CLINCAL TRIAL PROTOCOL

	Document Number:	**c02102551-08**
EudraCT No.:	2014-004794-16	
BI Trial No.:	1270.11	
BI Investigational Product(s):	BI 836826	
Title:	An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/allogeneic stem cell transplant	
Lay Title:	To determine the dose of BI 836826-GemOx and the efficacy of BI 836826-GemOx versus R-GemOx in patients with relapsed/refractory DLBCL	
Clinical Phase:	Ib/II	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Principal Investigator:	Phone: Fax:	
Status:	Final Protocol (Revised Protocol (based on global amendment 5))	
Version and Date:	**Version: 6.0**	**Date:14 September 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		not applicable	
Name of active ingredient:		BI 836826	
Protocol date: 11 Jun 2015	**Trial number:** 1270.11		**Revision date:** 14 September 2017

Title of trial:	An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/allogeneic stem cell transplant
Coordinating Investigator< for multi-center trial if applicable >:	Phone: Fax:
Trial site(s):	Multicenter trial in two parts • Part 1 (Phase Ib dose escalation) 12-14 sites mainly in Europe • Part 2 (randomized Phase II) 35-40 sites in Europe and rest of the world
Clinical Phase:	Phase Ib/ II
Objective(s):	**Part 1 (Phase Ib)** Primary objective: To establish the maximum tolerated dose (MTD) of BI 836826 in combination with GemOx Secondary objective: To evaluate pharmacokinetics of BI 836826 when administered in combination with GemOx To evaluate preliminary efficacy in terms of the overall response rate (ORR) based on investigator's assessment. **Part 2 (Phase II randomized)** Primary objective:

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	To investigate the efficacy by means of the overall response rate (PR+ CR) based on central review assessment in patients with relapsed DLBCL treated with BI 836826-GemOx compared to R-GemOx Secondary objective: To investigate the efficacy by means of the complete remission rate based on central review assessment in patients with relapsed DLBCL treated with BI 836826-GemOx compared to R-GemOx
Methodology:	**Part 1**: Open-label dose finding of BI 836826-GemOx **Part 2**: Open-label randomized trial of BI 836826-GemOx versus R-GemOx
No. of patients:	up to 153
total entered:	Part 1 and Part 2 = Up to 153
each treatment:	Part 1: Up to 33 patients treated with BI 836826-GemOx Part 2: 120 patients; 60 patients randomized to BI 836826-GemOx and 60 patients randomized to rituximab-GemOx (R-GemOx)
Diagnosis :	Relapsed/ refractory diffuse large B-cell lymphoma
Main criteria for inclusion:	1. Age 18 years or older 2. Patients with histologically confirmed, relapsed/refractory, diffuse large B-cell lymphoma (including transformed follicular lymphoma) • who have received an anti-CD20-supplemented, anthracycline-containing chemotherapy and • are not eligible for high dose therapy followed by an autologous stem cell transplant, or have relapsed/progressed after autologous/ allogeneic stem cell transplant Allogenic stem cell transplant performed at least 6 months prior to study entry is allowed if patients do not require

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	immunosuppressive treatment and have no evidence of active graft-versus-host disease 3. Patient has not received anti-lymphoma treatment prior to the first dose of trial medication: • within past 14 days or • within time that is shorter or equal to 5 half-lives of the drug if the last anti-lymphoma treatment contained an investigational agent 4. Screening computer tomography (CT) scan with involvement of at least 1 bi-dimensional lesion/node >1.5 cm 5. Screening [^{18}F]flourodeoxyglucose (FDG)- positron emission tomography (PET) scans must demonstrate positive lesion compatible with computer tomography (CT) defined anatomical tumor sites 6. ECOG performance status 0, 1, 2, see Table 5.2.3:1 7. Written signed informed consent consistent with ICH GCP and local legislation 8. Patients must have an acceptable organ function defined as in Table 3.3.2.1 : 9. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. Non-vasectomized male patients having a female sexual partner of childbearing potential must ensure their partner is using a highly effective method of birth control as described above, during the trial and for at least 12 months after the end of the trial. (See section 4.2.2.3 for details).
Test product(s):	BI 836826
dose:	Part 1: Five dose levels of BI 836826 (25mg, 50mg, 100mg, 150mg

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	and 200mg) will be administered intravenous (i.v.) on day 8 of each cycle. An additional intermediate dose might be tested. GemOx (gemcitabine 1000mg/m^2 plus oxaliplatin 100mg/m^2) will be administered i.v. on day 1 of each cycle. Each cycle is 14 days. Part 2: BI 836826-GemOx arm: Recommended dose of BI 836826 as identified in Part 1 in combination with GemOx. GemOx will be administered i.v on day 1 of each cycle. BI 836826 will be administered i.v. on day 8 of each cycle. Each cycle is 14 days
mode of administration:	Treatment arm with BI 836826-GemOx: BI 836826 i.v. Gemcitabine i.v. Oxaliplatin i.v.
Comparator products:	Part 2: Rituximab
dose:	Rituximab 375mg/m^2 i.v. on day 1 of every cycle. GemOx (gemcitabine 1000mg/m^2 plus oxaliplatin 100mg/m^2) i.v. on day 2 of each cycle. Each cycle is 14 days.
mode of administration:	Treatment arm with Rituximab and GemOx (R-GemOx): Rituximab i.v. Gemcitabine i.v. Oxaliplatin i.v.
Duration of treatment:	Six cycles
Endpoints	**Primary endpoints:** **Part 1** The number of patients with DLTs in cycle 1. The MTD of BI 836826 with GemOx based on the number of patients with DLTs in cycle 1. The MTD of BI 836826 with GemOx is defined as the highest dose studied for which the number of patients

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	with dose-limiting toxicity is 17% or less (i.e., 0-1/6 patients) during cycle 1. **Part 2** Overall response (OR) by central review assessment, i.e. partial response (PR) and complete remission (CR) by central review assessment, analyzed by the overall response rate (ORR) and compared between the two treatment arms. **Secondary endpoints:** **Part 1** The secondary endpoints will be pharmacokinetic parameters: AUC_t and C_{max} of BI 836826 when administered in combination with GemOx and the overall response based on investigator's assessment. **Part 2** The CR by central review assessment will be the secondary endpoint, and will be compared between the two treatment arms.
Safety criteria:	Incidence and intensity of adverse events graded according to common terminology criteria for Adverse Events (CTCAE) version 4.0. Changes in laboratory parameters.
Statistical methods:	Part 1: 3+3 design to evaluate the dose of BI 836826 in combination with GemOx. Part 2: Efficacy evaluation of BI 836826-GemOx compared to R-GemOx will be based on the binary endpoint for overall response (OR) analyzed by overall response rate. Suissa-Shuster exact test (including the Berger-Boos modification) will be used to compare the OR for the treatment groups. All analyses are descriptive and explorative.

FLOW CHART 1

PART 1: Dose Finding

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (- 1)**	**1**	**8 (+3)**	**1**	**8 (+3)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	Screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	EOT		FU
Informed consent Part1	X													
Demographics	X													
Height	X													
Weight	X	X				X		X		X		X		
ECOG	X	X				X		X		X		X		
Physical exam (incl. evaluation of B symptoms)	X	X				X		X		X		X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X		
Medical History	X													
In- and exclusion criteria review	X													
12-Lead ECG[7)]	X										X	X		
Tumor tissue biopsy[8)]	X													

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (- 1)**	**1**	**8 (+3)**	**1**	**8 (+3)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	Screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	EOT		FU
Safety labs														
Hematology	X	X	X	X	X	X	X	X	X	X	X	X		
Reticulocytes	X	X				X		X		X		X		
Biochemistry	X	X				X		X		X		X		
Serum β2–microglobulin	X													
Immunoglobulins	X	X				X		X		X		X		
Coagulation	X	X				X		X		X		X		
Urine	X	X				X		X		X		X		
Serum pregnancy test	X											X		
Screening for tumor lysis syndrome (TLS) [10)]			X											
Virology testing [11)]	X													
CMV viral load monitoring [12)]	X	X				X				X		X		
Flow cytometry [13)]		X								X		X		
Pharmacokinetics[14)]		X	X	X	X	X	X	X	X	X	X	X		

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (- 1)**	**1**	**8 (+3)**	**1**	**8 (+3)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	Screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	C3D1	C3D8	C4D1	C4D8	EOT		FU
IRT/ Dose assignment [16)]	X	X	X			X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	
PET/CT scan [17)]	X									X		X		
Eligibility for continuation						X		X		X				
Premedication for BI 836826			X				X		X		X			
Administration of BI 836826			X				X		X		X			
Antiemetics prior to GemOx		X				X		X		X				
Administration of Gemcitabine		X				X		X		X				
Administration of Oxaliplatin		X				X		X		X				
Disease assessment /vital status (remission/progression/death/new anti-lymphoma treatment) [18)]	X									X		X	X	X

1) The planned duration of a treatment cycle is 14 days; and up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days. In case of toxicity, the start of the next cycle maybe delayed by maximum of 14 days to allow for recovery.
2) EOT is the End of treatment visit and should be done at the earliest 30 days and no later than 42 days after the last dose for those patients completing all 6 cycles according to protocol. If a patient is prematurely withdrawn from treatment (i.e. earlier than the end of the 6th cycle), an EOT visit should be performed within 14 days after last dose (last administration of Gemcitabine, Oxaliplatin or BI836826, whichever is the latest).
3) FU AEs visit: The information collected at this visit should include all new AEs that occurred after the last dose and a follow-up of adverse events ongoing at the time of the last dose. If a patient has been prematurely withdrawn from treatment, the FU for AEs visit must be performed on site 30-42 days after the last dose. If a patient completes the 6 cycles according to the protocol the FU for AEs visit can be scheduled at the same time point as EOT visit.
4) Follow-up visits (FU) see section 6.2.5: After the FU for AEs, the patient will be followed for disease assessment/vital status (remission/progression/death/new anti-lymphoma treatment) and drug related SAEs and AESIs. These FU visits should take place every 3 months for the first year after FU for AEs visit, and then every 6 months until death, patient is lost to follow-up, patient withdraws consent for further follow up or the end of trial is reached. FU may be performed by telephone interview in case the patient is unable to visit the investigator.
5) In cycle 1, during the first infusion of BI 836826 the patients are required to be hospitalized for at least 24hrs under close surveillance with access to intensive care.
6) The naming of the visit follows the cycle number and day of treatment, i.e. Day 1 cycle 1 will read C1D1 and Day 8 cycle 2 will read C2D8.
7) Single electrocardiogram (ECG) to be performed before any blood sampling at screening, day 8 in cycle 4 (C4D8) and EOT. Please note that on C4D8, ECG has to be performed before the infusion and immediately after the end of the infusion of BI 836826.
8) Confirm availability of archival tissue. If the required amount of tumor tissue is not available, fresh biopsy is mandatory. Sample must be shipped to central laboratory. See Section 5.5.1.1

10) Screening for TLS has to be performed within 24hrs of first dose of BI 836826 in patients at risk of TLS (high tumor burden) see section 5.3.3.2.
11) Mandatory tests at screening: see 5.3.3.3 virology: HIV antibody, CMV- Ig G, CMV-IgM, HbsAg, anti-HBc, anti-HCV. If patient is positive for anti-HCV during screening, the HCV-RNA test can be performed to exclude false positive results. If HCV-RNA test is negative, patient may be enrolled

13) Flow cytometry: quantitative assessment of: B cells, T cells, NK cells required at C1D1, C4D1 and EOT visit. Blood samples to be sent to a Central laboratory.
14) Pharmacokinetics for dosing times and cycles see Appendix 10.1, Table 10.1:1

16) Patients will be registered via interactive response technology (IRT) at screening and at each time-point trial medication is dispensed as well as at EOT.
17) PET/CT Scan of neck, thorax, abdomen, and pelvis to be performed at each time.
    a) Baseline PET/CT scan: up to 28 days prior to C1D1
    b) Interim PET/CT scan: after C3, i.e. prior to C4D1
    c) Final PET/CT scan: 3-6 weeks after the last dose if 6 cycles have been completed.
18) Disease assessment/vital status is collected at baseline, after the interim PET/ CT scan, i.e. after the end of cycle 3 and before C4D1 at EOT and during follow up visits.

FLOW CHART 2

Part 2: BI 836826-GemOx arm

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (-1)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	EOT		FU
Informed consent Part 2	X									
Demographics	X									
Height	X									
Weight	X	X				X		X		
ECOG	X	X				X		X		
Physical exam (incl. evaluation of B symptoms)	X	X				X		X		
Vital signs	X	X	X	X	X	X	X	X		
Medical History	X									
In- and exclusion criteria review	X									
12-Lead ECG [7)]	X						X	X		

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (-1)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	EOT		FU
Safety labs										
Hematology	X	X	X	X	X	X	X	X		
Reticulocytes	X	X				X		X		
Biochemistry	X	X				X		X		
Serum β2–microglobulin	X									
Immunoglobulins	X	X				X		X		
Coagulation	X	X				X		X		
Urine	X	X				X		X		
Serum pregnancy test	X							X		
Screening for tumor lysis syndrome (TLS) [10)]			X							
Virology testing [11)]	X									
CMV viral load monitoring [12)]	X	X				X		X		)
Flow cytometry [13)]		X				X		X		
Pharmacokinetics[14)]			X			X	X	X		

Procedures/Cycles[1)]	**screen**	**Cycle 1**				**Cycle 2-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**8[5)]**	**9**	**11 (-1)**	**1**	**8 (+3)**		30-42 days after last dose	
Visit[6)]	screen	C1D1	C1D8	C1D9	C1D11	C2D1	C2D8	EOT		FU
IRT/ Randomization [16)]	X	X	X			X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	
PET/CT scan[17)]	X					X		X		
Eligibility for treatment continuation		X				X				
Premedication for BI 836826			X				X			
Administration of BI 836826			X				X			
Antiemetics prior to GemOx		X				X				
Administration of Gemcitabine		X				X				
Administration of Oxaliplatin		X				X				
Disease assessment/ vital status (remission/progression/death/new anti-lymphoma treatment) [18)]	X					X		X	X	X

1) The planned duration of a treatment cycle is 14 days; and up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days. In case of toxicity, the start of the next cycle maybe delayed by maximum of 14 days.
2) EOT is the End of treatment visit and should be done at the earliest 30 days and no later than 42 days after the last dose for those patients completing all 6 cycles according to protocol. If a patient is prematurely withdrawn from treatment (i.e. earlier than the end of the 6th cycle), an EOT visit should be performed within 14 days after last dose (last administration of Gemcitabine, Oxaliplatin or BI836826, whichever is the latest)
3) FU AEs: The information collected at this visit should include all new AEs that occurred after the last dose and a follow-up of adverse events ongoing at the time of the last dose. If a patient has been prematurely withdrawn from treatment, the FU for AEs visit must be performed on site 30-42 days after the last dose. If a patient completes the 6 cycles according to the protocol the FU for AEs visit can be scheduled at the same time point as EOT visit.
4) Follow-up visits (FU) see section 6.2.5: After the FU for AEs, the patient will be followed for disease assessment/ vital status (remission/progression/death/new anti-lymphoma treatment) and drug related SAEs and AESIs. These FU visits should take place every 3 months for the first year after FU for AEs visit, and then every 6 months until death, patient is lost to follow-up, patient withdraws consent for further follow up or the end of trial is reached. FU may be performed by telephone interview in case the patient is unable to visit the investigator
5) In cycle 1, during the first infusion of BI 836826 the patients are required to be hospitalized for at least 24hrs under close surveillance with access to intensive care.
6) The naming of the visit follows the cycle number and day of treatment, i.e. Day 1 cycle 1 will read C1D1 and Day 8 cycle 2 will read C2D8
7) Single electrocardiogram (ECG) are to be performed before any blood sampling at screening, day 8 in cycle 4 (C4D8) and EOT. Please note that on C4D8, ECG has to be performed before the infusion and immediately after the end of the infusion of BI 836826.

10) Screening for TLS has to be performed within 24hrs of first dose of BI 836826 in patients at risk of TLS (high tumor burden) see section 5.3.3.2.
11) Mandatory tests at screening: see 5.3.3.3 virology: HIV antibody, CMV- Ig G, CMV-IgM, HbsAg, anti-HBc, anti-HCV. If patient is positive for anti-HCV during screening, the HCV-RNA test can be performed to exclude false positive results. If HCV-RNA test is negative, patient may be enrolled.
12) Quantitative Cytomegalovirus (CMV), Deoxyribonucleic acid (DNA), polymerase chain reaction (PCR) to be performed at screening, C1D1,C2D1, C4D1, C6D1 and EOT.
13) Flow cytometry: quantitative assessment of: B cells, T cells, NK cells required at C1D1 C4D1 and EOT visit. Blood samples to be sent to a Central laboratory.
14) Pharmacokinetics for dosing times, days and cycles see Appendix 10.1, Table 10.1.2.

16) Patients will be registered via interactive response technology (IRT) at screening and at each time-point trial medication is dispensed as well as at EOT.
17) PET/CT Scan of neck, thorax, abdomen, and pelvis to be performed at each time.
    a) Baseline PET/CT scan : up to 28 days prior to C1D1
    b) Interim PET/CT scan : after C3, i.e. prior to C4D1
    c) Final PET/CT scan: 3-6 weeks after the last dose if 6 cycles have been completed.
18) Disease assessment/vital status is collected at baseline, after the interim PET/ CT scan, i.e. after the end of cycle 3 and before C4D1, at EOT and during follow up visits.

