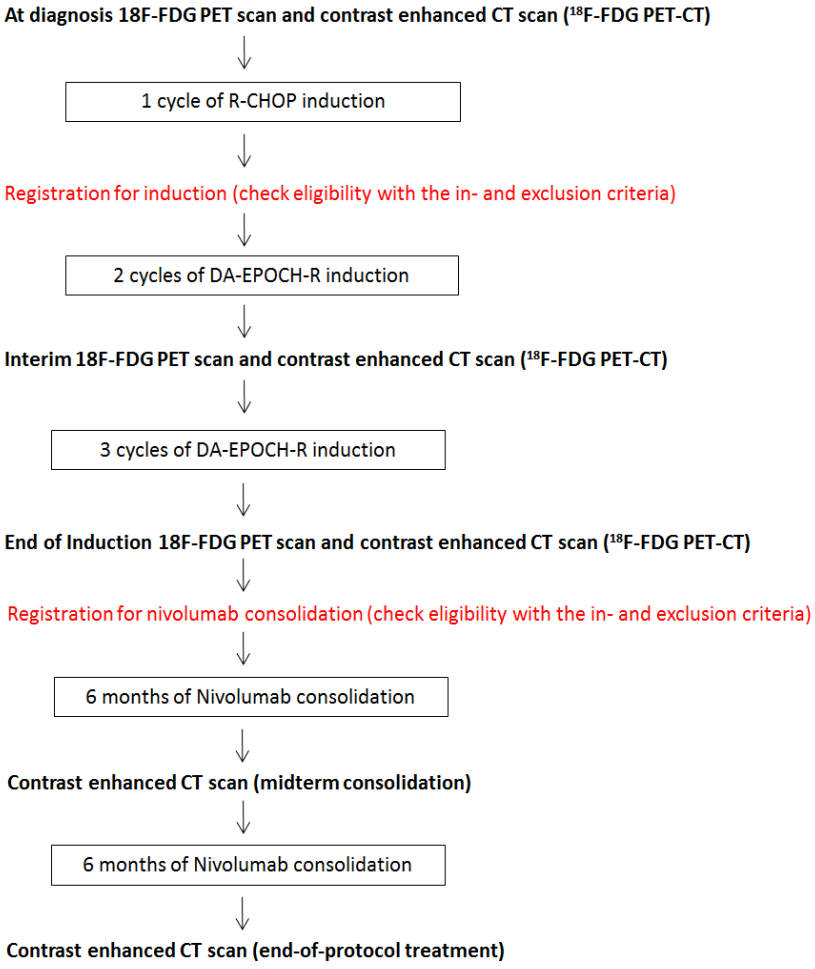
9 Treatment



9.1 Treatment with R-CHOP (cycle 1)

All patients receive 1 cycle of R-CHOP. This cycle will be given before registration during the screening period for *MYC, BCL2* and *BCL6* rearrangements.

9.1.1 Treatment schedule R- CHOP

Days	Drug	Dose/day	Route of administration
Day 1[a+b]	Cyclophosphamide	750 mg/m^2	i.v.
	Vincristine	1.4 mg/m^2 (max 2 mg)	i.v.
	Doxorubicin	50 mg/m^2	i.v.
	Rituximab	375 mg/m^2	i.v.
Day 1–5	Prednisone	100 mg	p.o

[a] reversed R-CHOP (cyclophosphamide, vincristine and doxorubicin on day 5) is allowed, mini R-CHOP is not allowed

[b] usage of rituximab IV biosimilar is allowed.

9.2 Treatment with DA-EPOCH-R (cycle 2-6)

For DA-EPOCH-R a (portable) infusion pump will be used for continuous infusion and if possible DA-EPOCH-R courses will be given on an out-patient basis (depending on the condition of the patient and logistics). For preparation details of DA-EPOCH-R see appendix E.

9.2.1 Treatment schedule DA-EPOCH-R

The first cycle of DA-EPOCH-R (=cycle 2) starts 21-28 days after d1 of the R-CHOP. Patients start DA-EPOCH-R treatment in **dose level 1** (9.2.1), according to the schedule below. In subsequent cycles the dose for doxorubicin, etoposide and cyclophosphamide will be reduced or increased as described in 9.2.2.

