Boehringer Ingelheim

Clinical Trial Protocol

Doc. No.: c02243064-09

EudraCT No.:	2013-001110-15
BI Trial No.:	1280.4
BI Investigational Product(s):	BI 836845
Title:	A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer
Clinical Phase:	Ib/II
Trial Clinical Monitor:	[redacted] Phone: + Fax: +
Co-ordinating Investigator:	[redacted] Phone: + Fax: +
Status, Version and Date of Protocol:	Final Protocol (Revised Protocol (based on global amendment(2)), version 3.0, 30 March 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 836845			
Protocol date: 13 December 2013	**Trial number:** 1280.4		**Revision date:** 30 March 2016
Title of trial:	A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer		
Co-ordinating Investigator:	[redacted] Phone: +[redacted] Fax: +[redacted]		
Trial site(s):	Multicenter trial, international		
Clinical phase:	Ib/II		
Objective(s):	Phase I part: To determine the maximum tolerated dose (MTD) and recommended Phase II dose of BI 836845 in combination with exemestane and everolimus in women with HR+/HER2− locally advanced or metastatic breast cancer Phase II part: To evaluate the anti-tumor activity of BI 836845 in combination with exemestane and everolimus versus exemestane and everolimus alone in women with HR+/HER2− locally advanced or metastatic breast cancer In addition, safety will be assessed [redacted]		
Methodology:	Open label, multicenter study in two parts: • Phase I – single arm, dose escalation with BI 836845 + everolimus + exemestane • Phase II – two arms, randomized, parallel design; arm 1: everolimus + exemestane ; arm 2: BI 836845 + everolimus + exemestane		
No. of patients:			
total entered:	Between 171 and 198		
each treatment:	Phase I: about 21–48; Phase II: approximately 75 patients per treatment arm (2-arm study)		
Diagnosis :	HR+/HER2− locally advanced or metastatic breast cancer		

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Main criteria for inclusion:	Histologically-confirmed locally advanced or metastatic breast cancer not deemed amenable to curative surgery or curative radiation therapy Tumors are positive for estrogen-receptor (ER) and/or progesterone receptor (PgR); HER2 negative Postmenopausal women Disease refractory to non-steroidal aromatase inhibitors Objective evidence of recurrence or progression on or after the last systemic therapy prior to the study entry Patients must have a measurable lesion according to RECIST version 1.1 or bone lesion ~~only~~: lytic or mixed (lytic + sclerotic) in the absence of measurable lesion
Test product(s):	BI 836845
dose:	Phase I: 750 mg weekly as starting dose; Phase II: RP2D as established in Phase I
mode of admin.:	Intravenous infusion over 60 minutes
Comparator products:	Exemestane plus Everolimus
dose:	Exemestane: 25 mg per day Everolimus: Phase I:10 mg per day as starting dose; Phase II: Arm 1: 10 mg per day, Arm 2: RP2D as established in Phase I
mode of admin.:	Oral
Duration of treatment:	Continuous treatment until disease progression, intolerable AEs, consent withdrawal or non-compliance with the study protocol

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Name of finished product: Not applicable			
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Criteria for *efficacy*:	The primary endpoint of the phase II part of this study is progression-free survival, as determined by RECIST 1.1. Secondary endpoints are: • Time to progression • Objective response (CR, PR) • Time to objective response • Duration of objective response • Disease Control (CR + PR + SD_{24w}+ Non-CR/Non-PD_{24w}) • Duration of disease control [redacted]		
Criteria for safety:	The primary endpoints of the phase I part of this study are occurrence of dose limiting toxicity and determination of MTD. Other safety endpoints including incidence and intensity of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, laboratory tests, physical examination, ECOG performance score, electrocardiogram (ECG) and vital signs		
Statistical methods:	Descriptive statistical analysis; exploratory design		

FLOW CHART

FLOW CHART – PHASE I PART

Study period	Screening (a)	Run-in (b)		Treatment Courses (c)									EOTV (d)	FU (e)
	SCR	R		Course 1					Course 2 onwards					
Visits (V)		1	2	1	2	3	4	5	1	2	3	4		
Days	-35 to -8	-7	-1	1	2	8 ±1	15 ±1	22 ±1	1 ±2	8 ±2	15 ±2	22 ±2		
Informed consent (1)	X													
Demographics	X													
Medical history	X													
Inclusion/exclusion criteria	X	X												
Physical exam (3)	X			X					X				X	X
Height	X													
Body weight	X			X					X				X	X
Vital signs (4)	X	X		X		X	X	X	X				X	X
ECOG performance status	X	X		X					X				X	X
12-lead ECG (triplicate) (5)	X			X		X	X		X		X (5)		X	X
Safety lab (6)	X	X		X		X	X	X	X		X (18)		X	X
HBV and HCV profile (7)	X													
Archival tumor tissue collection (8)	X													
[redacted]				■										
[redacted]		■		■	■	■	■	■	■				■	■
[redacted]			■	■	■	■	■	■	■		■		■	■
[redacted]		■	■	■	■	■								
[redacted]				■					■				■	■
Tumor assessment and bone scan by RECIST 1.1 (15)	X	See schedule below (15)												
Adverse event		X		X		X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X		X		X	X	X	X	X	X	X	X	X
Dispense EVE; Fill EXE (16)		X		X					X					
EVE+EXE treatment		Once daily continuous												
BI 836845 i.v.				X		X	X	X	X	X	X	X		
Compliance check EVE+EXE (17)				X					X				X	
Termination of trial medication													X	
Completion of the Phase I part														X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (Day -7 of Run-in). Safety lab at the screening assessment can serve as the Day -7 pre-treatment assessment of Run-in period if performed within 72 hours before the first treatment and does not need to be repeated

b Run-in: Consists of 7 days. During the run-in period, patients should take daily everolimus and exemestane treatment.

c Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Refer to Section 6.2.2. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4).

d EOTV: End of Treatment visit. If the decision to permanently discontinue all study treatments is taken during a scheduled visit, the End Of Treatment Visit (EOTV) should be performed instead of the scheduled visit (within 7 calendar days after last drug administration)

e FU: All patients should have a follow-up visit 42 days (+7days) after the permanent discontinuation of the study drugs

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting digital electrocardiogram (ECG) are recorded digitally and in triplicate. ECG will be performed at Screening, EOTV and FU. ECG will be repeated at Visit 1/Day 1, Visit 3/Day 8 and Visit 4/Day 15 of Course 1; Visit 1/Day 1 and Visit 3/Day 15 of Courses 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc.. ECG should be performed prior to and immediately after the end of BI 836845 infusion. PK samples will be taken immediately after ECG recording. See Section 5.2.4.
6. Safety labs: include hematology (CBC), coagulation and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. See Section 5.2.3 for detail. No need to repeat the safety lab on Day -7 of Run-in if within three calendar days of the screening safety lab and the patient is deemed stable by the investigator. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. HBV and HCV profile: All patients should be screened for hepatitis B and hepatitis C. Hepatitis B and C lab screen should include HBV-DNA and/or HBsAg, anti-HCV Ab and/or HCV RNA-PCR (local lab)
8. Archival tumor tissue collection: the most recent/appropriate archival tumor tissue must be collected prior to the start of run-in. Refer to Appendix 10.7 for tissue requirements

[redacted]

13. Everolimus and exemestane drug intake starting from Day -7 of Run-in and up to Course 1 Visit 3 Day 8 must be recorded in the patient diary card. The diary card should be returned on Day 1 and Day 8 of Course 1.
14. Immunogenicity (ADA): On days when BI 836845 is dosed, ADA samples are to be collected prior to BI 836845 infusion. ADA samples must be collected at Courses 1 through 12, EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.5
15. Tumor assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans should be performed at screening (see Section 5.1.2 for more detail).

    Assessment will be performed at the following time points until progression/start of further treatment (tumor assessments after start of BI 836845 should be performed no more than 7 days prior to the scheduled tumor assessment date up to week 48 AND no more than 14 days prior to the scheduled tumor assessment date after week 48):

    - At screening (within 28 days prior to starting of treatment)
    - Every 8 weeks: during week 8 (49-56 days after start of BI 836845), during week 16 (105-112 days after start of BI 836845), during week 24 (161-168 days after start of BI 836845), during week 32 (217-224 days after start of BI 836845), during week 40 (273-280 days after start of BI 836845), during week 48 (329-336 days after start of BI 836845)

- Every 12 weeks after week 48 (e.g. during week 59-60 (406 – 420 days after start of BI 836845), during week 71-72 (490 – 504 days after start of BI 836845), etc.)
  In the event of an interruption/delay to treatment, the tumor assessment schedule should not be changed.
  Patients who discontinue the trial for any reason other than imaging based progressive disease should have a tumour assessment (RECIST 1.1) performed at EOTV. Except in case of discontinuation from treatment due to imaging based progression, tumor assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
  Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF

16. Everolimus should be dispensed through IRT. The prescription of exemestane should be filled by pharmacy. Patient's screening, run-in, all drug dispensation visits and EOTV will be collected in the IRT system
17. Compliance check: on Day 1 of every course and at EOTV
18. For Course 2 only

FLOW CHART – PHASE II PART

Study period	Screen-ing (a)	Treatment Courses (c)								EOT V (d)	FU1 (f)	Add. FU (f)	OP (g)
	SCR	Course 1				Course 2 Onwards							
Visits (V)		1	2	3	4	1	2	3	4			FU2-FUn	
							Phone visit (h)						
Days	- 28 to -1	1	8 ±2	15 ±2	22 ±2	1 ±2	8 ±2	15 ±2	22 ±2				
Informed consent (1)	X												
Randomization (2)		X											
Demographics	X												
Medical history	X												
Inclusion/ exclusion	X	X											
Physical exam (3)	X	X				X				X	X		
Height	X												
Body weight	X	X				X				X	X		
Vital sign (4)	X	X	X	X	X	X				X	X		
ECOG	X	X				X				X	X		
12- lead ECG (triplicate) (5)	X	X	X	X		X				X	X		
Safety lab (6)	X	X		X		X		X (18)		X	X		
HBV, HCV profile (7)	X												
Archival tumor tissue collection (8)	X												
Blood sample for companion diagnostic development (21)		X											
[redacted]													
Tumor assessment and bone scan by RECIST 1.1 (15)	X	See schedule below (15)											
Adverse event		X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense/fill EVE+ EXE(16)		X				X							
Compliance check (17)						X				X			
EVE+ EXE treatment		Once daily continuous											
BI 836845 i.v. Arm 2 only(23)		X	X	X	X	X	X	X	X				
Termination of study medication										X			
Completion of the Phase II part (19)											X (19)	X (19)	
Collection of information on disease status and further therapies (20)													X

a Screening: The screening visit should be performed within 28 days prior to first drug administration. Safety lab at the screening assessment can serve as the Day 1 pre-treatment assessment of Course 1 if performed within 72 hours before the first treatment and does not need to be repeated.

c Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Refer to Section 6.2.2. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4).

d EOTV: If the decision to permanently discontinue all study treatments is taken during a scheduled visit, the End Of Treatment Visit (EOTV) should be performed instead of the scheduled visit (within 7 calendar days after last drug administration)

f FU1 and Additional FU: All patients should have a follow-up 1 (FU1) visit 42 days (+7days) after the permanent discontinuation of study drugs. Patients who have not progressed and not started further treatment at FU1 should have additional limited follow-up visits at scheduled tumor assessment until progression, start of further anti-cancer treatment, consent withdrawal, lost to follow-up or death. See Section 6.2.3

g OP: observation period every 90 ± 15 days after the last follow-up visit (visit or phone contact allowed)

h On Visits 2 and 4 of Courses 3 through 6, and on Visits 2, 3, 4 from Course 7 onwards, the study visit for patients on arm 1 (everolimus + exemestane) can be conducted via phone for collection of adverse events and concomitant medication