FLOW CHART 3

Part 2: R-GemOx arm

Procedures/Cycles[1)]	**screen**	**Cycle 1-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**2[5)]**		30-42 days after last dose	
Visit[6)]	screen	C1-C6 D1	C1-C6 D2	EOT		FU
Informed consent Part 2	X					
Demographics	X					
Height	X					
Weight	X	X		X		
ECOG	X	X		X		
Physical exam (incl. evaluation of B symptoms)	X	X		X		
Vital signs	X	X	X	X		
Medical History	X					
In- and exclusion criteria review	X					
12-Lead ECG [7)]	X		X	X		
Safety labs						
Hematology	X	X		X		
Reticulocytes	X	X		X		
Biochemistry	X	X		X		
Serum β2–microglobulin	X					
Immunoglobulin	X	X		X		
Coagulation	X	X		X		
Urine	X	X		X		

Procedures/Cycles[1)]	**screen**	**Cycle 1-6**		**EOT[2)]**	**FU[3)] AEs**	**FU[4)]**
Day of cycle	**-14 to <1**	**1**	**2[5)]**		30-42 days after last dose	
Visit[6)]	screen	C1-C6 D1	C1-C6 D2	EOT		FU
Serum pregnancy test	X			X		
Testing for tumor lysis syndrome (TLS) [10)]		X				
Virology testing [11)]	X					
CMV viral load monitoring [12)]	X	X		X		
Flow cytometry [13)]		X		X		
IRT/ Randomization [14)]	X	X	X	X		
Adverse events	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	
PET/CT scan [15)]	X	X		X		
Eligibility for treatment continuation		X				
Premedication for rituximab		X				
Administration of rituximab		X				
Antiemetics prior to GemOx			X			
Administration of Gemcitabine			X			
Administration of Oxaliplatin			X			
Disease assessment/ vital status (remission/progression/death/new anti-lymphoma treatment) [16)]	X	X		X	X	X

1) The planned duration of a treatment cycle is 14 days. In case of toxicity, the start of the next cycle maybe delayed by maximum of 14 days.
2) EOT is the End of treatment visit and should be done at the earliest 30 days and no later than 42 days after the last dose for those patients completing all 6 cycles according to protocol. If a patient is prematurely withdrawn from treatment (i.e. earlier than the end of the 6th cycle) an EOT visit should be performed within 14 days after last dose (last administration of Gemcitabine, Oxaliplatin or Rituximab, whichever is the latest)
3) FU AEs: The information collected at this visit should include all new AEs that occurred after the last dose and a follow-up of adverse events ongoing at the time of the last dose. If a patient has been prematurely withdrawn from treatment, the FU for AEs visit must be performed on site 30-42 days after the last dose. If a patient completes the 6 cycles according to the protocol the FU for AEs visit can be scheduled at the same time point as EOT.
4) Follow-up visits (FU) see section 6.2.5: After the FU for AEs, the patient will be followed for disease assessment/vital status (remission/progression/death/new anti-lymphoma treatment) and drug related SAEs and AESIs. These FU visits should take place every 3 months for the first year after FU for AEs visit, and then every 6 months until death, patient is lost to follow-up, patient withdraws consent for further follow up or the end of trial is reached. FU may be performed by telephone interview in case the patient is unable to visit the investigator
5) Day 2 is an outpatient visit. Patients do not need to stay overnight from day 1- day 2.
6) The naming of the visit follows the cycle number and day of treatment, i.e. Day 2 cycle 1 will read C1D2 and Day 2 cycle 2 will read C2D2.
7) Single electrocardiogram (ECG) is to be collected before any blood sampling at screening, on day 2 in cycle 4 (C4D2) and EOT. Please note that on C4D2, ECG to be performed before the infusion and immediately after the end of the infusion of GemOx.

10) Screening for TLS has to be performed within 24hrs of first dose of Rituximab in patients at risk of TLS (high tumor burden) see section 5.3.3.2
11) Mandatory tests at screening: see 5.3.3.3 virology: HIV antibody, CMV- Ig G, CMV-IgM, HbsAg, anti-HBc, anti-HCV. If patient is positive for anti-HCV during screening, the HCV-RNA test can be performed to exclude false positive results. If HCV-RNA test is negative, patient may be enrolled.
12) Quantitative Cytomegalovirus (CMV), Deoxyribonucleic acid (DNA), polymerase chain reaction (PCR) to be performed at screening , C1D1, C2D1,C4D1, C6D1, and EOT.
13) Flow cytometry: quantitative assessment of: B cells, T cells, NK cells required at C1D1 C4D1 and EOT visit. Blood samples to be sent to a Central laboratory.
14) Patients will be registered via interactive response technology (IRT) at screening and at each time-point trial medication is dispensed as well as at EOT.
15) PET/CT Scan of neck, thorax, abdomen, and pelvis to be performed at each time.
    a. Baseline PET/CT scan : up to 28 days prior to C1D1
    b. Interim PET/CT scan : after C3, i.e. prior to C4D1
    c. Final PET/CT scan: 3-6 weeks after the last dose if 6 cycles have been completed.
16) Disease assessment/vital status is collected at baseline, after the interim PET/ CT scan, i.e. after the end of cycle 3 and before C4D1, at EOT and during follow up visits.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ADCC	Antibody-dependent cell cytotoxicity
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
anti-HCV	hepatitis C antibody
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase
AUC_t	Area Under the Curve
BI	Boehringer Ingelheim
BI 836826-Gem	BI 836826+gemcitabine
BI 836826-GemOx	BI 836826+gemcitabine + oxaliplatin
BLQ	Below The Limit of Quantification
BSA	Body Surface Area
CA	Competent Authority
CDC	Complement dependent cytotoxicity
CHOP	cyclophosphamide, hydroxydaunorubicin, oncovin , and prednisolone
CLL	Chronic lymphocytic leukaemia
C_{max}	maximum plasma concentrations
CML	Local Clinical Monitor
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DEDP	Drug Exposure During Pregnancy
DILI	Drug-Induced Liver Injury
DLBCL	Diffuse Large B-cell lymphoma
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

e-CRF	Electronic Case Report Form
EDTA	Ethylendiaminetetraacetic acid
ELISA	Enzyme-Linked Immuno Assay
EMA	European Medicines Agency
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FCGR	Immunoglobulin G fragment C receptors
FDA	Food and Drug Administration
FDG	[^{18}F]flourodeoxyglucose
FISH	Fluorescence in-situ Hybridization
FL	Follicular Lymphoma
FU	Follow-up
G1	Grade 1 CTCAE
G2	Grade 2 CTCAE
G3	Grade 3 CTCAE
G4	Grade 4 CTCAE
GCP	Good Clinical Practice
GemOx	Gemcitabine and Oxaliplatin
GFR	Glomerular Filtration Rate
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HT	Histological Transformation
HMA CTFG	Heads of Medicines Agencies Clinical Trials Facilitation group
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IEC	Independent Ethics Committee
IgG	Immunoglobin G
IgM	Immunoglobin M
IgA	Immunoglobin A
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
mRNA	Messenger ribonucleic acid
MTD	Maximum Tolerated Dose
NC	Not Calculated

NCI	National Cancer institute
NHL	Non-Hodgkin's lymphoma
NK cells	Natural killer cells
NIMP	Non-Investigational Product
NOA	Not Analyzed
NOP	No peak detectable
NOR	No Valid Result
NOS	No Sample Available
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PLT	Platelets
p.o.	per os (oral)
PR	Partial Remission
5-PS	Five-point score
PT	Prothrombin Time
RBC	Red Blood Cell Count
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamics effects still likely to be present
R-Gem	Rituximab- + gemcitabine
R-GemOx	Rituximab + gemcitabine + oxaliplatin
RNA	Ribonucleic acid
RP2	Recommended dose in Part 2
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SPD	Sum of Product of Diameters
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUV	Standardized Uptake Value
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
THU	Tetrahydrouridine
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
TMM	Team Member Medicine

TMDS	Team Member Drug Safety
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WBC	White Blood Cell Count
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1. MEDICAL BACKGROUND

The Non-Hodgkin's Lymphoma (NHL) encompass a number of subtypes with variable clinical course and outcome. Approximately 90% of NHL in western countries are of B cell origin NHL (R10-4834) and belong to mature B cell malignancies according to the World Health Organization (WHO) classification (R10-6296).The incidence of NHL of B cell origin is 15-20 per 100.000 (seer.cancer.gov). About 72,240 new cases of NHL were estimated for 2017 and about 20,140 people will die (www.cancer.org) in the United States (US).
Historically, based on the clinical presentation, NHLs have been classified as indolent (low grade) lymphomas, or as (high grade) aggressive lymphomas. Most of the indolent types are nodular (or follicular) in morphology, and often with insidious presentation with slow growing lymphadenopathy, hepatomegaly, splenomegaly, and/or cytopenias. Early stages of indolent NHLs (stage I and stage II) can be effectively treated because the lymphomas are usually responsive to immunotherapy, radiation therapy, and chemotherapy. Patients with advanced stages cannot be cured (R15-0609), but have a relatively long median overall survival (up to 20 years) with a continuous rate of relapse over time, which can often be successfully re-treated as long as the disease histology remains low grade. The natural history and the clinical course of patients with B-cell indolent lymphomas are also characterized by the risk of histologic transformation (HT) to an aggressive lymphoma. This is a well-known phenomenon that has been extensively studied in terms of the incidence, risk factors, and outcome in patients with follicular lymphoma (FL), which transforms to a Diffuse Large B cell Lymphoma (DLBCL); and, less commonly, to Burkitt lymphoma, or other types of aggressive lymphomas. HT has also been described in other subtypes of B-cell indolent lymphomas. Patients who present with, or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.
Aggressive lymphomas commonly develop acutely or sub-acutely with a rapidly growing mass, systemic B symptoms (i.e., fever, night sweats, weight loss), and/or elevated levels of serum lactate dehydrogenase (LDH) and uric acid. Examples of lymphomas with this aggressive presentation include DLBCL, Burkitt lymphoma, adult T cell leukemia-lymphoma, or precursor B and T lymphoblastic leukemia/lymphoma. Untreated aggressive lymphomas have very short natural history, but with progress in recent years a significant number of patients can be cured with intensive combination regimens. DLBCL is the most common lymphoma and accounts for approximately 25 percent of all NHLs in the developed world (R15-0608, R10-6296). Advanced stage DLBCL is treated primarily with systemic chemotherapy (CHOP regimen: Cyclophosphamide, Hydroxydaunorubicin, Oncovin , and Prednisolone) with the addition of recombinant anti-CD20 antibody, rituximab. The addition of rituximab to CHOP-based therapy results in an approximately 10 to 15 percent overall increase in survival beginning at one year from initiation of therapy in patients of all ages with almost no increase in toxicity (R15-0607, R03-0720). The three year event free and overall survival for treated patients is 79 and 93% respectively (P12-05173). Unfortunately, a significant number of patients with DLBCL will not be cured with this approach, and will require subsequent treatments upon relapse. Relapsed or refractory DLBCL is treated with intense chemotherapy regiments with or without rituximab with plans to proceed to high-dose

chemotherapy and stem cell transplantation (SCT) in patients with chemotherapy-sensitive disease. The treatment of patients who (due to age and comorbidities) are not considered good candidates for SCT, who fail to respond to second-line chemotherapy regimens, or who relapse after SCT is generally palliative. In addition, patients with primary refractory disease rarely achieve a complete remission when treated with a second chemotherapy regimen. Recurrent or resistant DLBCL in patients ineligible for transplantation are particularly difficult to treat and have markedly reduced survival (P15-01473, P15-01472). Therefore, the need to develop more efficacious treatments for relapsed/refractory DLBCL patients who are not eligible for SCT is apparent. Since monoclonal anti CD20 antibodies have demonstrated utility in lymphoma treatment as part of chemoimmunotherapy approach, it is reasonable to assume that further combinations with other monoclonal antibodies targeting antigens present on tumor cells might also prove useful. While initial reports on the use of single agent rituximab for relapsed DLBCL demonstrated response rates of approximately 30 percent, the rate of response among patients who received rituximab as part of their initial treatment regimen is expected to be significantly lower. Therefore, rituximab may be of limited utility in these patients (P15-01471). Given that rituximab has become an inherent part of the standard first lane treatment in DLBCL, it is reasonable to expect that virtually all relapsed/refractory patients will have been pre-exposed to anti CD 20 antibody at some time in the past. Using a different then CD20 target seems particularly attractive as it may allow overcoming resistance to CD20 antibody in those patients.

CD37, a member of the tetraspanin superfamily, is a glycosylated cell surface protein which is predominantly expressed on normal B cells, with highest expression levels on mature peripheral blood B cells. The CD37 antigen is also expressed on the majority of malignant cells in patients with NHL and chronic lymphocytic leukaemia (CLL) (R08-2979, R08-2943, R08-2981, R08-2945, R08-2942, R14-3568, R14-3569). The physiological function of CD37 in humans remains unknown (R08-2979, R08-2946). Mice deficient for CD37 display no changes in development and cellular composition of lymphoid organs but have reduced levels of IgG1 and attenuated T-cell mediated immune reactions (R09-5412). Studies with CD37-/- T cells suggest a role for CD37 in T cell proliferation and regulation of immunoglobin A (IgA) response (R09-4740, R09-5414).

1.2. DRUGS PROFILE

1.2.1. BI 836826

BI 836826 is a mouse-chimeric antibody of the IgG1 isotype, directed against human CD37. BI 836826 has been investigated pre-clinically and in Phase 1 dose escalation trials in chronic lymphocytic leukemia and NHL.

In vitro assays demonstrated that BI 836826 specifically recognizes human CD37 and binds with high affinity to this antigen. BI 836826 is a potent inducer of apoptosis and antibody-dependent cell cytotoxicity (ADCC) in vitro, but lacks complement-dependent cytotoxicity (CDC) activity.
In vivo testing in nude mouse lymphoma xenograft models (Ramos DOHH2 cell lines) showed a statistically significant growth retardation of treated tumors with single agent BI 836826 and in combination with chemotherapy (R11-4834, n00232742, n00232752). The combination of BI 836826 with chemotherapeutics (bendamustine, chlorambucil,

fludarabine) or with the CD20 antibody rituximab in vitro results in additive or synergistic apoptosis induction on lymphoma cell lines and primary CLL cells (R12-4648).
The majority of effects observed in the general toxicity studies with BI 836826 in HuCD37 mice and with the surrogate BI 836847 (an anti-macaque CD37 surrogate antibody) in cynomolgus monkeys were directly related or secondary to the pharmacological activity of BI 836826 and BI 836847. The main target organs following repeat intravenous exposure to BI 836826 in HuCD37 mice and to the surrogate BI 836847 (an antimacque CD37 surrogate antibody) in cynomolgus monkeys were the blood and lymphoid system. BI 836826 induced B- but also T-cell reduction in HuCD37 mice in peripheral blood and lymphoid organs at all dose levels with the histopathological correlate of lymphoid depletion in B-cell areas in spleen and lymph nodes. In contrast, the surrogate BI 836847 induced reduction of lymphocytes, predominantly B cells and natural killer cells (NK cells) at low to moderate doses. T cells, granulocytes and platelets (PLT) were reduced at higher doses. Severe and sustained immunosuppression in monkeys treated with high doses led to several cases of septicaemia. Further details regarding the full safety profile from toxicological studies in animals can be found in the Investigator's Brochure (IB).

1.2.2. Human experience with BI 836826

Preliminary data from two ongoing Phase 1 monotherapy trials are available, one in relapsed CLL (study 1270.1, 37 patients) and the other in relapsed NHL (study 1270.2, 45 patients). Two different treatment schedules were used:

- in patients with r/r CLL (study 1270.1), BI 836826 was administered every 2 weeks until disease progression;
- in relapsed NHL (study 1270.2), BI 836826 was administered weekly in 3 courses of treatment with a total of up to 12 injections.

In summary, based on the experience with BI836826 monotherapy in CLL at doses up to 800mg and in NHL at doses up to 200mg, two (2) MTDs have been established: 400mg in monotherapy for CLL and 100mg for NHL. The MTD in the NHL study (1270.2) was determined based on DLTs seen at 150mg (asymptomatic laboratory abnormalities that resolved within 48 hours). Therefore, in the ongoing study (1270.11) in combination with GemOx, and using a different treatment schedule, it is legit to consider that a different dose of BI 836826 might be possible and might be higher than the 100mg defined as MTD in monotherapy in NHL.

For a more detailed description of the drug profile refer to the current IB which is included in the Investigator Site File (ISF).

1.2.3. Gemcitabine

Gemcitabine (dFdC), is a pyrimidine antimetabolite, which exerts its cytotoxic effect by inhibition of DNA synthesis. Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumor cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.
Gemcitabine is mostly used for treatment of variety of solid tumors as monotherapy, or in combinations with other chemotherapeutic agents. Recent studies in lymphoma indicate that gemcitabine in combination with oxaliplatin and rituximab (R-Gem-Ox regimen) can be considered as a salvage regimen for elderly patients with DLBCL because of its high clinical activity and relatively safe toxicity profile, (P13-00889, R14-2111)

The most common (in ≥10% of treated patients) adverse effects of gemcitabine include.
- Leukopenia, including G3-4 neutropenia
- Nausea and/or vomiting
- Elevation in liver enzymes (aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (AP))
- Hematuria and mild proteinuria
- Allergic skin reactions
- Dyspnea
- Influenza-like symptoms

On rare occasions a discontinuation of treatment with gemcitabine should be considered:
Rare AEs requiring permanent discontinuation of Gemcitabine:

- Severe pulmonary toxicity
- Severe hepatic toxicity
- At first evidence of microangiopathic hemolytic anemia or Hemolytic-Uremic Syndrome

1.2.4. For additional detailed information please refer to the summary of product characteristic (SmPC) located in the ISF. Oxaliplatin

Oxaliplatin is an antineoplastic drug belonging to a new class of platinum-based compounds which interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis and leading to cytotoxic and antitumor effects. Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumor activity in a variety of tumor model systems including human colorectal cancer models. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*. Oxaliplatin is indicated for treatment in combination with 5-Fluorouracil and folinic acid for treatment in patients with colorectal cancers.
Recent studies in lymphoma indicate that oxaliplatin in combination with gemcitabine and rituximab (R-Gem-Ox regimen) can be considered as a salvage regimen for elderly patients with DLBCL because of its high clinical activity and relatively safe toxicity profile (P13-00889, R14-2111),

Most common adverse effects reported for oxaliplatin are

- Neurological symptoms and peripheral neuropathy
- Thrombocytopenia, anemia, and neutropenia
- Infections
- Nausea, vomiting and diarrhea
- Infusion reactions with flushing, headache, dyspnea and/or hypotension.
- Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to oxaliplatin has been observed. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. **Re-challenge is contraindicated in those patients.**

For additional information please refer to the SmPC located in the ISF.

1.2.5. Rituximab (only in Part 2)

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

Rituximab targets CD20, a specific B-cell surface antigen. The binding of rituximab to the CD20 located on B lymphocytes results in cell destruction via three potential mechanisms: antibody-dependent cell cytotoxicity (ADCC), CDC and modest, if any, induction of apoptosis. This drug is administered intravenously, and is indicated for treatment of patients with various NHLs, CLL, and autoimmune diseases. Rituximab is also frequently used in clinical practice for treatment of patients with relapsed/refractory NHL either as part of multi-drug regimens, or less frequently, as monotherapy.

Rituximab **is contraindicated** in patients who are hypersensitive to the active substance or to murine proteins, or to any of the other excipients, in patients with active, severe infections, and in patients with severe immunosuppression.

The most common adverse events (>10% of treated patients) reported for treatment with rituximab are:

- Infections: bacterial and viral
- Hematologic toxicities: neutropenia, leucopenia, febrile neutropenia, and thrombocytopenia
- IRR, including angioedema
- nausea
- skin reactions: pruritus, rash, alopecia
- fever, chills, asthenia, headache
- decreased IgG levels

Special warnings and precautions for use of rituximab include:
- IRR
- skin reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome,
- serious infections, including hepatitis B reactivation
- rare, but fatal progressive multifocal leukoencephalopathy.

Tumor lysis syndrome and IRR usually occur in patients with high numbers of circulating tumor cells and in patients with high tumor burden, particularly if rituximab is administered in combination with chemotherapy. Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction are also reported. Therefore patients with a history of cardiac disease and/or cardio toxic chemotherapy should be monitored closely.

