CARMAN

Early treatment intensification in patients with high risk Mantle Cell Lymphoma using CAR-T-cell treatment after an abbreviated induction therapy with Rituximab and Ibrutinib and 6 months Ibrutinib maintenance (Arm A) as compared to standard of care induction and maintenance (Arm B)

Trial Short Title:	**CAR**-T-cell treatment for untreated high risk **MAN**tle Cell Lymphoma
Sponsor Code:	**CARMAN**
EU Clinical Trial Number	2022-502405-15-00
Protocol Version and Date:	Version 2.2_14 Jul 2023
Protocol Amendment:	
Sponsor:	Klinikum der Universität München, Germany

Table of Content

1 General information

1.1 Key roles and contact information

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MRD national reference labs
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1.2 Signatures

1.2.1 Protocol Signature Page Sponsor Level

Sponsor/sponsor delegated person (SDP):

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Munich, 27.02.2023_____ _____

City and Date Signature

Coordinating Investigator (multicenter):

Univ.-Prof. Dr. Georg Heß

Mainz, 27.02.2023_____ _____

City and Date Signature

Responsible Statistician:

Univ.-Prof. Dr. Eva Hoster

Munich, 27.02.2023_____ _____

City and Date Signature

1.2.2 Protocol Signature Page Site Level

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

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

Principle investigator:

Printed Name of Investigator:

_____

Name, first Name

_____ _____

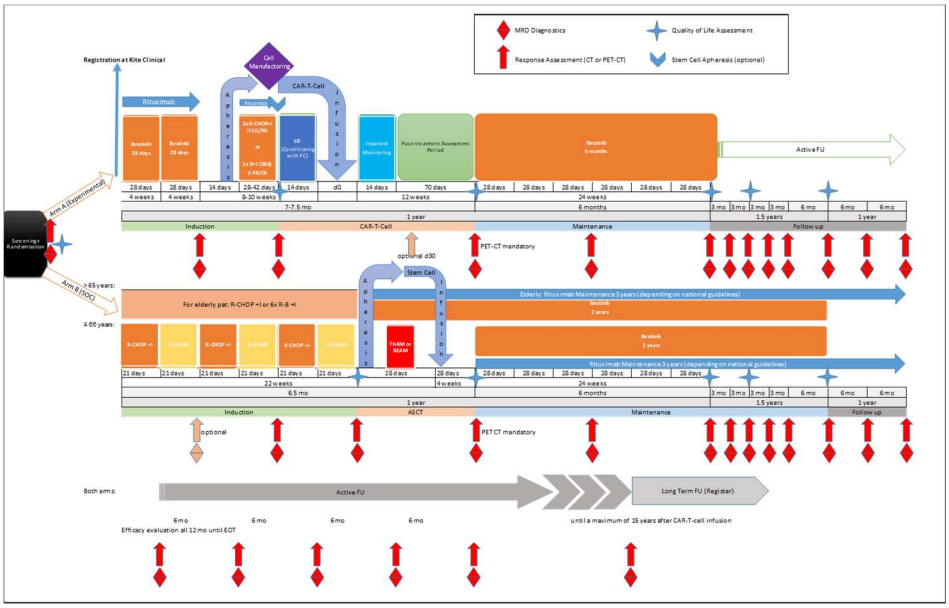
City and Date Signature

By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the Regulation (EU) No 536/2014, and local regulations governing the conduct of clinical studies.
I confirm that I was informed by a scientist, responsible for the pharmacological-toxicological test, about the findings of the test and the foreseeable risks involved in the clinical study.

1.3 Synopsis

Full Title	CARMAN: Early treatment intensification in patients with high risk Mantle Cell Lymphoma using CAR-T-cell treatment after an abbreviated induction therapy with Rituximab and Ibrutinib and 6 months Ibrutinib maintenance (Arm A) as compared to standard of care induction and maintenance (Arm B)
Clinical Phase	II
Short title	**CAR**-T-cell treatment for untreated high risk **MAN**tle Cell Lymphoma
Sponsor Code	CARMAN
EuCT No.	2022-502405-15-00
Investigational medicinal product, Dose and Mode of Application	**Both Arms:** **Trade name: Imbruvica** Investigational medicinal product: Ibrutinib Manufacturer: Janssen Pharmaceutica Dose: 560mg Mode of application: orally once daily Duration of treatment: depending of therapy arm. Minimal duration: 9 months (arm A), maximum duration: 2.5 years (Arm B) **Arm A (experimental):** **Trade Name: Tecartus (KTE-X19)** Investigational medicinal product: brexucabtagene autoleucel Manufacturer: Kite Pharma, Inc. Dose: 2 x 10^6 anti-CD 19 CAR-T-cells/kg Mode of application: intravenous application Duration of treatment: single dose **Arm A:** d1-28 with Ibrutinib and Rituximab for 2 cycles and d1-21 for 2 cycles with R-CHOP +/- Ibrutinib (in case of PD or SD after 2 cycles) or d1-28 Ibrutinib monotherapy (in case of PR or CR after 2 cycles) during abbreviated induction followed by 6 months of Ibrutinib maintenance after CAR T cell infusion. **Arm B:**Younger patients (≤ 65 years) will receive R-CHOP + Ibrutinib/ R-DHAP, followed by autologous stem cell transplantation (ASCT). Elderly patients (≥ 65 years) will receive 6 cycles of Bendamustine and Rituximab + Ibrutinib or R-CHOP + Ibrutinib without ASCT. Independently of age, control patients receive 2 years of maintenance therapy with Ibrutinib

Population	Adult patients with previously untreated high risk stage II-IV mantle cell lymphoma (MCL)
Study Design	Randomized controlled, international, multicenter, open-label phase II trial
Hypothesis	First-line CAR-T-cell consolidation after an abbreviated induction with 2 cycles of Rituximab and Ibrutinib prior to CAR-T-cell treatment and followed by 6 months of maintenance with Ibrutinib has superior efficacy than current standard of care treatment in patients with high risk MCL.
Treatment regimen	**Arm A (experimental):** The abbreviated induction phase consists of 2 cycles of Ibrutinib + Rituximab and 2 cycles of Ibrutinib + R-CHOP for primary tumor reduction followed by CAR-T-cell treatment. In case of good clinical response (PR or CR) after 2 cycles of Ibrutinib + Rituximab, Ibrutinib + R-CHOP can be omitted. In this case, one cycle of Ibrutinib monotherapy will be applied. T cell apheresis will be performed after the initial 2 cycles. Application of KTE-X19 will be performed after lymphodepleting chemotherapy with Fludarabine and Cyclophosphamide (FC). After stable hematopoietic recovery, maintenance with Ibrutinib will be applied for 6 months but not prior to day 60 post CAR. The follow-up period starts after the completion of Ibrutinib maintenance and takes 4.5 up to 7 years. **Arm B (control):** Younger patients (≤ 65 years) will receive 3 cycles R-CHOP + Ibrutinib/ 3 cycles R-DHAP alternating, followed by autologous stem cell transplantation (ASCT). Elderly patients (≥ 65 years) will receive 6 cycles of Bendamustine and Rituximab + Ibrutinib or R-CHOP + Ibrutinib without ASCT. Independently of age, control patients receive 2 years of maintenance therapy with Ibrutinib and 3 years of Rituximab maintenance if foreseen by national guidelines, in addition to Ibrutinib maintenance.

Study Flowchart	
Objectives	<u>Primary Objective:</u> To exploratively compare the efficacy of the experimental treatment (Arm A) with standard of care (Arm B) <u>Secondary Objectives:</u> To further assess efficacy, safety, and tolerability of CAR-T-cell treatment by means of secondary and exploratory endpoints in comparison to standard of care
Endpoints	Primary endpoint: Failure-free survival (FFS) from randomization. Failure events: • Any discontinuation of the per protocol treatment due to stable or progressive disease during induction • Stable disease at end of induction • Progressive disease at any time after end of induction treatment • Death from any cause at any time Secondary endpoints: • Progression-free survival (PFS) from randomization • Complete remission rate (CR) and overall response rate (ORR: CR, PR) 6 months from randomization (after completion of CAR-T-treatment or HDT, respectively) • Rate of PET negative CR (complete metabolic response rate, Lugano criteria) 6 months from randomization • PFS in responders 6 months from end of cytoreductive treatment • Best response during 2 years from randomization • Time to best response, time to first response from randomization

	• Overall survival (OS) from randomization • Safety: adverse events, serious adverse events, toxicities (CTCAE) Exploratory endpoints: • Molecular remission rate 6 months from randomization and during follow-up • Mutation profile at baseline and at relapse • Immunophenotype at relapse (e.g. CD19 expression) • Quality of life: physical functioning (assessed with the EORTC QLQ-C30), physical condition/fatigue (assessed with the EORTC QLQ-NHL-HG29) • Hematotoxicity associated with the CAR-T-cell therapy • Diversity and composition of the microbiome
Sample Size	A total number of 150 patients will be enrolled (approx. 75 patients in each arm).
Inclusion Criteria	1. Histologically confirmed diagnosis of MCL according to WHO classification, with documentation of either overexpression of cyclin D1 or presence of t(11;14) 2. At least one High Risk MCL – feature as defined as I. MIPI-c high intermediate (HI) or high (H) risk (i.e. high risk MIPI irrespective of Ki-67 or intermediate risk MIPI and Ki-67>=30% (Ki-67 based on local pathology) **and/or** II. TP53-mutation and/or TP53-overexpression by immunohistochemistry (> 50% of lymphoma cells) 3. No prior treatment for MCL 4. Stage II-IV (Ann Arbor) 5. 18-75 years 6. At least 1 measurable lesion according to the Lugano Response Criteria (>1.5 cm nodal lesion or > 1cm extranodal lesion); in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations. 7. ECOG performance status ≤ 2 8. The following laboratory values at screening (unless discrepancies are related to MCL): I. Absolute neutrophil count (ANC) ≥ 1000 cells/µL

	II. Platelets ≥75,000 cells/µL III. Creatinine <2 mg/dL or calculated creatinine clearance ≥60 mL/min IV. Transaminases (AST and ALT) < 2.5 x ULN V. Total bilirubin <= 2 x ULN unless other reason known (e.g. Gilbert-Meulengracht-Syndrome, or due to lymphoma involvement) 9. No evidence of CNS-disease 10. Written informed consent form according to ICH/EU GCP and national regulations, ability to follow study instructions and likely to attend and complete all required visits 11. Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods (combined oral contraceptives using two hormones, contraceptive implants, injectables, intrauterine devices, sterilized partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive caps) while on study; this should be maintained for 6 months after the last dose of KTE-X19 or for 3 months after last dose of Ibrutinib, whichever is longer 12. Negative serum or urine pregnancy test (Females of childbearing potential only, Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential) 13. Willingness not to drive a motor vehicle for 8 weeks post CAR T cell treatment 14. Possibility to reach the site within 2 hours in case of toxicity / emergency
Exclusion Criteria	1. Subjects not able to give consent 2. Subjects without legal capacity, unable to understand the nature, scope, significance and consequences of this clinical study 3. Known history of hypersensitivity to the investigational drug, to drugs with a similar chemical structure or to aminoglycosides 4. Simultaneously active participation in another clinical study involving an investigational medicinal product within 30 days prior to enrollment. Patients included in

follow up periods of other clinical trials without ongoing trial medication are allowed

5. Subjects with a physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the study results, or may interfere with the subject's participation in this clinical study
6. Known or persistent abuse of medication, drugs or alcohol
7. Serious concomitant disease interfering with a regular therapy according to the study protocol:
    I. Clinically significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, higher grade AV-block, unstable angina, myocardial infarction, cardiac angioplasty or stenting within 12 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below 50%
    II. Baseline oxygen saturation ≤ 92% on room air
    III. Clinical significant pleural effusion (if not lymphoma related)
    IV. Endocrinological (severe, not sufficiently controlled diabetes mellitus)
8. Current or planned pregnancy or nursing women. History of or active malignancy other than MCL, non-melanoma skin cancer, carcinoma in situ (e.g. cervix, bladder, breast) or prostate cancer unless disease-free for at least 3 years (and PSA within normal range in case of prostate cancer).
9. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.
10. Positive test results for chronic HBV infection (defined as positive HBsAg serology) (mandatory testing)
    Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable
11. Positive test results for hepatitis C (mandatory hepatitis C virus [HCV] antibody serology testing).
    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
12. Patients with known HIV infection (mandatory test)

	13. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement 14. History of or active autoimmune disease (e.g. Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression / systemic medication within the last 2 years 15. History of deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months of enrolment 16. Known severe primary immunodeficiency 17. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment 18. Live vaccine ≤ 6 weeks prior to planned start of study treatment 19. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule
Study Procedures	See list of visits that should be performed under section "schedule of activities"
Follow-up	All subjects who enter the study will continue to be followed for at least 4.5 and up to 7 years for disease progression, subsequent treatment, and survival, so the maximal duration of study participation per individual patient will be 7 years.
Scientific program	• Immune reconstitution • Minimal Residual Disease (MRD) • Quality of Life (QoL)
Investigational sites	This is a multi-center international study performed at approximately 40 sites in Europe.
Statistical Methods	**Primary estimand attributes**: population: previously untreated high-risk MCL as defined by inclusion and exclusion criteria; variable: FFS, population level summary: FFS hazard ratio (HR) Arm A vs. Arm B, strategies for handling intercurrent events: treatment policy following the intention-to-treat principle (ineligibility ascertained after registration, failure to receive IMP, new lymphoma treatment before treatment failure); while on treatment (loss to follow-up); composite endpoint (death from any cause).

Statistical design: two-sided stratified log-rank test with significance level of 10% using the following hypotheses:

Null hypothesis H_0: $FFS_A = FFS_B$ for all time points

Alternative hypothesis H_1: $FFS_A \neq FFS_B$ for at least one time point.

Stratification uses the randomization stratification factors country and MIPI risk group (high vs. intermediate/low risk).

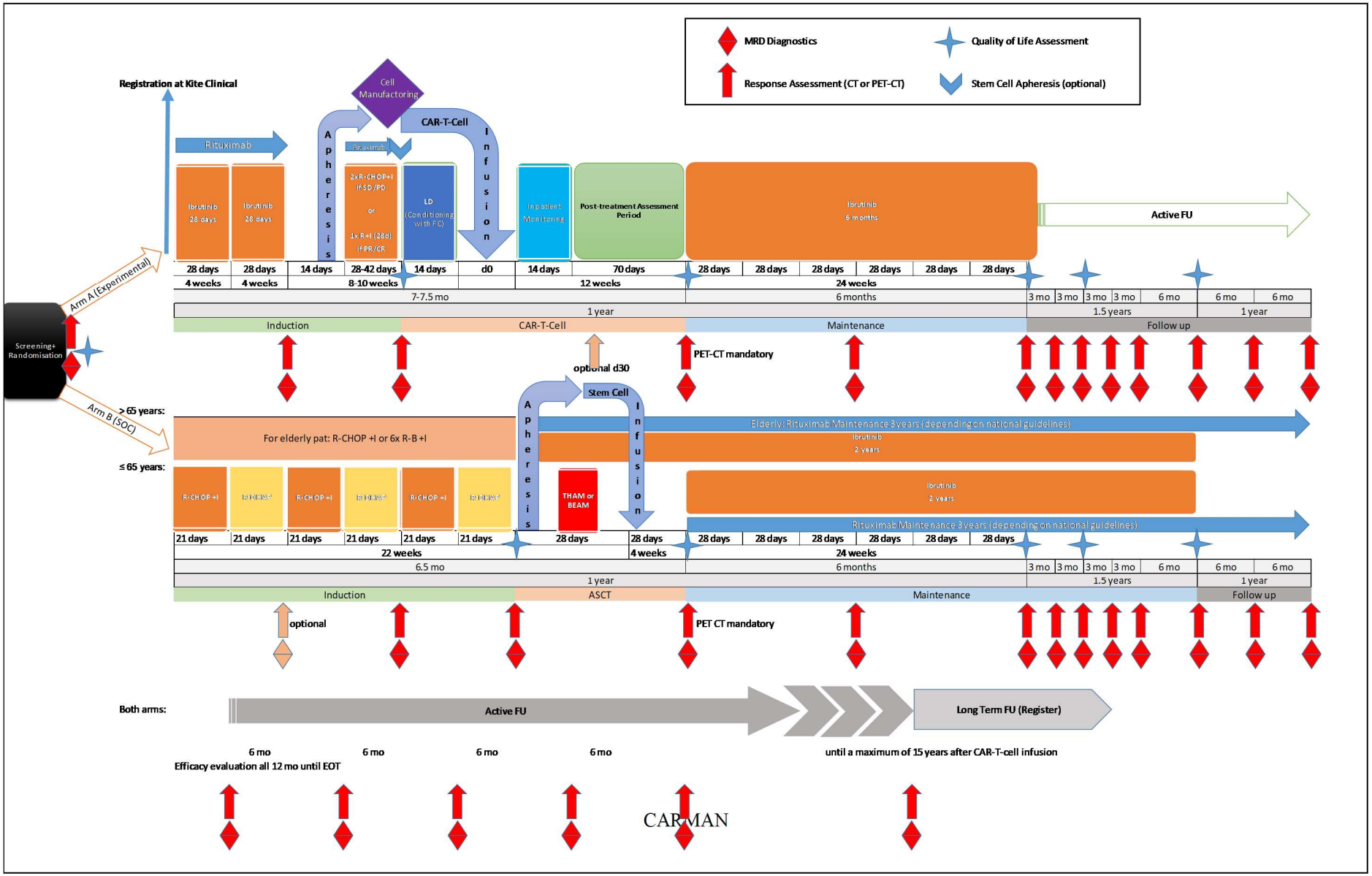
Sample size estimation: Based on the pooled European MCL Younger (Hermine et al., Lancet 2016) and MCL Elderly (Kluin-Nelemans et al., JCO 2020) trial data, we estimated a median FFS of 27 months for the control group B in the high-risk trial population (own unpublished calculation). With 150 patients randomized 1:1 between Arm A and B within 2 years of recruitment and at least 4.5 years of additional follow-up, allowing for 10% dropouts at 5 years, a power of 90% is achieved to decide against the null hypothesis in case of a true FFS-HR of 0.558 (median FFS in Arm A: 48 months). To detect this difference, 102 FFS events need to be observed. One interim analysis is planned after the observation of 51 FFS events to allow an early stop for superiority (O'Brien-Fleming boundaries) or inferiority (Pocock boundaries). The probability to stop early for superiority is 72% with a HR of 0.42 (median 65 months) and 32% with a HR of 0.56 (median 48 months). The probability to stop early for inferiority is 63% with a HR of 1.85 (median 15 months) and 22% with a HR of 1.36 (median 20 months). In case the FFS of the outcome is substantially better than projected (HR 0.75, median FFS in Arm B 36 months), 90% power is achieved to detect a true FFS-HR of 0.512 (median FFS in Arm A: 70 months).

Test of primary question: In the interim analysis, the standardized stratified log-rank statistic Z will be calculated and compared with the boundaries corresponding to the observed event number according to the pre-specified alpha-spending design. Stratified analysis stratifies for the randomization stratification factors country and MIPI risk group (high vs. low/intermediate risk). If the standardized two-sided stratified log-rank statistic Z exceeds the superiority or inferiority margin, superiority or inferiority of Arm A vs. Arm B is concluded, respectively. Otherwise the statistical test continues until the final evaluation in which the standardized stratified log-rank statistic Z is compared with the boundaries corresponding to the observed number of events according to the pre-specified alpha-spending design.

Analysis methods: ITT (primary) and PP (sensitivity) evaluations, Kaplan-Meier curves with estimates provided at yearly intervals and two-sided 95% confidence intervals for time to event outcomes, estimation of remission rates along with two-sided 95% confidence intervals, explorative comparison of all secondary and explorative outcomes between treatment groups, stratified for country and MIPI risk group (high vs. low/intermediate risk), exploratory subgroup analyses according to age (</>=65 years), sex and MIPI group

Time Schedule	Study set up:	Q4/2022
	First subject in:	Q2/2023
	Last subject in:	Q2/2025
	Last subject last treatment:	Q4/2027 (latest)
	Last subject out:	Q2/2030
	All sites closed:	Q4/2030
	Duration of the study	approx. 84 months
Duration of recruitment	Approximately 2 years	

1.4 Flow Chart of Study



1.5 Schedule of Activities

1.5.1 Arm A (experimental)

Table is separated into 4 parts based on:

- Time periods
    1. Screening - End of Consolidation Evaluation (EOC)
    2. Ibrutinib Maintenance – End of Study (EOS) + Long-term FU (separate study)
- Activities
    1. Assessments + Imaging
    2. Study treatment + Scientific program + Safety

Arm A experimental **Time period 1 Assements and Imaging**	Screening	Induction	Induction	Induction	Induction	First interim evaluation	Leukapheresis *	Induction	Induction	Induction	Induction	End of Induction Evaluation (EOI)	Conditioning Chemotherapy	CAR T cell infusion	inpatient monitoring	pCAR T cell infusion Evaluation	Post-treatment Assessment Period	End of Consolidation Evaluation (EOC)
	Within 28 days of enrolment	C1 D1	C1 D15	C2 D1	optional C2 D15	After completion of cycle 2		C3 D1	optional C3 D15	C4 D1 (in case of SD/PD after C2)	optional C4D15	after completion C3 / C4 before Lympho-depletion	Visit procedures at Day-5	D0	Day1-14 ** Visit procedures daily	Visit at Week 4	Visit at Week 8	Week 12 after CART cell infusion
Assessments																		
Histological diagnosis of MCL including at least one high-risk feature [1]	x																	
Reference Pathology [2]	x																	
Bone Marrow Assessment [3]	x					(x)						(x)						(x)
Inclusion/ exclusion criteria [4]	x																	
Demographic data	x																	
Informed consent	x																	
EMCL-Registry [5]	x																	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical history [6]	x																	
ECOG	x			x		x	x	x		x		x	x	x		x	x	x
Physical examination (A or B)[7]	A	A	B	B	B	A	B	B	B	B	B	A	B	B	B	x	x	A
Neurological assessment including MMSE [8]	x					x						x				x	x	x
Weight (+ height at screening)	x			x	x		x	x	x	x	x		x	x				x
Pregnancy test (fertile females only) [9]	Within 7 days before first induction dose	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	Within 7 days before Depletion	(x)	(x)	(x)	(x)	(x)
Consideration of sperm cryo-preservation and suppression of ovulation	x																	
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cardiac function evaluation (ECG, Echokardiography)	x											x						x
Blood draw (A, B, C or D) [10]	A	B	B	B	D	A	B	B	D	B	D	A	C	C	C or D	A	B	A
Blood draw cytokines [11]														D0 pre	D 1,7,14	x	x	x
CRS assessment, ICE score [12]														x	x			
Hepatitis/ HIV serology [13]	x																	
Imaging																		
Brain MRI	x																	
CT scan (neck, thorax, abdomen, pelvis)[14]	x					x						x				(x)		x
PET																		x

Arm A experimental **Time period 1 Study treatment, scientific program and safety**	Screening	Induction	Induction	Induction	Induction	First interim evaluation	Leukapheresis *	Induction	Induction	Induction	Induction	End of Induction Evaluation (EOI)	Conditioning Chemotherapy	CAR T cell infusion	inpatient monitoring	pCAR T cell infusion Evaluation	Post-treatment Assessment Period	End of Consolidation Evaluation (EOC)
	Within 28 days of enrolment	C1 D1	C1 D15	C2 D1	optional C2 D15	After completion of cycle 2		C3 D1	optional C3 D15	C4 D1 (in case of SD/PD after C2)	optional C4D15	after completion C3 / C4 before Lympho-depletion	Visit procedures at Day-5	D0	Day1-14 ** Visit procedures daily	Visit at Week 4	Visit at Week 8	Week 12 after CART cell infusion
Study treatment																		
CHOP (C) / Conditioning (FC) / Ibrutinib (I) / Rituximab (R) [15]		R+I	I	R+I	I			R+I (+C)	I	R+I+C	I		FC					
Leukapheresis (14 days after C2 Ibrutinib + Rituximab)							x											
KTE-X19 infusion														x				
Scientific program																		
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [16]	Within 7 days before first induction dose											x						x
Bag wash of KTE-X19 after infusion and CAR T quantification, immune status [17]														x				
1 x EDTA (MRD blood) [18] Optional: 1 x EDTA (MRD bone marrow) [19]	x					x						x		D0 pre	D 7 + 14	x		x
1 x EDTA (CAR T quant by PCR) [20]																		
CAR T quantification by flow [21]							x							D0 pre	D 7 + 14			
1 x EDTA (immune status and reconstitution and CAR-T quantification) [22]	x						x							D0 pre	D 7 + 14	x	x	x
2 x streck tubes (cfDNA) [23]	x					x						x		D0 pre	D 7 + 14	x	x	x
Stool samples [24]												x		x	D 7 + 14			
PBMC 20 ml PB	x																	
Serum 7,5 ml PB	x																	
Biobanking	x																	
Safety																		
Recording of AEs / SAEs [25]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Secondary malignancies		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FU in GLA-Registry																		

Arm A experimental **Time period 2 Assessments and imaging**	Ibrutinib maintenance (6 months)	Ibrutinib maintenance (6 months)	End of Treatment Evaluation (EOT)	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M7	Visit M10	approx. M13	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Assessments														For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Histological diagnosis of MCL including at least one high-risk feature [1]															
Reference Pathology [2]															
Bone Marrow Assessment [3]															
Inclusion/ exclusion criteria [4]															
Demographic data															
Informed consent															
EMCL-Registry [5]															
Concomitant medication	x	x	x	x											
Medical history [6]													x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x		
Physical examination (A or B)[7]	B	B	A	B	A	B	A	B	A	B	A	B	A		
Neurological assessment including MMSE [8]			x										x		
Weight (+ height at screening)															
Pregnancy test (fertile females only) [9]	(x)	(x)	x	(x)	(x)	(x)									
Consideration of sperm cryo-preservation and suppression of ovulation															
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x	x	x				
Cardiac function evaluation (ECG, Echokardiography)															
Blood draw (A, B, C or D) [10]	B	B	A	B	B	B	B	B	B	B	B	B	A		
Blood draw cytokines [11]															
CRS assessment, ICE score [12]															
Hepatitis/ HIV serology [13]															
Imaging															
Brain MRI															
CT scan (neck, thorax, abdomen, pelvis)[14]		x	x		x	x	x	x	x	x	x	x	x		
PET															

