistry, serum immunoglobulin [IgG, IgM, IgA], CRP). The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Serious adverse events will be reported according to applicable legislation. The DSMC will review data regarding safety as planned according to the DSMC Charter.

12.6 Analysis Populations

12.6.1 Core Analysis Population

As this study is a trial with only one treatment arm, all analyses will be performed only for one analysis population, the Core Analysis Population. This analysis population consists of all eligible patients included in the study who received at least one cycle of treatment. Patients without staging at regular end of treatment will be defined as non-responder (i.e. CR='NO').

The results on efficacy in the Core Analysis Population were considered to be the main efficacy results (confirmatory results). Forty eight patients are planned to belong to the Core Analysis Population, see part 12.3 above.

12.6.2 Safety population

The safety population and the Core Analysis Population are identical in this trial.

13. Independent Data Safety Monitoring Committee

An independent external Data Safety Monitoring Committee (DSMC) will review ongoing safety data throughout the study. The Data Safety Monitoring Board will include at least three independent members (2 experts in MZL and one independent statistician). Review of the safety data by the DSMC will take place based on the safety analyses after the first 6 patients and after the first 28 patients (50% of patient recrural) and 56 patients (100% patient recrural) have completed cycle 9 of treatment. All data presented at the meeting will be considered confidential. In addition, a review will be performed, when the last patient has ended treatment. Following each meeting the DSMC will prepare a report and may recommend changes in the conduct of the trial. Details on the work of the board will be described in a specific DSMC charter, to be jointly agreed upon the board and the sponsor.

14. Study monitoring and Data Management

14.1 Investigators Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. The sponsor staff or an authorized representative will evaluate and approve all investigators. The investigator is responsible to provide an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

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

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

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

14.2 Sponsor Responsibilities

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

At regular intervals during the study, the trial site will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team to review study progress, investigator and subject adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be scrutinized with the investigator: subject informed consent, inclusion and exclusion criteria, subject recruitment and follow-up, subject compliance to the study treatment, study treatment accountability (if applicable), concomitant therapy use, evaluations of response, serious/non serious adverse event documentation and reporting, and quality of data.

14.3 Source document requirements

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

14.4 Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that GCP and all aspects of the protocol are followed. The CRO will announce independent special trained monitors who will check on site on the basis of the patients records the fulfillment of e.g. inclusion/exclusion criteria, of diagnostic procedures at study entry, the presence of an informed consent, handling of remission criteria, performance of treatment and adverse events and correct documentation of patient’s data in the eCRF (Source Data Verification). The number of contacts will depend on the characteristics of the respective trial site, e.g., the number of recruited patients. Source documents will be reviewed for verification of agreement with data on case report forms. Details on the extent of data verification are described in the trial specific monitoring manual. The investigator/institution guarantees direct access to source documents by the representative of the CRO and appropriate regulatory authorities.

14.5 Use and completion of the (electronic) Case Report Forms (eCRF)

A professional study database and eCRF will be provided by a specialized CRO contracted and supervised by the sponsor. Study data will be processed and stored in the EU only.

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

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

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that 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.

All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

14.6 Study Drug Monitoring

Accountability for IMP Pembrolizumab and Rituximab at the clinical site is the responsibility of the investigator. The investigator will ensure that Pembrolizumab and Rituximab is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual.

Drug accountability records for the IMP indicating the drug's delivery date to the site, inventory at the site, use by each patient, or disposal of the drug will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol. The monitors assigned by the sponsor will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused IMP will be retained at the site until they are inventoried by the monitor. All used, unused or expired IMP will be treated and disposed of as hazardous waste in accordance with governing regulations.

15. Ethical and regulatory standards

15.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989), the 48th (Somerset West, 1996), the 52nd (Edinburg, 2000) World Medical Assemblies, notes for clarification added by the WMA General Assembly on paragraph 29 (Washington 2002) and on Paragraph 30 (Tokyo 2004) and amendment laid down by the 59th (Seoul, October 2008) World Medical Assemblies and the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

15.2 Laws and regulations

This study is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

15.3 Data Protection concept

The data protection concept stipulates that patients are only included in this clinical trial after they have been informed and after having signed the Informed Consent Form (ICF). The sponsor provides a data protection management and an information security management system. The Clinical Trial Centers are contractually obliged to comply with the GDPR and other data protection regulations, in particular the implementation of appropriate technical and organizational measures (Art. 32 GDPR). This also applies to involved third parties who are contractually obliged in accordance with Art. 28 GDPR to guarantee the implementation of appropriate technical and organisational measures in such a manner that the processing will meet the requirements of the Regulation and ensure the protection of the rights of the data subject. The data will not be used for any other purpose than the research project described in this protocol. It is guaranteed that the data protection provisions are followed.