For additional information please refer to the SmPC located in the ISF.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1. RATIONALE FOR PERFORMING THE TRIAL

A substantial number of patients relapse after first line therapy for DLBCL and many of them will not be good candidates for intensive treatment with curative intent due to age or co-morbidities (R10-4775, P12-05173). These patients will rather receive palliative treatment with the aim to control the disease, while maintaining reasonable quality of life. There are different options of combination chemotherapy in relapsed/refractory DLBCL setting, but none has proven superior, and there is no approved standard treatment in this group of patients. Treatment regimens used in elderly patients with relapsed/refractory DLBCL are reported to achieve response rates in the range of 50-70%, however many of those are partial responses and rather of short duration (P14-08836, P10-10101, R14-2310). The progression free survival and overall survival are generally short (P14-08836, P10-10101). One of the regimens used in patients ineligible for intensive therapy is a combination of rituximab, gemcitabine and oxaliplatin (R-GemOx) (R13-0204, P13-00889, R13-0203 and R14-2111). So far limited numbers of patients have been included in trials with this triple combination, but the results from Phase 2 multicenter trial with 48 patients are encouraging. The trial demonstrated an overall response rate (ORR (CR+PR)) of 61% after 4 cycles of treatment (R13-0204, P13-00889, R13-0203 and R14-2111). The 5 years progression free survival (PFS) and overall survival (OS) were 12.8 and 13.9% respectively. In addition, the R-GemOx regimen is relatively well tolerated with reversible hematologic toxicity and infections being the most frequent adverse events. Interestingly, prior exposure to rituximab seems to negatively affect responses in these patients (23 vs 65%). Emerging data from other trials in similar patient populations indicate that upon re-treatment with rituximab patients who received rituximab in their first line therapy have lower response rates and shorter event free survival compared to those who first received rituximab at relapse (R11-2236, P10-10101, R14-2111). Considering that rituximab became standard of care in western countries and almost all DLBCL patients receive rituximab as part of the initial therapy, it is concerning that combinations containing rituximab may not be the best treatment choice for those patients at relapse. One approach to avoid cross-resistance could be through targeting a different than CD20 antigen on the surface of tumor cells.

The majority of malignant cells in patients with NHL of B cell origin express the CD37 antigen, so targeting CD37 in malignancies may offer a valid treatment option (R08-2979, R08-2943, R08-2981, R08-2945, R08-2942, R14-3568, R14-3569). BI 836826 targets an epitope on the tumor cells which has not previously been therapeutically targeted, thus offering an advantage of avoiding cross-resistance with prior monoclonal antibody based therapies, The addition of BI 836826 to chemotherapy backbone in patients progressing after rituximab (or another anti-CD20 targeting mAb) offers a potential to overcome resistance to anti-CD20 monoclonal antibody and may improve the response rate and prolong survival in patients who are not eligible for high dose therapy.

The preliminary clinical experiences with targeting CD37 with MB-1, a radio-immuno-conjugate and TRU-016, a small modular immuno-pharmaceutical support the assumption

that targeting CD37 in man leads to lymphocyte reduction and consecutive lymph node shrinkage with an acceptable side effect profile (R10-2734, R10-2735, R10-6640).

The purpose of Part 1 (dose-escalation) of the trial is to establish the recommended dose of BI 836826 in combination with GemOx, based on safety profile. The purpose of Part 2 (randomized part) of the trial is to compare the overall response rate (ORR) of BI 836826-GemOx vs R-GemOx. An increase in ORR, especially in complete remission (CR) rate is considered a pre-requisite for improvement in PFS. Using the same chemotherapy backbone in both arms the trial will assess whether the preclinical superiority of BI 836826 to rituximab also translates into a clinical setting and results in improvement in efficacy.

2.2. TRIAL OBJECTIVES

Part 1 (Phase Ib)

Primary objective:
To establish the maximum tolerated dose (MTD) of BI 836826 in combination with GemOx.

Secondary objectives:
To evaluate pharmacokinetics of BI 836826 when given in combination with GemOx and to investigate preliminary efficacy in terms of the overall response rate based on investigator's assessment.

Part 2 (Phase II randomized)

Primary objective:
To investigate the efficacy by means of the overall response rate (PR+ CR) based on central review assessment in patients with relapsed DLBCL treated with BI 836826-GemOx compared to R-GemOx.

Secondary objective:
To investigate the efficacy by means of the complete remission rate based on central review assessment in patients with relapsed DLBCL treated with BI 836826-GemOx compared to R-GemOx.

2.3. BENEFIT - RISK ASSESSMENT

In preclinical studies, BI 836826 induced marked apoptosis and ADCC activity resulted in depletion of normal and neoplastic B cells. It is expected that these findings will translate into clinical setting, and will result in antitumor activity of BI 836826.
Targeting CD37 may potentially offer a benefit to patients with NHL, because BI 836826 is directed against an epitope on the tumor cells which has not previously been targeted by other drugs (for example rituximab), and therefore cross-resistance with prior therapies is not expected. In the preclinical settings the combination of BI 836826 with chemotherapy shows additive cytotoxic effect (R12-4648).

CD37 is not expressed outside of the hematopoietic and lymphatic system. The anticipated side effect profile of BI 836826 based on preclinical studies and initial clinical experience

comprises predominantly hematologic AEs and IRRs. The hematologic events are leukopenia, such as lymphocytopenia, neutropenia and thrombocytopenia. Lymphocytopenia and neutropenia may predispose to infections, including opportunistic infections. These adverse events are frequently reported in patients with hematological diseases and may be due to the underlying disease, previous and current treatment or combination of these. The neutropenia associated with BI 836826 is frequently immediate (within hours), and recovers few days after the administration. Hematologic toxicity has also been reported with GemOx combination with neutrophil nadir frequently reached around day 8 after administration. In order to avoid long lasting neutropenia the administration schedule in this trial has been structured in a way that the BI 836826 infusion is scheduled on day 8, when patients may already be neutropenic from the GemOx treatment received on day 1. We hypothesize that neutropenia resulting from BI 836826 administration will fall into nadir. While it is conceivable that further decrease in neutrophil counts may be observed, the overall duration of neutropenia should be affected minimally or, not at all. Accepting shorter periods of neutropenia with rapid recovery is considered safer then prolonged periods with low neutrophil counts when infections tend to develop. Together with adjustments of administration schedule, treatment and prophylaxis recommendations are provided in this protocol to ensure patients' safety see section 4.2.1.2. and 4.2.1.3. The allowance to use growth factors will further allow managing neutropenia in patients on this trial.
Severe neutropenia has rarely been observed with treatment with rituximab, therefore the administration schedule for R-GemOx arm will adhere to previously described dosing of Rituximab on day 1 and GemOx on day 2 of each cycle.

To mitigate IRRs the protocol specified precautions must be adhered to, i.e. rate controlled infusion schedule, premedication, monitoring of vital signs and access to intensive care facilities (see section 4.1.5). With the specified precautions IRRs have been manageable and no patient has been discontinued from BI 836826 due IRR.

There is an added risk associated with procedure of tumor tissue biopsy for patients who do not have archival tumor tissue available at screening and for whom a new tumor biopsy will be required. Those risks include: pain, swelling bleeding, and infection.
Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also section 5.3.3.1.

In summary, the prophylactic measures and guidance to investigators have been implemented in this protocol to protect patient's safety. In Part 1 the safety review team will analyze data after each cohort has been completed and decide whether dose escalation to the next level is safe. In Part 2, the internal Data Monitoring Committee (DMC) will be appointed for this trial to provide additional safety oversight. Considering the advanced stage of the underlying malignant disease in patients on this trial the potential benefit of therapy is expected to outweigh the treatment-related risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1. OVERALL TRIAL DESIGN AND PLAN

Population:
The trial will be conducted in patients with relapsed/refractory diffuse large B-cell lymphoma (including transformed follicular lymphoma) who have been previously treated with an anti-CD20 monoclonal antibody (e.g. rituximab) in combination with an anthracycline containing chemotherapy and who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant.

Part1 (Phase I dose escalation)
This trial consists of two parts. The Part 1 is an open-label (Phase Ib), dose-escalation according to a standard 3+3 design to determine the MTD of BI 836286 in combination with gemcitabine and oxaliplatin. The dose escalation phase will be followed by an extension cohort of 6 patients to be treated at the established MTD, so that a total of 12 patients will be treated at this established MTD.
Patients will receive maximum of 6 treatment cycles. Each cycle is 14 days (it can be up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days). In order to continue trial treatment, patients must fulfill all criteria as outlined in section 6.2.2.1. In case of toxicity, the start of the next cycle can be delayed by up to 14 days.
Following doses of BI 836826 will be tested in combination with GemOx: 25mg, 50mg, 100mg, 150mg and 200mg. An additional intermediate dose might be tested.

Table 3.1:1 Rules for dose escalation (for DLT definition see section 5.3.8)

Number of patients with DLT/dose level	Action
0/3	Proceed to the next dose level
1/3	Enroll additional 3 patients (up to 6 total) at the same dose
1/6	Proceed to the next dose level
≥2/6	Dose is exceeding MTD- stop escalation or examine lower, intermediate dose

Cycle duration= 14 days, MTD will be defined on the basis of DLT observed during the first cycle, i.e. the first 14 days of C1.

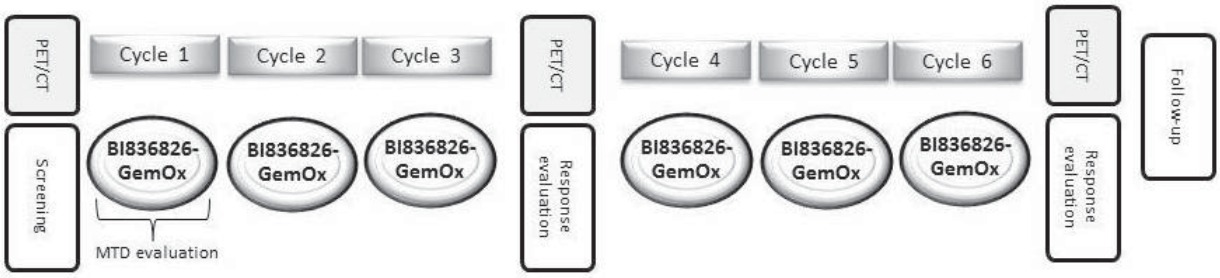

Figure 3.1:1 Part 1: Dose finding

Part 2 (open label randomized Phase II)
After the determination of the recommended dose of BI 836826 in combination with gemcitabine and oxaliplatin in Part 1, the randomized Part 2 of the trial will be initiated. Patients who have participated in Part 1 will not be eligible to participate in Part 2. Patients will be randomized (1:1) to one of the two treatment arms: BI 836826-GemOx or R-GemOx.

- R-GemOx arm

The treatment administration schedule for R-GemOx is in line with previously published regimen (R13-0204, P13-00889, R13-0203, R14-2111). Patients in R-GemOx arm will receive rituximab at 375mg/m^2 on day 1, and gemcitabine 1000mg/m^2 followed by oxaliplatin 100mg/m^2 on day 2 of each cycle. One cycle is 14 days, and treatment will be repeated on day 15 (i.e. D1 of the next cycle). Maximum number of treatment cycles is 6. In order to continue trial treatment, patients must fulfill all criteria as outlined in section 6.2.2.1. In case of toxicity, the start of the next cycle can be delayed by up to 14 days.

- BI 836826-GemOx arm

Patients randomized to BI 836826-GemOx arm will receive: gemcitabine 1000mg/m^2 followed by oxaliplatin 100mg/m^2 on day 1, and BI 836826 at the recommended dose from Part 1 on day 8 of each cycle. One cycle is 14 days (it can be up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days). Maximum number of treatment cycles is 6. In order to continue trial treatment, patients must fulfill all criteria as outlined in section 6.2.2.1. In case of toxicity, the start of the next cycle can be delayed by up to 14 days.

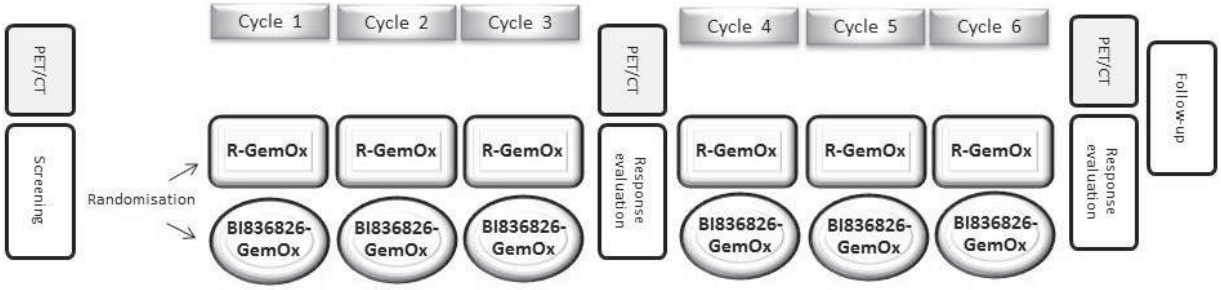

Figure 3.1:2 Part 2: Randomized

3.1.1. Administrative structure of the trial

This is a multicenter trial sponsored by Boehringer Ingelheim (BI) which will be conducted in two parts, Part 1 (Phase Ib dose escalation) with 12-14 sites mainly in Europe and randomized Part 2 (Phase II randomized) with 35-40 sites in Europe and the rest of the world.

The Coordinating Principal Investigator will be nominated for the trial. will be helping to provide an oversight to the execution of the trial at all centers, will be involved in dose escalation decisions in Part1. A Coordinating Investigator is responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities of all investigators will be defined in a contract. Relevant documentation on the participating investigators (Principal) and other important participants, including their curricula vitae, will be filed in the ISF and Trial Master File.

The Principal Investigators (PIs) will be hematologists experienced and specialized in the treatment of DLBCL. The PI at each site will be responsible for the daily conduct of the trial, complying with scheduled patients'visits, electronic case report form (e-CRF) completion, and for assisting the Clinical Research Associates (CRAs) in site monitoring.

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOP)s,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- insure appropriate training and information of Local Clinical Monitor (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs. Tasks and functions assigned in order to organize, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

In Part 1, a Safety Review Team consisting of the coordinating investigator, and principal investigators who have contributed by enrolling patients, Team member medicine (TMM), Team member drug safety (TMDS) and the TCM will review the clinical data regularly in order to assess safety (i.e. decide continuation, modification, or termination of the trial). The dose for the next cohort will be decided, based on the review of 3-6 patients in the same dose cohort, by the team.
After completion of Part 1, enrollment to the trial will be temporary stopped to allow for additional assessment of benefit/risk profile. The Safety Review Team will perform careful

analysis of safety profiles at tested doses and confirm the recommendation of dose for Part 2 of the trial.

In Part 2, an internal DMC, independent of the trial team, will review the data in order to assess the safety and efficacy data from the trial. Assessment of the data will be performed at specified intervals to recommend whether to continue, modify or stop the trial. The tasks and responsibilities and scheduling of meeting for the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

The sponsor may outsource some responsibilities related to trial activities like: monitoring, trial medication supply logistics, or others.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

In part 2, a vendor will be used for central review (response evaluation) and archiving of the PET/CT images collected in this trial. (See further details in sections 5.2.1. and 6.2.2.5).

Details on handling of the trial supplies are given in section 4 of this protocol.

3.2. DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The trial consists of two parts: Part 1, Phase Ib dose escalation and Part 2, a randomized Phase II. The MTD of BI 836826 established in Part 1 will be used to define the recommended dose for Part 2. The trial is designed as open label, since the administration schedule of the trial treatment is different in both arms, and blinding is not considered appropriate for this design.

Part 1
This is the first combination trial with BI 836826 and chemotherapy, therefore a careful dose escalation with starting dose below the MTD established for monotherapy is warranted. The starting dose has been selected at 25mg, which is two dose levels below the established monotherapy MTD of 100mg, and it is predicted to be safe. The planned 5 dose escalation levels should allow reaching the monotherapy MTD with the minimum required number of patients to gather safety data, while allowing the patients to be exposed to drug levels that might provide some clinical benefit.
From the definition of the MTD, and extension cohort will recruit 6 patients at that established MTD. The total number of patients treated at this MTD will be 12.

Part 2
Once the MTD dose has been established in Part 1, and the recommended dose to be used is confirmed by the safety review team, Part 2 will be initiated.
Patients will be randomized (1:1) to one of two treatment arms: BI 836826-GemOx, or R-GemOx. The randomized design will allow exploring the clinical activity of BI 836826-GemOx regimen versus R-GemOx and provide comparison data on safety for both arms. This randomized design will help to inform whether CD37 antibody is a valid target in this patient

population, and whether it has greater therapeutic potential than rituximab in setting of relapsed/refractory aggressive lymphomas in patients who are not eligible for stem cell transplant.

Relapsed or refractory DLBCL is treated with systemic chemotherapy with or without rituximab with plans to proceed to high-dose chemotherapy and hematopoietic cell transplantation (HCT) in those with chemotherapy-sensitive disease. The treatment of patients who are not candidates for HCT, who fail to respond to second-line chemotherapy regimens, or who relapse after HCT is generally palliative. In the absence of HCT, conventional chemotherapy regimens provide only transient disease control for the majority of patients with relapsed or refractory DLBCL. Patients with primary refractory disease rarely achieve a complete remission when treated with a second chemotherapy regimen. Following relapse from a first complete remission, a subset of patients will achieve a second complete remission with chemotherapy; however, these remissions are generally not durable and long term disease-free survivors are rare (P15-01852). Patients that cannot tolerate the intensive standard chemotherapy followed by stem cell transplant are candidates for regimens designed for elderly patients. Examples of such regimens include: CEPP (P15-01777) (cyclophosphamide, etoposide, prednisone, procarbazine), DA-EPOCH (P14-08837, P14-08836) (dose-adjusted cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone), CEOP (P15-01909) (cyclophosphamide, etoposide, vincristine, prednisone), GDP (R15-0717) gemcitabine, dexamethasone, cisplatin), or GemOx (R14-2111, R13-0203) (gemcitabine, oxaliplatin). All of those regimens can be given with, or without addition of rituximab. Alternatively, single agent therapy with anthracyclines, cytarabine, or alkylating agents may be used for palliation of symptoms. None of the above combination regiments is clearly superior over the other, and in clinical practice the choice of treatment at relapse frequently relies on experience of treating physician, patient's comorbidities and possible toxicities. The R-GemOx combination is one of possible treatments in this setting which has proven safe in patients with relapsed/refractory DLBCL who are not eligible for high dose chemotherapy (R14-2111).