Arm A experimental **Time period 2 Study treatment, scientific program and safety**	Ibrutinib maintenance (6 months)	Ibrutinib maintenance (6 months)	End of Treatment Evaluation (EOT)	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M7	Visit M10	approx. M13	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Study treatment															
CHOP (C) / Conditioning (FC) / Ibrutinib (I) / Rituximab (R) [15]	x	x													
Leukapheresis (14 days after C2 Ibrutinib + Rituximab)															
KTE-X19 infusion															
Scientific program															
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [16]			x			x			x						
Bag wash of KTE-X19 after infusion and CAR T quantification, immune status [17]															
1 x EDTA (MRD blood) [18] Optional: 1 x EDTA (MRD bone marrow) [19]	x	x	x	x		x	x	x	x	x	x		x		
1 x EDTA (CAR T quant by PCR) [20]								x	x	x	x				
CAR T quantification by flow [21]															
1 x EDTA (immune status and reconstitution and CAR-T quantification) [22]	x	x	x	x									x		
2 x streck tubes (cfDNA) [23]	x	x	x	x		x		x	x	x	x		x		
Stool samples [24]															
PBMC 20 ml PB															
Serum 7,5 ml PB															
Biobanking															
Safety															
Recording of AEs / SAEs [25]	x	x	x	x	x	x		x	x	x	x	x	x		
Secondary malignancies	x	x	x	x	x	x		x	x	x	x	x	x		
FU in GLA-Registry															x

For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study

1	High risk MCL features are defined in the inclusion criteria (section 10.3)
2	See section 15.1, 5-8 FFPE from diagnostic biopsies will be used to define predictive MCL ecotypes by integrating Gene Mutation Data, Genomic Copy Number Alterations (CNA) and Immune Tumor Microenvironment (TME) Profiles. 500ng of genomic DNA needed for targeted DNA next-generation sequencing (NGS), 200ng of total RNA needed for digital multiplex gene expression profiling DMGEP. At relapse 5-8 FFPE or fresh material needed for RNAseq, capture/ CAN seq and Immune status.
3	BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.
4	See section 10.3 und 10.4
5	Enrolment in the eMCL registry is strongly recommended.
6	Concomitant diseases, allergies
7	A: examination of head, eyes, ear, nose, throat, lymph nodes, liver and spleen; cardiovascular, respiratory, gastrointestinal, dermatological and musculoskeletal system, B symptoms. B: Targeted PE, systems of primary relevance: cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) as described in section 14.2.1
8	Examination of brain nerves, application of the Mini Mental State Examination (MMST), see Appendix 3
9	Urine or blood test; monthly tests mandatory as long as contraception is recommended (refer to 16.11 and appendix 13)
10	A: Hematology (RBC, WBC, Platelets, Differential BC), Serum Chemistry (Na, K, Ca, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP). Coagulation (Quick and/or INR, aPTT), ß2-microgluboline, Vitamine D and IgG. TSH mandotory at baseline and at days with planned CT. All laboratory parameters have to be checked -7days prior to first induction dose. B: Blood count, serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP), Coagulation (Quick and/or INR, aPTT), TSH in case of planned CT C: as B + IL-6+Ferritine+PCT D: Blood count, serum Chemistry (Na, K, Crea, Urea, LDH, CRP),
11	Central assessment (Kiel) from plasma samples: IL-1, IL-2, IL-6, IL-8, IL-10, TNFα, interferone gamma,(IFNγ) soluble Interleukin-2 receptor (sIL-2R)
12	CRS assessment starts before the CAR T cell administration at day 0 by using the CRS grading. At least 1x per shift an assessment of the CRS - severity must be performed and documented in the file, see section 11.1.6.5.1., appendices 4-8
13	Mandatory screening for HIV, HBV (HbsAg, consider HBV DNA for occult or prior HBV infection) and HCV (HCV antibody serology, if positive: HCV RNA PCR mandatory), please check with local transfusion center if special serology is needed prior to Leukapheresis
14	Response evaluation with (PET) CT scans using contrast media is the preferred radiology method. PET-CT is mandatory at EOC, otherwise PET is optional.
15	For details on chemotherapy in Arm A see section 11.1 and section 11.2 for Arm B
16	Will be provided by EORTC
17	Local assessment (Mainz). For a wash out of the CAR T cell product rinse CAR T bag with NaCl after infusion: draw up 20 ml medium into perfusor syringe; connect to bag using 3-way stopcock; rinse bag; take up cell suspension into shipping containers; immediate shipping (refrigerated)
18	Central assessment (Kiel), see Appendix 11 for details on biosampling and shipping.
19	Central assessment (Kiel), see section 14.1.3 or MRD diagnostics from bone marrow (strongly recommend) and Appendix 11 for details on biosampling and shipping.
20	Local assessment, see appendix 9 for details.
21	Local assessment, see appendix 10 for details.
22	Local assessment, see appendix 9 for details.
23	Central assessment (Kiel), e.g. for cytokine analysis from plasma samples
24	Central assessment (Munich), fill two tubes (Omnigene Gut) at each visit, storage at room temperature, long-term storage at -80°C, see Appendix 9 and Appendix 10 for details and shipping
25	Period of observation for adverse events extends from registration up to 30 days after the last trial medication application. SPMs and hematotoxicity are followed until the the end of study. For more details see section 16.6

* Examination of peripheral venous status for Leukapheresis + registration at local transfusion center must be checked at least 2 weeks before the planned Leukapheresis or according to local standards. Check local requirements of virus serology before leukapheresis with local transfusion center at least 2 weeks (or according to local standards) before planned leukapheresis. Leukapheresis will be performed according to local procedures after reconstitution of leukocytes (ANC at least 500/nl). For biosampling 2.5ml of leukapheresed cells are needed for CAR T flow and Immune status, see section 11.1.3 and Appendix 11 for details.

** see section 11.1.6, at least 10 days of hospitalization after CAR T cell infusion recommended, up to 14 days or longer possible if required for medical reasons

1.5.2 Arm B (Standard of care)

A) Schedule of Activities – Arm B (R-CHOP + I / R-DHAP for patients ≤ 65 years)

Table is separated into 4 parts based on:

- Time periods
  1. Screening - End of Consolidation Evaluation (EOC)
  2. Ibrutinib Maintenance – End of Study (EOS) + Long-term FU (registry)
- Activities
  1. Assessments + Imaging
  2. Study treatment + Scientific program + Safety

Arm B ≤65 years ASCT Time period 1 Assessments and imaging	Screening	Induction	Induction	Induction	Induction	Induction	Induction	Induction	Induction	First interim evaluation	Apheresis	End of Induction Evaluation (EOI)	THAM or BEAM	ASCT	p ASCT	p ASCT	p ASCT	End of Consolidation Evaluation (EOC)
	Within 28 days of enrolment	optional C1D0	C1D1	C1D8	C1D15	optional C2-6 D0	C2-C6 D1	optional C2-C6 D8	optional C2-C6 D15	optional C4D15	C4 or C6 D10	C6D21	D -7	D 0	D 8	optional D 15	optional D 21	3 to 5 weeks after ASCT approx. month 7
Assessments																		
Histological diagnosis of MCL including at least one high-risk feature [1]	x																	
Reference Pathology [2]	x																	
Bone Marrow Assessment [3]	x									(x)								
Inclusion/ exclusion criteria [4]	x																	
Demographic data	x																	
Informed consent	x																	
EMCL-Registry [5]	x																	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x					x
Medical history [6]	x																	
ECOG	x	x	x	x	x	x	x			x		x	x					x
Physical examination (A or B) [7]	A	A	A	B	B	B	B	B	B	A		A	B	B	B	B		A
Neurological assessment including MMSE [8]																		
Weight (+ height at screening)	x						x			x		x						
Pregnancy test (fertile females only) [9]	within 7 days before first induction dose	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Consideration of sperm cryo-preservation and suppression of ovulation	x																	
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cardiac function evaluation (ECG, Echokardiography)	x											x						x
Blood draw (A, B, C or D) [10]	A	(A)	B	D	D	(A)	B	D	D	B	B	B	B	D	B or D	B or D	B or D	A
Hepatitis/ HIV serology [11]	x																	
Imaging																		
Brain MRI	x																	
CT scan (neck, thorax, abdomen, pelvis) [12]	x									x		x						x
PET																		x

Arm B ≤65 years ASCT Time period 1 Study treatment, scientific program and safety	Screening	Induction	Induction	Induction	Induction	Induction	Induction	Induction	Induction	First interim evaluation	Apheresis	End of Induction Evaluation (EOI)	THAM or BEAM	ASCT	p ASCT	p ASCT	p ASCT	End of Consolidation Evaluation (EOC)
	Within 28 days of enrolment	optional C1D0	C1D1	C1D8	C1D15	optional C2-6 D0	C2-C6 D1	optional C2-C6 D8	optional C2-C6 D15	optional C4D15	C4 or C6 D10	C6D21	D -7	D 0	D 8	optional D 15	optional D 21	3 to 5 weeks after ASCT approx. month 7
Study treatment																		
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]		R	C+R+I	I	I	R	C+R+I (C3,C5)	I (C3, C5)	I (C3, C5)									I
G-CSF [14]														x	(x)	(x)	(x)	
Stem cell apheresis											x							
Check availibility of stem cells													x					
THAM or BEAM													x					
PBSCT														x				
Scientific program																		
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [15]	Within 7 days before first induction dose											x						x
1 x EDTA (MRD blood) [16] Optional: 1 x EDTA (MRD bone marrow) [17]	x									x		x						x
1 x EDTA (immune status and reconstitution) [18]	x																	x
2 x streck tubes (cfDNA) [19]	x									x								x
Stool samples [20]												x		x	x	x		
PBMC 20 ml PB	x																	
Serum 7,5 ml PB	x																	
Biobanking	x																	
Safety																		
Recording of AEs / SAEs [21]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Secondary malignancies		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FU in GLA-Registry																		

Arm B ≤65 years ASCT Time period 2 Assessments and imaging	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)	Active Follow-up (+Rituximab)	Active Follow-up (+Rituximab)	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Year 4 Visit Visit M49	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Assessments														For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Histological diagnosis of MCL including at least one high-risk feature [1]															
Reference Pathology [2]															
Bone Marrow Assessment [3]															
Inclusion/ exclusion criteria [4]															
Demographic data															
Informed consent															
EMCL-Registry [5]												x			
Concomitant medication	x	x	x	x	x	x	x								
Medical history [6]												x	x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x		
Physical examination (A or B)[7]	B	A	A	A	A	A	A	B	B	B	B	B	A		
Neurological assessment including MMSE [8]															
Weight (+ height at screening)							x						x		
Pregnancy test (fertile females only) [9]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)					
Consideration of sperm cryo-preservation and suppression of ovulation															
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x						
Cardiac function evaluation (ECG, Echokardiography)															
Blood draw (A, B, C or D) [10]	B	B	B	B	B	B	A	B	B	B	B	B	A		
Hepatitis/ HIV serology [11]															
Imaging															
Brain MRI															
CT scan (neck, thorax, abdomen, pelvis)[12]	x	x	x	x	x	x	x		x	x	x	x	x		
PET															

Arm B ≤65 years ASCT Time period 2 Study treatment, scientific program and safety	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)	Active Follow-up (+Rituximab)	Active Follow-up (+Rituximab)	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Year 4 Visit Visit M49	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Study treatment														For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]	I	I	I	I	I	I									
G-CSF [14]															
Stem cell apheresis															
Check availibility of stem cells															
THAM or BEAM															
PBSCT															
Scientific program															
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [15]		x		x			x								
1 x EDTA (MRD blood) [16] Optional: 1 x EDTA (MRD bone marrow) [17]	x	x		x		x	x	x	x	x	x		x		
1 x EDTA (immune status and reconstitution) [18]	x	x													
2 x streck tubes (cfDNA) [19]	x	x		x		x	x	x	x	x	x		x		
Stool samples [20]															
PBMC 20 ml PB															
Serum 7,5 ml PB															
Biobanking															
Safety															
Recording of AEs / SAEs [21]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Secondary malignancies	x	x	x	x	x	x	x	x	x	x	x	x	x		
FU in GLA-Registry															X

1	High risk MCL features are defined in the inclusion criteria (section 10.3)
2	See section 15.1, 5-8 FFPE from diagnostic biopsies will be used to define predictive MCL ecotypes by integrating Gene Mutation Data, Genomic Copy Number Alterations (CNA) and Immune Tumor Microenvironment (TME) Profiles. 500ng of genomic DNA needed for targeted DNA next-generation sequencing (NGS), 200ng of total RNA needed for digital multiplex gene expression profiling DMGEP. At relapse 5-8 FFPE or fresh material needed for RNAseq, capture/ CAN seq and Immune status.
3	BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.
4	See section 10.3 und 10.4
5	Enrolment in the eMCL registry is strongly recommended.
6	Concomitant diseases, allergies
7	A: examination of head, eyes, ear, nose, throat, lymph nodes, liver and spleen; cardiovascular, respiratory, gastrointestinal, dermatological and musculoskeletal system, B symptoms. B: Targeted PE, systems of primary relevance: cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) as described in section 14.2.1
8	Examination of brain nerves, application of the Mini Mental State Examination (MMST), see Appendix 3
9	Urine or blood test; monthly tests mandatory as long as contraception is recommended (refer to 16.11 and appendix 13)
10	A: Hematology (RBC, WBC, Platelets, Differential BC), Serum Chemistry (Na, K, Ca, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP). Coagulation (Quick and/or INR, aPTT), ß2-microgluboline, Vitamine D and IgG. TSH mandotory at baseline and at days with planned CT. All laboratory parameters have to be checked -7days prior to first induction dose. B: Blood count, serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP), Coagulation (Quick and/or INR, aPTT), TSH in case of planned CT C: as B + IL-6+Ferritine+PCT D: Blood count, serum Chemistry (Na, K, Crea, Urea, LDH, CRP),
11	Mandatory screening for HIV, HBV (HbsAg, consider HBV DNA for occult or prior HBV infection) and HCV (HCV antibody serology, if positive: HCV RNA PCR mandatory), please check with local transfusion center if special serology is needed prior to Leukapheresis
12	Response evaluation with (PET) CT scans using contrast media is the preferred radiology method. PET-CT is mandatory at EOC, otherwise PET is optional.
13	For details on chemotherapy in Arm A see section 11.1 and section 11.2 for Arm B
14	Will be provided by EORTC)
15	Central assessment (Kiel), see Appendix 11for details on biosampling and shipping.
16	Central assessment (Kiel), see section 14.1.3 for MRD diagnostics from bone marrow (strongly recommend) and Appendix 11 for details on biosampling and shipping.
17	Local assessment, see appendix 10 for details.
18	Local assessment, see appendix 9 for details.
19	Central assessment (Kiel), e.g. for cytokine analysis from plasma samples
20	Central assessment (Munich), fill two tubes (Omnigene Gut) at each visit, storage at room temperature, long-term storage at -80°C, see Appendix 9 and Appendix 10 for details and shipping
21	Period of observation for adverse events extends from registration up to 30 days after the last trial medication application. SPMs and hematotoxicity are followed until the the end of study. For more details see section 16.6

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

B) Schedule of Activities – Arm B (R-Benda + Ibrutinib <u>for patients > 65 years</u>)

Table is separated into 4 parts based on:

- Time periods
    1. Screening - End of Induction Evaluation (EOI)
    2. Ibrutinib Maintenance – End of Study (EOS) + Long-term FU (registry)
- Activities
    1. Assessments + Imaging
    2. Study treatment + Scientific program + Safety

Arm B >65 years R-Benda + Ibrutinib Time period 1 Assessments and imaging	Screening	Induction	Induction	Induction	Induction	Induction	Induction	Induction	Induction	First interim evaluation	End of Induction Evaluation (EOI)
	Within 28 days of enrolment	optional C1D0	C1D1	C1D2	optional C1D8	optional C1D15	optional C2-C6 D0	C2-C6 D1	C2-C6 D2	C4D15	end of C6 approx. month 7
Assessments											
Histological diagnosis of MCL including at least one high-risk feature [1]	x										
Reference Pathology [2]	x										
Bone Marrow Assessment [3]	x									(x)	
Inclusion/ exclusion criteria [4]	x										
Demographic data	x										
Informed consent	x										
EMCL-Registry [5]	x										
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x
Medical history [6]	x										
ECOG	x		x					x		x	x
Physical examination (A or B)[7]	A	A	B	B	B	B	B	B	B	A	A
Neurological assessment including MMSE [8]											
Weight (+ height at screening)	x		x					x		x	x
Pregnancy test (fertile females only) [9]	within 7 days before first induction dose	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Consideration of sperm cryo-preservation and suppression of ovulation	x										
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x	x	x
Cardiac function evaluation (ECG, Echokardiography)	x										x
Blood draw (A or B) [10]	A	(A)	A		(A)	(A)	(A)	A		A	A
Hepatitis/ HIV serology [11]	x										
Imaging											
Brain MRI	x										
CT scan (neck, thorax, abdomen, pelvis)[12]	x									x	
PET											x

Arm B **>65 years R-Benda + Ibrutinib** **Time period 1** **Study treatment, scientific program and safety**	Screening	Induction	Induction	Induction	Induction	Induction	Induction	Induction	Induction	First interim evaluation	End of Induction Evaluation (EOI)
	Within 28 days of enrolment	optional C1D0	C1D1	C1D2	optional C1D8	optional C1D15	optional C2-C6 D0	C2-C6 D1	C2-C6 D2	C4D15	end of C6 approx. month 7
Study treatment											
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]		R	R+B+I	B+I	I	I	R+I	R+B+I	B+I	I	I
Scientific program											
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [14]	Within 7 days before first induction dose										x
1 x EDTA (MRD blood) [15] Optional: 1 x EDTA (MRD bone marrow) [16]	x									x	x
1 x EDTA (immune status and reconstitution) [17]	x										
2 x streck tubes (cfDNA) [18]	x									x	
Stool samples [19]											x
PBMC 20 ml PB	x										
Serum 7,5 ml PB	x										
Biobanking	x										
Safety											
Recording of AEs / SAEs [20]		x	x	x	x	x	x	x	x	x	x
Secondary malignancies		x	x	x	x	x	x	x	x	x	x
FU in GLA-Registry											

Arm B >65 years R-Benda + Ibrutinib Time period 2 Assessments and imaging	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)	Active Follow-up (+Rituximab)	Active Follow-up (+Rituximab)	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Year 4 Visit Visit M49	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Assessments														For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Histological diagnosis of MCL including at least one high-risk feature [1]															
Reference Pathology [2]															
Bone Marrow Assessment [3]															
Inclusion/ exclusion criteria [4]															
Demographic data															
Informed consent															
EMCL-Registry [5]												x			
Concomitant medication	x	x	x	x	x	x	x								
Medical history [6]												x	x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x		
Physical examination (A or B) [7]	B	B	B	B	B	B	A	B	A	B	B	A	A		
Neurological assessment including MMSE [8]															
Weight (+ height at screening)							x						x		
Pregnancy test (fertile females only) [9]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)					
Consideration of sperm cryo-preservation and suppression of ovulation															
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x						
Cardiac function evaluation (ECG, Echokardiography)															
Blood draw (A or B) [10]	A	A	A	A	A	A	A	A	A	A	A	A	A		
Hepatitis/ HIV serology [11]															
Imaging															
Brain MRI															
CT scan (neck, thorax, abdomen, pelvis) [12]	x	x	x	x	x	x	x		x	x	x	x	x		
PET															

Arm B **>65 years R-Benda + Ibrutinib** **Time period 2** **Study treatment, scientific program and safety**	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)	Active Follow-up (+Rituximab)	Active Follow-up (+Rituximab)	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Year 4 Visit Visit M49	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Study treatment														For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]	I	I	I	I	I	I									
Scientific program															
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [14]		x		x			x								
1 x EDTA (MRD blood) [15] Optional: 1 x EDTA (MRD bone marrow) [16]	x	x		x		x	x	x	x	x	x		x		
1 x EDTA (immune status and reconstitution) [17]	x	x													
2 x streck tubes (cfDNA) [18]	x	x		x		x	x	x	x	x	x		x		
Stool samples [19]															
PBMC 20 ml PB															
Serum 7,5 ml PB															
Biobanking															
Safety															
Recording of AEs / SAEs [20]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Secondary malignancies	x	x	x	x	x	x	x	x	x	x	x	x	x		
FU in GLA-Registry															X

1	High risk MCL features are defined in the inclusion criteria (section 10.3)
2	See section 15.1, 5-8 FFPE from diagnostic biopsies will be used to define predictive MCL ecotypes by integrating Gene Mutation Data, Genomic Copy Number Alterations (CNA) and Immune Tumor Microenvironment (TME) Profiles. 500ng of genomic DNA needed for targeted DNA next-generation sequencing (NGS), 200ng of total RNA needed for digital multiplex gene expression profiling DMGEP. At relapse 5-8 FFPE or fresh material needed for RNAseq, capture/ CAN seq and Immune status.
3	BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.
4	See section 10.3 und 10.4
5	Enrolment in the eMCL registry is strongly recommended.
6	Concomitant diseases, allergies
7	A: examination of head, eyes, ear, nose, throat, lymph nodes, liver and spleen; cardiovascular, respiratory, gastrointestinal, dermatological and musculoskeletal system, B symptoms. B: Targeted PE, systems of primary relevance: cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) as described in 14.2.1
8	Examination of brain nerves, application of the Mini Mental State Examination (MMST), see Appendix 3
9	Urine or blood test; monthly tests mandatory as long as contraception is recommended (refer to 16.11 and appendix 13)
10	A: Hematology (RBC, WBC, Platelets, Differential BC), Serum Chemistry (Na, K, Ca, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP). Coagulation (Quick and/or INR, aPTT), ß2-microgluboline, Vitamine D and IgG. TSH mandotory at baseline and at days with planned CT. All laboratory parameters have to be checked -7days prior to first induction dose. B: Blood count, serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP), Coagulation (Quick and/or INR, aPTT), TSH in case of planned CT
11	Mandatory screening for HIV, HBV (HbsAg, consider HBV DNA for occult or prior HBV infection) and HCV (HCV antibody serology, if positive: HCV RNA PCR mandatory), please check with local transfusion center if special serology is needed prior to Leukapheresis
12	Response evaluation with (PET) CT scans using contrast media is the preferred radiology method. PET-CT is mandatory at EOI, otherwise PET is optional.
13	For details on chemotherapy in Arm A see section 11.1 and section 11.2 for Arm B
14	Will be provided by EORTC
15	Central assessment (Kiel), see Appendix 11 for details on biosampling and shipping.
16	Central assessment (Kiel), see section 14.1.3 for MRD diagnostics from bone marrow (strongly recommend) and Appendix 11 for details on biosampling and shipping.
17	Local assessment, see appendix 10 for details.
18	Local assessment, see appendix 9 for details.
19	Central assessment (Munich), fill two tubes (Omnigene Gut) at each visit, storage at room temperature, long-term storage at -80°C, see Appendix 9 and Appendix 10 for details and shipping
20	Period of observation for adverse events extends from registration up to 30 days after the last trial medication application. SPMs and hematotoxicity are followed until the the end of study. For more details see section 16.6

B) Schedule of Activities – Arm B (R-CHOP + Ibrutinib for patients > 65 years)

Table is separated into 4 parts based on:

- Time periods
    1. Screening - End of Treatment Evaluation (EOT)
    2. Active-Follow-up – End of Study (EOS) + Long-term FU (registry)
- Activities
    1. Assessments + Imaging
    2. Study treatment + Scientific program + Safety

Arm B >65 years R-CHOP + Ibrutinib Time period 1 Assessments and imaging	Screening	Induction	Induction	Induction	Induction	First interim evaluation	End of Induction Evaluation (EOI)	Second interim evaluation	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)
	Within 28 days of enrolment	optional C1D0	C1D1	optional C2-C6 D0	C2-C6 D1	End of C4	end of C6 approx. month 5	Visit M7	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31
Assessments															
Histological diagnosis of MCL including at least one high-risk feature [1]	x														
Reference Pathology [2]	x														
Bone Marrow Assessment [3]	x					(x)									
Inclusion/ exclusion criteria [4]	x														
Demographic data	x														
Informed consent	x														
EMCL-Registry [5]	x														
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical history [6]	x														
ECOG	x		x		x	x	x	x	x	x	x	x	x	x	x
Physical examination (A or B)[7]	A	A	A	B	B	A	A	A	B	B	B	B	B	B	A
Neurological assessment including MMSE [8]	x														
Weight (+ height at screening)	x		x		x	x	x	x							x
Pregnancy test (fertile females only) [9]	within 7 days before first induction dose	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Consideration of sperm cryo-preservation and suppression of ovulation	x														
Vital signs (BP, HR, O2 Saturation, temperature)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cardiac function evaluation (ECG, Echokardiography)	x						x	x							
Blood draw (A or B) [10]	A	B	B	B	B	A	A	A	B	B	B	B	B	B	A
Hepatitis/ HIV serology [11]	x														
Imaging															
Brain MRI															
CT scan (neck, thorax, abdomen, pelvis)[12]	x					x	x		x	x	x	x	x	x	x
PET								x							

Arm B **>65 years R-CHOP + Ibrutinib** **Time period 1** **Study treatment, scientific program and safety**	Screening	Induction	Induction	Induction	Induction	First interim evaluation	End of Induction Evaluation (EOI)	Second interim evaluation	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	Ibrutinib maintenance (2 years)	End of Treatment Evaluation (EOT)
	Within 28 days of enrolment	optional C1D0	C1D1	optional C2-C6 D0	C2-C6 D1	End of C4	end of C6 approx. month 5	Visit M7	Visit M10	Year 2 Visit M13	Year 2 Visit M16	Year 2 Visit M19	Year 2 Visit M22	Year 3 Visit M25	approx. M31
Study treatment															
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]		R	R+C+I	R+I	R+C+I	I	I	I	I	I	I	I	I	I	
Scientific program															
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [14]	Within 7 days before first induction dose						x			x		x			x
1 x EDTA (MRD blood) [15] Optional: 1 x EDTA (MRD bone marrow) [16]	x					x	x		x	x		x		x	x
1 x EDTA (immune status and reconstitution) [17]	x								x	x					
2 x streck tubes (cfDNA) [18]	x					x			x	x		x		x	x
Stool samples [19]							x								
PBMC 20 ml PB	x														
Serum 7,5 ml PB	x														
Biobanking	x														
Safety															
Recording of AEs / SAEs [20]		x	x	x	x	x	x		x	x	x	x	x	x	x
Secondary malignancies		x	x	x	x	x	x		x	x	x	x	x	x	x
FU in GLA-Registry															

Arm B >65 years R-CHOP + Ibrutinib Time period 2 Assessments and imaging	Active Follow-up (+Rituximab) Year 3 Visit M31	Active Follow-up (+Rituximab) Year 4 Visit M37	Active Follow-up Year 4 Visit M43	Active Follow-up Year 4 Visit Visit M49	Active Follow-up Annual thereafter until EOS (max. 7 years)	End of Study Evaluation (EOS) / Time of Progression visit (TOP) at the end of FU or at time of PD	Survival Follow up every 6 months after TOP	Long-term FU (registry) Until a maximum of 15 years
Assessments							For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Histological diagnosis of MCL including at least one high-risk feature [1]								
Reference Pathology [2]								
Bone Marrow Assessment [3]								
Inclusion/ exclusion criteria [4]								
Demographic data								
Informed consent								
EMCL-Registry [5]					x			
Concomitant medication								
Medical history [6]					x	x		
ECOG	x	x	x	x	x	x		
Physical examination (A or B)[7]	B	A	B	B	A	A		
Neurological assessment including MMSE [8]								
Weight (+ height at screening)						x		
Pregnancy test (fertile females only) [9]	(x)	(x)	(x)	(x)				
Consideration of sperm cryo-preservation and suppression of ovulation								
Vital signs (BP, HR, O2 Saturation, temperature)	x	x						
Cardiac function evaluation (ECG, Echokardiography)								
Blood draw (A or B) [10]	B	B	B	B	B	A		
Hepatitis/ HIV serology [11]								
Imaging								
Brain MRI								
CT scan (neck, thorax, abdomen, pelvis)[12]		x	x	x	x	x		
PET								