1. Written informed consent must be obtained before any protocol specific screening assessment is performed. Additional informed consent must be obtained prior to fresh tumor biopsy
2. Randomization: the randomization may take place up to 3 days prior to the C1V1 if site procedures require advance randomization to accommodate the logistics of dispensing study medication to patients. Sites that use this option must include a copy of site policy or documented justification in the ISF and submit a copy to the sponsor. If randomization is performed prior to C1V1, the subsequent visits must be scheduled with reference to C1V1. Arm 1 treatment: everolimus + exemestane; Arm 2 treatment: BI 836845 + everolimus + exemestane. Patient's screening, randomization and EOTV will be collected in the IRT system
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status. No need to repeat the physical exam on C1V1D1 if within three calendar days of the screening physical exam and the patient is deemed stable by the investigator
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting digital electrocardiogram (ECG) are recorded digitally and in triplicate. ECG will be performed at Screening, EOTV and FU1. ECG will be repeated at Visit 1/Day 1, Visit 2/Day 8 and Visit 3/Day 15 of Course 1; Visit 1/Day 1 of Course 2; and at Visit 1/Day 1 of Courses 3, 6,9,12, etc. ECG should be performed prior to BI 836845 infusion and/or everolimus+ exemestane administration, and immediately after BI 836845 infusion (for arm 2 patients) OR one hour after the administration of everolimus+ exemestane (for arm 1 patients). See Section 5.2.4
6. Safety labs: include hematology (CBC), coagulation and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. See Section 5.2.3 for detail. No need to repeat the safety lab on C1V1D1 if within three calendar days of the screening safety lab and the patient is deemed stable by the investigator. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. HBV and HCV profile: All patients should be screened for hepatitis B and hepatitis C. Hepatitis B and C lab screen should include HBV-DNA and/or HBsAg, and anti-HCV Ab and/or HCV RNA-PCR (local lab)
8. Archival tumor tissue collection: the most recent/appropriate archival tumor tissue must be collected prior to C1V1 treatment. Refer to Appendix 10.7 for tissue requirements

[redacted]

[redacted]

14. Immunogenicity (ADA): ADA sampling is mandatory only for patients receiving BI 836845 containing regimen in arm 2. On days when BI 836845 is dosed, ADA samples are to be collected prior to BI 836845 infusion. ADA samples must be collected at Courses 1 through 12, EOTV and FU1 visit. For detailed sampling schedule, refer to Appendix 10.5
15. Tumor assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) according to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study, and during the phase II part of the trial imaging guidelines should be observed. Bone scans should be performed at screening (see Section 5.1.2 for more detail).

    Assessment will be performed at the following time points until progression/start of further treatment (tumor assessments after randomisation should be performed no more than 7 days prior to the scheduled tumor assessment date up to week 48 AND no more than 14 days prior to the scheduled tumor assessment date after week 48):
    - At screening (within 28 days prior start of treatment):
    - Every 8 weeks: during week 8 (49-56 days after randomisation), during week 16 (105-112 days after randomisation), during week 24 (161-168 days after randomisation), during week 32 (217-224 days after randomisation), during week 40 (273-280 days after randomisation), during week 48 (329-336 days after randomisation)
    - Every 12 weeks after week 48 (e.g. during week 59-60 (406 – 420 days after randomisation), during week 71-72 (490 – 504 days after randomisation), etc.)

    In the event of an interruption/delay to treatment, the tumor assessment schedule should not be changed. Patients who discontinue the trial for any reason other than imaging based progressive disease should have a tumour assessment (RECIST 1.1) performed at EOTV. Except in case of discontinuation from treatment due to imaging based progression, tumor assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
    Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF
16. Everolimus, if supplied by the sponsor, should be dispensed through IRT. The prescription of everolimus (if not supplied by the sponsor) and exemestane should be filled by pharmacy. Patient's screening, randomization, all drug dispensation visits and EOTV will be collected in the IRT system
17. Compliance check: on Day 1 of course 2, 3, 4, 5, etc. and at EOTV
18. For Course 2 only
19. Completion of the phase II part: Completion of the phase II part of the study should be recorded at FU (the last FU visit) when PD/death occurs, starting of new treatment, consent withdrawal or death
20. Collection of information on disease status and further therapies: information on progression, further anti-cancer treatment and death should be collected from patient's notes or by telephone contact with the patient. A formal study visit is not required
21. At visit C1V1D1 of the Phase II part, 3 mL of blood will be taken before any treatment is administered in both Arms 1 and 2. The samples will be used for future companion diagnostic development needs or for measurement of other putative predictive biomarkers in serum.
22. [redacted]
23. If extremely necessary, for arm 2 patients receiving BI 836845 infussion at a subsequent visit, the transaction with the IVRS/IWRS system can be done up to one day before the actual visit date. Please refer to BI 836845 Preparation Storage and Administration instructions for more information about BI 836845 stability and storage conditions once diluted in the infusion bag.
24. On Course 5 Day 1 only (After 16 weeks of treatment)

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS

aBC/mBC	Locally advanced/metastatic Breast Cancer
ADA	Anti-Drug Antibody
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)
[redacted]	[redacted]
BOLERO-2	Breast cancer trials of OraL EveROlimus-2
[redacted]	[redacted]
CI	Confidence Interval
CML	Local Clinical Monitor
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DC	**Disease Control (also called Clinical Benefit)**
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
Dlco	Carbon Monoxide Diffusing Capacity
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
ER+	Estrogen Receptor positive
EOTV	End of Treatment Visit
FAS	Full Analysis Set
[redacted]	[redacted]
FU	Follow up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
HER2–	Human Epidermal growth factor Receptor 2 negative
HR+	Hormone Receptor positive
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IGF	Insuline-like Growth Factor
IGF-1R	Insuline-like Growth Factor-1 Receptor
IGF-2R	Insuline-like Growth Factor-2 Receptor
[redacted]	[redacted]
INR	International Normalized Ratio
InsR	Insulin Receptor

IRB	Institutional Review Board
IRT	Interactive Response Technologies
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
mTOR	mammalian Target Of Rapamycin
OPU	Operative Unit
p.o.	per os (oral)
PD	Pharmacodynamics
PD	Progressive Disease
PFS	Progression Free Survival
[redacted]	[redacted]
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PR	Partial Response
PTM	Planned Time
q.d.	quaque die (once a day)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Stable Disease
SNPs	Single nucleotide polymorphisms
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TMM	Team Member Medicine
TSAP	Trial Statistical Analysis Plan

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Breast cancer is the most common malignancy in women worldwide. It is estimated that more than 1.6 million new cases of breast cancer occurred globally among women in 2010 (R13-2186). Even though death rates have fallen steadily since 1990, reflecting improvements in early detection and treatment, currently breast cancer is the second leading cause of cancer-related death in women (R09-5656). This high death rate reflects the limited effectiveness of current therapeutic options, particularly in patients with advanced disease.

Approximately 75% of primary breast cancers are positive for hormone receptor (HR+). These cancers express Estrogen Receptor (ER) and/ or Progestone Receptor (PgR). Therapies directed at endocrine receptors are important treatment option. For postmenopausal HR+ breast cancer, an aromatase inhibitor (AI), such as letrozole and anastrozole, is the recommended first-line therapy for management (P13-05504). Unfortunately, not all patients have a response to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). On disease progression, second-line treatment options include other classes of aromatase inhibitors (steroidal or nonsteroidal) and the estrogen-receptor (ER) antagonists fulvestrant and tamoxifen (R13-2054).

De novo and acquired resistance to endocrine therapy presents a major challenge in the management of HR+ breast cancer and is an area under intense investigation. The mammalian target of rapamycin (mTOR) pathway has been shown to play an important role in the resistance to endocrine therapy. Two recently published reports showed that a novel mTOR inhibitor everolimus combined with endocrine therapies were of benefit. In hormone refractory, hormone receptor-positive, HER2-negative metastatic breast cancer patients, tamoxifen plus everolimus resulted in increased clinical benefit compared to tamoxifen alone with improved time to progression (PFS 8.6 vs. 4.5 months) and overall survival (55% reduction in the risk of death associated with combination therapy, HR, 0.45; 95% CI, 0.24 to 0.81; exploratory P=007) (R13-1976). In a similar patient population, the Phase III Breast Cancer Trial of Oral Everolimus 2 (BOLERO-2) (R12-5635) demonstrated that treatment with everolimus plus exemestane more than doubled median progression-free survival to 7.8 months compared with 3.2 months for those treated with exemestane alone (hazard ratio, 0.45; 95% confidence interval, 0.38 - 0.54; one-sided log rank P < .0001) by local investigator assessment (R12-5281). The overall response rate was also improved compared to exemestane alone (12.6 % vs. 1.7%) (R12-5281). Based on the result of this trial, everolimus, as the first drug in the mTOR class, was approved by the regulatory agency for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole (R12-5281).

The insulin-like growth factor (IGF) pathway holds 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); and six ligand-binding proteins, 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. Certain transcription factors have been identified to be impaired by this IGF-mediated signaling process and involved in breast carcinogenesis (R13-1986, R13-1995, R13-1996).

Preclinical and clinical data indicated that aberrant regulation of the IGF system is attributed to the pathogenesis of breast cancer and also contributes to various stages of breast carcinogenesis. IGF-1R over-expression is common in breast cancer cell lines and fresh tumor biopsies (R13-2004, P13-05525, R13-2010), and IGF activity captured in a microarray signature has been associated with poor clinical outcome (P13-05658). Bidirectional crosstalk between the oestrogen and the IGF signalling pathways is well documented (R13-1983, R13-1984) with activation of the latter mediating endocrine resistance (R13-2185). In ER+ breast cancer resistant to hormonal therapy, InsR-A isoform is the predominant insulin receptor, suggesting an important role for IGF-2 signaling (R13-1976). Therefore, the IGF signalling network represents a promising target in advanced breast cancer.

Currently there are three different strategies inhibiting IGF pathways including anti-receptor monoclonal antibodies (ganitumab, cixutumumab, and dalotuzumab), tyrosine kinase inhibitors (TKI, including dual IGF-1R and InsR tyrosine kinase inhibitors BMS-754807, KW2450, and linsitinib), and anti-IGF ligand antibodies (dusigitumab (MEDI-573, [redacted]) and BI 836845) (R13-1980). These agents are now being tested in the clinic either as monotherapy or in combination with cytotoxic agents and/or other molecularly targeted agents (P13-05658).

The major advantage of neutralizing antibodies for both IGF-1 and IGF-2 is that the sequestration of the ligands ensures that receptor activation by IGF-1 or IGF-2 does not occur, and eliminates the possibility of activation of the InsR-A by IGF-2. Hence it offers a balanced approach with therapeutic potential in a variety of cancers, with few of the pitfalls of targeting the IGF-1R with monoclonal antibodies (mAbs). Currently, BI 836845 and dusigitumab are the only agents in development using this approach (R13-1980).

A potential mechanism of resistance to mTOR inhibitor therapy is the induction of AKT phosphorylation, which is frequently observed in both preclinical and clinical studies [R13-3257, R08-5567, R11-4665, R11-4672]. Furthermore, up-regulation of AKT activity is dependent on Insulin-like growth factor (IGF)/Insulin like growth factor type 1 receptor (IGF-1R) signaling [R13-3257, R08-5567, R11-4665, R11-4672]. It has been shown in tumors that inhibition of mTOR with rapalogs releases a negative feedback loop on growth factor receptors, including the insulin-like growth factor-1 receptor/insulin receptor substrate (IRS)-1 complex, resulting in activation of IGF-1R signaling and ultimately phosphorylation of AKT (R08-5567, R11-4672), which in turn could potentially counteract the anti-tumor effects of mTOR inhibitors. The activation may be prevented if IGF signaling is blocked simultaneously (R13-2053).