15.4 Ethics Committee and competent authorities submission

The sponsor must submit this study to country central ethics review committee, and to competent authorities and it is required to forward a copy of written approvals / advices signed to the investigators.

16. Administrative procedures

16.1 Curriculum vitae

An updated copy of the curriculum vitae of each investigator and sub-investigator will be provided to the sponsor prior to the beginning of the study.

16.2 Secrecy agreement

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

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

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

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

16.3 Record retention in investigating trial sites

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

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

The investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any trial site will notify the sponsor before destroying any data or records.

The sponsor is responsible for archiving the trial master file according to applicable regulations.

16.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms, or in the form of a report, with or without comments and with or without analysis, in order to submit them to the competent authorities.

16.5 Publication

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

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no efficacy or safety data may be published before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the coordinating investigator. This is applicable to any individual patient registered in the trial, or any subgroup of the trial patients. Such a publication cannot include an analysis of any of the study end-points unless the final results of the trial have already been published.

16.6 Insurance compensation

The sponsor of the study will obtain insurance coverage for each patient for eventually occurring damage caused by the treatment or any actions taken according to the treatment plan, a certificate of insurance will be provided to the investigator.

16.7 Company audits and inspections by regulatory agencies

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

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

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

The sponsor will in all cases help the investigator prepare for an inspection by any regulatory agency.

16.8 Clinical study report

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees according to law following the end of the study. A study report will be prepared under the responsibility of the sponsor less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees

16.9 Protocol amendments

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or

amendment(s) have been fully discussed and agreed upon by the Study Coordinators and the sponsor.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the coordinating investigators and by the sponsor and the signed amendment will be appended to this protocol.

Approval / advice of amendments by Ethics Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, study amendment must be submitted to regulatory agencies, where applicable, except under emergency conditions.

16.10 Contract of Investigation

The participating institutions are selected by the coordinating investigator, based on the proven qualification in the framework of previous trials in the cooperative groups. The clinical trial sites will document their appropriate qualification and capacities for taking part in the trial, in order to allow for a qualified decision of the (local) ethical committee on the participation

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

Every participating trial site has the duty to be cooperative if inspections will be performed at the trial site.

16.11 Financing

The coordinating investigator and the sponsor will take care of the financing/funding of the study. The study will be funded in part by MSD SHARP & DOHME GMBH. The study drug, “Pembrolizumab” will be provided by MSD SHARP & DOHME GMBH free of charge, Truxima will be provided free of charge by Celltrion Healthcare Co., LTD.

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APPENDICES

Appendix A: Study Flowchart

Treatment – Phase

		Screening	Treatment Period (1 cycle = 21 days)						EOT/ ET Visit (4 weeks after C18/D1)
	Section	SD -28	C1/D1	C1/D2	C1/D8 + D15	C2/D1 – C9/D1	C10D1	C11/D1 – C18/D1	
Informed consent incl. discussion of fertility issues and sperm banking (in patients of childbearing age)*	10.1	X							
Verify Inclusion/exclusion criteria*	7.1 + 7.2	X	X						
Pathological diagnosis (local and reference pathology – incl. MYD88 and PD-L1*)	9.1.1	Within 12 months before C1D1							
Demographics, Medical history and Ann Arbor Stage*	9.1.4	X							
Patients with gastric extranodal MZL: Gastroduodenal endoscopy [a]	9.1.2	Within 12 weeks before C1D1					X[c]		X[c]
Patients with non-gastric extranodal MZL: Assessments according section 9.1.2	9.1.2	Within 12 weeks before C1D1					X[c]		X[c]
Bone marrow aspirate and biopsy [b]	9.1.3	Within 12 weeks before C1D1					X[b]		X[b]
CT/MRI scan and tumor assessment	9.1.2	Within 6 weeks before C1D1					X[c]		X[c]
12-lead ECG + Echocardiography	9.1.9	X					X[d]		X[d]
B Symptoms	9.1.6	X	X			X[l]	X[l]	X[l]	X
Physical examination [e]	9.1.5	X	(X)			(X)	X	(X)	X
Vital signs	9.1.7	X	X	X	X	X	X	X	X
ECOG Performance Status*	9.1.8	X	X			X	X	X	X
Concomitant medication	9.3 – 9.4	X	X	X	X	X	X	X	X
Adverse events / Toxicity	11		X	X	X	X	X	X	X