It is controversial whether rituximab should be included in the treatment of all patients with relapsed/refractory disease. This is partially because older studies that have demonstrated a benefit from rituximab in the setting of relapsed disease have included few patients who received rituximab as part of their initial treatment. It is important to note that according to newer emerging data patients who have received rituximab in their first line therapy have lower response rates and shorter event free survival compared to those who are rituximab-naïve at time of their relapse (P10-10101, R14-2111). All patients enrolled into this trial will have been previously exposed to an anti-CD20 monoclonal antibody (see, section 3.3.2. inclusion criterion #3). The trial will provide initial data on whether such pre-exposure limits the beneficial effect of rituximab in the salvage regimen, when compared with novel anti CD37 antibody targeting another antigen on tumor cells. The trial will also provide initial data whether CD37 antibody can be effectively used in this setting, and how the activity of BI 836826-GemOx compares to clinical activity to R-GemOx regimen.

3.3. SELECTION OF TRIAL POPULATION

3.3.1. Main diagnosis for trial entry

3.3.1.1. Patient population

Patients with relapsed/refractory DLBCL (including transformed folicullar lymphoma) who have been pretreated with an anti-CD20 monoclonal antibody (e.g. rituximab) in combination with an anthracycline containing chemotherapy and who are not eligible for, or have relapsed/progressed after autologous/allogeneic stem cell transplant.

Number of patients to be enrolled:

Part 1:
Up to 33 evaluable patients will be enrolled during dose escalation. Patients who received, full treatment in the first cycle, but did not complete the 14 days observation period (D1 to 14 of the first cycle) for reasons other than a DLT, will be replaced at the same dose level.

Part 2:
A total of 120 patients will be randomized (1:1) to either of two treatment arms: R-GemOx, or BI 836826-GemOx, see section 4.1.2.

Patients participating in Part 1 will not be eligible for Part 2 of this trial.

3.3.2. Inclusion criteria

1. Age 18 years or older
2. Patients with histologically confirmed, relapsed/refractory, diffuse large B-cell lymphoma (including transformed follicular lymphoma)
    - who have received an anti-CD20-supplemented, anthracycline-containing chemotherapy

    and
    - are not eligible for high dose therapy followed by an autologous stem cell transplant, or have relapsed/progressed after autologous/ allogeneic stem cell transplant

    Allogenic stem cell transplant performed at least 6 months prior to study entry is allowed if patients do not require immunosuppressive treatment and have no evidence of active graft-versus-host disease.
3. Patient has not received anti-lymphoma treatment prior to the first dose of trial medication:
    - within past 14 days
      or
    - within time that is shorter or equal to 5 half-lives of the drug if the last anti-lymphoma treatment contained an investigational agent
4. Screening computer tomography (CT) scan with involvement of at least 1 bi-dimensional lesion/node >1.5 cm

5. Screening [^{18}F]flourodeoxyglucose (FDG)- positron emission tomography (PET) scans must demonstrate positive lesion compatible with computer tomography (CT) defined anatomical tumor sites.
6. ECOG performance status 0, 1, 2, see Table 5.2.3:1
7. Written signed informed consent consistent with ICH GCP and local legislation
8. Patients must have an acceptable organ function defined as in Table 3.3.2.1 :

Table 3.3.2:1 Definition of acceptable organ function

Laboratory investigation	**Value required at screening**
Hb[1)]	≥ 8g/dL
Absolute neutrophil count (ANC)[1)]	≥ 1000/µL
Platelets (PLT)	≥ 75000/µL
Glomerular filtration rate (GFR) [2)]	≥ 45mL/min
Serum creatinine	≤ 2xULN
AST and ALT	≤ 3xULN
Bilirubin (total) (Exceptions: patients with diagnosed Gilbert's syndrome)	≤ 1.5xULN
International Normalized Ratio (INR) (If treated with anticoagulants prolonged INR is acceptable)	≤ 1.5XULN

1) growth factor support and transfusions are allowed
2) GFR calculated based on local practices

9. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. Non-vasectomized male patients having a female sexual partner of childbearing potential must ensure their partner is using a highly effective method of birth control as described above, during the trial and for at least 12 months after the end of the trial. (See section 4.2.2.3 for details)

3.3.3. Exclusion criteria

1. Eligible for curative salvage high dose therapy followed by stem cell transplant
2. Primary central nervous system lymphoma or known Central nervous system (CNS) involvement
3. Prior history of malignancy other than DLBCL except basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the uterine cervix or breast which has been treated with curative therapy. Other prior malignancies are allowed only if patient has been free of disease and without treatment other than hormones for at least past three years.
4. Refractory to gemcitabine and/or oxaliplatin

5. Contraindications for gemcitabine, oxaliplatin and/or rituximab as judged by the investigator. Hypersensitivity to oxaliplatin.
6. Unresolved toxicity of CTCAE grade > 1from prior anti-lymphoma therapy (except alopecia)
7. Significant concurrent medical disease or condition which according to the investigators judgment would either compromise patient safety or interfere with the evaluation of the safety of the test drug. e.g. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring therapy with the exception of extra systoles of minor conduction abnormalities
8. An infection requiring treatment at the start of the trial medication.
9. Active hepatitis B or hepatitis C, or laboratory evidence for a chronic infection or HIV infection (test results done in routine diagnostics are acceptable if done within 14 days before the first study treatment dose)
10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. This includes the female sexual partners of a male participant.
11. Known alcohol or drug abuse which could potentially interfere with trial participation according to investigator's judgment
12. Prior treatment with CD37 antibody

3.3.4. Removal of patients from therapy or assessments

3.3.4.1. Removal/Replacement of individual patients

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- Occurrence of toxicity other than lymphopenia which does not recover to Grade 1 or less within 14 days after the end of the 14-days cycle (meaning not recovered at D28 of cycle 1 and maximum D31 from cycle 2 in case the D8 was delayed by maximum 3 days), or to a degree that allows treatment continuation (see section 6.2.2.1)
- Progressive disease
- Development of any other concomitant disease/symptom, including deterioration of general condition, which results in patient's inability to continue trial treatment.

The patient will undergo the procedures for premature treatment discontinuation and follow up as outlined in the Flow Chart 1, 2, 3.

For all patients who discontinue or withdraw from the study, the reason must be recorded in the eCRFs. At the time of discontinuation of the study treatment, the next scheduled visit assessments and the EoT visit assessments will be performed whenever possible, as described in the study procedures (see section 6.2.3), and the information will be recorded in the eCRF. Although treatment is discontinued, patients who do not withdraw consent for follow-up, nor die, nor become lost to follow-up will enter the follow-up period (see section 6.2.4 and 6.2.5). The data will be recorded in the trial database and will be reported.

If a patient or patient's partner should become pregnant during the trial, all trial treatment must immediately be stopped, and this female patient is not allowed to receive trial medication from that point onward. The female patient or patients' partner will be followed up until delivery or termination of pregnancy (see section 5.3.7). The data of the female patient or patients' partner will be collected and reported in the clinical trial report (CTR) until last patient last visit and any events occurring thereafter will be reported in BI drug safety database.

Patients who have not received BI 836826 on D8 in cycle 1 will be replaced. Patients who received, full treatment in the first cycle, but did not complete the 14 days observation period (D1 to 14 of the first cycle) for reasons other than DLT, will be replaced at the same dose level. Patients who experienced a DLT prior to BI 836826 infusion will be replaced.

3.3.4.2. Discontinuation of the trial by the sponsor

BI reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals,
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial,
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of termination of the trial (except in case of the third reason).

3.3.4.3. Trial stopping rules in case of unacceptable toxicities

All AEs, including Serious Adverse Event (SAEs) and deaths will be carefully analyzed. Unacceptable toxicity will be defined as:

- Clinically relevant adverse events that are unexpected considering the mode of action, and are not manifestations of underlying disease or background events typical of the trial population
  - and/or are debilitating, non-reversible, not manageable
  - or lead to a fatal outcome where evidence suggests that there was a reasonable possibility that the drug caused the adverse event
- Higher than expected frequency of specific events (such as known consequences of the underlying disease or other events that commonly occur in the trial population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than would be expected in the trial population.

If one or both of the above criteria are met, the enrolment to the trial will be stopped for in-depth analysis of the safety profile of BI 836826-GemOx. The risk-benefit profile of BI 836826-GemOx will be re-assessed by the sponsor's trial team, coordinating investigator and internal DMC (in Part 2). The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a possible re-start of enrolment. In case the benefit/risk assessment is no longer considered to be positive, the trial will be stopped.

4. TREATMENTS

4.1. TREATMENTS TO BE ADMINISTERED

All drug products listed in section 4.1.1 will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1. Identity of BI investigational product(s) and comparator backbone product(s)

Table 4.1.1:1 BI 836826

Substance:	BI 836826
Pharmaceutical formulation:	Concentrate for solution for infusion
Strength:	100mg/vial
Posology	Rate controlled infusion
Route of administration:	Intravenous
Doses	25, 50, 100, 150, 200mg*

* An additional intermediate dose level might be tested.

Table 4.1.1:2 Gemcitabine

Substance:	Gemcitabine
Pharmaceutical formulation:	Concentrate for solution for infusion
Strength:	1000mg/vial
Posology	Rate controlled infusion
Route of administration:	Intravenous
Dose	1000mg/m^2

Table 4.1.1:3 Oxaliplatin

Substance:	Oxaliplatin
Pharmaceutical formulation:	Concentrate for solution for infusion
Strength:	100mg/vial
Posology	Rate controlled infusion
Route of administration:	Intravenous
Dose	100mg/m^2

Table 4.1.1:4 Rituximab

Substance:	Rituximab
Pharmaceutical formulation:	Concentrate for solution for infusion
Strengths:	500mg/vial
Posology	Rate controlled infusion
Route of administration:	Intravenous
Dose	375mg/m^2

4.1.2. Method of assigning patients to treatment groups

The treatment group will be assigned via Interactive Response Technology (IRT). The IRT will be used to register the patient at screening and at all time-points trial medication is dispensed as well as at EOT visit. The time points for accessing the IRT system are shown in the Flow chart 1, 2, 3.
The complete trial medication, including BI 836826, rituximab, gemcitabine and oxaliplatin will be supplied by BI and managed through the IRT system. Please note that the medication number is the trial medication identification and is different from the patient number.
An IRT manual, describing how to access and use the IRT, will be distributed to the investigator, pharmacist and site personnel prior to start of the trial.

Part 1
All patients enrolled in Part 1 will receive BI 836826 in combination with GemOx. The following dose levels of BI 836826 will be tested in cohorts of 3-6 patients: 25-50-100-150-200mg (an additional intermediate dose level might be tested). The assignment to a cohort /dose level will be facilitated by the IRT system.

Part 2
In Part 2, patients will be randomized in a 1:1 ratio to BI 836826-GemOx, or R-GemOx. Patients who have participated in Part 1 will not be eligible for Part 2. Randomization will be carried out centrally using IRT. The company that provides the IRT will receive the randomization list from Boehringer-Ingelheim Clinical Trial Support Group or a Clinical Research Organisation (CRO) appointed by the sponsor. The BI standard validated random number generating system will be used to generate the randomization schedules which will be verified by an independent statistician who is not involved in the trial. The access to the randomization code will be supervised by the Clinical Trial Support Group. People who are directly involved in the conduct and analysis of the trial will have no access to the randomization schedule.

4.1.3. Selection of doses in the trial

BI 836826 will be given as a flat dose i.e. without any adjustment for body surface area (BSA) or weight, in a biweekly dosing schedule (every 2 weeks). The starting dose has been selected at 25mg, which is two dose levels below the established monotherapy MTD of 100mg, and it is predicted to be safe. During the dose escalation, the dose will be doubled in the 2 first subsequent cohorts (next dose levels: 50 and 100mg) and then escalate to 150 and

200mg cohorts. This approach was selected because it is to be safe and allows the achievement of an efficacious dose with minimum number of patients treated below MTD. The patients in a cohort will be evaluated for occurred DLTs during the 14 days observation period (D1 to 14 of the first cycle). Any patient withdrawing from study participation before D15, for reasons other than DLT, will be replaced in the cohort by a new patient, as the withdrawn patient is considered not evaluable. The safety profile of the cohort has to be assessed as tolerable by the safety review team before the next cohort can be opened for enrolment. The IRT system will be closed during this evaluation and it will not be possible to enter a patient in the trial. The investigators will be able to obtain the information about the next dose level from the IRT system.

The doses of gemcitabine (1000mg/m^2) and oxaliplatin (100mg/m^2) in a biweekly dosing schedule were selected based on tolerability and efficacy data from the literature (R13-0203). Both, gemcitabine and oxaliplatin are dosed by BSA. Patient's weight from C1D1 should be used or initial calculation of BSA and the same value can be used throughout the trial as long as patient's weight does not change by 10% or more. If body weight changes by >10% the BSA needs to be recalculated and doses of both: gemcitabine and oxaliplatin need to be adjusted accordingly.

One cycle is 14 days (it can be up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days), and repeated cycle starts on day 15 (or D18 in case of D8 delayed by maximum 3 days). In case of toxicity, the next cycle start might be delayed by a maximum of 14 days. Patients who do not recover from toxicity within 14 days will be removed from the trial for toxicity reasons, and will not be allowed to re-enter the trial treatment.

Part 1

Table 4.1.3:1 Part 1 Doses and administration of BI 836826-GemOx

Trial Medication	Dose levels	Administration
BI 836826 [1)]	25mg-50mg-100-150-200mg iv in 250mL normal saline at rate controlled infusion for details see Table 4.1.5.1:1	Day 8 of each cycle (up to 6 cycles)
Gemcitabine	1000mg/m^2 iv in 500mL normal saline at 10mg/m^2/min	Day1 of each cycle (up to 6 cycles)
Oxaliplatin	100mg/m^2 iv in 5% glucose solution administered after Gemcitabine as 2hrs infusion	Day1 of each cycle (up to 6 cycles)

1) An additional intermediate dose level might be tested.

Part 2
BI 836826-GemOx arm
BI 836826 will be given as a flat dose, i.e. without any adjustment for body surface area or weight.
The recommended BI 836826 dose in combination with GemOx will be based on the observed AEs of the combination with GemOx from cycle 1 in Part 1 and on all additional safety data available from subsequent treatment cycles in Part 1. The recommended dose in Part 2 may be equal or lower than the MTD determined in Part 1.

Table 4.1.3:2 Part 2 Doses and administration of BI 836826–GemOx

Trial Medication	Dose levels	Administration
BI 836826	Recommended dose iv from Part 1 in 250mL normal saline at rate controlled infusion for details see Table 4.1.5.1:1	Day 8 of each cycle (up to 6 cycles)
Gemcitabine	1000mg/m^2 iv in 500mL normal saline at 10mg/m^2/min	Day1 of each cycle (up to 6 cycles)
Oxaliplatin	100mg/m^2 iv in 5% glucose solution administered after Gemcitabine as 2hrs infusion	Day1 of each cycle (up to 6 cycles)

R-GemOx arm
The rituximab dose will be given at the approved dose of 375mg/m^2. Rituximab will be given in combination with GemOx as documented in the literature (R13-0203).

Table 4.1.3:3 Part 2 Doses and administration of R–GemOX

Medication	Dose levels	Administration
Rituximab	375mg/m^2 iv in 500mL normal saline at rate controlled infusion for details see section 4.1.5.2.	Day 1 of each cycle (up to 6 cycles)
Gemcitabine	1000mg/m^2 iv in 500mL normal saline at 10mg/m^2/min	Day 2 of each cycle (up to 6 cycles)
Oxaliplatin	100mg/m^2 iv in 5% glucose solution administered after Gemcitabine as 2hrs infusion	Day 2 of each cycle (up to 6 cycles)

4.1.4. Drug administration of doses for each patient

Standard or routine prophylactic measures (including antiemetic's and hydration) should be used prior to administration of GemOx chemotherapy to reduce the incidence of adverse events from these infusions.

For premedication before antibody infusion see section 4.1.5.4.
For handling of IRRs see section 6.2.2.3, and for tumor lysis syndrome (TLS), see section 6.2.2.6.

The use of transfusions and growth factors is allowed throughout the trial as clinically indicated.

A cycle is 14 days in length (it can be up to 17 days from Cycle 2, in case the D8 is delayed by maximum 3 days). The repeat cycle starts on day 15 (= day 1 of the next cycle; up to D18 in case D8 is delayed by maximum 3 days). Up to 6 cycles can be administered, if the treatment is well tolerated and the patient has no clinical and/or radiologic signs of progression, as judged by the investigator.
Before the initiation of each subsequent cycle, each patient has to be evaluated for eligibility to receive further treatment. If the patient does not fulfill **all** criteria to continue treatment as outlined in section 6.2.2.1, the start of the next cycle can be delayed by a maximum of 14 days to allow recovery. Patients who do not recover during those additional 14 days will be withdrawn from the trial for toxicity reasons.
The actual duration of all the infusions need to be documented in the e-CRF including actual start and end time, actual time points for interruptionand restart of the infusion and the actual infusion rates, including all steps in rate changes.

Part 1
Gemcitabine and oxaliplatin (GemOx) will be administered as intravenous infusions on day 1of each cycle (see section 4.1.5.3). BI 836826 will be administered as an intravenous infusion, on day 8 of each cycle under the supervision of the investigator or designated personnel.

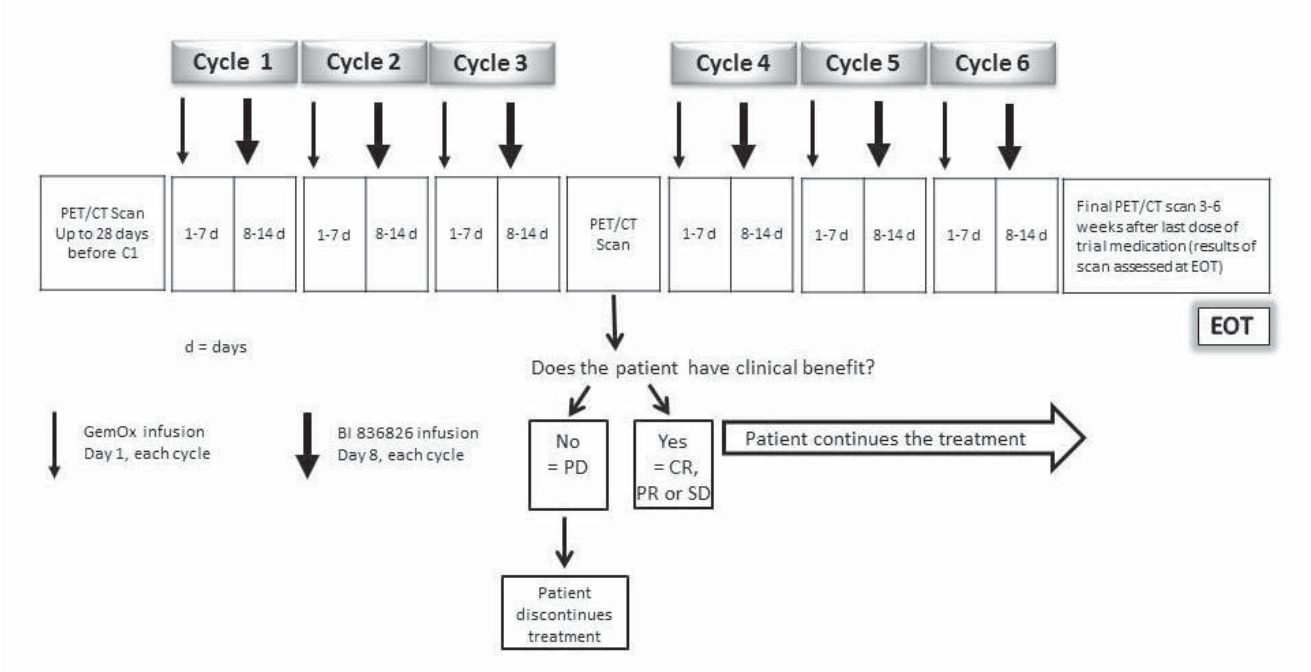

Figure 4.1.4:1 BI 836826-GemOx arms Part 1 and 2

In order to facilitate blood sampling for pharmacokinetic (PK) analyses, it is recommended to start the BI 836826 infusion during the morning, preferably before 12 noon.