In preclinical models, dual inhibition of both IGF-1R, with monoclonal antibodies or tyrosine kinase inhibitors, and mTOR, results in a superior anti-proliferative effect compared with inhibition of each target alone (R13-1987). In a Phase I trial using IGF-1R antibody cixutumumab in combination with temsirolimus in a heavily treated metastatic breast cancer patients, no objective response were observed, but four patients experienced stable disease that lasted for at least 4 months (R13-2183).

Another Phase I clinical study combining ridaforolimus (a rapalog) and dalotuzumab (an antibody targeted against IGF-1R) reported remarkable clinical activity in breast cancer (R13-2056). More specifically, of 23 breast cancer patients enrolled at the time of analysis, 5 had efficacy signals (2 PRs, 1 SD for 9 months, and 2 partial metabolic responses (PMRs) on FDG-PET scan); all 5 patients were ER+, and 4 had high Ki67 breast tumors. This combination is now being explored in a larger, Phase II study restricted to women with HR-positive metastatic breast cancer (R13-2047).

Taken together, these results justify the evaluation of the IGF network as a therapeutic target in HR+ breast cancer, in combination with Everolimus.

1.2 DRUG PROFILE

1.2.1 BI 836845

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.

The BI 836845 molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy polypeptide chain of ~ 50 kDa (447 amino acids) and a light polypeptide chain of ~ 23 kDa (216 amino acids). The four polypeptide chains of the antibody molecule are linked together by disulfide bonds. Each heavy polypeptide chain contains one consensus sequence for N-linked glycosylation, which is occupied. There are two binding sites for IGF-1 and IGF-2 per antibody molecule. The antibody protein has a molecular mass of approximately 146 kDa.

BI 836845 binds with high affinity to IGF-1 and IGF-2, and potently neutralizes the proliferative and prosurvival cellular signaling triggered by both proteins. The mode of action of BI 836845 is different from IGF-1 receptor targeted mAbs. In particular, BI 836845 can inhibit IGF-2 stimulated Insulin Receptor-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, BI 836845 may achieve antitumor activity without perturbing glucose homeostasis.

Preclinical study showed that 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 BI 836845 (P12-07179).

In animal study, the Cynomolgus monkeys and rats were selected as relevant species for the investigation of the preclinical safety because the monkeys show a 100% sequence homology to human IGF-1 and IGF-2, and comparable binding affinities to BI 836845 were demonstrated in rats. For BI 836845, safety pharmacology (core battery) endpoints integrated in the Cynomolgus monkeys toxicity study demonstrated a favourable safety profile. There were no effects of treatment on neurological parameters, auditory response, respiratory rate, body temperature or cardiovascular function.

Repeat-dose toxicity studies with once weekly intravenous administration of BI 836845 for 13 weeks in Cynomolgus monkeys and for 13 or 26 weeks in rats revealed a variety of dose related and essentially reversible effects. The treatment related changes included the body as a whole (growth retardation) in both species and liver functions, the haematolymphatic system, kidneys, bone, teeth, and ovaries in rats only.

Most if not all observed effects were attributable to the pharmacodynamic potential of BI 836845, i.e. reflecting the neutralization of specific growth factors in these species during a phase of rapid body growth. Consequently, signs of general growth retardation, e.g. reduced body weight gain and body size were apparent in both species examined. The effects on the haematolymphatic system and liver function seen in the rat studies were considered to be of no toxicological relevance.

Glomerulopathy (PAS positive granules in podocytes and dilated Bowman's spaces) was observed in individual rats (7-8 weeks old at the commencement of treatment) at all dose levels of the 13-week study, but not in those of the 26-week study (10-11 weeks old). This rat glomerulopathy is therefore considered an age dependent change. On the other hand, a higher incidence and severity of interstitial structures called 'persistent granulosa cell nests within remnants of atretic follicles' were observed in the ovaries of rats at dosages of 20 and 200 mg/kg which was reversible after a 12-week recovery period. However, a number of follicles showed normal maturation and the incidences of the different stages of the menstrual cycle were not affected. The only effects noted in rats and Cynomolgus monkeys exposed similarly to rats were a dose-dependent reduction of body growth and alkaline phosphatase activity. Otherwise, young adult monkeys did not show any of the effects observed in rats, even though fully pharmacologically active doses were achieved in both species in terms of the reduction of IGF-1R phosphorylation potential (IGF bioactivity) in the plasma. Similar to rats, exposure to BI 836845 induced a weak increase in blood glucose levels up to upper limit of normal, fructosamines and HbA1c in male Cynomolgus monkeys given 30 or 100 mg/kg (equivalent to 10 to 32 mg/kg human equivalent dose - HED).

Based on the studies summarized above, the preclinical safety profile of BI 836845 is considered to be favorable for the intended oncological indications (U10-2830).

Two Phase I studies with BI 836845 monotherapy given weekly or every three weeks are conducted in patients with advanced solid tumors. 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 BI 836845 were observed 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 in the order of 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. The incidence of anti-drug antibodies (ADA) was approx. 19% in 1280.1 and 30% in 1280.2. Overall, the ADA-response was weak, dose-independent and in many cases transient and had no impact on PK or PD.

No deviations from dose-proportional pharmacokinetics have been observed in the dose range tested (10-1050 mg qw in 1280.1 and 10-3600 mg q3w in 1280.2). Steady state plasma concentrations of BI 836845 were achieved after 5-7 weeks. Repeated weekly dosing resulted in about 1.5 fold accumulation of 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 BI 836845 are mainly cleared by catabolism. This mechanism of clearance is not shared or overlapping with the clearance mechanism for small molecules. Thus, BI 836845 is not predicted to directly affect the hepatic, renal, or biliary elimination of small molecules. Furthermore, 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 BI 836845 to alter the pharmacokinetics of co-medication is considered low.

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

As of July 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 hemorrhage, 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 1280.2 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 BI 836845, an alternative explanation may have been an underlying paraneoplastic syndrome. However, consequently, investigators should carefully monitor electrolytes and excretion under treatment with 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 BI 836845 are possibly abnormal liver function tests 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 62-year old male with a recurrent nasopharyngeal carcinoma (NPC) and multiple lung metastases after concurrent chemoradiotherapy; secondly, in a 19-year old woman with a peripheral primitive neuroectodermal tumor (pPNET). In addition, twelve (25.0%) and four (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 BI 836845 (U10-2830).

1.2.2 Everolimus

Everolimus (RAD001, Afinitor®, [redacted]) is the 40-O-(2-hydroxyethyl) derivative of sirolimus; it inhibits mTOR by binding with high affinity to its intracellular receptor FKBP12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibits mTOR kinase activity.

Everolimus has been developed as both an immunosuppressant for the treatment of transplant organ rejection and as an anticancer agent (R13-2184). A phase 1 study conducted in solid tumor patients identified mucositis and fatigue as dose-limiting toxicities when everolimus was administered as a single agent using a weekly schedule. Everolimus was rapidly absorbed with a Tmax of 0.5-2.5 h, exposure was dose proportional over the therapeutic dose range (2.5 – 25 mg), with steady-state concentrations achieved within 7 days or less following once-daily dosing (R08-5716, R13-0654, R13-0655). Its terminal half-life is 30 h (range, 26–38 h). Metabolism of everolimus occurred primarily in the gut and liver by cytochrome P450 3A4, 3A5 and 2C8, with the majority of drug (approximately 98%) excreted in the bile in the form of metabolites (R08-5716).

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6 (R12-5281).

Everolimus is approved for various conditions: advanced hormone receptor-positive, HER2-negative breast cancer, advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, renal angiomyolipoma with tuberous sclerosis complex and subependymal giant cell astrocytoma with tuberous sclerosis complex. Additionally, biologic activity has been seen in a variety of tumors, including gastric cancer, hepatocellular carcinoma and lymphoma; worthy of mention, phase III trials are under way, in the aforementioned malignancies [website clinicaltrials.gov]. The approved treatment dose of everolimus in advanced HR+ BC is 10 mg daily (please refer to the most current drug precribing information for update).

1.2.3 Exemestane

Exemestane is an irreversible, steroidal aromatase inactivator. Exemestane structure is related to androstenedione, a natural substrate of the aromatase enzyme. Exemestane binds irreversibly to the active site of the enzyme and causes its inactivation. Exemestane inhibition of aromatase results in deep suppression of circulating estrogen concentrations in postmenopausal women, which is frequently below the detection limits of standard assays, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. Unlike tamoxifen, exemestane has no partial estrogen agonist activity (R13-0738).

Following oral administration to healthy postmenopausal women, exemestane is rapidly absorbed with a mean Tmax of 1.2 hours. After maximum plasma concentration is reached, levels decline polyexponentially with a mean terminal half-life of about 24 hours. The pharmacokinetics of exemestane is dose proportional after single (10 to 200 mg) or repeated oral doses (0.5 to 50 mg). Its steady-state was achieved within 7 days following once-daily dosing (R13-0766). Exemestane is extensively distributed and is cleared from the systemic circulation primarily by metabolism. Studies using human liver preparations indicate that CYP 3A4 is the principal isoenzyme involved in the oxidation of exemestane. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Exemestane plasma levels increased after a high-fat breakfast. Exemestane is mainly excreted from urine and feces (R13-0738).

Exemestane is associated with myalgias and arthralgias, as well as reduced bone mineral density and increased risk of fracture, which do not appear to persist at follow-up, with subsequent return to pretreatment values. Compared with tamoxifen, there is a reduced incidence of endometrial changes, thromboembolic events, and hot flashes. Limited evidence shows nonadherence in 23%–32% of patients. Evidence is growing in support of exemestane in all clinical settings. It is generally more efficacious and has a better safety profile than tamoxifen (R13-0738). How it compares with the nonsteroidal aromatase inhibitors remains to be established (R13-1990).

Exemestane is indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen or anti-oestrogen therapy. The approved treatment dose of exemestane is 25 mg taken once daily after a meal (please refer to the most current drug precribing information for update).

2. RATIONALE, OBJECTIVES, AND BENEFIT – RISK ASSESSMENT

2.1 RATIONAL FOR PERFORMING THE TRIAL

Dysregulation of both insulin-like growth factor signaling and the phosphatidylinositol 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) signaling pathways are linked to acquired resistance to hormonal therapy in breast cancer (R13-1977, R13-1980). Pre-clinical studies demonstrated that BI 836845 treatment inhibited the rapamycin-induced feedback phosphorylation of AKT. Similarly, rapamycin resulted in an increase in the IGF bioactivity (IGF-1R phosphorylation potential) of mouse serum, which could also be inhibited by BI 836845 (P12-07179, R13-1979). A dual-targeted combination of mTOR and IGF-1R inhibitors has been shown to have a synergistic clinical anti-tumor activity by disrupting an IGF-mediated AKT activation mechanism induced by mTOR inhibition using ridaforolimus and dalotuzumab (R13-2056). Furthermore, targeting on IGF pathway using BI 836845, a ligand blocker, could address the concern about insulin receptor serving as a bypass pathway of using IGF-1R blocker. Preliminary clinical anti-tumor activity has been observed with BI 836845 monotherapy (U10-2830).

Taken together, this study hypothesizes that BI 836845 in combination with everolimus and exemestane will block the negative feedback loop between IGF and PI3K–Akt –mTOR pathways, produce a synergistic anti-tumor effect and therefore enhance sensitivity and/or overcome resistance to endocrine therapy in HR+/HER2– advanced/metastatic breast cancer. The combination treatment with everolimus and exemestane based on BOLERO-2 trial will serve as an active control in the randomized Phase II part.