Treatment – Phase (continued)

		Screening	Treatment Period (1 cycle = 21 days)						EOT/ ET Visit (4 weeks after C18/D1)
	Section	SD -28	C1/D1	C1/D2	C1/D8 + D15	C2/D1 – C9/D1	C10D1	C11/D1 – C18/D1	
Laboratory Assessments	9.1.10								
HIV, HBV, HCV testing [f]	9.1.10	X				X[f]	X[f]	X[f]	X[f]
Pregnancy test	9.2 – 9.4 + App. C	X	X			X	X	X	X
Hematology	9.1.10	X	X		X	X	X	X	X
Serum chemistry [g, h]	9.1.10	X	X		X	X	X	X	X
Electrophoresis (If M Protein present: add. Serum Protein Immunofixation)	9.1.10	X	X		X	X	X	X	X
Coagulation	9.1.10	X				X	X	X	
Thyroid hormones	9.1.10	X				X[m]	X[m]	X[m]	
Leukocyte immunophenotyping (FACS)[j]	9.1.10	X					X		X
Quantitative Immunoglobulins (IgG, IgA, IgM)	9.1.10	X					X		X
Urine analysis [i]	9.1.10	X				X[i]	X[i]	X[i]	X[i]
UPCR	9.1.10	X	X[d]		X[d]	X[d]	X[d]	X[d]	X[d]
GFR (acc. MDRD formula)	9.1.10	X				X	X	X	X
QoL questionnaire (FACT-Lym)*	9.1.11		X			X (Day 1 of every third cycle)			X
Tumor tissue sample at time of relapse or transformation	9.1.2					(X)[k]			
New anti-lymphoma treatment	9.5								X
Biological Material for Biobank (optional)*	9.1.12 + App. B	X					X		X

Treatment – Phase (continued)

C=Cycle; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; ET=early termination; FACS=fluorescence-activated cell sorter; HBV=hepatitis B virus; HCV=hepatitis C virus; IPI=International Prognostic Index; MRI=magnetic resonance imaging; UPCR= Urine Protein to Creatinine Ratio (UPCR) measurement.

Only activities/procedures marked with an asterisk (*) are study specific. All other activities/procedures are performed according to routine/guidelines.

Notes: **On treatment days, all assessments should be performed prior to dosing unless otherwise noted.** The C1, D1 visit should be scheduled to allow subsequent visits to occur without delay. Study visits during treatment should occur on the scheduled day (±3 days), with the exception of delays resulting from toxicities.

[a] In patients with gastric extranodal MZL, the initial staging should include a gastroduodenal endoscopy with multiple biopsies from the stomach, duodenum, gastroesophageal junction, and any site that seems abnormal. If any disease sites are identified in this manner at screening, a subsequent gastroduodenal endoscopy and biopsy are required to confirm a CR. H. pylori status must be evaluated. Endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration should be performed.
[b] A bone marrow examination must be performed at screening unless performed within 12 weeks prior to C1, D1. If positive at screening, a subsequent bone marrow examination is required at completion of cycle 9 (C10D1) for all patients who may achieved a CR and at the EOT visit for patients to confirm a CR. In patients with continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later timepoint. Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.
[c] If initially positive
[d] When clinically indicated
[e] At Screening a complete physical examination includes all systems described in Section 9.1.5. As part of tumor assessment including assessment of lymph nodes, hepatomegaly, and splenomegaly. At other timepoints physical examination should only include systems of most clinical relevance = (X)
[f] CxD1 HBV DNA PCR in patients who are HBsAG neg. and HBcAb pos.
[g] ß2 microglobulin only at screening;
[h] Phosphate, total cholesterol, LDL and triglycerides will be determined at Screening, on Day 1 of every 2nd cycle (2, 4, 6 etc.) and at the EOT visit. On these days patients must be fasting prior to sampling according to local standards. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
[i] At Screening in a fresh sample of midstream urine, a dipstick testing for proteinuria is required and microscopy including protein, specific gravity, glucose and blood. For further urine testing only dipstick, microscopy as clinically indicated
[j] PB and bone marrow aspirate will be taken for the assessment of circulating lymphoma cells: mandatory: CD5, CD10, CD19, CD20, CD23, CD27, CD43, FMC7, kappa/lambda light chains.
[k] an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time.
[l] B-Symptoms on Day 1 of each third cycle (i.e. on Day 1 of Cycles 1, 4, 7, 10, 13 and 17)
[m] TSH is assessed before each treatment cycle, T3 and T4 only in case of labortatory abnormalities.

