SYNOPSIS

<table>
<tr><td>Title</td><td>A prospective, multicenter randomized phase II trial investigating Gemcitabine/Oxaliplatin/Rituximab with or without Mor208 for patients with relapsed/refractory aggressive lymphoma</td></tr>
<tr><td>Short title</td><td>GOAL II</td></tr>
<tr><td>EudraCT</td><td>2019-002373-59</td></tr>
<tr><td>Sponsor trial code</td><td>19-00153</td></tr>
<tr><td>Indication</td><td>Malignant B-cell lymphoma
- aggressive variants, spec. Diffuse large B-cell lymphoma, aggressive Lymphoma NOS, High grade Lymphoma, PMBCL, (Plasmablastic Lymphoma (if CD 19 positive)), etc.
- follicular lymphoma grade 3B, transformed indolent lymphoma, (Quorum not more than 20 % of the patient population)
- transformed indolent lymphoma, (Quorum not more than 20 % of the patient population)
- Relapsed disease, no curative option available</td></tr>
<tr><td>Phase</td><td>II</td></tr>
<tr><td>Treatments</td><td>Test product: Tafasitamab (Mor208)
Reference therapy: R-Gem/Ox (non-IMP / standard of care)

<u>Standard Group A:</u>
<table>
<tr><th>Drug</th><th>Dose</th><th>Schedule</th></tr>
<tr><td>Rituximab</td><td>375 mg/m^2 iv or 1400mg sc</td><td>day 1</td></tr>
<tr><td>Gemcitabine</td><td>1000 mg/m^2</td><td>day 1 (or 2 for organizational reason at discretion of investigator)</td></tr>
<tr><td>Oxaliplatin</td><td>100 mg/m^2</td><td>day 1 (or 2 for organizational reason at discretion of investigator)</td></tr>
<tr><td colspan="3">cycle length 14 days; max. 8 cycles</td></tr>
</table>
<u>Experimental Group B:</u>
Induction:
<table>
<tr><th>Drug</th><th>Dose</th><th>Schedule</th></tr>
<tr><td>Tafasitamab</td><td>12 mg/kg body weight</td><td>day 1 and day 8</td></tr>
<tr><td>Rituximab</td><td>375 mg/m^2 IV or 1400mg sc</td><td>day 1 (or 2 for organizational reason at discretion of investigator)</td></tr>
<tr><td>Gemcitabine</td><td>1000 mg/m^2</td><td>day 1 (or 2 for organizational reason at discretion of investigator)</td></tr>
<tr><td>Oxaliplatin</td><td>100 mg/m^2</td><td>day 1 (or 2 for organizational reason at discretion of investigator)</td></tr>
<tr><td colspan="3">cycle length 14 days; max. 8 cycles</td></tr>
</table>
Consolidation:
<table>
<tr><th>Drug</th><th>Dose</th><th>Schedule</th></tr>
<tr><td>Tafasitamab</td><td>12 mg/kg body weight</td><td>day 1 and 15 in cycle cC1 - cC12</td></tr>
<tr><td>Tafasitamab</td><td>12 mg/kg body weight</td><td>day 1 in cycle cC13 - cC24,</td></tr>
<tr><td colspan="3">cycle length 28 days; max. 24 cycles (cC=consolidation Cycle)</td></tr>
</table></td></tr>
<tr><td>Primary objective</td><td>Improvement of ORR in the experimental arm versus the standard treatment
(Analysis will be based on Lugano -Criteria)</td></tr>
<tr><td>Secondary objectives</td><td>Improvement of CR-Rate, PFS, OS
Improvement ORR based on Cheson 2007-criteria
Improvement of QoL (global QoL, physical functioning, fatigue)</td></tr>
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Exploratory objectives	Improvement of other QoL dimensions
Trial design	Prospective, open label, randomized trial Randomized 2:1 comparison of the Mor208-R-Gem/Ox combination to R-Gem/Ox. A safety analysis will be performed after 20 patients in experimental arm B have reached End of Induction (regular or individual).
Trial population	Main inclusion criteria: Subjects meeting all of the following criteria will be considered for enrollment to the trial: - Histologically proven diagnosis of a) diffuse large cell B-cell lymphoma, and other aggressive B-cell lymphomas according to the WHO 2016 revision (specified in detail in the protocol) b) follicular lymphoma grade 3B and c) transformed indolent B-cell lymphoma (not more than 20 % of the patient population) according to the WHO classification (central pathology review) - Relapsed disease or refractory disease, at least one but no more than two prior treatment lines - age ≥ 18 years - No curative option available (age ≥ 65yr and/or HCT-CI Score > 2) or s.p. HDT - At least 1 measurable tumor mass (>1.5 cm x >1.0 cm) or bone marrow infiltration - Adequate bone marrow reserve: a) Platelets of at least 100 000/µl b) absolute neutrophil count of at least 1000/µl - Adequate hepatic and renal function: a) Alanine aminotransferase (ALT) <2.5 x upper limit of normal (ULN) b) Aspartate aminotransferase (AST) <2.5 x upper limit of normal (ULN) c) Total bilirubin <1.5 x upper limit of normal (ULN) unless related to lymphoma - Measured or calculated eGFR >50 ml/min (institutional standard) - Eastern Cooperative Oncology Group (ECOG) performance Status ≤2, unless tumor associated and expected to improve on treatment - Signed informed consent - Adequate contraception (if needed) Main exclusion criteria: - CNS involvement (brain MRI is required only in cases of clinically suspicious involvement) - no adequate pretreatment (R-CHOP-like) - systemic treatment within last 6 weeks, steroids for bridging are allowed - prior allogeneic transplantation and prior anti CD19 CAR T-cell therapy - pregnant or breast-feeding women - severe concomitant disease (e.g. uncontrolled arterial hypertension, heart failure (NYHA III-IV), uncontrolled diabetes mellitus, pulmonary fibrosis, uncontrolled hyperlipoproteinemia) - Prolongation of QTc interval > 450 ms, demonstrated in electrocardiogramm (two separate or one in triplicate) or family history for Long QT-syndrome - active uncontrolled infections including HIV-positivity, active Hep B or Hep C - Medical or psychological condition that would not permit completion of the trial or signing of informed consent - Diagnosed or treated for a malignancy other than NHL except: a) adequately treated non-melanoma skin cancer b) curatively treated in-situ cancer of the cervix c) ductal carcinoma in situ (DCIS) of the breast d) other solid tumors curatively treated with no evidence of disease for >2 years e) prostate cancer with a life expectancy of more than 2 years - Concurrent treatment with another investigational agent or within the last 6 weeks prior to treatment initiation. Concurrent participation in non-treatment studies is not excluded. - Known intolerance to any of the study drugs or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product
Trial duration and dates	First subject in (FSI): Q2/2020 Last subject in (LSI): Q2/2022 Last subject last treatment: Q3/2024 Last subject out (LSO): Q3/2027 (LPLT + max. 3 years or latest patient alive followed for 3 years) Expected final study report: Q1/2028 Overall expected trial duration: Q4/2020 – Q3/2027

	Publication plan: - Protocol publication 2019 upon activation - Safety Analysis (20 patients arm B, EoI) Lugano 2021 - Primary analysis (ORR) ASH 2022 or ASCO 2023 - Final analysis (ORR) 2025 - Peer reviewed publication of the study results 2025/26
Number of subjects	It is planned to screen up to 140 subjects, Enrollment will be stopped if 126 subjects are randomized with a randomization ratio of 2:1.
Number of sites	Approx. 25-30 trial sites in Germany are planned to participate.
Primary endpoint	ORR of the regimen after cycle 8 (end of induction) or the individual treatment end, tested in the entire cohort of patients.
Secondary endpoints	- ORR (Cheson 2007-criteria) - Progression free survival (Lugano) - Overall survival - Improvement of CR-Rate (Lugano) - Best response (Lugano) - Quality of Life measured with EORTC QLQ C30 and NHL-HG29 - ORR in separate GCB vs. non GCB-analysis is planned
Safety Endpoints	Safety and tolerability as measured by rate of AE, SAE compared between Arm A and B
Exploratory endpoints	- MRD-course during induction, maintenance and follow up - immune reconstitution in maintenance and follow up
Statistical analysis	The primary analysis for stage 1 is to assess the tolerability of the test product. Therefore, only safety parameters like adverse events will be analyzed. This will be done by descriptive methods. The significance level will not be adjusted for this analysis. The primary analysis parameter for the second stage will be the ORR after cycle 8. The ORR of the test product will be compared to the ORR of the reference therapy by a chi-square test on a one-sided level of significance of α=5%. The primary analysis population will be the ITT population consisting of all randomized patients. Missing values will be regarded as if no response is achieved. PFS and OS will be analyzed secondary with methods of survival analysis like Kaplan-Meier Plots and exploratory Logrank-Tests. Quality of life will be analyzed using linear mixed models.