Required investigations at entry, during treatment and during follow up

	Before (-21 days) R-CHOP (=cycle 1)	**before enrollment (registration)**	**at day 1 of every cycle of DA-EPOCH-R**	**Twice a week during DA-EPOCH-R (=cycle 2-6)**	**Response evaluation: Mid treatment after cycle 3 (1 R-CHOP + 2 DA-EPOCH-R)**	**Response evaluation: End of induction treatment**	**Start of nivolumab consolidation**	**Day 1 of every cycle of nivolumab**	**Response evaluation: During nivolumab consolidation after 6 and 12 months**	**During follow up every 6 months during the first two years and yearly thereafter [1)]**
Medical history	x	x[2)]	x							x
Physical examination	x	x[2)]	x		x	x	x	x		x
Hematology	x	x[2)]	x	x	x	x	x	x		
Blood chemistry	x	x[2)]	x	o.i.	x	x	x	x		
Blood coagulation	x	x[2)]								
Blood endocrinology (TSH)	x	x[2)]					x	x		
Virus serology (PCR when serology is positive)	x	x[2)]	o.i.				o.i.			
Lymph node biopsy	x									
MYC/BCL2/BCL6 FISH	x									
Bone marrow	x[3)]	not necessary[3)]								
aspirate	x[3)]									
biopsy	x[3)]									
ECG	x	x[2)]								
ECHO or MUGA in case of cardiac history	x	x[2)]								
^{18}F-FDG PET [4)]	X[5)]				X[6)]	X[6)]				x[8)]
Contrast enhanced CT scan [4)]	X[5)]				X[6)]	X[6)]			x[7)]	x[8)]
Pregnancy test	x	x[2)]								
CSF (liquor analysis)		x[9)]	x[10)]							
PB for central analysis MRD and T cell subsets (appendix F)			x[11)]		x		x	x[12)]		

1) Disease status and survival until 5 years after registration
2) If not performed and documented 21 days before start of1 cycle of R-CHOP
3) If bone marrow aspirate/biopsy was not done at diagnosis, it's not necessary to do this at time of registration
4) Please refer to 10.3 for more information; In case patient goes off protocol after cycle 4 or 5 because of toxicity, an end-of-treatment PET-CT should be performed.
5) Baseline 18F-FDG PET and contrast enhanced CT scan should have been made within 21 days before start of the first cycle of R-CHOP.
6) Mid induction treatment ^{18}F-FDG PET-CT should be made preferably 3 days prior to the start of the next DA-EPOCH-R cycle, end of induction treatment 18F-FDG PET-CT should be made 6 weeks after day 1 of last DA-EPOCH-R cycle (see 10.3)
7) Contrast enhanced CT after nivolumab consolidation at 6 and 12 months (+ or – 14 days).
8) Contrast enhanced CT only in case of if suspicion of progression, PET-CT is advised
9) CSF analysis before start of treatment only in case of suspected CNS involvement
10) CSF analysis when prophylaxis is administered
11) Please extract PB for MRD and T cell subsets, only at day 1 of first DA-EPOCH-R cycle
12) Sample MRD at consolidation before start nivolumab treatment and at 3, 6, 9 and 12 months (allowable sample period: + or – 14 days, or at day 1 of the nearest nivolumab cycle).

Medical history

Standard medical history, with special attention for:

WHO performance status and auto-immune diseases

Only at entry:

Prior and present other diseases

Antecedent hematological or oncological diseases

Previous chemotherapy or radiotherapy

Physical examination

Standard physical examination including body weight and height (height only at entry), with special attention for:lymphadenopathy and hepato-splenomegaly

Histological diagnosis

A diagnosis of DH/TH-HGBL should be based on a representative histological excision biopsy of a lymph node or extra-nodal site and made according to the criteria of the WHO classification 2016, including morphological and immunohistochemical parameters. *MYC, BCL2* and /or *BCL6* translocation assessment by FISH should be performed by one of the pathology laboratories in the Netherlands designated by the HOVON Pathology Group for this technique and reported according to the guidelines of the HOVON Pathology Group (see laboratory addendum available on the HOVON website (www.hovon.nl).

Hematology

Hemoglobin, Leukocyte count, differential count (automatically), Platelets

Blood chemistry

Sodium, Potassium, Creatinine, ALT, AST, Total bilirubin, Alkaline phosphatase, gamma GT, LDH, Calcium, Albumin.