Follow-up – Phase for patients who have CR, PR or SD at the EOT visit

After last treatment cycle or after early termination	Follow-up Year 1 + 2 (every 3 months ± 14 days)								Follow-up Year 3 - 5 (every 6 months ± 14 days)						At the end of study or time of progression
	FU1	FU2	FU3	FU4	FU5	FU6	FU7	FU8	FU9	FU10	FU11	FU12	FU13	FU14	
Physical examination [a]	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
B symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X														
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine analysis [c]		X		X		X		X		X		X		X	X
HBV DNA PCR [d]	(X)	(X)	(X)	(X)											
New anti-lymphoma treatment [e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Survival follow-up [e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CT/MRI scan and tumor assessment (if initially positive)		X		X		X		X		X		X		X	X
Gastroduodenal endoscopy [f]		X		X		X		X		X		X		X	X
Leukocyte immunophenotyping (FACS) [g]		X		X		X		X		X					X
Quantitative immunoglobulins (IgA, IgG, IgM)		X		X		X		X		X					X
Serum protein immunofixation (if initially positive)		X		X		X		X		X					X
Bone marrow aspirate and biopsy [h]															X
Tumor tissue sample at time of relapse															(X)[i]
Adverse events [j]	X	X													
QoL questionnaire (FACT-Lym)				X				X		X		X		X	X
Biological Material for Biobank (optional)															X (at progress)

Follow-up – Phase (continued)

CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; FACS=fluorescence-activated cell sorter; HBV=hepatitis B virus; SAE=serious adverse event.

(x)=conditional/optional; refer to footnote for details.

[a] The physical examination should only include systems of most clinical relevance.
[b] Without Phosphate, total cholesterol, LDL and triglycerides
[c] For further urine testing only dipstick, microscopy as clinically indicated
[d] Only if clinically indicated. HBV DNA levels will be measured by real-time PCR using an assay with a sensitivity of at least 10 IU/mL.
[e] **Patients with disease progression will be followed for new anti-lymphoma treatment and survival twice per year until the end of the study.**
[f] In patients with gastric extranodal MZL. If clinically indicated it may be performed even more often. If there were no disease sites detectable at the last investigation, endoscopy should be performed every 6 months in year 1 to 2, and then once a year in year 3, 4 and 5 of follow-up. In the case of persistent disease sites endoscopy should be performed every three months until negativity.
[g] A blood sample will be taken for the assessment of circulating lymphoma cells: mandatory: CD5, CD10, CD19, CD23, CD27, CD43, FMC7, kappa/lambda light chains
[h] If initially positive or clinically indicated or in the case of progression
[i] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time.
[j] All AEs will be recorded up to 110 days after the last dose of study drug, study drug–related SAEs will be recorded indefinitely (even if the study has been closed).

Appendix B: Biological samples for further ancillary studies

Only German study sites will participate in the biological sampling project.

In the case of patient's consent, the following biological samples will be obtained:
a) Bone marrow cells

- before start of treatment

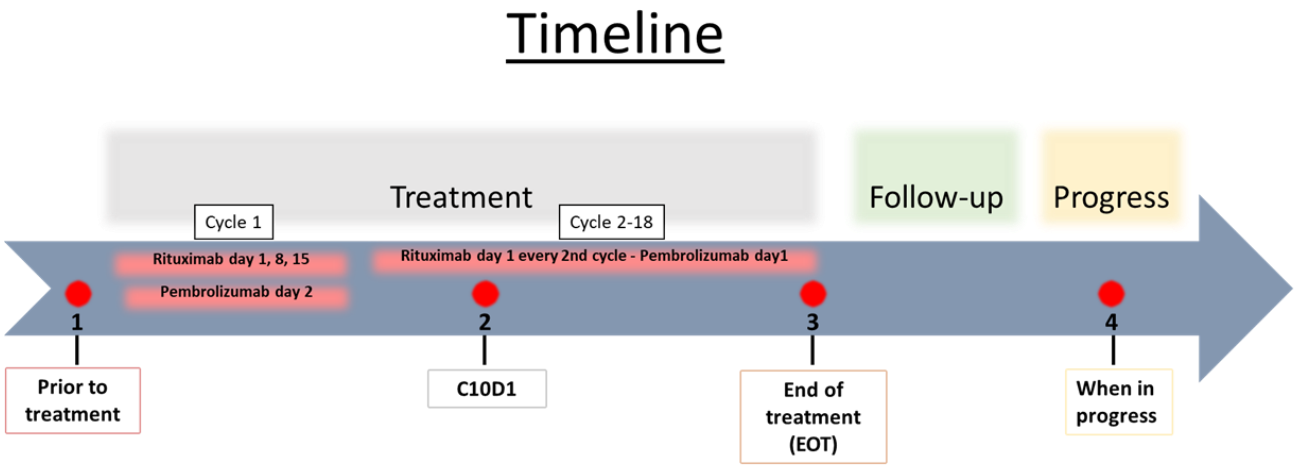
- during treatment/ at EOT only in those patients in whom bone marrow aspiration is performed to confirm CR or to document delayed response (see Appendix A).

