Clinical Trial Protocol

Doc. No.: c02190401-06

BI Trial No.:	1280.16
BI Investigational Product:	Xentuzumab (BI 836845)
Title:	A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors
Clinical Phase:	Ib
Trial Clinical Monitor:	Telephone: Fax: Email:
Co-ordinating Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol based on Global Amendment 3)
Version and Date:	**Version: 4.0** **Date: 02 Nov 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: N.A.			
Name of active ingredient: Xentuzumab (BI 836845)			
Protocol date: 28 Mar 2014	**Trial number:** 1280.16		**Revision date:** 02 Nov 2016
Title of trial:	A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors		
Co-ordinating Investigator :	Phone: Fax:		
Trial sites:	Multi-centre trial conducted in 4 countries (Korea, Taiwan, Singapore and Japan) Approximately 12 sites		
Clinical phase:	Ib		
Objectives:	**Primary objectives** • **Part A:** To determine the Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) based on evaluation of safety and tolerability of Xentuzumab (BI 836845) when administered in combination with afatinib in patients with non-small cell lung cancer with progression following prior treatment (EGFR TKI or platinum-based chemotherapy**)** • **Part B:** To evaluate the early anti-tumour activity of Xentuzumab (BI 836845) in combination with afatinib in patients with EGFR mutant non-small cell lung cancer with progression following prior irreversible EGFR TKIs. **Secondary objectives Part A and Part B:** • To evaluate the safety of Xentuzumab (BI 836845) in combination with afatinib in patients with non-small cell lung cancer		

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Name of finished product: N.A.			
Name of active ingredient: Xentuzumab (BI 836845)			
Protocol date: 28 Mar 2014	**Trial number:** 1280.16		**Revision date:** 02 Nov 2016
Methodology:	Open-label, 3+3 dose escalation (Part A) study of Xentuzumab (BI 836845) in combination with afatinib, followed by an expansion phase (Part B)		
No. of patients:			
total entered:	Approximately 42 patients		
each treatment:	Part A: Approximately 24 patients / Part B: Approximately 18 patients		
Diagnosis :	**Part A:**Patients with pathologic confirmation of advanced and/or metastatic stage IIIb/IV non-small cell carcinoma of lung **Part B:** Patients with pathologic confirmation of advanced and/or metastatic stage IIIb/IV non-small cell carcinoma of lung who have failed at least one irreversible EGFR TKI therapy		

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Main criteria for inclusion:

1. Patients with pathologic confirmation of advanced and/or metastatic stage IIIb/IV non-small cell carcinoma of lung
2. Documented activating EGFR mutation (exon 19 deletion, L858R, G719X, L861X). Exception: patient with squamous cell predominant histology in Part A
3. Presence of EGFR activating mutation and absence of EGFR T790M mutation in the tumour associated with the latest disease progression. Only applicable in Part B
4. Adequate fresh or archival tumour tissue at the latest disease progression immediately prior to the study entry must be made available for central EGFR mutation test and/or resistance analysis
5. Part A: Progression of disease (RECIST v1.1) while on continuous treatment with single agent EGFR TKI (e.g. erlotinib or gefitinib or afatinib) or for histology other than adenocarcinoma and without prior EGFR TKI treatment: progression of disease (RECIST v1.1) on platinum-based chemotherapy.
   Part B: Progression of disease (RECIST v1.1) while on continuous treatment with single agent of the second generation irreversible EGFR TKI (e.g. afatinib or dacomitinib)
   Note: In both parts, patients whose disease progresses only in the central nervous system (CNS) are not eligible
6. No intervening systemic therapy between cessation of EGFR TKI and initiation of the treatment in the study. Exception: patient with squamous cell predominant histology in Part A
7. Patients must have measurable disease per RECIST v1.1 (R09-0262 - Appendix 10.5) presented after tumour biopsy for the latest disease progression
8. Recovered from any previous therapy related toxicity to ≤ Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia)

Test product(s):	Xentuzumab (BI 836845) in combination with afatinib
dose:	Xentuzumab (BI 836845) 1000 mg with 30 mg afatinib (starting dose level)
mode of admin.:	Xentuzumab (BI 836845): Intravenous infusion over 60 minutes/ afatinib: Once daily oral dosing
Comparator products:	NA
dose:	NA
mode of admin.:	NA

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Duration of treatment:	Continuous treatment until disease progression, intolerable adverse events (AEs), consent withdrawal or non-compliance with the study protocol
Criteria for *efficacy*:	<u>Primary endpoint (for Part B)</u> • Objective response (OR), defined as complete response (CR) or partial response (PR) according to RECIST v1.1 <u>Secondary endpoints (for Part B)</u> • Disease control, defined as complete response (CR), partial response (PR) or stable disease (SD) • Time to objective response, defined as the duration of time from the date of first treatment administration until objective response • Duration of objective response, defined as the duration of time from objective response to the date of first objective tumour progression or death due to any cause
Criteria for safety:	• MTD of Xentuzumab (BI 836845) in combination with afatinib (primary endpoint for Part A only) • Dose limiting toxicity (DLT) during the first treatment course (primary endpoint for Part A only) • Adverse Events (AEs) according to Common Terminology Criteria (CTCAE version 4.03), physical examination, vital signs, ECOG performance score, safety laboratory parameters, electrocardiogram (ECG), and Left Ventricular Ejection Fraction (LEVF)
Statistical methods:	Descriptive and exploratory analyses

FLOW CHART

Refer to Part A and Part B

Study Periods	**Screening**	**Treatment courses****									**FU** ****		**OP** *****
	SCR*	**Course 1**				**Couse 2 Onwards**							
Visit		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**EOT** ***	**FU1**	**FU2 – FUn**	
Days	-42 to -1	1	8 (±2)	15 (±2)	22 (±2)	1 (±2)	8 (±2)	15 (±2)	22 (±2)				**Every 90 (±15)**
Informed consent[1]	X												
Demographics	X												
Medical history	X												
In- /Exclusion criteria (eligibility)	X[2]	X[2]											
Physical examination[3]	X	X				X				X	X		
Body height	X												
ECOG performance score	X	X				X				X	X		
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X		
Body weight	X	X				X				X	X		
12 lead –ECG[5]	X	X		X		X				X			
Left ventricular ejection fraction[6]	X												
Safety lab parameters[7]	X	X	X	X	X	X		X		X	X		
Urinalysis[8]	X					X							
Pregnancy test	X									X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X[9]
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X[10]		
Tumour assessment by RECIST v1.1[11]	X					X				X		X	
Tumour biopsy[12]	X									X[12]			
Medication diary card dispense[18]		X	X	X	X				X				
Afatinib compliance check			X	X	X	X	X	X	X	X			
BI836845 i.v. administrationweekly		X	X	X	X	X	X	X	X				
Afatinib administration[20] daily			Continuous daily administration.										

Study Periods	**Screening**	**Treatment courses****									**FU** ****		**OP** *****
	SCR*	**Course 1**				**Couse 2 Onwards**							
Visit		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**EOT** ***	**FU1**	**FU2 – FUn**	
Days	-42 to -1	1	8 (±2)	15 (±2)	22 (±2)	1 (±2)	8 (±2)	15 (±2)	22 (±2)				**Every 90 (±15)**
Dispense afatinib		X				X							
Termination of trial medication										X			
Conclusion of Patient Participation[21]											X		X
Patient status (Part B)													X[22]

*Screening visit should be performed within 42 days prior to first drug administration. Safety lab at the screening assessment can serve as the C1/V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated.
**A treatment course consists of 28 days and will be repeated until tumour progression (according to RECIST v1.1) confirmed by tumour imaging.
*** End Of Treatment (EOT) visit must be performed within 14 days of the last administration of study drug, i.e. both Xentuzumab (BI 836845) and afatinib. If last administration of the study drug occurs during a scheduled visit, examinations as defined for EOT should be performed instead of examinations for the scheduled visit.
****First Follow-up (FU) visit 42 calendar days (up to +7 days) after the last administration of study drug for all patients (part A and part B). Additional FU visits (only for patients who discontinue not due to progressive disease) at 8-week intervals until progression, lost to follow-up or initiation of other anti-cancer treatment.
*****Observation period only for part B. For details see Section 6.2.3.3.

[1]Written informed consent must be obtained before any trial specific screening assessments are performed.
[2]In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered.
[3] Physical examination: includes cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status.
[4]Vital signs: include pulse, temperature and blood pressure.
[5] ECG to be performed at Screening/ pre-infusion, during infusion (after 30±5 mins) and immediately prior to the end of the infusion (-10 mins) on Day 1 of Course 1/ a single ECG to be taken on Day 15 of Course 1/ thereafter a single ECG to be taken pre-infusion at the start of every course on Day 1, and also at EOTV.
[6]MUGA scan or echocardiogram not older than 28 days prior to start of treatment. Further scans may be performed post treatment if clinically indicated
[7]Haematology, biochemistry and coagulation parameters. Safety labs may be collected up to two days prior to the scheduled time points. Safety lab result at course 1 visit 1 should be reviewed by investigator before first administration of study medications. From course 2 onwards, safety lab assessment will be done at visit 1 and 3 of each course. For details see Section 5.2.3.
[8]Urinalysis (Dipstick).
[9] For observation period (after the patient completed last follow-up and when progression occurred or when new anti-cancer therapy started), the investigator may report SAE if she/he becomes aware of and considers relevant.
[10]During Follow-up, concomitant therapy only needs to be recorded if indicated for the treatment of an AE.
[11]Tumour assessment will be performed every 4 weeks after start of treatment with Xentuzumab (BI 836845) and afatinib for first 8 weeks (prior to courses 2 and 3), in 8-week intervals thereafter (e.g. prior to courses 5, 7, 9, etc.) and in 12-week interval after course 16 until PD or start of further anti-cancer treatment. It should include CT scans or MRI. CT images not older than 30 days at start of treatment will suffice as screening images and don't have to be repeated. The EOT tumour assessment is optional if performed in the previous 4 weeks. Imaging may be performed within 7 days of scheduled time point. Additional imaging follow up will be required for patients who discontinued not due to progressive disease at 8-week intervals until progression, lost to follow-up or initiation of other anti-cancer treatment.
[12]Tissue biopsies to determine EGFR mutations and other relevant pathways at study entry and following progression may be obtained after obtaining informed consent. (Optional at the time of progression) In case there is a documented result of EGFR mutations available before study entry for Part A, local result is acceptable. For Part B, tumour sample provision to central laboratory is mandatory for confirmation of the result. Prior to any biopsy, patients must have controlled hematology parameters (INR and PTT within normal range) and platelet count (≥100,000 /µL). See Section 4.2.2 for restriction of

antiplatelet and anticoagulant medications. For tissue biopsy at the time of progression after study treatments, separate informed consent must be obtained.

[18]Part A: afatinib intake starting from Course 1 Day 8 up to Course 2 Day 1 and Course 3 Day 1 must be recorded in the patient diary and it should be dispensed to the patient on Day 1, 8, 15 and 22 of Course 1and Day 22 of Course 2.
Part B: afatinib intake from Course 2 Day 1 and Course 3 Day 1 must be recorded in the patient diary and the diary card should be dispensed to patient on Day 22 of Course 1 and Day 22 of Course 2.
Completed diary card should be returned from the patient at next visit.

Afatinib treatment oral continuous daily administration. Patients should take the study medication at the same time every day to ensure a dose interval of approximately 24 hours.
[21]Refer to Section 6.2.3.
[22] All patients in Part B will be followed-up for overall survival at 3 monthly intervals (90±15 days) after the last follow-up visit. For details see Section 6.2.3.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT (SGPT)	Alanine amino Transferase (Serum Glutamate Pyruvate Transaminase)
AST (SGOT)	Aspartate amino Transferase (Serum Glutamic Oxaloacetic Transaminase)
BI	Boehringer Ingelheim
CI	Confidence Interval
CM	Clinical Monitor
CML	Local Clinical Monitor
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Echocardiogram
ECHO	Electronic Data Capture
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOTV	End of Treatment Visit
EudraCT	European Clinical Trials Database
HER2	Human Epidermal growth factor Receptor 2
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IGF	Insulin-like Growth Factor
IGF-1R	Insulin-like Growth Factor -1 Receptor
IGF-1	Insulin-like Growth Factor 1
IGF-2	Insulin-like Growth Factor 2
IGFBP	Insulin Growth Factor Binding Protein
INR	International Normalized Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technologies
ISF	Investigator Site File
i.v.	Intravenous
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Subteam
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition
NSCLC	Non Small Cell Lung Cancer
OPU	Operative Unit
OS	Overall Survival
p.o.	per os (oral)
PCC	Protocol Challenge Committee
P-gp	P-glycoprotein
PR	Partical Response
q.d.	quaque die (once a day)
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Stable Disease
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TK	Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor
TMF	Trial Master File
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The epidermal growth factor receptor (EGFR) is a membrane-bound receptor tyrosine kinase that belongs to a subfamily of four closely related receptors: HER1/EGFR/ERBB1, HER2/ERBB2, HER3/ERBB3, and HER4/ERBB4. EGFR tyrosine kinase (TK) mutations can be found in about 10% of Caucasian patients with non-small cell lung cancer (NSCLC) and about 40–50% in East Asian patients with NSCLC. EGFR mutant NSCLC is a special type of lung cancer with distinct biology (P11-11496). EGFR mutation is a "driver" mutation because mutation of EGFR TK results in constitutional kinase activation and is oncogenic (R14-1169). It has been suggested that transformed lung cancer cells are dependent on EGFR activation and its downstream signalling related to proliferation and survival, a phenomenon called oncogene addiction (R14-1169). As a consequence, apoptosis is inhibited. Application of selective EGFR tyrosine kinase inhibitor (TKI) to EGFR mutant tumours abruptly breaks this balance and makes tumours regress through apoptosis, a phenomenon called oncogenic shock (R14-1169).

Exon 19 deletion (LREA deletion) and exon 21 L858R substitution are the two most common EGFR mutations in NSCLC. These two so-called common mutations attribute to more than 85% of EGFR mutations and are sensitive to selective EGFR TKIs (P13-03214). There are other less common EGFR mutations, such as G719X, L861X, T790M, and exon 20 insertion. Among these uncommon mutations G719X and L861X are sensitive to EGFR TKIs (P11-11496, P13-03214, R13-4230, R10-0095).

With almost one decade of intensive clinical investigations, mono therapy with EGFR TKIs has been established as standard first-line treatment for advanced EGFR mutant NSCLC. As of 2013, there are three EGFR TKIs approved for the first-line treatment of EGFR mutant NSCLC (R09-4437, R12-1015, P13-07382). Compared to chemotherapy, first-line EGFR TKI treatment provides a marked clinical benefit with response rates of about 60–70% and a progression-free survival of about 9–13 months in patients with common EGFR mutations (R09-4437, R12-1015, P13-07382).

Despite an initial response or disease stabilization to first-line EGFR TKIs, patients will invariably develop acquired resistance (P11-11496). It is crucial to understand the mechanisms of resistance in order to prolong the clinical benefit in patients with EGFR mutant lung cancer. Several mechanisms have been identified in clinical or non-clinical studies (R12-5206, P13-03214, P14-00839, P14-04205). After exclusion of factors such as drug-drug interactions and suboptimal drug exposure (pharmacokinetic reasons or the blood-brain barrier), the most common mechanism for acquired resistance is the development of secondary mutations in EGFR. EGFR T790M alone is responsible for 50–60% of acquired resistance (P14-00839, P13-03214, R12-5206). Other mechanisms of resistance include alternative pathway activation (e.g. c-MET in 5–10%, PIK3CA in ~5%, ~1% BRAF) and histological transformation. The molecular basis of about 30–40% of acquired resistance cases is still unknown. Caution should be exercised because most of the aforemtioned data were obtained from patients treated with first generation reversible TKIs (erlotinib and

gefitinib). Mechanisms of acquired resistance to irreversible EGFR TKIs (e.g. afatinib, dacomitinib, AZD 9291) are poorly characterized thus far.

Therefore, the current strategy to overcome acquired resistance to EGFR inhibitors may be divided to T790M-directed and non-T790M-directed. To effectively develop treatments for acquired resistance, the importance of tumour biopsies cannot be overestimated (R12-5206, P14-00839). Two EGFR wild-type sparing and T790M-specific irreversible TKIs, i.e. AZD 9291 and CO-1686, are currently under clinical investigations. According to preliminary phase I results of AZD 9291, there were 7 partial responses out of 12 patients with EGFR T790M (R14-1166). In contrast, so far there is no such promising molecular-targeted therapy for non-T790M acquired resistance. Indeed, many targeted therapies are under investigation, e.g. heat shock protein inhibitor, mTOR inhibitor, c-MET inhibitor, and dual targeting of the EGFR by combining an antibody and a TKI. Although chemotherapy added to an EGFR TKI could provide benefit to patients with acquired resistance (R14-1167), it is desirable to develop mechanism-based therapies with a favourable safety profile.

The insulin-like growth factor (IGF) pathway holds a crucial role in cell growth, differentiation and proliferation. The insulin-like growth factor family encompasses three ligands, IGF-1, IGF-2, insulin; their corresponding receptors IGF-1 receptor (IGF-1R), IGF-2 receptor (IGF-2R), Insulin-Receptor (InsR) (two isoforms: InsR-A and InsR-B); as well as six, IGF-binding proteins (IGFBP1-6) and IGFBP degrading enzymes known as proteases (R13-2052, P13-05658). Activation of IGF-1R triggers a cascade of reactions involving two main signal transduction pathways: the Ras–Raf–mitogen-activated protein kinase (MAPK) network and the phosphatidylinositol 3-kinase (PI3K)–Akt–mTOR pathway.

Among various non-T790M mechanisms, IGF signalling pathway has been implicated in the acquired resistance to EGFR TKIs (R12-5206, P14-00839, R14-1168). However, thus far, there is no clear evidence derived from a clinical study. Cortot et al. established a resistant cell line by incubating PC9 cells, which harbor exon 19 deletions, in high concentration of irreversible EGFR TKI or T790M selective TKI. IGF-1R activation was noted in this resistant cell line though T790M was not identified. The growth of the IGF-1R activated resistant cells can be effectively inhibited by treatment with an IGF-1R blocker. Interestingly, the preemptive combination of an EGFR TKI and an IGF-1R blocker prevented the emergence of resistant cells (R14-1168).