[redacted]

2.2 TRIAL OBJECTIVES

Primary objectives:

Phase I part: To determine the Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D) of BI 836845 and everolimus in combination with exemestane in women with HR+/HER2- advanced breast cancer.

Phase II part: To evaluate the antitumor activity of BI 836845 in combination with exemestane and everolimus compared to exemestane and everolimus alone in women with HR+/HER2– advanced breast cancer.

Secondary objectives:

To determine the safety of BI 836845 in combination with exemestane and everolimus in HR+/HER2– advanced breast cancer patients.

[redacted]

[redacted]

2.3 BENEFIT - RISK ASSESSMENT

Despite recent advances which came with the introduction of mTOR targeted treatment, hormone-positive advanced or metastatic breast cancer still has a dismal prognosis with median PFS of less than a year; almost all patients will develop resistance to endocrine treatment and succumb to their disease eventually.

Preclinical and clinical data indicate that aberrant regulation of the IGF system is attributed to the pathogenesis of breast cancer and also contributes to the resistance to endocrine therapy. Early evaluations of ongoing clinical trials of anti-IGF/IGF-1R agents including BI 836845 as a single agent, as well as pharmacodynamic studies of BI 836845 on neoplastic cell lines, indicate the possibility of disease stabilization, or tumor responses in patients with advanced and otherwise incurable cancers. It has also been shown in preclinical model that addition of BI 836845 to everolimus could enhance treatment effect. Therefore, it is believed that patients with HR+ breast cancer treated with BI 836845 plus everolimus and exemestane will have better efficacy compared to everolimus plus exemestane alone.

This study will be the first one combining the BOLERO-2 regimen with the IGF-1/-2 co-neutralizing monoclonal antibody BI 836845. The BOLERO-2 trial showed that the combination of everolimus and exemestane treatment is tolerated. The most common adverse reactions (incidence ≥30%) include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite. The most frequently reported grade 3/4 AEs in the everolimus arm were stomatitis, anemia, dyspnea, fatigue and hyperglycemia. These AEs were generally manageable with treatment interruption and/or dose reduction (R13-1647, R12-5635).

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 BI 836845 monotherapy. The AE profile observed has generally been consistent with the underlying neoplastic conditions with most of the AEs were CTCAE grade 1 or 2. As the clinical experience with BI 836845 is limited, safety will be carefully monitored throughout the duration of treatment with BI 836845; supportive treatments, and/or dose modification/discontinuation of BI 836845 will be mandated as necessary.

As of 16 Apr 2014, the ten most common treatment-emergent AEs regardless of relatedness are shown below:

- 1280.1 (weekly schedule): decreased appetite, anemia, back pain, weight decreased, dizziness, fatigue, cough, dyspnea, abdominal distension, and ALT increased.
- 1280.2 (3-weekly schedule): abdominal pain, diarrhea, nausea, vomiting, fatigue, decreased appetite, constipation, hypokalemia, back pain, and dyspnea.

No listed AEs are established so far. Since there is currently no relationship with dose and with IGF-mediated mechanisms, AEs which are truly drug-related and those that are possibly a reflection of the underlying cancer or concomitant illnesses cannot be differentiated at this point in time.

Although 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 BI 836845; no infusion reaction has been observed (U10-2830). The immune responses to BI 836845 mAb will be assessed through anti-drug antibody in the study.

The class-effect AEs of everolimus include: epithelia-cutaneous events (stomatitis and skin rash), metabolic abnormalities (hyperglycemia and hyperlipidemia), immunosuppression (infection), and non-infectious pneumonitis. The toxicity profile of BI 836845 and everolimus plus exemestane appears not overlapping. However, some caution is warranted when co-targeting both systems. mTOR inhibitors disrupt negative intracellular feedback loops and enhance IGF/insulin signaling and subsequent PI3K/AKT activation (R11-4670), which in turn may aggravate everolimus-related adverse events (especially mucositis and metabolic disturbance including hyperglycemia). Therefore, it is conceivable that BI 836845 may increase the efficacy as well as the side effects of everolimus, depending on whether resistance to mTOR inhibition is restricted to the tumor - or also occurs in normal tissue, for example the mucosae (stomatitis). Evidence of support may be seen from a phase II study of single agent temsirolimus in patients with metastatic breast cancer (R13-1971), in which 16% of patients experienced grade 2 stomatitis. In contrast, in a similar patient population using a combination of cixutumumab (a monclonal antibody targeting IGF-1R) and temsirolimus, 36% of patients experienced grade 2 or higher stomatitis (R13-1991). The possibility of enhanced class-effect AEs of everolimus by adding BI 836845 could be considered from the underlying mechanisms of those class effects. The stomatitis lesions of everolimus are similar to aphthous or herpetic ulcers and are different to chemotherapy-induced mucositis. mTOR inhibitor-induced stomatitis is believed to be caused by a T cell mediated inflammatory reaction. Non-infectious pneumonitis is a non-malignant inflammatory infiltration of the lungs that is associated with the use of rapamycin derivatives. The immunosuppressive properties of mTOR inhibitors may predispose patients to localized and systemic infections. So far, the clinical AE pattern of BI 836845 is less likely to be associated with immunosuppression, immune cells disturbance, or inflammation.

Early, proactive, and effective management of stomatitis is mandated in this study (see Section 4.4 for guideline). Fasting serum glucose level and lipid profiles will be assessed

monthly throughout the study for metabolic related adverse events; endocrinologist or specialist care access is required in case of grade 3 or higher event including hyperglycemia. Furthermore, patients with grade 2 or higher hyperglycemia will be excluded at the study entry; prolonged systemic corticosteroid treatment will also be prohibited during the study. 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 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.

A steering committee will oversee the conduct of the trial. A Data Monitoring Committee (DMC, internally at the sponsor) will be appointed to periodically review and monitor the data from Phase II part of the trial.

In conclusion, given the life-threatening situation of the advanced/metastastic breast cancer, potential benefits expected from BI 836845 in combination with everolimus and exemestane treatment is anticipated to outweigh its risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This clinical trial will involve two components: a dose finding Phase I part followed by a two-arm, open-label, randomized Phase II part. As the steady state of everolimus and exemestane is reached in about 7 days (R08-5716, R13-0654, R13-0655), to assess the pharmacokinetic and biomarker effect, a run-in treatment with exemestane and everolimus for 7 days prior to commencing the combination therapy with BI 836845 in the Phase I part is mandated. In addition, given the elimination half-life of all study drugs, the (first) follow-up visit is scheduled 42 days after last dose of study drug administration in order to assess the PK, biomarker and immunogenicity of BI 836845 when study drugs have been eliminated from the body.

Patients are included in the study once the informed consent is signed. The screening period will be up to 4 weeks (28 days) during which time the eligibility will be confirmed. 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.

Tumor response and progression will be assessed using RECIST 1.1 (R09-0262). Assessment at the investigator site will be used to make decisions on eligibility and continuation of treatment.

Phase I part:

Initially a "3+3" Phase I dose finding study will be performed to determine the Maximum Tolerated Dose (MTD), Recommended Phase II dose (RP2D) and pharmacokinetics of BI 836845, everolimus and exemestane in women with HR+/HER2– advanced breast cancer. It is estimated that approximately 18 patients at RP2D are needed to evaluate pharmacokinetics and a potential impact of BI 836845 on the pharmacokinetics of exemestane and everolimus. Once the RP2D is determined in approximately 12 evaluable patients, the Phase II part of the trial will commence. Meanwhile, 6 additional patients will continue to be enrolled at RP2D in the phase I part to evaluate pharmacokinetics and a potential impact of BI 836845 on the pharmacokinetics of exemestane and everolimus.

After screening, eligible patients will start the run-in with everolimus and exemestane for seven consecutive days prior to commencing the combination therapy of everolimus and exemestane with BI 836845. Patients participating in the Phase I part will be concluded after the completion of the follow-up visit.

The diagram below depicts the stages of a patient's participation in the Phase I part of the protocol.

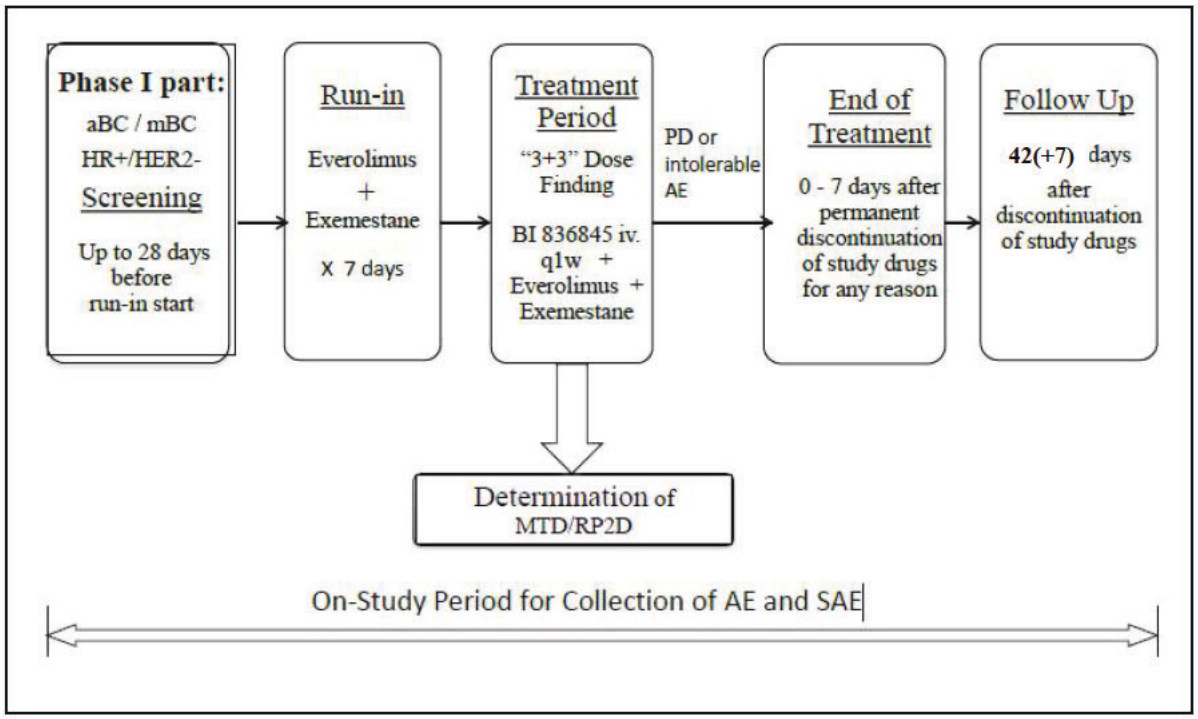


Figure 3.1: 1 Study diagram – Phase I part

Phase II part:

Once the RP2D is determined (see Section 5.2.7), an open-label, two-arm randomized Phase II study will commence to further assess the anti-tumor activity of BI 836845 in combination with exemestane and everolimus in women with HR+/HER2– locally advanced or metastatic breast cancer. Eligible patients will be randomly assigned in 1:1 ratio to one of the two treatment arms as listed below. Each arm will enroll approximately 75 patients (total of approximately 150 patients). Randomization will be stratified by visceral involvement (yes vs. no). Visceral involvement refers to lung, liver, brain, pleural and peritoneal metastasis.

Treatment arms for the Phase II part are as the following:

> **Arm 1 (control arm)**: Once daily everolimus 10 mg plus once daily exemestane 25 mg orally
>
> **Arm 2 (experimental arm)**: BI 836845 and everolimus plus exemestane. BI 836845 will be administered intravenously once weekly, exemestane is dosed at 25 mg once daily. The treatment doses of BI 836845 and everolimus will be that of the RP2D from the Phase I part of the study

Patients will receive continuous daily treatment of everolimus plus exemestane with or without weekly infusions of BI 836845.