Part 2

BI 836826-GemOx

Gemcitabine and oxaliplatin (GemOx) will be administered as intravenous infusions on day 1of each cycle (for details see section 4.1.5.3). BI 836826 will be administered as an intravenous infusion on day 8 of each cycle under the supervision of the investigator or designated personnel. For administration scheme see Figure 4.1.4:1

R-GemOx

Rituximab will be administered on day 1 of each cycle and gemcitabine and oxaliplatin (GemOx) will be administered as intravenous infusions on day 2 of each cycle (see section 4.1.5.3). For administration scheme see Figure 4.1.4:2

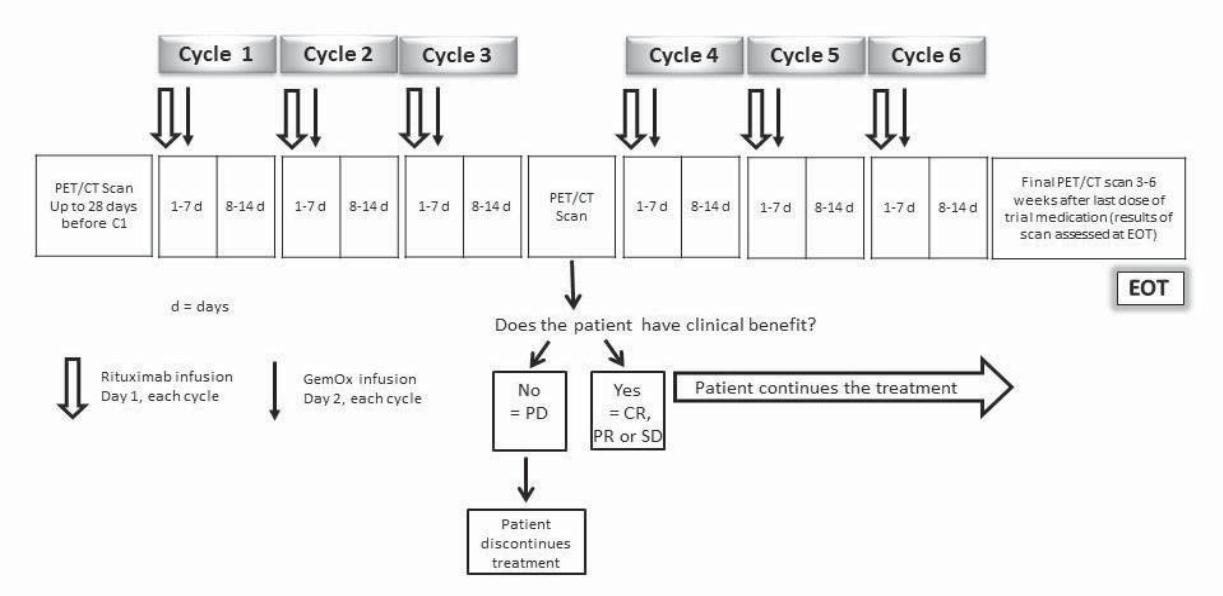

Figure 4.1.4:2 Rituximab-GemOx arm Part 2

4.1.5. Infusion schedules

All patients (Part 1 and Part 2) need to fulfil criteria to continue treatment prior to starting the next cycle (C2-6), for details see section 6.2.2.1. The initiation of the next cycle may be postponed for up to 14 days to allow patients to fulfil these criteria (meaning the next cycle has to be started at the latest on D29, or maximum on D32 from cycle 2 and in case the D8 was delayed by maximum 3 days).
For dose adjustment recommendations please see details below and see Table 6.2.2.1:1.

4.1.5.1. BI 836826 infusion

BI 836826 is to be diluted into 250mL of normal saline. Premedication is mandatory (see section 4.1.5.4). All patients have to be hospitalized for at least 24hrs after the first infusion of BI 836826. Please refer to table 4.1.5.1:1 for the first infusion schedule.

Table 4.1.5.1:1 Infusion schedule for BI 836826:

Time (+/- 10min)	Rate mL/h in 250mL	Total Volume (ml) infused
0-29 min	10	5
30-59 min	20	15
60-89 min	30	30
90-119 min	40	50
120-149 min	50	75
150-179 min	60	105
180-209 min	70	140
210-293 min	80	250

Subsequent infusions may be faster or steps maybe omitted if considered safe. The maximum speed of infusion should not exceed 120mL/h.

The total duration of the infusion may not extend 24 hours. If interruptions are necessary for IRR treatment, the time from the initial start of infusion until the end of infusion must be ≤ 24 hours. Any remaining solution needs to be discarded after this time.

No dose reduction or dose delay of BI 836826 is allowed in cycle 1. From Cycle 2, the D8 can be delayed by maximum 3 days.
Only one dose of BI 836826 may be omitted from cycle 2.

4.1.5.2. Rituximab infusion

The rituximab dose of 375mg/m^2 is to be diluted into 500mL normal saline. Premedication is mandatory, see section 4.1.5.4. The first dose of rituximab should be given cautiously, starting at a slow rate and increased slowly. As recommended in the SmPC of rituximab, the initial rate for infusion should be a maximum of 50mg/h. After 30 minutes, the infusion rate can be escalated in 50mg/h increments every 30 minutes, to a maximum rate of 400mg/h.

No dose reduction or skipped dose of rituximab is allowed.

4.1.5.3. Gemcitabine and Oxaliplatin

Gemcitabine 1000mg/m^2 (diluted into 500mL of normal saline) is administered at a fixed dose rate of 10mg/m^2/min on:

- day 1 if patients are participating in Part 1 or, are randomized to the BI 836826-GemOx treatment arm in Part2

or

- day 2 if patients are randomized to R-GemOx arm in Part2.

This prolonged administration schedule has been shown to achieve superior intracellular drug concentrations than the standard 30 min i.v. schedule (R14-4504).

No dose reduction or skipped dose of gemcitabine is allowed.

Oxaliplatin 100 mg/m^2 is to be administered after gemcitabine in a 2hrs infusion on:

- day 1 if patients are participating in Part 1 or are randomized to the BI 836826-GemOx treatment arm in Part2

or

- day 2 if patients are randomized to R-GemOx arm in Part 2.

Only one dose of oxaliplatin may be omitted during the trial.

Reduction of dose is allowed as per events described in table 6.2.2.1:1.

4.1.5.4. Premedication for BI 836826 and Rituximab

Premedication and close monitoring of the rate of infusion are the main precautions to minimize infusion related reactions. Premedication is mandatory and has to be administered 30-120 minutes prior to the administration of monoclonal antibody, *i.e.* BI 836826 or rituximab. The premedication in the first and second cycle should include:

- Acetaminophen/paracetamol 1000 mg per os (p.o.), or equivalent
- Antihistamine p.o. or i.v., equivalent to diphenhydramine 50mg i.v.
- Glucocorticoid i.v., equivalent to prednisolone 100mg

If patients tolerate the infusions with BI 836826 or rituximab well during the first 2 cycles, the dose of glucocorticoid premedication may be reduced by:
- 50% at the third cycle, (i.e. glucocorticoid i.v., equivalent to 50mg prednisolone)
- 75% at the fourth and subsequent cycles (i.e. glucocorticoid i.v., equivalent to 25mg prednisolone)

4.1.6. Blinding and procedures for unblinding

4.1.6.1. Blinding

This is an open label trial. Blinding is not applicable, see section 3.2. However, to reduce bias, the BI trial team will be blinded for the aggregated data in Part 2 until the database has been locked.

4.1.6.2. Un-blinding and breaking the code

This is an open label trial. Procedures for emergency un-blinding are not applicable.

4.1.7. Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).
Boxes and vials of BI 836826, rituximab, gemcitabine and oxaliplatin will be labelled according to local regulations and will include the following as a minimum:

- The trial number (1270.11)
- Product name
- Contents of the bottle/carton box
- Strength
- Batch number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement indicating that the medication is for clinical trial use only
- A caution statement

Examples of the labels will be filed in the ISF.

The BI 836826, rituximab, gemcitabine and oxaliplatin drug supply will be managed through IRT by the trial sites and BI personnel.

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

Refer to the ISF for details of packaging and the description of the label as well as the process for resupply of trial drug.

4.1.8. Storage conditions

All trial medication will be kept in original packaging in a secure limited access storage area according to the recommended storage conditions on the label.

Temperature logs must be maintained to make certain that the drug supplies are stored at the correct temperature. In case temperature would be out of range, the sponsor has to be notified.

For a more detailed description of the BI 836826 drug profile refer to the current IB which is included in the ISF.

For gemcitabine, oxaliplatin and rituximab please refer to SmPC in ISF.

4.1.9. Drug accountability

The investigator or the pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / ethics committee/ / Health Authority (HA)
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol
- If applicable, availability of the proof of a medical license (*e.g.* Form 1572 in US) for the principal investigator

The investigator or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the medication kit numbers assigned to the investigational products and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. The investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient.

Any opened vials of BI 836826, rituximab, gemcitabine and oxaliplatin should be discarded after use following local regulations and local hospital practices.

4.2. CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1. Rescue medication, emergency procedures, and additional treatment(s)

4.2.1.1. Rescue medication

Rescue medication in term of an antidote to reverse the action of BI 836826 is not available. Potential side effects of BI 836826 have to be treated symptomatically.

4.2.1.2. Supportive care

Patients should receive supportive care according to local guidelines regarding treatment of any AEs, IRRs (section 6.2.2.3), TLS (section 6.2.2.6), blood product support, growth factor support, analgesics, skin and mouth care, etc.

4.2.1.3. Antibiotics and antivirals

Prophylactic antibiotics, antivirals, and antifungals are allowed. For patients who are considered to have an increased risk for herpes and/or pneumocystis jiroveci infections, the prophylaxis is mandatory. For patients who are considered to have an increased risk for other infections, prophylactic therapy is recommended.

Prophylactic antiviral therapy is recommended for patients with a history of recurrent herpes virus infections, herpes infection during previous anti-lymphoma therapy e.g. acyclovir 400 mg three times a day orally.

CMV reactivation during treatment should be treated according to institutional standards.

4.2.1.4. Concomitant treatments

All concomitant therapies to provide adequate care may be given as clinically necessary. Any other anti-lymphoma therapy besides trial treatment is not allowed. All concomitant treatments should be recorded in the e-CRF except for vitamins or nutrient supplements. Trade name, indication and dates of administration of concomitant therapies will be documented. For parenteral nutrition during the trial, the components need not to be specified in detail. It should just be indicated as ‘parenteral nutrition’. If a patient needs general anesthesia, it will be sufficient to indicate ‘general anesthesia’ without specifying the details.

Systemic immune-suppressive therapy other than corticosteroids is not allowed during treatment. Short term pulsatile glucocorticoid medications may be used as clinically indicated to treat IRRs or autoimmune phenomena, at any dose. Long term (>5 days) daily oral steroid treatment may be administered at doses equivalent to prednisolone 20mg per day or below. Higher doses of daily steroid treatment should be discussed and agreed upon between investigator and sponsor.

Concomitant therapy should be recorded in the e-CRF during the screening and treatment period, starting at the date of signature of informed consent, and ending at FU for AEs visit. (i.e. this is equivalent to the Residual Effect Period (REP) 30-42 days after the last dose). If new anti-lymphoma therapy is administered during this period, it will be captured on a separate follow up therapy e-CRF page.

4.2.2. Restrictions

4.2.2.1. Restrictions regarding concomitant treatment

- No concomitant anti-neoplastic therapies are allowed during the trial
- No other investigational therapy is allowed
- Additional glucocorticoid medications may be used as clinically indicated only to treat IRRs at any dose

4.2.2.2. Restrictions on diet and life style

No restrictions apply with regard to diet or life style exception the contraception rules see section 3.3.2., (inclusion criterion 9) and section 4.2.2.3.

4.2.2.3. Restrictions regarding women of childbearing potential

Women of childbearing potential* (WOCBP) must be ready and able to use highly effective methods of birth control per ICH M3 (R2) and in accordance with the recommendations related to contraception and pregnancy testing in clinical trials by Heads of Medicines Agencies Clinical Trials Facilitation Group (HMA CTFG) [R16-0373] that result in a low failure rate of less than 1% per year when used consistently and correctly, and this during the trial and for at least 12 months after the end of the trial.

*Women of childbearing potential (WOCBP) are defined as:

- A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile, which also includes the female sexual partner of a male patient.
- Women who underwent tubal ligation/occlusion, a highly effective method of contraception but not a method of permanent sterilisation, are still considered of childbearing potential, which means that they must be tested for pregnancy during the study period [R16-0373].

Women not of childbearing potential are defined as:

- Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

Highly effective methods of birth control for WOCBP are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, taken as oral, intravaginal or transdermal formulation.
- Progestogen-only hormonal contraception associated with inhibition of ovulation, taken as oral, injectable or implantable formulation.

- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS).
- Surgical sterilisation (vasectomy) of the sexual male partner.
- Complete sexual abstinence: a preferred or usual life-style where you refrain from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur.

An explanation is also provided in the patients informed consent information form.

4.3. TREATMENT COMPLIANCE

BI 836826- GemOx and R-GemOx will be administered as intravenous infusions at the investigational site under supervision of authorized personnel. Any discrepancies in drug accountability are to be documented in the e-CRF by the investigator or his/her deputy.

5. VARIABLES AND THEIR ASSESSMENT

5.1. TRIAL ENDPOINTS

5.1.1. Primary Endpoints

Part 1
- The number of evaluable patients with DLTs in cycle 1.
- The MTD of BI 836826 with GemOx based on the number of evaluable patients with DLTs in cycle 1. The MTD of BI 836826 with GemOx is defined as the highest dose studied for which the number of evaluable patients with dose-limiting toxicity is 17% or less (i.e., 0-1/6 patients) during cycle 1.
- The observation time for both endpoints is 14 days from first trial medication administration.

Part 2
- Overall response (OR) by central review assessment, i.e. partial response (PR) and complete remission (CR) by central review assessment, analyzed by the ORR and compared between the two treatment arms.
- The observation time for OR is up to 32 weeks from first trial medication administration.

5.1.2. Secondary Endpoints

Part 1
- Pharmacokinetic parameters: AUC_t and C_{max} of BI 836826 when administered in combination with GemOx.
- Overall response based on investigator's assessment
- The observation time for all secondary endpoints is up to 32 weeks from first trial medication administration.

Part 2
- The CR by central review assessment will be the secondary endpoint, and will be compared between the two treatment arms.
- The observation time for this endpoint is up to 32 weeks from first trial medication administration.

5.2. ASSESSMENT OF EFFICACY

5.2.1. Criteria for response

Response will be evaluated using PET/CT scan. Scans will be performed locally and in Part 2 images will be sent for central reading. The response evaluation criteria will follow the criteria for NHL as published in the literature in 2007 (R10-1462) and with refined evaluation for the PET scan introducing the 5-PS score in 2014 (R14-3387) see Table 5.2.1:1.

Table 5.2.1:1 Criteria for Response

Response	Definition	Nodal disease	Spleen, Liver	Bone marrow
Complete remission	Disappearance of all evidence of disease	a) FDG-avid or PET + prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal* size on CT	Not palpable, nodules disappeared	Infiltrates cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
Partial remission	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET + prior to therapy; one or more PET + at previously involved site b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of spleen or liver	Irrelevant if positive prior to therapy, cell type should be specified

Table 5.2.1:1 Criteria for Response (cont'd)

Response	Definition	Nodal disease	Spleen, Liver	Bone marrow
Stable disease	Failure to attain: Complete remission Partial remission Or Progressive disease	a) FDG-avid or PET + prior to therapy; PET + at prior sites of disease and no new sites on CT or PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or progressive disease**	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET + if FDG-avid lymphoma or PET+ prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

FDG = [^{18}F]flourodeoxyglucose; PET = positron emission tomography; CT = computer tomography; SPD = sum of product of diameters

*Normal size of lymph nodes and nodal masses on CT scan is defined as ≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy. For previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

**For relapsed disease or progression, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

The PET scan should be evaluated in accordance with recent guideline (R14-3383). The PET/CT scan should use a fixed display and color table scaled to standardized uptake value (SUV). The focal uptake in aggressive DLBCL is sensitive to bone marrow involvement and may make the need for a bone marrow biopsy unnecessary.
The PET scan should be evaluated with the use of the 5-PS which has been validated for use both as an interim and as end of treatment.
The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions

In addition, as written in the published reference (R14-3383) new areas of uptake, unlikely to be related to lymphoma, are marked by (X).

If the PET scan performed after 3 cycles, demonstrates a disease progression the patient has to be withdrawn from the trial treatment.

5.2.3. ECOG Performance Status

The ECOG performance status is a scale used to assess how a patient's disease affects daily living abilities. Performance status is graded using the following scale from 0 to 5:

Table 5.2.3:1 ECOG performance status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up to about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

5.3. ASSESSMENT OF SAFETY

5.3.1. Physical examination & B symptoms

A physical examination including height (only at screening), weight and ECOG performance score as well as the tumor size determination (by palpation) will be performed at screening and at the time points specified in the Flow Chart 1, 2, 3. During the physical examination, the patient should be assessed for possible adverse events.
Patients may present with constitutional symptoms at baseline, which may improve on treatment, or may develop constitutional symptoms in the context of progression which may indicate the need for a subsequent therapy.

All patients will be evaluated for lymphoma related B symptoms at the same time points when a physical examination is indicated in the Flow Charts 1, 2, 3.
An evaluation of B symptoms will be based on the following parameters which have to be reported in the e-CRF:

- Weight loss ≥10% in 6 months or less
- Fever higher than 38.0°C
- Night sweats.

5.3.2. Vital Signs

Vital signs (blood pressure, pulse rate and body temperature) will be recorded at every visit during screening, treatment and follow-up, before proceeding with any other clinical procedure and after at least 5 minutes of rest. Additional measures of vital signs need to be collected at the time of trial drug administration in order to detect possible IRRs which must be reported as AEs. In case of IRR, the investigator should decide whether to intensify or prolong the monitoring of vital signs and to adapt patient's surveillance during subsequent infusions.