Days	drug	Dose	Route	Time
Day 1[a] (before infusions)	Rituximab	375 mg/m^2	i.v.	Local protocol
Day 1 (cycle 2-6)[b]	Methotrexate Or Cytarabin	15 mg 70 mg	i.t.	
Day 1 (cycle 2-6)[c]	*Optional:* Dexamethasone *or* Prednisolone	 4 mg 25 mg	i.t.	
Day 1-4	Etoposide	acc. to dose level (see 9.2.2)	i.v.	continuous infusion 96 hours
Day 1-4	Doxorubicin	acc. to dose level (see 9.2.2)	i.v.	continuous infusion 96 hours
Day 1-4	Vincristine	0.4 mg/m^2 /day	i.v.	continuous infusion 96 hours
Day 5[d+a] (cycle 2 and 3 only), before cyclophosphamide	Rituximab	375 mg/m^2	i.v.	Local protocol
Day 5	Cyclophosphamide	acc. to dose level (see 9.2.2)	i.v.	bolus
Day 1-5	Prednisolone	120 mg/m^2 /day	p.o.	60 mg/m^2 b.i.d.
Day 6-15 or further until ANC > 5 x10^9/l past nadir	G-CSF	≤ 80 kg 300 µg /day > 80 kg 480 µg /day	s.c.	

[a] Usage of rituximab IV biosimilar is allowed. The rituximab IV may be substituted with a rituximab SC 1400 mg flat dose. Rituximab may also be given on day 2.

[b] In total 5 prophylactic intrathecal injections should be given. The intrathecal injections may be administered on a different day to that specified in the protocol and this is permissible as long as 5 doses are completed

[c] i.t. dexamethasone or prednisolone may be given to avoid arachnoiditis according to local protocol

[d] In total 8 infusions of rituximab should be given; in cycle 2 and 3 a loading dose of two infusions (at day 1 and day 5) and from cycle 4 only one infusion on day 1 should be given.

Repeat cycle after 21 days. Delay cycle until ANC > 1.0 x10^9/l and platelets >75 x10^9/l. If no recovery at 21 days, continue G-CSF to increase ANC and begin next cycle as soon as ANC recovers. If ANC is not recovered at day 35, the patient will go off protocol.

All patients will receive intrathecal (i.t.) prophylaxis with methotrexate (MTX) or cytarabin 5 doses i.t. according to local practice (see also 5.1.6).

Patients will receive 5 cycles of DA-EPOCH-R in total. After 1 cycle of R-CHOP plus 2 cycles of DA-EPOCH-R a response evaluation with ^{18}F-FDG PET-CT scan will take place, preferably within 3 days before start of the next cycle. Another 3 cycles of DA-EPOCH-R will be given to patients without progressive disease.

9.2.2 Dose adjustments for doxorubicin, etoposide, cyclophosphamide and vincristine

Patients start treatment with DA-EPOCH-R in **dose level 1** during the first cycle after R-CHOP (=cycle 2). For every next cycle doses for doxorubicin, etoposide, and cyclophosphamide will be based on measurements of the previous cycle ANC or platelet nadir whichever is lower. Therefore it is important to measure blood counts twice a week. Dose adjustment is based on measurements of twice weekly blood counts only, even if additional blood counts are obtained (the lowest level will always be taken in account). Twice weekly blood counts must be at least 3 days apart. Adjustments apply only to etoposide, doxorubicin, and cyclophosphamide. Levels -1 and -2 only involve 20% reduction in cyclophosphamide.

- If ANC ≥ 0.5 x10^9/l on all measurements: ↑ One level above last cycle
- If Nadir ANC < 0.5 x10^9/l on 1 or 2 measurements: = Same level as last cycle
- If Nadir ANC < 0.5 x10^9/l ≥ 3 measurements: ↓ One level below last cycle

Or

- If nadir platelet < 25 x10^9/l on ≥ 1 measurement: ↓ One level below last cycle

Drug	**Drug Doses per Dose Levels**						
	-2	**-1**	**1**	**2**	**3**	**4**	**5**
Doxorobucin (mg/m^2/day)	10	10	10	12	14.4	17.3	20.7
Etoposide (mg/m^2/day)	50	50	50	60	72	86.4	103.7
Cyclophosphamide (mg/m^2/day)	480	600	750	900	1080	1296	1555

Dose adjustments for vincristine in case of polyneuropathy will be made at the investigator discretion.

9.2.3 Special precautions and supportive care during DA-EPOCH-R

Central venous access

All infusions will be administered through central venous access (PICC line, port-a-cath, or central venous line).

Tumor Lysis Syndrome

Management of patients with high suspicion of tumor lysis may consist of allopurinol or rasburicase and/or hospitalization with aggressive IV hydration at the discretion of the investigator. In case of renal obstruction hemodialysis and/or insertion of a nephrostomy should be considered.