The end of treatment visit (EOTV) should be performed when the study treatment is permanently discontinued followed by a Follow-up visit (FU1) 42 days after the termination of all study medications. Patients who discontinue study drug for reasons other than disease progression may continue the scheduled tumor assessments according to the Flow Chart. The last follow-up visit will be defined as the last visit of on-study period for this trial. Afterwards, patients will be monitored for vital status in the Observation Period. Adverse events occurring from the date when informed consent is obtained until the start of observation period will be collected.

The Phase II part of the trial will be concluded as soon as the last patient has completed the first Follow-up Visit (FU1).

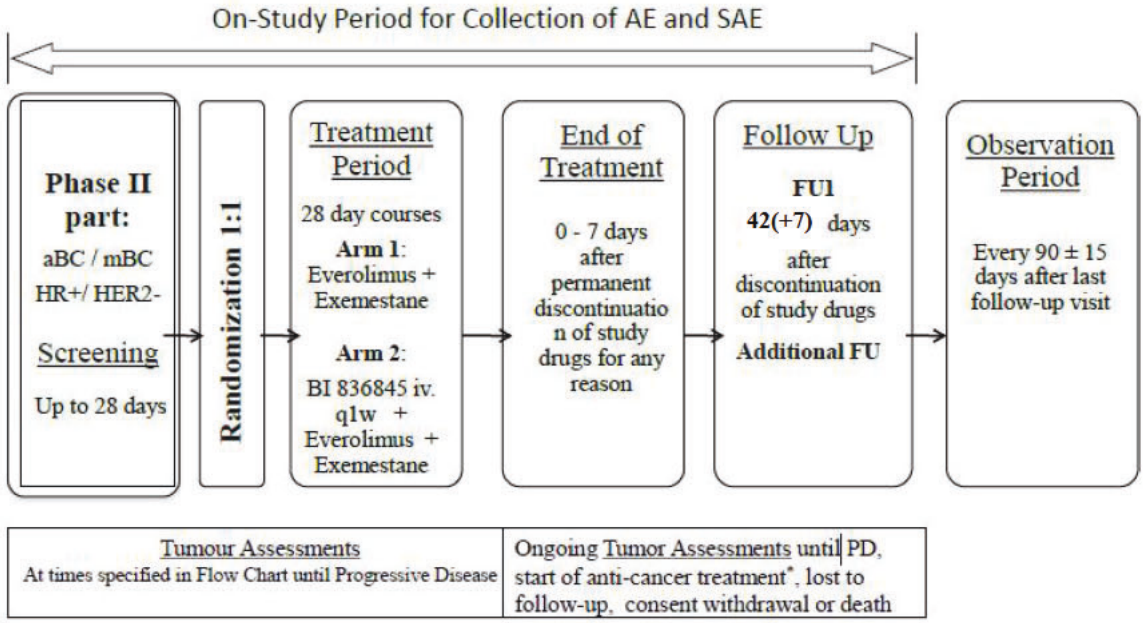


Figure 3.1: 2 Study diagram – Phase II Part

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 breast cancer.

A steering committee including the coordinating investigator, experienced investigators and BI representatives will monitor the trial on a regular basis (all operational aspects,

recruitment issues, data quality, etc.). A steering committee charter will be prepared to specify the objectives of the committee.

A BI internal data monitoring committee (DMC) will be appointed to periodically assess the Phase II data, including the aggregated data at the treatment level to ensure overall safety and integrity of the trial. Moreover, the DMC will meet at two additional pre-specified timepoints to have a look at efficacy data with emphasis on the primary endpoint. More details on the evaluations and the DMC responsibilities can be found in Section 7.3.4 as well as in the DMC charter.

Inclusion of patients in the Phase II trial will continue during the scheduled meetings of the DMC. Decisions on trial termination, amendment or cessation of patient recruitment, based on safety or outcome findings will be made after recommendations from the DMC have been assessed by the trial team and steering committee.

BI will appoint CROs and independent service providers for special services such as storage and potential central analysis of tumour images, central laboratory services for biomarker testing and part of bioanalytical testing, biosample collection and logistics, ECG, and Interactive Response Technologies (IRT) for randomisation and trial medication 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 Contract Research Organisations (CRO) appointed by BI.

All trial relevant documentation will be stored in the clinical trial master file (CTMF) 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

Phase I part

The ‘3+3’ up-and-down design is a classic dose-finding design for Phase I clinical studies in oncology, requiring no control group. As no data on the optimal dose for the BI 836845/ everolimus/exemestane combination therapy exist so far, the study will first determine the MTD and RP2D of the triple drug regimen prior to further exploring its anti-tumor activity in the Phase II part.

Phase II part

Due to the inherent differences between the two treatment arms, i.e. continuous oral treatment with intravenous infusion in the BI 836845 containing arm versus continuous oral treatment only in the control arm, the trial will be open-label. Since the only way to conduct this as a blinded trial would have been the addition of an i.v. placebo to the control arm, which is not ethically acceptable in an exploratory Phase II setting.

However, steps to minimize potential bias are in place for this open-label clinical trial. These include the use of a central randomisation method and the blinding of the trial team to treatment level aggregated data until database lock.

3.3 SELECTION OF TRIAL POPULATION

Phase I part

It is estimated that a total of about 21 to 48 evaluable patients will be necessary to determine the MTD, the Recommended Phase II Dose and pharmacokinetics of BI 836845, everolimus and exemestane.

The Phase I part of the trial will be conducted in about six to twelve centers in Europe. If needed, centers from other region such as Asia may also participate. Each center is expected to enroll about one to three patients. If center(s) are unable to recruit patients, additional centers may be opened and underperforming centers may be closed.

Phase II part

In the Phase II part, approximately 150 patients will be randomized at approximately 45 study sites globally. The rate of randomization will vary by study site, but is expected to be approximately 3 to 4 patients per site. Additional country may be added if necessary.

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.

Enrollment is competitive. Investigators will be notified when the appropriate number of patients has 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 and are eligible prior to notification of the termination of recruitment will be allowed to continue in the study.

3.3.1 Main diagnosis for study entry

3.3.2 Inclusion criteria

1. Histologically-confirmed locally advanced (aBC) or metastatic breast cancer (mBC) not deemed amenable to curative surgery or curative radiation therapy
2. Tumors are positive for estrogen-receptor (ER) and/or progesterone receptor (PgR). Tumors must be negative for HER2 per local lab testing. ER, PgR and HER2 status previously assessed by local lab is acceptable
3. Must have adequate archival tumor tissue from surgery or biopsy (refer to Section 5.3.3 and Section 5.6.3.3 for details). If multiple surgeries/biopsies are available for individual patient, the most recent and/or the most appropriate tissue material is requested

4. Postmenopausal female patients aged ≥18 years old. Postmenopausal status is defined either by:

    a. Age ≥ 55 years and one year or more of amenorrhea
    b. Age < 55 years and one year or more of amenorrhea, in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and FSH and estradiol within postmenopausal ranges as per insititution standard/normal practice.
    c. Surgical menopause with bilateral oophorectomy

5. Objective evidence of recurrence or progressive disease on or after the last line of systemic therapy for breast cancer prior to study entry

6. The patient is disease refractory to non-steroidal aromatase inhibitor (letrozole and/or anastrozole): defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of aromatase inhibitor treatment for locally advanced or metastatic disease

    Note: Letrozole or anastrozole do not have to be the most recent treatment. Prior anticancer therapy, e.g. tamoxifen, fulvestrant are allowed

7. Patients must have
    a. Measurable lesion according to RECIST version 1.1 (R09-0262) **or**
    b. Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable lesion as defined above

Both, 7a and 7b above must fulfil the condition described in Section 5.1.2 for irradiated tumors.

8. Eastern Cooperative Oncology Group (ECOG, R01-0787) performance score ≤ 2. Refer to APPENDIX 10.2

9. Life expectancy of ≥ 6 months in the opinion of the investigator

10. Fasting plasma glucose < 8.9 mmol/L (< 160 mg/dL) and HbA1c < 8.0%

11. Adequate organ function, defined as all of the following:

    a) Absolute neutrophil count (ANC) ≥ 1500/mm^3
    b) Platelet count ≥100,000/mm^3
    c) International Normalized Ratio (INR) ≤ 2.0
    d) Serum creatinine ≤ 1.5 times ULN.
    e) Total Bilirubin ≤ 1.5 times upper limit of institutional normal (patients with Gilbert syndrome total bilirubin must be < 4 times institutional upper limit of normal)

f) Aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤ three times the upper limit of institutional normal (ULN) (if related to liver metastases ≤ five times ULN)
g) Fasting triglycerides ≤300 mg/dL or 3.42 mmol/L
h) Hemoglobin (Hgb) ≥ 9.0 g/dL

12. Recovered from any previous therapy related toxicity to ≤ Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia)

13. Written informed consent that is consistent with ICH-GCP guidelines and local regulations

Optional fresh biopsy substudy for the Phase II part:

Inclusion criteria for the biopsy substudy are identical to the main study of the phase II part except for the following two inclusion criteria:

- Fresh tumor biopsy should be taken when deemed safe and feasible by the investigator and upon informed consent by the patient. Bone lesion is not recommended for biopsy

- Patients eligible to undergo tumor biopsy should have normal coagulation parameters (INR and PTT within normal range)

3.3.3 Exclusion criteria

Phase I part:

1. Previous treatment with agents targeting on IGF pathway, phosphoinositide 3-kinase (PI3K) signaling pathway, protein kinase B (AKT), or mammalian target of rapamycin (mTOR) pathways (sirolimus, temsirolimus, etc.)

2. Prior treatment with exemestane (except adjuvant exemestane stopped > 12 months prior to start of study treatment as long as the patient did not recur during or within 12 months after the end of adjuvant exemestane)

3. Known hypersensitivity to monoclonal antibody, mTOR inhibitors (e.g. sirolimus), or to the excipients of any study drugs

4. Ovarian suppression by ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate)

5. Less than one week after receiving immunization with attenuated live vaccines prior to study treatment

6. Radiotherapy within 4 weeks prior to the start of study treatment, except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within two weeks prior to study treatment

7. Chemotherapy, biological therapy (other than bevacizumab), immunotherapy or investigational agents within 5 half-life of the drug or within two weeks prior to the start of study treatment, whichever is longer; bevacizumab treatment within 4 weeks prior to start of study treatment (this criterion concerns anti-cancer therapy only)

8. Hormonal treatment for breast cancer within 2 weeks prior to start of study treatment

9. Major surgery in the judgement of the investigator within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study

10. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use except in cases outlined below:
    a. Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed
    b. Patients on stable low dose of corticosteroids for at least two weeks before study entry are allowed

11. Chronic hepatitis B infection (defined as presence of HBsAg and/ or HBV- DNA), chronic hepatitis C infection (defined as presence of anti-HCV Ab and/or HCV-RNA) and/or known HIV carrier

12. QTcF prolongation > 470 ms or QT prolongation deemed clinically relevant by the investigator (e.g., congenital long QT syndrome).The QTcF will be calculated as the mean of the 3 ECGs taken at screening (see Section 5.2.4)

13. 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 tumor (subjects who are intended for urgent chemotherapy)

14. History or current presence of brain or other CNS metastases

15. Bilateral diffuse lymphangitic carcinomatosis (in lung)

16. Hypokalemia of Grade >1

17. History of another primary malignancy within 5 years, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer

18. Family history of long QT syndrome

19. Any concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety and anti-tumor activity of the test drug(s) such as:

    a) History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure, New York Heart Association (NYHA, refer to Appendix 10.1) functional classification of 3 or 4, unstable angina or poorly controlled arrhythmia, including any type of atril fibriliation. Myocardial infarction within 6 month prior to the study entry
    b) Impairment of gastrointestinal function or who have gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome) , or any GI disorders of Grade > 1
    c) Active skin, mucosa or ocular disorders of Grade > 1
    d) Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O_2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates

20. Patients being treated with drugs recognized as being strong or moderate CYP3A4 and/or P-glycoprotein (PgP) inhibitors and/or strong CYP3A4 inducers within 2 weeks (or use of amiodarone within 6 months) prior to study entry. Refer to Section 10.3

21. Patients unwilling or unable to comply with study and follow-up procedures in the opinion of the investigator

22. Patients received more than two lines of chemotherapy for locally advanced or metastatic breast cancer

    Note: A chemotherapy line in advanced/metastatic disease is an anticancer regimen(s) that contains at least 1 cytotoxic chemotherapy agent and given for 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a "prior line of chemotherapy". Locally advanced / metastatic disease is to be understood as not amenable for curative therapy/surgery. Therefore chemotherapy agents in the adjuvant/neoadjuvant setting should not be considered here.