b) Cheek swab
- once before start of treatment

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

Questions and notifications regarding biological sampling should be sent via e-mail to:

gla.biosampling@uni-ulm.de



Time points

Four eligible time points are described for bio-sampling:

1. Prior to treatment
2. C10D1 (during treatment)
3. EOT (month 18)
4. When in progress

Sample	Usage
30 mL of peripheral blood in CELL-FREE DNA blood collection tubes (BCT®) (Streck)	Storage of plasma for cell free DNA (cfDNA), storage of DNA (cell pellet) for MRD measurement
15 mL of bone marrow	- Storage of freshly isolated cells - Storage of DNA and RNA from sorted bone marrow B cells
10 mL of serum	Storage of serum proteins
10 mL EDTA	Storage of DNA (cell pellet) for MRD
Cheek swab	Storage of DNA of non-hematopoietic cells (FTA cards)

The biological samples should be sent as follows:

Sample	Delivery
30 ml of peripheral blood	Peripheral Blood should be collected on site in CELL-FREE DNA blood collection tubes (BCT®) (Streck), which will be provided by the Sponsor. Tubes will be sent to the University of Ulm at ambient temperature with overnight carrier for next day delivery
15 ml of bone marrow aspirate	EDTA tube at ambient temperature should be sent to the University of Ulm with overnight carrier for next day delivery
1 x 10 ml of serum	Serum tubes at ambient temperature with overnight carrier for next day delivery
1 x 10 ml EDTA	EDTA tubes at ambient temperature with overnight carrier for next day delivery
Cheek swab	DNA of non-hematological cells will be collected by cheek swabs and the Whatman® FTA® card technology (Sigma-Aldrich). The kit will be provided by the Sponsor. Genomic DNA stored on FTA Cards at room temperature is stable for years. FTA cards will be sent to the University of Ulm with overnight carrier for next day delivery

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

Appendix C: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

1. Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4 during the protocol-defined time frame in.

Table 4 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception associated with inhibition og ovulation[b,] ○ Oral ○ Intravaginal ○ Transdermal
● Progestogen-only hormonal contraception associated with inhibition og ovulation[b,] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 110 days after the last dose of study treatment.

Please note: If a patient experiences nausea or diarrhea, oral contraception is not considered a reliable method.

Combined contraceptive methods (additional use of condoms for female participants and their partners) are recommended.

2. Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Appendix D: Selection of Lesions and Response Criteria for Nodal Marginal Zone Lymphoma and Extragastric MALT Lymphoma

Response should be determined on the basis of radiographic and clinical evidence of disease adapting the modified 2007 Cheson criteria below[5].

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 ≥ 1.5 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 1.5 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 for Nodal Marginal Zone lymphoma and extragastric MALT lymphoma and for measurable disease (≥1.5 cm) shown by radiographic evidence. For the assessment of extranodal gastric MALT lymphoma and splenic MZL, see Appendices E and F **in addition** to the information below.

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.

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

1. 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 Timepoint Response Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Timepoint 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 E: Response Criteria for Extranodal Gastric Marginal Zone lymphoma (MALT)

The histological grading system of the GELA for posttreatment evaluation of gastric MALT lymphoma should be used[7]. If there is a measurable extragastric extranodal or nodal disease, it should be documented additionally on the basis of radiographic and clinical evidence of disease using the modified 2007 Cheson criteria (see Appendix D).