5.3.3. Safety laboratory parameters

5.3.3.1. General safety laboratory parameters

Blood samples and urine have to be collected at the time points specified in the Flow Chart 1, 2, 3 and before the infusion of trial medication, and will include the following analysis:

Hematology	At each study visit: Hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), PLT.
Reticulocytes	At screening, D1 of each cycle and at the EOT.
Biochemistry	At screening, D1 of each cycle and EOT: Glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), total bilirubin (if elevated provide direct bilirubin), total protein, albumin, uric acid
Immunoglobulins	At screening, D1 of each cycle and EOT: IgG, IgM, IgA, direct antiglobulin test are to be measured.
Serum β2–microglobulin	At screening visit only
Coagulation	At screening, D1 of each cycle and EOT: Activated partial thromboplastin time (aPTT), prothrombin time (PT)/international normalized ratio (INR).
Urine	At screening, D1 of each cycle and EOT: pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed by dipstick and reported as semi-quantitative measurements.
Pregnancy test	A serum pregnancy test needs to be obtained at screening and at EOT in female patients of childbearing potential.

5.3.3.2. Screening for laboratory evidence of TLS

To allow for early treatment in case TLS develops, vigilant monitoring after the first dose of BI 836826 or rituximab is recommended. During the first 24 hours after the start of the first dose of BI 836826 or rituximab the following laboratory parameters need to be checked at least once in patients who considered at risk for TLS, (e.g. large tumor burden, leukemic manifestation of the lymphoma). The actual date and time of the blood samples should be recorded in the e-CRF.

Testing for tumor lysis syndrome	Uric acid, potassium, sodium, calcium, inorganic phosphate, LDH, creatinine.

5.3.3.3. Screening for hepatitis B, hepatitis C, CMV and HIV

At the time points indicated in the Flow Charts 1, 2, 3 local laboratory will be used.
For HIV, HBV, HCV, test results done in routine diagnostics are acceptable if done within 14 days before C1D1.

Patients with active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or laboratory evidence of a chronic infection have to be excluded from the trial. The same applies to patients with HIV infection or detection of a HIV infection at screening.

The following laboratory parameters have to be determined at the screening visit and reported in the eCRF: Hepatitis B Surface Antigen (HBsAG), Hepatitis B Core Antibody (anti-HBc), HBV DNA and HCV RNA by quantitative assays. HIV Antibody (anti-HIV).

Patients can be treated with BI 836826 if:

9 9 HBV DNA negative
9 9 HCV RNA negative
9 9 HIV antibody negative

Patients who are HBC antibody positive at screening will be monitored for potential HBV reactivation by quantitative HBV DNA at visit 1 of every even course and at the EOT visit. If there is evidence for HBV reactivation, immediately discontinue BI 836826 and start appropriate treatment for HBV.

5.3.3.4. CMV monitoring

Monitoring of CMV has to be performed at the time points indicated in the Flow Chart 1, 2, 3 according to local standards. Cytomegalovirus serology (CMV, Ig G and Ig M) should be included in screening assessment to allow for differentiation between a primary CMV infection and reactivation of CMV during the trial. Quantitative polymerase chain reaction (PCR) assays to detect CMV DNA are considered acceptable for the purpose of this trial. The same method should be used for all treated patients in the same investigational site. Results have to be reported in the e-CRF.

5.3.3.5. Flow cytometry/quantitative lymphocyte phenotyping

At the time points indicated in the Flow Chart 1, 2 and 3, lymphocyte sub-populations (B cells, CD4+ T cells, CD8+ T cells, NK cells) will be quantitatively analyzed by a standard flow cytometry protocol in a central laboratory. Detailed instructions are included in the laboratory manual in the ISF.

Table 5.3.3.5:1 Lymphocyte surface markers

B cells	CD19
T cells	CD3+ CD4+ CD8+
NK cells	CD56+

5.3.4. Electrocardiogram

Single 12-lead ECG will be performed in all patients as specified in the Flow Chart 1, 2, 3. Please note ECG to be performed before any blood sampling.

The ECG time-points for the **Part 1** are defined as the following:

- Screening

- On trial: C4D8 (-60 min. to -5 min. prior to administration of BI 836826) and immediately after the end of infusion
- EOT visit

The ECG time-points for **Part 2** are defined in **BI 836826-GemOx** Treatment arm:
- Screening
- On trial: C4D8 (-60 min. to -5 min. prior to administration of BI 836826) and immediately after the end of infusion
- EOT visit

The ECG time-points for **Part 2** are defined in **R-GemOx** Treatment arm:
- Screening
- On trial: C4D2 (-60 min. to -5 min. prior to administration of GemOx) and immediately after the end of infusion
- EOT visit

The ECGs will be recorded using calibrated equipment 12-lead ECGs at site. The ECG recordings must also be reviewed and checked for abnormality by the investigator. Any ECG findings that are clinically significant should be reported as AE. Any QT prolongation not related to a baseline condition must be followed up sufficiently as deemed by the investigator. Additional ECGs should be done whenever the investigator deems necessary.

5.3.5. Other safety parameters

Not applicable

5.3.6. Assessment of adverse events

5.3.6.1. Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event
A SAE is defined as any AE which:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or

- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the Remote Data Capture (RDC). A copy of the latest list of "Always Serious AEs" will be provided to you upon request. These events should always be reported as SAEs as described in section 5.3.6.1.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see section 5.3.7.

The following are considered AESIs in this trial:

- **DLT**
  Any event that qualifies for DLT refer to section 5.3.8.

- **IRR**
  IRRs CTCAE grade 3 -5 are defined to be AESIs.

- **Late onset infections**
  Infections occurring during the "extended follow-up" period see Figure 5.3.7:1, which are clinically relevant and considered related to BI 836826 by the investigator, are to be reported as AESIs.

- **Hepatic injury**
  Drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators and is considered an AESI in this trial. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters, is necessary to

distinguish an effect of the underlying malignancy on liver function from other causes. This is important for patient safety.
In patients with normal transaminases and bilirubin at baseline, a hepatic injury is defined by any of the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

In patients with elevated transaminases and/or bilirubin at baseline in line with in- and exclusion criteria of this protocol, a hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥5 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

Work-up as outlined in the "Drug-Induced Liver Injury (DILI)-checklist" will serve to confirm the initial abnormality, obtain a comprehensive history and medical assessment, assess the severity of liver injury, evaluate data for potential alternative causes and decide on management of trial drug. Follow-up of the potential DILI case should be initiated within 48 hours of the initial laboratory alert, or as soon as possible if timelines cannot be met. When performing all of the required examinations, the investigator may use clinical judgment, based on the patient's disease, comorbidities, clinical situation, past viral infections and risk for reactivation, exposure, prior therapy for malignant disease, co-medications and other factors as applicable. The sequence of tests in the DILI checklist may be used as guidance. The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process and/or on the respective CRF pages. In the event the aetiology of the abnormal liver test results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), the "DILI checklist" must be completed. Virus reactivation should be assessed by viral load and PCR testing where possible. Diagnostics for auto-immune hepatitis, Wilson's disease and haemochromatosis can be completed at the end of all assessments, as these examinations will not change within a short time period but can be considered proof of a long persisting chronic condition. In case a laboratory parameter of the DILI checklist cannot be performed, the investigator should provide a comment including a brief assessment of the relevance of this parameter for the overall evaluation of DILI.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

If the investigator determines any AESI is related to trial drug, the administration of the trial drug must be managed according to Table 6.2.2.1:1.

Any elevation of ALT and/or AST and total bilirubin qualifying as laboratory hepatic injury alert should lead to reflex testing on the initial blood sample. The reflex testing should include (if appropriate specimen is available):

- direct bilirubin
- acetaminophen level
- lactate dehydrogenase
- haptoglobin
- additional single PK sample should be drawn
- liver imaging should be performed within 48 hours of identifying a liver event
  If the reflex testing at the local laboratory is initiated by the investigator the results need to be entered in the e-CRF.

Severity of AEs
The severity of adverse events should be classified and recorded in the e-CRF according to the CTCAE version 4.0 (R10-4848)

Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Yes: There is a reasonable causal relationship between the trial medication administered and the AE.
No: There is no reasonable causal relationship between the trial medication administered and the AE.

Every adverse event must be assessed for causal relationship by the investigator. The investigator needs to determine according to their best ability whether given adverse event is related to BI 836826, rituximab and/or GemOx.

The causal relationship needs to be documented on the SAE form. The causal relationship also needs to be documented in the patient's source data.

5.3.7. Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate e-CRF by the investigator:

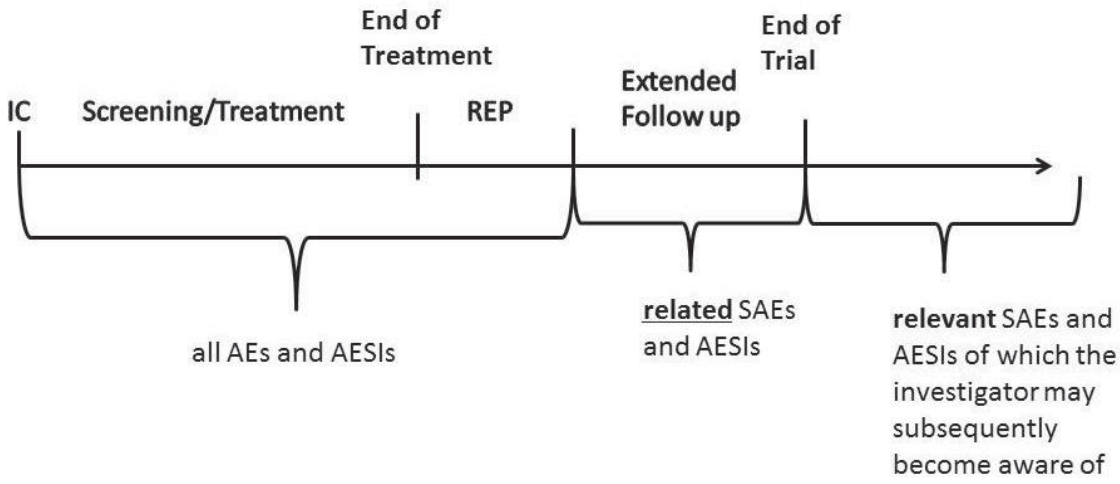

Figure 5.3.7:1 AE Collection

- From signing the informed consent onwards until FU for AEs visit all AEs (non-serious and serious), and AESIs (this is the REP period).
- After the FU for AEs visit until the last per protocol contact, all those SAEs and AESIs which are considered related to trial medication .
- However, if only vital status information is collected for a patient after PD and/or new anti-lymphoma treatment, from then on until the patient's participation in the trial ends, the investigator does not need to actively monitor the patient for AEs. Fatal AEs, relevant SAEs and relevant AESIs, which the investigator may become aware of, should be reported.

The FU for AEs / (end of REP) is scheduled 30-42 days after the last dose of trial medication (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI836826, whichever is the latest).All AEs which occurred during treatment up until FU for AEs visit are considered as "on treatment" AEs. Please see section 7.3.4. Events which occurred after the FU for AEs visit are considered " post- treatment" AEs.

After the last per protocol contact, the investigator does not need to actively monitor patients for AEs. However, if the investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the investigator to the sponsor if considered relevant by the investigator. The rules for AE reporting exemptions still apply.

AE reporting to sponsor and timelines
The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

Information required
For each AE, the investigator should provide the information requested on the appropriate e-CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The investigator should determine the causal relationship to the trial medication, and any possible interactions between the investigational drug(s) and a non-investigational product (NIMP)
The following should also be recorded as an (S)AE in the e-CRF and SAE form (if applicable):

- Worsening of pre-existing conditions other than the underlying disease
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The investigator must also report pregnancies that occurred in a female partner of a male subject. The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

Exemptions to SAE Reporting
Progressive disease (PD) in oncology trials is a trial endpoint for analysis of efficacy. PD is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy will be recorded in the appropriate pages of the e-CRF as part of efficacy data collection. Death due to PD is to be recorded on the appropriate e-CRF page and not on a SAE form.
Examples of exempted events of PD are:

- Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.

- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

When there is evidence suggesting a causal relationship between the drug and the event of progression of the underlying disease, the event must be reported as (S)AE in the eCRF and on the SAE form.

5.3.8. Dose limiting toxicity for Part 1

The MTD will be defined on the basis of DLT observed during the first cycle, *i.e.* the first 14 days of C1.

Any patient who has been replaced will not be considered evaluable for MTD determination.

The following adverse events will qualify as DLT:

- Any ≥ G3 non hematologic adverse event considered related to any trial medication with the following exceptions:
    - Laboratory abnormalities that can be corrected with treatment within 48 hours (for example: electrolyte abnormalities).
    - nausea, vomiting, diarrhea which resolve within 48hrs with adequate treatment
    - neuropathy considered related to oxaliplatin
    - IRR

- Any hematologic adverse event related to any trial medication defined as follows:
    - G4 neutropenia lasting >7 days despite growth factors support
    - Any febrile neutropenia which does not resolve within 48 hours with appropriate treatment (antibiotics, antifungal, antiviral agents and growth factors)
    - G4 thrombocytopenia lasting >7 days, or G3-4 thrombocytopenia with clinically significant bleeding
    - Failure to recover platelets (PLT) ≥ 75 x 10^9/L by 4 weeks after start of the cycle (meaning by D28 of the cycle)
    - Failure to recover neutrophils (ANC) ≥1.0 x 10^9/L by 4 weeks after start of the cycle (meaning by D28 of the cycle)

A DLT has to be reported as Adverse Event of Special Interest (AESI) section 5.3.6.1 .

The MTD will be defined on the basis of DLT observed during the first treatment cycle (D1 to 14). However, for those patients who receive more than one cycle of BI 836826 plus gemcitabine and oxaliplatin, all adverse events corresponding to the above definition of DLT as well as other adverse events and laboratory assessments will be considered for the purpose

of confirming the selection of the recommended dose for BI 836826 with GemOx in Part 2 of the trial.

5.4. DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1. Assessment of pharmacokinetics

Blood samples will be collected for determining the pharmacokinetic parameters of BI 836826 and exposure of gemcitabine and oxaliplatin in plasma. Oxaliplatin exposure will be assessed by means of the free platinum concentrations in plasma.
In addition samples will be collected for determining potential immunogenicity of BI 836826.
The dates and the "start and stop" times of infusions along with additional information on respective infusion conditions, e.g. total dose and interruptions of infusion, should be documented for BI 836826, gemcitabine and oxaliplatin on all days of PK sampling.

These actual administration and sampling times will be used for determination of pharmacokinetic parameters.
Concentrations will be used for graphs and calculations in the format that is reported in the bio-analytical report.

If data allow, the following pharmacokinetic parameters of BI 836826 will be evaluated using noncompartmental analysis methods according to the internal BI Standard Operating Procedure:

- Maximum measured plasma concentration of the analyte (C_{max})

- Area under the plasma concentration-time curve over the time interval from 0 to the time of the last quantifiable data point after drug administration (AUC_{0-tz})
- Area under the plasma concentration-time curve over the time interval from zero extrapolated to infinity ($AUC_{0-\infty}$)

Others pharmacokinetic parameters can be calculated if considered relevant considering the available data.

5.4.2. Methods of sample collection

For quantification of BI 836826 plasma concentrations, 3mL blood will be taken in an ethylendiaminetetraacetic acid (EDTA) anticoagulant blood drawing tube at the time points specified in Appendix 10.1. For the early time points on the day of drug administration the sample has to be taken from the opposite arm to the one where the infusion is/was administered in order to prevent contamination of blood samples with the infusion solution.

For quantification of gemcitabine and free platinum plasma concentrations, 3mL blood will be taken in an EDTA blood drawing tube at the time points specified in Appendix 10.1. For the early time points on the day of drug administration the sample has to be taken from the opposite arm to the one where the infusion is/was administered in order to prevent contamination of blood samples with the infusion solution. Since gemcitabine is highly unstable in blood and plasma, blood samples have to be stabilized with tetrahydrouridine (THU) immediately after collection. To accurately determine free platinum concentrations, the blood samples have to be immediately centrifuged after collection. The resulting plasma has to be subsequently ultra-filtrated before freezing. The details are described in the ISF and it is important note that the ultra-filtration process must be started less than 20 minutes after blood draw.

Correct, complete and legible documentation of drug administration and blood sampling times as well as adequate handling and identification of PK samples is mandatory to obtain data of adequate quality for the pharmacokinetic analysis.

Details about sample collection, preparation, required cryovials, labels, storage and shipment are described in the laboratory manual included in the ISF.

5.4.3. Analytical determinations

BI 836826 will be determined using a validated enzyme-linked immuno assay (ELISA). Plasma concentrations of oxaliplatin will be determined as free platinum by a validated inductively coupled plasma mass spectrometry (ICP-MS) assay and gemcitabine concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The procedures and specifications of the analytical methods are available at the determination site.
A detailed description of the assays will be available prior to the start of sample analysis.

5.6. APPROPRIATENESS OF MEASUREMENTS

Determination of MTD of BI 836826 is based on toxicities graded according to CTCAE version 4.0 (R10-4848). The CTCAE criteria are commonly used for the assessment of adverse events in cancer patients. In the randomized part of the trial the response is assessed according to the International recommendation for lymphoma which is well established (R10-1462, R14-3383, R14-3387).

6. INVESTIGATIONAL PLAN

6.1. VISIT SCHEDULE

The allowable time windows for visits are included in the Flow Charts 1, 2, 3.

- Screening period is 14 days to 1 day prior C1D1.
- The planned duration of a treatment cycle is 14 days (+ maximum 3 days from cycle 2 in case of delayed D8). In case of toxicity, the start of the next cycle may be delayed by maximum of 14 days to allow for recovery.
- Day 1, 2 and 8 of cycle 1 must be strictly respected. Only C1D11 can be done with -1 day window (applicable only with BI 836826-GemOx). From Cycle 2, D8 can be delayed by maximum 3 days.
- EOT:
    - If a patient has been prematurely withdrawn from treatment (i.e. earlier than the 6th cycle), EOT must be performed within 14 days after last dose (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI 836826, whichever is the latest).
    - If a patient completed all 6 cycles according to protocol, EOT must be performed at the earliest 30 days and no later than 42 days after the last dose (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI836826, whichever is the latest).
- FU AEs visit: The information collected at this visit should include all new AEs that occurred after the last dose and a follow-up of adverse events ongoing at the time of the last dose or EOT visit.
    - If a patient has been prematurely withdrawn from treatment, the FU for AEs visit can be performed on site 30-42 days after the last dose.
    - If a patient completed the 6 cycles according to the protocol, the FU for AEs visit can be scheduled at the same time point as EOT visit.
- Follow-up visits (FU): After the FU for AEs, the patient will be followed for disease assessment/vital status (remission/progression/death/new anti-lymphoma treatment) and drug related SAEs and AESIs. These FU visits should take place every 3 months for the first year after FU for AEs visit, and then every 6 months until death, patient is lost to follow-up, patient withdraws consent for further follow up or the end of trial is reached. FU may be performed by telephone interview in case the patient is unable to visit the investigator

6.2. DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1. Screening period

Patients who failed screening may repeat the screening once after discussion between the investigator and sponsor providing that reasons for screening failure were reversible and have been resolved.