Arm B **>65 years R-CHOP + Ibrutinib** **Time period 2** **Study treatment, scientific program and safety**	Active Follow-up (+Rituximab)	Active Follow-up (+Rituximab)	Active Follow-up	Active Follow-up	Active Follow-up	End of Study Evaluation (EOS) / Time of Progression visit (TOP)	Survival Follow up	Long-term FU (registry)
	Year 3 Visit M31	Year 4 Visit M37	Year 4 Visit M43	Year 4 Visit Visit M49	Annual thereafter until EOS (max. 7 years)	at the end of FU or at time of PD	every 6 months after TOP	Until a maximum of 15 years
Study treatment							For Patients in Survival Follow-Up: Salvage Therapy or Maintenance to be documented half-yearly from Time of Progression until end of Study	
Chemotherapy (C) / Ibrutinib (I) / Rituximab (R) [13]								
Scientific program								
QoL (EORTC-QLQ-C30, EORTC QLQ-NHL-HG29) [14]								
1 x EDTA (MRD blood) [15] Optional: 1 x EDTA (MRD bone marrow) [16]	x	x	x	x		x		
1 x EDTA (immune status and reconstitution) [17]								
2 x streck tubes (cfDNA) [18]	x	x	x	x		x		
Stool samples [19]								
PBMC 20 ml PB								
Serum 7,5 ml PB								
Biobanking								
Safety								
Recording of AEs / SAEs [20]	x	x	x	x	x	x		
Secondary malignancies	x	x	x	x	x	x		
FU in GLA-Registry								X

1	High risk MCL features are defined in the inclusion criteria (section 10.3)
2	See section 15.1, 5-8 FFPE from diagnostic biopsies will be used to define predictive MCL ecotypes by integrating Gene Mutation Data, Genomic Copy Number Alterations (CNA) and Immune Tumor Microenvironment (TME) Profiles. 500ng of genomic DNA needed for targeted DNA next-generation sequencing (NGS), 200ng of total RNA needed for digital multiplex gene expression profiling DMGEP. At relapse 5-8 FFPE or fresh material needed for RNAseq, capture/ CAN seq and Immune status.
3	BM biopsy mandatory if BM was involved at screening, optional if BM was free of lymphoma at screening, but strongly recommended.
4	See section 10.3 und 10.4
5	Enrolment in the eMCL registry is strongly recommended.
6	Concomitant diseases, allergies
7	A: examination of head, eyes, ear, nose, throat, lymph nodes, liver and spleen; cardiovascular, respiratory, gastrointestinal, dermatological and musculoskeletal system, B symptoms. B: Targeted PE, systems of primary relevance: cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) as described in 14.2.1
8	Examination of brain nerves, application of the Mini Mental State Examination (MMST), see Appendix 3
9	Urine or blood test; monthly tests mandatory as long as contraception is recommended (refer to 16.11 and appendix 13)
10	A: Hematology (RBC, WBC, Platelets, Differential BC), Serum Chemistry (Na, K, Ca, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP). Coagulation (Quick and/or INR, aPTT), ß2-microgluboline, Vitamine D and IgG. TSH mandotory at baseline and at days with planned CT. All laboratory parameters have to be checked -7days prior to first induction dose. B: Blood count, serum Chemistry (Na, K, Crea, Urea, Urea Acid, LDH, CRP), Hepatology (yGT, ALT, AST, Bilirubin, AP), Coagulation (Quick and/or INR, aPTT), TSH in case of planned CT
11	Mandatory screening for HIV, HBV (HbsAg, consider HBV DNA for occult or prior HBV infection) and HCV (HCV antibody serology, if positive: HCV RNA PCR mandatory), please check with local transfusion center if special serology is needed prior to Leukapheresis
12	Response evaluation with (PET) CT scans using contrast media is the preferred radiology method. PET-CT is mandatory at EOI, otherwise PET is optional.
13	For details on chemotherapy in Arm A see section 11.1 and section 11.2 for Arm B
14	Will be provided by EORTC
15	Central assessment (Kiel), see Appendix 11 for details on biosampling and shipping.
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17	Local assessment, see appendix 10 for details.
18	Local assessment, see appendix 9 for details.
19	Central assessment (Munich), fill two tubes (Omnigene Gut) at each visit, storage at room temperature, long-term storage at -80°C, see Appendix 9 and Appendix 10 for details and shipping
20	Period of observation for adverse events extends from registration up to 30 days after the last trial medication application. SPMs and hematotoxicity are followed until the the end of study. For more details see section 16.6

1.6 List of abbreviations

AR	Adverse (Drug) Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz
ASCT	Autologous Stem Cell Transplantation
BOB	Bundesoberbehörde
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BP	Blood pressure
BTK	Brutone's Tyrosine Kinase
CA	Competent Authority
CT	Computed Tomography
CNA	Copy number alterations
CNS	Central Nervous System
CPF	Cell Processing Facility
CR	Complete Remission
CRA	Clinical Research Associate
CRES	CAR-T cell-related encephalopathy syndrome
CRF	Case Report Form
CRO	Contract Research Organisation
CRS	Cytokine Release Syndrome
CSC	Clinical Study Center (CSC_{LMU}), Munich
CSF	Cerebrospinal fluid
CTIS	Clinical trial information system (the EU Portal)
CTR	Clinical Trial Regulation No 536/2014
DMSC	Data monitoring safety committee
EC	Ethics Committee
EMA	European Medicine Agency
EOT	End of Treatment
FFPE	Formalin-fixed paraffin-embedded tissue
FFS	Failure-free Survival
FPFV	First Patient First Visit
FU	Follow Up
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HR	Heart rate
ICANS	Immune effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune effector cell-associated encephalopathy
ICH	International Council on Harmonization
IMP	Investigational Medicinal Product

ISF	Investigator Site File
I.V.	intravenously
ITT	Intention to Treat
LD	Lymphodepleting Chemotherapy
LPLV	Last Patient Last Visit
MIPI	Mantle Cell International Prognostic Index
MRD	Minimal Residual Disease
NGS	Next-generation sequencing
NHL	Non Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PEI	Paul Ehrlich Institut
PFS	Progression-free Survival
PD	Progressive Disease
p. o.	per os (orally)
PP	Per Protocol
PR	Partial Remission
QoL	Quality of Life
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SDP	Sponsor Delegated Person
SDV	Source Data Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	total body irradiation
TME	Tumor Microenvironment
ToP	Time-of-Progression-Visit
UAR	Unexpected Adverse Reaction
WBC	White Blood Cells
YOB	Year of birth

2 Introduction

Mantle cell lymphoma (MCL) is a rare lymphoma subtype that accounts for 3-10% of Non-Hodgkin lymphomas (NHL) in adults. Recent biologic and therapeutic developments improved prognosis by optimizing first and subsequent treatment lines, nevertheless MCL is considered incurable with current treatment options. Defined prognostic parameters, namely alterations of TP53 (mutations, overexpression), Ki-67 proliferation index ≥30%, blastoid or pleomorphic morphologic characteristics as well a high-risk Mantle Cell Lymphoma International Prognostic Index C (MIPI-c) predict poor outcome. Treatment approaches as chemoimmunotherapy and non-chemotherapeutic targeted therapies such as Bruton's tyrosine kinase inhibitors (BTKi) may induce disease remission, but in high risk patients these options frequently fail early. Today, achieving cure in patients with high-risk MCL remains a major challenge, with allogeneic transplantation considered the only option, however, only a minority of patients qualifies for this treatment modality, which is associated with high rates of treatment-related morbidity and mortality.

Lately, the anti-CD19 chimeric antigen receptor T-cell (CAR-T) product brexucabtagene autoleucel (KTE-X19) has shown promising efficacy in patients with relapsed or refractory aggressive MCL with up to 5 prior regimens and failure of previous BTK inhibitor therapy [1]. These results led to approval by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for patients with relapsed disease (EMA: After failure of at least two lines of therapy including BTKi). Although this adds substantially to current treatment options, restricting CAR-T cell therapy to later treatment lines increases the risk of disease evolution over time, thereby potentially limiting treatment efficacy of this modality. Especially in high-riskdisease, this negative effect may be accentuated. Therefore, it seems reasonable to apply this approach already in first line, when the disease might be more susceptible, thereby exploiting the full therapeutic potential. In this intent the European Mantle Cell Lymphoma Network, an international academic research network (www.european-mcl.net) has developed a phase II study concept exploring early treatment intensification by the integration of CAR-T-cells into the first line treatment for high-risk MCL patients.

3 Background

MCL is an uncommon (3-10% of adult NHL in Western countries) and usually aggressive, incurable subtype of NHL[2-4]. Approximately 4000 new cases are diagnosed yearly in the US, and approximately 800-1200 cases in Germany. Median age at diagnosis is 68 years, there is a clear male predominance and most patients are diagnosed with advanced stage [5].The staging is based on the Ann Arbor classification or the modified Lugano classification [6].A subset of patients may initially present with an indolent disease course (leukemic, non-nodalvariants), but most patients require systemic treatment at the time of diagnosis [7-10]. Amongvarious genetic alterations, MCL is usually characterized by the translocation t(11;14) leadingto Cyclin D1 overexpression, however secondary genetic aberrations such as TP53 alterations frequently occur during the later disease course [11].

Several risk factors have been determined to predict prognosis and guide management, suchas the simplified MCL International Prognostic Index, MIPI [12]. The following four independent prognostic parameters are incorporated: age, performance status, serum LDH level, and leukocyte count. High-risk patients have a significantly lower 5-year OS than patients with low- or intermediate features (34% versus 83% and 63%, respectively) when treated with chemoimmunotherapy [13, 14]. In addition, high Ki-67 (>30%), TP53 alterations and

blastic/pleomorphic histology predict poor outcome in newly diagnosed MCL. Poor performance status, elderly age group, significant comorbidities and disease characteristics such as CNS involvement, disease transformation and BTK-inhibitor-refractory MCL are further high risk features [15-18]. In relapsed patients, complex karyotype and disease progression within 12-24 months after first-line therapy indicate poor prognosis [19, 20].

Although different risk groups have been defined, treatment selection in newly diagnosed MCL still mainly is based on age and performance status rather than on prognostic scores or biological outcome predictors, such as TP53 aberrations and proliferation index.

First-line therapy for MCL typically includes polychemotherapy in combination with a CD20 targeting antibody. Intensification of therapy by adding high-dose cytarabine to induction chemotherapy has sustainably improved response and prognosis of young patients with MCL. While the median overall survival at the beginning of the millennium change was still around 2-3 years, modern induction regimens can achieve progression-free survival times of 5 years or longer [21, 22].

Table 1 provides an overview of results of clinical studies in high risk MCL.

Protocol Used	No. of Patients With Blastoid and/or Pleomorphic MCL/Total No. of Patients	Median Follow-Up Time	ORR/CR (%)	TTF/PFS	OS	Clinical High-Risk Marker
Front-line single-arm studies/pooled analyses						
MDACC; R-HCVAD/MTX-Ara-C[73,109,110] (no ASCT)	14/97	13.4 years	NA/79	35% (8 years)	43% (8 years)	The PFS and OS did not differ significantly between blastoid and non-blastoid MCL.
						Blastoid MCL did not affect survival in multivariable analysis.
						At 10-year follow-up,[109] patients with high MIPI score (n = 16) had significantly inferior 8-year TTF (18%) and OS (29%) compared with other MIPI categories.
Nordic MCL2; R-maxi-CHOP/R-HiDAC (with ASCT)[71,72,111]	31/160	6.8 years	NA/54[a]	44% (10 years)	51% (10 years)	At 11.6-year follow-up, blastoid MCL showed a nonsignificant trend for inferior OS but no significant difference with respect to PFS compared with nonblastoid MCL.
						Thirty-seven (24%) of patients had high-risk MIPI, and the OS time was 4 years and PFS time was 2.5 years.
						Patients with *TP53* mutations and deletions demonstrated significantly inferior OS and PFS (combined cohort of MCL2 and MCL3).
CALGB study; R-MTX-augmented CHOP; HiDAC and etoposide with R and G-CSF then ASCT and two doses of R[112]	12/78	4.7 years	NA/69[a]	56% (5 years)[a]	64% (5 years)[a]	Small cohort of blastoid MCL; subset-specific responses not described.
BR, R-HiDAC, and ASCT[113]	11/88	33 months	91/82	66% (3 years)	92% (3 years)[a]	Patients with blastoid MCL had inferior PFS compared with patients with classic MCL (P = .038).
						Seventeen patients had high-risk MIPI; ORR was 88%, CR was 75%, and 3-year PFS was 76%, which were significantly inferior results compared with other MIPI groups.
						Twenty-one patients had Ki-67 > 30%, and in these patients, the ORR was 95% and CR was 85%.
Front-line randomized studies						
MCL Younger; R-CHOP-ASCT (n = 234) *v* R-CHOP alternating with R-DHAP-Ara-C and ASCT (n = 232)[17]	28/466	6.1 years	81/23[23]	18 months	32 months	Five-year OS was significantly inferior in blastoid MCL compared with classic MCL (38% *v* 75%, respectively; P = .0001), whereas PFS was borderline negative for blastoid MCL (P = .05).
						In Ara-C arm, 31 patients had high MIPI, and the median TTF was approximately 1.5 years.
MCL Elderly; R-CHOP *v* R-FCM followed by R *v* IFN maintenance[114,115]	34/287	3 years	NA	19 months	29 months	Five-year OS was significantly inferior in blastoid MCL than in nonblastoid MCL (29 *v* 78 months, respectively; P = .0085).
						Five-year PFS was not significantly different between patients with blastoid and nonblastoid MCL.
R-BAC500[116]	6/57 blastoid, 8/57 pleomorphic	35 months	NA	6 months in blastoid, 40 months in pleomorphic	NA	Median PFS was approximately 16 months in patients with Ki-67 ≥ 30% (n = 16).
						In multivariable analysis, Ki-67 ≥ 30% and blastoid morphology predicted for higher hazard for progression compared with low Ki-67 and nonblastoid morphology.
VR-CAP[117]	9/134	82 months	NA	NA	NA	Improved OS in patients with high Ki-67 (> 30%) on VR-CAP (n = 19; median OS, 38 months) compared with R-CHOP (n = 15; median OS, 17 months).
BR-bortezomib[118]	10/71 blastoid	52 months	NA	NA	NA	Thirty of 51 patients had high Ki-67 (≥ 30%).
						Subgroup analysis demonstrated histology type and Ki-67 did not predict for PFS or OS.
						Median PFS in patients with high Ki-67 was 45 months *v* not reached in those with low Ki-67.
BR (Canadian study)[119]	13/190	3.1 years	NA	NA	NA	StiL and BRIGHT studies do not provide data on high-risk subgroups of MCL.
						Canadian retrospective cohort study showed that patients with high-risk MIPI (n = 21), high Ki-67 (> 50%; n = 45), and blastoid histology (n = 13) have poorer outcomes and higher fraction of nonresponders with BR regimen compared with patients with low-or intermediate-risk MIPI, low Ki-67, and classic histology.
						High-risk patients had inferior PFS and OS.

Relapsed MCL						
Ibrutinib[74]	36/370	3.5 years	50/NA	5.1 months	12.8 months	Duration of response was 8.5 *v* 18.8 months in patients with blastoid and nonblastoid MCL, respectively.
						Twenty patients had mutated *TP53*.
						Response rate in patients with mutated *TP53* was 55%, with a median PFS and OS of 4 months and 10.3 months, respectively. Response rate was 71% in patients with wild-type *TP53*.
Ibrutinib plus rituximab[76]	7/49	4 years	71/43	21 months	30 months	Patients with relapsed blastoid MCL had inferior outcomes and lower response rates compared with patients with nonblastoid MCL; however, the number of patients with blastoid MCL was small.
						Eighteen patients with high-risk MIPI had significantly inferior OS of 34 months.
						Eleven patients with high Ki-67 (> 50%) had significantly inferior PFS (8 months) and OS (14 months) compared with patients with low Ki-67 (not reached).
Nordic study[66]; ibrutinib, lenalidomide, and rituximab	8 *TP53* mutated/49	17.8 months	73/64	8 months	—	Responses were similar in patients with *TP53* mutation compared with patients with wild-type *TP53*.
						Double deletion (*CDKN2A* and *TP53*) did not affect prognosis.
Acalabrutinib[77]	26/124	2 years	77/35	15 months	NA	Response rates and outcomes were inferior in patients with blastoid compared with nonblastoid MCL.
						Twenty-one patients had high-risk MIPI, with a median PFS of 5.7 months compared with 25 months in other groups.
						Thirty-two patients with Ki-67 (≥ 50%) had a median PFS of 6.4 months, compared with 28 months in patients with low Ki-67.
Zanubrutinib[3]	12/86	18.4 months	75/–	16.8 months	—	Patients with blastoid MCL had an ORR of 75% *v* 87% in patients with nonblastoid MCL.
						In 15 patients with *TP53* mutations compared with *TP53* wild-type patients, ORR was 80% *v* 87%, respectively, and median PFS was 14.2 *v* 22.1 months, respectively.
Retrospective studies (miscellaneous regimens)						
Jain et al[22]; largest retrospective analysis of 183 patients with blastoid/ pleomorphic MCL from a single center	183	19.6 months	78/56	13 months	33 months	Patients with de novo blastoid disease had superior outcomes compared with patients with transformed blastoid MCL.
						Patients with pleomorphic MCL had inferior failure-free survival after first-line treatment compared with patients with blastoid MCL, but clinical features in patients with blastoid and pleomorphic MCL were similar.
						Patients with high Ki-67 (≥ 50%) demonstrated significantly inferior OS and failure-free survival (20 and 10 months, respectively) compared with patients with Ki-67 < 50% (118 and 27 months, respectively).
Bhatt et al[120] (pre-BTK inhibitor era)		31 (24) evaluable	58/45	16% (5 years)	24% (5 years)	Patients with blastoid and diffuse classic MCL had inferior PFS compared with patients with nodular classic MCL.
Bernard et al[121] (pre-rituximab era), CHOP/CVP	24	33	NA/36	13 months	14.5 months	Median OS was significantly shorter in patients with blastoid MCL compared with patients with classic MCL.

Abbreviations: Ara-C, cytarabine; ASCT, autologous stem-cell transplantation; BR, bendamustine and rituximab; BTK, Bruton tyrosine kinase; CALGB, Cancer and Leukemia Group B; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; G-CSF, granulocyte colony-stimulating factor; HiDAC, high-dose cytarabine; IFN, interferon; MCL, mantle cell lymphoma; MDACC, The University of Texas MD Anderson Cancer Center; MIPI, Mantle Cell Lymphoma International Prognostic Index; MTX, methotrexate; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; R-DHAP, rituximab, dexamethasone, cisplatin, and cytarabine; R-BAC500, rituximab 375 mg/m2 on day 1, bendamustine 70 mg/m2 on days 2 and 3, and cytarabine 500 mg/m2 on days 2 to 4 (all administered intravenously) every 4 weeks for up to six cycles; R-FCM, rituximab, fludarabine, cyclophosphamide, and mitoxantrone; R-HCVAD/MTX-Ara-C, rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; TTF, time to treatment failure; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

*Data not solely from patients with blastoid MCL; these data are obtained from all patients in this study.

Table 1: Overview of Clinical Studies With Data on High-Risk MCL as published by Dreyling et al.[5]

Younger patients are treated with intensified chemoimmunotherapy treatments, e.g. alternating R-CHOP/ R-DHAP (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Prednisone / Rituximab, Dexamethasone, Cytarabine, Cisplatin) followed by consolidative autologous stem-cell transplantation. In elderly patients, treatment options are R-CHOP, BR (Bendamustine, Rituximab) or VR-CAP CAP (Bortezomib, Rituximab, Cyclophosphamide, Doxorubicine, Prednisone). Regardless of patients' age, Rituximab maintenance therapy is given on a regular basis.

Despite high initial response rates to these therapies, almost all patients eventually develop progressive disease (PD). Especially in patients with TP53 alterations, responses to regimens including cytarabine, Rituximab, and ASCT are often poor: in MCL patients from the Nordic

MCL2 and MCL3 trials, TP53-mutated cases had a dismal outcome, with a median OS of 1.8 years, and 50% relapsed at 1.0 years, compared to a median OS of 12.7 years for TP53-unmutated cases (P < .0001) [23]. Therefore, alternative front-line treatment options are needed in high-risk MCL patients.

Ibrutinib, an oral BTKi, has marked a major advance in relapsed or refractory MCL, demonstrating an overall response rate (ORR) of 68%, with 46% of patients achieving partial response (PR) and 22% achieving complete remission (CR) [24]. Its benefit in the first-line therapy of MCL was recently confirmed in the SHINE study, demonstrating a significantly increased progression-free survival of 80.6 months for BR + Ibrutinib compared to 52.9 months for BR + Placebo in elderly patients with newly diagnosed MCL [25].

The TRIANGLE study, a randomized European MCL Network trial, is addressing the question of whether an autologous stem cell transplantation in times of targeted therapies is still needed by evaluating the current standard therapy (3 cycles of R-CHOP / R-DHAP and consolidating ASCT) with Ibrutinib-containing induction therapy (3 cycles of Ibrutinib+R-CHOP / R-DHAP) with and without consolidating ASCT and each with Ibrutinib maintenance therapy in a three-arm design. The study completed recruitment in December 2020 and first results are still to be expected (EudraCT#: 2014-001363-12).

Other clinical trials investigate whether the addition of a novel BTK-Inhibitor (e.g. BR +/- acalabrutinib, EudraCT-Nr.: 2015-005220-26) or replacement of chemotherapy by a targeted agent such as venetoclax can further improve results. Venetoclax, a potent and selective BCL2 antagonist, as monotherapy or in combination with anti-CD20 monoclonal antibodies, has also demonstrated moderate efficacy in BTKi – refractory MCL (40-50% response rates) [26]. However, outcome of patients with progressive disease following BTK inhibition remains poor.

Whether the current research protocols will improve PFS and OS cannot be answered at this time, however, a curative potential has not been assumed with the treatment concepts under evaluation and especially improvement for high risk MCL patients' needs to be evaluated carefully.

For relapsed patients following autologous stem-cell transplantation, allogeneic stem cell transplantation with "reduced intensity" conditioning may be considered, resulting in in long-term disease-free survival in about 30% of the patients, however, therapy-associated mortality at one year was 24%, primarily caused by graft versus host disease (GvHD) and infections [27].

Anti-CD19 Chimeric antigen receptor T-cells (CAR T) are autologous human T cells that have been engineered to express an extracellular single-chain variable fragment with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

CAR T cell therapy with the anti-CD19 directed product brexucabtagene autoleucel (KTE-X19) was primarily investigated in the ZUMA-2 study, a single-arm, international, multicenter, phase II trial that included 68 patients with relapsed MCL after in median three prior therapy lines including BTK therapy [1, 28] and is now FDA and EMA approved for this indication. Patients underwent leukapheresis and lymphodepleting chemotherapy followed by KTE-X19 infusion at a targeted dose of 2x10^6 CAR-T cells/kg. KTE-X19 dosing was determined on the basis of trials with axicabtagene ciloleucel in patients with refractory aggressive lymphoma [29, 30]. Seventeen patients (25%) had blastoid histology, six had TP53 mutations, and 32 exhibited Ki-67 > 50%. In ZUMA-2 the ORR was 93% in blastoid, TP53-mutated, and high Ki-67 patients.

After a median follow-up of 35.6 months, 91% of patients had an objective response (68% CR). The median progression-free and overall survival was 25.8 and 46.6 months [31].

Progression free survival was consistent in patients with high Ki-67, TP53 mutation and blastoid morphology, indicating that CAR-T-cell treatment might overcome the dismal prognosis that is linked to these biological risk factors. Common grade ≥ 3 adverse events were cytopenias (94%) and infections (32%). Grade ≥ 3 cytokine release syndrome and neurologic events occurred in 15% and 31% of patients, respectively, but none were fatal. There had been no comparator arm in this trial, however, a current analysis of the post BTK-failure results with standard treatments underlined the favorable results of CAR-T-cell treatment as compared to currently available options ("KTE- X19 versus standard of care for relapsed/refractory MCL previously treated with BTK inhibitors: real-world evidence from Europe", Hess et al. 2021, EHA abstract EP786).

Another trial evaluated a similar anti-CD19 CAR T-cell product lisocabtagene maraleucel (liso-cel) in r/r MCL patients with similar promising results (ORR of 84% with 66% CR), supporting the potency of this treatment approach [32]. However, long-term follow-up data of the durability of remissions on CAR T studies are needed. The potential major advantages of CAR-T cell products over allogeneic SCT include reduced morbidity and mortality, preservation of T-cell function, and lower risk of infections. It is yet unknown, whether earlier administration of CAR-T alone or in combination with BTK-inhibitors would reduce risk of future relapses in high-risk MCL. The phase II TARMAC study in Australia currently investigates the efficacy and safety of the combination of Ibrutinib and Tisagenlecleucel in twenty patients with relapsed or refractory MCL or who had sub-optimal response to standard therapy in the presence of TP53 mutation (ClinicalTrials.gov identifier: NCT04234061).

4 Study Rationale

Over the last decades, specific standards of care have been developed for MCL. Namely, for younger patients for the initial treatment the introduction of cytarabinoside, the use of consolidation high dose therapy with autologous stem cell support and the use of Rituximab maintenance treatment have impacted on recent standards. In elderly patients, the use of immunochemotherapy and the use of Rituximab-maintenance treatment is the most widely accepted treatment strategy in first line therapy. Although good response rates and in some cases long remissions can be achieved with this therapeutic options, high risk MCL patients rapidly fail upon standard immunochemotherapy: 50% will relapse at 1.0 years, and prognosis after relapse is poor with a median OS of 1.8 years [23].

The advent of inhibitors of the Bruton's Tyrosine Kinase (BTKi), namely Ibrutinib, has markedly impacted on the outcome of patients with relapsed MCL, especially for those with poor or short-lived responses to chemotherapy. The positive results have stimulated subsequent clinical trials, in which the combination of BTKi to standard regimen has been explored.

Recently, results from the Phase 3 SHINE study were published [25].