GELA histological grading system for post-treatment evaluation of gastric MALT lymphoma

Score	Lymphoid infiltrate	LEL	Stromal changes
CR	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/orfibrosis
pMRD	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD	Dense, diffuse, or nodular extending around glands in the LP	Focal LEL or absent	Focal empty LP and/or fibrosis
NC	Dense, diffuse, or nodular	Present, “may be absent”	No changes

CR = complete remission, pMRD = probable minimal residual disease, rRD= responding residual disease, NC = no change, MM, muscularis mucosa; LP, lamina propria; SM, submucosa; LEL, lymphoepithelial lesions.

According to this histological scoring system, criteria for treatment response in GMZL can be defined as follow:

1. Complete remission (CR) is defined as normalization of endoscopic findings and negative histology (CR or pMRD) in two subsequent follow-up investigations.
2. Partial remission (PR) is defined as normalization or reduction of macroscopic findings, histological signs of lymphoma regression (rRD) and no signs of progressive disease.
3. Stable disease (SD) is characterized by unmodified gastroscopic findings and/or unmodified histology (NC).
4. Progressive disease (PD) is defined by worsening of macroscopic findings or dissemination of gastric MALT lymphoma or transformation into diffuse large B-cell lymphoma.
5. Relapse is defined as the re-occurrence of histologically- confirmed lymphoma after a CR was previously documented.

Appendix F: Response Criteria Splenic Marginal Zone lymphoma

The following criteria should be used for response evaluation[6, 15]. Splenomegaly as well as nodal or extranodal disease should be documented using the modified 2007 Cheson criteria[5] (see Appendix D).

Response Criteria for Splenic MZL **Response Category**	**Definition**
Complete response (CR)	• Resolution of organomegaly, normalization of the blood counts (Hb >12 g /dl; platelets > 100 x 10^9/l; neutrophils >1.5 x 10^9/l and no evidence of circulating clonal B cells). No evidence or minor BM infiltration detected by immunohistochemistry.
Partial response (PR)	• 50% or greater improvement in the disease manifestations. This should include resolution or decrease in spleen size, improvement on cytopenias and resolution or decrease in lymphadenopathy if present. BM should show a decrease in the level of lymphoid infiltration and improvement of the hemopoietic reserve.
No response (Stable Disease (SD))*	• No response: Less than 10% improvement on the disease manifestations
Progressive Disease (PD)*	• Progressive disease: Deterioration of the above, i.e. > 50% of measurable signs of the disease from nadir.
<u>Splenectomy:</u> Response will be considered when there is at least 50% improvement on the blood counts, non-progressive lymphocytosis and no change or improvement in the degree of BM infiltration. *: Based on (Dreyling, 2013), this category will be split into two separate response categories	

Appendix G: Ann Arbor Stage

Ann Arbor Stage

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 more 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+IIIE = Both IIIS+IIIE

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 H: ECOG Performance Status Criteria

The following table presents the ECOG performance status scale[32]:

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

Appendix I: Functional Assessment of Cancer Therapy for Lymphoma (FACTLym) (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					

GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Appendix J: Pathology Reference Centers

Country	Name of institution and address
Germany	**Prof. Dr. med. Alfred Feller** [redacted] **Prof. Dr. med. Falko Fend** [redacted] **Prof. Dr. med. Dr. h.c. Martin-Leo Hansmann** [redacted] **Prof. Dr. med. Wolfram Klapper** [redacted] **Prof. Dr. med. Peter Möller** [redacted] **Prof. Dr. med. German Ott** [redacted]

	[redacted] **Prof. Dr. med. Andreas Rosenwald** [redacted] **Prof. Dr. med. Dr. h.c. Harald Stein** [redacted]
Austria	**Prof. Dr. Ingrid Simonitsch-Klupp** [redacted]

Appendix K: Data Safety Monitoring Committee

Name, institution and address
Prof. Dr. med. Eva Kimby [redacted] **ao Univ. Prof. Dr. med. Alexander Egle** [redacted] **Dr. rer. nat. Michael Unterhalt** [redacted]

Appendix L: Patient Insurance

If required according to the national regulations for each participating country, the sponsor of the study will obtain insurance coverage for eventually occurring damage caused by the treatment or any actions taken according to the treatment plan. A certificate of insurance will be provided to the investigator in countries in which this document is required. The investigator, or an individual who is designated by the investigator, will inform the patient of the existence of the insurance, including the obligations arising from it. The study patients must be given access to the insurance documents and, on request, a copy of the general conditions of insurance.