Taken collectively, it is conceivable that there is a subset of patients with non-T790M acquired resistance who could potentially be identified with a predictive biomarker and whose disease may be controlled by the administration of an IGF pathway inhibitor such as Xentuzumab (BI 836845). This clinical trial is therefore aiming to investigate the safety and efficacy of an IGF ligand antibody (Xentuzumab (BI 836845)) in combination with an EGFR TKI (afatinib) in patients previously treated with reversible or irreversible EGFR TKIs. The mechanism of acquired resistance to irreversible TKI will be explored in this study as well.

1.2 DRUG PROFILE

1.2.1 Xentuzumab (BI 836845)

Xentuzumab (BI 836845) is a fully human monoclonal antibody of the IgG1 isotype that binds to human insulin-like growth factor-1 and insulin-like growth factor-2 and thereby neutralizes the growth-promoting activities of IGF-1 and IGF-2.

Xentuzumab (BI 836845) binds with high affinity to IGF-1 and IGF-2, and potently neutralizes proliferative and prosurvival cellular signalling triggered by both proteins. The mode of action of Xentuzumab (BI 836845) is different from IGF-1 receptor targeted mAbs. In particular, Xentuzumab (BI 836845) can inhibit IGF-2 stimulated Insulin Receptor-A (InsR-A) activation, which is an additional proliferative and prosurvival pathway not blocked by IGF-1R targeted mAbs (U10-2830). In addition, by sparing InsR-B and its hybrid receptors, Xentuzumab (BI 836845) may achieve anti-tumour activity without perturbing glucose homeostasis.

Preclinical studies showed that Xentuzumab (BI 836845) treatment inhibited the rapamycin-induced feedback phosphorylation of AKT in PI3K-AKT-mTOR pathway. Similarly, rapamycin resulted in an increase in the IGF bioactivity (IGF-1R phosphorylation potential) of mouse serum, which could be inhibited by Xentuzumab (BI 836845) (P13-16103).

Expansion cohorts in two phase I studies with Xentuzumab (BI 836845) monotherapy given weekly or every three weeks are currently ongoing in patients with advanced solid tumours. These studies are intended to determine the safety, maximum tolerated dose and/ or relevant biological dose, pharmacokinetics (PK) and PK/pharmacodynamic (PD) correlation. Preliminary interim data from these trials indicate that maximum plasma concentrations of Xentuzumab (BI 836845) are reached at the end of the infusion or shortly thereafter. After reaching the peak, plasma concentrations showed an at least biphasic decay with a terminal half-life of about 6 days. The estimated volume of distribution was about 5.8 L (approx. two times the plasma volume) and the total plasma clearance was about 0.5 mL/min.

No deviations from dose-proportional pharmacokinetics have been observed in the dose range analyzed (10-1050 mg q1w in 1280.1 and 10-3600 mg q3w in 1280.2). Steady state plasma concentrations of Xentuzumab (BI 836845) were achieved after 5-7 weeks. Repeated weekly dosing resulted in about 1.5 fold accumulation of Xentuzumab (BI 836845) plasma concentration at steady state, while only limited accumulation was observed after repeated infusions every three weeks.

It is known that human IgGs like Xentuzumab (BI 836845) are mainly cleared by catabolism. This mechanism of clearance is not shared or overlapping with the clearance mechanism for small molecules. Thus, Xentuzumab (BI 836845) is not predicted to directly affect the hepatic, renal, or biliary elimination of small molecules. Furthermore, Xentuzumab (BI 836845) is not targeting cytokines, and mAbs targeting upstream IGFs have not been related to modulation of CYP450 isozymes or drug transporters (P13-02270). Hence, the potential of Xentuzumab (BI 836845) to alter the pharmacokinetics of co-medication is considered low.

Xentuzumab (BI 836845) has been formulated for i.v. infusion and will be provided as a liquid formulation. The appropriate dose of Xentuzumab (BI 836845) should be diluted in physiological sodium chloride solution (0.9%) prior to intravenous administration.

As of Jul 10, 2013, 48 and 33 patients have been dosed in 1280.1 and 1280.2 trial using weekly and every three-week schedule, respectively. Among these two trials, only one dose limiting toxicity (DLT), a pulmonary haemorrhage, was observed at 450 mg (in the trial using weekly schedule), which was considered drug-related by the investigator. Consequently, 3 additional patients were dosed at this level for a total of 6 patients, no additional DLT was observed. Four subjects in study 1280.1 discontinued treatment due to non drug-related AEs. A CTCAE grade 3 hyponatraemia (syndrome of inappropriate antidiuretic hormone secretion – SIADH) occurred in a single patient in the 3600 mg q3w cohort. As there is no connection to the mechanism of action of Xentuzumab (BI 836845), an alternative explanation may have been an underlying paraneoplastic syndrome. However, consequently, investigator should carefully monitor electroytes and excretion under treatment with Xentuzumab (BI 836845).

Dose escalation to 1800 mg weekly or 3600 mg q3w did not identify a maximum-tolerated dose (MTD).

Based on toxicity studies the side effects expected with Xentuzumab (BI 836845) are possibly abnormal liver function test and changes in haematological parameters (reduced white and red blood cells). However, abnormal liver function tests as well as anaemia and decreased white blood cells were only infrequently observed in the 81 patients treated thus far in Phase I and generally of low grade (Grade 1 and 2).

Infusion reactions have not been observed. Metabolic AEs involving perturbed glucose homeostasis, among the most common toxicities documented for IGF-1R-targeting mAbs and small molecule TKIs, were observed at low frequencies: Two out of 81 subjects reported transient hyperglycemia; 1 patient (Grade 2) in 1280.1 and 1 patient (Grade 3) in 1280.2.

Of note, two confirmed partial responses (PR) have been reported in the weekly schedule trial; firstly, in a -year old with a recurrent nasopharyngeal carcinoma (NPC) and multiple lung metastases after concurrent chemoradiotherapy; secondly, in a -year old with a peripheral primitive neuroectodermal tumour (pPNET). In addition, 12 (25%) and 4 (12.1%) patients with confirmed stable diseases were reported in study 1280.1 and 1280.2, respectively.

Full details of the clinical pharmacology, toxicology, clinical pharmacokinetics and safety data can be found in the current Investigator Brochure for Xentuzumab (BI 836845) (U10-2830).

1.2.2 Afatinib

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning afatinib refer to the free base compound afatinib BI which is used as the oral formulation.

Afatinib (BIBW2992) is a small molecule, selective and irreversible ErbB family blocker. In preclinical models it effectively inhibits EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4) phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors. Afatinib is under regulatory review for treatment of patients with EGFR mutation-positive NSCLC and has already been approved for first-line use in the USA, the EU, Taiwan, Korea, Singapore and other countries. Afatinib is also in clinical development as a therapy for several other ErbB-driven cancers.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for $AUC_{0-\infty}$ and C_{max} when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators.
In pre-clinical studies afatinib is not irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two phase I open label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumours at 40mg and 50mg daily, respectively (U03-3218 and P12-14433). Adverse events (AE) observed with afatinib are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent investigator defined drug-related AEs were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects, epistaxis, fatigue and decreased appetite. Early and proactive management of diarrhoea, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies (R07-4077, P07-11507, R07-4078, P13-03658 and P13-03659).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Somatic mutations in exons encoding the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) are positively associated with increased sensitivity of non-small cell lung cancer (NSCLC) patients to the selective EGFR TK inhibitors (TKIs), gefitinib (Iressa™) and erlotinib (Tarceva™) (R04-4507, R04-4508, R06-1259). Prospective trials have demonstrated an impressive ~75% response rate for patients whose tumours harbor these mutations (R06-1403, R09-4439), which occur as either multinucleotide in-frame deletions in exon 19 (e.g., delE746-A750) or as single missense mutations (e.g., L858R). Unfortunately, the EGFR TKI-driven improvement in patient outcome is only limited because virtually all NSCLC patients with erlotinib/gefitinib-sensitizing EGFR mutations eventually acquire resistance after a median of 6–12 months of EGFR TKI therapy and eventually succumb to their disease (R06-1403, R06-1311). In approximately half of cases, the tumour cells present after disease progression contain second-site mutations that alter drug binding to the EGFR TK domain. The most common lesion (>90%) is the so-called "gatekeeper mutation", which involves a substitution of methionine for threonine at position 790 (T790M).

More recently, in addition to other second-site mutations associated with acquired resistance to EGFR TKIs (e.g., L747S and D761Y in exon 19 or T854A in exon 21), novel EGFR-independent mechanisms have been discovered that contribute to EGFR TKI resistance, either in the absence or presence of the EGFR T790M mutation (R11-4674, P09-09950). Another such mechanism of gefitinib/erlotinib resistance is the MET receptor tyrosine kinase (RTK) gene amplification: "oncogene kinase switch". EGFR T790M and MET amplification, which can be detected in up to 20% of EGFR NSCLCs with acquired resistance to EGFR TKIs, account for approximately 60–70% of all known causes of acquired resistance to gefitinib/erlotinib. Consequently, ongoing research is attempting to identify the mechanisms that may account for the 30–40% of EGFR TKI-resistant, EGFR-mutated tumours that do not carry EGFR mutations or MET amplification. Another possible kinase switch mechanism could involve hyperactivity of the IGF/IGF-1R system. Although increased activation of insulin-like growth factor-1 receptor (IGF-1R) through IGF overexpression, the loss of IGF-binding proteins and loss or reduction of the tumour suppressor PTEN have been associated with acquired resistance to EGFR TKIs in laboratory models (R09-1568, R14-1339, R14-1338), this hypothesis has not yet been tested in a clinical trial with EGFR TKI-resistant patients.

IGF pathway signalling is important in many physiological functions and also in carcinogenesis. IGF pathway signalling shares some downstream effector pathways and biological functions with EGFR signalling. Several evidences show there is a signalling cross-talk between IGF-1R and EGFR; this cross-talk may be involved in a compensatory mechanism. Along this line, several non-clinical reports have shown that the IGF pathway is involved in the resistance to EGFR targeted therapy in EGFR mutant NSCLC (P09-09950, R14-1173, R14-1172, R14-1168, R14-1171). For instance, as described in Section 1.1, IGF

pathway activation has been reported to be responsible for acquired resistance to irreversible EGFR TKIs in an EGFR mutant cell line (R14-1168). It is therefore conceivable that the addition of an IGF signalling inhibitor to an EGFR TKI can overcome drug resistance to an EGFR TKI alone. So far, there is no evidence that IGF signalling plays an important role in the development of resistance in the presence of EGFR T790M. This subset of patients may rather fall in the category of acquired resistance without T790M. Nevertheless, no clinical trial has tested this concept until now.

To test this hypothesis, an EGFR TKI, afatinib, will be continued in this resistant setting. It is assumed that once IGF-mediated resistance is controlled by the IGF antibody Xentuzumab (BI 836845), afatinib will still inhibit EGFR-addicted cells in the absence of T790M mediated drug resistance. This strategy is supported by the results of Cortot et al., showing that the combination of an IGF-1R TKI and an EGFR TKI achieved better inhibition of downstream phospho-Akt and phospho-ERK (R14-1168).

To date, several studies using an IGF-1R antibody (R-1507 or cixutumumab) in combination with an EGFR TKI (erlotinib) reported disappointing results in patients with NSCLC. The main reasons were a lack of a predictive biomarker for patient selection and an unfavourable safety profile stemming from the receptor-targeting approach (R13-0059, R12-5650, R16-4930). At present, there is no IGF ligand antibody, with a potentially more favourable safety profile, under clinical investigation in EGFR mutant NSCLC.

Afatinib has been studied in an EGFR-TKI pretreated setting and shown encouraging efficacy results. In patients who met Jackman's criteria of acquired resistance, the PFS was 4.5 months in afatinib group and 1.0 month in the placebo group (P12-03682).

Xentuzumab (BI 836845) has been investigated in two phase I studies, with expansion cohorts till ongoing. A favourable safety profile without the typical class side-effects of IGF-1R-targeted agents (antibodies or TKIs) has been observed. Moreover, a preliminary efficacy signal was noted with two partial responders and several disease stabilizations (U10-2830). Taken collectively, these studies suggest that co-targeting the IGF and EGFR pathways with Xentuzumab (BI 836845) and afatinib may offer synergistic therapeutic benefits for EGFR mutant NSCLC.

Since the mechanism of acquired resistance to irreversible EGFR TKI is largely unknown, a better molecular characterization could improve the selection of treatment for individual patients. Consequently, in addition to tumour biopsies, circulating free DNA (so-called liquid biopsies) will be collected to support the investigation of unknown resistance pathways and to identify candidate predictive biomarkers for future patient enrichment.

This clinical trial is intended as a pilot study before a larger, randomized proof-of-clinical-concept study. The purpose is 1) to establish an acceptable safety profile as well as a recommended Phase II dose for the combination of Xentuzumab (BI 836845) and afatinib and 2) to identify an initial efficacy signal before embarking on a larger and broader clinical development in other EGFR mutant cancer indications.

2.2 TRIAL OBJECTIVES

The overall objective of this trial is to evaluate the safety and anti-tumour activity of Xentuzumab (BI 836845) combined with afatinib in patients with EGFR mutant lung cancer.

2.2.1 Primary objectives

Part A – Dose confirmation:

- To determine the Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D) of Xentuzumab (BI 836845) in combination with afatinib in patients with non-small cell lung cancer with progression following prior treatment (EGFR TKIs or platinum-based chemotherapy)

Part B – Expansion cohorts:

- To evaluate the early anti-tumour activity of Xentuzumab (BI 836845) in combination with afatinib in patients with EGFR mutant non-small cell lung cancer with progression following prior irreversible EGFR TKIs

2.2.2 Secondary objectives

Part A and Part B:

- To evaluate the safety of Xentuzumab (BI 836845) in combination with afatinib in patients with non-small cell lung cancer

For details on endpoints and their assessments, see Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Most patients with EGFR mutant NSCLC will develop acquired resistance to EGFR TKI despite initial benefit. Consequently, most patients with locally advanced or metastatic tumours will succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic EGFR mutant NSCLC.

Aberrant ErbB (HER) family expression and signalling contribute to the malignant phenotype in many tumour types including squamous cell carcinoma of lung. It is therefore expected that treatment with an ErbB family blocker may result in tumour control. Afatinib is a potent, irreversible, orally available ErbB family blocker studied in more than 3000 patients to date. The combination of afatinib with Xentuzumab (BI 836845) may further improve EGFR/ErbB1 target inhibition and overcome acquired resistance to EGFR TKIs.

Based on toxicological findings and the experience with other EGFR (ErbB1) and HER2 (ErbB2) inhibitors, as well as results from Phase I studies, the risks of anti-EGFR/HER2 therapy with afatinib primarily consist of gastrointestinal (GI) AEs (including diarrhoea, nausea, and vomiting), and skin AEs. Skin and subcutaneous tissue disorders primarily consist of erythematous, maculo-papular and papular skin rashes, pruritus, acne, eczema, folliculitis, and pustular rash.

Xentuzumab (BI 836845) has been tested in two separate Phase I clinical trials. As of the database cut-off date of July 10, 2013, 81 patients received Xentuzumab (BI 836845) monotherapy. The AE profile observed has generally been consistent with the underlying neoplastic conditions with most AEs being CTCAE grade 1 or 2. As the clinical experience with Xentuzumab (BI 836845) is limited, safety will be carefully monitored throughout the duration of treatment with Xentuzumab (BI 836845); supportive treatments, and/or dose modification/discontinuation of Xentuzumab (BI 836845) will be mandated as necessary.

Although Xentuzumab (BI 836845) is a fully humanised antibody given intravenously, there may be a potential for infusion-related reactions and immune responses to occur. Such infusion reactions will be graded and treated following standard of care or local guidance. Out of 81 patients who received Xentuzumab (BI 836845), no infusion reaction has been observed (U10-2830). The immune responses to Xentuzumab (BI 836845) mAb will be assessed through measurement of anti-drug antibodies in the study.

Because IGF-1R signalling could be a compensatory pathway to EGFR inhibition, and IGF-1R shares a similar downstream effector pathway, AEs, e.g. cutaneous side effects and diarrhoea due to afatinib might be augmented by combining afatinib and Xentuzumab (BI 836845). Nevertheless, these side effects are not expected to become life-threatening as they can be identified early and treated appropriately with comprehensive supportive treatment and/or interruption or dose adaptation of the study treatment. In this study, detailed recommendations on management of expected side effects of afatinib will be provided to minimize the intensity and duration of side effects.

Weight loss should be monitored closely. Nutritional consultation may be recommended early and nutrition support including tube feeding or total parenteral nutrition should be provided if indicated.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients safety.

Given the high unmet medical need in NSCLC, the potential benefits to be expected from afatinib in combination with Xentuzumab (BI 836845) are likely to outweigh its risks in this study population.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, open-label, phase Ib clinical trial to evaluate the safety, tolerability and anti-tumour activity of the combination of Xentuzumab (BI 836845) and afatinib. This trial will consist of a dose confirmation part (Part A) and an expansion part (Part B). Part A and Part B will be conducted sequentially.

Initially, recruitment in Part A will follow an escalation/de-escalation "3+3" design (R07-0220) to determine the Maximum Tolerated Dose (MTD) and/or recommended dose for Part B of Xentuzumab (BI 836845) in combination with afatinib in patients with NSCLC who have had progression following prior treatment (EGFR TKIs or platinum-based chemotherapy). The starting dose of afatinib will be one level below the registered dose and for Xentuzumab (BI 836845) the current monotherapy RP2D will be used. The safety of the RP2D of Xentuzumab (BI 836845) in combination with afatinib will be confirmed in a total of 12 patients across. Thus, 6 additional patients will be treated at the MTD/RP2D dose level.

After conclusion of Part A (determination of RP2D), Part B of the trial will commence in one expansion cohort to evaluate the safety, tolerability and preliminary anti-tumour activity in patients with EGFR mutant non-small cell lung cancer who have progressed on irreversible EGFR TKIs (e.g. afatinib, dacomitinib). In the expansion cohort,18 additional patients will be treated.

Patients are enrolled in the study once the informed consent form is signed. The screening period will be up to 6 weeks (42 days) during which time the eligibility will be confirmed. In order to meet the eligibility criteria regarding EGFR genotypes and/or to characterize resistance mechanisms, all patients need to provide archived tumour sample which is associated with EGFR TKI (or other treatment in EGFR wild type) resistance or undergo a fresh tumour biopsy. In the Part B, the EGFR genotypes must be confirmed by the authorized central laboratory. The eligibility criteria will be reconfirmed prior to the first administration of study medications. Eligible patients will be treated continuously with the study regimen in the absence of disease progression, intolerable adverse events, or other reason necessitating withdrawal (refer to Section 3.3.4). The treatment will be administered as courses of 28 days. Continued treatment beyond disease progression will not be allowed in the study.