In brief, the primary endpoint of the trial, improvement of progression free survival, was met, however, no impact on overall survival was noted. Although, contributing factors to the lack of benefit in OS are not entire clear, added toxicity in very elderly patients may have impacted on the results. Another trial, the TRIANGLE trial of the European Mantle Cell Lymphoma network, has tested whether the addition of Ibrutinib to the dose dense standard treatment can improve results and even if toxic high dose therapy may be omitted by the use of additional BTKi. Results

have been presented at ASH 2022 (manuscript in preparation, Dreyling et al.) (ref). In brief, the addition of Ibrutinib clearly improved progression free survival in comparison to the not-BTKi treatment arm. This held true for the arm containing HDT and the one without. Preliminary, a benefit in OS seems to be possible, however longer follow up is needed, especially for high risk patients. The impressive results have led to acceptance of the approach by payers e.g. in Germany. Albeit the trial has been conducted as an academic collaborative trial, approval in Europe based on the results in currently under discussion. Although the trial has set a new standard of care, recurrence of disease is still being noted, defining a field of unmet medical need.

Besides the implementation of BTKi the succesfull introduction of CAR-T-cell treatment has been the one of major advances during the last decade. The results of the ZUMA-II-trial have established brexucabtagene autoleucel (formerly KTE-X19, brexu-cel) as the treatment of choice of patients failing a BTKi inhibitor (Wang et al.). Notably, even after 3 prior lines, overall response rates of 91% were noted with substantial PFS after 4 years (n.r.) as compared to a median overall survival in an equivalent population of 8-12 months in the past. Recently, (Lugano Wang, LisoCel) similar results have been obtained with a comparable product, lisocabtagene maraleucel (liso-cel), which underline the therapeutic potential of the principle. Interesting, with either of the products even high risk patients (e.g. with TP53 alteration) responded well with long term remission. The results of the controlled trials have been confirmed by a series of real world data, the largest series comprising more than 150 patients[33].

As T-cell fitness required for KTE-X19 efficacy declines with increasing immunochemotherapy exposure [34], administering KTE-X19 as part of first-line treatment without preceding chemotherapy could therefore be an especially effective way to take advantage of the unique capacities of CAR-T-cell treatment.

In addition, besides BTK-inhibition directly impacting B-cell-proliferations, Ibrutinib inhibits interleukin-2-inducible T-cell kinase (ITK) and thereby depletes T helper 2 (Th2) cells and induces a shift towards Th1 cells [1] or increase Th17 subsets [35]. In CLL patients, it was reported that Ibrutinib can reverse the exhausted T-cell phenotype by reducing PD1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression [35]. Of note, CAR-T-cell generation in presence of Ibrutinib resulted in increased cell viability and expansion of CAR-T-cells and decreased the expression of exhaustion markers PD-1, TIM-3 and LAG-3 [36]. Interestingly, the efficacy of a second CAR-T-cell therapy in relapsed NHL patients was improved in patients receiving Ibrutinib prior to and during the anti-CD-19-CAR T-cell treatment [37]. These data suggest that Ibrutinib might induce synergistic effects with CAR T cells by increasing the viability and expansion of T cells while inhibiting T-cell exhaustion.

Recent results of the TARMAC-trial underline the potential of the combination of BTKi and CAR-T-cell treatment. In this trial, another commercially available CAR-T-cell product, tisagenlecleucel (tisa-cel), has been tested together with a BTKi priming strategy prior to leukapheresis and continuous BTKi treatment. Importantly, it had been continued even throughout conditioning and a period of 6 months after CAR-T-cell infusion. Importantly, again with promising response rates, no increase in toxicity as compared to the above mentioned CAR-T-cell trials was noted, which underlines the safety of the approach of post CAR-T-infusion BTKi-treatment.[38]

As CAR-T-cell treatment may – in contrast to currently used immunochemotherapy-based approaches – harbor a curative potential, unlimited use of BTKi seems neither justified nor required in first line treatment.

Finally, results from different trials show the efficacy of chemotherapy free induction, even in high risk patients, with a BTKi based treatment[39]. Furthermore, the combination with Rituximab has been proven to be safe and efficacious and offers an additional in vivo purging efficacy[40].

In summary, the use of a BTKi based induction prior to leukapheresis and CAR-T-cell treatment is justified in terms of efficacy, safety (and reduced toxicity as compared to conventional chemotherapy) and with potential benefit for the functioning of the CAR-T-cell product.

Therefore, the phase II clinical trial will compare the efficacy, safety and tolerability of first-line treatment with KTE-X19 after a shortened induction with Rituximab and Ibrutinib to conventional immunochemotherapy and Ibrutinib followed by ASCT in younger patients in high-risk MCL patients or immunochemotherapy plus BTKi for elderly, but still fit patients (need to be CAR-T-cell eligible). As primarily the potential of CAR-T-cell treatment is evaluated within this trial, in case of failure to achieve a partial response will be treated with 2 additional cycles of R-CHOP, which can be omitted in case of sufficient response to Ibrutinib-based treatment.

5 Risk Benefit Assessment

Ibrutinib is widely used in CLL and MCL. With continuous Ibrutinib monotherapy, the majority of adverse events were grade 1 or 2. Most common non-hematological AEs were diarrhea (50%), fatigue (41%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory tract infection (23%), vomiting (23%), and decreased appetite (21%). Pneumonia was the most common infection of grade 3-5. Most common grade 3-4 hematologic AEs included neutropenia (16%), thrombocytopenia (11%) and anemia (10%). Severe bleeding events of grade 3 occurred in 5 of 111 patients with no grade 4 or 5 events [24]. The cardiovascular risk especially atrial fibrillation have been found to be increased in patients treated with Ibrutinib.

Pharmacologic interactions between Ibrutinib and P-glycoprotein substrates (digoxin and dabigatran), CYP3A4-inhibitors and inducers including anti-arrhythmic drugs (verapamil and amiodarone) and direct oral anticoagulants (apixaban, rivaroxaban), antimicrobials (azoles, macrolides, rifampicin or carbamazepine) and antiepileptic drugs must be carefully considered [41].

Potential risks associated with KTE-X19 treatment are mostly hematological and infectious adverse events, as reported in the ZUMA-2 trial [1]. In 99% of the patients treated within the trial, AEs of grade 3 were recorded. 94% of the patients had cytopenias of grade 3 or higher (of these, neutropenia in 85% of the patients, thrombocytopenia in 51% of the patients and anemia in 50% of the patients) and 32% of the patients had infections. One third of the patients had cytopenias of grade 3 or higher which lasted more than 90 days after the KTE-X19 administration.

Furthermore, cytokine release syndrome (CRS) and neurotoxicity are common after immune effector cell therapy such as CAR T cell therapy. Patients with immune effector cell-associated neurotoxicity syndrome (ICANS), alternatively known as CAR-T cell-related encephalopathy syndrome (CRES), may present with delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, or cerebral oedema, its precise pathophysiology is still unclear [42].

In patients treated within the ZUMA-2 trial, CRS occurred in 91% of the patients, most of them grade 1 and 2 and 15% grade 3 or higher. 59% of all treated patients received tocilizumab, an interleukin-6 receptor antibody, 22% received glucocorticoids, and 16% received vasopressors. No patients died from CRS.

Neurologic events occurred in 63% of the patients, 31% of these were grade 3 or higher. 26% of all treated patients received tocilizumab and 38% received glucocorticoids.

Although patients reported an impairment of health-related quality of life 4 weeks after the CAR-T cell therapy within the ZUMA-2 trial, self-reported scores improved after 3 months and after 6 months some of the patients reported a better status than before CAR T cell therapy. We do also expect a benefit in health-related quality of life for the patients treated within the CARMAN study.

In the CARMAN study, patients will also be closely monitored for neurologic events and CRS by validated scores, e.g. the CRS Grading per Lee [42, 43]or the Immune Effector Cell-associated Encephalopathy Score (ICE score), see Appendix 6. Management of these toxicities include symptomatic therapy such as application of fluids, antipyretics and vasopressors as well as, if indicated, the application of tocilizumab or corticosteroids, see section 11.1.6.5 (Toxicity management).

In case of Ibrutinib-related adverse events, therapy will be held or the dose will be reduced according to section 11.3.4

Patients will be furthermore closely monitored for other observed toxicities during the whole therapy so early identification of currently unknown safety risks is ensured. These data will be discussed by an independent Data Safety Monitoring Committee to minimize the potential risk for all study participants.

The pivotal trial by Wang et al. [1] demonstrated a surprising efficacy in heavily pre-treated high risk MCL patients. We expect at least similar safety data as described in the ZUMA-2 trial with even better efficacy results since patients are not pre-treated and therefore, T-cell fitness is unimpaired. However, the potential benefit of an Ibrutinib pretreatment still needs to be evaluated.

Given the poor prognosis of high risk MCL (see above), the described promising efficacy of KTE-X19 in earlier trials with manageable toxicities and no reported therapy-emergent deaths portrays benefits that outweigh the potential risks. Ibrutinib is already approved for the treatment of relapsed MCL and is generally well tolerated with manageable side effects. The assumed additional efficacy of Ibrutinib in this high-risk cohort with poor overall survival outweighs its predictable risks.

6 Study Design

This study is a randomized controlled, international, multicenter, open-label phase II trial evaluating the safety and efficacy of KTE-X19 following an abbreviated induction and 6 months Ibrutinib maintenance (Arm A) as compared to standard of care induction and maintenance plus Ibrutinib (Arm B). The abbreviated induction phase consists of 2 cycles of Ibrutinib + Rituximab and 2 cycles of Ibrutinib + R-CHOP for primary tumor reduction. In case of good clinical response (PR or CR) after 2 cycles of Ibrutinib + Rituximab, Ibrutinib and R-CHOP can be omitted. In this case, one additional cycle of Ibrutinib + Rituximab will be applied.

7 Study Duration

The maximal duration of the study will be 7 years; with up to 2 years recruitment, 2.5 years of treatment (Arm B) and up to 2,5 years additional follow-up.

Per Subject:

- All subjects who enter the study will continue to be followed for at least 4.5 and up to 7 years for disease progression, subsequent treatment, and survival, so the maximal duration of study participation per individual patient will be 7 years

Long term FU will be performed outside this study in the EMCL registry (arm B) or separate follow up study (arm A).

8 Study Objectives and Endpoints

8.1 Primary Objective

The primary objective is to exploratively compare the efficacy of a CAR-T-cell treatment strategy with KTE- X19 in patients with previously untreated high risk mantle cell lymphoma (MCL) following experimental treatment (Arm A) as compared with standard of care (Arm B).

8.2 Primary Endpoint

The primary endpoint is the probability of failure-free survival from randomization. Events of interest are any discontinuation of the per protocol treatment due to stable or progressive disease during induction, stable disease at the end of induction, progressive disease at any time after end of induction treatment and death from any cause.

8.3 Secondary Objectives

Secondary objectives are to evaluate the efficacy, safety, tolerability, and quality of life (QoL) associated with a CAR-T-cell treatment strategy in terms of additional efficacy endpoints including molecular remission after induction and during maintenance in both arms.

8.4 Secondary Endpoints

- Progression-free survival from randomization
- Complete remission rate (CR) and overall response rate (ORR: CR, PR) 6 months from randomization (after completion of CAR-T-treatment or HDT, respectively)
- Rate of PET negative CR (complete metabolic response rate, Lugano criteria) 6 months from randomization
- Progression-free survival in responders 6 months from end of cytoreductive treatment
- Best response during 2 years from randomization
- Time to best response, time to first response from randomization
- Overall survival (OS) from randomization
- Safety: adverse events, serious adverse events, toxicities (CTC AE)

8.5 Exploratory endpoints

- Molecular remission rate 6 months from randomization and during follow-up
- Mutation profile at baseline and at relapse Immunophenotype at relapse (e.g. CD19 expression)
- Quality of life: physical functioning (assessed with the EORTC QLQ-C30), physical condition/fatigue (assessed with the EORTC QLQ-NHL-HG29)
- Hematotoxicity associated with the CAR T cell therapy
- Diversity and composition of the microbiome (asservation of stool samples)

9 Participating study sites

Approximately 40 sites in Europe will participate in the study.

Therapy with KTE-X19 imposes special logistical and organizational requirements on the treatment facilities.

All study sites must be approved for the application of CAR-T cells in accordance with local laws and regulations (e.g. for Germany: "Decision on Measures for Quality Assurance of CAR-T Cells in B-Cell Neoplasms according to Section 136a Paragraph 5 of the Fifth Book of the German Social Code (SGB V)" or France: requirements of the order of May19, 2021 on CAR-T-cell use according to the provisions of Article L. 1151-1 of the Public Health Code).

Only sites already been qualified by the manufacturer Kite Gilead for apheresis and application of Kite CAR T-cell preparations and thus comply with the above-mentioned regulations will be approved for this study.

10 Study Population and Selection Criteria

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

Eligible patients are between 18-75 years old, diagnosed with high risk MCL with need for systemic treatment (see section 10.3 for inclusion criteria).

A multidisciplinary tumor board decision-making process promotes greater diagnostic accuracy, tailors treatment plans to individual patient needs, and may improves overall patient outcomes by leveraging different perspectives and expertise. We recommend that all patients are discussed in an multidisciplinary board before starting the consenting process with the individual patient. For patients in France, a tumor board decision is a prerequisite for patient inclusion in the study due to a requirement of the competent authority.

10.1 Number of Subjects

A total number of 150 patients will be enrolled (approx. 75 in each arm).

10.2 Gender Distribution

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

in terms of efficacy and safety. It is expected that a male predominance will be observed, in line with the higher incidence of MCL in men.

10.3 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Histologically confirmed diagnosis of MCL according to WHO classification, with documentation of either overexpression of cyclin D1 or presence of t(11;14)
2. At least one High Risk MCL – feature as defined as
   I. MIPI-c high intermediate (HI) or high (H) risk (i.e. high risk MIPI irrespective of Ki-67 or intermediate risk MIPI and Ki-67>=30% (Ki-67 based on local pathology)

   and/or

   II. TP53-mutation and/or TP53-overexpression by immunohistochemistry (> 50% of lymphoma cells)
3. No prior treatment for MCL
4. Stage II-IV (Ann Arbor) (Appendix 2)
5. 18-75 years
6. At least 1 measurable lesion according to the Lugano Response Criteria (>1.5 cm nodal lesion or > 1cm extranodal lesion); in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations.
7. ECOG performance status ≤ 2
8. The following laboratory values at screening (unless discrepancies are related to MCL):
   I. Absolute neutrophil count (ANC) ≥ 1000 cells/µL
   II. Platelets ≥75,000 cells/µL
   III. Creatinine <2 mg/dL or calculated creatinine clearance ≥60 mL/min
   IV. Transaminases (AST and ALT) < 2.5 x ULN
   V. Total bilirubin <= 2 x ULN unless other reason known (e.g. Gilbert-Meulengracht-Syndrome, or due to lymphoma involvement)
9. No evidence of CNS-disease
10. Written informed consent form according to ICH/EU GCP and national regulations, ability to follow study instructions and likely to attend and complete all required visits
11. Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods (combined oral contraceptives using two hormones, contraceptive implants, injectables, intrauterine devices, sterilized partner) together with one of the barrier methods (latex condoms, diaphragms, contraceptive

caps) while on study; this should be maintained for 6 months after the last dose of KTE-X19 or for 3 months after last dose of Ibrutinib, whichever is longer

12. Negative serum or urine pregnancy test (Females of childbearing potential only, Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential)
13. Willingness not to drive a motor vehicle for 8 weeks post CAR T cell treatment
14. Possibility to reach the site within 2 hours in case of toxicity / emergency

10.4 Exclusion Criteria

Subjects presenting with any of the following exclusion criteria may not be included in the study:

1. Subjects not able to give consent
2. Subjects without legal capacity, unable to understand the nature, scope, significance and consequences of this clinical study
3. Known history of hypersensitivity to the investigational drug, to drugs with a similar chemical structure or to aminoglycosides
4. Simultaneously active participation in another clinical study involving an investigational medicinal product within 30 days prior to enrollment. Patients included in follow up periods of other clinical trials without ongoing trial medication are allowed.
5. Subjects with a physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the study results, or may interfere with the subject's participation in this clinical study
6. Known or persistent abuse of medication, drugs or alcohol
7. Serious concomitant disease interfering with a regular therapy according to the study protocol:
    I. Clinically significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, higher grade AV-block, unstable angina, myocardial infarction, cardiac angioplasty or stenting within 12 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below 50%
    II. Baseline oxygen saturation ≤ 92% on room air
    III. Clinical significant pleural effusion (if not lymphoma related)
    IV. Endocrinological (severe, not sufficiently controlled diabetes mellitus)
8. Current or planned pregnancy or nursing women. History of or active malignancy other than MCL, non-melanoma skin cancer, carcinoma in situ (eg, cervix, bladder, breast) or prostate cancer unless disease-free for at least 3 years (and PSA within normal range in case of prostate cancer).
9. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.

10. Positive test results for chronic HBV infection (defined as positive HBsAg serology) (mandatory testing)
    Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable
11. Positive test results for hepatitis C (mandatory hepatitis C virus [HCV] antibody serology testing).
    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
12. Patients with known HIV infection (mandatory test)
13. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement
14. History of or active autoimmune disease (e.g. Crohn's disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression / systemic medication within the last 2 years
15. History of deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months of enrolment
16. Known severe primary immunodeficiency
17. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
18. Live vaccine ≤ 6 weeks prior to planned start of study treatment
19. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule

10.5 Prohibitions and restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

- Because delayed toxicities may occur in rare cases after CAR T-cell therapy, the management of which requires experience in handling CAR T-cell specific side effects, subjects must be able to reach the study site within 2 hours during a 30-day period after CAR T-cell therapy.
- Because CAR T-cell therapy can very rarely cause delayed neurotoxicity, including seizures, patients must agree not to drive a motor vehicle within 8 weeks of CAR T-cell therapy.

Prohibited medications and precautions with concomitant medications are detailed in section 11.4.2 respectively.

10.6 Subject Information, Recruitment and Randomization

If a subject appears to be eligible for the study, the investigator will inform the subject about the study and ask the subject for his/her written consent (see section 23.8 for further information).

It is a requirement that written consent is obtained prior to any study-specific procedures. The informed consent process has to be recorded into the patients' file by the investigator with date, time and signature.

After verification of eligibility, patient registration and randomization will be performed via the EDC system. Registration is only accepted from authorised investigators and must be done before the start of any treatment. Randomization will ensure equal probability for assignment to the two treatment arms (1:1 randomization). Randomization will be stratified according to country and MIPI risk group (high risk vs. intermediate/low risk). Stratification is implemented to reduce confounding by unequal proportions of potentially prognostic variables in the two treatment groups. In our data from the European MCL Younger/Elderly trials, MIPI high vs. low/intermediate risk still had an influence on FFS and OS within the high-risk biology MCL subgroup. A stratification by Ki-67 or p53 will not be implemented as no clear prognostic value of these variables within the high-risk biology MCL subgroup was observed in our data.

11 Study Treatment

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

Each subject will proceed through the following study periods:

1. Screening
2. Registration
3. Randomization
4. Treatment
    I. **Arm A:** Abbreviated induction phase: 2 cycles of Rituximab and Ibrutinib (IR), Leukapheresis, 2 cycles IR-CHOP (in case of good clinical response (CR/PR), R-CHOP can be omitted and instead one additional cycle of IR can be applied), lymphodepleting therapy, CAR T cell application, 6 months Ibrutinib maintenance

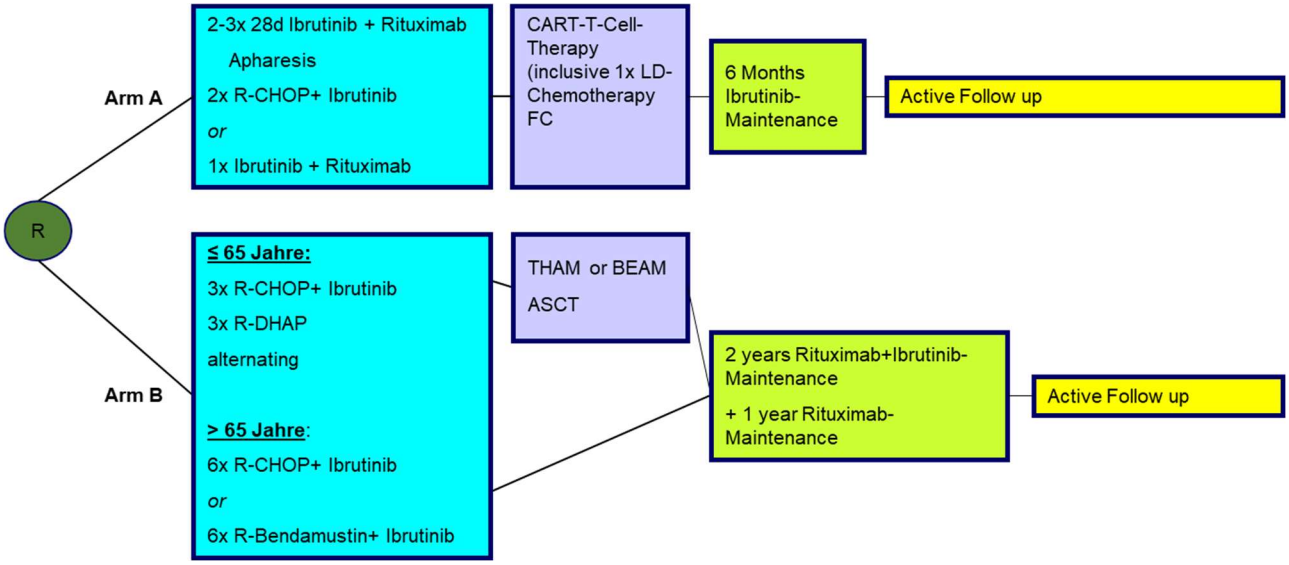
    OR

    II. **Arm B:** 3 cycles of IR-CHOP / R-DHAP followed by high-dose therapy with BEAM or THAM and ASCT; **for elderly patients:** 6 cycles of BR-I or IR-CHOP without ASCT; followed independent of age by 2 years Ibrutinib maintenance
5. Active Follow Up
6. Long Term Follow Up (outside of study protocol within the eMCL registry (arm B, strongly recommended) or separate follow up study (arm A).

All treatments will be given open-label because it is not feasible to apply all treatment components (Ibrutinib, immunochemotherapy, CAR-T-cells, ASCT, Rituximab maintenance) in a blinded way.

Treatments with R-CHOP, R-DHAP and BR are considered standard of care in MCL patients and will be administered according to the standard preparation and infusion procedures of each investigational site.

The apheresis of a stem cell backup is not part of this trial but allowed if it is required according to local standards.



11.1 Arm A: Experimental Arm

IR (Cycle 1+2 ; cycle of 28 days):		
Rituximab	375 mg/m²	i.v. D0 or D1
Ibrutinib	560 mg	orally D1-28
Leukapheresis	14 days after cycle 2 of IR (see 11.1.3)	
R-CHOP + Ibrutinib (Cycle 3+4; cycle of 21 days):		
Rituximab	375mg/m²	i.v. D0 or D1
Cyclophosphamide	750 mg/m²	D1 i.v.
Vincristine	1.4 mg/m²	D1 i.v.
Doxorubicine	50 mg/m²	D1 i.v.
Predniso(lo)ne	100 mg/d	D1-5 i.v.
Ibrutinib	560 mg/d	D1-21 oral
in case of PR or CR after 2 IR cycles:		
IR (Cycle 3); cycle of 28 days)		
Rituximab	375 mg/m²	i.v. D0 or D1
Ibrutinib	560 mg/d	orally for 28 days

Conditioning chemotherapy	within 14 days after reconstitution after cycle 4 or 3 (Ibrutinib monotherapy in responders), respectively (see 11.1.4) in responding patients
CAR T cell infusion	D0
Maintenance therapy	for six 28-day-cycles starting approximately 12 weeks post CAR T cell infusion
Ibrutinib	560mg orally for 6 months

11.1.1 Rituximab + Ibrutinib (Cycles 1+2 and 3 [in case of PR/CR after 2 cycles])

Rituximab will be applied according to local standards. Refer to specific product information and package inserts for premedication, preparation, administration and storage guidelines.

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

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

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

11.1.2 R-CHOP+I (cylces 3+4 in case of SD or PD after 2 cycles of Ibrutinib+Rituximab)

R-CHOP will be applied according to local standards. Refer to specific product information and package inserts for premedication, preparation, administration and storage guidelines.

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

Rituximab will be given at a dose of 375 mg/m2 on the first day of CHOP or BR+I or delayed until the circulating number of lymphoma cells is < 100 x 109/L, to avoid CRS (more frequently observed in leukemic lymphoma). That criterion has to be reconsidered before each consecutive course.

For the use of Ibrutinib refer to section 11.1.1.

11.1.3 Leukapheresis for CAR T cell therapy

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [WBCs]) for the manufacturing of KTE-X19 only when the diagnosis has been confirmed via central histopathological review. Mononuclear cells will be obtained by leukapheresis (12 to 15 liter apheresis with a goal to target approximately 5 to 10 x 10^9 mononuclear cells).

The leukapheresed cells obtained at participating centers are then packaged for expedited shipment to the CPF as described in the Investigational Product Manual.

Upon arrival at the CPF, each subjects' leukapheresed product will be processed to enrich for the T cell containing peripheral blood mononuclear cell (PBMC) fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the IP per CPF standard operating procedures (SOPs). After the product has passed all required analysis, it will be shipped back to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective KTE-X19.

In rare cases, the manufactured CAR-T cell product does not meet the specifications for KTE-X19 as stated in the IB. In this case, production is considered to have failed and no out-of-specification KTE-X19 is supplied, as an effective alternative is available within the standard arm. For procedure in case of KTE-X19 production failure see section 11.5.

11.1.4 Conditioning Chemotherapy (lymphodepleting chemotherapy = LD)

Administration of conditioning lymphodepleting chemotherapy is likely to have a correlation with clinical responses to adoptive cell therapy [44]. Specifically, there appears to be a link between adequate lymphodepletion and adoptively-transferred T-cell expansion and function. The depth and duration of the lymphodepletion in pre-clinical models correlate with the anti-tumor activity of the adoptively-transferred, tumor-specific CD8+ T cells [45]. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating regulatory T- cells, or enhancing the activation of antigen-presenting cells [46]. Combined treatment with cyclophosphamide and fludarabine represents a potent lymphodepleting regimen. The ZUMA-1 trial of axicabtagene ciloulecel in aggressive large B-cell lymphoma used the same cyclophosphamide/fludarabine conditioning regimen that has been used in the ZUMA-2 trial [29, 30], resulting in in a favorable risk-benefit profile. Similar doses of cyclophosphamide and fludarabine have been administered to subjects with B-cell malignancies prior to anti-CD19 CAR T cell infusion (NCI Protocol 09-C-0082) and were shown to increase levels of cytokines known to support T-cell expansion and survival [47].

Subjects will receive LD chemotherapy consisting of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day, administered on D-5 to D-3 to create an optimal environment for expansion of anti-CD19 CAR T cells in vivo. KTE-X19 infusion will be applied at D0.

LD chemotherapy should only commence when the KTE-X19 product is available.