Phase II Part:

Exclusion criteria for the Phase II part are identical to the Phase I part except that exclusion criteria number 22 of the Phase I part is replaced with the following exclusion criteria:

- Patients received more than one line of chemotherapy for locally advanced or metastatic breast cancer

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be withdrawn from study therapy in case any of the following applies:

1. The patient withdraws consent from study treatment
2. Documented progressive disease
3. The patient is no longer able to receive any of the study treatments (e.g. adverse events, concomitant diagnoses, surgery, concomitant medications or administrative reasons)
4. An increase in QT/QTc to >500 ms or of >60 ms over baseline
5. Significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made after discussion between the sponsor and the investigator
6. Further dose reductions considered necessary but not allowed according to the protocol (for exceptions, refer to Section 4.1.4.3)

A patient has to be considered to have completed the trial and any further study assessment (except the observation period for collection of vital status and further therapies) in case any of the following applies:

1. Documented progressive disease (refer to Section 5.1.2)
2. Start of new anti-cancer treatment
3. Withdrawal of consent

If possible, a patient who discontinues treatment for reasons other than the above criteria should continue to be followed up based on the tumor assessment schedule.

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, disturbing the appropriate conduct of the trial,
4. Decision to terminate the trial by the sponsor.

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

3.3.5 Replacement of patients

Phase I part:

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

Patients will be replaced for the assessment of Dose Limiting Toxicity in cases of:

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

2) Patients who do not experience DLT but miss ≥ one BI 836845 administration or ≥ 6 doses of everolimus in first treatment course

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

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

5) Patients who miss more than one dose of everolimus or exemestane during the run-in period may be replaced after discussion between the sponsor and the investigator.

Patients that have been replaced might continue treatment in the trial should criteria in Section 4.1.4.2 apply; however these patients will not be considered for the evaluation of DLT.

Phase II part:

Patients who withdraw from the trial after randomisation/entering active treatment phase will not be replaced.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will receive BI 836845 plus everolimus and exemestane triple-drug combination or everolimus plus exemestane doublet therapy. The manufacturers for each of the products are listed in Section 4.1.1.

4.1.1 Identity of BI investigational product and comparator products

4.1.1.1 BI 836845 (investigational product)

Substance:	BI 836845 human monoclonal antibody
Pharmaceutical form:	Liquid formulation
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml of BI 836845 supplied in 20 ml vials (200 mg/vial)
Weekly dose	1000 mg, 750 mg (starting dose)
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
Route of administration:	Intravenous infusion. Appropriate dose of 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

Detailed preparation and handling of BI 836845, including information on infusion equipment and infusion procedure, will be described in ISF.

4.1.1.2 Everolimus (Afinitor®) (investigational product)

Everolimus is a registered commercially available drug and will be provided by the sponsor. However, if the recommended phase II dose of Everolimus is on label, e.g. 10 mg daily, for countries starting the trial with the phase II part, and if local regulation permits, Everolimus will be considered non-investigational product and hence, will be supplied by a pharmacy. For countries starting the trial with the phase I part, Everolimus will be supplied by the sponsor throughout the trial.

Pharmaceutical form: Tablets

Source:	[redacted] (for EU countries)
Unit strength:	2.5 mg and 5 mg
Daily dose:	Phase I part: Starting dose 10 mg continous daily at Cohort 1a. If necessary, dose deescalation will occur as outlined in Section 4.1.3 until determination of MTD and RP2D. In Phase II part, starting dose will be 10 mg in arm 1 and RP2D in arm 2 as outlined in Section 3.1.1
Duration of use:	Continuous dosing in the absence of disease progression, intolerable AEs or other reason necessitating withdrawal
Route of administration:	Oral (swallowed)
Posology:	Once daily after a meal
Additional information:	Drug should be administered according to the summary of product characteristics for EU or the prescribing information for respective country

4.1.1.3 Exemestane (Aromasin®) (non-investigational product)

Exemestane is a registered commercially available drug; the generic version of exemestane is now available. Exemestane will not be provided by the sponsor. Instead, it will be provided by a pharmacy.

Pharmaceutical form:	Tablets
Source:	[redacted] or other companies with therapeutic equivalents
Unit strength:	25 mg
Daily dose	25 mg
Duration of use:	Continuous dosing in the absence of disease progression, intolerable AEs or other reason necessitating withdrawal
Route of administration:	Oral (swallowed)
Posology:	Once daily after a meal
Additional information:	Drug should be administered according to the summary of product characteristics for EU or the prescribing information for respective country. From the start of run-in period through Course 1 Day 8 of

phase I part, exemestane from the same manufacture must be used for PK evaluation

4.1.2 Method of assigning patients to treatment groups

4.1.2.1 The Phase I part:

Treatment slots are assigned by the BI Clinical Monitor (CM) in close communication (email/phone/fax) with the recruiting sites and IRT system 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 reasonable period of time until patient signs ICF. If more than one site notifies potential patients and there are no slots for all proposed candidates, BI Clinical Monitor will allocate the slot prioritizing by planned calendar, balanced number of patients per site and other parameters as needed.

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 Phase II part:

Patients that meet the eligibility criteria and who have given their written informed consent will be randomized in a 1:1 ratio to everolimus plus exemestane (Arm 1) or BI 836845 plus everolimus and exemestane (Arm 2) treatment regimen.

Randomisation will be carried out centrally using Interactive Response Technologies (IRT, also called IVRS/IWRS). The company that provides the IRT will receive the randomisation list from [redacted] or a CRO appointed by the sponsor. The BI standard validated random number generating system will be used to generate the randomisation schedules which will be verified by an independent statistician who is not involved in the study. The access to the randomisation code will be supervised by the [redacted]; persons directly involved in the conduct and analysis of the trial will have no access to the randomisation schedule.

4.1.3 Selection of doses in the trial

4.1.3.1 Run-in treatment with everolimus and exemestane in the Phase I part

Prior to commencing the combination therapy with BI 836845 in the Phase I part, patients will receive treatment with exemestane 25 mg and everolimus for 7 days (from Day -7 to -1). The treatment dose of everolimus will depend on the treatment cohort the patient has been assigned to (e.g. 5 mg/d, 7.5 mg/d or 10 mg/d).

4.1.3.2 Determination of MTD in the Phase I part

In this study, the dose of exemestane is 25 mg daily continuous based on the label. The starting dose of everolimus is 10 mg daily, which is the approved dose for the study population (please refer to the latest version of SPC or PI).

In a Phase I study of everolimus plus ganitumab in patients with advanced solid tumors, the RP2D of everolimus is 10 mg daily (R13-2441). The approval of 10 mg daily dose of everolimus in breast cancer patient population is based on BOLERO-2 study in which, 50% patients reported grade 3 or 4 AEs (R12-5281) with 67% patients had dose reduction or treatment interruption (R13-1647). The first dose reduction in BOLERO-2 is 50% or 5 mg daily dose. The mean dose intensity of everolimus is 7.1 mg/day and 7.9 mg/day for patients at least 65 years old and those below 65 years old, respectively. All of these implied that everolimus can be tolerated at different dose levels. As the toxicity profile of everolimus could be augmented by the inhibition of IGF pathway, several dose levels of everolimus might be tested in case the occurrence of DLT is related to everolimus.

Based on biological effects observed in two dose finding studies using monotherapy of BI 836845 (please refer to the current version of the Investigator's Brochure, U10-2830), a dose level of 750 mg with weekly dose schedule are selected as the starting dose for this study.

BI 836845 is to be administrated weekly without a loading dose. The plan is to start with everolimus 10 mg daily in combination with escalating/de-escalation dose tiers of BI 836845 until determination of MTD and RP2D (refer to Sections 5.2.6 and 5.2.7 for definition). Intra-patient dose escalation is not permitted. If 10 mg everolimus dose is not tolerated, cohort with lower dose level of everolimus will be started.

Cohorts of 3 patients are to be entered sequentially into escalating/deescalating dosage tiers of BI 836845/everolimus/exemestane and observed until the end of the first course for the occurrence of a DLT. If no DLT is observed, the dose will be escalated in the next cohort and three more patients will be treated at the next higher dose; if one patient experiences DLT, then three additional patients will be treated at the same dose; if two or more patients have DLT, then the MTD has been exceeded and the dose will be deescalated or the trial may be terminated. To further approximate the MTD, the dose may be re-escalated, as long as it remains lower than the dose which exceeded the MTD.

Starting doses are outlined in Table 4.1.3.2: 1 / Cohort 1a. The dose of BI 836845 for the successive cohort is to be increased directly to that of Cohort 1b unless two or more patients out of six with DLTs are observed, in which case, if the DLT is mainly related to BI 836845, the dose level of Cohort 1a will be determined as MTD; if the DLT occurred in Cohort 1b is mainly related to everolimus, the Cohort -1b should be followed. If one or none DLT occurred at Cohort 1b out of six evaluable patients, the dose level of Cohort 1b will be determined the MTD. Cohort -1b could be the MTD, or be followed by Cohort -1a or Cohort -2b, depending on the number of DLT observed and the relatedness of DLT to the study drugs.

On the other hand, if two or more DLT is observed at Cohort 1a, Cohort -1a may be followed, subsequently followed by Cohort -1b, Cohort -2b or Cohort -2a depending on the DLT observed. If two or more DLTs are observed at Cohort -2a, the trial may be terminated.

Examples of dose escalation/deescalation plan are illustrated in Figure 4.1.3.2: 1 and 4.1.3.2: 2. During dose finding stage, safety profile as well as DLT will be discussed with the investigators and the steering committee. The decision on the next dose level or determination of MTD and RP2D will be documented.