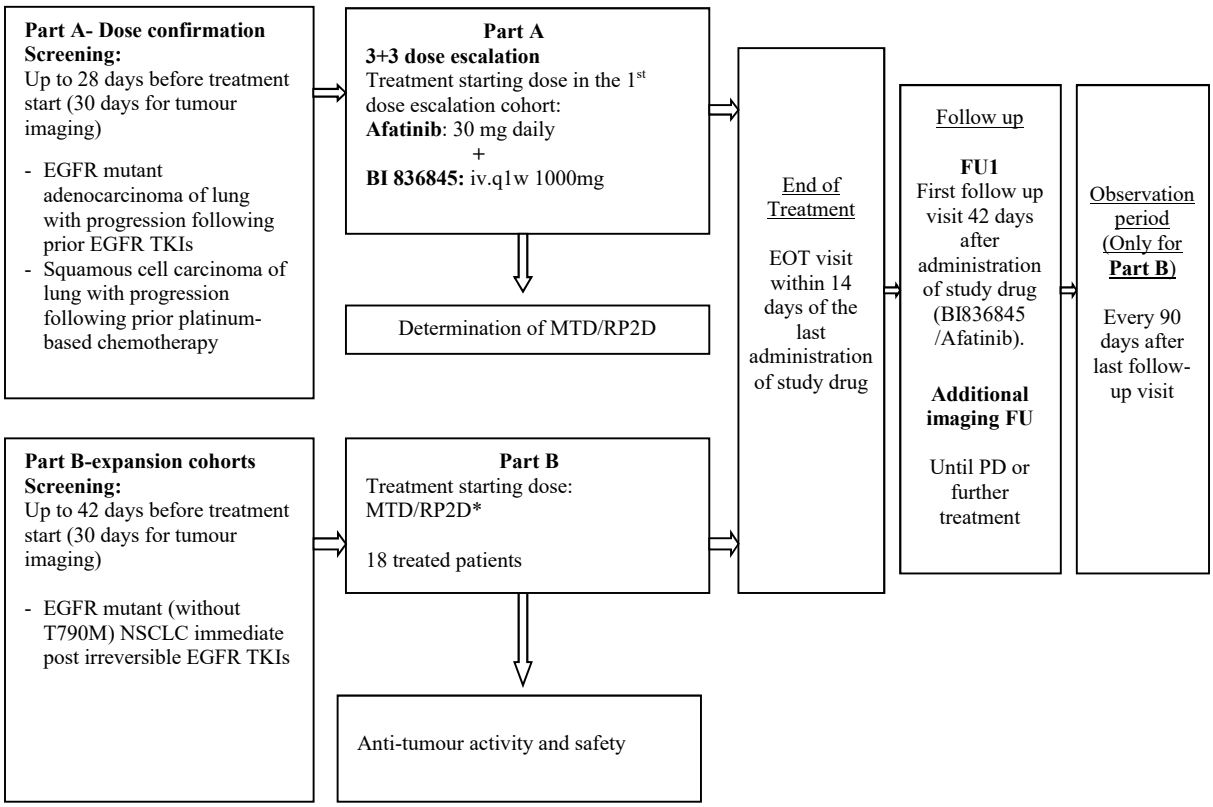
All patients will have regular assessment of safety parameters as detailed in the Flow Chart.

Tumour assessment by imaging according to RECIST version 1.1 will be conducted at baseline and at fixed time points as specified in the Flow Chart.

An End of Treatment (EOT) visit is to be completed when a patient permanently discontinues both study drugs, for any reason listed in Section 3.3.4.

The assessments required are listed in the Flow Chart. Patients who permanently discontinue both study drugs due to other reason than progressive disease will continue to have tumour assessments according to the Flow Chart until disease progression, lost to follow-up or initiation of other anti-tumour therapy, whichever occurs first.

A Follow-up visit (FU1) will be completed 42 (+ 7) days after the last administration of study drug. Refer to the Flow Chart and Figure 3.1: 1 below for details. FU1 will be defined as the end of on-treatment period for this trial. After disease progression, patients will be monitored for vital status in the observation period (**for Part B only**).



* Part B only: For patients who had disease progression while on afatinib less than 40 mg/day, the starting dose is the last dose of afatinib. Alternative starting dose of afatinib must be discussed and agreed by Sponsor.

Figure 3.1: 1 Study design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim.

The coordinating investigator is an oncologist with experience in this type of trial and investigations. The coordinating investigator has been designated by Boehringer Ingelheim and will sign the clinical trial report. The investigators participating in the trial must have experience in diagnosing and treating patients with locally advanced or metastatic non-small cell lung cancer. Each decision on dose escalation or de-escalation steps will be taken in agreement between the Sponsor and the principal investigators at each site and safety will be closely monitored by a BI monitor or a Contract Research Organisation (CRO) appointed by BI. There will be no steering committee or data monitoring committee for this trial.

Regular teleconferences (or online meeting) will be held for decision of dose escalation, discussion of ongoing patients, discussion and determination of MTD/RP2D, and discussion of operational aspects. The participants are the investigators and BI study team. Relevant safety, laboratory, and efficacy data should be checked by on-site monitoring or review of eCRF before the teleconference. During the regular teleconferences with the investigators and study team, the next higher dose level will be determined from the progress of existing patients at the current dose level and in consideration of available AE and PK-PD data. Any potential patients for the trial will also be discussed. Conclusion of dose escalation decision should be agreed by the investigators and BI study team. All teleconference details will be documented accordingly.

BI will appoint CROs and independent service providers for special services such as central laboratory services for biomarker testing and part of bioanalytical testing, biosample collection and logistics, and Interactive Response Technologies (IRT) for trial medication assignment/logistics. The analysis of biomarker and PK will be performed by BI or a CRO appointed by BI.

On-site monitoring will be performed by BI or a Contract Research Organisation (CRO) appointed by BI.

All trial relevant documentation will be stored in the Trial master file (TMF) at BI. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The ‘3+3’ dose finding design (R07-0220) for phase I clinical studies in oncology with escalating/de-escalating steps will be used to determine the MTD of Xentuzumab (BI 836845) combined with daily dosing of afatinib. No control group is needed.

As no data regarding the optimal dose for Xentuzumab (BI 836845) combined with a daily dose of afatinib exist so far, the assessment of MTD will be performed in part A prior to further exploring the anti-tumour activity of the combination regimen in Part B. In part B, for patients who had disease progression while on afatinib less than 40 mg/day, the starting dose is the last dose of afatinib. Alternative starting dose of afatinib must be discussed and agreed by Sponsor. (P16-10813).

Patients will continue trial treatment until any reason listed in Section 3.3.4 is met.

3.3 SELECTION OF TRIAL POPULATION

Since the objective is to evaluate the tolerability of Xentuzumab (BI 836845) plus afatinib for patients with NSCLC who have failed previous treatment (EGFR TKI or platinum based chemotherapy), it is important to conduct the dose confirmation part (Part A) in a closely related patient population and to conduct the expansion part (Part B) for the exploration of a preliminary efficacy signal in a well-defined group of patients with resistance to EGFR TKIs. Squamous cell carcinoma, a subtype of NSCLC, will be also eligible in Part A because emerging data shows that afatinib provides clinical benefit in this patient group (P15-06906). Both EGFR mutant NSCLC and SCC of lung are more likely expected to obtain benefit from afatinib-based therapy. The safety and tolerability profiles of afatinib between EGFR mutant NSCLC and SCC are similar. Ideally, a clear signal whether the experimental treatment can work in truly resistant disease will be obtained; a false positive signal has a very low likelihood as no response is to be expected from resistant clones.

Part A

An estimated total of about 9 to 18 patients will be necessary to establish the MTD for the combination of Xentuzumab (BI 836845) plus afatinib. If 6 evaluable patients have been treated at the MTD dose level, an additional 6 patients will be recruited to determine the RP2D, i.e., a total of 12 patients with resistance to EGFR TKIs will be treated at the MTD level. If the RP2D is different from the MTD dose, a total of 12 patients should be treated at the RP2D dose prior to commencing the Part B of the study.

Part B

Once the RP2D has been determined, 18 additional patients will be treated in the expansion cohort of Part B. In part B, for patients who had disease progression while on afatinib less than 40 mg/day, the starting dose is the last dose of afatinib. Alternative starting dose of afatinib must be discussed and agreed by Sponsor(P16-10813).

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

3.3.1 Main diagnosis for study entry

3.3.2 Inclusion criteria

1. Male or female patients aged 18 years or older
2. Patients with pathologic confirmation of advanced and/or metastatic stage IIIb/IV non-small cell carcinoma of lung

   Note: In Part A and B, diagnosis is not necessarily based on the latest tumour sample. Small cell lung cancer transformation must be excluded.

3. Documented activating EGFR mutation (exon 19 deletion, L858R, G719X, L861X). Exception: patient with squamous cell predominant histology in Part A
4. Presence of EGFR activating mutation and absence of EGFR T790M mutation in the tumour associated with the latest disease progression. Only applicable in Part B
5. Adequate fresh or archival tumour tissue at the latest disease progression immediately prior to the study entry must be made available for central EGFR mutation test and/or resistance analysis
6. Part A: Progression of disease (RECIST v1.1) while on continuous treatment with single agent EGFR TKI (e.g. erlotinib or gefitinib or afatinib) or for histology other than adenocarcinoma and without prior EGFR TKI treatment: progression of disease (RECIST v1.1) on platinum-based chemotherapy.

   Part B: Progression of disease (RECIST v1.1) while on continuous treatment with single agent of the second generation irreversible EGFR TKI (e.g. afatinib or dacomitinib).

   Note: In both parts, patients whose disease progresses only in the central nervous system (CNS) are not eligible
7. No intervening systemic therapy between cessation of EGFR TKI and initiation of the treatment in the study. Exception: patient with squamous cell predominant histology in Part A
8. Patients must have measurable disease per RECIST v1.1 (R09-0262 - Appendix 10.5) presented after tumour biopsy for the latest disease progression
9. Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1 (Refer to Appendix 10.4)
10. Life expectancy of ≥ 3 months in the opinion of the investigator
11. Fasting plasma glucose < 8.9 mmol/L (< 160mg/dL) and HbA1C < 8%
12. Adequate organ function as defined by the following criteria:
    - LVEF >50% or within institutional values
    - Absolute neutrophil count (ANC) ≥1,500/ mm^3
    - Platelet count ≥100,000/ mm^3
    - Estimated creatinine clearance > 45ml/ min Appendix 10.2.
    - Total bilirubin ≤1.5 times upper limit of institutional normal.
    - Aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤3 x upper limit of institutional normal (ULN) (if related to liver metastases ≤ 5xULN)
13. Recovered from any previous therapy related toxicity to ≤ Grade 1 at study entry (except for stable sensory neuropathy ≤ Grade 2 and alopecia)
14. Written informed consent that is consistent with ICH-GCP guidelines and local regulation.

15. No known potentially targetable mutation other than IGF signalling pathway or EGFR or no available treatment for potentially targetable mutation

3.3.3 Exclusion criteria

1. Part A only: For patient who has been treated with afatinib,last treatment at reduced dose below the assigned dose level
2. Patient whose disease progressed on insufficient dose of EGFR TKI immediately prior to study in the opinion of the investigator
3. Part B only: More than 2 prior EGFR TKI treatment regimens for relapsed or metastatic NSCLC
4. Chemotherapy, biological therapy or investigational agents (except EGFR TKIs) within 4 weeks prior to the start of study treatment.
5. Use of previous EGFR TKIs except afatinib within 3 days of treatment administered.
6. Radiotherapy within 4 weeks prior to the start of study treatment, except as follows:

   (a) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to the start of study treatment, and

   (b) Single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling.
7. Patients with active brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids or have been on stable dose of corticosteroids for at least 4 weeks before starting study treatment. Any symptoms attributed to brain metastases must be stable for at least 4 weeks before starting study treatment.
8. Meningeal carcinomatosis.
9. Major surgery (as judged by the investigator) within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study.
10. Known hypersensitivity to afatinib, monoclonal antibody or the excipients of any of the trial drugs.
11. Prior severe infusion-related reaction to a monoclonal antibody
12. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (Refer to Appendix 10.3), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior start treatment.
13. Female patients of childbearing potential (see Section 4.2.2.3) and male who are able to father a child who:

    (a) are nursing or

    (b) are pregnant or

(c) are not using an acceptable method of birth control (see Section 4.2.2.3) or do not plan to continue using this method throughout the study and/or do not agree to submit to pregnancy testing required by this protocol.

14. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug.
15. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.
16. Disease that is considered by the investigator to be rapidly progressing or life threatening such as extensive symptomatic visceral disease including hepatic involvement and pulmonary lymphangitic spread of tumour (subjects who are intended for urgent chemotherapy)
17. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2 that cannot be stopped for the duration of trial participation.
18. Known pre-existing interstitial lung disease (ILD).
19. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption).
20. Active hepatitis B infection active hepatitis C infection and/or known HIV carrier.
21. Use of alcohol or drugs incompatible with patient participation in the study in the investigator's opinion.
22. Previous treatment with agents targeting the IGF signalling pathway.
23. Patients unwilling or unable to comply with protocol in the opinion of the investigator
24. Previous treatment with EGFR TKI which can't be documented as either reversible or irreversible (Part B only)
25. Part B only: Prior treatment with third generation irreversible EGFR TKI (e.g. AZD9291 or CO-1686)

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be removed from the trial in case any of the following criteria applies:

- A patient denies further trial participation (patients are free to discontinue their participation in this study at any time without the need to justify this decision).

In this event, the patient will be asked to have their end of treatment assessments and the data collected until the point in time when withdrawal occurred will be included in the final analysis of the trial data. No further follow-up will be performed in case the patient does not agree to follow-up.

A patient has to be discontinued from study treatment in case any of the following applies:

1. A patient requests discontinuation of active treatment but agrees to be followed-up.
2. Documented progressive disease (Section 5.1.2)
3. The patient is no longer able to participate in the study (e.g., AE, pregnancy, surgery, concomitant diagnoses, concomitant therapies or administrative reasons). The investigator may also stop a patient's treatment, if the patient is no longer able to attend study visits e.g. due to worsening of disease; in such a case the Investigator's reason for a patient's removal must be recorded on the appropriate page of the Electronic Case Report Form (eCRF).
4. Significant deviation from the protocol. The decision to continue or withdraw treatment will be made after discussion between the sponsor and the investigator.
5. Diagnosis of ILD.
6. Further dose reductions considered necessary but not allowed according to the protocol for both study drugs (Section 4.1.4.3).
7. An interruption of both drugs for more than 14 days as counted from the next planned treatment administration. If an interruption of more than 14 days is necessary and clinically justified, the patient may continue study treatment after discussion and agreement between the investigator and the BI Clinical Monitor.

Patient withdrawal will be documented and the reason for withdrawal recorded and discussed in the final study report.

As soon as a patient has withdrawn from the trial, the EOT visit should be performed where feasible. Every effort should be made to follow up patients in case an adverse event is still ongoing at the time of withdrawal.

All patients who are included into the trial (i.e. having given informed consent) will have their data entered into the trial database. This includes patients who are considered screen failures i.e. do not commence study drug treatment.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim 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 overall or at a particular trial site,

2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial.

3. Violation of GCP, the CTP, or the contract by a trial site or investigator, affecting the appropriate conduct of the trial.

4. Discontinuation of the clinical development programme with Xentuzumab (BI 836845) or the combination of Xentuzumab (BI 836845) with afatinib.

5. Any other administrative reason

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

3.3.4.3 Replacement of patients

Replacement of entered patients is only applicable in part A before the determination of MTD.

Patients will be replaced for the assessment of Dose Limiting Toxicities in case of:

1) Patient's withdrawal during the first course of treatment for reasons other than DLT, e.g. patient no longer wishes to participate, or lost to follow up during first course

2) Patients who do not experience DLT, but miss more than one visit during the first course of treatment

3) Patients who do not experience DLT but miss ≥ one Xentuzumab (BI 836845) administration or ≥ 5 doses of afatinib in first treatment course

4) Patients who miss one complete course at any time beyond the first course of treatment may be replaced after discussion between the sponsor and the investigator

5) Patients who are non-evaluable with respect to DLT

Patients that have been replaced might continue treatment in the trial upon agreement between investigator and sponsor however these patients will not be considered for the evaluation of MTD.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will receive Xentuzumab (BI 836845) weekly in combination with afatinib once daily. The manufacturers for each of the products are listed in Section 4.1.1.

4.1.1 Identity of BI investigational product and comparator product

4.1.1.1 Xentuzumab (BI 836845) (investigational product)

Substance:	Xentuzumab (BI 836845) human monoclonal antibody
Pharmaceutical form:	Liquid formulation
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml of Xentuzumab (BI 836845) supplied in 20 ml vials (200 mg/vial)
Weekly dose:	1000 mg (starting dose), 750 mg
Posology:	Once weekly administrated through one hour intravenous infusion. Infusion duration may be extended to over one hour and up to a maximum of three hours in cases of grade ≥ 2 infusion reactions. See Section 4.1.3 for dose selection
Route of administration:	Intravenous infusion. Appropriate dose of Xentuzumab (BI 836845) will be diluted in isotonic sodium chloride solution (0.9%)
Duration of use:	Continuous weekly dosing (days 1, 8, 15 and 22 in a 28-day course) in the absence of disease progression, intolerable AEs or other reason necessitating withdrawal

4.1.1.2 Afatinib (investigational product)

Substance:	Afatinib
Brand name:	Giotrif
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg, 30 mg or 40 mg (the dose of afatinib in tablets is related to the free base equivalent of afatinib)

Route of administration:	Oral
Posology:	Once daily. Take afatinib at least 1 hour before or 3 hours after a meal. See Section 4.1.3 for dose selection
Duration of use:	Continuous daily dosing until criterion in Section 3.3.4.1 is met

4.1.2 Method of assigning patients to treatment groups

4.1.2.1 The dose confirmation Part A

Treatment slots are assigned by the BI Clinical Monitor (CM) in close communication (email/phone/FAX) with the recruiting sites and will be assigned on a competitive basis. After the BI Clinical Monitor has been notified by a site about a potential patient, the slot will be reserved to this site for a maximum of seven calendar days. If the informed consent form (ICF) has not been signed by the potential patient within this time window, the slot will be opened up again for all recruiting sites.

Patients that meet the eligibility criteria and who have given their written informed consent will be entered into the study.