<u>Conditioning (LD chemotherapy)</u>		
Fludarabine	30 mg/m2	D -5 to D -3 I.V. over approx. 30 min
Cyclophosphamide	500 mg/ m2	D -5 to D -3 I.V. over approx. 60 min
<u>KTE-X19 infusion on D 0</u>		

11.1.4.1 Requirements for the start of conditioning therapy (LD chemotherapy)

- Availability of the CAR T cell product
- No suspected or active systemic infection
- No fever ≥ 38°C that is unrelated to the underlying disease
- No signs of progressive disease
- No need of oxygen
- No cardiac arrhythmias that cannot be controlled by medical treatment
- No hypotension requiring vasopressor support
- No CTCAE grade 2 or higher neurotoxicity No CTC Grade 3 or higher organ toxicity (other than hematologic toxicity)
- No use of any of the prohibited drugs described in section 11.4.2
- Negative PCR test for SARS-CoV-2 (see 11.1.6.4)
-

Sites should refer to the current product label for guidance on packaging, storage, preparation, administration and toxicity management associated with the administration of both agents.

The application of the conditioning chemotherapy is considered standard of care for CAR-T-cell treatment and should be given according to local practice.

11.1.5 Dose adjustments of LD chemotherapy (conditioning)

Administration of conditioning lymphodepleting chemotherapy correlates with clinical responses to CAR-T-cell treatment. Prior to initiation of LD chemotherapy, the patients' requirements for CAR-T cell administration must have been confirmed. Dose reductions should be done according to the local institutional guidelines for lymphodepletion prior to CAR-T-cell-therapy.

11.1.6 Application of KTE-X19

Please refer to section 12 for IMP details.

All subjects will be hospitalized to receive treatment with KTE-X19 followed by an inpatient observation period of at least 10 days unless otherwise required by country regulatory agencies. Subjects should not be discharged from the hospital until all anti-CD19 CAR T cells-related non-hematological toxicities return to Grade ≤ 2 or return to baseline. Subjects should remain hospitalized for ongoing anti-CD19 CAR T cells-related CRS or ongoing central neurological toxicity > Grade 1, or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurologic events in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the principal investigator or seek immediate medical attention. It is strongly recommended that patients stay near the treatment center for at least 4 weeks after infusion and it is mandatory that they do not drive a motor vehicle for 8 weeks.

11.1.6.1 Requirements for the start of KTE-X19 infusion

- No suspected or active systemic infection
- No fever ≥ 38°C that is unrelated to the underlying disease
- No need of oxygen
- No cardiac arrhythmias that cannot be controlled by medical treatment
- No hypotension requiring medical intervention
- No CTCAE grade 2 or higher neurotoxicity
- No unresolved serious adverse events from earlier treatment
- No CTCAE Grade 3 or higher organ toxicity (other than hematologic toxicity)
- No use of any of the prohibited drugs described in Section 11.4.2
- Negative PCR test for SARS-CoV-2 (see 11.1.6.4)

Application of premedication before anti-CD19 CAR T cells infusion should be administered according to local standards.

11.1.6.2 Preparation for infusion:

- **Tocilizumab and emergency equipment must be available prior to infusion and during follow-up.**
- Verify that the identity (ID) of the patient matches the patient identifiers on the product metal cassette.
- The KTE-X19 infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Remove the infusion bag from the metal cassette after the patient ID has been confirmed.
- Make sure that the patient information on the label of the metal cassette matches that on the label of the bag.
- Inspect the infusion bag for integrity before thawing. If the bag is damaged, comply with local regulations for handling waste materials of human origin and contact the sponsor.
- Place the infusion bag in a second bag.
- Thaw KTE-X19 at approximately 37 °C using a water bath or dry thaw method until no ice is visible in the infusion bag.
- Gently mix the bag contents to break up clumps of cellular material. If clumps of cellular material continue to be visible, continue to gently mix the bag contents. Small clumps of cellular material should dissolve with careful manual mixing.
- KTE-X19 should not be washed, centrifuged and/or resuspended in new medium prior to infusion. Thawing should take approximately 3 to 5 minutes.
- After thawing, KTE-X19 is stable for up to 3 hours at room temperature (20 °C - 25 °C). However, KTE-X19 infusion should start within 30 minutes after complete thawing.

11.1.6.3 Administration of KTE-X19

- For autologous single use only.
- A leukocyte-depleting filter must not be used.
- Central venous access is recommended for administration.

- Re-verify the patient ID to match the patient identifiers on the KTE- X19 bag.
- Flush the tubing with sodium chloride injection solution 9 mg/ml (0.9%) (0.154 mmol sodium per ml) prior to infusion.
- Infuse the entire contents of the KTE-X19 bag within 30 minutes.
- Gently shake the bag during infusion to avoid clumping of cells.
- After the entire contents of the bag have been infused, flush the tubing with the same infusion rate of sodium chloride injection solution 9 mg/ml (0.9%) (0.154 mmol sodium per ml) to ensure that the entire dose has been administered

11.1.6.4 Special precautions for handling KTE-X19

Participating treatment centers must be qualified to administer Kite Gilead CAR-T cells.

KTE-X19 must be administered only by personnel trained for this purpose and experienced in the management of patients treated with CAR-T cells. At least 1 dose of tocilizumab must be available for use prior to infusion, as well as emergency equipment in case of cytokine release syndrome (CRS).

The qualified treatment center must have access to another dose of tocilizumab within 8 hours of each previous dose.

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling KTE-X19 must take appropriate precautions following local standards to avoid potential transmission of infectious diseases.

KTE-X19 is a subject-specific product, and the intended subject will be identified by a unique subject ID number and year of birth (YOB). Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, YOB, subject ID number) is essential. **Do not infuse the product if the information on the subject-specific label does not match the intended subject.** The volume of KTE-X19 infused, the thaw start/stop time, and KTE-X19 administration start/stop time will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion. Refer to the Investigational Product Manual for details and instruction on storage, thawing, and administration of KTE-X19.

KTE-X19 treatment and SARS-CoV-2 infections

The pronounced B-cell aplasia and persistent hypogammaglobulinemia predisposes CAR T-cell treated patients to complication-prone courses after infection with the SARS-CoV-2 virus. All patients must be tested with PCR before treatment. Generally, KTE-X19 treatment is not allowed if the PCR test is positive. In case of positive PCR tests after a successful recovery after a SARS-CoV-2 infection the sponsor's medical advisor must be consulted.

As members of the high-risk group, patients should be asked to consistently adhere to the appropriate hygiene measures (such as proper masking, hand hygiene, social distancing). Depending on the overall condition and the situation at home, vaccination of the family carer should be considered (no trial procedure!). According to the current status, patients should be vaccinated after CAR T-cell therapy from month 3. No data are available on the likelihood of vaccine response. It is possible that COVID-19 vaccination does not lead to a protective immune response in the patient.

In the case of a new SARS-CoV-2 vaccination before the start of therapy, sufficient distance to lymphodepletion (6 weeks before the start of lymphodepletion) should be ensured in order to guarantee the maximum possible vaccination protection and to avoid interactions.

In case of SARS-CoV2 infections the treating physicians should be aware that patients may stay asymptomatic or show minimal symptoms for some time before deteriorating. SARS-CoV-2 treatment should be performed according to local standards for treatment of high risk SARS-CoV-2 patients (e.g. antiviral medication early after diagnosis of SARS-CoV2 infections).

11.1.6.5 Toxicity Management

To date, the following important risks have been identified with KTE-X19: CRS, neurologic toxicity, infections, cytopenias and hypogammaglobulinemia. Refer to section 11.1.6.5.1 for CRS management and to section 11.1.6.5.2 for neurotoxicity management. Infections and hypogammaglobulinemia are to be treated according to local standards.

As the safety experience with KTE-X19 increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the KTE-X19 IB for guidance regarding managing KTE-X19 related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with KTE-X19.

11.1.6.5.1 Cytokine Release Syndrome (CRS)

The underlying cause of CRS is the activation of T cells. These cells secrete proinflammatory cytokines such as IL-6, TNFα and IFNγ. This also results in stimulation of bystander cells such as dendritic cells and monocytes/macrophages, which in turn secrete cytokines such as IL-6 and IL-1 in large quantities. Thus, as a result of the therapeutically intended T-cell activation, an immunological cascade is initiated, which clinically manifests itself in the form of CRS.

After infusion of CAR T cells, CRS usually occurs with a delay (median after 3 days for anti-CD19 CAR T cells in refractory/relapsed DLBCL). In individual cases, however, it may occur weeks after infusion. CRS symptoms are based on a T cell expansion in vivo, which usually does not occur immediately after infusion, but with a time lag.

The main characteristic and often the first symptom of CRS is fever. In addition, CRS is usually accompanied by a number of general symptoms (shivering, bone and joint pain, general feeling of illness) and may lead to life-threatening complications up to multi organ failure, DIC and shock. Therefore, the IL-6 antibody tocilizumab must be available before infusion of the IMP (see section 11.4.1 for dosing).

CRS cannot be distinguished from sepsis clinically or by laboratory assessment, which is why blood cultures and anti-infective therapy (following local standards) is usually indicated.

Monitoring of heart rate, RR, O2 saturation every eight hours, temperature every four hours and neurological checks every twelve hours is required. Assessment of the CRS - severity must be performed accordingly and documented in the patients file, see Appendix 4 for the grading.

Refer to section 6.5 of the current IB for details regarding management guidance for CRS. A shortened version of the guidelines can be found at Appendix 5 of this protocol.

11.1.6.5.2 Neurotoxicity (ICANS)

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) is the most common side effect of CAR T cell therapy after CRS. ICANS can occur in combination with CRS or after CAR T cell therapy independent of CRS up to four weeks after cell transfusion. The exact pathophysiology of ICANS remains unclear. It is postulated that mechanisms leading to an increase in the permeability of the blood-brain barrier play a role. This allows passive diffusion of cytokines into brain tissue and, secondarily, chemokine-mediated migration of infused CAR T cells or myeloid cells into the CNS. Furthermore, additional infections, liver and kidney dysfunction can trigger encephalopathy [48].

Neurotoxicity can occur early, usually in association with CRS within the first days after CAR T cell transfusion, and less frequently later, about two to four weeks after CAR T cell transfusion. Both forms may be severe and may be associated with a rapid, even life- threatening deterioration of the patients' general condition. Symptoms are initially discrete, e.g.: attention deficit, change in personality, changes in writing, speech disorders, coordination disorders and can progress to status epilepticus with cerebral edema and lethal course. In 2018, the American Society for Transplantation and Cellular Therapy (ASTCT) published a grading system for ICANS [42]. ICANS will be assessed by the ASTCT grading, as shown in Appendix 6 (using immune effector cell-associated encephalopathy scores as determined by Appendix 7). However, neurotoxicity management will only be based on the Common Terminology Criteria for Adverse Events (CTCAE) grading as described in section 11.1.6.5.2 or in the current Investigator's Brochure (IB).

<u>The following extended diagnostic measures are recommended when there is evidence for ICANS:</u>

- Brain MRI
- Neurological consultation
- EEG
- Examination of cerebrospinal fluid (CSF)

Refer to section 6.5 of the current IB for details regarding management guidance for neurological events. A shortened version of the guidelines can be found at Appendix 8 of this protocol.

11.1.7 Ibrutinib Maintenance

Patients randomized to Arm A will receive additional oral Ibrutinib 560 mg (4x 140mg capsules) daily maintenance for 6 months in case of CR or PR at EoI evaluation.

For details of Ibrutinib application and dose adjustments refer to 11.1.1 and 11.3.4.

Ibrutinib maintenance will start after regeneration of peripheral blood count after treatment with KTE-X19.

Requirements for start of Maintenance:

- ANC ≥ 1,000 cells/mm³ (1.0 X 109/L);
- Platelets ≥ 50,000 cells/mm³ (50 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity

- Any other AE related to induction treatment or treatment with KTE-19 not requiring discontinuation has resolved to Grade ≤ 2 severity.

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

11.2 Arm B: Standard of care treatment

11.2.1 For patients ≤ 65 years

11.2.1.1 IR-CHOP/R-DHAP

Alternating 3 cycles IR-CHOP / 3 cycles R-DHAP induction followed by ASCT (THAM or BEAM):

IR-CHOP: (Cycle 1,3,5; cycle of 21 days)

Rituximab	375mg/m²	D0 or D1 i.v.
Cyclophosphamide	750mg/m²	D1 i.v.
Vincristine	1.4mg/m²	D1 i.v.
Doxorubicine	50mg/m²	D1 i.v.
Predniso(lo)ne	100mg/d	D1-5 i.v.
Ibrutinib	560mg/d	D1-19 oral

R-DHAP (Cycle 2,4,6; cycle of 21 days)

Rituximab	375mg/m²	D0 or D1 i.v.
Dexamethasone	40mg	D1-4 oral or i.v.
Cytarabine	2000mg/m²	D2 twice daily over 3h
Cisplatin	100mg/m²	D1 continously for 24h
(alternatively Oxaliplatin	130mg/m²	D1 i.v.)
G-CSF	5µg/kg	D6 daily SC[#]

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

Stem cell apheresis will be performed after the second or third cycle R-DHAP according to local standards.

ASCT conditioning: THAM or BEAM, stratified per site before trial activation at site.

THAM:

TBI 10 Gy	D –7 to –5
Ara-C 2x 1,5 g/m2 q12h	D –4, –3 IV 30 min
Melphalan 140 mg/m2	D –2 IV 1h

OR

BEAM:

BCNU 300 mg/m2	D –7,IV 1h

Etoposide 2x 100 mg/m2 q12h	D –6 to –3 IV 1 h
Cytarabine 2x 200 mg/m2 q12h	D –6 to –3 IV 30 min
Melphalan 140 mg/m2	D –2 IV 1h

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

Ibrutinib maintenance (560mg/d) will be administered for 2 years after ASCT.

Rituximab maintenance may be added for 3 years after ASCT depending on national guidelines.

G-CSF administration according to local standards.

R-CHOP / R-DHAP will be applied according to local standards.

Refer to specific product information and package inserts for premedication, preparation, administration and storage guidelines.

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

Rituximab will be given at a dose of 375 mg/m2 on the first day of or the day before CHOP or DHAP or delayed until the circulating number of lymphoma cells is < 100 x 109/L, to avoid CRS (more frequently observed in leukemic lymphoma). That criterion has to be reconsidered before each consecutive course.

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

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

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

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

11.2.1.2 Stem cell mobilization and harvest (Arm B, patients < 65 years)

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

Stem cell separation will be performed after achievement of a WBC count > 1 x 109/l following the WBC nadir (minimal 2 x 10^6/kg body weight CD34+ cells for each transplantation and optional "back-up". Whether a backup dose is collected depends on local standards). Separation and asservation will be done according to the accepted local practice at the participating institution.

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

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

11.2.1.3 ASCT conditioning (Arm B, patients < 65 years)

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

THAM

The myeloablative radioimmunochemotherapy and peripheral stem cell transplantation should follow the end of induction visit within 4 weeks.

This procedure depends on the following requirements:

- continuous complete or partial remission
- number of stored CD34+ cells > 2x 10^6/kg body weight for transplantation
- no medical contraindications to myeloablative radioimmunochemotherapy

The myeloablative treatment consists of a combined radiochemotherapy with fractionated total body irradiation with a total of 10 Gray (d-7 d-6, d-5), Ara-C 1,5 g/m2, q12h (d-4 and d–3), and Melphalan 140 mg/m2 (d-2). The total body irradiation (TBI) will be applied according to local institutional guidelines.

The peripheral stem cells will be retransfused on day 0 (2 days after Melphalan) and should contain at least 2,0 x 106/kg body weight CD34+ positive cells. The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 109/l is recommended, but not mandatory.

BEAM

The myeloablative chemotherapy and peripheral stem cell transplantation should follow the end of induction visit within 2 weeks. This procedure depends on the following requirements:

- continuous complete or partial remission
- number of stored CD34+ cells > 2 - 4x 106/kg body weight for transplantation and "back-up"
- no medical contraindications to myeloablative chemotherapy

The myeloablative treatment consists of a combined chemotherapy with Carmustine 300 mg/m2 (d-7), Cytarabine 200 mg/m2, q12h (d-6 to d–3), Etoposide 100mg/m2, q12h (d-6 to d-3) and Melphalan 140 mg/m2 (d-2).

The peripheral stem cells will be retransfused on day 0 (2 days after Melphalan) and should contain at least 2,0 x 106/kg body weight CD34+ positive cells. The subsequent administration of G-CSF at a dose of 5 µg/kg body weight until a peripheral granulocyte count 2 x 109/l is recommended, but not mandatory.

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

11.2.1.4 Ibrutinib Maintenance

Patients randomized to Arm B will receive additional oral Ibrutinib 560 mg (4x 140mg capsules) daily maintenance for 2 years in case of CR or PR at EoI-assessment.

For details of Ibrutinib application refer to 11.2.1.1.

Ibrutinib maintenance will start after regeneration of peripheral blood count after ASCT, respectively.

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

Requirements for start of Maintenance:

- ANC ≥ 1,000 cells/mm³ (1.0 X 109/L);
- Platelets ≥ 50,000 cells/mm³ (50 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related to induction treatment or ASCT not requiring discontinuation has resolved to Grade ≤ 2 severity.

11.2.1.5 Rituximab Maintenance

Rituximab maintenance is not under investigation in this trial but is allowed for patients randomized to Arm B after Induction and ASCT in case of CR or PR at ASCT or EoI-evaluation according to national guidelines.

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

11.2.2 For patients > 65 years

11.2.2.1 IR-CHOP / BR+I

Investigators' choice: 6 cycles IR-CHOP or BR+I without ASCT

IR-CHOP (Cycle 1-6; cycle of 21 days):		
Rituximab	375mg/m²	D0 or D1 i.v.
Cyclophosphamide	750mg/m²	D1 i.v.
Vincristine	1.4mg/m²	D1 i.v.
Doxorubicine	50mg/m²	D1 i.v.
Prednisone	100mg/d	D1-5 orally
Ibrutinib	560mg/d	D1-21 orally
OR		
BR-I (Cycle 1-6; cycle of 28 days):		
Bendamustine	90mg/m²	D1 and D2 i.v.
Rituximab	375mg/m²	D0 or D1 i.v.
Ibrutinib	560mg/d	D1-28 orally
G-CSF support is not mandatory but allowed as of investigators discretion		
Ibrutinib maintenance (560mg/d) will be administered for 2 years after ASCT.		
Rituximab maintenance may be added for 3 years depending on national guidelines.		

R-CHOP or BR will be applied according to local standards.

Refer to specific product information and package inserts for premedication, preparation, administration and storage guidelines.

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

Rituximab will be given at a dose of 375 mg/m2 on the first day of CHOP or BR+I or delayed until the circulating number of lymphoma cells is < 100 x 109/L, to avoid CRS (more frequently observed in leukemic lymphoma). That criterion has to be reconsidered before each consecutive course.

For details about Ibrutinib treatment refer to 11.1.1 and 11.3.4

11.2.2.2 Ibrutinib Maintenance

Patients randomized to Arm B will receive additional oral Ibrutinib 560 mg (4x 140mg capsules) daily maintenance for 2 years in case of CR or PR at EoI-assessment.

For details of Ibrutinib application refer to 11.1.1 and 11.3.4.

Ibrutinib maintenance will start after regeneration of peripheral blood count after the end of the last cycle of induction therapy respectively.

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

Requirements for start of Maintenance:

- ANC ≥ 1,000 cells/mm³ (1.0 X 109/L);
- Platelets ≥ 50,000 cells/mm³ (50 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related to induction treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.

11.2.2.3 Rituximab Maintenance

Rituximab maintenance is not under investigation in this trial but is allowed for patients randomized to Arm B after Induction and ASCT in case of CR or PR at ASCT or EoI-evaluation according to national guidelines.

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

11.3 Dose adjustments

No dose modification will be made in the first course.

11.3.1 R-CHOP (Arm A and Arm B)+ I / R-DHAP (Arm B)

Requirements for therapy resumption:

- ANC ≥ 1000 cells/mm³ (1.0 X 109/L) – except related to MCL
- Platelets ≥ 75,000 cells/mm³ (75 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related to induction treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.

Recommendations for postponing or stopping treatment or dose reduction

- If ANC < 1.0 x 109/l or thrombocytes < 75 x 109/l at the day of the next course (d22 or d21 if Rituximab is applied at d0) it is strongly recommended to postpone treatment (including Ibrutinib) for 1 week.
- If an insufficient hematologic recovery after one week delay (d29) remains, it is strongly recommended to postpone treatment until the requirements for therapy resumption outlined above are fulfilled. Then a two-step-approach of dose modifications is recommended:

- In a first step reduce the next R-DHAP regimen according to the rules outlined below (depending on d29 blood levels)
- In a second step, dose modifications of the next R-CHOP (depending on d29 blood levels) are recommended according to the rules outlined in 11.3.3.

- In the event of insufficient blood level recovery or persistent AEs grade > 2 severity contact trial office or medical advisor to discuss permanently stop of study treatment
- In the event of severe treatment associated toxicity (CTC grade IV) in the last cycle but with complete recovery at d29 the investigator may reduce the next dosing of chemotherapy to 75% of Cyclophosphamide and Doxorubicin in case of CHOP or 75% of Cytarabine and Cisplatinum/Oxaliplatinum in case of DHAP.

Dose reduction strategy

Postpone treatment until ANC > 1000 cells/mm3 (1.0 x109/L) and platelets > 75.000 cells/mm3 (75.0 x109/L), then follow dose reduction recommendations

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

11.3.2 Dose modifictions of DHAP

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

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

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

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

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

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

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

11.3.3 Dose modifications of R-CHOP (with or without Ibrutinib)

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

ANC/µl on d29	Platelets/µl on d29	Cyclophos-phamide	Doxo-rubicin	Vincristine	Prednisone	Rituximab
>1.000/µl	>75.000/µl	100%	100%	100%	100%	100%
.500–1.000/µl	50.000-75.000/µl	75%	75%	100%	100%	100%
< 500/µl	< 50.000/µl	50%	50%	100%	100%	100%

Dose reduction of CHOP

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

11.3.4 Dose modifications of Ibrutinib

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

Ibrutinib-treatment should be interrupted for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Study drug may be interrupted for a maximum of 28

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

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

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

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

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

Resumption of Ibrutinib-dosing may begin if:

- The ANC is ≥ 1,000 cells/mm³ (1.0 X 109/L);
- The platelet count is ≥ 50,000 cells/mm³ (50 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.
- During induction therapy if R-CHOP is postponed due to toxicity, Ibrutinib has to be also postponed.
- If tolerated, for maintenance therapy Ibrutinib can be resumed at full dose even if it had to be reduced in induction therapy because of hematologic toxicity.

11.3.5 Bendamustine Hydrochloride

Bendamustine hydrochloride administration should be delayed in the event of Bendamustine-related ≥ Grad 3 hematologic toxicity or clinically significant Grade ≥ 2 non-hematologic toxicity.

Requirements for therapy resumption:

- ANC ≥ 1000 cells/mm³ (1.0 X 109/L) – except related to MCL
- Platelets ≥ 75,000 cells/mm³ (75 X 109/L);
- Rituximab or Ibrutinib related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity
- Any other AE related to induction treatment not requiring discontinuation has resolved to Grade ≤ 2 severity.

In addition, dose reduction may be warranted as follows:

Dose modifications for Grade 4 hematologic toxicity:

- reduce the dose to 70 mg/m2 on Day 1 and Day 2 of each cycle.
- If Grade 4 toxicity recurs, the dose may be reduced to 45 mg/m2 on Day 1 and Day 2 of each cycle.

Dose modifications for Grade ≥ 3 non-hematologic toxicity:

- reduce the dose to 70 mg/m2 on Day 1 and Day 2 of each cycle.
- If Grade 3 or greater toxicity recurs, the dose should be reduced to 45 mg/m2 on Day 1 and Day 2 of each cycle.

Bendamustine may be held for a maximum of 28 consecutive days; a hold >28 days must be reviewed and approved by the sponsor. Discontinue Bendamustine permanently if it cannot be restarted within 28 days due to toxicity. If Bendamustine is discontinued for toxicity, treatment with Rituximab and/or Ibrutinib may be continued. Dose re-escalation of Bendamustine hydrochloride is not permitted.

11.3.6 Dose adjustments of LD chemotherapy (conditioning)

See section 11.1.5.

11.4 Prior and Concomitant Therapy/Medication

11.4.1 Concomitant medication

Supportive therapy (e.g., antiemetics, antipyretics etc.) is usually necessary during the treatment of patients with complex chemotherapy protocols and should be applied in accordance with local guidelines and local practices, unless specifically prohibited in the "Prohibited therapy" section.

All concomitant therapy or medication needs to be documented in the subjects' medical record and in the appropriate eCRF from study registration until 60 days after the last study-specific therapeutic intervention.

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

Primary prophylaxis with granulocyte colony stimulating factors (G-CSFs) is obligatory during the R-DHAP cycles of induction and recommended after KTE-X19 (Arm A) and autologous stem cell transplantation (Arm B).

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

Tocilizumab

Tocilizumab is a humanized monoclonal antibody directed against the interleukin-6 (IL-6) receptor. It is approved for the treatment of CAR-T cell-induced severe CRS (≥°2).

The recommended dose for the treatment of CRS is **8 mg/kg**, administered as a 60-minute intravenous infusion. If there is no clinical improvement in the signs and symptoms of CRS after the first dose, up to 3 additional doses of Tocilizumab may be administered. The interval between successive doses must be at least 8 hours. Doses greater than 800 mg per infusion are not recommended in patients with CRS.

If there is no improvement within 24 hours, the severity level increases by 1 grade. Early use of catecholamines (if necessary also additional use of Terlipressin/Vasopressin) is recommended.

For details on Tocilizumab therapy, see the Tocilizumab SmPC and CRS treatment guidelines outlined in the KTE-X19 IB.

11.4.2 Prohibited therapy / Concomitant medication

Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19 related toxicities

Live vaccines are prohibited for a period of 6 weeks before study treatment until 90 days after the last dose of study treatment.

Treatment for MCL such as chemotherapy, immunotherapy, targeted agents, radiation, high dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after study treatment.

If permissibility of a specific medication/treatment is in question, contact the medical adviser of the sponsor team.

CYP3A4/5 Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4/5 (Section 2.1.3). Co-administration of Ibrutinib with strong CYP3A4/5 inducers (such as Carbamazepine and Rifampicine) can decrease Ibrutinib plasma concentrations and should be avoided. Since no exposure data are available in patients treated concomitantly with strong inhibitors of CYP3A4/5 (e.g., Ketoconazole, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Clarithromycin, Telithromycin, Itraconazole, and Nefazadone), these inhibitors should be avoided. If Ibrutinib must be administered with a strong inhibitor the national coordinating investigator should be consulted before use, and a dose reduction of Ibrutinib to 140 mg daily or a temporary hold of Ibrutinib should be considered. Patients should be monitored for signs of Ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, monitor patient for toxicity and follow dose modification guidance as needed.