Table 4.1.3.2: 1 Concomitant dosing schedule schemes of the Phase I part

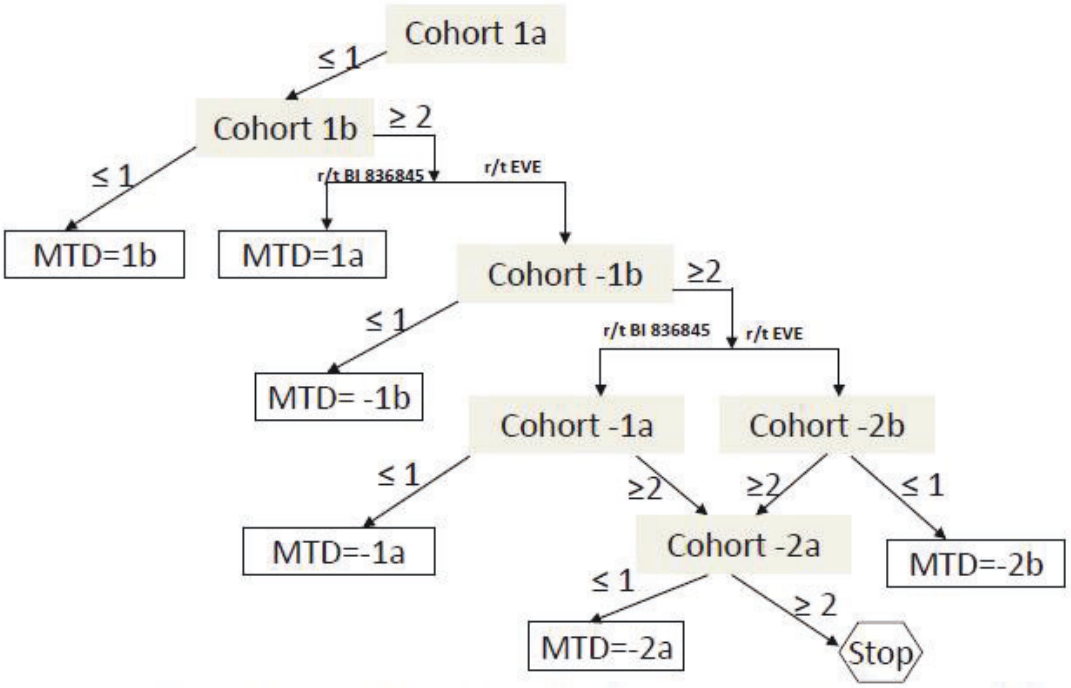
Cohort	BI 836845 (mg)	Everolimus (mg)	Exemestane (mg)
Cohort -2a	750	5	25
Cohort -2b	1000	5	25
Cohort -1a	750	7.5	25
Cohort -1b	1000	7.5	25
*Cohort 1a	750	10	25
Cohort 1b	1000	10	25

*-Starting dose level

Additional patients can be enrolled at MTD/RP2D if required for safety and/or PK analysis. If the RP2D is different from the MTD, a total of 18 patients should be treated at the RP2D of the phase I part.

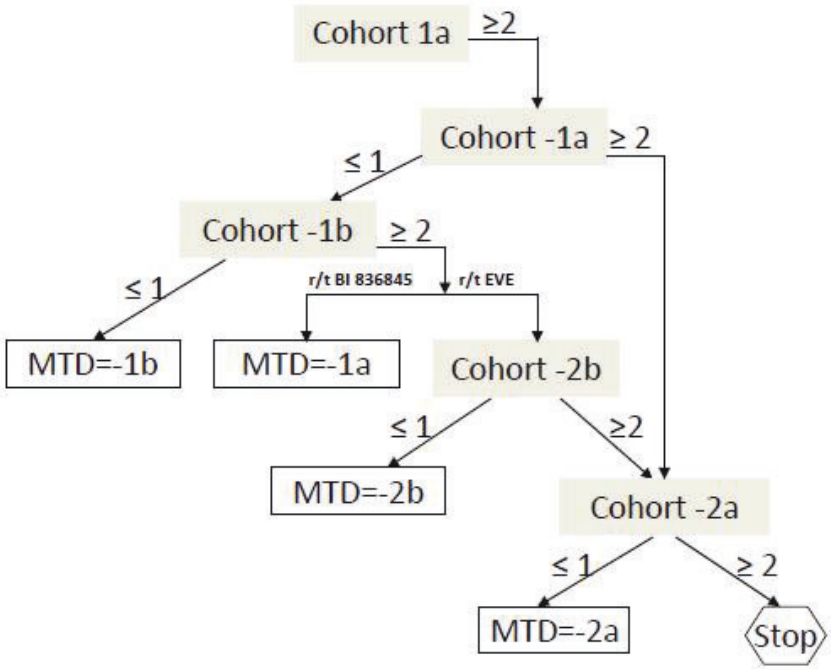
Above dose levels may be modified and/or additional dose levels/administration regimens may be added based on safety profile and other emerging data upon discussion and agreement between the sponsor and investigators.

Examples of dose decision tree are illustrated as following:



Note: The numerical values (≤**1** or ≥**2**) indicate # of DLTs occurred in three or six evaluable patients at each cohort. 1a, 1b, -1a, -1b and -2a, -2b indicate the dose level of the cohort. r/t BI 836845: related to BI 836845; r/t EVE: related to everolimus. MTD is determined based on the occurrence of DLT during the first treatment cycle

Figure 4.1.3.2: 1 Dose decision tree example one



Note: The numerical values (≤**1** or ≥**2**) indicate # of DLTs occurred in three or six evaluable patients at each cohort. 1a, 1b, -1a, -1b and -2a, -2b indicate the dose level of the cohort. r/t BI 836845: related to BI 836845; r/t EVE: related to everolimus. MTD is determined based on the occurrence of DLT during the first treatment cycle

Figure 4.1.3.2: 2 Dose decision tree example two

Refer to Sections 5.2.6 and 5.2.7 for definition of DLT, MTD and RP2D.

4.1.3.3 Selection of phase II dosing schedule

The decision on dose escalation/deescalation, MTD and RP2D will be determined in discussion with steering committee comprised of at least BI Trial Clinical Monitor, BI project physician (TMM) and Coordinating Investigator and taking into account patient safety. This decision will be documented.

4.1.4 Drug assignment and administration of doses for each patient

The treatment medication assignment for BI 836845 and everolimus, if supplied by BI, will be managed through IRT system. However, if everolimus is used on label in the phase II part, it will be prescribed by the investigator and supplied by a pharmacy in some countries; under this circumstance, everolimus will not be managed through IRT system. Exemestane will not be supplied by the sponsor throughout the study; therefore, it will not be managed through IRT system.

In addition, patient's screening, run-in, randomization, 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 in this study regardless of IRT is described in below sections of individual study drug. The medication kit as well as the treatment will be assigned with the support from IRT. The detailed information regarding handling of medication number will be described in ISF.

Before entering patients at the next dose level of the phase I part, 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 BI 836845

Patients will start treatment with their assigned dose tier (see Section 4.1.3) or RP2D of BI 836845 from course 1 day 1. 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. If scheduled infusion of BI 836845 is not performed within the time window, this treatment will be skipped and will not be made up. Subsequent visits should follow the original visit date schedule. Mannitol is used in the formulation of 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 $\geq$ 2 infusion reactions (see Section 4.4.2 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.

At days of PK sampling during the Phase I and II part, everolimus and exemestane should be administrated within 5 minutes after start of BI 836845 infusion.

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

4.1.4.1.2 Everolimus

Everolimus should be taken orally once daily after a meal at the same time every day. The blisters for everolimus tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. All blisters will conform to local regulatory requirements. The tablets should not be crushed or chewed. Everolimus should be swallowed whole with a large glass of water.

At days of PK sampling, **patients should NOT take study medication at home prior to their visits to the study site.**

Missed doses of everolimus can be made up if taken within 6 hours of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Patients must not take 2 doses to make up for the missed dose. **Missed doses of everolimus should be recorded in the eCRF throughout the study.**

Everolimus will be prescribed by the investigator. If everolimus is supplied by the sponsor, it will be dispensed at visits described in Flow Chart either by the investigator, site staff or affiliated pharmacy through IRT. Otherwise, the prescription of everolimus should be filled by pharmacy. During the study, patients may be administered a combination of different dose strengths of everolimus to reach the expected dose level as outlined per protocol. For example, 10 mg everolimus can be given with two tablets of 5 mg or one tablet of 5 mg plus two tablets of 2.5 mg.

4.1.4.1.3 Exemestane

The recommended treatment dose for exemestane is one 25 mg tablet once daily after a meal. Complete guidelines for management and administration of exemestane can be found in EU Summary of Product Characteristics or the prescribing information of respective country.

At days of PK sampling, **patients should NOT take study medication at home prior to their visits to the study center.**

Missed doses of exemestane can be made up if taken within 6 hours of the regularly scheduled time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Patients must not take 2 doses to make up for the missed dose. **Missed doses of exemestane should be recorded in the eCRF throughout the study.**

There will be no investigational supply of exemestane. Exemestane will be prescribed by the investigator at visits described in Flow Chart and filled by pharmacy.

4.1.4.1.4 Special instructions for the Run-in period and up to Course 1 Day 8 of the Phase I part

During the study period critical for DDI analysis (Run-in period and up to Course 1 Day 8 of the Phase I part), the timing of drug administration and food intake are specified in the following:

Patients should be advised to take everolimus and exemestane at approximately the same clock time in the morning after breakfast when taking study drugs at home.

At days of PK sampling critical for DDI analysis **(on Day -1 of Run-in and C1D1, C1D2 of the Phase I part)**, **patients need to come fasted to the study site and should not take study medication at home prior to their visits.** Breakfast should be taken at approximately the same clock time on these days. The content and amount of the breakfast must be as close as possible on Day -1 of Run-in and C1D1, i.e. containing the same ingredients in a very similar amounts.

The breakfast and drug administration should be timed according to the following schedule:

1. Patients start breakfast 30 min prior to start of infusion AND/OR 35 min prior to administration of everolimus and exemestane. Patients should complete their breakfast within 25 min

2. The pre-treatment sample should be taken 5 min prior to BI 836845 infusion AND/OR 10 min prior to administration of everolimus and exemestane.

3. 5 min after start of infusion AND/OR 35 min after start of breakfast, everolimus and exemestane are administered.

Information on drug and food intake during the Run-in and up to C1D8 should be recorded on the diary card and the **eCRF**.

Sites should be encouraged to schedule PK visits in the early morning to accommodate consistent dosing schedules.

4.1.4.2 Additional course of treatment in Phase I part

The dose of BI 836845, everolimus and exemestane assigned upon entry to this trial will be used on all the scheduled administrations described in the Flow Chart unless the patient experienced DLT or treatment related adverse events which require dose modification.

Patients demonstrating a clinical benefit (i.e., with either an objective tumor 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

DLT or those AEs requiring dose adjustment as indicated on the label, 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 4.4 for additional recommendations. In Phase I, both BI 836845 and everolimus must be paused when DLT occurs during the first treatment course.

To prevent the development of more severe adverse events, treatment related stomatitis, non-infectious pneumonitis and metabolic events should be closely monitored and managed early as described in Section 4.4.

The treatment should be paused until patient has recovered from the drug-related toxicity to grade ≤1 or baseline. Baseline is defined as the CTCAE grade at the start of treatment. For patients who develop DLT, treatment may be resumed at reduced dose according to dose reduction scheme of the patient's starting dosage. If a patient has not recovered to Grade ≤1 or baseline within 28 days, study treatment must be permanently discontinued. In the event

that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with study drug(s) will be decided in agreement between the sponsor and the investigator.

Dose reductions will apply to individual patients only. Doses of BI 836845 and/or everolimus can be reduced independent of each other. Once the treatment dose is reduced for a particular patient, it should not be increased back to the previous dose.

Table 4.1.4.3: 1 Dose reduction scheme

Dose level	BI 836845	BI 836845	Everolimus dose (1)	Everolimus dose(2)	Everolimus dose (3)
0 = starting dose	1000 mg	750 mg	10 mg daily	7.5 mg daily	5 mg daily
-1 dose level	750 mg	500 mg	5 mg daily	5 mg daily	2.5 mg daily
-2 dose level	500 mg	Off-drug	2.5 mg daily	2.5 mg daily	2.5 mg every other day

Stomatitis, non-infectious pneumonitis, and metabolic events including hyperglycemia and dyslipidemia are common side-effects of everolimus listed on drug label. Please refer to the current everolimus prescribing information for dose adjustment recommendations (except for the Course 1 of the Phase I part where DLT occurs, in which 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, first dose modification is recommended to be made to everolimus preferentially.

No dose reduction is allowed below 500 mg for BI 836845 or 2.5 mg every other day for everolimus.

Alternative dose modification scheme can only be considered after discussion and agreement between the investigator and the BI clinical monitor.

