Title of the study:	Ibrutinib and standard immuno-therapy R-CHOEP-14 in younger, high risk patients with diffuse large B-cell lymphoma
Short title of study:	R-CHOEP - brut
Sponsor's Study Code:	UKM17_0017
EudraCT-No.:	2017-003256-22
Sponsor:	Universitätsklinikum Münster
Coordinating investigator:	Prof. Dr. med. Norbert Schmitz Medizinische Klinik A Hämatologie, Hämostaseologie, Onkologie und Pneumologie Universitätsklinikum Münster
Indication:	First-line therapy of diffuse large B-cell lymphoma (DLBCL) in younger patients (18-60 years) with age-adjusted International Prognostic Index (aaIPI) 2-3.
Study design:	Prospective, multicenter, non-randomized, open-label, phase II study with safety run-in phase.
Investigational Medicinal Product:	Imbruvica 140 mg hard capsules (active substance: Ibrutinib).
Treatment:	<u>Ibrutinib:</u> Ibrutinib capsules will be administered orally once daily at a dose of 560 mg (4 x 140 mg hard capsules) for 112 days (max. until day 14 of cycle 8 of R-CHOEP). <u>R-CHOEP-14:</u> All patients will receive 8 cycles of immunochemotherapy every two weeks with the following doses per cycle: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (dose capped at 2 mg), etoposide 300 mg/m^2, prednisolone 500 mg. <u>Radiotherapy:</u> All patients with bulky disease (≥ 7.5 cm) or extralymphatic involvement will receive radiotherapy at a dose of 39.6 Gy.
Primary objectives:	The primary objective is to estimate the 2-year progression-free survival (PFS) achieved with ibrutinib in combination with immunochemotherapy with rituximab, cyclophosphamide,

	doxorubicin, vincristine, etoposide, and prednisone (R-CHOEP) in younger, high-risk patients.
Secondary objectives:	The secondary objectives for efficacy are to evaluate overall survival (OS), event-free survival (EFS), rate of complete remission (CR), rate of partial remission (PR), overall response rate (ORR) (CR+PR), progression rate, relapse rate and the duration of response. Other secondary objectives of the trial are to assess the • rate of treatment-related deaths, • feasibility, safety, toxicity, and protocol adherence of ibrutinib when combined with R-CHOEP and • outcome according to biological parameters of the tumor.
Primary endpoint:	2-year PFS with 95% confidence intervals (CI) in 75 patients without CNS disease.
Secondary endpoints:	Secondary endpoints for efficacy: OS, EFS, CR rate, PR rate, ORR, progression rate, relapse rate, duration of response. Other secondary endpoints: AEs, SAEs, treatment-related deaths, Secondary malignancies, Number and duration of therapy cycles, Cumulative doses of cyclophosphamide, doxorubicin, vincristine, etoposide, rituximab and ibrutinib, outcome according to biological parameters.
Pre-planned additional analysis	Another objective for efficacy is to compare patients and the PFS achieved in this study with patients from the previous R-MegaCHOEP phase III trial (DLBCL patients with aaIPI 2 or 3 treated with R-CHOEP-14) (Schmitz et al., Lancet Oncol 2012).
Study population:	Patients with primary diagnosis of DLBCL aged 18 - 60 years and aaIPI 2 or 3.
Patient number:	75 patients with DLBCL
Number of Study Centers:	12 institutions will participate.
Inclusion Criteria:	1. Sign (or their legally-acceptable representatives must

	sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study. 2. Age between 18-60 years 3. Risk score 2 or 3 according to aaIPI 4. Histology: Primary diagnosis of - DLBCL (NOS) or - High-grade B-cell Lymphoma with MYC and BCL2 and/or BCL6 rearrangements or - High-grade B-cell lymphoma, NOS 5. Performance status: ECOG 0-3 6. Stage: all stages according Ann Arbor 7. ANC: > 1000 cells/microliter (independent of growth factor support) 8. Platelet count ≥ 100.000/mm^3 or ≥ 50.000/mm^3 if bone marrow involvement independent of transfusion support in either situation. 9. ALT and AST: < 3 x ULN 10. Total Bilirubin: < 1.5 x ULN 11. Serum Creatinine: < 2 x ULN or estimated GFR (GFR [Cockcroft-Gault]) ≥ 40 ml/min 12. Women of childbearing potential and men who are sexually active must be practising a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For male subjects, these restrictions apply for 6 months after last dose of study drug. For female subjects, they apply for 12 months after last dose of study drug. 13. Women of childbearing potential must have negative serum or urine beta-human chorionic gonadotropin pregnancy test at screening. Women who are pregnant or breast-feeding are ineligible for this study. 14. Willing/ able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion Criteria:	1. Vaccinated with live, attenuated vaccines within 4 weeks of inclusion. 2. Major surgery within 4 weeks of inclusion. 3. Any prior lymphoma-directed therapy (except pre-phase treatment). 4. Known central nervous system involvement. 5. Diagnosed or treated for malignancy other than DLBCL, in particular any other (indolent) lymphoma. 6. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional classification. 7. Bone marrow involvement > 25% 8. History of stroke or intracranial hemorrhage within six months of inclusion. 9. Requires anticoagulation with warfarin or equivalent vitamin K antagonist. 10. Known history of human immunodeficiency virus or active hepatitis C virus or active hepatitis B virus infection or any uncontrolled active systemic infection requiring IV antibiotics. 11. Requires treatment with strong CYP3A inhibitors. 12. Use of preparations containing St. John's Wort. 13. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk. 14. Concurrent treatment with other investigational agent or X-ray therapy. 15. Previous chemo- or radiotherapy for any other malignancy, in particular indolent lymphoma. 16. Any psychological, cognitive, familial, sociological or geographical condition that, in the investigator's opinion, compromises the patient's ability to understand the patient

	information, to give informed consent or to comply with the study protocol. 17. Participation in another interventional clinical trial during this trial. There may be exceptions at the discretion of the coordinating investigator.
Visits:	<u>Screening visit</u> • Patients will undergo a screening visit prior to any treatment to verify study eligibility. <u>Treatment period:</u> • Prephase therapy (highly recommended prior the first R-CHOEP cycle). • Patients will receive 8 therapy cycles of R-CHOEP, each lasting 2 weeks. • Interim restaging (approx. 10 to 14 days after start of cycle 4). <u>Final restaging:</u> For patients without radiotherapy after immunochemotherapy: • Final restaging (Approx. 6 to 8 weeks after commencement of the last cycle of R-CHOEP). For patients with radiotherapy after immunochemotherapy: • Restaging before radiotherapy (Approx. 2 to 4 weeks after start of cycle 8 of R-CHOEP). • Final restaging after radiotherapy (Approx. 2 to 4 weeks after completion of radiotherapy). <u>Follow up visits:</u> • For patients responding to R-CHOEP plus ibrutinib at final restaging, a first follow-up should be performed 3 months after final restaging. Thereafter, 3-monthly follow-up examinations are recommended during the first 2 years after the completion of chemotherapy, followed by 6-monthly follow-up visits. Follow-up observation will end for all patients 2 years after the last patient enrolled in the study.
Analysis of feasibility and safety in the run-in phase:	A first safety analysis will be done after 5 patients completed all per-protocol treatment. A detailed analysis of all adverse

	events (AE) and serious adverse events (SAE) occurring during all documented treatment cycles in all patients included will be performed and compared to AE experienced in patients given R-CHOEP only in a previous trial (Schmitz et al., Lancet Oncology 2012), and presented to the Data Safety Monitoring Committee (DSMC). A further safety analysis will be done after the completion of final restaging of the first 25 patients.
Statistical Methods:	2-year PFS with 95% CI will be calculated. A Cox regression analysis with adjustments for known clinical and biological risk factors will be performed. PFS and OS will be compared to PFS and OS achieved with R-CHOEP-14 in previous trials. When comparing PFS curves a precision of app. +/ - 10% (95% confidence interval) will be achieved. If study treatment with ibrutinib improves PFS to 85% the precision will be app. +/ - 9%.
Major analyses:	All major analyses will be done according to the intention-to-treat principle. Kaplan-Meier curves will be used to present PFS; projection of 2-year PFS with 95% CI will be calculated. Cox regression models will be used to adjust for prognostic factors.
Timelines:	First patient in: February 2018 Last patient in: February 2020 Follow up ends: February 2022
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