Protocol Synopsis DSHNHL 2015-1

Trial number:	DSHNHL 2015-1
Short title of study:	Niveau
Title of study:	Improvement of Outcome in Elderly Patients or Patients not eligible for high-dose chemotherapy with Aggressive Non-Hodgkin Lymphoma in first Relapse or Progression by adding Nivolumab to Gemcitabine, Oxaliplatin plus Rituximab in case of B-cell lymphoma.
Indication:	Patients with first relapse or progression of aggressive Non-Hodgkin's Lymphoma who are not eligible neither for autologous nor allogeneic stem cell transplantation.
Primary objective of study:	Improvement of 1-yr PFS by nivolumab plus (R)-GemOx followed by nivolumab consolidation instead of (R)-GemOx alone.
Secondary objectives:	• To determine whether survival can be increased by adding nivolumab to standard (R)-GemOx. • To determine whether outcome can be improved by adding nivolumab to standard (R)-GemOx. • To determine toxicity and protocol adherence of standard (R)-GemOx with or without nivolumab. • To evaluate quality of life of patients with relapsed or refractory aggressive Non-Hodgkin's Lymphoma treated with (R)-GemOx with or without Nivolumab. • To analyze outcome according to biological parameters.
Study design, statistics and patient numbers:	International, multicentre, randomised, open-label, treatment optimisation study, preceded by safety run-in phases conducted for B-cell and T-cell lymphoma separately. It is the aim to demonstrate an improvement in 1-years PFS rate from 27% to 42% (i.e. a hazard ratio of 0.66). The two-sided question will be answered with an error probability of alpha= 5% (two sided) and a power of 80%. Therefore, it will be necessary to analyze 292 B cell lymphoma patients (146 patients in each arm). Approximately 5% of patients are expected to be lost to follow-up. Therefore 310 patients with B-cell lymphoma will be randomized. In parallel a maximum of 78 patients with T-cell lymphoma will be included.
Study population:	Patients with first relapse or progression of aggressive Non-Hodgkin's Lymphoma who are not eligible for neither autologous nor allogeneic stem cell transplantation, defined as age >65 years or > 18 years old with HCT-CI score >2 or patients who underwent prior autologous stem cell transplantation and are not eligible for allogeneic stem cell transplantation
Treatment:	Immunochemotherapy consists in eight cycles (R)-GemOx (Gemcitabine 1000 mg/m^2, d1, Oxaliplatin 100 mg/m^2, d1, Rituximab 375 mg/m^{2}in case of B-cell lymphoma disease, repeated every 2 wks) **Standard arm:** eight cycles of (R)-GemOx. **Experimental arm:** eight cycles of nivolumab (240 mg) plus (R)-GemOx in 2-wk intervals followed by additional 9 infusions of Nivolumab (480mg) in 4-wk intervals as consolidation or up to progression or unacceptable toxicity, whatever occurs first. Switching to flat-dosing 240 mg every 2 weeks (Q2W) and 480 mg given every 4 weeks (Q4W) should start

	immediately when protocol version 6.0 will be activated. All patients are treated in the experimental arm in the safety run-in phases
Primary endpoint:	1-year Progression-free survival
Secondary endpoints:	• complete response rate after eight cycles of (R)-GemOx • partial response rate after eight cycles of (R)-GemOx • overall response rate after eight cycles of (R)-GemOx • duration of response • progression rate • rate of treatment-related deaths • relapse rate • Event-free survival • Overall survival • Toxicity • Protocol adherence • quality of life as assessed by the EQ-5D-5L. • outcome according to PD-L1 and PD-1 expression, cell of origin, 9p24.1 alterations
Analysis of safety run-in phases	Safety analysis will be done, when both 10 patients with B-cell lymphoma as well as 5 patients with T-cell lymphoma have been included. In case the intended number of patients both B-cell as well as T-cell lymphoma will not be recruited, a safety analysis will be performed after inclusion of either 15 patients with B-cell or 7 patients with T-cell lymphoma at the latest. The analysis will be done immediately after the last patient received the interim restaging after four cycles of (R)-GemOx. A detailed description of AEs/SAEs and therapy-associated deaths will be performed in B-cell and T-cell lymphoma separately. A substantial amendment will be submitted before inclusion of any further patients in the randomized treatment phase.
Safety analysis in the randomisation phase.	The analysis will be performed after the randomisation of thirty patients in the experimental arm. A detailed description of AEs/SAEs, hematotoxicity, dose of (R)-GemOx, dose of Nivolumab, duration of therapy and therapy-associated deaths will be performed for both treatment arms (with and without Nivolumab), also separately for B- and T-cell patients and presented to the Data Safety Monitoring Committee.
Major Analysis:	All major analyses will be done according to the intention-to-treat principle. The log-rank test will be used in a primary analysis to compare the progression-free survival (PFS) for the two treatment strategies ((R)-GemOx vs. Nivolumab plus (R)-GemOx followed by Nivolumab consolidation). Kaplan-Meier curves will be used to represent the PFS. In addition, a projection of the 1-year PFS rate with 95% CI will be prepared for the two treatment strategies. Cox regression modells will used to adjust for prognostic factors/strata.
Timelines:	For recruitment of 310 patients with B-cell lymphoma we expect a slower recruitment during the first year of the study with a recruitment rate of 30 patients and 70 patients per year in the following years resulting in a recruitment period of 5 years, followed by 2 years of observation after inclusion of the last patient. With the expected start of recruitment in Q4/2017, the recruitment period will finish in Q4/2022 and the follow-up in Q4/2024. During the recruitment period of 5 years a maximum of 78 patients with T-

	cell lymphoma will be included.
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