Before entering patients at the next dose level it will be ensured that all patients at an ongoing cohort have completed the first course. Prior to inclusion of a new patient, the investigator should confirm the respective dose with the BI clinical monitor.

4.1.2.2 The expansion Part B

The enrolment in Part B is competitive. In order to reach an adequate number, eligible patients need to be communicated to the BI Clinical Monitor (CM). These communications may be done by FAX/e-mail and will be documented. Patients that meet the eligibility criteria and who have given their written informed consent will be entered into the Part B of the study. Investigators will be notified by the sponsor when the appropriate number of patients have been screened and screening is complete, thereafter additional patients will not be allowed to recruit for this study. Patients who have signed an informed consent form and are eligible prior to notification of the termination of recruitment will be allowed to participate in the study.

4.1.3 Selection of doses in the trial

4.1.3.1 Planned dose levels in the Part A

The Part A will follow an escalation/de-escalation “3+3” design. The starting dose level consists of 1000 mg weekly Xentuzumab (BI 836845) in combination with 30mg/day of afatinib.

The approved dose of afatinib in first-line monotherapy treatment of EGFR mutant NSCLC is 40 mg daily. Afatinib has also been studied in NSCLC with settings of EGFR TKI failure. In the LUX-Lung 1 study, afatinib was administered as monotherapy with a daily dose of 50 mg (P12-03682). Afatinib at 40 mg daily in combination with bi-weekly cetuximab of 500 mg/m^2 has been established as recommended dose for patients who failed prior EGFR TKI (P12-11350). In the current trial, an afatinib dose of 30 mg daily, a dose lower than the registered dose, has been chosen as a starting dose level. Given the cross-talk between IGF-1R and EGFR, it is conceivable that side-effects as well as efficacy of EGFR TKIs might be potentiated when an IGF pathway inhibitor is added (R16-4930, R12-5650). Hence, to mitigate this risk, a lower than labeled dose is chosen for the first dose cohort.

The starting dose level of Xentuzumab (BI 836845) has been determined as 1000 mg every week. Based on data from two phase I studies, the recommended monotherapy dose of Xentuzumab (BI 836845) is 1000 mg every week. In these two studies, a formal MTD was not established in the absence of DLT from 1000 mg per week up to 1800 mg per week. About 90% neutralization of IGF-1 can be achieved with dose of 1000 mg every week. Tolerability and safety are considered favourable even at dose levels above 1000 mg every week. Therefore, a dose of 1000 mg Xentuzumab (BI 836845) every week is chosen as starting dose to combine with 30 mg QD of afatinib.

Table 4.1.3.1: 1 Planned dose levels

Dose level		**Xentuzumab (BI 836845) (mg/week)**	**Afatinib (mg /day)**
Dose level -1		750	30
Dose level 1	Starting dose	1000	30
Dose level 2	Intended RP2D	1000	40

Study treatment will be administered in 4-week (28 days) courses.

To determine the maximum tolerated dose (MTD), patients will be entered sequentially into escalating/de-escalating dosage tiers of BI836845 and afatinib (see Table 4.1.3.1: 1). Three patients will be treated at the starting dose level (dose level 1). If 1 out of 3 patients at that dose level experiences a dose limiting toxicity (DLT), then 3 additional patients will be treated at that dose level. If more than 1 out of 3 or more than 1 out of 6 patients at dose level 1 have a DLT, then the MTD has been exceeded and the dose is de-escalated to dose level -1. If 1 out of 3 patients experience a DLT at any dose level, then 3 additional patients will be treated at that dose level. If at dose level 1, 0 out of 3 patients or 1 out of 6 experiences a DLT, the dose will be escalated to dose level 2. If 0 or 1 out of 3 patients experience a DLT and dose level 2, then 3 additional patients will be treated at that dose level. If more than 1 out of up to 6 patients experiences a DLT at the lowest dose level -1, the trial will be discontinued, and no MTD could be established. Intra-patient dose escalation is not permitted.

For decision on dose escalation, please see Section 3.1.1. During the dose confirmation stage (Part A) of the study, the safety profile as well as DLTs will be discussed with the

investigator as well as a coordinating investigator. The decision on the next dose level or determination of the MTD will be documented.

Table 4.1.3.1: 2 Rules for dose escalation/de-escalation

Number of Patients with DLT at a Given Dose Level	**Escalation/de-escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2 out of 3	Dose de-escalation will commence. Three (3) additional patients will be entered at the lower dose level.
1 out of 3	Enter up to 3 more patients at this dose level. If 0 of these 3 additional patients experience DLT, proceed to next dose level. If 1 or more of these 3 additional patients experience DLT, then dose de-escalation will commence.
≤ 1 out of 6 at the highest dose level	This is the MTD (or maximal administered dose) to be considered as RP2D

4.1.3.2 Part B – dosing schedule

The decision on dose escalation/de-escalation, MTD and RP2D will be determined in discussion with a group of BI Trial Clinical Monitor, BI project physician (TMM) and investigators including Coordinating Investigator and taking into account patient safety. This decision will be documented and patients will be treated at the MTD/RP2D determined from Part A. For decision on MTD/RP2D determination, please see Section 3.1.1.

MTD/RP2D has been determined as Xentuzumab (BI 836845) 1000 mg/week plus afatinib 40 mg/day and it will be used as starting dose in Part B. However, in part B, for patients who had disease progression while on afatinib less than 40 mg/day, the starting dose is the last dose of afatinib. Alternative starting dose of afatinib must be discussed and agreed by Sponsor.

4.1.4 Drug assignment and administration of doses for each patient

The treatment medication assignment for Xentuzumab (BI 836845) and afatinib will be managed through an IRT system. In addition, patient's screening, dose assignment, all drug dispensation visits and EOTV will be collected in the IRT system.

4.1.4.1 Initial study drug assignment and administration

General information that applies to this study regardless of the IRT is described in below sections of each individual study drug. The medication kit as well as the treatment will be assigned with the support of the IRT system. The detailed information regarding handling of medication number will be described in ISF.

Before entering patients at the next dose level of Part A, it will be ensured that all patients at the current ongoing dose level have completed at least one course of treatment.

4.1.4.1.1 Xentuzumab (BI 836845)

Patients will start treatment with their assigned dose tier (see Section 4.1.3) or RP2D of Xentuzumab (BI 836845) from course 1 day 1. Xentuzumab (BI 836845) will be administered at the investigator site intravenously over one hour with a constant infusion rate on the treatment day as specified in the Flow Chart. No prophylaxis for infusion-related reaction is recommended at Course 1 Visit 1. Mannitol is used in the formulation of Xentuzumab (BI 836845), so an infusion duration of less than one hour must be avoided. The infusion time may be extended to over one hour and up to a maximum of three hours in cases of CTCAE grade ≥ 2 infusion reactions (see Section 4.2.3.4) for grading and management of infusion reactions). Further information on infusion equipment and procedure is described in the ISF. In case of a delay or an interruption of infusion, the reason and the exact time of deviation must be recorded in the eCRF. The accuracy of this information is crucial for the proper evaluation and appraisal of the pharmacokinetics and other data.

Detailed information of dispensation, preparation, and handling of Xentuzumab (BI 836845) will be described in ISF.

4.1.4.1.2 Afatinib

Patients will take a single oral dose of afatinib each day starting at their assigned dose-level (Part A) or RP2D (Part B), continuously during each treatment course. The medication should be taken at the same time each day (± 2 hours) without food (at least one hour before or at least three hours after a meal) to ensure a dose interval of approximately 24 hours.

If a dose is missed, it should be taken within the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped and the next scheduled dose at the usual time should be taken. Patients with emesis must not take a replacement dose.

The tablet should be swallowed with a glass of water (approximately 250 mL). Afatinib tablets should not be chewed or crushed, but may be administered after dispersing the afatinib tablets according to the following procedure: If dosing of whole tablets is not possible, afatinib tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 min until the tablet is broken up into very small particles. The dispersion should be drunk immediately. The glass should be rinsed with approximately 100 ml of water which should also be drunk. The dispersion can also be administered through a naso-gastric tube.

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment course. Treatment will start when the patient is taking the first dose of medication at course 1 Day1. Study drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

4.1.4.2 Additional course of treatment

The doses of Xentuzumab (BI 836845) and afatinib assigned upon entry to this trial will be used on all scheduled administrations described in the Flow Chart unless the patient experiences DLTs or treatment related adverse events which require dose modification.

Intra-patient dose escalation of either afatinib or BI 836345 is not allowed in this trial.

Patients demonstrating a clinical benefit (i.e., with either an objective tumour response or the absence of disease progression) with the trial drug, and who have recovered from any clinically relevant drug-related AE, are eligible for further treatment courses as per the Flow Chart until any of the conditions in Section 3.3.4.1 is met.

4.1.4.3 Temporary treatment interruption and dose reduction

DLTs or those AEs requiring dose adjustment as indicated within the prescribing information, should be managed by treatment interruptions and subsequent dose reductions of the presumed causal study drug(s) according to the schedule described in Table 4.1.4.3: 1. Please also refer to Section 4.2.3 for additional recommendations. In Part A, both Xentuzumab (BI 836845) and afatinib must be paused when a DLT occurs during the first treatment course. Dose reductions will apply to individual patients only and dose of Xentuzumab (BI 836845) and/or afatinib may be reduced independent of one another. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related AEs should be closely monitored and managed early and proactively as described in Section 4.2.3.

Treatment should be paused until a patient has recovered from a drug-related AE to grade ≤1 or baseline. Baseline is defined as the CTCAE grade at the start of treatment. For patients who develop a DLT, treatment may be resumed at reduced dose according to the dose reduction scheme of the patient's starting dosage (Table 4.1.4.3: 1). If a patient has not recovered to Grade ≤1 or baseline within 14 days, study treatment must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with study drug(s) will be decided in agreement between the sponsor and the investigator.

Diarrhoea and skin-related AEs are common side-effects of afatinib listed within the prescribing information. Please refer to the current afatinib prescribing information/SmPC for dose adjustment recommendations (except for the Course 1 of Part A if a DLT occurs, in which case both drugs need to be interrupted until AE recovery, refer to Section 5.2.6). When these AEs occur and are considered related to study treatment, the first dose modification is recommended to be made preferentially for afatinib.

In the event of any unrelated AEs or related non-DLT AEs, the investigator may choose to interrupt the medication (Xentuzumab (BI 836845) and/or afatinib) for up to 14 days, but no dose reduction should occur unless indicated in the current drug label/SmPC of afatinib. If the medication is interrupted for more than 14 days, the decision to continue with

Xentuzumab (BI 836845) and/or afatinib will be made by the BI clinical monitor in agreement with the investigator.

Applicable dose levels for weekly Xentuzumab (BI 836845) are 1000 mg and 750 mg. For afatinib, the applicable dose levels are 40 mg, 30 mg, and 20 mg. No dose reduction is allowed below 750 mg for Xentuzumab (BI 836845) or below 20 mg for afatinib. Patients who need further dose reduction which is not allowed according to protocol should be discontinued from that drug treatment. An exception to this rule can be considered upon discussion with BI's Clinical Monitor in patients who derive obvious clinical benefit according to the investigator's judgement. Alternative dose modification scheme can only be considered after discussion and agreement between the investigator and the BI clinical monitor.

Management of afatinib related adverse reaction and dose adjustment should be based on the European SPC or current prescribing information for afatinib of the respective country or institutional standard if not specified by protocol.

During temporary treatment interruption of Xentuzumab (BI 836845), the scheduled drug infusion will be skipped and will not be retrospectively administered.

Table 4.1.4.3: 1 Dose reduction scheme by AE type and CTCAE Grade (Part A and Part B)

AE type and CTCAE Grade	Action	Dose reduction scheme
Events related to study drug: - Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration - Nausea and/or Vomiting Grade 2 persisting for 7 or more consecutive days despite anti-emetic treatment/hydration - Reduced renal function to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline - Drug-related skin AE Grade ≥3	Pause afatinib treatment until patient has recovered to Grade ≤1 or baseline1. Xentuzumab (BI 836845) may be paused at the discretion of the investigator Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤1 or baseline within 14 days study treatment must be permanently discontinued[2].	**Afatinib** If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib. **Xentuzumab (BI 836845)** Reduce Xentuzumab (BI 836845) at investigator's discretion after interruption, but by no more than one level at a time. (1000mg (starting dose)->750mg (-1 dose level)) If patient need further dose reduction below 750 mg, discontinue BI836845.
Drug-related DLTs (see Section 5.2.6) or any other drug-related AE ≥ 3[3]	Pause afatinib and/or Xentuzumab (BI 836845) treatment until patient has recovered to Grade ≤1 or baseline1. In Part A, both afatinib and Xentuzumab (BI 836845) must be paused when DLT occurs in the first course. Resume treatment at reduced dose according to schedule opposite. Drug without interruption will maintain dose level. If patient has not recovered to Grade ≤1 or baseline within 14 days study treatment must be permanently discontinued[2].	**Afatinib** (if interrupted) If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib. **Xentuzumab (BI 836845)** (if interrupted) Reduce Xentuzumab (BI 836845) by not more than one level at a time. (1000mg (starting dose)->750mg (-1 dose level)) If patient need further dose reduction below 750 mg, discontinue BI836845.

Table 4.1.4.3: 1 Dose reduction scheme by AE type and CTCAE Grade (Part A and Part B) (Cont'd)

AE type and CTCAE Grade	Action	Dose reduction scheme
Acute onset and/or unexplained worsening of pulmonary systems (dyspnoea, cough, fever)	Pause afatinib and Xentuzumab (BI 836845) while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not drug-related, resume afatinib and Xentuzumab (BI 836845) at current dose. If AEs are drug-related, follow directions in row above. If ILD is confirmed, discontinue afatinib and Xentuzumab (BI 836845).
Xentuzumab (BI 836845) induced CTCAE grade ≥3 infusion-related reaction	No action on afatinib Pause BI836845	See specific guideline in Section 4.2.3.4

[1] Baseline is defined as the CTCAE Grade at the start of treatment
[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib and/or Xentuzumab (BI 836845) will be decided in agreement between the BI clinical monitor and the investigator.
In the event of any unrelated adverse events, the investigator may choose to interrupt the medication (afatinib and/or Xentuzumab (BI 836845)) for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with afatinib and/or Xentuzumab (BI 836845) will be made by the BI clinical monitor in agreement with the investigator.
[3] except alopecia, infusion reaction and allergic reaction

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable. This is an open-label trial.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

For details of drug supply, refer to Section 4.1.1.

Boxes and vials of Xentuzumab (BI 836845) and boxes of afatinib will be labelled according to local regulations and will include the following as a minimum:

- The study number (1280.16)

- 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 Xentuzumab (BI 836845) and afatinib drug supply will be managed through Interactive Response Technologies (IRT) by the study sites and BI personnel. Refer to the ISF for details of packaging and the description of the label as well as the process for resupply of study drug.

4.1.7 Storage conditions

Trial medication (afatinib and Xentuzumab (BI 836845)), which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined below until supplied/administered to patient. 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, this has to be reported in the ISF and the sponsor be notified.

4.1.7.1 Afatinib

Afatinib must be stored in the original package in order to protect from light. Film-coated tablets are humidity-sensitive; therefore, bottles must be kept tightly closed to protect from moisture. Tablets must be stored according to label instructions.

4.1.7.2 Xentuzumab (BI 836845)

Investigational drug supply of Xentuzumab (BI 836845) must be stored in the original packaging and will be stored in accordance with the instructions on the label.

A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator (e.g. pharmacist or study drug storage manager) will receive the study drug(s) delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- 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 licence for the principal investigator.

The investigator or delegate 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 product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator or delegate 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. At the time of return to the sponsor and/or appointed CRO, the investigator or delegate must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment

Rescue medications to reverse the action of afatinib or Xentuzumab (BI 836845) are not available. Potential side effects of afatinib and/or Xentuzumab (BI 836845) have to be treated symptomatically.

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, analgesia etc., according to local practice/guidelines where appropriate. Anti-emetic medication should be prescribed according to local practice.

Precaution should be taken to avoid extravasation of Xentuzumab (BI 836845). Patients should be asked to report any pain or burning at the site of injection immediately. If extravasation is suspected the infusion should be stopped immediately. Treatment should be initiated according to local practice

Common adverse events of treatment with afatinib or Xentuzumab (BI 836845) with specified management recommendations and/or requirements include diarrhoea, and rash/acne. To improve tolerability and the probability of clinical benefit, patients should

receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described in Section 4.2.3.

Symptomatic treatments of side effects or tumour-associated symptoms are allowed.

Concomitant treatments

Concomitant medications or therapy to provide adequate care may be given as clinically necessary.

After study enrolment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for tumour response assessment. During palliative radiotherapy, study treatment should be delayed and may be resumed once the patient has recovered from any radiation associated AE. If medication is interrupted for more than 14 days, the decision to continue will be made by the BI clinical monitor in agreement with the investigator. Continuous interruption of >14 days due to palliative radiotherapy will not be allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib/Xentuzumab (BI 836845) around one week prior to the surgery, and to restart treatment after complete wound healing. If afatinib/Xentuzumab (BI 836845) is interrupted for more than 14 days, the decision to continue will be made by the BI Clinical Monitor in agreement with the investigator.

Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.

Palliative radiotherapy may be given as described in Section 4.2.1.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate for decreased appetite), or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Any concomitant medication should be reduced to the clinically necessary minimum on the days of Xentuzumab (BI 836845) infusion.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with P-gp modulators. For a list of potent P-gp inhibitors and inducers (refer to Appendix 10.1).

Antiplatelet medications (e.g. acetylsalicylic acid) should be discontinued 7 days prior to tumour biopsy. Anticoagulant medications should be discontinued prior to tumour biopsy. Warfarin should generally be discontinued at least 5 days prior to tumour biopsy. In all patients, the risk of discontinuing antiplatelet and/or anticoagulant medications must be weighed against the (potential) risk of bleeding during/after biopsy. Antiplatelet and anticoagulant may be restarted after tumour biopsy by the judgment of the investigators.

4.2.2.2 Restrictions on diet and life style

Patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea see Section 4.2.3.1.

To prevent skin related AEs, intense irradiation with UV light should be avoided, see also Section 4.2.3.2.

Patient has to show up in fasting condition at the site for analysis of specific blood parameters when safety lab is required.

4.2.2.3 Women of Child-Bearing Potential and Pregnancy Prevention

Patients who are not of childbearing potential due to being postmenopausal (1 year without menstruations and at least 2 years without menstruation following chemotherapy) or surgical sterilisation (oophorectomy and/or hysterectomy) do not need to use contraception to be eligible for the trial.