SAEs and /or AESI occurring in patients who are classed as screening failures, (i.e. those patients who did not receive any trial medication), are to be **reported if the Investigator**

considers the SAEs and /or AESI to be related to the screening procedure. SAEs and /or AESI during the screening period are to be reported according to standard procedures.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not

6.2.2. Treatment period(s)

A treatment cycle is defined as 14 days, with the start of next cycle on day 15 (from cycle 2, D8 can be delayed by maximum 3 days, meaning that the cyle could be up to 17 days, with the start of the next cycle on day 18). However if it is medically indicated a cycle may be postponed by maximum of 14 days due to toxicity reasons. Any additional visits (not foreseen by flow charts) will be recorded in the e-CRF.

In Part I, Cycle 1, no dose reduction or dose skipped is allowed.
In Part 1 and 2 in Cycle 1, there is the need for hospital stay for a minimum of 24 hours for PK sampling and safety monitoring. Please see Flowchart 1 and 2 and Appendix 10.1.

Patients may continue trial medication for maximum of 6 cycles. Patients who develop PD, or toxicity or who are considered intolerable, or withdraws consent, are to discontinue the trial according to the discontinuation rules described in section 3.3.4.

Please refer to section 4.1.4 for drug administration.

6.2.2.1. Criteria to continue next treatment cycle (C2-6) and guidance to dose reduction

The following criteria need to be fulfilled on D1 of each treatment cycle for Cycles 2-6:

- no active infection
- no evidence of progressive disease
- recovery from any AE except lymphopenia to ≤ G1, or to baseline
- peripheral blood counts recovery defined as:
  - PLT ≥ 75 x 10^9/L
  - ANC ≥1.0 x 10^9/L

Patients who experienced toxicity suspected as DILI need to demonstrate recovery of AST/ALT/bilirubin values as defined in section 5.3.6.1.

Guidance for dose reduction:

- **BI 836826**:

The following criteria need to be fulfilled on D8 of each treatment cycle for Cycles 2-6, prior to start of the infusion with BI 836826:

- In case elevations of AST and or ALT > 3 x ULN are considered drug related or related to a hepatic injury, a decline to ≤ 3 x ULN has to be documented prior to administration of the next dose of BI 836826. In case an elevation of bilirubin to >1,5 x ULN is considered drug related or related to a hepatic

injury, a decline to ≤ 1.5 x ULN or baseline (for patients with elevated levels at trial entry) has to be documented prior to administration of the next dose of BI 836826.

From cycle 2, the infusion can be delayed by maximum 3 days, until D11. In that case, the next cycle should not start before at least 7 days between the BI 836826 infusion and the next D1.

If needed, the dose of BI 836826 should be omitted. If more than one dose of BI 836826 is skipped, the patient must be removed from the study.

Reduction of dose is allowed as per events described in table 6.2.2.1:1.

- **Rituximab:**

No dose reduction or skipped dose of rituximab is allowed.

- **Oxaliplatin:**

Only one oxaliplatin dose can be omitted for toxicity reasons during the duration of the trial (6 cycles). If due to toxicity, related to oxaliplatin (Table 6.2.2.1:1), a patient is unable to receive oxaliplatin, the treatment can continue with BI 836826-Gem, or R-Gem for one cycle. If at the time of the next cycle the patient still cannot receive oxaliplatin due to oxaliplatin related toxicities, this patient needs to be withdrawn for toxicity reasons, and will not be allowed to re-enter the trial.
Reduction of dose is allowed as per events described in table 6.2.2.1:1.

- **Gemcitabine:**

No dose reduction or skipped dose of gemcitabine is allowed.

The criteria below are serving as basic guidance to investigators. They should not replace a sound clinical judgment in case of occurrence of other serious toxicities not listed in the table below.

Table 6.2.2.1:1 Criteria for dose reduction and treatment discontinuation

Finding	**Recommended action**
Hepatitis B or C reactivation	Withdraw patient from trial
Serum creatinine >2xULN	Reduce* Oxaliplatin dose to 75mg/m^2
G2 neurosensory AEs lasting ≤ 14days	Reduce* Oxaliplatin dose to 75mg/m^2
G2 neurosensory AEs lasting > 14days:	Omit one Oxaliplatin dose
G3 neurosensory AEs (single occurrence)	Omit one Oxaliplatin dose
G3 neurosensory AEs (prolonged >14 days, or recurrent)	Withdraw patient from trial
Hypersensitivity to oxaliplatin	Withdraw patient from trial

Finding	**Recommended action**
CMV reactivation: -with clinical signs of infection	Withdraw patient from trial, implement treatment according to local standards
-raising CMV viral load without clinical signs	Continue following viral load bi-weekly (every 2 weeks), and monitor patient for clinical signs of infection. If viral load continues to rise on two consecutive assessments consider pre-emptive antiviral treatment and withdrawal from trial
Hepatic injury fulfilling DILI criteria see section 5.3.6.1	Consider delaying next cycle or dose reduction of BI 836826 by 25%
Recurrent febrile neutropenia	Primary prophylaxis with colony-stimulating factors is not permitted, but if a chemotherapy cycle is delayed, then filgrastim [granulocyte colonystimulating factor (G-CSF)] is administered with subsequent cycles to aid maintenance of the dose intensity. Use of filgrastim is also recommended if febrile neutropenia had been observed during a previous treatment cycle.
Infusion related reactions (IRR) (see 6.2.2.3) to BI 836826: • Grade 1 • Grade 2-3 Grade 4	 • G1: Reduce BI 836826 infusion rate by 50%, or temporarily interrupt and restart infusion when considered clinically manageable • G2-3: Stop infusion until all symptoms are resolved. Resume BI 836826 at lower infusion rate, e.g. to 50%, and increase infusion rate as tolerated to the target rate. • G4: Stop infusion immediately and do not re-expose to B 836826 after the event.

***Dose adjustment of oxaliplatin** was carried out in the event of peripheral neuropathy. The oxaliplatin dose was to be reduced to 75 mg/m² in the event of significant paresthesia lasting between 7 and 13 days after each administration. In the event of abnormal results by neurological examination or if a patient experienced significant paresthesia lasting for 14

days or more, oxaliplatin was to be stopped until symptoms improved and then restarted at a dose of 75 mg/m². In the event of pharyngolaryngeal dysesthesia, the duration of the oxaliplatin infusion was to be prolonged from 2 to 6 h.

6.2.2.2. Monitoring for infusion-related reactions

Close monitoring of the patients during and after the infusions of BI 836826 or rituximab in combination with GemOx is required for the evaluation of IRR. The monitoring includes:

- During the first infusion of BI 836826 the patients are required to be hospitalized under close surveillance with access to intensive care for at least 24 hours.
- Subsequent infusions of BI 836826 may be administered in outpatient facilities with access to intensive care unit.
- The infusions of rituximab can be administered in an outpatient setting if well tolerated.
- Frequent measurements and documentation of blood pressure and heart rate (see section 5.3.2.

6.2.2.3. Handling of infusion-related reactions

In case of an IRR, the infusion has to be stopped immediately for ≥ G2 reactions. Appropriate actions depending on the type and severity of the reaction should be taken according to best medical judgment and local guidelines. Supportive therapy including steroids may be used as clinically indicated. If IRR has been managed successfully, and if in the investigators' judgment the infusion can be re-started at lower rate, the total time between original start and end of infusion cannot exceed 24 hrs. If infusion cannot be completed within 24 hours the remaining solution needs to be discarded, and the total dose received appropriately documented in e-CRF.

IRR should be reported as other AEs according to CTCAE version 4.0 with the term infusion related reaction. Together with this term the individual symptom, e.g. chills should also be grade according to CTCAE. IRRs are defined to be AESIs if they are classified CTCAE grade 3-5. AESIs have to be reported in an expedited manner according to SAE-reporting (see section 5.3.7).

The following recommendations for the management of IRRs may be considered by the investigator as guidance (see also table 6.2.2.1:1):

- In the case of G1 IRR, the infusion rate of BI 836826 should be reduced, e.g. to 50% of the target rate, or the infusion should be temporarily interrupted and resumed as soon as considered clinically manageable by the investigator.
- In the case of G2-3 IRR, the infusion with BI 836826 should be stopped immediately. Only in case all symptoms have resolved, administration of BI 836826 may be resumed at a slower infusion rate, e.g. of 50% of the target rate, and increase the infusion rate as tolerated to the target rate.
- In the case of G4 IRR, the infusion has to be stopped immediately. These patients should not be re-exposed to BI 836826 after the event.

6.2.2.4. Laboratory analyses:

The safety laboratory analyses (see section 5.3.3) will be performed at the investigator's site, i.e. local hospital laboratories. The certification/accreditation for each laboratory or evidence that it participates in an established quality program must be provided by the investigator and filed in the sponsor's and in the local ISF. The normal ranges of each test performed are to be documented in e-CRF.

Blood samples for pharmacokinetic analyses (PK), and flow cytometry (lymphocyte immune-phenotyping) will be shipped to a central laboratory in both Part 1 and 2.

6.2.2.5. Disease assessments (PET-CT)

PET/CT Scan of neck, thorax, abdomen, and pelvis has to be performed at:

- Baseline PET/CT scan : up to 28 days prior to C1D1
- Interim PET/CT scan : after end of C3, i.e. prior to C4D1 infusion
- Final PET/CT scan: 3-6 weeks after the last dose if 6 cycles have been completed.

In Part 1, image acquisition and readings will be performed locally, and appropriate data and measurements will be entered into e-CRF.

In Part 2 image acquisitions will be performed locally, however the images will be sent to an appointed vendor for central readings, and central archiving. A copy of the images are to be retained at the site. Local readings should be used for treatment decisions (i.e. discontinuation from trial participation due to PD) local results are to be entered in e-CRF.

6.2.2.6. Tumor lysis syndrome (TLS)

During the first 24 hours after the start of the first dose of BI 836826 or rituximab, laboratory parameters need to be checked at least once in patients who considered at risk for TLS (e.g. large tumor burden, leukemic manifestation of the lymphoma) (see section 5.3.3.2).
In case of clinical or laboratory signs of TLS appropriate treatment and hydration needs to be instituted immediately according to local standards.

6.2.3. End of Treatment

For patients completing all 6 cycles: the end of treatment visit and should be done at the earliest 30 days and no later than 42 days after the last dose (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI836826, whichever is the latest).

If a patient is prematurely withdrawn from treatment (i.e. earlier than the 6th cycle) an EOT visit should be performed within 14 days after last dose (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI836826, whichever is the latest).

6.2.4. Follow-Up for AEs

A Follow up visit for AEs collection needs to be performed between 30- 42 days after the last dose (last administration of Gemcitabine, Oxaliplatin, Rituximab or BI836826, whichever is the latest). The information collected at this visit should include all new AEs that occurred after the last dose and a follow-up of adverse events ongoing at the time of the last dose.

If a patient completes the 6 cycles according to the protocol the FU for AEs visit can be scheduled at the same time point as EOT visit.

If a patient has been prematurely withdrawn from treatment, the FU for AEs visit can be performed on site 30-42 days after the last dose.

6.2.5. Follow Up Period and Trial Completion

After the FU for AEs, the patient will be followed for disease assessment/vital status (remission/progression/death/new anti-lymphoma treatment) and drug related SAEs and AESIs. These FU visits should take place every 3 months for the first year after FU for AEs visit, and then every 6 months until death, patient is lost to follow-up, patient withdraws consent for further follow up or the end of trial is reached. FU may be performed by telephone interview in case the patient is unable to visit the investigator

If patient progresses or relapses, only data on the new anti-lymphoma treatment and survival will be collected.

Prior to primary and final analyses, all applicable patients will be contacted for vital status regardless of whether the next FU visit is due or not.

The end of the trial is defined as when the last ongoing patient has completed treatment and has been followed for at least a year or when at least 50% of the patients have died, whichever occurs last.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1. STATISTICAL DESIGN MODEL

This trial will be conducted as an open-label trial in two parts. The primary objective of the Part 1 (Phase Ib) is to determine the dose of BI 836826 for the combination with GemOx using the classical 3+3 design (R04-0569) based on the number of patients with DLTs and the resulting MTD.

In the second randomized part of the trial safety and efficacy of the combination BI 836826-GemOx vs. R-GemOx will be evaluated. The primary endpoint for efficacy is OR by using PR+CR rates, analyzed when the last patient in the trial has completed 6 cycles of trial medication, or has been withdrawn for other reasons.
Only descriptive and exploratory analyses are planned and no formal statistical testing will be performed.

7.2. NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. This is an exploratory Phase Ib/II trial with the main objective of treatment effect estimation. The primary endpoint for Part 2 will be overall response analyzed by PR+CR rate. All analysis and p-values provided need to be understood in an exploratory way.

7.3. PLANNED ANALYSES

All patients who have received any amount of trial drug of BI 836826 or rituximab or gemcitabine or oxaliplatin will be included into safety analyses. All patients randomized for the Part 2 of the trial will be included in all efficacy analyses, using the intent-to-treat approach. Every effort will be made to evaluate response and progression for all patients who receive treatment, including those who discontinue prematurely.

During Part 1, cohorts of patients treated with BI 836826 in combination with GemOx will be evaluated continuously based on the totality of the safety data in order to determine the recommended BI 836826 dose for Part 2 of the trial. Results from data snapshots will be provided as needed to the trial team and involved investigators to support the determination of the dose for the randomized Part 2 of the trial.

Summary outputs of efficacy analyses will include all patients entered in Part 2 of the trial. Both treatment arms in Part 2 will be compared.

Safety analyses will be summarized separately for patients treated in Part 1 and Part 2 of the trial.

No per protocol set will be used in the analyses. However potential important protocol violations will be summarized and violations of inclusion and exclusion criteria will be

provided in a subject data listing. The Core Trial Statistical Analysis Plan will specify the potential important protocol violations in detail.

The analyses of all primary, secondary and further endpoints in Part 1 and Part 2 will be performed when the last patient entered in Part 2 has completed 6 cycles of trial medication or has been withdrawn for other reason; a CTR will be written at this time point.
The final CTR will be written at the end of the trial.

7.3.1. Primary endpoint analyses

Part 1: The primary endpoint of the Phase Ib is to determine the MTD of BI 836826 in combination with GemOx analyzed via the number of patients with DLTs during the MTD evaluation period. In order to identify the MTD, the number of patients with DLTs at each dose level will be presented.

Part 2: The primary endpoint of the randomized Phase II is overall response analyzed by the PR+CR rate. The 95% confidence interval will be provided for the PR and CR rate in each arm. Comparisons between treatment groups will be performed using the Suissa-Shuster exact test (including the Berger-Boos modification), for which an exploratory p-value will be provided.

7.3.2. Secondary endpoint analyses

Part 1: PK endpoints will be analysed as described in Section 7.3.5. Overall response by investigator's assessment will be analysed descriptively in terms of the OR rate.

Part 2:
Complete remission

Best overall response is the best response (CR, PR, stable disease (SD) or PD) with respect to all time points. Complete remission is defined as CR and will be analyzed descriptively and compared between the two treatment arms.
Frequency distributions and other descriptive statistical measures will be used to examine this endpoint.

7.3.4. Safety analyses

All patients who have received any amount of trial drug will be included in the safety analysis. The number of patients with dose limiting toxicity (during the MTD observation

period in the Part 1 as well as during the on-treatment period in Part 1) as well as the incidence and intensity of adverse events, graded according to CTCAE version 4.0 and reported according to BI standards, laboratory parameters and vital signs will be evaluated. The safety analysis will be descriptive and exploratory and results for the Part 1 and Part 2 will be presented separately. No hypothesis testing is planned.
Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

The overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment with BI 836826 will be reported for all dose cohorts in Part 1 and for both treatment arms in Part 2. SAEs, fatal AEs and AESIs will be tabulated. In addition, events leading to treatment discontinuation will be examined.

Events that start from any administration of trial medication until 30 days after the last administration of any trial medication will be considered as having occurred “on treatment” see section 5.3.8.
In general, adverse events occurring after the FU for AEs visit (after REP) will be attributed to the post-treatment period and will be presented separately. However, post-treatment events will be examined to determine whether they need to be combined with on-treatment events in an additional table.

Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical significance will be reported. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5. Pharmacokinetic analyses

Refer to Section 5.5.1 for PK parameters to be calculated.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic and geometric mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

The following descriptive statistics will be calculated for analytic concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of

decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.3.5.1. Plasma concentration - time profiles

Concentration data identified with no sample available (NOS), no valid result (NOR), not analyzed (NOA), and below the limit of quantification (BLQ) will be ignored and not replaced by zero at any time point (applies also to the lag Phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included).

7.3.5.2. Pharmacokinetic assessment

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. All other BLQ values of the profile will be ignored.

If the pre-dose concentration before the first dose is less than or equal to 5% of C_{max} value in that subject, the subject’s data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the pre-dose value will not be changed to zero). If the pre-dose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.4. INTERIM ANALYSES

The dose selection for Part 2 will be based on the safety and PK data after the last patient in Part1 has completed cycle 1. After the discussion with the treating investigators the decision will be documented and shared with the investigators.
Details for the evaluations to be performed will be outlined in the trial statistical analysis plan (TSAP).
During Part 2 of the trial regular monitoring by the internal DMC will be performed to ensure the positive benefit-risk for the patients. See section 3.1.1

7.5. HANDLING OF MISSING DATA

In general, missing data will not be imputed. Every effort will be undertaken to obtain the date of progression or remission for patients known to have progressed or experienced a remission and to obtain complete information on all AEs. Consequently no missing data will be imputed unless otherwise specified.
For partial or missing AE onset and/or end dates, BI internal rules will be applied for imputation.

7.6. RANDOMISATION

Part 1:

No randomization will be performed. Patients will be assigned into escalating dose groups by order of admission into the trial.

Part 2:

In the second part of the trial patients will be randomized in a 1:1 ratio to BI 836826-GemOx or R-GemOx.
Patients will be randomized in blocks to one of the treatment groups. Approximately equal numbers of patients will be randomized to each treatment group. Randomization will be performed using IRT. BI, Clinical Trial Support Group or a CRO appointed by the sponsor will provide the randomization lists using a validated randomization number generating system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7. DETERMINATION OF SAMPLE SIZE

7.7.1. Part 1

In the first part (Phase Ib) of the trial the classical 3+3 design will be used. The overall number of the patients for the 3+3 design is not fixed.

Up to-33 will be enrolled. The classical 3+3 design allows for flexibility and additional patients might be recruited to determine the BI 836826 dose to be used in the combination BI 836826-GemOx.