Laxation

Prolonged vincristine administration may cause obstipation; laxatives like bisacodyl 5 mg/day or according to local practice are advised.

Proton pump inhibition (for example esomeprazole 40 mg daily) is advised.

Anti-emetics will be administered according to local protocol, ondansetron 8 mg is suggested.

Pneumocystis jirovecii Pneumonia prophylaxis

Pneumocystis jirovecii Pneumonia (PJP) prophylaxis is mandatory in all patients; cotrimoxazole 480 mg p.o once daily is suggested until 4 weeks after the last DA-EPOCH-R. In case of cotrimoxazole intolerance this can be replaced by pentamidine inhalation (300 mg every 4 weeks) or according to local protocols.

Antimicrobial prophylaxis: in case of granulocytopenia < $0.5x10^9$/L despite the use of G-CSF, antimicrobial prophylaxis (SDD) should be considered at least until ANC has increased to a minimum of $0.5x10^9$/L, according to local practice.

Fungal infections: If symptomatic oral or esophageal candidiasis oral fluconazole 100 mg is recommended, or according to local practice.

Prophylaxis for hepatitis B reactivation

Patients who receive chemotherapy and/or rituximab may undergo hepatitis B virus reactivation, particularly if they have persistent hepatitis B infection as defined by Hepatitis Surface Antigen positivity and/or detectable hepatitis B virus in the blood by PCR. Patients who have serologic evidence of previous hepatitis B infection (hepatitis B core antibody positive; HBcAb) may have low

levels of hepatitis B viremia, which should be excluded by a PCR test for hepatitis B viral load (HBV DNA). If positive, they will be considered to be at high risk of reactivation and should receive antiviral prophylaxis according to hepatology advice and local protocols, from pre-treatment to 6 months after completing treatment. Even if HBV DNA negative, there is a risk of HBV reactivation if HBcAb positive, and these patients should be monitored (with or without antiviral prophylaxis as per local protocol). All patients at risk of reactivation will have a PCR analysis of blood for viral loads performed pre-treatment and after cycles 2, 4 and 6 of chemotherapy treatment.

Cystitis prophylaxis: in dose level 5 of DA-EPOCH-R, Mesna may be administered according to local protocols.

Contraceptive advice

Due to insufficient data for the effects of the IMP (DA-EPOCH-R and nivolumab) during pregnancy and lactation, patients must consent to use a method of contraception until 6 months post last treatment administration. If a patient or the partner of a male trial patient becomes pregnant during the trial, the sponsor must be informed immediately. (see section 12.5 for details on the reporting procedure).

Menstruating premenopausal female trial patients will be started on **anovulatory drugs**; for instance Orgametril (Lynestrenol) 10 mg.

9.3 Treatment with nivolumab

9.3.1 Treatment schedule nivolumab

Nivolumab consolidation has to start 2 weeks (+ or – 3 days) after end-of- treatment local PET-CT scan shows CMR (Deauville 1-3), and after the patient has been registered for consolidation.
In case of Deauville 4 or 5 on end-of-treatment PET-CT after DA-EPOCH-R, 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. If this repeated scan shows Deauville 3 or less, patients are allowed to proceed to nivolumab consolidation treatment within 2 weeks.

Nivolumab 480 mg flat dose will be given for a maximal period of one year (12 months) from the moment of consolidation registration or until relapse, for a maximum of 13 cycles according to the schedule below. Every next cycle starts at day 29.

Agent	Dose	Route	Days
Nivolumab	480 mg	Intravenous	Day 1

9.3.2 Premedication nivolumab

Antiemetic premedications should not be routinely administered prior to nivolumab. See section 9.3.5 for premedication recommendations following a nivolumab related infusion reaction.

9.3.3 Administration of nivolumab

Nivolumab is to be administered as a 30-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It must not be administrated as an intravenous push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

9.3.4 Nivolumab schedule modifications and management of immune mediated reactions

Dose modifications are not allowed. Nivolumab administration should be delayed (for maximum of 6 weeks) according to the table below. Please refer to the nivolumab investigators brochure for the most up to date information.

