2.2 Protocol Synopsis DSHNHL 2009-1

Trial number:	DSHNHL 2009-1
Short title of study:	OPTIMAL>60
Title of study:	Improvement of outcome and reduction of toxicity in elderly patients with $CD20^+$ aggressive B-cell lymphoma by an optimised schedule of the monoclonal antibody rituximab, substitution of conventional by liposomal vincristine and FDG-PET based reduction of therapy in combination with vitamin D substitution.
Indication:	Elderly patients (61-80 years) with aggressive $CD20^+$ B-NHL
Primary objective of study:	"OPTIMAL>60 Less Favourable" Patients with less favourable prognosis: • To test whether progression-free survival (PFS) can be improved by substituting conventional by liposomal vincristine; • To test whether PFS can be improved by 12 optimised applications instead of 8 2-week applications of rituximab. "OPTIMAL>60 Favourable": Patients with favourable prognosis: • Comparison of neurotoxicity of conventional and liposomal vincristine; • Determination of PFS for the treatment strategy of reducing treatment in patients with negative FDG-PET after 4 x R-CHOP/CHLIP-14 (PET-4) and comparison with the corresponding patient population in RICOVER-60.
Secondary objectives:	"OPTIMAL>60 Favourable" and "OPTIMAL>60 Less Favourable": • Comparison of the prognostic value of a pre-treatment FDG-PET (PET-0) with conventional CT/MRT. • Investigation of the prognostic value of different FDG-PET derived imaging biomarkers for lymphoma load (SUV, SUR, MTV, TLG, TLG_{SUR}). • Comparison of the FDG-PET-based individualised treatment strategy in OPTIMAL>60 with the fixed (pre-defined) treatment strategy in RICOVER>60. • Estimation of the vincristine-related neurotoxicity ("OPTIMAL>60 Less Favourable only, since vincristine related neurotoxicity is primary objective of the study in favourable patients) and other toxicities (all patients). • Determination of the therapeutic efficacy of a vitamin D substitution by comparing the first patients without vitamin D substitution with patients with a vitamin D substitution. • Comparison of the vincristine related neurotoxicity before and after amendment #4. • Comparison of CNS events before and after amendment #4. • Comparison of the Cheson, Lugano and RECIL response criteria. • Evaluation on the role of (metabolic) tumor volume to confirm or refute the hypothesis that optimized rituximab should improve the outcome of patients with a high (metabolic) tumor volume more than that of patients with low MTV and to analyse the substitution of conventional vincristine by liposomal. • Estimation of the prognostic value of the pre- and post-prephase treatment ECOG performance state. • Estimation of the prognostic value of the reference pathology biomarkers. • Estimation of the prognostic value of plasma biomarkers. "OPTIMAL>60 Favourable": • Determination, if the addition of 2xCHOP/CHLIP-14 plus involved-node radiotherapy can compensate for the assumed worse prognosis of patients with a positive PET after 4xR-CHOP/CHLIP -14 compared to patients with a negative PET after 4xR-CHOP/CHLIP -14. Comparison of PET positive patients who receive two additional R-CHOP-14 plus radiotherapy with those who do not.