7.7.2. Part 2

For the determination of sample size in the second part we assume as a best case scenario a target ORR of the BI 836826-GemOx combination of 81% and for the reference combination R-GemOx an ORR of 61%. In this case the true treatment difference is 20%. Due to stochastic nature of the process the true treatment difference is usually not the same as the treatment difference observed in the trial. Therefore we evaluate the probability to observe a difference of at least 10% under the assumption that the true difference lies somewhere between 0% and 20% (see table 7.7.2:1).

Table 7.7.2:1 Evaluation of probabilities to observe a treatment difference in OR-rate dependent on true difference and sample size.

Number of patients per arm	True treatment difference	Treatment difference at least observed in the trial	Probability to observe a treatment difference of at least 10%
30	0 %	10 %	17.7%
30	10 %	10 %	44.6%
30	15%	10 %	61.3%
30	20 %	10 %	76.8%
60	0 %	10 %	11.2%
60	10 %	10 %	46.3%
60	15%	10 %	69.2%
60	20 %	10 %	87.2%

Results are based on 1000000 simulations in SAS version 9.2.

If the true difference is 20%, the probability to observe a treatment difference of at least 10% should be above 80% in order to provide sufficient credibility for the trial results. This probability is 87.2% with 60 patients per arm. At the same time if there is no difference in ORR between the treatments, the probability to observe a treatment difference of at least 10% by chance in the trial with 60 patients per arm is very low (11.2%).

The sample size of 60 patients per arm and the requirement that the observed treatment difference is at least 10% allows clear differentiation between these two scenarios and therefore is considered adequate for efficacy evaluation in the second part of this trial.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: http://trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF

8.1. TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2. DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3. RECORDS

Electronic case report forms (e-CRF) for individual patients will be provided by the sponsor. For drug accountability, refer to section 4.1.9.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the trial master file (TMF). Coding of the data obtained will be done by using the MedDRA and the World health organization drug dictionary (WHO-DD).
Changes in laboratory parameters and adverse events will be graded according to US National Cancer Institute (NCI) CTCAE version 4.0 (R10-4848).

8.3.1. Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the e-CRF must be consistent with the source data or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For the e-CRF, all data need to be derived from source documents.

8.3.2. Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data / documents. e-CRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's Clinical Research Associate (CRA), auditor and inspection by health authorities (e.g. Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / on site monitor and auditor may review all e-CRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3. Storage period of records

Trial site(s):
The trial site(s) must retain the source documents and essential documents for a period defined in the trial site's contract with the sponsor.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.
When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor must notify the head of trial site.

8.4. LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1. Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided.

For BI 836826 this is the current version of the Investigator's Brochure.

For the comparator, rituximab, the SmPC of the originator Mabthera will be used. For the non-investigational trial medication, gemcitabine and oxaliplatin, the SmPCs of the originator products GEMZAR and Eloxatin will be used will be used. The current versions of these reference documents are to be provided in the ISF.

8.4.2. Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5. STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to

- appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6. END OF TRIAL

The end of the trial is defined as when the last ongoing patient has completed treatment and has been followed for at least a year or when at least 50% of the patients have died, whichever occurs last.

The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

When the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7. PROTOCOL VIOLATIONS

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8. COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

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10.APPENDICES

10.1. BLOOD SAMPLING TIMES FOR PHARMACOKINETICS

Table 10.1:1 Part 1, Cycle 1

Blood sampling times for Pharmacokinetics (PK) for BI 83682-GemOx arm

Procedures	**screen**	**Cycle 1**								
Day of cycle	**-14 to <1**	**1**				**8**[2)]			**9**	**11(- 1)**
Visit	**Screen**	**C1D1**				**C1D8**			**C1D9**	**C1D11**
Time point after dose [h:min]		Up to 6hrs before gemcitabine infusion	Shortly before end gemcitabine infusion	Shortly before end oxaliplatin infusion	8hrs (+/-30 min) after start gemcitabine infusion	Up to 6hrs before BI 836826 infusion	Shortly before end BI 836826 infusion	8hrs (+ /-30 min) after start BI 836826 infusion	23hrs (+/- 2hrs) after start BI 836826 infusion	96hrs (- 24hrs) after start BI 836826 infusion
Write in e-CRF Actual date and time point		T_0 (G) 0:00	1:00*	3:00**	8:00	T_0 (BI 836826) 0:00	4:00***	8:00****	23:00	96:00
BI 836826 analysis						X	X	X	X	X
Gemcitabine analysis		X	X	X	X					
Oxaliplatin analysis										

*This is an indication as the total duration of Gemcitabine infusion duration is based on BSA (10mg/m²/hour). The PK sample must be drawn shortly **before the end** of the Gemcitabine infusion.

** This is an indication as the start of the Oxaliplatin infusion depends on the Gemcitabine infusion duration. The PK sample must be drawn shortly **before the end** of the Oxaliplatin infusion.
*** This is an indication, the PK sample must be drawn just **before the end** of the BI 836826 infusion, meaning if the infusion is longer than 4 hours, the PK sample must be drawn later than 4 hours but shortly before the end of the infusion.
**** This is an indication; the post-infusion PK sample must be drawn **4 hours after the end** of the infusion.

T_0 (G) Time zero is when gemcitabine infusion starts
T_0 (BI 836826) Time zero is when BI 836826 infusion starts

[2)] Day 8, in cycle 1, the patient will stay over-night allowing a morning PK sample to be taken day 9
If the investigator determines a need for an unscheduled safety lab, a concomitant sampling of PK is required

Table 10.1:1 Part 1, Cycle 3 cont`d

Blood sampling times for Pharmacokinetics (PK) for BI 836826 and GemOx arm

Procedures	**Cycle 3**						
Day of cycle	**1**				**8**		
Visit	**C3D1**				**C3D8**		
Time point after dose [h:min]	Up to 6hrs before gemcitabine infusion	Shortly before end gemcitabine infusion	Shortly before end oxaliplatin infusion	8hrs (+/-30 min) after start gemcitabine infusion	Up to 6hrs before BI 836826 infusion	Shortly before end BI 836826 infusion	8hrs (+ /-30 min) after start BI 836826 infusion
Write in e-CRF Actual date and time point	T_0 (G) 0:00	1:00*	3:00**	8:00	T_0 (BI 836826) 0:00	4:00***	8:00****
BI 836826 analysis	X				X	X	X
Gemcitabine analysis	X	X	X	X			
Oxaliplatin analysis							

*This is an indication as the total duration of Gemcitabine infusion duration is based on BSA (10mg/m²/hour). The PK sample must be drawn shortly **before the end** of the Gemcitabine infusion.
** This is an indication as the start of the Oxaliplatin infusion depends on the Gemcitabine infusion duration. The PK sample must be drawn shortly **before the end** of the Oxaliplatin infusion.
*** This is an indication, the PK sample must be drawn just **before the end** of the BI 836826 infusion, meaning if the infusion is longer than 4 hours, the PK sample must be drawn later than 4 hours but shortly before the end of the infusion.
**** This is an indication; the post-infusion PK sample must be drawn **4 hours after the end** of the infusion.

T_0 (G) Time zero when gemcitabine infusion starts
T_0 (BI 836826) Time zero when BI 836826 infusion starts

If the investigator determines a need for an unscheduled safety lab, a concomitant sampling of PK is required

Table 10.1:1 Part 1, Cycle 2,4,5,6 and EOT cont`d

Blood sampling times for Pharmacokinetics (PK) for BI 836826-GemOx arm

Procedures	**Cycle 2, 4, 5, 6**			**EOT**
Day of cycle	**1**	**8**		
Visit	C2D1, C4D1, C5D1, C6D1	C2D8, C4D8, C5D8, C6D8[1)]		
Time point after dose [h:min]	Up to 6hrs before gemcitabine infusion	Up to 6hrs before BI 836826 infusion	Shortly before end BI 836826 infusion	
Write in e-CRF Actual date and time point	T_0 (G) 0:00	T_0 (BI 836826) 0:00	4:00*	
BI 836826 analysis	X	X	X	X

* This is an indication, the PK sample must be drawn just **before** the end of the infusion, meaning if the infusion is longer than 4 hours, the PK sample must be drawn later than 4 hours but shortly before the end of the infusion.

T_0 (G) Time zero when gemcitabine infusion starts
T_0 (BI 836826) Time zero when BI 836826 infusion starts

If the investigator determines a need for an unscheduled safety lab, a concomitant sampling of PK is required

Table 10.1:2 Part 2, Cycle 1

Blood sampling times for Pharmacokinetics (PK) for BI 836826-GemOx arm

Procedures	**screen**						
Day of cycle	**-14 to <1**	**1**				**8**[2)]	
Visit	**Screen**	**C1D1**				**C1D8**	
Time point after dose [h:min]		Up to 6hrs before gemcitabine infusion	Shortly before end gemcitabine infusion	Shortly before end oxaliplatin infusion	8hrs (+/-30 min) after start gemcitabine infusion	Up to 6hrs before BI 836826 infusion	Shortly before end BI 836826 infusion
Write in e-CRF Actual date and time point		T_0 (G) 0:00	1:00*	3:00**	8:00	T_0 (BI 836826) 0:00	4:00***
BI 836826 analysis						X	X

*This is an indication as the total duration of Gemcitabine infusion duration is based on BSA (10mg/m²/hour). The PK sample must be drawn shortly **before the end** of the Gemcitabine infusion.
** This is an indication as the start of the Oxaliplatin infusion depends on the Gemcitabine infusion duration. The PK sample must be drawn shortly **before the end** of the Oxaliplatin infusion.
*** This is an indication, the PK sample must be drawn just **before the end** of the BI 836826 infusion, meaning if the infusion is longer than 4 hours, the PK sample must be drawn later than 4 hours but shortly before the end of the infusion.
**** This is an indication; the post-infusion PK sample must be drawn **4 hours after the end** of the infusion.

T_0 (G) Time zero when gemcitabine infusion starts
T_0 (BI 836826) Time zero when BI 836826 infusion starts

[2)] Day 8, in cycle 1, the patient will stay over-night allowing a morning PK sample to be taken day 9

If during an unscheduled visit the investigator determines a need for a safety lab a concomitant sampling of PK is required

Table 10.1:2 Part 2, Cycle 3 cont`d

Blood sampling times for Pharmacokinetics (PK) for BI 836826-GemOx arm

Procedures	**Cycle 3**						
Day of cycle	**1**				**8**		
Visit	**C3D1**				**C3D8**		
Time point after dose [h:min]	Up to 6hr before gem-citabine infusion	Shortly before end gemcitabine infusion	Shortly before end oxaliplatin infusion	8hrs (+/-30 min) after start gemcitabine infusion	Up to 6hr before BI 836826 infusion	Shortly before end BI 836826 infusion	
Write in e-CRF Actual date and time point	T_0 (G) 0:00	1:00*	3:00**	8:00	T_0 (BI 836826) 0:00	4:00***	
BI 836826 analysis	X				X	X	

*This is an indication as the total duration of Gemcitabine infusion duration is based on BSA (10mg/m²/hour). The PK sample must be drawn shortly **before the end** of the Gemcitabine infusion.

** This is an indication as the start of the Oxaliplatin infusion depends on the Gemcitabine infusion duration. The PK sample must be drawn shortly **before the end** of the Oxaliplatin infusion.

*** This is an indication, the PK sample must be drawn just **before the end** of the BI 836826 infusion, meaning if the infusion is longer than 4 hours, the PK sample must be drawn later than 4 hours but shortly before the end of the infusion.

T_0 (G) Time zero when gemcitabine infusion starts

T_0 (BI 836826) Time zero when BI 836826 infusion starts

If during an unscheduled visit the investigator determines a need for a safety lab a concomitant sampling of PK is required

Table 10.1:2 Part 2, Cycle 2,4,5,6 and EOT cont`d

Blood sampling times for Pharmacokinetics (PK) for BI 836826-GemOx arm

Procedures	**Cycle 2, 4, 5, 6**[1)]			**EOT**
Day of cycle	**1**	**8**		
Visit	**C2D1, C4D1, C5D1 C6D1**	**C2D8,C4D8,C5D8,C6D8**		
Time point after dose [h:min]	Up to 6hrs before gemcitabine infusion	Up to 6hrs before BI 836826 infusion	Shortly before end BI 836826 infusion	
Write in e-CRF Actual date and time point	T_0 (G) 0:00	T_0 (BI 836826) 0:00	4:00*	
BI 836826 analysis	X	X	X	X
ADA[1)] analysis		X[1)]		X

* This is an indication, the PK sample must be drawn just **before** the end of the infusion, meaning if the infusion is longer than 4 hours, the sample must be drawn later than 4 hours but shortly before the end of the infusion.

T_0 (BI 836826) Time zero when BI 836826 infusion starts
T_0 (G) Time zero when gemcitabine infusion starts

If the investigator determines a need for an unscheduled safety lab, a concomitant sampling of PK is required

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		13 OCTOBER 2016
EudraCT number		2014-004794-16
BI Trial number		1270.11
BI Investigational Product(s)		BI 836826
Title of protocol		An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title, Protocol Synopsis, Flow chart, List of abbreviations, section 1.2.2, 1.2.4, 1.2.5, 3.3.2, 3.3.3, 3.3.4, 4.1, 4.1.1, 5.3.3, 6.1, 6.2.
Description of change		- Clarification of the protocol Title, to match with inclusion criteria. - Correction of the Protocol Synopsis to match with changes made in other sections. - Flow chart: correction of the visit window allowed, blood safety tests added at C1D1 and EOT, Weight added at EOT, footers numbering corrected, rewording of the notes. - List of abbreviations: some have been added. - section 1.2.2: updated section with latest data

		- section 1.2.4 & 1.2.5: reference to SMPC located in the ISF rather than a specific version to avoid upcoming amendment in case of change in the referenced SMPC. - section 3.1: clarifications and rewordings - section 3.3.1: clarification of the observational period (D& to 14 Cycle 1) - section 3.3.2: clarification of inclusion criteria 2. - section 3.3.3: clarification of exclusion criteria 7 & 9 - section 3.3.4: clarification of the removal of patients - section 4.1.1: renaming of "comparator products" to "comparator backbone products" - section 4.1.2 – 4.1.3- 4.1.4- 4.1.5- 4.1.7: clarifications and rewordings - section 4.2.2.3: correction of the section based on the recommendations to contraception and pregnancy testing in clinical trials (HMACTFG) - section 5.3: rewording and clarifications within the section. - section 6.1: clarifications and description added - section 6.2: rewording and various clarifications within the section. - section 8: some administrative changes In general: Rewording of Administrative changes. Corrections of unclear sentences, typos.
Rationale for change		Biochemistry test added on C1D1 is on request of Belgian HA. Other changes are made to make the protocol more clear, correct some mistakes, unclarities, and add consistency.

Number of global amendment		2
Date of CTP revision		03 November 2016
EudraCT number		2014-004794-16
BI Trial number		1270.11
BI Investigational Product(s)		BI 836826
Title of protocol		An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Flow chart, Sections 5.3.3.3 , 11
Description of change		Flow chart: Part 3: weight assessment moved to EoT. Section 5.3.3.3: HBV tests described in more detail. Section11: tick box “to be implemented after..” is ticked: was missing for amendment 1
Rationale for change		Flow chart: Part 3: weight assessment was put on FU for AE in error Section 5.3.3.3.: Regular HBV DNA tests is required in case HBsAg and/or anti-HBc are positive at screening. Section11: tick box was not ticked in error

Number of global amendment		3
Date of CTP revision		10 January 2017
EudraCT number		2014-004794-16
BI Trial number		1270.11
BI Investigational Product(s)		BI 836826
Title of protocol		An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	X	
Section to be changed		3.3.4.1 & 5.1.1 & 5.3.8
Description of change		3.3.4.1: Clarification by addition of the sentence: "Patients who experienced a DLT prior to BI 836826 infusion will be replaced." 5.1.1: clarification about DLT and MTD determination based on "evaluable" patients. 5.3.8 Clarification by addition of the sentence: "Any patient who has been replaced will not be considered evaluable for MTD determination. "
Rationale for change		MTD can only be determined on "evaluable" patients.

Number of global amendment		4
Date of CTP revision		09 June 2017
EudraCT number		2014-004794-16
BI Trial number		1270.11
BI Investigational Product(s)		BI 836826
Title of protocol		An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis, Sections 1.1, 1.2.2, 2.2, 3.1, 3.2, 3.3, 4, 5.1.2, 7.3.2, 7.3.2, 7.7.1
Description of change		Synopsis: - addition of a secondary endpoint (evaluate the preliminary efficacy in terms of the ORR based on investigator's assessment) -total number of patients entered increased in Part 1 (from 12 to 18, to a total up to 33) - addition of two dose cohorts: 150 & 200mg Section 1.1.Introduction: update for number of NHLM cases in 2017, based on www.cancer.org. Section 1.2.2: rationale for addition of 2 doses cohorts, and updated data.

		Section 2.2: addition of a secondary endpoint: evaluate the preliminary efficacy in terms of the ORR based on investigator's assessment Section 3.1 & 3.2: addition of 6 to 9 patients will be recruit at the established MTD to have a total of 12 patients treated at this MTD Section 3.3: correction of the number of patients in Part 1: up to 33 Section 4: additional dose cohorts: 150 and 200mg Section 5.1.2 & 7.3.2: addition of the secondary endpoint: ORR based on investigator's assessment Section 7.7.1: sample size adapted to new numbers Section 7.3.2: addition of secondary endpoint part 1
Rationale for change		Addition of 2 dose cohorts (150 and 200mg) and addition of patients to be treated at the established MTD.

Number of global amendment		5
Date of CTP revision		14 Sep 2017
EudraCT number		2014-004794-16
BI Trial number		1270.11
BI Investigational Product(s)		BI 836826
Title of protocol		An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/ allogeneic stem cell transplant
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis, Section 3.3.2
Description of change		Synopsis: Change of inclusion criteria 4 from two to at least 1 bi-dimensional lesion/node >1.5 cm Section 3.3.2: Change of inclusion criteria 4 from two to at least 1 bi-dimensional lesion/node >1.5 cm
Rationale for change		The initial inclusion criteria did not allow patients with one large single lesion to participate to the study. This amendment will allow these patients to enter the study and to be treated

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-6

Title: An open label multicenter Phase Ib/II trial to determine the dose of BI 836826 in combination with gemcitabine and oxaliplatin (GemOx) and the efficacy of BI 836826-GemOx versus rituximab (R)- GemOx (R-GemOx) in patients with relapsed/ refractory diffuse large B-cell lymphoma (DLBCL) who are not eligible for, or have relapsed/progressed after autologous/allogeneic stem cell transplant

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		14 Sep 2017 15:17 CEST
Approval-Trial Clinical Monitor		18 Sep 2017 13:56 CEST
Approval-Clinical Program		18 Sep 2017 16:42 CEST
Author-Clinical Pharmacokineticist		20 Sep 2017 12:57 CEST
Verification-Paper Signature Completion		25 Sep 2017 14:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed