6 Study objectives

6.1 Primary objective

- To increase 12 months DFS of DH/TH-HGBL patients in CMR after DA-EPOCH-R from 70% to 85% with nivolumab consolidation treatment

6.2 Secondary objectives

- To evaluate CMR rate after completion of DA-EPOCH-R
- To evaluate 18 months PFS and OS of all patients
- To evaluate 12 months overall survival under consolidation (OSc) of patients registered for consolidation
- To evaluate safety of nivolumab treatment
- To explore the accuracy of mid-treatment ^{18}F-FDG PET-CT to predict CMR end-of-treatment.
- To explore the efficacy of nivolumab with regard to induction of MRD negativity by circulating tumor DNA and extracellular vesicle associated microRNA
- To explore PD1/PDL1 expression in relation to NGS, GEP and to outcome
- To explore T cell subsets and clonality during treatment and in relation to MRD

7 Study design

The trial is designed as a prospective, multicenter, non-randomized phase II trial. All eligible patients will be registered during or after first R-CHOP, but before start of DA-EPOCH-R treatment and before start of nivolumab treatment. Details of all treatments (dose and schedule) are given in paragraph 9

8 Study population

8.1 Eligibility for registration for induction

All patients must be registered before start of DA-EPOCH-R treatment and must meet all of the following eligibility criteria.

8.1.1 Inclusion criteria for DA-EPOCH-R induction

- High-grade B-cell lymphoma, with *MYC* in combination with *BCL2* and/or *BCL6* rearrangements as assessed by FISH according to the WHO 2016 classification.
- Age ≥ 18 year.

- Patient started with or has received one course of full dose R-CHOP. [Reversed R-CHOP (cyclophosphamide, vincristine and doxorubicin on day 5) is allowed; local radiation or short course (max 7 days) of steroids (max 100 mg/day) before R-CHOP is allowed. Mini-R-CHOP is not allowed].
- WHO performance status 0-3 during or after the first R-CHOP cycle (see appendix C).
- Ann Arbor stage II-IV at diagnosis (see appendix A).
- ^{18}F-FDG PET scan and contrast enhanced CT-scan performed within 21 days before start first cycle of R-CHOP.
- Measurable disease: on contrast enhanced CT-scan at least 1 lesion/node with a long axis of >1.5 cm and at least one ^{18}F-FDG avid lesion.
- Negative pregnancy test at study entry.
- Patient is willing and able to use adequate contraception until 6 months post last treatment administration.
- Written informed consent.
- Patient is capable of giving informed consent.

8.1.2 Exclusion criteria for induction with DA-EPOCH-R

- All histopathological diagnoses other than DH/TH-HGBL (like testicular large B-cell lymphoma or primary mediastinal B-cell lymphoma) according to WHO 2016 classification.
- Known history of indolent lymphoma with the execption of localization of an indolent lymphoma component in the bone marrow detected during pre-treatment screening procedures.
- Inadequate renal function or creatinine clearance < 30 mL/min (after rehydration). Creatinine clearance may be calculated by Cockcroft –Gault formula:

$$\text{CrCl} = \frac{(140 - \text{age [in years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ for females})}{(0.815 \times \text{serum creatinine [µmol/L]})}$$

- Inadequate hepatic function: bilirubin > 3 times ULN (total) except patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin.
- Inadequate hematological function: ANC < 1.0×10^9/L or platelets < 75×10^9 /L before R-CHOP unless lymphoma related.
- CNS localization of the lymphoma. CSF analysis before start of treatment is only necessary in case of suspicion of CNS localization.
- Female subject pregnant or breast-feeding.
- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma.

- Active symptomatic ischemic heart disease, myocardial infarction, or congestive heart failure within the past year. In case of cardiac history, an echo or MUGA should be obtained and LVEF should exceed 40% to be eligible.
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.) that would jeopardize the patient's ability to receive the regimen with reasonable safety.
- HIV positivity.
- Active Hepatitis B or C infection as defined by positive serology and transaminitis. Non-active Hepatitis B carriers may be included if protected (see 9.2.3).
- Severe pulmonary dysfunction (CTCAE grade III-IV, see appendix D).
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD1, anti-PDL1, anti-PDL2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
- Severe neurological or psychiatric disease.
- Current participation in another clinical trial interfering with this trial.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- Claustrophobia precluding PET-CT.

8.2 Eligibility for registration for nivolumab consolidation

Patient eligible for nivolumab consolidation must be registered before start of the nivolumab treatment and must meet all of the following eligibility criteria.

8.2.1 Inclusion criteria for nivolumab consolidation

- Complete metabolic response on end of induction ^{18}F-FDG PET-CT assessed with the Deauville response criteria (see 10.3)
- Patient has completed at least R-CHOP plus four cycles of DA-EPOCH-R induction treatment

8.2.2 Exclusion criteria for nivolumab consolidation

- Inadequate renal function or creatinine clearance < 30 mL/min (after rehydration). Creatinine clearance may be calculated by Cockcroft –Gault formula:

$$CrCl = \frac{(140 - \text{age [in years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ for females})}{(0.815 \times \text{serum creatinine [µmol/L]})}$$

- Inadequate hepatic function: bilirubin > 3 times ULN (total) except patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.