Creatinine clearance: only at entry and at start nivolumab

Phosphate, Mg, Uric acid: only at entry and in case of tumor lysis suspicion

Serology

HIV 1/2, Hepatitis B and C, EBV, CMV, VZV, HSV, HTLV. In case of positive serology for HCV and HBV, PCR for viral load should be performed.

Blood coagulation

aPTT, PT (only at study entry, otherwise on indication)

Blood endocrinology

TSH at entry and at day 1 of every nivolumab cycle

Pregnancy test

In all premenopausal women a pregnancy test should be performed at entry.

Bone marrow

Bone marrow aspirate and biopsy for morphology at diagnosis. If bone marrow aspirate/biopsy was not done at diagnosis, it's not necessary to do this at time of registration.

CSF (liquor analysis)

Cell counts, morphology and flow cytometry

At diagnosis only in case of suspicion of CNS localization (exclusion criterion)

At cycle 2-6 when intrathecal therapy is administered

PET and CT scans

Preferably, ^{18}F-FDG PET-CT will be performed on the same scanner throughout the whole treatment period. For every PET-CT scanner, EARL accreditation is strongly advised (see http://earl.eanm.org/cms/website.php?id=/en/projects/fdg_pet_ct_accreditation.htm and http://earl.eanm.org/cms/website.php?id=/en/projects/fdg_pet_ct_accreditation/accreditation_specifications.htm).

^{18}F-FDG PET-CT whole body will be made

- During R-CHOP and DA-EPOCH-R induction: before treatment, mid-induction treatment and end-of induction treatment, and at suspicion of relapse.
- During nivolumab consolidation: no PET scans are required, but are advised at suspicion of relapse.

Contrast-enhanced CT scans of neck, thorax, abdomen and pelvis will made

- During R-CHOP and DA-EPOCH-R induction: before treatment, mid-treatment, end-of treatment (combined with ^{18}F-FDG PET scan)
- During nivolumab consolidation: at 6 and 12 months

Cardial evaluation

- ECG
- ECHO or MUGA only in case of cardiac history

10.3 Response evaluation

Prior to therapy, mid treatment and after completion of induction therapy ^{18}F-FDG PET-CT will be performed and evaluated according to appendix B1 and B2. If, on mid treatment or end-of-induction scan progression is diagnosed, the patient will go off protocol treatment.
Assessment of the on study ^{18}F-FDG PET-CT scan will be performed for involvement only (appendix B1). Assessment of the midterm and end end-of-(DA-EPOCH-R) treatment ^{18}F-FDG PET scans will be performed using the 5 points scale of Deauville (appendix B1)[44].
The interim ^{18}F-FDG PET-CT should preferably be made 3 days prior to the next DA-EPOCH-R treatment cycle. The end-of-induction ^{18}F-FDG PET-CT scan should be scheduled 6 weeks (+ or – 3 days) after day 1 of last DA-EPOCH-R . In case prolonged administration of growth factors is necessary a maximum delay of 2 weeks is allowed.
In case of Deauville 4 or 5 on end of (DA-EPOCH-R) treatment ^{18}F-FDG PET-CT, every attempt should be made to confirm or to rule out active lymphoma by biopsy. If this is not possible, it is allowed to repeat the ^{18}F-FDG PET-CT scan after another 4 weeks. In case this repeated scan shows Deauville 3 or less, patients are allowed to proceed to nivolumab consolidation treatment. In case of uncertainty about the response, please contact the principle investigator.
Assessment of the ^{18}F-FDG PET-CT made during consolidation (advised only at suspicion of relapse) will be according to the refined criteria[45].
Assessment of the CT scans will be according to Lugano classification (in appendix B2) with the modification that an negative bone marrow examination is not necessary for the definition of complete remission.
Please note that when the patient goes off protocol after cycle 4 or 5 of DA-EPOCH-R because of toxicity, an end-of-treatment PET-CT should be performed. When a patient goes off protocol during nivolumab, an end-of-treatment CT should be performed.

10.4 Central review

10.4.1 Pathology review

All diagnostic lymphoma samples will be collected and reviewed by 2 central pathologists according to HOVON Pathology Working Group guidelines (http://hovon.nl/working-groups/technical-commissions/hovon-pathology-facility-and-biobank-hop-.html). The logistic process will be performed and supported by the HOVON Pathology Facility and Biobank (HOP), which will be notified by the