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

QT Prolonging Agents

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

Other Drug Interactions

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

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

Bleeding risk

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. Warfarin or other vitamin K antagonists should not be administered concomitantly with Ibrutinib. Supplements, such as fish oil and vitamin E preparation should be avoided. Use Ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than Vitamin K antagonist) during the course of the study should have treatment with Ibrutinib held, the sponsor’s medical monitor should be contacted, and Ibrutinib should not be restarted until the subject is clinically stable and the re-initiation of Ibrutinib is approved by the sponsor’s medical

monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

11.5 Rescue/ Salvage Therapy / Treatment in case of KTE-X19 production failure

In case of progression of disease or stable disease after the first 2 cycles during induction therapy in Arm A, two additional cycles of R-CHOP + I will be administered. In case of progressive disease during induction therapy in Arm B, study treatment has to be stopped but patient remains in study for survival follow-up. In case of progressive disease (proven by CT scan) after induction therapy, study treatment has to be stopped but patient remains in study for survival follow-up. Any salvage therapy according to institutional standard can be used after stopping study treatment.

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

For younger patients with KTE-X19 manufacturing failure stem cell apheresis, consolidation with high dose chemotherapy and ASCT followed by Rituximab maintenance should be performed according to local standards.

Elderly patients with KTE-X19 manufacturing failure who are not qualifying for ASCT should be treated with R-CHOP or R-Bendamustin followed by Rituximab maintenance according to local standards.

Patients with a KTE-X19 product available who cannot be treated according to the CARMAN study protocol (due to PD before LD or toxicity) could be treated with the KTE-X19 product in routine clinical care according to the published label for TECARTUS®. In any case, the expiry date of KTE- X19 must not be exceeded.

12 Investigational Medicinal Product(s) (IMP)

In this trial KTE-X19 (brexucabtagene autoleucel) and Ibrutinib are considered as investigational medicinal products (IMP).

KTE-X19 (brexucabtagene autoleucel) consists of autologous T cells genetically modified ex vivo with a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a mouse anti-CD19 single-chain variable fragment (scFv) linked to the CD28 costimulatory domain and the CD3-zeta signaling domain.

KTE-X19 is manufactured for subjects with lymphomas that are characterized by having high numbers of CD19-expressing circulating tumor cells (B-cell acute lymphoblastic leukemia, CLL, and MCL). Briefly, from the leukapheresis product, the T cells in the harvested leukocytes are enriched by binding to magnetic beads coated with anti-CD4 and anti-CD8 antibodies. T cells are activated by culturing with anti-CD3 and anti-CD28 antibodies, and are then transduced with a retroviral vector containing an anti-CD19 CAR gene. These engineered T cells are then propagated in culture to generate a sufficient number of cells for administration.

This product contains 300 mg of sodium. Each dose contains 0.05 ml of dimethyl sulfoxide (DMSO) per ml of KTE-X19.

Refer to the current version of the IB regarding KTE-X19 and related clinical experience. Refer to the Investigational Product Manual for details and instruction on storage and administration of KTE-X19.

If any problems related to the use of KTE-X19 or any products that support the management of KTE-X19 (eg, cryostorage bags, subject identification labels) required in this study are identified, refer to the current Investigational Product Manual for information regarding issue reporting and resolution.

Ibrutinib is an oral Bruton's Tyrosine Kinase inhibitor (BTKi) which is approved for relapsed or refractory MCL. It is widely used also in other lymphatic neoplasia such as CLL.

Product	**Authorised**	**Used in accordance with the terms of their marketing authorisations**
KTE-X19	yes	No (approved for relapsed or refractory MCL after TKI use
Ibrutinib	yes	No (approved for relapsed or refractory MCL)

12.1 Packaging and Labelling of IMP

12.1.1 KTE-X19

KTE-X19 is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing KTE-X19 arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen, and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KTE-X19 is a subject-specific product, and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (e.g. initials, subject ID number) is essential.

If any problems related to the use of KTE-X19 or any products that support the management of KTE-X19 (e.g. cryostorage bags, subject identification labels) required in this study are identified, refer to the current Investigational Product Manual for information regarding issue reporting and resolution.

12.1.2 Ibrutinib

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

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

Each bottle contains 120 capsules of Ibrutinib.

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

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

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

12.2 Transport of IMP

12.2.1 KTE-X19

The transport of both the IMP (from the manufacturer to the treatment center) and the starting material (from the treatment center to the manufacturer) is organized and carried out by the manufacturer Kite Gilead.

For the organization of the transport logistics it is necessary that the IMP has to be ordered via Kite Clinical Platform Online System (KC) to schedule subject-specific IMP production.

The registration will be done pseudonymously with the patient ID after study registration during the first cycle of induction therapy.

The details regarding the apheresis date, the collection of the apheresate, the delivery date of KTE-X19 and the infusion date will be arranged with the manufacturer Kite Gilead and the sponsor electronically via email and by using the KC ordering portal.

For details see the Product Order Manual in the ISF.

12.2.2 Ibrutinib

The Sponsor will arrange the supply of IMP to investigational sites in a timely manner. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

12.3 Storage requirements

12.3.1 KTE-X19

KTE-X19 must be stored in the vapor phase of liquid nitrogen (≤ -150 °C) and must remain frozen until the patient is ready for treatment to ensure that viable, live autologous cells are available for administration to the patient.

The investigator bears the responsibility for the proper storage in a secure location at the site. Personnel who have access to the study drug need to be listed (name and responsibilities) on the Authorization and Delegation Log in the study specific Investigator Site File (ISF).

The investigator should ensure that the IMP is only used according to the protocol.

12.3.2 Ibrutinib

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

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

12.4 Dosage and Mode of Application

12.4.1 KTE-X19

This study is designed to evaluate safety and efficacy of a target anti-CD19 CAR T cell dose of 2 x 106 anti-CD19 CAR T cells/kg.

Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 ml for a target dose of 2 × 106 anti-CD19 CAR-positive viable T cells per kg body weight (range: 1 × 106 – 2 × 106 cells/kg), with a maximum of 2 × 108 anti-CD19 CAR-positive viable T cells for subjects ≥ 100 kg.

The recommended treatment regimen is based on the favorable safety and efficacy profile as seen in the ZUMA-1 trial, a Phase ½ multicenter study investigating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, which met its primary endpoint with an ORR of 82% and CR rate of 54% [29] and is further supported by the favorable safety and efficacy profile seen in subjects treated with KTE-X19 in ZUMA-2 Cohort 1.

KTE-X19 is considered to be used as a single dose. For application details see section 11.1.6 of this protocol.

12.4.2. Ibrutinib

Ibrutinib is administered at an oral dose of 560 mg per day in both arms. For details see section 11. The recommended treatment regimen is based on the favorable safety and efficacy profile as seen in previous trials.

12.5 Handling of IMP at the Site and Drug Accountability

In accordance with all applicable regulation requirements the investigator or another appropriate individual who is designated by the investigator (pharmacist, member of transfusion medicine department), should maintain records to document receipt of the IMP, the stocks of IMP at the site, the dispense and use by the individual subjects (drug accountability), the reconciliation, and the return of unused investigational medicinal products to the sponsor (or manufacturer) or their disposal on appropriate forms filed in the study site file.

All the forms relevant for the documentation of drug handling will be confirmed by signature of the investigator or a pharmacist, or another appropriate individual who is designated by the investigator.

12.5.1 KTE-X19

For further details, please refer to the current investigators brochure.

12.5.2 Ibrutinib

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

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

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

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

12.6 Return and Disposal of IMP

In case IMP cannot be used for the subject it has to be returned to manufacturer, stored at study site or destructed and records have to achieved at study site. Each single case needs to be evaluated by Sponsor and Study Site and decision to be communicated to monitor and manufacturer for planning the further steps. Destruction has to be done accordingly to national regulations and site's standards.

13 Auxiliary medicinal products used in the clinical trial

Product	**Authorised**	**Used in accordance with the terms of their marketing authorisations**
Rituximab	yes	no (no MA for MCL but standard of care according to national and international guidelines)
Cyclophosphamide	yes	yes
Vincristine	yes	Yes

Doxorubicine	yes	yes
Predniso(lo)ne	yes	yes
Dexamethasone	yes	yes
Cytarabine	yes	yes
Cisplatin	yes	No (no MA for MCL but standard of care according to national and international guidelines as combination agent in polychemotherapy regimen)
Oxaliplatin	Yes	No (no MA for MCL but standard of care according to national and international guidelines as combination agent in polychemotherapy regimen)
Melphalan	yes	No (no MA for MCL but standard of care according to national and international guidelines as combination agent in polychemotherapy regimen)
BCNU	yes	yes
Etoposide	yes	yes
Thiotepa	yes	yes
G-CSF	yes	yes
Bendamustine	yes	No (no MA for MCL but standard of care according to national and international guidelines)
Fludarabine	yes	no (no MA for lymphodepletion before CAR-T-cells but standard of care for this indication in national and international guidelines and mentioned in the SmPCs of several CAR-T-cell-products)
Tocilizumab	yes	yes

The investigator will be responsible for ensuring the correct storage and sufficient stocks of the auxiliary medicinal products at the site.

14 Study Procedures

For the schedule of treatment and assessments, see flow chart figure in section 1.4 and Schedule of Activities tables in 1.5

All scheduled assessments and treatments can be performed within a timeframe of +/- 4 days unless otherwise noted.

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

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

14.1 Methods of Assessment

The following section will give a general overview and adequate explanations to the examinations and procedures to be performed in this study. Regarding the exact procedure of the visit-specific examinations, see section 14.2

14.1.1 Physical Examination

A **complete physical examination (A)** should include an evaluation of head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems and recording of the ECOG/ WHO performance status (see Appendix 1). Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

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

14.1.2 Neurological assessments

Neurological assessments are necessary to assess to the potential presence of neurological abnormalities. In this study the Mini-Mental State Examination (MMSE) standard version 2.0. (see Appendix 3) will be used at defined time points. The MMSE is a 5 to 10 minute, 11- question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

14.1.3 Tumor and Response Assessments

Response assessments will be performed by the investigator, based on physical examinations, (PET)-CT scans of neck, thorax, abdomen and pelvis, laboratory results and bone marrow examinations through use of the Lugano Classification (Cheson 2014).

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

Bone marrow examinations:

Bone marrow examinations should include a biopsy for morphology, an aspirate and up to 3 blood smears for local hematology (optional, if part of standard of care at site), and an aspirate for MRD determination. Bone marrow examinations are required up to 90 days prior registration for staging purposes and for determination of MRD baseline levels in all patients.

- If bone marrow is free of lymphoma by morphology at screening, subsequent bone marrow aspirates for MRD is not mandatory
- If there is bone marrow involvement at screening, then subsequent bone marrow biopsies at the response assessment time points are mandatory for clinical response evaluation until EoT. In patients with PR due to continued bone marrow involvement, subsequent bone marrow examinations should be performed to confirm CR at a later time point.
- If the bone marrow changed from involved to not involved further bone marrow biopsies are not mandatory, but strongly recommended for MRD assessment. Bone marrow aspirations for MRD should be performed even in cases which are negative in conventional cytomorphological examination (see above). An additional bone marrow aspirate may be done if that is standard of care at the site.
- Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

Response evaluation with (PET)-CT scans using contrast media are the preferred radiology method at the following time points (± 1 week):

	Month 2	Month 3/4	Month 5	Month 6/7
Arm A	x	x	(x)	PET-CT
Arm B				
≤65 years, ASCT		x	x	PET-CT
>65 years, R-CHOP + I		x	x	PET-CT
>65 years, BR – I		x		PET-CT

- Month 2: End of cycle 2
  - Arm A: **mandatory**
- Month 3/4:
  - Arm A: End of Induction, after C3 (Ibrutinib) or C4 (in case of CHOP+I)
  - Arm B: First interim Evaluation, end of cycle 4
- Month 5:
  - Arm A: post CAR-T cell transfusion, approx. 4 weeks after transfusion, **optional**
  - Arm B:
    - ≤65 years, ASCT: End of Induction, prior ASCT, **mandatory**

    - >65 years, R-CHOP + I: End of Induction (after 6 cycles), **mandatory**
- Month 6/7, **PET-CT mandatory:**
    - Arm A: End of Consolidation, 12 weeks after CAR-T-cell transfusion
    - Arm B:
        - ≤65 years, ASCT: End of Consolidation, 3 to 5 weeks after ASCT
        - >65 years, R-CHOP + I: approx. 8 weeks after End of Induction
        - >65 years, BR – I: End of Induction
- Thereafter:
    - Every 3 months during the first 2 years after registration
    - Every 6 months during the following 2 years (until 4 years after registration)
    - Every 12 months thereafter until the end of study

Only at Month 6/7, a PET CT scan is mandatory. If additional PET-CT scans are performed by the sites, results can still be recorded in the CRF.

Complete physical examination (including /WHO Performance Status and B symptoms, as described in section 14.1.1.) should be performed during each response assessment by (PET)-CT scans.

14.1.4 Laboratory Examinations / Biological Specimens

Samples for the laboratory assessments will be analyzed at the study site's local laboratory. Depending on treatment phase and day different examinations are relevant (A, B, C or D) (for details refer to 1.5). All laboratory parameters have to be checked -7days prior to first induction dose.

Tumor tissue samples will be sent for central pathology review (for details refer to15.1).

MRD peripheral blood and bone marrow samples will be sent to central MRD laboratories (for details refer to 15.2 and Appendix 11).

Protection of patient confidentiality will extend to any data generated from the analysis of these samples.

All clinically significant findings will be documented in the source data and in the eCRF as adverse events. Clinically significant findings at baseline visit will be documented as concomitant disease under medical history.

14.1.5 Quality of Life Assessment

For Quality of Life (QoL) assessment the EORTC-QLQ-C30 and EORTC QLQ-NHL-HG29 questionnaires will be used. All patients are required to perform a QoL assessment at baseline.

See Schedule of events for further time points of QoL assessment until final evaluation at month 31.

14.1.6 Stool asservation

Stool asservations will be performed to analyze the diversity and composition of the microbiome. In Arm A at 4 different time points (before lymphodepleting therapy, day 0, day +7, day + 14), in Arm B ≤65 years at 4 different time points (C6D21 before THAM or BEAM, day 0, day +8, day + 15),

14.2 Visit specific examinations

14.2.1 Baseline Examination

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

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

Results of standard-of-care tests or examinations performed within a time period of 28 days (bone marrow 90 days) prior to study entry may be used; such tests do not need to be repeated for baseline. The subject's eligibility has to be evaluated during the baseline period prior to registration and administration of the first cycle of chemotherapy. The baseline period of 28 days is the time frame from obtaining informed consent to start of study therapy.

Please see the schedule of activities and assessments provided in section 1.5 for baseline assessments and for MRD samples see 15.2.

14.2.2 Examinations during induction

Assessments scheduled on the day of study drug administration should be performed prior to immuno(chemo)therapy infusion, unless otherwise noted.

Please see section 1.5 for schedule of activities and assessments to be performed during induction treatment.

However, if baseline or standard of care labs are drawn within 2 weeks before therapy on cycle 1 day 1, they do not need to be repeated.

14.2.3 Examinations before leukapheresis (Arm A)

Please see section 1.5 for schedule of activities and assessments to be performed before leukapheresis.

14.2.4 Evaluations for response during treatment (Induction, Consolidation and Maintenance)

For response assessment during interim evaluations please see section 14.1.3 Tumor and Response evaluation and for MRD Samples see section 15.2.

14.2.5 End of Treatment (EOT) Evaluation

The end of treatment evaluation has to be performed after end of Ibrutinib maintenance. As Rituximab can be given during follow up in Arm B based on investigators discretion, it is not considered for end of treatment evaluation.

In case of clinically suspected progressive disease, the evaluation can be performed at any time.

For schedule of assessments for EOT evaluation please see chapter 1.5.

14.2.6 Assessments during Active FU

During active FU (in patients who are responding) all visits must occur within ± 4 weeks from the scheduled date, unless otherwise noted.

Please see section 1.5 for schedules of assessments to be performed during follow-up. For response assessments during follow up see 14.1.3 (tumor and response evaluations) and for MRD samples see section 15.2. For Quality of Life assessment see section 14.1.5.

In case of treatment stop (e.g. due to toxicity) without progression of the disease patient should proceed to active follow–up.

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

If a patient has progressive disease any time after completion of induction therapy or discontinues per protocol treatment due to stable or progressive disease during induction treatment, any study medication will be stopped and a “Time-of-Progression-visit” (ToP) will be performed.

For the ToP visit all assessments of the End-of-Treatment (EoT)-visit should be performed as outlined in section 1.5.

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

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

14.2.8 Long term Follow Up

After the end of this study patients will be followed up for late effects of therapy, regarding survival and the administration of further MCL therapies in a separate registry outside of this study (eMCL registry, arm B) or separate follow up study (arm A).

Additionally registration in the European MCL registry and the EBMT registry (DRST registry for Germany) is strongly recommended for Arm A patients but not mandatory.

15 Reference assessments

15.1 Pathology Review

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

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

The review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of MCL (both by morphology and immunophenotyping including CD5, CD20, CD23, SOX11 and Cyclin D1) and recording of the morphological variants including prognostic factors such as Ki67 expression and TP53 expression.

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, will be sent to the designated national pathology platform. National review will revise diagnosis, cytology subtype, TP53 expression status and Ki67 according to the published guidelines of the network [49].

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

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

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction at the national reference pathology center; both will be used to study the expression of markers which may influence the prognosis of mantle cell lymphoma. At the end of the induction and during 6 months of follow up, frozen tumor tissue will be requested and organized by the designated national pathological platform. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of MCL patients.

15.2 Minimal Residual Disease (MRD) assessment and cellular immune reconstitution

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

In this study, we will use the expertise of the EU MCL network to assess MRD status using Next Generation Sequencing of clonal immunoglobulinrearrangements (IG-NGS) to determine each individual patient's MRD status. IG-NGS is currently the most sensitive, specific and standardized method for MRD assessment in MCL allowing to detect one lymphoma cell in 106 peripheral blood mononuclear cells and has been successfully used for MCL.

For IG-NGS, it will be necessary to determine the dominant clonotype in the diagnostic peripheral blood or bone marrow from each patient. This will be possible from diagnostic peripheral blood and bone marrow analysis prior to any treatment. Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

Peripheral blood, bone marrow and plasma will be collected at the timepoints specified in the schedule of activities (section 1.5): For each time point, samples (see MRD Appendix for description of the samples required for each time point) will be sent to the national reference laboratories listed in section 1 of the protocol. MRD analysis will be performed in the national reference laboratory and reported centrally to the Sponsor.

MRD in plasma will be analyzed by mutational profiling using a targeted capture sequencing panel optimized for the short fragments of cell free tumor DNA or IG-NGS.

To understand potential treatment effects on cellular immune reconstitution and identify prediction parameters for patients with favorable responses, T cell populations will be evaluated in both treatment arms.

This will include the quantitative and phenotypic evaluation of T cell subsets, separated in CD4+ and CD8+ T-cells with naïve or memory phenotypes, incl. Treg markers as well as activation (CD69, CD44, and HLA-DR) and inhibitory / exhaustion markers (NKG2A, PD-1) that may contribute to or suppress anti-tumor immune responses [50].

For antibody directed anti-tumor immune responses, innate immune cell recognition by Fc receptors bearing cells is essential and mediated by antibody dependent cellular cytotoxicity (ADCC) by monocytes / macrophages and NK cells [51], while tumor cell phagocytosis (ADCP) is mostly mediated by monocytes / macrophages [52].It will of particular interest to analyze monocyte subsets, as slan+ monocytes have recently been described to be involved in the elimination of B-cell lymphomas by ADCC and ADCP [53]. However, recent reports highlight the relevance of neutrophils in ADCC and ADCP, which has been underestimated so far [54]

Exploratory analyses of these immune cell subsets will be performed at baseline, D7, D14, week 4, EOT, maintenance and follow up to account for treatment related changes in cellular distributions. The data sets obtained will be analyzed over time in both treatment arms and correlated with established clinical and laboratory based prognostic parameters.

16 Safety Parameters

16.1 Definitions

Please see the standard definitions for Adverse Event (AE), Adverse (drug) reaction (AR), Unexpected Adverse (Drug) Reaction (UAR), Serious Adverse Event (SAE) and (Suspected Unexpected Serious Adverse Reaction ((S)USAR) in Appendix 12.

All Adverse Event have to be documented according to the specifications given in this chapter:

16.2 Protocol-defined Adverse Events of Special Interest (AESI) and special reporting situations

The following adverse events of special interest and special reporting situations will need to be reported to the Sponsor without regard to causality and seriousness (for reporting instructions, please see the following):

- Secondary primary malignancies (SPM)
- Drug Interaction
- Exposure to medicinal product from breastfeeding

The above mentioned events or special reporting situations should be recorded in the eCRF within 24 hours after awareness by the investigator to the sponsor. **(AE Page)**

All SPMs occurring from the time of registration up to the end of the trial must be considered as an "Important Medical Event" and reported as serious adverse events regardless of causal relationship to study treatment.

16.3 Exclusion of Treatment related SAEs from immediate reporting

No SAEs are excluded from immediate reporting.

16.4 Onset and end date of AEs and SAEs

The onset date of the AE is defined as the date when new signs or symptoms or worsening of a pre-existing condition first occur. The onset date of the SAE is defined as the date when at least one of the criteria for seriousness (see Appendix 12) occurs.

The end date of the AE is defined as the date when the symptoms resolve, or the event is considered stable by the investigator. The end date of the SAE is defined as the time the seriousness criteria are no longer applicable. The end date of the SAE must not be later than the end date of the corresponding AE. AEs and SAEs that are ongoing at the time of death, but not the cause for the death, are considered ongoing, not resolved or resolving (e.g. no change of the outcome). If an AE is the cause of death, the outcome has to be changed to "fatal".

16.5 Assessment of AEs by investigator (1st assessment)

Subjects must be carefully monitored for adverse events by the investigator. The intensity of the adverse events and the causal relation to trial medication and/or procedures are to be assessed.

The terms "serious" and "severe" are not synonymous but are often used interchangeably. The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache).

This is not the same as "serious", which is based on the existence of one of the regulatory defined seriousness criteria (see Appendix 12).

16.5.1 Assessment of Intensity/Severity

The intensity (severity) of adverse events will be scored according to the NCI Common Terminology Criteria for Adverse Events, CTCAE, version 5.0 [published on Nov 27th, 2017].

Adverse events not explicitly included in the NCI Common Toxicity Criteria list should be described in detail and graded according to the five points system below:

GRADE	Clinical description of severity
1	MILD
2	MODERATE
3	SEVERE
4	LIFE-THREATENING OR DISABLING
5	DEATH

16.5.2 Assessment of Seriousness

See detailed definition of Serious Adverse Event in Appendix 12. As mentioned above, the criterion "serious" serves as guide for regulatory (expedited) reporting obligations.

The criterion Seriousness is met, if an Adverse Event

- results in death,
- is life threatening,
- results in unplanned hospitalization (overnight stay) or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity for the subject,
- is associated with a congenital anomaly or birth defect,

or

- qualifies as "other" medically significant event or condition at investigator's discretion,

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

16.5.3 Assessment of causal relation to trial medication/procedures

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating yes or no accordingly. The following guidance should be taken into consideration:

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence,science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.

NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

Further examples for the assessment of causality of an adverse event with IMP:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

16.6 Period of observation

In this trial, the period of observation for collection of adverse events extends from registration up to 30 days after the last trial medication application. SPMs and hematotoxicity are followed until the end of study and should be reported by the investigator unless it is clearly attributed to new lymphoma treatment in case of disease progression.

If the investigator detects a serious adverse event in a trial subject after the end of the period of observation, and considers the event (at least possibly) related to the trial treatment or study medication, it should be documented and reported as SAE as described.

After the end of the trial all patients will be asked to be followed in a separate GLA register for possible late toxicity (e.g. SPM) so a period of 15 years of observation is maintained.

16.7 Documentation of AEs and Follow-up

All AEs (whether serious or not) reported by the subject or detected by the investigator will be documented in the patients records and on the appropriate pages of the eCRF.

If the adverse event is serious (see section 16.5.2), the investigator must complete, in addition to the “Adverse Event Page”, the “Serious Adverse Event” information at the time the serious adverse event is detected.

Except of the assessments specified in the following section (16.7.1 Source Data to be entered directly in the eCRF), all assessments related to AE documentation should be done in the patient’s file.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up, but no longer than 30 days after the end of the whole trial.

Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

AEs and SAEs that are ongoing at the time of death are kept as "ongoing" in the eCRF.

Necessary criteria for adverse event evaluation by the investigator:

- Event term or specification
- Duration (start date and stop date)
- Outcome
- Severity grade (according to CTCAE, see above)
- Seriousness of Event (according to seriousness criteria)
- Drug relationship of the AE to the investigational product (Causality assessment)

16.7.1 Source Data to be entered directly in the eCRF

The assessment of AEs by investigator may be recorded directly on the respective eCRF page (e.g. Adverse event page) and is to be considered as **Source Data**.

This is applicable only for the following data fields

- toxicity (severity) grading,
- the assessment of causality for all IMPs,
- the period of AE occurrence
- and for the seriousness criteria.

The Source documentation of all other assessments related to AE documentation should be done in the patient's file.

To ensure the availability of SAE documentation, the applicable eCRF page should additionally be stored during the conduct of the study locally (e.g. print out or copy of the respective page).

16.8 Immediate reporting of SAEs by investigator

SAEs, AESIs, Special reporting situations should be reported in the eCRF within 24h after awareness by the investigator.

In case of technical problems of the eCRF, the investigator will record the safety information on the provided paper SAE-Form, sign and send it to the immediately (at latest within 24 hours) to the Pharmacovigilance department PV-KUM:

FAX No. +49 89 4400-7- 7900 / 7901

E-Mail: PVKUM@med.uni-muenchen.de

The investigator should provide additional information on the clinical course and the outcome of each SAE as soon as possible (Follow up report).

The investigator can contact studyce@med.uni-muenchen.de (+49 89 4400-74900) in case of questions according documentation or reporting of SAEs.

16.9 Safety evaluation and Reporting by sponsor

The sponsor will ensure that all legal reporting requirements are met. According to GCP the sponsor is responsible for the continuous safety evaluation of the investigational product and the clinical trial.

On behalf of the sponsor PV-KUM will conduct the management of SAEs and the expedited reporting as required by the applicable laws and regulations.

A suspected unexpected serious adverse reaction (SUSAR) will be reported electronically to the Eudravigilance database (Art. 40 CTR) as soon as possible but not later than 15 calendar days, and 7 calendar days if it was fatal or life-threatening. Follow-up information is to be reported within further 8 days. The clock for the initial reporting starts as soon as the information containing the minimum reporting criteria has been received by the sponsor. If a reported SUSAR becomes fatal it must be reported within 7 days (Annex III, Nr. 13 CTR).

The members of the DMC will be informed within the same timeframes. The marketing authorization holder of the IMP should be informed too.

The participating investigators are informed once a month with a list of all SUSARs occurred in the whole clinical trial, together with a summary analysis of safety profile and updated benefit risk for the ongoing clinical trial. If there is any change of benefit risk which might influence the treatment decision of investigators the information will be given as soon as possible.

The sponsor will notify the Member States concerned through CTIS of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not SUSARs. This notification will be made without undue delay but no later than 15 days from the date the sponsor became aware of this event.

Work flow and procedures concerning Safety management will be described in a separate document.