Adverse reaction	NCI CTCAE grade version 4.03			
	Severity * #	Clinical signs	Dose Modification	Management
Skin	Grade 1-2	mild rash, <30% body surface	Continue	topical steroids, antihistaminica
	Grade 3	rash > 30% body suface, suspected SJS or TEN[b]	Withhold dose[a]	biopsy, prednison 1-2 mg/kg
	Grade 4	confirmed SJS or TEN[b]	Permanently discontinue	biopsy, prednison 1-2 mg/kg
Colitis	Grade 1	diarrhea < 4/day	Continue	loperamide
	Grade 2	diarrhea 4-6/day	Withhold dose[a]	exclude infectious cause, coloscopy if persistent, prednisolone 1 mg/kg
	Grade 3	diarrhea > 7/day	Withhold dose[a]	exclude infectious cause, coloscopy if persistent, prednisolone 2 mg/kg
	Grade 4	diarrhea >7 /day, life threatening	Permanently discontinue	exclude infectious cause, coloscopy if persistent, prednisolone 2 mg/kg, anti TNF
Pneumonitis	Grade 1	only radiologic	Continue	repeat X-thorax
	Grade 2	mild cough/dyspnoe	Withhold dose[a]	BAL, CT etc, consider prednisolone 1 mg/kg
	Grade 3 or 4	serious cough/dyspnoe	Permanently discontinue	BAL, CT etc, prednisolone 2 mg/kg
Hepatitis	Grade 1	AST or ALT <3 ULN and/or total bilirubin< 1.5 ULN	Continue	exclude infectious cause
	Grade 2	AST or ALT >3 ULN and/or total bilirubin > 1.5 - 3 ULN	Withhold dose[a]	exclude infectious cause, prednisolone 1 mg/kg
	Grade 3-4	AST or ALT >5 ULN and/or total bilirubin > 3 ULN	Permanently discontinue	exclude infectious cause, prednisolone 2 mg/kg
Hypophysitis	Grade 2 or 3 hypophysitis	moderate symptoms	Withhold dose[a]	substitute, consider methylprednisolon 1-2 mg/kg once followd by 1-2 mg prednisone/day
	Grade 4 hypophysitis	severe symptoms, hospitalisation	Permanently discontinue	substitute, consider methylprednisolon 1-2 mg/kg once followd by 1-2 mg prednisone/day
Adrenal Insufficiency	Grade 2 adrenal insufficiency	moderate symptoms	Withhold dose[a]	substitute, consider methylprednisolon 1-2 mg/kg once followd by 1-2 mg prednisone/day
	Grade 3 or 4 adrenal insufficiency	severe symptoms, hospitalisation	Permanently discontinue	substitute, consider methylprednisolon 1-2 mg/kg once followd by 1-2 mg prednisone/day
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	fasting glucose 13.9- 27.8 mmol/L	Withhold dose[a]	substitute insuline
	Grade 4 hyperglycemia	fasting glucose > 27.8 mmol/L	Permanently discontinue	substitute insuline

Nephritis and Renal Dysfunction	Grade 2-3	Serum creatinine > 1.5 - 6 ULN	Withhold dose[a]	consider prednisolone 1-2 mg/kg
	Grade 4	Serum creatinine > 6 times the ULN	Permanently discontinue	consider prednisolone 1-2 mg/kg
Encephalitis	New-onset moderate or severe neurologic signs or symptoms		Withhold dose[a]	consider prednisolone 1-2 mg/kg
	Immune-mediated encephalitis		Permanently discontinue	consider prednisolone 1-2 mg/kg
Other	Other Grade 3 adverse reaction			
	- First occurrence		Withhold dose[a]	
	- Recurrence of same Grade 3 adverse reactions		Permanently discontinue	
	Life-threatening or Grade 4 adverse reaction		Permanently discontinue	
	Grade 3 myocarditis		Permanently discontinue	
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks		Permanently discontinue	
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer		Permanently discontinue	

* In case of grade > 2 ; consult a specialist

[#] Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4).

[a] Resume treatment when adverse reaction improves to Grade 0 or 1.

[b] Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)

9.3.5 Treatment of nivolumab related Infusion reactions (IRR)

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the HDC safety desk and reported as an SAE only if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines.

Adverse event	NCI CTCAE IRR grade version 4.03				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anaphylaxis	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/ angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ⩽24 h	Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Allergic reaction	Transient flushing or rash, drug fever <38 °C; intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for⩽24 h	Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (for example, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ⩽24 h	Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (for example, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death

NCI CTCAE IRR grade	Management
1	The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.
2	Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg(acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid (wat, hoeveel?) or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
3 or 4	Immediately discontinue infusion of nivolumab . Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids)

9.4 Investigational Medicinal Products DA-EPOCH-R

All drugs from the treatment regimen DA-EPOCH-R, which are not used as supportive care or prophylaxis, are IMP in this trial.

- Cyclophosphamide
- Vincristine
- Doxorubicin
- Rituximab (i.v.), may be Mabthera® or biosimilar, Rituximab S.C. is allowed
- Etoposide
- Prednisolone (p.o.)