All other patients are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until end of trial participation or 2 months after last dose of trial medication, whichever is later).

Acceptable methods of contraception include surgical sterilisation and double barrier method, and must be in accordance with local regulations where applicable. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and intrauterine device (UID) (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). Those using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in Section 5.2.2.2.

4.2.3 Management of expected adverse events

Dermatologic AEs and diarrhoea are the most common side effects associated with treatment with afatinib. Treatment of these side effects should be proactive and should be started as early as possible after onset of symptoms, and recommendations for management are described below.

4.2.3.1 Management of diarrhoea and hydration status

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to study treatment with afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.3.1: 1). At the time of initiation of treatment with afatinib and Xentuzumab (BI 836845), patients should be given a supply of loperamide to keep with them at all times; and patients should be counselled on the appropriate use. In addition to diarrhoea management described in Table 4.2.3.1: 1, upon onset of diarrhoea CTCAE grade ≥1, patient should take racecadotril (Tiorfan 100 mg), if available, 1 tablet twice daily (morning and evening) to be continued until recovery at the investigator's discretion.
For the use of anti-diarrhoeal medication, please refer to latest version of local drug label.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea.

Table 4.2.3.1: 1 Grade specific treatment recommendations for diarrhoea

Severity (CTCAE grade)	**Description****	**Intervention concerning afatinib**	**Specific intervention**
Grade 1	• Increase of <4 stools per day over baseline • Mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Grade 2	• Increase of 4-6 stools per day over baseline • i.v. fluids indicated <24 hours • Moderate increase in ostomy output compared with baseline • Not interfering with activity of daily life (ADL)	Continue same dose **unless grade 2 diarrhoea continues for ≥ 2 days (48 hours)** in which case afatinib must be interrupted until recovered to grade ≤1 followed by dose reduction	• Continue loperamide • Assess for dehydration and electrolyte imbalance • Consider i.v. fluids and electrolyte replacement
Grade 3	• Increase of ≥7 stools per day over baseline • Incontinence • i.v. fluids >24 hours • Hospitalisation • Severe increase in ostomy output compared with baseline • Interfering with ADL	Also see Section 4.1.4.3. Dose interruption until recovered to grade ≤1 followed by dose reduction*	• See grade 2, plus: • An infectious process should be ruled out with stool cultures • Aggressive i.v. fluid replacement ≥24 hours • Hospitalisation to monitor progress • Consider prophylactic antibiotics if patient is also neutropenic
Grade 4	• Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to grade ≤1 followed by dose reduction*	• See grade 3

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTCAE Grade ≤ 1 within 14 days, treatment with afatinib and/or Xentuzumab (BI 836845) must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib and/or Xentuzumab (BI 836845) will be decided in agreement between the sponsor and the investigator.
** May refer to CTCAE version 4.03 for updated description of grading

4.2.3.2 Management recommendations for dermatological AEs

Dermatologic AEs include rash, acneiform, dermatitis and dry skin. A proactive and early approach to management is crucial, and depending on the investigator's own clinical experience, early involvement of a dermatologist and/or prompt institution of therapy such as

a topical (e.g. clindamycin) and /or oral (e.g. minocycline) antibiotic amongst other measures (Table 4.2.3.2:1 & Table 4.2.3.2:2) should be considered at onset of a rash CTCAE grade ≥1.

Dermatological events can be managed by a variety of treatment options to relieve symptoms and reduce skin reaction. General recommendations for prophylaxis are summarized in Table 4.2.3.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.3.2: 2. Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered (adapted from Potthoff et al., R11-0826).

Table 4.2.3.2: 1 General recommendation for skin reactions prophylaxis

Personal hygiene	• Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water • Use of very mild shampoos for hair wash • Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided • Fine cotton clothes should be worn instead of synthetic material • Shaving has to be done very carefully • Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	• Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended • Patients should be encouraged to consequently stay out of the sun • Protective clothing for sun protection and wearing a hat should be recommended
Moisturizer treatment	• It is important to moisturize the skin as soon as anti-EGFR therapy is started • Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness • Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications
Prevention of paronychia	• Patients should keep their hands dry and out of water if ever possible • They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail • Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions

Severity (CTCAE grade)	Description[1)]	Specific intervention
ACNEIFORM RASH		
Grade 1	Macular or papular eruptions or erythema without associated symptoms	• Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1% • Isolated scattered lesion: cream preferred • Multiple scattered areas: lotion preferred
Grade 2	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	• Topical treatment as for grade 1, *plus* • short term topical steroids, e.g. prednicarbate cream 0.02%, *plus* • an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d.
Grade 3	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	• Topical and systemic treatment as for grade 2. • Consider referral to dermatologist • Consider systemic steroids • See Section 4.1.4.3 for dose modification
Grade 4	Generalized exfoliative, ulcerative, or bullous dermatitis	• See grade 3 • Systemic steroids are recommended
EARLY AND LATE XEROTIC SKIN REACTIONS – PRURITUS		
Grade 1	Mild or localized	• Topical polidocanol cream • Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine)
Grade 2	Intense or widespread	• See grade 1, *plus* • oral antihistamines • Consider topical steroids, e.g. topical hydrocortisone
Grade 3	Intense or widespread and interfering with ADL	• See grade 2 • See Section 4.1.4.3 for dose modification
XEROSIS (DRY SKIN)		
Grade 1	Asymptomatic	• Soap-free shower gel and/or bath oil • Avoid alcoholic solutions and soaps • Urea- or glycerine-based moisturizer • In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Grade 2	Symptomatic, not interfering with ADL	• See grade 1 • In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Grade 3	Symptomatic, interfering with ADL	• See grade 2 • Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) • Consider oral antibiotics • See Section 4.1.4.3 for dose modification

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions (con'd)

Severity (CTCAE grade)	Description[1)]	Specific intervention
FISSURES		
Grade 1	Asymptomatic	• Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths) • Topical application of aqueous silver nitrate solutions to fissures
Grade 2	Symptomatic, not interfering with ADL	• See grade 1 • Consider oral antibiotics. • Afatinib and/or Xentuzumab (BI 836845) treatment interruption
Grade 3	Symptomatic, Interfering with ADL	• See grade 2

1) May refer to CTCAE version 4.03 for updated description of grading

* If grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause afatinib and/or Xentuzumab (BI 836845) treatment up to 14 days followed by a reduction in the dose of afatinib and/or Xentuzumab (BI 836845) according to the dose reduction scheme in Table 4.1.4.3: 1.
If despite optimal supportive care and a treatment pause, grade 2 rash does not resolve to CTCAE Grade ≤ 1 within 14 days, treatment with afatinib and/or Xentuzumab (BI 836845) must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib and/or Xentuzumab (BI 836845) will be decided in agreement between the sponsor and the investigator.

**CTCAE grade 3 (or greater) rash: may be treated in a manner similar to CTCAE grade 2 rash. In the event of CTCAE grade ≥3 rash, treatment with afatinib and/or Xentuzumab (BI 836845) should be paused until recovery to CTCAE grade ≤1. Treatment should be resumed at a reduced dose (Table 4.1.4.3: 1). If CTCAE grade ≥3 rash does not resolve to CTCAE grade ≤1 within 14 days of stopping afatinib and/or Xentuzumab (BI 836845) treatment and despite optimal supportive care, the patient should not receive any further treatment with afatinib and/or Xentuzumab (BI 836845) and the End of Treatment visit should be performed.

4.2.3.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.3.3:1. For dose adjustment refer to Section 4.1.4 and for restrictions on concomitant therapies refer to Sections 4.2.2 and Appendix 10.1.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.3.3:1 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from P11-09424)

Mouth washed with steroids (not to be swallowed) should be considered for oral ulcers as soon as they appear for CTCAE grade ≥1 until recovery at the investigator's discretion.

Table 4.2.3.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description*	Treatment recommendations	Intervention concerning afatinib treatment/ dose modification
Grade 1	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash with steroids (not to be swallowed), normal saline, diluted salt and baking soda solution .	No change .
Grade 2	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Grade 3	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4
Grade 4	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4

* May refer to CTCAE version 4.03 for updated description of grading

4.2.3.4 Management and grading of infusion reactions

The study drug infusions should always be administered in a hospital environment and under close supervision of the medically qualified staff member with immediate availability of appropriate resuscitation facilities.

Infusion reactions may occur during infusion with Xentuzumab (BI 836845) and include pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension and hypertension. **A one hour observation period is recommended following each infusion.** Mild to moderate infusion reactions may be managed with a slower infusion rate and prophylactic antihistamines for subsequent dosing. Severe reactions require immediate and permanent discontinuation of infusion. The grading of hypersensitivity reactions will be according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R10-4848).

Table 4.2.3.4: 1 Infusion reaction management

Infusion Reaction Grade	Management
CTCAE Grade 1 or 2	In the event of a mild to moderate CTCAE grade 1 or 2 non-allergic infusion event, the infusion rate should be reduced by 50%. Once the event has resolved the investigator should wait and deliver the infusion at the reduced rate for another 30 minutes. If tolerated, the infusion rate may then be increased to the next close rate on the patient's infusion schedule. In case of a Grade 2 event that requires therapy (e.g., antihistamines, NSAIDs, steroids, narcotics, IV fluids) or infusion interruption and resolves promptly the infusion may also be re-started at half of the infusion rate at the time of onset of the reaction.
CTCAE Grade 3	For patients experiencing CTCAE grade 3 infusion related event, infusion should be interrupted immediately and patients should receive aggressive symptomatic treatment. Only after all the symptoms have disappeared the infusion should be started. The infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.
CTCAE Grade 4	Patients experiencing CTCAE grade 4 such as anaphylaxis during an infusion should have infusion immediately stopped and receive appropriate treatment including use of resuscitation medications and equipment that must be available. Such patients should be withdrawn from treatment and should be followed up.

The infusion duration may be extended to over one hour and up to a maximum of three hours, see Section 4.1.4.1.1.

The infusion reactions should be treated symptomatically as judged clinically relevant by the investigator. For symptomatic treatment of infusion reactions: hydrocortisone, antihistamines such as chlorphenamine accompanied by an antipyretic/analgesic and/or a bronchodilator is recommended.

4.2.3.5 Management of hyperglycemia

In case of hyperglycaemia, treatment should follow standard and/or local guidelines and may include oral antidiabetics such as metformin 1g to 2.5 g/d. The appropriate expert advice should be considered in the management of hyperglycemia.

In case of a grade 3 or higher hyperglycemic event, the patient should have immediate access to consultation with an endocrinologist or specialist. When treatment with the study drug is discontinued, the need for further antidiabetic treatment has to be evaluated depending on the blood glucose levels of the patient.

4.3 TREATMENT COMPLIANCE

Xentuzumab (BI 836845) will only be administered by trained staff in participating sites. Date and time of start and end of infusion, the exact amount of drug administered at each infusion will be documented in the eCRF/ study medication form.

Afatinib will be given in accordance with the protocol and the instructions of a site investigator.

The appropriate number of afatinib tablets for 4-week treatment course will be provided to patients to be self-administered at home. Patients will be asked to bring the remaining trial medication at the end of each 4-week course to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each 4-week course, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. For afatinib, a maximum of 6 consecutive doses or 7 non-consecutive doses may be missed for other reasons than drug-related AEs. Patients who miss afatinib treatment more frequently are considered non-compliant.

Afatinib should not be taken more than once a day. Patient experiencing emesis should not take a replacement dose.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy (anti-tumour activity)

5.1.1.1 Dose confirmation Part A

There are no formal efficacy endpoints for the dose confirmation part, as this is mainly concerned with the determination of the MTD/RP2D of Xentuzumab (BI 836845) in combination with afatinib. However, anti-tumour activity will also be assessed by tumour measurement and evaluation.

5.1.1.2 Expansion Part B

Primary endpoint

The primary endpoint for Part B is the objective response (OR), defined as complete response (CR) or partial response (PR).

Secondary endpoints

- Disease control (DC), defined as complete response (CR), partial response (PR) or stable disease (SD).
- Time to objective response, defined as the duration of time from the date of first treatment administration until objective response.
- Duration of objective response, defined as the duration of time from first objective response to the date of first objective tumour progression or death due to any cause.

Patients with measurable and evaluable disease should have assessment according to RECIST version 1.1.

5.1.2 Assessment of efficacy

The assessment by the investigator and the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety).

Tumour assessment will be performed every 4 weeks after start of treatment with Xentuzumab (BI 836845) and afatinib for first 8 weeks (prior to courses 2 and 3),in 8-week intervals thereafter (e.g. prior to courses 5, 7, 9, etc.) and in 12-week interval after course 16

until PD or start of further anti-cancer treatment . Imaging may be performed within 7 days of scheduled time point. In case of tumour response (CR or PR), confirmation will be performed with a repeat assessment no less than 4 weeks after the RECIST criteria for response have been met. In the case of SD, measurement must have met the SD criteria at least once after study entry at an interval of not less than 6 weeks.

CT/MRI images not older than 30 days at start of treatment will suffice as screening images and don't have to be repeated. The EOT tumour assessment is optional if performed within the previous 4 weeks. At baseline, the investigator along with the radiologist will record the target (five target lesions maximum and maximum two per organ) and non-target lesions at baseline in the eCRF before the start of treatment. The same method of assessment and the same technique should be used to characterise each reported lesion at baseline and during follow up. Measurable lesion should be available after tumour biopsy. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. Response will be evaluated according to the response evaluation criteria in solid tumours (RECIST version 1.1, R09-0262 – Appendix 10.5). In the event of a delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule. The schedule should be followed until progression is observed or until the patient commences further treatment for disease, whichever occurs first.

5.2 SAFETY

5.2.1 Endpoints of safety

5.2.1.1 Dose confirmation Part A

The determination of the MTD/RP2D is the primary objective of Part A of this study and it will be based in occurrence of DLTs during the first treatment course. The MTD, together with the safety profile (if required, pharmacokinetic- and pharmacodynamic parameters) will serve to define the recommended phase II dose (RP2D) to be used for further trials in the development of Xentuzumab (BI 836845) in combination with afatinib.

Primary endpoints:
- Maximum tolerated dose (MTD) of Xentuzumab (BI 836845) in combination with afatinib
- Dose limiting toxicity (DLT) during the first treatment course

5.2.1.2 Expansion Part B

There are no formal safety endpoints for the expansion cohort in Part B of this trial. However, evaluation of safety data will be performed and presented separately for the expansion cohort.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Patients may be hospitalized for administrative reasons during the trial (e.g. days on which pharmacokinetics sampling takes place). These and other hospitalizations planned at the beginning of the trial will not be considered as SAE if they have been reported at the screening visit in the source documents and performed as planned. Pre-existing conditions at baseline other than the disease will not be recorded as Adverse Events if they remain unchanged during the trial.

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the eCRF.

Causal relationship of adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

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

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

If progressive disease occurs and is associated with symptoms , the term “Progressive Disease” should not be reported as AE, however, signs and symptoms of progressive disease will be reported as an (S)AE (if applicable). In this case Progressive Disease should be

documented on the CRF referencing also the AEs documented in the AE module of the CRF. Exception to this: Death due to progressive disease and where no signs or symptoms are available should be reported as "malignant neoplasm progression (grade 5, outcome fatal)."

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Protocol-specified Adverse Events of Special Interest (AESI)

The following are considered as Protocol-specified Adverse Events of Special Interest:

- Hepatic injury defined by the following alterations of liver parameters:
    - For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits) at baseline:
      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 draw sample. Patients showing these lab abnormalities need to be followed up according to Appendices 10.6 this clinical trial protocol and the "DILI checklist" provided in *ISF*.

    - For patients with abnormal liver function tests at baseline (AST and/or ALT>ULN):
      an elevation of transaminase ≥ (baseline + 4 fold ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, with the exclusion of the causes due to underlying diseases. Patients with abnormal liver function tests must have their abnormalities and the etiology documented in detail as baseline conditions. Every effort should be made to exclude the worsening of liver function due to underlying diseases.

  Although rare, drug-induces liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety

- DLT occurs in the Part A. Please refer to Section 5.2.6 for definition of DLTs.

Protocol-specified AESI are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the end of the follow-up period)

will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The residual effect period (REP) for Xentuzumab (BI 836845) is 42 days. Therefore all events reported within 42 days after the last trial medication will be considered on treatment. All adverse events will be reported up until last follow up visit. The investigator does not need to actively monitor patients for adverse events during the observation period or once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred during the observation period or after the patient has completed the clinical trial, it should be reported by the investigator to the sponsor if considered relevant by the investigator, see Table 5.2.2.2:1.

Table 5.2.2.2: 1 AE/SAE reporting requirements

Time period	Reporting requirements
From signing of informed consent until last follow up visit (including 42 days after last trial drug administration and beyond if required)	Report all AEs and SAEs regardless of relatedness or whether the trial drug was administered. This includes all deaths.
Observation period (after the patient completed last follow-up and when progression occurred or when new anti-cancer therapy started)	The investigator may report SAE if s/he becomes aware of and considers relevant. Death should not be reported as an SAE except when it is considered related to trial treatment or trial design (because death is an outcome endpoint and will be followed up separately).

If not stipulated differently in the ISF, the investigator must report the following events via telephone/fax or if available for the trial, using the electronic submission process (RDC) immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant to the SAE(s), and protocol-specified AESI.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the

item “serious” needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

With receipt of any further information to the adverse events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File) or by using the electronic submission process. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified AESI becomes available.

AEs which are not yet recovered at the End of Treatment (EOT) visit will be followed up until recovery or, in case of persistence, sufficient characterization of the AEs has been achieved and the investigator and the BI Clinical Monitor agree not to pursue them further.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Blood samples, including fasting serum samples (fasting state for at least 12 hours) will be collected up to two days prior to the scheduled time points as specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations include hematology, coagulation, biochemistry and urine examination. See Table 5.2.3: 1 for details. In case of abnormal findings such as neutropenia or thrombocytopenia, blood will be examined as clinically indicated at the discretion of the investigator. All analyses are to be performed by the local clinical laboratory. Unscheduled safety laboratory examinations will be documented in the eCRF along with the results.