During the clinical trial **the sponsor** will submit annually a safety report of the investigational medicinal product in accordance with the requirements in Article 43 CTR through the Eudravigilance database to the Agency. This report will be a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2). The Sponsor is conducting this clinical trial with IMPs from different Pharmaceutical Companies, therefore, it seems more sensible to create a single ASR for the study.

This report will also be sent to the pharmaceutical manufacturers and to the members of the DMSC.

16.10 Documentation of Abuse, Misuse, Overdose and Medication errors

All special events such as study medication abuse, misuse, overdose and medication errors (including dilution and infusion rate errors) have to be documented in the subject's eCRF and source documents. In case of hazard to patient safety the sponsor has to be informed immediately.

If they lead to an adverse event, then this has to be documented and reported as an AE/SAE.

16.11 Pregnancy

Women of childbearing potential (WOCBOP)[1] are required to have a urine or serum ß-hCG pregnancy test to exclude a pregnancy before enrolment in the clinical study.

Additional pregnancy testing will be conducted within 28 days prior to the first dose of study drug, monthly during the period of contraception (see below) and during the whole study if clinically indicated.

Subjects of both sexes (WOCBP, fertile men)[2] must be willing to use highly effective contraception during treatment and for at least 6 months after receiving lymphodepleting chemotherapy or KTE-X19, at least 3 months after last dose of Ibrutinib and women 12 months after last dose of Rituximab, whichever is longer.

As most of the auxiliary products require contraception, please see additionally the current version of the SmPCs for the required time of contraception for all auxiliary products used in the treatment of this trial. An overview of required contraception (valid July 2023) can be found in Appendix 13.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. 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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

[2] A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy

Methods considered as highly effective birth control methods when used consistently and correctly are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[3]:
  - oral[4]
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[3]:
  - oral[4]
  - injectable
  - implantable[5]
- intrauterine device (IUD)[5]
- intrauterine hormone-releasing system (IUS)[5]
- bilateral tubal occlusion[5]
- vasectomised partner[5,6]
- sexual abstinence[7]

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Actions to be taken if pregnancy occurs to female subjects or partners of male subjects

If a female subject becomes pregnant or suspect to be pregnant (including a positive pregnancy test regardless of age or disease state) while participating in this study, the investigator has to be informed immediately about this event.

Likewise, if the partner of a male study subject becomes pregnant or suspects to be pregnant while the subject participates in this study, the investigator has to be informed immediately by the male subject about this suspected or confirmed pregnancy.

The investigator will provide this information to the Sponsor's Pharmacovigilance Department in the following cases:

- Any pregnancy in a female subject or a female partner of a male subject under study treatment
- Any pregnancy in a female subject dosed with KTE-X19, regardless of the time after KTE-X19 infusion.

[3] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[4] In case of vomiting and nausea the efficacy of oral contraception may be reduced

[5] Contraception methods that are considered to have low user dependency

[6] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman is considered of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success

[7] 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

- If the pregnancy occurs in a female partner of a male subject within 6 months after the administration of KTE-X19.
- If the pregnancy occurs in a female subject or a female partner of a male subject within 3 months after last dose of Ibrutinib
- If the pregnancy occurs in a female subject within 12 months after dose of Rituximab

The investigator will record and report pregnancy information on the appropriate pregnancy report form as an initial report and fax or email it immediately (latest within 24h) to

FAX No. +49 89 4400-7- 7900 / 7901

E-Mail: PVKUM@med.uni-muenchen.de

The pregnancy itself is not considered to be an AE or SAE, but should be reported and followed up until early termination or completion and the outcome of pregnancy should be notified to the sponsor/ the sponsor delegated person inclusive information regarding maternal or newborn complications. For this purpose, the investigator will actively seek and provide follow- up information using the paper the Pregnancy Report Form. The timeframe to follow up the details of birth will be no longer than 2 years following the planned delivery date.

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

- spontaneous, therapeutic abortion or voluntary termination,
- stillbirth,
- all neonatal and infant deaths, that occur within 2 years of birth without regard to causality
- presence of birth defects
- congenital anomaly (including that in an aborted fetus, stillbirth or neonatal death)

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

17 Safety Run In Phase

So far combination data for CAR-T-cells with Ibrutinib are only available from smaller trials. Thus there will be an initial safety run-in phase of 27 patients randomized in the experimental arm which will be closely monitored for the observed toxicities during induction and maintenance therapy with special focus on observation to CAR-T-cell related toxicity (grade 5 AEs, CRS and ICANS) and hematotoxicity. After observation of four grade 5 AEs (not related

with lymphoma progression) or completion of 90 days after the KTE-X19 treatment of the first 27 patients randomized in the experimental arm, the Data and Safety Monitoring Committee (DSMC) will advise the sponsor delegated person / principal coordinating investigator and the international coordinating investigators about the continuation of the study.

During Safety Run In Phase additional blood counts will be done once a week from day of discharge after CAR-T-cell treatment till complete recovery of hematopoiesis (for criteria of full recovery refer to "Requirements for start of Maintenance" in section 11.1.7)

The following events which occurred between CAR-T-cell-treatment and d90 after CAR-T-cell infusion qualify as severe toxicity in the safety run in phase (Safety Events in Run-In) and should be monitored closely and reported in a timely manner (at the latest 1 week after occurrence):

- grade ≥ 3 neurologic toxicity
- grade ≥ 3 CRS / MAS
- grade ≥ 3 non-hematologic toxicity
- grade 4 neutropenia lasting ≥ 14 days
- death whatever the cause, except death due to lymphoma

with the following restrictions:

- Laboratory abnormalities grade 3 are only considered if they persist for > 2 weeks or if they do not return to ≤ grade 1
- Any infection/fever requiring iv antibiotics is not considered to be safety event, only grade 4 infections are considered
- If an event is attributed to progressive disease, it will not be counted as safety event.

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

- Rate of occurrence of at least one safety event per patient stratified by treatment arm
- Number of occurrences of safety events as defined above stratified by treatment arm
- percentage of patients randomized to the experimental arm who did not receive KTE-X19 treatment as planned and percentage of patients randomized to the experimental arm who did not start ibrutinib maintenance as planned

The DSMC may recommend stopping the study after analysing the data from the safety run-in phase.

18 Data Monitoring Safety Committee (DMSC)

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

The DMSC advises the sponsor regarding the continuity safety of study participants and should make recommendations on the discontinuation, modification or continuation of the study. The independent Data Monitoring Committee will review safety data considering efficacy of the IMP treatment.

Frequency and contents of the DMSC meetings are detailed in the DMSC Charter.

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

19 Statistical Methods

19.1 Primary estimand attributes

The primary objective is to exploratively compare the efficacy, measured by FFS, of KTE-X19 with current standard of care in patients with previously untreated high-risk MCL.

The population comprises previously untreated patients with high-risk MCL as defined by the inclusion and exclusion criteria.

Variable is the failure-free survival from randomization. Primary events of interest are any discontinuation of the per protocol treatment due to stable or progressive disease during induction, stable disease at the end of induction, progressive disease at any time after end of induction treatment and death from any cause.

Most relevant intercurrent events include ineligibility ascertained after registration, failure to receive IMP, application of a new lymphoma treatment before treatment failure, loss to follow-up, and death from any cause.

Intercurrent events are treated as follows: ineligibility, failure to receive IMP (e.g. because of out of specification product), and application of new lymphoma treatment are ignored (treatment policy strategy following the intention-to-treat principle), loss of follow-up is censored (while on treatment strategy), and death from any cause is considered an event (composite variable strategy).

Population level summary is the hazard ratio of FFS estimate, comparing Arm A vs. Arm B.

19.2 Statistical design

A two-sided stratified log-rank test with significance level of 10% will be performed using the following hypotheses:

Null hypothesis H_0: $FFS_A = FFS_B$ for all time points

Alternative hypothesis H_1: $FFS_A \neq FFS_B$ for at least one time point.

Stratified analysis is done for the randomization stratification factors country and MIPI risk group (high vs. intermediate/low risk) in order to increase statistical power without increasing type 1 error probability.

19.3 Sample size

Based on the pooled European MCL Younger [13] and MCL Elderly [55] trial data, we estimated a median FFS of 27 months for the control group B in the high-risk trial population (own unpublished calculation). With 150 patients randomized 1:1 between Arm A and B within 2 years of recruitment and at least 4.5 years of additional follow-up, allowing for 10% dropouts at 5 years, a power of 90% is achieved to decide against the null hypothesis in case of a true FFS-HR of 0.558 (median FFS in Arm A: 48 months). To detect this difference, 102 FFS events need

to be observed. One interim analysis is planned after the observation of 51 FFS events to allow an early stop for superiority (O'Brien-Fleming boundaries) or inferiority (Pocock boundaries). The probability to stop early for superiority is 72% with a HR of 0.42 (median 65 months) and 32% with a HR of 0.56 (median 48 months). The probability to stop early for inferiority is 63% with a HR of 1.85 (median 15 months) and 22% with a HR of 1.36 (median 20 months). In case the FFS of the outcome is substantially better than projected (HR 0.75, median FFS in Arm B 36 months), 90% power is achieved to detect a true FFS-HR of 0.512 (median FFS in Arm A: 70 months).

19.4 Analysis populations

The intention-to treat (ITT) population comprises all subjects randomized in the study after informed consent and eligibility check, even if they did not receive the treatment that they were randomized to. The ITT population will be analyzed based on the treatment group that the subjects were randomized to. The ITT population will be used for the primary hypothesis test and all the efficacy questions.

The per-protocol (PP) population comprises randomized subjects who fulfill the inclusion criteria and not fulfill exclusion criteria, and received the treatment that they were randomized to. The PP population will be analyzed based on the treatment group that the subjects were randomized to. The PP population applies to all efficacy questions as sensitivity analyses.

The induction safety population comprises all subjects who start induction treatment and applies to induction safety analysis. The induction safety population will be analyzed based on the induction treatment that the subjects actually started. As sensitivity analysis we will restrict the safety population of arm A to the patients who received KTE-X19.

19.5 Statistical analysis

19.5.1 Definition and analysis of primary endpoint

The primary endpoint is failure-free survival, defined as time from randomization to any discontinuation of the per protocol treatment due to stable or progressive disease during induction, stable disease at the end of induction, progressive disease at any time after end of induction treatment and death from any cause, whichever occurred first. Stable disease at end of induction is defined as failure event because it represents a regular indication for salvage treatment in MCL. Patients without any failure event will be censored at the latest follow-up showing the absence of an event. For patients without a restaging result at end of induction or without any contact after randomization, FFS is censored 1 day after randomization.

FFS will be described using Kaplan-Meier curves with estimates of FFS probability at yearly intervals. In the interim analysis, a two-sided stratified log-rank test with significance level 10% will be performed and the statistic will be compared with the boundaries corresponding to the observed event number according to the pre-specified alpha-spending design. Stratified analyses stratify for the randomization stratification factors country and MIPI risk group (high vs. low/intermediate risk). If the standardized two-sided stratified log-rank statistic Z exceeds the superiority or inferiority margin, superiority or inferiority of Arm A vs. Arm B is concluded, respectively. Otherwise the statistical test continues until the final evaluation in which the standardized stratified log-rank statistic Z is compared with the boundaries corresponding to the observed number of events according to the pre-specified alpha-spending design. Hazard ratio of FFS comparing Arm A and B with 95% confidence interval and corresponding p value will

be calculated from a stratified Cox proportional hazard model, stratifying for country and MIPI risk group (high versus low/intermediate risk).

19.5.2 Analysis of secondary endpoints

Progression-free survival (PFS) is time from randomization to progression or death from any cause, whichever occurred first. Patients without documented progression and alive at last contact will be censored at the latest staging where progression was excluded. For patients without any staging result or without any contact after randomization, PFS is censored 1 day after randomization.

PFS in responders will be calculated from the date of response (CR or PR within 6 months from randomization) to progression or death from any cause, whichever occurred first. Patients without CR/PR recorded by 6 months from randomization will be excluded from the analysis. Responders without documented progression and alive at last contact will be censored at the latest staging where progression was excluded.

Complete remission (CR) rate, overall response (ORR) rate, and complete metabolic response rate are calculated as percentage of patients with CR, CR/PR, PET negative CR (Lugano criteria, Deauville score 1-2), respectively, among all patients with evaluable staging result by 6 months from randomization.

The best response achieved within 2 years from randomization will be recorded for each patient. Time to best response is calculated from the date of randomization to the date of best response. For patients with the same best response at multiple time points, the time of the first response recorded is considered as time to best response. Median time to best response will be summarized for each best response group (CR, PR, SD, PD).

Time to first response is calculated from the date of randomization to the date of first response (CR or PR). Patients with PD or death as their first response are censored at the date of PD or death. Patients with SD as their best response are censored at eventual first progression or at last contact in SD or at date of death. Patients without any recorded response are censored 1 day after randomization.

Overall survival is time from randomization to death. Patients alive at last contact will be censored at their last contact. Patients without any contact after randomization will be censored 1 day after randomization.

In PP analyses, time-to-event endpoints will be censored at major protocol violations such as initiation of a new anti-lymphoma treatment.

All the time-to-event endpoints will be described using Kaplan-Meier curves with estimates of probability at yearly intervals with two-sided 95% confidence intervals, and compared between treatment Arm A and B by stratified log-rank tests. Hazard ratios of Arm A vs. B with 95% confidence intervals and corresponding p values will be calculated from stratified Cox proportional hazard models. Response rates will be estimated with two-sided 95% confidence intervals, and compared by the stratified Cochran-Mantel-Haenszel test between two treatment groups. In all stratified analyses stratification is done for the randomization stratification factors country and MIPI risk group (high vs. low/intermediate risk).

19.5.3 Analysis of subgroups

Exploratory subgroup analyses for all efficacy questions will be performed for age (≤65, >65 years), sex (female, male), and MIPI risk groups (low, intermediate, high).

19.5.4 Interim analyses

An interim analysis is planned for the primary efficacy hypothesis tests after the observation of 51 FFS events. The standardized stratified log-rank statistic will be calculated and compared with the boundaries corresponding to the observed number of events according to the pre-specified alpha-spending design to allow early stop for superiority or inferiority.

19.5.5 Analysis of adverse events

The percentage of patients completing the treatment as planned will be described for each arm.

The maximal grades of Common Terminology Criteria for Adverse Events (CTCAE) will be determined for each patient who received treatment. The frequencies of CTCAE grades 0, 1 or 2, 3, 4 or 5 will be calculated for each category of adverse events for each treatment group and time frame (induction, consolidation, follow-up). Cytokine Release Syndrome (CRS) and Neurologic Toxicity Associated with Immune Effector Cells (ICANS) will be additionally graded according to ASTCT.

19.5.6 Analysis of exploratory endpoints

Molecular remission rate

Molecular remission rate is calculated as percentage of patients with negative MRD result within 6 months from randomization.

Immunophenotypes at relapse

For patients who have achieved CR/PR within 6 months from randomization and have a relapse later, the frequency and percentage of their immunophenotypes at relapse will be summarized.

Analysis of quality of life (QoL)

QoL during induction therapy and follow-up will be measured by physical functioning (assessed with the EORTC QLQ-C30) and physical condition/fatigue (assessed with the EORTC QLQ-NHL-HG29). The scale scores from each questionnaire will be calculated for each patient who received treatment and summarized descriptively at each time point for each treatment group. The proportion of missing observations per time-point will be taken into account; a proportion of at least 70% completed questionnaires out of all eligible patients at each time point is considered to be required for reliable estimates. The scores will be compared with references values from the EORTC data repository.

Diversity and composition of the microbiome

Stool asservations will be performed at 4 different time points in Arm A (before lymphodepleting therapy, day 0, day +7, day + 14) to analyze the diversity and composition of the microbiome by performing 16s RNA-Sequencing and Shotgun Metagenomic Sequencing (see appendices 9 + 10). At the same time points, stool asservations will be performed in Arm B, serving as control group samples.

CAR-Hematotoxicity

Hematotoxicity represents a frequent CAR T-cell related adverse event that is still poorly understood. Rejeski et al. analyzed patterns of hematopoietic reconstitution and evaluated potential predictive biomarkers of hematotoxicity [56]. They calculated the CAR-HEMATOTOX model, which includes markers associated with hematopoietic reserve (e.g. platelet count, hemoglobin and ANC) and baseline inflammation (e.g. C-reactive-protein, ferritin) and is predictive for neutropenia, thrombopenia and anemia. The model will be validated in our study.

19.6 Consideration of Protocol violations in the statistical evaluation

All protocol violations will be listed and the impact on the evaluation of the subjects concerned will be discussed prior to statistical analysis.

In the primary efficacy analysis, ITT patients will be evaluated ignoring any protocol violations as far as possible. In sensitivity PP analyses, time to event variables will be censored at major protocol violations (e.g. start of a new anti-lymphoma treatment without preceding treatment failure).

19.7 Handling of drop-outs, withdrawal, and missing data

In general, missing data e.g. due to drop-outs or withdrawal will not be imputed before statistical analyses. A maximal percentage of 10% of patients with missing data for primary evaluation after 5 years is considered in the power calculation. In the primary evaluation of FFS, drop-outs are censored at their last tumor staging without a failure event. A sensitivity analysis for the primary efficacy question will be performed counting drop-outs as failure events.

20 Data Management

Data management will be performed at the study center of the sponsor. Details on data management (responsibilities, data collection by eCRF, data handling, audit trail, record keeping, etc.) will be described in a Data Management Plan prior to the study. During the study, the performance of data management and any deviations from the data management plan will be documented in a data management report.

20.1 (Electronic) Case Report Form (eCRF)

In this clinical study, the GCP compliant Electronic Data Capture (EDC) System “MARVIN” by XClinical will be used to implement the eCRF and the related study database. Before any

data entry is performed, the eCRF will be validated according to the requirements for computerized systems used in clinical studies, and the technical specifications will be documented. In event of future protocol amendments their impact on the eCRF has to be verified. If necessary the eCRF will be modified adequately and the changes will be validated.

The investigator has ultimate responsibility for completeness, accuracy, authenticity as well as timely collection and reporting of all clinical, safety, and laboratory data in the eCRF. All data may only be entered into the eCRF by authorized qualified study personnel. The study sites should provide the sponsor with the valid and up to date list of persons to whom data entry currently has been assigned. The sponsor will make sure that these persons receive timely an adequate training with documented license for controlled access to the production eCRF and are provided with written data entry and processing guidelines. The study sites will be made aware to contact the study center for assistance. A separate eCRF manual is available to support the data entry.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably within two weeks after a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

Data will be collected on the eCRF according to this protocol and providing the essential data quality to document eligibility, safety, and efficacy parameters, compliance to treatment schedules, and parameters necessary to evaluate the study endpoints. Any corrections to entries made in the source documents must be dated, signed, and explained (if necessary). Any corrections to entries made in the eCRF must be explained. All entries and corrections on the eCRF are automatically documented via “audit trail” provided by the EDC system. The data in the eCRF must match with the data in the source documents. Inconsistencies will be queried and discussed with the investigator. In most cases, the source documents are the hospitals’ or the physician's subject chart. In these cases data collected on the eCRF must match the data in those charts. In some cases, the eCRF, or parts of the eCRF, may also serve as source documents (see section 16.7.1). After data clearance the data base will be locked against further changes, and data will be used for statistical analysis.

The monitor is responsible to verify the eCRF data at regular intervals throughout the study to verify the adherence to the protocol, completeness, accuracy, and consistency with the source data. Therefore, the monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRF are resolved and will be avoided in future.

All study data in the eCRF are collected pseudonymously; entering of identification data of a patient in the eCRF is not allowed. The preudonymisation code for a patient at registration is generated by the eCRF using only a fixed administrative string for the study, the number of previous notified patients and a check code to prevent mistakes by typing the code. No parts of name or birthdate are used for the preudonymisation code. Only the year of birth but no initials and not the complete birthdate will be submitted at notification of a patient in the eCRF.

The investigator has to sign the Signature Form for this eCRF study to confirm the completeness, accuracy, and authenticity of all data entered in the eCRF for the patient at the end of study.

20.2 Investigator Site File (ISF)

The study site will be provided with an Investigator Site File (ISF) containing all sponsor-specific essential and study specific documents. The monitor will regularly check the ISF for accuracy and completeness. The ISF has to be stored locked and secured. After the end of the study or early termination of the study the ISF should be retained for at least 25 years at the site.

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

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

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

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

20.3 Archiving

In compliance with the CTR the essential documents of the trial will be stored. The sponsor and the investigator will archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law. The essential documents will be located in files as specified in ICH/GCP Section 8. The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and acces¬ sible, upon request, to the competent authorities.

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

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

21 Reporting

21.1 Statistical Report

During the conduct of the trial, regular reports on trial performance, baseline comparability, efficacy in the whole patient groups pooled from all treatment groups, and safety will be prepared twice a year. Baseline comparability and safety may be reported according to treatment groups, whereas efficacy results according to treatment groups will not be disclosed to any other person than the trial statisticians or the DMSC before the decision of the confirmatory statistical test.

The statistical evaluation and the statistical report are performed, evaluated and signed by the responsible statistician for the trial.

21.2 Annual progress report

During the clinical trial the sponsor will submit annually a safety report of the investigational medicinal product in accordance with the requirements in Article 43 CTR through the Eudravigilance database to the Agency. This report will be a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2). Please see section 16.9 for further explanations.

21.3 End of study report (Clinical Study Report)

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study as well as a summary of the results for Laypersons.

The final trial report will be written and signed in co-operation between the sponsor/coordinating investigator.

21.4 Publication Policy

The right of publication is primarily with the sponsor, the coordinating investigator and the other investigators involved. All data collected in connection with the clinical study will be treated in confidence by the sponsor/coordinating investigator and all others involved in the study, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the sponsor) and the coordinating investigator. This is indispensable for a full exchange of information between the above-named parties, which will ensure that the opinions of all parties involved have been heard before publication.

22 Monitoring, Audits and Inspections

During the clinical subject, quality control and quality assurance will be endured through monitoring, auditing and inspections by authorities.

22.1 Monitoring

According to the guidelines on Good Clinical Practice, the investigator’s sites and study procedures will be monitored by a representative of the sponsor (study monitor) to ensure

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

Source data verification will be performed in order to verify the accuracy and completeness of the entries in the electronic case report form (eCRF) by comparing them with the source data, and to ensure and increase the quality of the data.

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

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

22.2 Audits and Inspections

In accordance with ICH GCP this study may be selected for audit by representatives of the sponsor or for inspection by site responsible representatives of the local regulatory authority. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

The investigator agrees to give the auditors and regulatory authorities access to all relevant documents for review and to support the sponsor to solve possible findings concerning the study conduct at the respective site.

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

23 Ethics and Good Clinical Practice

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice, the relevant European and national regulations and the Declaration of Helsinki.

23.1 Responsibilities of the Sponsor

According to German law (§§ 40 – 42 AMG) and CTR the sponsor is responsible for obtaining the approval from the respective competent authority and the respective responsible research ethics committee before initiation of the study.

It is the sponsor’s responsibility to ensure that all required regulatory and administrative documents are provided to the investigational sites before shipment of study drug and before enrollment of the first patient. This will always include an approval of the Member State

concerned for the investigational site. Each investigational site will be notified when all requirements are met, and enrollment can start.

The overall responsibility for the clinical trial lies with the sponsor. This includes the compliance with all applicable European and national laws and guidance (Good Clinical Practice and related).

23.2 Responsibilities of the Investigator

By signing this protocol the local investigator declares his/her commitment:

- to not enrol any person dependent on him/her or the sponsor in accordance with the principles of ICH-GCP
- to follow the regulations for data security according to DGPR
- to inform the subjects of the transmission of their pseudonymized data according to documentation and transmission obligations (Article 28f CTR) and to make sure that subjects unwilling to give consent to the processing of their data are not included into the study
- to certify that he/she was informed of the pharmacological – toxicological issues and risks of the clinical subject according to Article 29 CTR
- to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
- to be thoroughly familiar with the appropriate use of the study drug(s), as described in the protocol, the product information and other information sources provided by the sponsor
- to be aware of, and comply with GCP and the applicable regulatory requirements
- to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties (if applicable).
- to promptly report a (suspected) serious breach to the sponsor.
- to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

23.3 Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the sponsor and the investigator. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/authority/ethics committee.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the Member State(s) concernedto eliminate immediate risks to the subject. The deviation or amendment should subsequently be reported to the sponsor or sponsor delegated person. The sponsor reports the incident, if necessary, the Member State(s) concerned, giving reasons.

After a subject has been enrolled, it is the investigator's responsibility to make all reasonable efforts to document all protocol deviations and to continue the subject's per protocol participation in the study as far as possible. Protocol deviations do not constitute a justification for withdrawal of a subject from the study in general.

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator. Protocol deviations will be

reported to the sponsor during the course of the study in the eCRF. Besides a description of the deviation, the reason for deviation and preventive actions are mandatory.

23.4 Serious breaches

A serious breach is any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

Suspected serious breach means an incident which at the time of communication from investigators or from service providers to the sponsor has not yet been assessed by the sponsor to be a serious breach.

The sponsor will provide a detailed training and guidance of reporting possible serious breaches.

The investigator should provide detailed information of each suspected serious breach and corrective and preventive measures (if applicable) as soon as possible to the sponsor using following E-mail address:

MED3.hematology-SSB@med.uni-muenchen.de

The investigator can contact the sponsor in case of questions (during business hours): Tel: +49 89 4400-74900

The incoming suspected serious breaches will be processed during business hours (Monday to Thursday from 8 a.m. to 4 p.m., Friday 8 a.m. to 3 p.m., except for the public holidays in Bavaria).

If the sponsor has reasonable grounds based on evidence to believe that a serious breach has occurred, it is expected to report the serious breach first, within 7 days, and investigate and take action simultaneously or after the notification.

23.5 Notification of General Modifications to the Protocol

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

Substantial Modifications are changes that likely affect and /or change:

- the safety of the persons concerned,
- the interpretation of the scientific study documents or the scientific informational value of the study results,
- the nature of management or conduct of the clinical trial,
- the pharmaceutical quality or safety of the investigational medicinal products
- the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical subjects with drugs consisting of or containing genetically modified organisms

A substantial modification requires an authorization of Part I and/or Part II by the member states concerned of the modification. The clinical trial may only be continued when an approval has been obtained.

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

23.6 Notification of the start and end of recruitment of the study

The sponsor shall notify each Member State concerned of the start of a clinical trial in relation to that Member State through CTIS. The sponsor shall notify each Member State concerned of the first visit of the first subject in relation to that Member State through CTIS. The sponsor shall notify each Member State concerned of the end of the recruitment of subjects for a clinical trial in that Member State through CTIS. These notifications shall be made within 15 days.

23.7 Notification of the end of the study

The end of the clinical study is the date of the last visit of the last subject undergoing the study. The sponsor shall notify each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS. The sponsor shall notify each Member State concerned of the end of a clinical trial in all Member States concerned through CTIS. These notifications shall be made within 15 days.

Therefore, all investigators are required to report the all patients' last visit of their site immediately to the sponsor

In case the study is ended prematurely, that notification shall be made without undue delay but not later than in 15 days of the date of the temporary halt or early termination. The notification shall include the reasons for such action and specify follow-up measures.