	"OPTIMAL>60 Less Favourable": • To determine whether the assumed worse prognosis of patients with bulky disease PET-positive after chemotherapy compared to patients with a PET-negative bulk after chemotherapy can be compensated by radiotherapy to PET-positive bulky disease. • Comparison of patients with a positive PET who receive radiotherapy with those who do not.
Study design, statistics and patient numbers:	"OPTIMAL>60 Less Favourable": Multi-centre open-label randomised 2 x 2 factorial phase III study design powered to detect a reduction of the hazard rate to 0.68 or less (corresponding to a 9% improvement in the 3-yr PFS-rate) in each of the two questions independently (alpha = 5%, Power 80%). For this goal 864 patients are required. "OPTIMAL>60 Favourable"*:* A multi-centre cohort study designed to demonstrate that neurotoxicity can be reduced by liposomal vincristine and that 3-yr PFS is close to 88% (with a 95%-confidence limit of +/- 4%) and to compare toxicity of conventional to liposomal vincristine. For this goal 288 patients are required. The total of 1152 patients should be sufficient to achieve the secondary objectives
Study population:	Patients with untreated aggressive $CD20^+$ B-cell lymphoma 61 to 80 years of age with any stage according to Ann Arbor and any risk factor according to the International Prognostic Index (IPI) without major accompanying disorder.
Treatment:	All patients receive R-CHOP/CHLIP-14 with either conventional or liposomal vincristine and will receive vitamin D substitution with a target serum level of 65 ng/ml. Due to the DSMC recommendation of 09th November 2018 all patients receive conventional vincristine. "OPTIMAL>60 Favourable": Favourable patients (IPI=1 [age>60], no bulky disease) receive 4 cycles of R-CHOP~~/CHLIP~~14 induction and 2x R-CHOP~~/CHLIP~~-14+2x R + involved-site radiotherapy (39.6 Gy) as consolidation therapy unless FDG-PET is negative after 4 cycles (PET-4), in which case consolidation consists of 4x R only. "OPTIMAL>60 Less Favourable": Less favourable patients receive 6x R-CHOP/CHLIP-14+2x R or 6x CHOP/CHLIP-14 +12x Opti-R with radiotherapy (39.6 Gy) to bulky disease in both arms except for bulky areas that are negative in FDG-PET after 6 cycles (Opti-) R-CHOP/CHLIP-14 (PET-6). (Recruitment goal reached on 05th October 2018)
Primary endpoint:	Progression-free survival
Secondary endpoints:	for efficacy: rate of complete remissions (CR rate), rate of partial responses (PR rate), rate of primary progressions, relapse rate, event-free survival (EFS) and overall survival (OS); rate and CTC grades of polyneuropathy. Prognostic value of the FDG-PET derived imaging biomarkers for lymphoma load: SUV (standardized uptake value), SUR (standardized uptake ratio), metabolic tumor volume (MTV), total lesion glycolysis (TLG), SUR-derived TLG (TLG_{SUR}). Different reference pathology biomarkers from tumor tissue and circulating tumor DNA in the plasma
Analysis:	**Primary objectives:** "OPTIMAL>60 Less Favourable": To test the effects of substitution of conventional by liposomal vincristine and of a 2-week applications of 8x rituximab by an optimised application of 12 x rituximab stratified log rank tests will be performed for each question (stratified for IPI-factors). Proportional hazard models will be used to investigate treatment interaction and to obtain estimates for the single treatment effects (HR) adjusting for the IPI-factors. "OPTIMAL>60 Favourable" Grade of neurotoxicity will be estimated and indicated with a 95% confidence interval (CI) separated to each type of vincristine. To investigate the 3-year PFS with 95% CI the Kaplan-Meier estimator will be used.

	Secondary objectives: To analyze how (i. e. in which direction) and how often a pre-treatment FDG-PET-based assignment (PET-0) would have affected the assignment of a patient to a different stage, IPI risk group or treatment, respectively. The different FDG-PET derived imaging biomarkers for lymphoma load (SUV, SUR MTV, TLG, TLG_{SUR}) will be analyzed for their relationship with CR-rate, PR-rate, rate of primary progressions, relapse rate, EFS, PFS and OS. To compare the efficacy and side effects of the (post-induction therapy FDG-PET-based) individualised treatment strategy in OPTIMAL>60 with the fixed (pre-defined) treatment strategy in RICOVER-60. Rates and grades of polyneuropathy will be determined according to CTC-v4.03. Comparison of the patients without vitamin-D-substitution with patients receiving a vitamin-D-substitution. The vincristine related neurotoxicity rates before and after amendment #4 will be documented and statistical tests will be performed. The time to CNS event will be described in an exploratory way. Kaplan-Meier curves will be used to represent the time to CNS event. The 3-year rates will be estimated and presented with 95% confidence interval. All analyses will also be performed with respect to known prognostic factors for CNS event. Crosstabs for Cheson, Lugano and RECIL responses will be presented and statistical tests will be performed. Kaplan-Meier curves and Cox models for survival endpoints will be performed to confirm or refute the hypothesis that optimized rituximab should improve the outcome of patients with a high (metabolic) tumor volume more than that of patients with low MTV and to analyse the substitution of conventional vincristine by liposomal. The change of ECOG due to prephase treatment will be described. Kaplan-Meier curves for survival endpoints according to the variation of the ECOG (before and after prephase) will be presented. Univariable and multivariable (adjusted for known prognostic factors) analyses will also be performed. Kaplan-Meier curves for PFS and OS according to biomarkers will be presented. Univariable and multivariable analyses will also be performed with respect to IPI factors and strata. The sensitivity and the specificity of the demonstration of circulating lymphoma-derived DNA in the peripheral blood of patients will be determined at pre-defined time points and its prognostic value will be analysed in a prospective fashion. The sensitivity and specificity of the ctDNA assay will be compared with the diagnostic imaging techniques used for staging and restaging and their prognostic value will be compared with respect to survival endpoints. Kaplan-Meier curves for survival endpoints according to PET-positive (bulky) patients with and without radiotherapy and PET-negative patients will be presented. Univariable and multivariable (adjusted for known prognostic factors) analyses will also be performed. Survival rates with 95% confidence interval will be presented.
Timelines:	Start of study 11/2011, assumed end of recruitment 12/2020, assuming a recruitment rate of 112 patients in the first and 130 patients per year in the following 8 years. Follow-up observation within the study will end for all patients recruited in amendment 3, 4, 5 and 6 3 years after the end of therapy of the last patient enrolled in the study, presumably ending in 05/2024. Follow-up observation within the study will end 03/2020 for all patients recruited before amendment 3. Duration of follow-up within the clinical study at least 3 years, not longer than 7.5 years for the individual patient. Outside this trial patients will be followed-up life-long.
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