Safety laboratory assessment may be performed according to local practice but must include at least the following parameters:

Table 5.2.3: 1 Clinical laboratory tests

Category	Parameters
Hematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, white blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	Blood urea/blood urea nitrogen (BUN), creatinine, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), bilirubin (total and direct), albumin, total protein, creatine phosphokinase (CPK); in case of pathological CPK further evaluation (e.g by determination of isoenzymes, troponin assays, ECG exam) should be performed as clinically indicated
Electrolytes	Sodium, potassium, calcium, magnesium
Other (fasting)	Glucose and HbA1C
Urinalysis	pH, protein, glucose, erythrocytes, leucocytes, ketones and nitrite will be analyzed by dipstick (semi-quantitative measurements: -, +, ++, +++); in case of pathological finding further evaluation should be performed and results documented

5.2.4 Electrocardiogram

A standard 12-lead resting ECG will be performed locally at the time points specified in the Flow Chart.

- Screening
- Pre-infusion, during infusion (after 30±5 min) and immediately prior to the end of the infusion (-10 min) on Day 1 of Course 1
- A single ECG to be taken pre-infusion on Day 15 of Course 1, pre-infusion at the start of every course on Day 1
- EOT visit

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination, vital signs, height and weight

The physical examination must include cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination must be clarified. Wherever possible the same investigator should perform this examination.

The physical examination will be done at screening visit and at the time points specified in the Flow Chart. A symptom-directed examination is to be performed on all other visits.

Vital sign measurements of blood pressure (systolic blood pressure, diastolic blood pressure), pulse rate, temperature and measurement of height (in cm, at screening) and body weight (in kg) and the evaluation of the ECOG performance status will be performed at the times specified in the Flow Chart.

5.2.5.2 Left ventricular fraction

Left ventricular ejection fraction (LVEF) as measured by echocardiography or multiple gated acquisition (MUGA) will be assessed at time points specified in the Flow Chart. LVEF assessment after start of study treatment may be performed if clinically indicated. The same method of measurement should be used throughout the study.

5.2.6 Dose Limiting Toxicity

The primary endpoint of Part A of this trial is the occurrence of Dose Limiting Toxicity (DLT).

For definition of DLT, it is essential that patients are treated sufficiently according to supportive care standards. DLT is assessed throughout the Part A. A study drug-related adverse event constitutes a DLT, if one of the following applies:

- CTCAE Grade 4 neutropenia ($< 0.5 \times 10^9$/L) lasting ≥ 7 days
- Febrile neutropenia ANC$< 1.0 \times 10^9$/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour.
- Documented infection with ANC $< 1.0 \times 10^9$/L
- CTCAE Grade 4 thrombocytopenia ($< 25.0 \times 10^9$/L) or CTCAE Grade 3 thrombocytopenia associated with bleeding requiring platelet transfusion.
- CTCAE Grade 2 or higher decrease in cardiac left ventricular function
- CTCAE Grade 2 diarrhoea lasting for 7 days or more, despite appropriate use of standard anti-diarrhoeal therapy
- CTCAE Grade ≥3 diarrhoea despite appropriate use of standard anti-diarrhoeal therapy for at least two days

- CTCAE Grade ≥3 nausea and/or vomiting despite appropriate use of standard anti-emetics for at least three days
- CTCAE Grade ≥3 skin rash despite standard medical management as outlined in Section 4.2.3.2
- AST or ALT > 5x ULN (for baseline AST/ALT ≤ ULN) or > (baseline value + 4x ULN) (for baseline AST/ALT > ULN)
- CTCAE Grade ≥3 fatigue/asthenia lasting for more than seven days
- CTCAE Grade ≥3 hyperglycemia lasting > 48 hours
- All other non-hematologic adverse events of CTCAE Grade ≥3 (except alopecia, infusion reaction, and allergic reaction) leading to an interruption of afatinib and/or Xentuzumab (BI 836845) for more than 14 days until recovery to baseline or Grade 1, whichever is higher
- Any other study drug related toxicity considered significant enough to be qualified as DLT in the opinion of the investigators (e.g. AE which not defined as DLT but requires dose reduction according to afatinib label) and confirmed by the safety review with the BI clinical monitor and BI project physician (TMM), will be reported as a DLT.

For the purposes of MTD determination, only DLT events that occur during the first treatment course of 28 days will be considered. Decisions regarding dose escalation/de-escalation steps will be made only after discussion between the sponsor and the investigators at all sites, and in consideration of the available AE data. DLTs occurring after first treatment course and all unusual/unexpected AE during the whole treatment will be considered for the purpose of recommending the dose for Part B.

5.2.7 Maximum Tolerated Dose and recommended phase II dose

The Maximum Tolerated Dose (MTD) is defined as the highest dose level studied for which the incidence of DLT is no more than one out of 6 patients during the first course. DLTs occurring after the start of the second treatment course will be analyzed separately. DLTs will only be investigated in Part A of the study.

For the definition of DLT and determination of MTD refer to Sections 5.2.6 and 4.1.3.1.

The MTD will be defined on the basis of DLT observed during the first treatment course only. However, also DLTs after that time period will be considered for the purpose of determination of recommended phase II dose (RP2D). The MTD, maximal administered dose, or a lower dose level will be chosen as the RP2D based on the totality of the safety data available. The discussion and agreement on dose selection between the investigator and the sponsor will be documented and communicated to all participating sites.

5.3 OTHER

5.3.4 Demographics and medical history

The following patient demographic, baseline characteristics and medical history will be collected on the eCRF:

- Demographics including sex, date of birth, ethnicity, race if allowed by local law, information on smoking and alcohol history.
- Medical history and baseline conditions will be collected during the screening visit. Relevant concomitant diagnoses and/or therapies present at study entry and/or during screening and relevant to the patient's safety during the study as judged by the investigator will be recorded in the eCRF.
- History of lung cancer will also be obtained. The histological subtype, the date of the first histological diagnosis (month and year may be sufficient), tumour Stage according to the

TNM-classification at diagnosis, and the primary tumour site will be reported on the eCRF. The differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated), the number and location of metastatic sites (bone, liver, lung, pleural effusion, brain, other) at study entry will be provided.

- Previous surgeries and radiotherapy will be reported. Previously administered chemotherapy, tyrosine kinase inhibitors treatment, vaccine-therapy, antibodies therapy, immuno-therapy, and hormone-therapy will be reported including start and end dates (month and year may be sufficient) as well as the number of courses (when applicable), the best response obtained (complete response, partial response, stable disease, progressive disease, unknown), the reason leading to treatment discontinuation (completion, PD, AE) as well as the therapy mode (neoadjuvant, adjuvant or palliative). The date of tumour progression after previous line(s) of therapy for advanced or metastatic disease will be documented.
- Previous EGFR mutation status of the original tumour will be recorded if available.

5.4 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumours. Response evaluation criteria in solid tumours (RECIST version 1.1) are used for assessment of the change in tumour burden. These criteria are well established and well received by the regulatory authorities and scientific community.

The CTCAE criteria are used in the assessment of adverse events in cancer patients. In the present trial CTCAE version 4.03 (R10-4848) will be used.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients must provide written informed consent (ICF) before any study related screening procedures can be performed. A diagram of the stages of a patient's participation in this trial is included in Section 3.1, and allowable time windows for visits are included in the Flow Chart.

Investigational drugs Xentuzumab (BI 836845) and afatinib will be dispensed at visit according to the Flow Chart. Patients will receive a new medication kit through the IRT system on each occasion for medications supplied by the sponsor.

Tumour assessments at screening must be completed within 30 days of start of treatment. However, upon clinical assessment if a patient presents with clinical symptoms of progressive disease, the investigator may use clinical judgement to determine whether to have the patient undergo another scan prior to starting treatment. All other screening assessment must be completed within 42 days of start of treatment.

All patients are to adhere to the visit schedule as specified in the Flow Chart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. The date and reason for the rescheduled visit should be noted in the source documentation. In the event of any study drug interruption or delay of treatment, the tumour assessment schedule should not be changed. Scheduled visit which coincides holiday and can't be adjusted within time window may be skipped after discussion with BI Clinical Monitor.

Blood samples for pharmacokinetics, biomarkers and pharmacogenetics will be collected from all patients. Tissue and blood samples will be collected for biomarkers from both treatment arms; For specific PK, biomarker and pharmacogenetics sampling schedule refer to Section 5.3, 5.5 and Appendix 10.7. Actual clock time for study drug administration and for each blood draw needs to be documented in the eCRF.

On visit days when PK sampling is scheduled, afatinib should be administrated during the clinical visit. On visit days when safety lab is scheduled, patients should show up in fasting condition.

Adverse events and concomitant medication must be collected starting from the date of ICF being obtained until the last follow-up visit.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Refer to the Flow Chart for procedure details. Please review Sections 3.3.2 and 3.3.3 for specific eligibility criteria for Part A and Part B.

Screening procedures must be performed within 42 days of start of treatment. Patients who failed screening may repeat the screening after discussion between investigator and sponsor providing that reasons for screening failure were reversible and have resolved.

The provision of tumour tissue is mandatory. An archival tumour tissue must be collected at screening visit for biomarker analysis. If an archival tumour sample is not available, tumour biopsy must be performed during screening period.

In case there is a documented result of EGFR mutations available before study entry, local result will be accepted in Part A. In the Part B, the eligibility criteria of EGFR mutations must be based on the results of the authorized central laboratory.

6.2.2 Treatment period

Every treatment course is 28 days. In case a patient misses the scheduled study visit but reports to the investigative site before the next scheduled study visit, the missed visit will be performed. The current date and reason for the delayed visit will be noted in the source documentation. All subsequent study visits should take place at the next scheduled visit the Flow Chart. In the event of any study drug interruption or delay of treatment, the tumour assessment scheduled will not be changed. The missed scheduled Xentuzumab (BI 836845) administration will be skipped if the patient reports to the investigator outside the time window specified in Flow Chart.

In this trial, patients may be hospitalized for the day of treatment and PK sampling at the discretion of the investigator; patients may be discharged if tolerated the treatment well and no safety concerns are present as judged by the investigator.

Refer to the Flow Chart for procedure details.

6.2.3 End of trial and follow-up period

6.2.3.1 End of treatment visit

The End of Treatment (EOT) visit should be performed within14 days after permanent discontinuation of study drug (Xentuzumab (BI 836845) and afatinib). If the last administration of study drug occurs during a scheduled visit, examinations as defined for EOTV should be performed instead of the examination for the scheduled visit.

The patient must return all study drugs, and the site must document why the patient is discontinuing the treatment.

Blood samples for soluble biomarkers, PK and immunogenicity must be obtained.

In patients who are experiencing disease progression at EOTV, an optional fresh tumour biopsy might be performed from those with appropriate informed consent in case patient agrees to provide tumour samples after progression.

Refer to Flow Chart for details.

6.2.3.2 Follow-up

The residual effect period (REP) for Xentuzumab (BI 836845) is 42 days. Therefore all events reported within 42 days after permanent discontinuation of trial medication will be considered as 'on treatment'. At the end of REP, the first follow-up visit (FU1) is to be performed.

All patients should have a follow-up visit 42 days (+ **7** days) after permanent discontinuation of study drugs. At this follow-up visit, an end of trial assessment will be performed and documented in the e-CRF.

Additional follow-up visits at 8-week intervals should be performed for patients who are not progressed or new anti-cancer treatment has not been started according to the Flow Chart.

Follow-up period for every patient will end at the earliest of the following events:

- Lost to follow-up
- Disease progression
- Initiation of a new anti-cancer therapy
- Death
- End of whole trial as specified in Section 6.2.3.5

The following will be obtained and/or performed during the follow-up visits.

- Record any new AEs or SAEs and follow-up of ongoing adverse events
- Concomitant medications for treatment of an adverse event including trade name, indication and dates of administration
- Tumour assessment and imaging will be performed if applicable.
- Treatment and date with any other anti-cancer drug and/or best supportive care including the name and type of the anti-cancer drug
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD will be recorded)

Follow-up of patients with AEs which have not recovered at the last planned follow-up visit, please refer to Section 5.2.2.2.

6.2.3.3 Observation period

There is no observation period in Part A.

All patients in Part B will be followed-up for overall survival every 90 days (± 15 days) after the last follow-up visit (as specified in Section 6.2.3.2) until death, lost to follow-up or completion of the whole trial (as specified in Section 6.2.3.5) whatever occurs earlier.

For patients who progressed on treatment, this period starts after the FU1 visit. For patients who have not progressed on treatment, this period starts after the last follow up visit.
No further AE/SAE collection is needed unless considered relevant by the investigator.
Follow-up of AEs not yet recovered at the last follow up visit will continue.

These visits may also be performed by telephone interview in case the patient is unable to visit the investigator.
The following information will be collected during the observation period:

- Date and method of contact
- Further anti-cancer treatment : regimen and drugs name, start and stop dates, reason for stopping this treatment
- Information on death
- Follow-up of adverse events in case they were not yet recovered at last follow up visit

6.2.3.4 Patient completion

A patient has to be considered to have completed the trial if no further information is collected, i.e. in case any of the following applies:

- Completion of planned observation period
- Lost to follow-up
- Death

6.2.3.5 End of whole Trial

The end of the trial (both parts) will be when the last patient has completed the first follow-up visit (FU1) as defined in Section 6.2.3.2.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The trial will be performed as an open label study. The primary objective of the dose confirmation part of the trial is to determine the MTD/RP2D of Xentuzumab (BI 836845) in combination with afatinib in patients with NSCLC with progression following prior treatment (EGFR TKI or platinum based chemotherapy). To do so, patients are entered sequentially into escalating/de-escalating dose tiers. Patients will be included into the study following a3+3 design with escalating/de-escalating steps (Edler and Burkholder in Crowley R07-0220, see also Section 4.1.3). After the determination of MTD for Xentuzumab (BI 836845) in combination with afatinib, 6 additional patients will be included at this dose level for the evaluation of the RP2D.

In the expansion cohort of Part B, 18 additional patients will be entered. These patients must be diagnosed with EGFR mutant NSCLC and must have been progressed following prior TKIs. They will be treated with Xentuzumab (BI 836845) in combination with afatinib at the RP2D found in the dose confirmation part of the study. For patients who had disease progression while on afatinib less than 40 mg/day, the starting dose is the last dose of afatinib.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this trial are descriptive and exploratory. No formal statistical tests will be performed.

7.3 PLANNED ANALYSES

All patients who are treated with at least one single dose of Xentuzumab (BI 836845) or afatinib will be included in all efficacy and safety analyses.

During Part A, cohorts of patients treated with Xentuzumab (BI 836845) in combination with afatinib will be evaluated continuously based on the totality of the safety data in order to determine the MTD and the RP2D.

Summary outputs of efficacy analyses will include all patients entered in Part B of the trial and patients entered in RP2D level in Part A. All endpoints defined in Section 5.1.1 will be summarized descriptively.

Safety analysis will be summarized separately for patients treated in Part A and Part B.

7.3.1 Primary analyses

7.3.1.1 Part A

The primary objective of the dose confirmation part is to determine the MTD of Xentuzumab (BI 836845) in combination with afatinib. The analysis will be based in occurrence of DLT during the first treatment course.

Section 5.2.6 specifies adverse events that qualify for DLT, and Section 7.3.3 below gives further information about the safety analyses.

7.3.1.2 Part B

Early efficacy signals of Xentuzumab (BI 836845) in combination with afatinib will be explored in the second part of this trial, and objective response rate will be used as primary endpoint. Tumour assessments will be performed according to RECIST v1.1.

Descriptive statistics for objective response rate (CR or PR) will be provided for all treated patients. The primary analysis will be performed when the last patient in Part B completes the first follow-up visit (FU1) as specified in Section 6.2.3.2.

7.3.2 Secondary analyses

Disease control (CR, PR or SD), time to objective response, duration of objective response, will be summarized using descriptive statistics.
Kaplan-Meier curves will be plotted to graphically display the progression-free survival and overall survival for the expansion cohort in Part B.

7.3.3 Safety analyses

The occurrence of dose limiting toxicity (DLT) as well as the incidence, intensity, duration and causality of adverse events graded according to CTCAE Version 4.03 (R10-4848), laboratory parameters and vital signs will be evaluated in both parts of the study.

AEs will be evaluated using the CTCAE grading scheme. The overall incidence and intensity of adverse events, as well as their relatedness to the study medication will be reported for all treatment arms and combinations. Serious adverse events and events leading to dose reduction or treatment discontinuation will be tabulated. Descriptive statistics will be used to describe changes in laboratory parameters over time. In addition, all abnormalities of potential clinical relevance will be reported.

AEs that started within the period starting with first administration of the trial drug and ending 42 days after permanent discontinuation of study drugs (both Xentuzumab (BI 836845) and afatinib) will be considered as having occurred during ‘on treatment’. Later events will be attributed to the post-treatment period and and events occurring between IC date and first drug intake will be presented separately.

7.3.4 Interim analyses

No formal interim analysis is planned.

The data will be evaluated as they accumulate. DLTs and other AEs will be reviewed by the sponsor before each dose escalation/de-escalation. In addition, although no formal interim clinical trial report will be produced, a limited set of tables and listings will be provided to document the MTD/RP2D of Xentuzumab (BI 836845) in combination with afatinib. Snapshots of the database (e.g., as a basis for presentation of preliminary study results at

conferences, or for safety reasons, or for regulatory documents) may be taken at any time during the study conduct.

7.4 HANDLING OF MISSING DATA

Every effort will be made to obtain complete information in this phase I study, especially on all adverse events with particular emphasis on dose limiting toxicities. No imputation will be performed on missing data unless otherwise specified.

Missing baseline laboratory values will be imputed by the respective values from the screening visit. Missing or incomplete AE dates will be imputed according to BI guidelines.

7.5 RANDOMISATION

In this open-label, Phase Ib study, randomisation is not applicable. Patients will be assigned, not randomised, independently and sequentially to each dose level in both parts of the study.

7.6 DETERMINATION OF SAMPLE SIZE

Part A follows a 3+3 design with escalating/de-escalating steps (R07-0220) for the determination of the MTD of Xentuzumab (BI 836845) in combination with afatinib. According to this design as described in Section 4.1.3, up to 18 evaluable patients may be needed to identify the MTD. Six additional patients will be treated at the RP2D level before commencing Part B.

The patients in Part B will be treated at the RP2D. In the expansion cohort, 18 additional patients will be treated. Assuming a true response rate of 20% a sample size of 18 patients leads to a probability of 73% of observing at least 3 objective responses (CR or PR). If the true response rate is higher i.e. 25%, then the probability to observe at least 3 objective responses is 86%. The probability of a false positive signal is <0.1%.