23.8 Subject Information and Informed Consent

According to Chapter V of the CTR and to § 40b German Drug Law (Arzneimittelgesetz, AMG) every participating subject will be informed of nature, importance, treatment methods, risks and consequences of the study by the local investigator. Details of indemnity and insurance are also stated.

The local investigator is responsible for obtaining written informed consent from a subject before any protocol-specific screening procedures will be performed or any investigational products will be administered. The written informed consent document has to be prepared and provided in the language(s) of the potential subject population.

The subject is to be informed by an investigator who is a physician, or by a member of the investigating team who is a physician, about the nature, significance, risks and implications of the clinical trial as well as about his/her right to withdraw from the clinical trial at any time; a generally comprehensible information sheet is to be handed out to him. Furthermore, the person concerned is to be given the opportunity to have a counselling session with an investigator or a member of the investigating team who is a physician about the other conditions surrounding the conduct of the clinical trial.

The subject is to be informed of the purpose and scope of the processing of personal data, especially medical data. The person concerned is to be informed especially of the fact that some data have to be processed in a pseudonymized manner according to legal obligations (e.g. safety reporting obligations) and that the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

It is also the responsibility of the investigator for asking the subject if he/she agrees to have her primary care physician informed of his/her participation in the clinical trial. If the subject agrees

to such notification, the investigator shall inform the primary care physician of the subject's participation by sending a message.

Subjects must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, subjects must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The subject will be given ample of time and opportunity to obtain answers to any open questions. All questions relating to the clinical subject should be answered to the satisfaction of the subject and/or his/her legal representative. On the other hand by signing the consent form subjects give their consent to the evaluation, recording and usage of their personal data.

The written consent form will be personally dated and signed by the subject and the by investigator conducting the informed consent discussion. The informed consent forms will be filed in the ISF at each site.

The acquisition of informed consent and the subject's agreement or refusal of the notification of the primary care physician should be documented in the subject's medical record.

A copy of the signed and dated informed consent form will be given to the subject or legally acceptable representative and a copy will be held in the subject's medical notes. The existence of written informed consent will have to be confirmed before any study-specific test/treatment has been performed.

In the case of substantial modifications, e.g. any new data providing information on the safety profile of any of the investigational medicinal product and leading to significant changes in the risk-benefit ratio, the subject must be informed with an appropriately revised subject information and the consent of the subject has to be obtained again.

Changed study procedures can only be carried out if they have been approved by the member states concerned, and if the subject has been appropriately informed and has given his/her written consent.

23.9 Subject Insurance

Every subject participating in the study is insured against any study -related illness/injuries pursuant to the legal requirements which may occur during the study, in accordance with national laws and institutional guidelines of each respective country..

The investigator will inform the subject of the existence of the insurance, including the obligations arising from it. The subjects have access to insurance documents and provided with a copy of the general conditions of insurance on request.

23.10 Data Protection and Subject Confidentiality

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

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

The subjects must be informed that:

1. Any subject related data in this study are handled confidentially and will be captured in pseudonymized form (subject ID number for the study – subject number-, year of birth) and will only be transmitted to
    a. the coordinating investigator/sponsor/sponsor delegated person/data monitoring safety board for scientific and adverse event evaluation
    b. the responsible regulatory authority(ies), the responsible ECs via CTIS and Eudravigilance database for verifying the proper conduct of the study and for assessment of study results and adverse events
2. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the local regulatory authority(ies) must have direct access to personal data. In this case, the investigator is released from confidential medical communication.

Details will be described in the data protection concept.

23.11 Financing of the Study

The present study is an investigator initiated study (IIS). The study is financially supported by Kite Pharma and Janssen Pharmaceutica.

24 Termination of the Study

24.1 Regular Termination of the Study

The regular end of the study is defined by the last visit of the last subject entering the study ("Last Subject – Last Visit").

24.2 Early Termination by the Subject

Patients can leave the study at any time for any reason if they wish to do so without any consequences. Please inform the sponsor if a patient withdraws consent. Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

For patients who have withdrawn their consent no further information will be collected.

In this case safety information regarding AE should be published as spontaneous report on suspected side-effects also known as suspected adverse drug reactions for authorized medicines in the European Economic Area (EEA).

24.3 Early Termination by the Investigator

Subjects may also be withdrawn from study treatment at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, e.g.:

- Occurrence of intolerable adverse events which would constitute an unacceptable high risk for the subject
- Lack of efficacy

- Medically indicated e.g. because it is found that inclusion / exclusion criteria were violated
- Continuation is unacceptable because risks outweigh the benefits
- Pregnancy
- Lack of compliance of the subject (e.g. taking prohibited medication)
- Significant protocol violations
- Logistical reasons (e.g. subject changes his/her doctor or hospital or moves to another location where participation in this study is not possible)

Whenever a subject is withdrawn from the study treatments, the circumstances of the discontinuation have to be recorded in detail in the eCRF and patient will continue to follow up or survival follow up as described in section 14.2.6 or 14.2.7.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal. The subject should be followed-up regarding any unresolved adverse events.

24.4 Follow-up of Patients Withdrawn from Treatment

Patients who are withdrawn from treatment by the investigator for other reasons than death or lack of efficacy (defined as stable disease at end of induction or progression of disease at any time) will go to Follow Up as described in section 14.2.6for follow up.

Patients who are withdrawn from treatment because of lack of efficacy or progressive disease will go to survival follow up as described in section 14.2.7for survival follow up.

For patients who are withdrawn from treatment because afterwards they did not fulfil the eligibility criteria at time of enrollment contact sponsor and coordinating investigator to evaluate the further proceedings.

24.5 Early Termination of the Study Sites

Both the investigator and the sponsor have the right to terminate the study at one of the centers at any time for the following instances:

- Unforeseeable circumstances have arisen at the respective study center which preclude the continuation of the clinical subjects.
- The investigator or the sponsor considers that the resources for continuation are no longer available.
- The investigator or the sponsor considers that the continuation of the study is no longer ethically or medically justifiable.
- Subject recruitment is inadequate.
- Serious problems arise regarding the quality of the collected data which cannot be resolved.
- Withdrawal of the opinion of the agency.

Early termination at one of the study centers does not automatically mean the discontinuation of study participation with already enrolled study subjects. A separate

decision on further treatment must be made for each subject, depending on the overall situation.

- An adequate further treatment and follow-up of already enrolled study subjects must be ensured.
- The documentation of already enrolled study subjects will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the center is closed. These queries must be answered properly by the center.
- The agency must be duly notified of the center's closure, including reasons, within the specified period(s).
- The respective study center will be closed in stages by the CRA when a decision has been made on the further treatment of the subjects concerned.

24.6 Early Termination of the Entire Study

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

- The stopping rule has been reached (see 19.5.4).
- There is evidence of an unacceptable risk for study patients (i.e. safety issue).
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrollment of more patients; for example insufficient enrollment that cannot be improved.
- The DMSC recommends to end the study based on viable arguments other than described above.

The sponsor will promptly notify all concerned investigators of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

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26 Appendices

Appendix 1 ECOG/WHO Performance Status Criteria

GRADE	PERFORMANCE STATUS – WHO CLASSIFICATION
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more 50% of waking hours
3	Capable of only limited self-care confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed and chair.

Appendix 2 Categories of Staging according to Ann Arbor

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

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

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

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

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

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

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

-IIIS+E = Both IIIS+IIIE *.

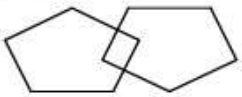
*(*Of note, in FLIPI, spleen involvement is categorized as stage IV)*

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

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

Appendix 3 Mini Mental State Examination (MMSE)

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Interpretation of the MMSE:

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Interpretation of MMSE Scores:

Score	Degree of Impairment	Formal Psychometric Assessment	Day-to-Day Functioning
25-30	Questionably significant	If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.	May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.
20-25	Mild	Formal assessment may be helpful to better determine pattern and extent of deficits.	Significant effect. May require some supervision, support and assistance.
10-20	Moderate	Formal assessment may be helpful if there are specific clinical indications.	Clear impairment. May require 24-hour supervision.
0-10	Severe	Patient not likely to be testable.	Marked impairment. Likely to require 24-hour supervision and assistance with ADL.

Appendix 4 Cytokine Release Syndrome Grading per Lee, 2014

Grade	Symptoms
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO_2 or Hypotension responsive to fluids or low dose of 1 vasopressor[a] or Grade 2 organ toxicity[b]
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or Hypotension requiring high-dose or multiple vasopressors[a] or Grade 3 organ toxicity or Grade 4 transaminitis[b]
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)[b]
Grade 5	Death

Abbreviations: FiO2, fraction of inspired oxygen

Appendix 5 CRS Management Guidelines

(The cross-references refer to the corresponding sections of the KTE-X19-IB)

CRS Grade[a]	Supportive Care	Tocilizumab	Steroids	Follow-up
Grade 1				
• Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	• Supportive care per institutional standard of care • Closely monitor neurologic status	N/A	N/A	Not improving after 24 hours: • Tocilizumab as per Grade 2 guidance (below) Not improving after 3 days: • Dexamethasone 10 mg IV x 1
Grade 2				
• Symptoms require and respond to moderate intervention • Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of 1 vasopressor or Grade 2 organ toxicity	• Continuous cardiac telemetry and pulse oximetry as indicated • IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids • Vasopressor support for hypotension not responsive to IV fluids • Supplemental oxygen as indicated	• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	• Dexamethasone 10 mg IV once daily	Improving Manage as above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Manage as appropriate grade below
Grade 3				
• Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	• Management in monitored care or intensive care unit	• Manage as Grade 2 (above)	• Dexamethasone 10 mg IV 3 times a day	Improving • Manage as appropriate grade above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Manage as Grade 4 (below) • Contact Medical Monitor
Grade 4				
• Life-threatening symptoms • Requirements for ventilator support or CVVHD • Grade 4 organ toxicity (excluding transaminitis)	• Manage as Grade 3 (above) • Mechanical ventilation and/or renal replacement therapy may be required	• Manage as Grade 2 (above)	• Methylprednisolone 1000 mg IV once daily x 3 days	Improving • Manage as appropriate grade above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Consider 1 g twice a day to 3 times a day of methylprednisolone or alternative therapy[b] • Contact Medical Monitor

Abbreviations: CRS, cytokine release syndrome; CVVHD, continuous veno-venous hemodialysis; FiO_2, fraction of inspired oxygen; IV, intravenous(ly); N/A, not applicable.
a Modified {Lee 2014}.
b Initiation of alternative therapy should be considered and includes (but is not limited to) antithymocyte globulin, neurosurgical intervention, anakinra, siltuximab, ruxolitinib, cyclophosphamide, IV immunoglobulin, and intrathecal chemotherapy/steroids.

Appendix 6 ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolved rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviation: ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable.
Notes: The ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, and raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified with Grade 3 ICANS.

a A patient with an ICE score of 0 may be classified with Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified with Grade 4 ICANS if unarousable.
b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE, but they do not influence the ICANS grading.
d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE.

Appendix 7 Immune effector cell-associated encephalopathy (ICE) score

Task		Score
Orientation:	Orientation to year, month, city, hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands:	Ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Writing:	Ability to write a standard sentence (eg, "Our national bird is the bald eagle")	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

Appendix 8 Neurologic Events – Management

(The cross-references refer to the corresponding sections of the KTE-X19-IB)

Neurologic Event (Grading Assessment CTCAE version 5.0)	Supportive Care	Tocilizumab	Corticosteroids	Follow-up
Grade 1				
Examples include the following: • Somnolence-mild drowsiness or sleepiness • Confusion-mild disorientation • Encephalopathy-mild limiting of ADLs • Dysphasia-not impairing ability to communicate	• Supportive care per institutional standard of care • Closely monitor neurologic status • Consider prophylactic levetiracetam[a]	Concurrent CRS • Per Grade 1 CRS guidance from Table 47	Dexamethasone 10 mg IV x 1	Not improving after 2 days: • Repeat dexamethasone 10 mg IV x 1 • Continue supportive care
Grade 2				
Examples include the following: • Somnolence-moderate, limiting instrumental ADLs • Confusion-moderate disorientation • Encephalopathy-limiting instrumental ADLs • Dysphasia-moderate impairing ability to communicate spontaneously • Seizure(s)	• Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications	Concurrent CRS • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period. • Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS	• Dexamethasone 10 mg IV 4 times a day	Improving • Manage as above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Manage as appropriate grade below • Consider contacting Medical Monitor
Grade 3				
Examples include the following: • Somnolence-obtundation or stupor • Confusion-severe disorientation • Encephalopathy-limiting self-care ADLs • Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Management in monitored care or intensive care unit	• Manage as Grade 2 (above)	• Methylprednisolone 1000 mg IV once daily	Improving • Manage as appropriate grade above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Manage as Grade 4 (below) • Contact Medical Monitor
Grade 4				
• Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation • Consider cerebral edema (see Table 53 for management of suspected cerebral edema)	• Manage as Grade 3 (above) • Mechanical ventilation may be required	• Manage as Grade 2 (above)	• Methylprednisolone 1000 mg IV twice a day	Improving • Manage as appropriate grade above • Continue corticosteroids until the event is Grade 1 or less, then quickly taper as clinically appropriate Not improving • Consider 1 g of methylprednisolone 3 times a day or alternative therapy[b] • Contact Medical Monitor

Abbreviations: ADL, activity of daily life; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; IV, intravenous(ly); MRI, magnetic resonance imaging.

a Prophylactic levetiracetam applies to all grades.

b Initiation of alternative therapy should be discussed with the Medical Monitor and includes (but is not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, IV immunoglobulin, and antithymocyte globulin.

Appendix 9 **Stool asservation flow chart**

Asservierung von Stuhlproben für Diversität und Komposition des Mikrobioms

* LD = Lymphodepletion

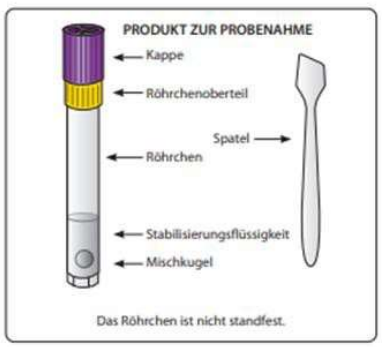
Zeitpunkte
1. Vor Lymphodepletion
2. Tag 0 (Tag der CAR T-Zelltransfusion)
3. Tag 7
4. Tag 14

Protokoll
1. Zwei Röhrchen (Omnigene Gut) pro Zeitpunkt
2. Lagerung bei Raumtemperatur
3. Längerfristige Lagerung bei -80°C
4. Versand nach München

Genzentrum LMU München
AG Subklewe – Viktoria Blumenberg
Feodor-Lynen Straße 25
81377 München

Appendix 10 User Manual for Stool Asservation

OMNIgene·GUT
für Mikrobiom



Zusammenfassung und Erläuterung des Kits:
OMNIgene-GUT stellt das Material und die Gebrauchsanweisung zur Verfügung, mit denen mikrobielle DNS aus einer Stuhlprobe entnommen und stabilisiert werden kann.

Warnhinweise und Vorsichtsmaßnahmen:
- NUR ZUR ÄUSSERLICHEN ANWENDUNG.
- KEINESFALLS das gelbe Oberteil des Röhrchens abnehmen.
- Die Stabilisierungsflüssigkeit im Röhrchen NICHT verschütten.
- Mit den Augen oder der Haut in Kontakt gekommene Stabilisierungsflüssigkeit mit Wasser abspülen. NICHT verschlucken.
- Wenn die entnommene Stuhlprobe flüssig ist, sind die separat bereitgestellten Gebrauchsanweisungen zu beachten.
- Kleinteile können eine Erstickungsgefahr darstellen.

Lagerung: 15 °C bis 25 °C

Transport gemäß den geltenden Vorschriften über den Transport von biologischen Proben. Siehe MSDS (Sicherheitshinweise für den Umgang mit gefährlichen Substanzen) unter www.dnagenotek.com

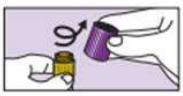
Etikettenlegende:
- Probenahme bis (verwendbar bis)
- REF Katalognummer
- Hersteller
- 15°C 25°C Lagervorschriften
- Achtung, Gebrauchsanweisung lesen
- LOT Losnummer

BENUTZERANLEITUNG

Vor der Probenentnahme alle Anweisungen lesen

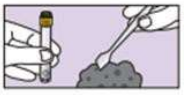
Verfahren:

1 **WICHTIGE SCHRITTE ZUR VORBEREITUNG:**
- Bevor Sie mit der Probenahme beginnen, die Blase leeren.
- Eine Stuhlprobe nehmen, die frei von Urin und Toilettenwasser ist.
- Eventuell ist der Gebrauch von Toilettenpapier oder Taschentüchern erforderlich.



2 Das gelbe Oberteil des Röhrchens festhalten und NUR die lila Kappe vom Kit abschrauben und zur späteren Verwendung beiseite legen.

WICHTIG:
KEINESFALLS das gelbe Oberteil des Röhrchens abnehmen. Die Stabilisierungsflüssigkeit im Röhrchen NICHT verschütten.



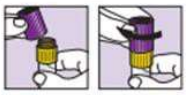
3 Mit dem Spatel eine kleine Menge Stuhlprobe aufnehmen.

4 Die Stuhlprobe in das gelbe Oberteil des Röhrchens hineingeben. Diese Schritte wiederholen, bis die Probe das gelbe Oberteil des Röhrchens ausfüllt.

WICHTIG: KEINESFALLS die Probe in das Röhrchen drücken.

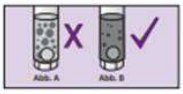
5 Mit dem Spatel waagerecht über die Oberkante des Röhrchens streifen, um überschüssiges Probenmaterial zu entfernen.

Die Außenflächen des Röhrchens und des Oberteils nach Bedarf mit Toilettenpapier oder Taschentuch abwischen.



6 Die lila Kappe mit der geschlossenen Fläche nach unten auf das gelbe Röhrchenoberteil aufschrauben, bis das Röhrchen fest verschlossen ist.

7 Das dicht verschlossene Röhrchen so kräftig und so schnell wie möglich 30 Sekunden lang hin- und herschütteln.



8 Die Stuhlprobe vermischt sich mit der Stabilisierungsflüssigkeit im Röhrchen. Nicht alle Teilchen lösen sich auf.

WICHTIG: Wenn größere Teilchen übrig bleiben, wie in Abbildung A gezeigt, weiter schütteln.

9 Den Spatel in die Originalverpackung zurücklegen oder in Toilettenpapier wickeln und über den Hausmüll entsorgen.

WICHTIG: Die Probe zur Bearbeitung einschicken und dabei die separat bereitgestellte Versandanleitung des Herstellers beachten.

DNA genotek
Überlegene Proben
Bewährte Leistung

Hergestellt in Kanada
DNA Genotek Inc.
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Ottawa, ON, Kanada K2V 1C2

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Appendix 11 **Biosampling and shipping**

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

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

All patients will be screened for an MRD marker by NGS in diagnostic PB or BM samples and residual disease will be tracked in subsequent follow-up samples.

Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

For the sampling of plasma specific tubes are required. When Peripheral Blood (PB) samples are going to be collected in Cell-Free DNA BCT tubes [Streck's black/baige vacutainers], please follow carefully the instructions:

- At predefined time points in the protocol, **20 ml of PB** will be collected in a total of 2 Cell-Free DNA BCT tubes (Streck's, 10 ml each).
- Cell-Free DNA BCT is a direct draw whole blood collection tube intended for collection, stabilization and transportation of plasmatic circulating tumor DNA (ctDNA). The formaldehyde-free preservative reagent contained in Cell-Free DNA BCT stabilizes nucleated blood cells, preventing the release of cellular genomic DNA, and inhibits nuclease-mediated degradation of ctDNA, contributing to the overall stabilization of ctDNA. Samples collected in Cell-Free DNA BCT tubes are stable for up to 14 days at room temperatures, allowing convenient sample collection, transport and storage (Fig1).

Cell-Free DNA BCT specification	
Blood Draw Volume	10.0 ml
Anticoagulant	K_3EDTA
Additive	Proprietary Stabilizing Agent
Storage Prior to use	Room Temperature
Shipment temperature	Room Temperature

Fig1. Cell-Free DNA BCT specification

Since Cell-Free DNA BCT CE contains chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions:

- keep patient's arm in the downward position during the collection procedure;

- hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection;
- release tourniquet once blood starts to flow in the tube, or within 2 minutes of application. Fill tube completely.
- remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180 degrees, and back (Fig 2).

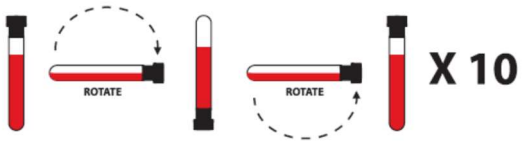

Fig 2. Cell-Free DNA BCT tubes after PB recovering

When stored at 18°C - 30°C, unused Cell-Free DNA BCT is stable through expiration date.
Do not freeze unfilled Cell-Free DNA BCT.
Do not refrigerate or freeze Cell-Free DNA BCT.

Samples will be shipped by courier to the national reference lab at the time pints specified below.

Arm A

	TIME POINTS	SAMPLES
INDUCTION PHASE Year 1	Prior treatment: for all patients before any treatment	10 ml EDTA Blood, 20 ml STRECK tube Blood
		3 ml EDTA Bone marrow
	First treatment evaluation C2D15	10 ml EDTA Blood, 20 ml STRECK tube Blood
	Second treatment evaluation	10 ml EDTA Blood, 20 ml STRECK tube Blood
	D 0, 7, 14 after CAR-T cell infusion	10 ml EDTA Blood, 20 ml STRECK tube Blood
	Week 4 and 10 after CAR-T cell infusion	10 ml EDTA Blood, 20 ml STRECK tube Blood
	Visit months 6,9,12 after CAR-T cell infusion	10 ml EDTA Blood, 20 ml STRECK tube Blood
		Optional 3ml EDTA Bone marrow if routine bone marrow is assessed

Year 2	Visit months 18, 24 after CAR-T cell infusion	10 ml EDTA Blood, 20 ml STRECK tube Blood
Year 3	Visit months 30, 36	10 ml EDTA Blood, 20 ml STRECK tube Blood
Year 4	Visit months 42, 48	10 ml EDTA Blood
	6 monthly intervals until year 7	10 ml EDTA Blood

Arm B

	TIME POINTS	**SAMPLES**
INDUCTION PHASE	Prior treatment: for all patients before any treatment	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5 ml EDTA Bone marrow
	First interim analysis	010 ml EDTA Blood, 20 ml STRECK tube Blood
	Second interim analysis	
	End of treatment C6D21	10 ml EDTA Blood, 20 ml STRECK tube Blood
		5ml EDTA Bone marrow
Year 1	Visit months 6,9,12	10 ml EDTA Blood, 20 ml STRECK tube Blood
Year 2	Visit months 18, 24 after CAR-T cell infusion	10 ml EDTA Blood, 20 ml STRECK tube Blood
Year 3	Visit months 30, 36	10 ml EDTA Blood, 20 ml STRECK tube Blood
Year 4	Visit months 42, 48	10 ml EDTA Blood
	6 monthly intervals until year 7	10 ml EDTA Blood

Information for shipment will be provided

Appendix 12 Safety Definitions

Please see the standard definitions for Adverse Event (AE), Adverse (drug) reaction (AR), Unexpected Adverse (Drug) Reaction (UAR), Serious Adverse Event (SAE) and (Suspected Unexpected Serious Adverse Reaction ((S)USAR) in ANNEX 13

Adverse Event (AE),
An Adverse Event (AE) is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or in a clinical investigation subject who has administered a medicinal or pharmaceutical product or is participating in a clinical study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

This may include the following:

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

Adverse (drug) reaction (AR),
Adverse drug reactions (ADR) are all noxious and unintended responses 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, i.e., the relationship cannot be ruled out.

Unexpected Adverse (Drug) Reaction (UAR),
This is defined to be an adverse drug reaction which nature and severity is not consistent with the applicable product information (e.g. Summary of Product Characteristics for an authorized product or Investigator's Brochures for an unauthorized investigational medicinal product), or an event which has not previously been observed or documented and which is thus not on the basis of what might be anticipated from the pharmacological properties of the product.

Serious Adverse Event (SAE) / Serious Adverse (Drug) Reaction (SAR)

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

- results in death (regardless of cause)

- is life threatening
  - places the subject, in the view of the investigator, at immediate risk of death at the time of event
  - It does not refer to an event that, which hypothetically might have caused death if it were more severe
- results in hospitalization (overnight stay) or prolongation of existing hospitalization, excluding the following:
  - Hospitalization that does not necessitate an overnight stay.
  - routine scheduled treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Hospitalisation planned before subject entered in the study
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication treated in the study and which has not worsened since the start of treatment with the investigational medicinal product
- results in persistent or significant disability or incapacity for the subject
  - disability is a substantial disruption of a person's ability to conduct normal life functions
- is associated with a congenital anomaly or birth defect
- is qualified as "other" important medically significant event or condition e.g. the event may jeopardize the subject or may require intervention to prevent one of the outcome listed above (e.g. intensive treatment in an emergency room or at home).

Serious Adverse (Drug) Reaction (SAR)
This is defined as an adverse drug reaction that is serious and at least possibly related to IMP (see SAE criteria above).

(Suspected Unexpected Serious Adverse Reaction ((S)USAR)

A SUSAR is an adverse reaction, which is both serious and unexpected because the nature or severity of this event is not consistent with the reference safety information.

Appendix 13 **Recommendations for contraception**

The period of contraception depends on the used drugs during the study. The recommendations may change during the study conduction. The following specifications are based on the SmPCs of the auxiliary products valid at the start of the study (as of July 2023). The specifications may change during the course of the study. It is the responsibility of the investigators to take into account possible changes in the SmPCs of the auxillary drugs locally used during the course of the study.

Please refer to chapter 16.11 for definitions and additional information.

Auxiliary Product	**Contraception for women of childbearing potential**	**Contraception for fertile men**
BCNU	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Bendamustine	while on treatment	while on treatment and for at least 6 months after treatment
Carmustine	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Cisplatin	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Cyclophosphamide	while on treatment and for at least 12 months after treatment	while on treatment and for at least 12 months after treatment
Cytarabine	not defined (6 months recommended by sponsor based on other chemotherapy drugs)	Not defined
Dexamethasone	Not defined	Not defined
Doxorubicin	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Etoposide	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Fludarabine	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Melphalan	while on treatment and for at least 6 months after treatment	while on treatment and for at least 6 months after treatment
Neupogen	while on treatment	Not defined
Oxaliplatin	while on treatment and for at least 4 months after treatment	while on treatment and for at least 6 months after treatment
Prednisolone	Not defined	Not defined

Rituximab	while on treatment and for at least 12 months after treatment	
Tocilizumab	while on treatment and for at least 3 months after treatment	
Thiotepa	while on treatment	while on treatment and for at least 12 months after treatment
Vincristine	while on treatment	while on treatment