True Response Rate	# Patients per cohort	Probability to observe at least				
		1 event	2 events	3 events	4 events	5 events
0.15	16	0.92575	0.71610	0.43862	0.21011	0.07905
0.15	18	0.94635	0.77595	0.52034	0.27976	0.12056
0.15	20	0.96124	0.82444	0.59510	0.35227	0.17015
0.20	16	0.97185	0.85926	0.64816	0.40187	0.20175
0.20	18	0.98199	0.90092	0.72866	0.49897	0.28365
0.20	20	0.98847	0.93082	0.79392	0.58855	0.37035
0.25	16	0.98998	0.93652	0.80289	0.59501	0.36981
0.25	18	0.99436	0.96054	0.86470	0.69431	0.48133
0.25	20	0.99683	0.97569	0.90874	0.77484	0.58516
0.01	16	0.14854	0.01093	0.00051	0.00002	0.00000
0.01	18	0.16549	0.01376	0.00073	0.00003	0.00000
0.01	20	0.18209	0.01686	0.00100	0.00004	0.00000

Altogether the total sample size is anticipated to be approximately 42 entered patients. Naturally this represents only a rough estimation since the number of patients needed is induced by the “3+3” design and is subject to different influencing factors. Assuming a 60% of screen fail rate, 105 patients are anticipated to be enrolled in the trial.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

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 general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY 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 Institutional Review Board (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 patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs 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

eCRFs for individual patients will be provided by the sponsor via RDC. For drug accountability, refer to Section 4.1.8.

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 entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must 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. CRFs/eCRFs 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 trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

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 Xentuzumab (BI 836845), this is the current version of the Investigator's Brochure (U10-2830). For afatinib, this is the current version of the Company Core Data Sheet (CCDS). The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

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.

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

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10. APPENDICES

10.1 LIST OF POTENT INHIBITORS AND INDUCERS OF P-GLYCOPROTEIN

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

As the information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess the status of each concomittant therapies and in case of questions contact BI clinical monitor.

While caution needs to continue to be exercised in concomitant use of P-gp inhibitors/inducers with afatinib, based on new data from two drug-drug interaction (DDI) trials (U03-3218) investigating the effect of ritonavir and rifampicin, respectively, on 40 mg afatinib, their use in patients needing such therapies is no longer prohibited. It cannot be excluded that the plasma exposure to afatinib may increase under concomitant treatment with strong P-gp inhibitors. Conversely, strong P-gp inducers may decrease the plasma concentrations of afatinib. However, maximum observed effects are rather mild to moderate and could even be avoided for the potent inhibitor ritonavir when given simultaneously or 6 h after afatinib. Therefore caution has to be exercised when combining afatinib with potent P-gp modulators.

10.2 COCKCROFT-GAULT FORMULA

Estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula

$$eC_{CR} = \frac{\textbf{(140-Age)X Mass (in kilograms) X (0.85 } \textit{\textbf{if Female}}\textbf{)}}{\textbf{72 X Serum Creatinine (in mg/dL)}}$$

Or when serum creatinine is measured in µmol/L

$$eC_{CR} = \frac{\textbf{(140-Age)X Mass (in kilograms) X } \textit{\textbf{Constant}}}{\textbf{Serum Creatinine (in µmol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women

10.3 NYHA CLASSIFICATION OF HEART FAILURE

Class	Patient Symptoms
Class I (Mild)	No intention of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	ECOG
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. R01-0787

10.5 RECIST (VERSION 1.1)

The criteria below are based on RECIST 1.1 (R09-0262).

The preferred method of assessment is a spiral CT scan with IV and oral contrast, unless IV and/or oral contrast are medically contraindicated. CT scans of the chest, abdomen and other areas of known or newly suspected disease must be performed. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

Skin lesions followed as target lesions must be documented by colour digital photography and must include in the image a ruler with millimetre subdivisions and a label that includes the patients ID and date.

Bone scans (using ^{99}m-technetium polyphosphonate scintigraphy) are recommended at baseline if the patient has any signs and symptoms consistent with bone metastasis or a history of bone metastasis. Bone metastasis identified at baseline must be documented and assessed according to RECIST 1.1 at the times of the other tumour measurements indicated in the flow chart. During the study bone scans should be repeated as clinically indicated in patients without bone metastasis at Baseline.

Tumour assessment will be performed every 4 weeks after start of treatment with Xentuzumab (BI 836845) and afatinib for first 8 weeks (prior to courses 2 and 3), in 8-week intervals thereafter (e.g. prior to courses 5, 7, 9, etc.) and in 12-week interval after course 16 until PD or start of further anti-cancer treatment. In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

Follow-up tumour assessments must utilize the same CT/MRI/photographic method and acquisition technique (including use or non-use of IV contrast) as were used for screening assessments to ensure comparability. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of CT/MRI/bone scan.

Measurability of tumour at baseline

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15mm are also measurable.

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. Measurable lesion if limited to either small (<2cm) solitary visceral lesion or scant (<5cm) lymph nodes only

metastasis should be evaluated for additional evidence of malignant nature and discussed with BI trial clinical monitor before enrolling.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

New lesions in irradiated fields

Previously irradiated lesions should not be used as indicator lesions unless there has been demonstrated progression in the lesion. However, new lesions occurring in previously irradiated fields can be used to assess the anti-tumour response.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5mm should be applied. If the lesion is not visible, a default measurement of 0mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is obligatory.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured (longest diameter = LD) and numbered at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Lymph nodes must be ≥15mm in order to be considered as target lesions.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.5:1).

Table 10.5: 1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression (PD)	At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started, together with an absolute increase in the sum of LD of at least 5mm or the appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, taking as reference the baseline SoD, nor sufficient increase to qualify for PD taking as reference the smallest SoD since the treatment started.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.5:2).

Table 10.5: 2 Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesions or/and maintenance of tumour marker level above normal limits.
Progression (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

In case of tumour response (CR or PR), confirmation will be performed with a repeat assessment no less than 4 weeks after the RECIST criteria for response have been met. In the case of SD, measurement must have met the SD criteria at least once after study entry at an interval of not less than 6 weeks.

Evaluation of best response to study treatment

The best response to study treatment (Table 10.5: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.5: 3).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.5: 3 Algorithm for evaluation of overall response*

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.6 CLINICAL EVALUATION OF LIVER INJURY

10.6.1 Introduction

Alterations of liver parameters, as described in Section 5.2.2.1 (Protocol-Specified Adverse Events of Special Interest), are to be further evaluated using the following procedures:

10.6.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.

If the alert is confirmed on initial sample, or it is not possible to repeat testing using initial sample, the following must be completed:

1) Evaluate patient within 48 hours and

2) Perform the following laboratory tests:

1. Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
2. Haptoglobin
3. Complete blood count and cell morphology
4. Reticulocyte count
5. Creatine Kinase (CK)
6. Lactate dehydrogenase (LDH)
7. Alkaline Phosphatase

The results of these laboratory tests must be reported to BI as soon as possible.

If the initial alert values (*ie* AST,ALT, and bilirubin) are confirmed on the second sample described as above, then an abdominal ultrasound or clinically appropriate alternate imaging (to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm) must be completed within 48 hours.

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. In the event the etiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), then the "DILI checklist" must be completed. Details of the "DILI checklist" are provided in the ISF. The following assessments need to be performed in order to complete the "DILI checklist" and results will be reported via the eCRF:

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF;
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;

- complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:

Clinical chemistry

alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin*, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology

Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*

Hormones, tumour marker

Thyroid-stimulating hormone(TSH)*

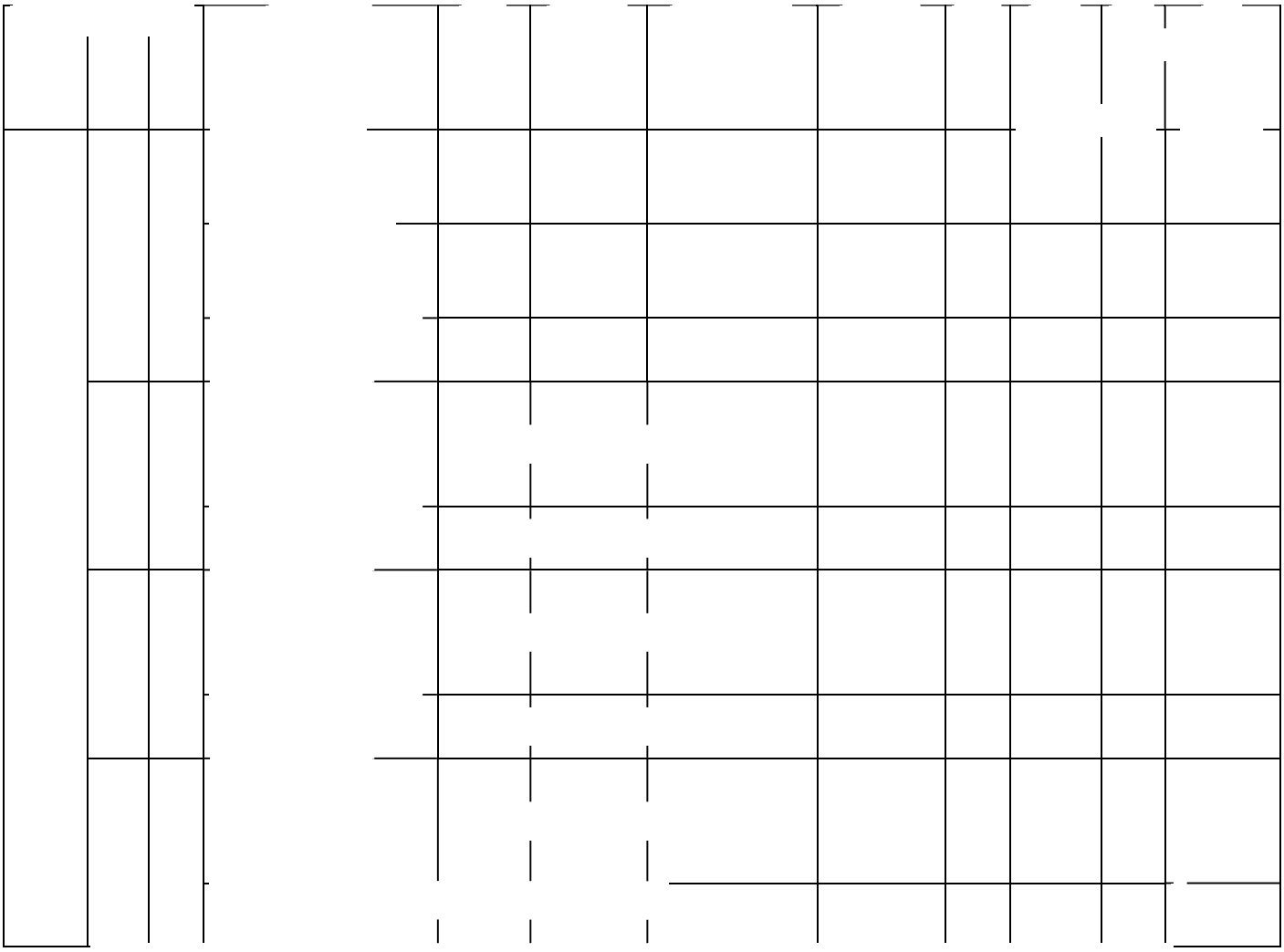
Haematology

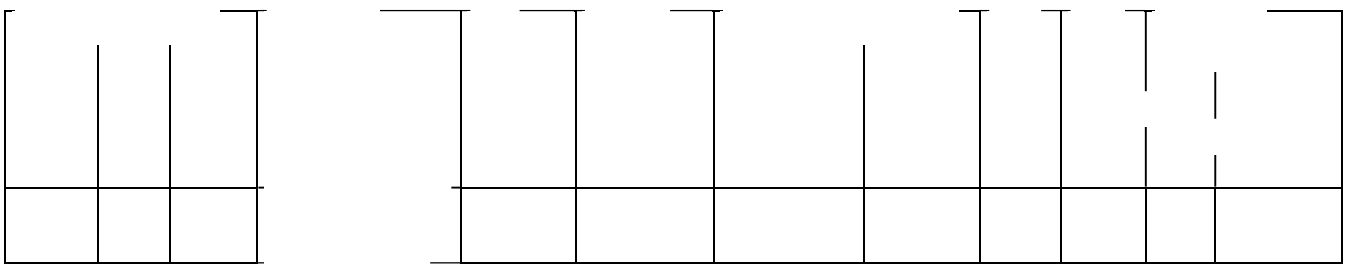
Thrombocytes, eosinophils

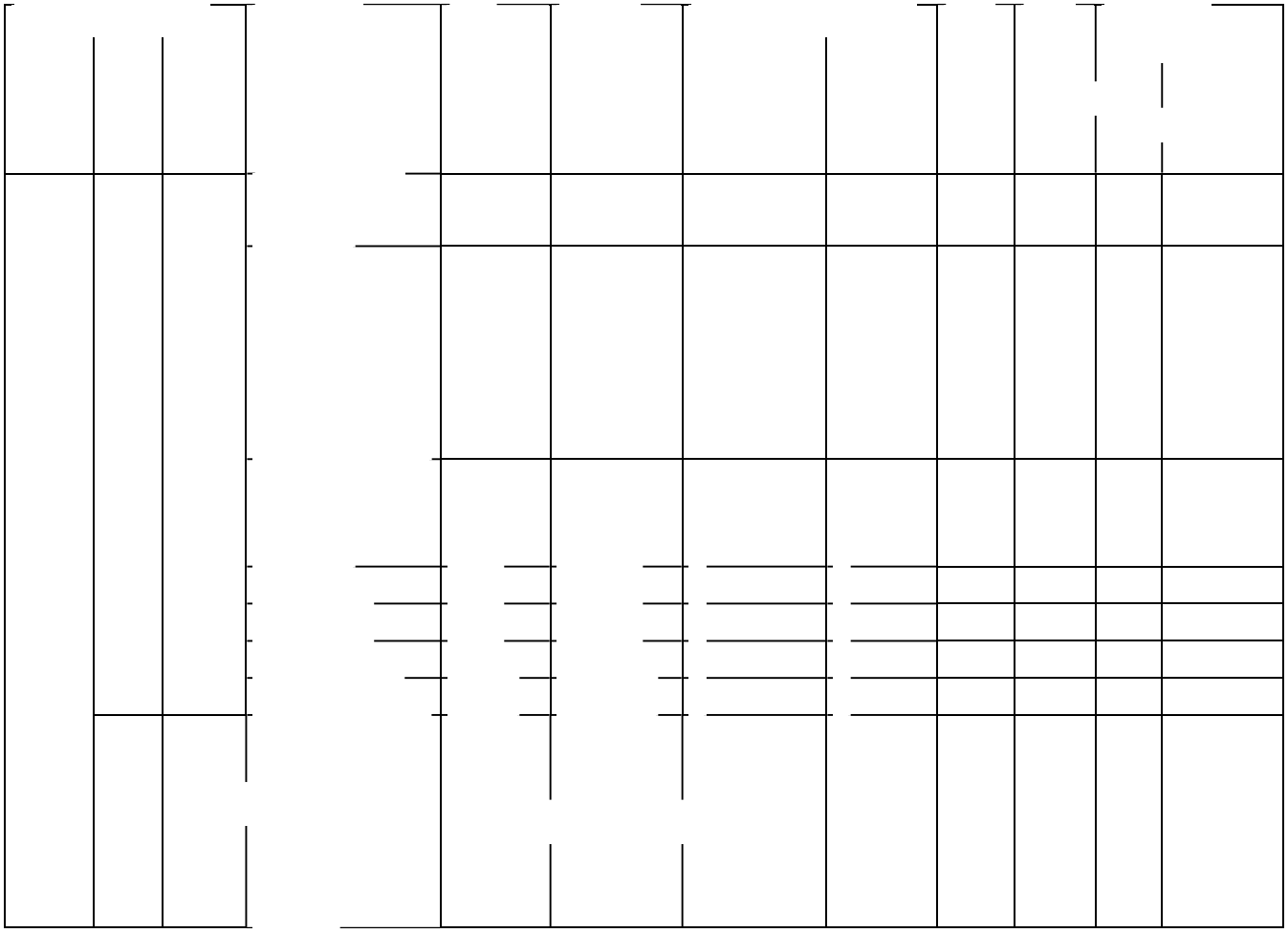
*If clinically indicated (e.g. immunocompromised patients)

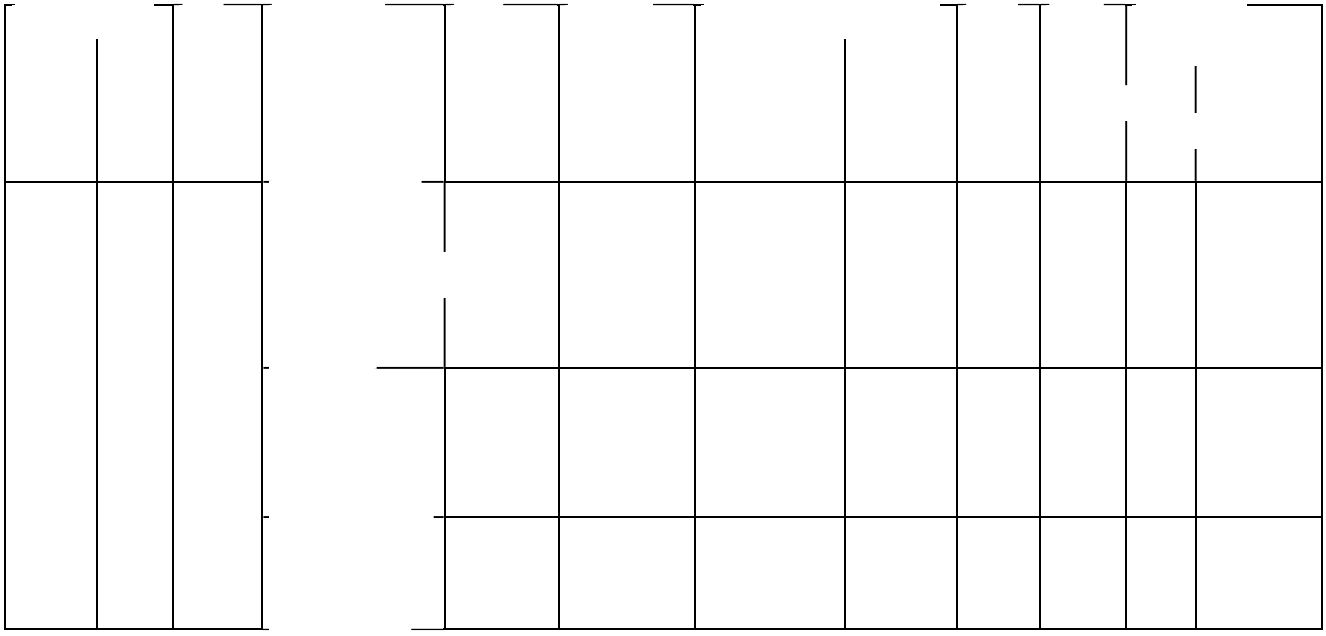
Long term follow-up

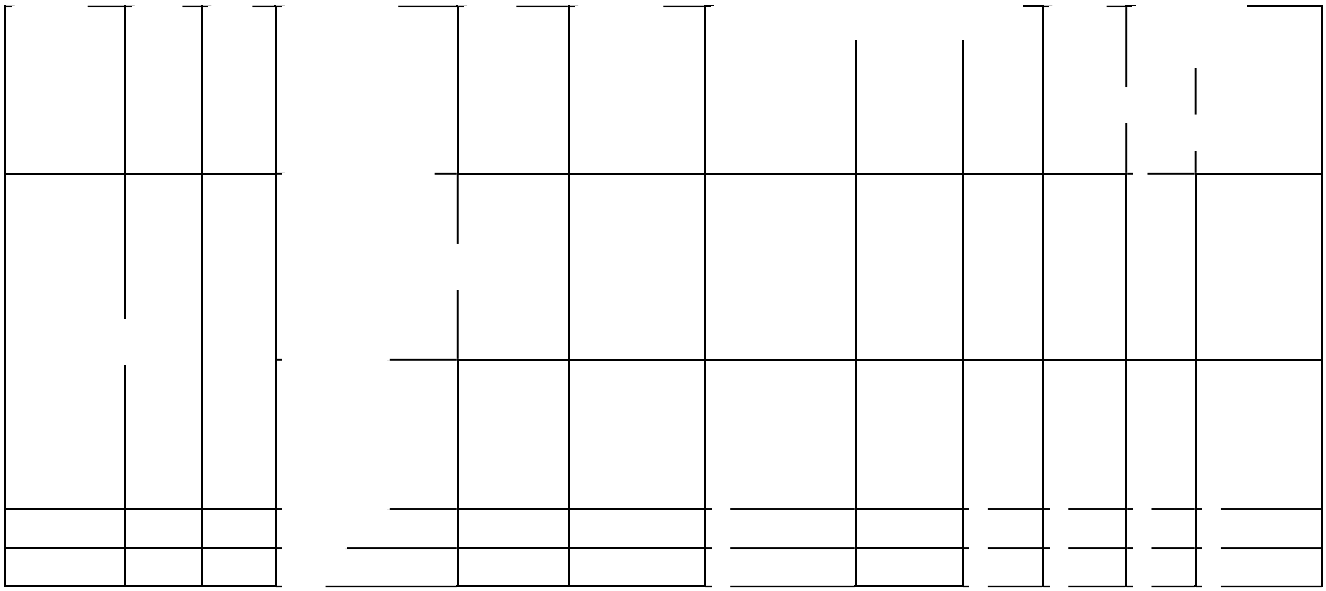
Initiate close observation of subjects by repeat testing of ALT, AST, and bilirubin (with fractionation to total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

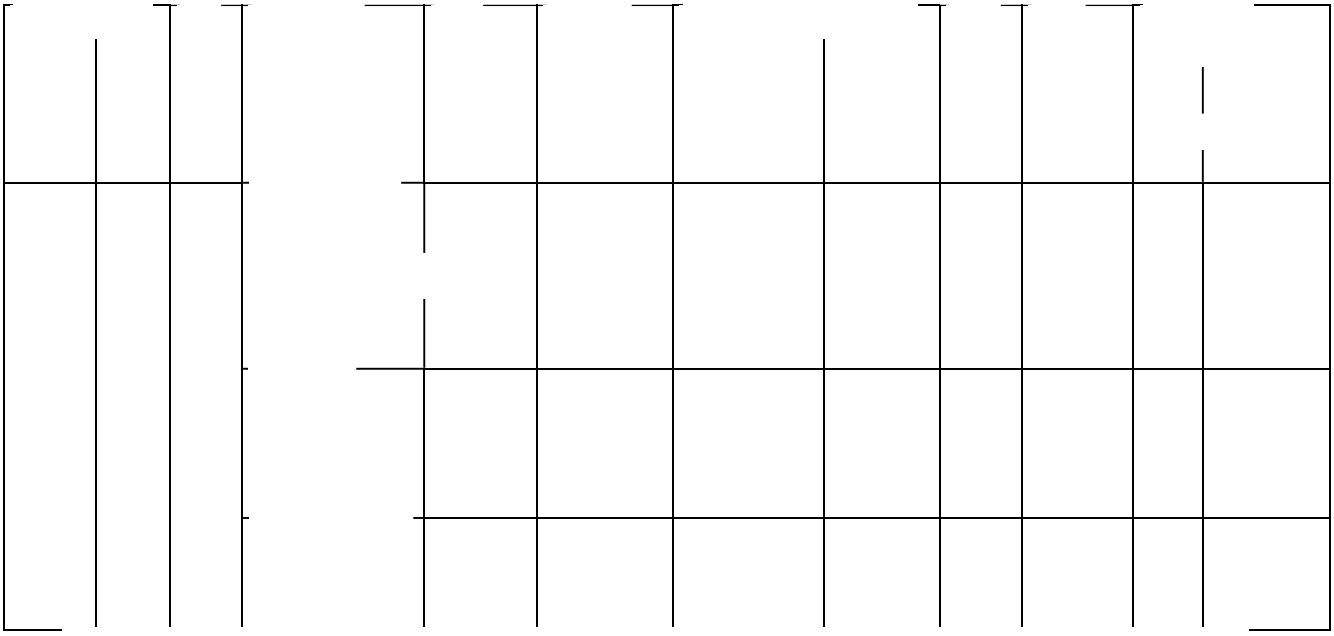


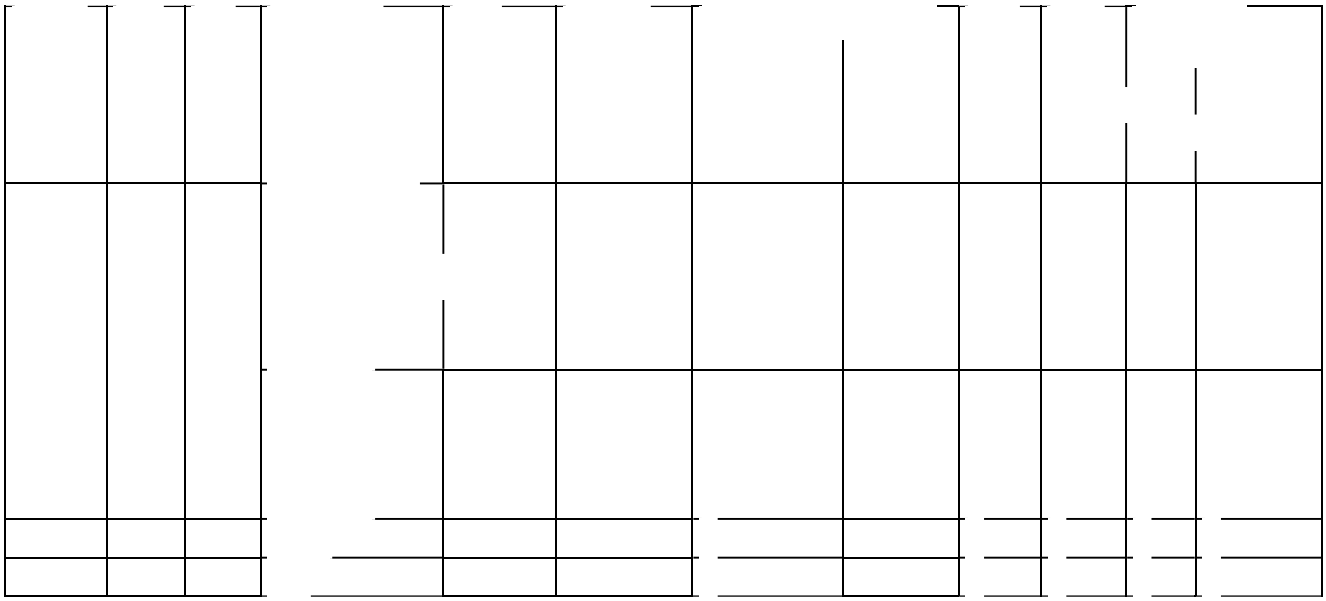












11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		*15 Jul 2015*
EudraCT number		*Not applicable*
BI Trial number		*1280.16*
BI Investigational Product(s)		*Xentuzumab (BI 836845)*
Title of protocol		A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors
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		Change 1: Cover page Change 2: Clinical Trial Protocol Synopsis- Trial sites Change 3: Clinical Trial Protocol Synopsis- Objective, Diagnosis and Main criteria for inclusion Change 4: Flow Chart and 6.2.1 Screening period Change 5: 2.2.1 Primary objectives, 2.2.2 Secondary objectives, 3.1 Overall Trial Design and Plan, Figure 3.1: 1 Study design , 3.3 Selection of Trial Population and 7.1 Statistical Design – Model Change 6: 2.3 Benefit-Risk Assessment, 3.3

Number of global amendment		1
		Selection of Trial Population, 3.3.2 Inclusion criteria, criteria no. 2, 3, 5, 6 and 7 and 5.3.2 Pharmacogenomic evaluation Change 7: 3.3.2 Inclusion criteria, criteria no. 2 Change 8: 3.3.2 Inclusion criteria, criteria no. 4 Change 9: 3.3.2 Inclusion criteria, criteria no. 6 Change 10: 3.3.2 Inclusion criteria, criteria no. 12 Change 11: 3.3.2 Inclusion criteria, criteria no. 15 Change 12: 3.3.3 Exclusion criteria, criteria no.3 Change 13: 3.3.3 Exclusion criteria, criteria no.25 Change 14: 4.1.4.3 Temporary treatment interruption and dose reduction Change 17: 9.1 Published references and 9.2 Unpublished references
Description of change		Change 1: Change of TCM Change 2: Addition of Japan as a participating country and update of number of participating sites Change 3: Change in statement of objective, diagnosis and main inclusion criteria Change 4: Clarification on allowance of local result of EGFR mutation in Part A Change 5: Change in statement of primary objective and target population in Part A Change 6: Inclusion of squamous cell carcinoma of lung in Part A and its related changes and justification Change 7: Clarification on histology and need of diagnosis based on the latest tumour sample, Exclusion of small cell lung cancer transformation Change 8: Removal of T790M status in Part A Change 9: Removal of 30 days interval between progression of disease and initiation of study treatment and addition of limitation of TKI free period in Part B Change 10: Clarification of ALT and AST criteria Change 11: Addition of inclusion criteria on patients with known potentially targetable mutation Change 12: Removal of limitation of number of

Number of global amendment		1
		prior TKI in Part A and change of limitation of number of prior TKI in Part B Change 13: Addition of exclusion criteria on prior treatment with third generation irreversible EGFR TKI in Part B Change 14: Correction of typo on section to be referred Change 15: Rephrasing Change 17: Addition of new and missing references/ rearrangement of reference in alphabetic and numeric order
Rationale for change		Change 1 and 17: Administrative change Change 2: Japan to be participated in Part B Change 3: To align the texts to the information in section 2.2.1 and 3.3.2 Change 4: To clarify that T790M result at baseline will be collected in Part A even though patients can be enrolled in Part A regardless of T790M status Change 5, 6 and 8: To investigate safety of this combination in broader spectrum of NSCLC for part A as a dose escalation cohort Change 7: To make a clarification for the patients with mixed histology of cancer Change 9: To reflect the clinical practice Change 10: To make a clarification on ALT and AST criteria for eligibility Change 11: To make a clarification for known potentially targetable mutation other than IGF signalling pathway or EGFR Change 12: To reflect the clinical practice and treatment guideline Change 13: To make a clarification for prior treatment with third generation irreversible EGFR TKI in Part B Change 14: To correct typo error Change 15: To make it more clear

Number of global amendment		2
Date of CTP revision		*17 May 2016*
EudraCT number		*Not applicable*
BI Trial number		*1280.16*
BI Investigational Product(s)		*Xentuzumab (BI 836845)*
Title of protocol		A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors
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		- **Change 1:** Clinical Trial Protocol Synopsis-Objective, No. of patients, Diagnosis and Main criteria for inclusion, 2.2.1 Primary objectives, 3.1 Overall Trial Design and Plan, Figure 3.1: 1 Study design , 3.3 Selection of Trial Population, 3.3.2 Inclusion criteria, criteria no. 6, 4.1.2.2 The expansion Part B, 5.1.2.2 The expansion Part B, 7.1 Statistical Design – Model, 7.3.1.2 Part B and 7.3.2 Secondary analyses - **Change 2**: 7.6 Determination of sample size - **Change 3:** Flow chart foot note 12 and 6.2.1 Screening period - **Change 4**: Flow chart foot note 15 - **Change 5**: 2.3 Benefit-risk assessment - **Change 6:** Figure 3.1: 1 Study design - **Change 7:** 3.3.4.3 Replacement of patients

Number of global amendment		2
		- **Change 8:** Table 4.1.4.3: 1 Dose reduction scheme by AE type and CTCAE Grade (Part A and Part B) - **Change 9:** Table 4.2.3.1: 1 Grade specific treatment recommendations for diarrhea, Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions and Table 4.2.3.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis - **Change 10:** Table 4.2.3.2: 1 General recommendation for skin reactions prophylaxis - **Change 11:** 5.2.1.1 Dose confirmation Part A - **Change 12:** 5.2.2.1 Definitions of adverse events - **Change 13:** - **Change 14:** 6.2.3.4 Patient completion - **Change 15:**
Description of change		- **Change 1 and 2:** Group 2 in Part B has been removed and no. of target patient has been adjusted accordingly. - **Change 3:** Requirement on the separate informed consents for tissue biopsy has been clarified. - **Change 4:** - **Change 5:** Recommendation to monitor weight loss has been added. - **Change 6:** Allowable time frame for baseline imaging at screening has been corrected as described in flowchart, footnote 11. - **Change 7, 10 and 12:** Typo errors have been corrected. - **Change 8:** Clarification on dose reduction scheme for any drug-related AEs ≥CTCAE grade 3 has been added. - **Change 9:** Reference for AE descriptions by CTCAE grade has been added. - **Change 11:** Supporting data in determination

Number of global amendment		2
		of RP2D has been clarified. - **Change 13:** l - **Change 14:** Incorrect information has been deleted. No PC page in eCRF - **Change 15:**
Rationale for change		- **Change 1:** Decision in the consideration of scientific merits based on the evolving treatment options in EGFR mutated NSCLC, **Change 2:** To correct and adjust the number of patients anticipated to be enrolled in the trial according to modification on expansion cohort. - **Change 3:** - **Change 4:** To align the information in section 5.3.2 - **Change 5:** Patients well-being - **Change 6:** To align the information in flowchart, footnote 11 - **Change 7, 10 and 12:** Correction of typo errors - **Change 8:** To clarify that dose reduction is required only for drug-related AEs described in table 4.1.4.3: 1. - **Change 9:** Clarification on AE descriptions and CTCAE reference version - **Change 11:** Clarification on supporting data in determination of RP2D - **Change 13:** - **Change 14:** Deletion of incorrect information, No PC page in eCRF - **Change 15:**

Number of global amendment		3
Date of CTP revision		*02 Nov 2016*
EudraCT number		*Not applicable*
BI Trial number		*1280.16*
BI Investigational Product(s)		*Xentuzumab (BI 836845)*
Title of protocol		A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors
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		- **Change 1:** Throughout document - **Change 2:** Flowchart, footnote 7 in flowchart, 3.1 Overall trial design and plan, Figure 3.1: 1 Study design, 3.3.2 Exclusion criteria, exclusion no. 1 and 6.1 visit schedule - **Change 3:** Figure 3.1: 1 Study design, 3.2 Discussion of trial design, including the choice of control group, 3.3 Selection of trial population, 4.1.3.2 Part B – dosing schedule and 7.1 Statistical desing-model - **Change 4:** 3.3.2 Inclusion criteria, inclusion no. 6 - **Change 5:** Women of Child-Bearing Potential and Pregnancy Prevention - **Change 6:** 9.1 Published references - **Change 7:** 1.2.2 afatinib, 2.1 Rationale for performing the trial, 3.3 Selection of trial

Number of global amendment		3
		population, 4.1.3.1 planned dose levels in Part A, 9.1 published references and 9.2 unpublished references
Description of change		- **Change 1:** addition of xentuzumab to the name of BI investigational product - **Change 2:** extension of screening period from 28 days to 42 days and addition of the statement that safety lab result should be reviewed before first administration of study treatment - **Change 3:** allowance of lower dose of afatinib as a starting dose in part B for the patients who have progressed on afatinib less than 40mg after discussion and agreement by sponsor - **Change 4:** deletion of TKI-free period - **Change 5:** deletion of tubal from a method of permanent sterilization - **Change 6:** addition of new publication - **Change 7:** replacement with updated publication/reference
Rationale for change		- **Change 1:** new name added for completeness - **Change 2:** 28 days of screening period is too short to complete re-biopsy procedures at in some circumstances. For safety confirmation before initiating study treatments, the safety laboratory result at course 1 visit 1 should be reviewed by investigators before first study medications. - **Change 3:** To reflect the clinical practice of afatinib use. - **Change 4:** To reflect the clinical practice - **Change 5:** The recommendation related to contraception and pregnancy testing in clinical trials by Clinical Trial Facilitation group (CTFG) has been updated. - **Change 6:** The publication supports afatinib 30mg as a starting dose for the patients who have progressed on reduced dose of afatinib 30mg due to adverse events of afatinib - **Change 7:** To reflect the updated publication/reference

APPROVAL / SIGNATURE PAGE

Document Number: c02190401 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol-revision-03

Title: A phase Ib open-label clinical trial of once daily oral treatment of afatinib plus weekly intravenous infusion of Xentuzumab (BI 836845) in patients with EGFR mutant non-small cell lung cancer with progression following prior EGFR tyrosine kinase inhibitors

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		08 Nov 2016 10:04 CET
Approval-Clinical Program		08 Nov 2016 10:04 CET
Approval-Team Member Medicine		08 Nov 2016 10:31 CET
Approval-Therapeutic Area		08 Nov 2016 13:04 CET
Approval-Dept or or		08 Nov 2016 15:43 CET
Approval-Biostatistics		09 Nov 2016 09:17 CET
Author-Trial Clinical Pharmacokineticist		10 Nov 2016 01:43 CET
Verification-Paper Signature Completion		10 Nov 2016 06:27 CET

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