Management of everolimus related adverse reaction and dose adjustment should be based on the European SPC or current prescribing information for everolimus of respective country or institutional standard, except for the Course 1 of the phase I part, for which, protocol should be followed in case of DLT.

Patients who need to reduce the dose of the same drug for more than two times should be discontinued from that drug treatment. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgement could be considered upon discussion with BI's Clinical Monitor.

During temporary treatment interruption of BI 836845, the scheduled drug infusion will be missed and will not be administered retrospectively.

In the event of any unrelated AEs or related non-DLT AEs, the study drug(s) may be interrupted for up to 28 days, but no dose reduction should occur unless indicated in the current drug label/SPC of everolimus or exemestane. Otherwise, the decision to continue with the study treatment will be made by the BI Clinical Monitor in agreement with the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label study. Blinding is not applicable. However, to reduce bias, the BI trial team will be blinded for the aggregated phase II part data at the treatment level until the trial database lock for the primary readout.

The prespecified looks by the DMC (see section 7.3.4) will not lead to an unblinding of the trial team in order to prevent potential introduction of operational bias. A logistics plan prepared and approved in accordance with BI's specific procedures will detail procedures used to ensure that all members of the trial team remain blinded. All subsequent actions requested by the DMC will be performed by an independent team as defined in the DMC charter. The logistics plan will also contain a detailed list of functions that need to be unblinded to perform this analysis.

4.1.5.2 Procedures for emergency unblinding

This is an open-label study. Procedures for emergency unblinding are 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 BI 836845 and boxes of everolimus (if supplied by BI) will be labelled according to local regulations and will include the following as a minimum:

- The study number (1280.4)
- Product name
- Contents of the bottle/carton box
- Strength
- Batch number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement indicating that the medication is for clinical trial use only
- A caution statement

Examples of the labels will be filed in the ISF.

The BI 836845 and Everolimus (if provided by BI) 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

BI 836845 and everolimus (for those provided by the sponsor) must be kept in a secure, limited access storage area under the storage conditions defined on the drug label. Temperature logs must be maintained to assure that drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor as provided in the list of contacts.

Investigational drug supply of BI 836845 and everolimus must be stored in the original packaging.

4.1.8 Drug accountability

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

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

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

Any opened vials of BI 836845 should be discarded after use following local regulations and local hospital practices.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

4.2.1.1 Rescue medication

Rescue medications to reverse the effects of BI 836845, everolimus, and exemestane are not available. Side effects of these treatments should be treated symptomatically with treatment interruption and dose reduction when needed. There is no specific antidote to overdosage of everolimus or exemestane.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

Precaution should be taken to avoid extravasation of 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 reinitiated according to local practice.

4.2.1.3 Concomitant treatments

Symptomatic treatments of tumor-associated symptoms are allowed. Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After study enrollment, palliative radiotherapy may be given for analgesic purposes, lytic lesions at risk of fracture or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range to non-target lesion according to institutional standards. Information on palliative radiotherapy will be captured in e-CRF. It is at the investigator's discretion to withhold the study treatment during palliative radiotherapy. The investigators should assess the signs/symptoms carefully to exclude the progressive disease prior to the administration of the palliative radiotherapy.

The acute use of bisphosphonates for symptomatic treatment of bone metastases is permitted during the study, but chronic use for the prevention of bone metastases is prohibited (see Section 4.2.2.1). Bisphosphonate therapy for the treatment of osteoporosis, at the doses indicated under prescribing information, is permitted during the study. If bisphosphonate therapy is initiated after enrollment, the reason for its use must be clearly documented clearly documented in the eCRF.

All medications (other than study drug), including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, and significant non-drug therapies (including physical therapy and blood transfusions) starting or changing after the patient

signed informed consent must be listed on the concomitant medication page of eCRF including trade name, start and end dates, indication for use etc. as specified in the Flow Chart. Subsequent anti-cancer therapy received after discontinuation of the study treatment must also be recorded in the eCRF for patients participating in the Phase II part of the study.

If patients receive parenteral nutrition during the trial, the components need not be specified in detail. It should just be indicated as "parenteral nutrition". If a patient requires anesthesia, it will be sufficient to indicate "anesthesia" without specifying details.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with BI 836845 and/or everolimus around one week prior to the surgery, and to restart treatment after complete wound healing. If the patient can't recover within 28 days since stopping study medication, she should be removed from the study. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgement could be agreed upon discussion with BI's Clinical Monitor.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

For everolimus: Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Systemic concomitant strong CYP3A4 inhibitors and PgP inhibitors should not be used with everolimus. (refer to Appendix 3 for a list of examples).
Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided (refer to Appendix 3 for a list of examples). If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the everolimus dose is returned to the dose used prior to initiation of the co-administration.

Avoid the use of concomitant potent CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, dexamethasone or St. John's wort). If patients require co-administration of a potent CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the co-administration.

St.John's Wort may decrease everolimus exposure unpredictably and therefore should be avoided.

For exemestane: Exemestane is a substrate of CYP3A4. Pharmacokinetic study showed that co-medications that induce CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine,

phenobarbital, dexamethasone or St. John's wort) may significantly decrease exposure to exemestane.

Since the clinical relevance of this interaction has not been evaluated, the co-administration of drugs, known to induce CYP3A4 may reduce the efficacy of exemestane.

Exemestane does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Nevertheless, exemestane should be used cautiously with drugs that are metabolised via CYP3A4 and have a narrow therapeutic window.

In order to effectively assess the pharmacokinetics of exemestane, everolimus and BI 836845 and to investigate potential alterations of pharmacokinetics during co-administration, **strong and moderate CYP3A4 inhibitors/inducers and/or strong and moderate P-gp inhibitors are prohibited during the run-in period and the first treatment course at the Phase I part** (refer to Appendix 3 for a list of examples)**.** Switching to a different class of drug that is not a strong or moderate CYP3A4 inhibitor/inducer and/or strong or moderate P-gp inhibitor at least 14 days prior to the run-in period is permitted.

Starting from Day 1 of Course 2 of the Phase I part and Day 1 of Course 1 of the Phase II part, follow the respective drug package insert/SPC when considering concomitant treatment with CYP3A4/PgP inhibitors/inducers.

Antiplatelet medications (e.g. acetylsalicylic acid) should be discontinued 7 days prior to tumor biopsy. Anticoagulant medications should be discontinued prior to tumor biopsy. Warfarin should generally be discontinued at least 5 days prior to tumor 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. These medications may be restarted after tumor biopsy at the discretion of the investigators.

In addition, the following concomitant treatments are not allowed during the study:

1) Chronic concomitant bisphosphonate therapy for the prevention of bone metastases (the use of any other agent for the prevention of bone metastasis is not allowed during the study).
2) Investigational or commercial anticancer treatment and/or standard chemo-, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than exemestane
3) Growth hormones or growth hormone inhibitors
4) Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene)
5) Prolonged systemic corticosteroid treatment, except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections

(e.g. intraarticular) should not be given. A short duration (<2 weeks) of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease, anti-emetic)

6) Hematopoietic growth factors (e.g. erythropoietins, G-CSF and GM-CSF) are not to be administered prophylactically. Use of these should be reserved to cases of severe neutropenia and anemia as per the labelling of these agents

7) The use of concomitant medications that prolong the QT/QTc interval (refer to website crediblemeds.org for the list of medications) should be avoided, except in those cases where treatment is necessary after a risk-benefit evaluation by the investigator and provided that the drug in question cannot be substituted by any other agent.

It is to be noted that

1) Everolimus may affect the response to vaccinations making it less effective. Live vaccines should be avoided while a patient is treated with everolimus.

2) Lipid-lowering drugs may be given in case of hyperlipidemia according to local best clinical practice.

3) Antihyperglycemic drugs may be given in case of hyperglycemia according to local best clinical practice.

Otherwise, the use of other concomitant medication/therapy deemed necessary for the care of the patient is allowed.

4.2.2.2 Restrictions on diet and life style

Patients should avoid grapefruit and grapefruit juice while treated on everolimus. Patients also have to show up in fasting condition at the site when blood draw for safety lab is required.

Everolimus and exemestane tablets should be administered with a large glass of water (~ 240 mL). Patients should be advised not to eat within 2 hours after drug administration and not to drink within 1 hour after drug intake.

For specific instructions on food and drug intake during the Run-in period and up to C1D8 of the phase I part for DDI analysis, refer to section 4.1.4.1.4.

4.3 TREATMENT COMPLIANCE

The study medications will be given in accordance with the protocol and the instructions of a site investigator. The investigator should instruct the patient to take the study drugs exactly as prescribed to promote compliance.

4.3.1 BI 836845

BI 836845 will be administered as a single infusion under supervision of the investigator or dedicated study personnel. In the event that the full dose of BI 836845 is not administered to the patient, it must be documented and explained.

A maximum of three BI 836845 infusions may be skipped for the recovery from AEs. Missing BI 836845 treatment for any other reasons is considered non-compliant.

4.3.2 Everolimus and exemestane

Patients should be given appropriate number of everolimus and exemestane tablets to be self-administered. During the run-in phase and up to the Visit 3 (Day 8±1) in first treatment course of the Phase I part, the patient will be requested to record each dose of medication in a diary. The medication diary will be returned to clinic staff at the end of run-in phase and at Visit 3 of the first treatment course.

Patients will be asked to bring the remaining investigational oral medication everolimus on Day 1 of each treatment course to the investigator site. Compliance of investigational everolimus will be assessed by the investigator and/or study personnel using pill counts and information provided by the patient or caregiver. This information and discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. The compliance of exemestane and non-investigational everolimus (if applicable) will be assessed following the local regulation and practice, using either patient diary, pill counts, information provided by the patient or caregiver or the combination of any of them. If a patient is eligible for further treatment, medications of everolimus and exemestane must be made available.

During the run-in phase, everolimus and exemestane must be taken daily without skipping any dose. If doses of everolimus or exemestane are missed during run-in period, treatment with BI 836845 may commence and the reason for not taking everolimus and exemestane as per protocol requirement must be documented in the eCRF (refer to section 3.3.4.1). During the treatment phase, a maximum of 25% of the planned doses per four-week period may be missed for reasons other than recovering from AEs; patients who miss everolimus/exemestane treatment more frequently are considered non-compliant.

4.3.3 Compliance Assessment

Patients who do not attend a minimum of 75% of scheduled study visits, unless due to exceptional circumstances, should be discussed with BI clinical monitor and be evaluated for compliance.

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.

4.4 MANAGEMENT OF EXPECTED ADVERSE EVENTS

The following recommendation should be followed unless institutional guidelines can be implemented based on the investigator's judgement. The EU Summary of product characteristics or prescribing information of respective country for everolimus and exemestane should also be referred to when managing drug related adverse events.

In everolimus SPC, non-infectious pneumonitis, infections, hypersensitivity reactions, concomitant use of angiotensin-converting enzyme inhibitors, oral ulceration, renal failure events, and some lab tests and monitoring are described under "Special warnings and precautions for use". For updated information regarding warning and precautions of everolimus and exemestane, please refer to the most current version.

4.4.1 Management of oral mucositis

4.4.1.1 Mouth care

- Routine and systematic oral hygiene is extremely important to reduce the incidence and severity of the side effects of cancer treatment.
- Correct oral hygiene should be maintained with daily brushing of the teeth, tongue and gums, performed after meals and before going to bed, using a non-irritant toothpaste, a soft toothbrush and dental floss to clean between the teeth. This should be followed by rinsing the mouth with a mouthwash.
- Mouthwashes eliminate food particles that can accumulate and favour bacterial growth. The preferred solutions are normal saline, sodium bicarbonate, or a mixture of the two, to be used after each meal and before going to bed; solutions containing alcohol should be avoided as they dehydrate the mucosa. If the mucosa is ulcerated, do not use hydrogen peroxide solution as this will interfere with the formation of granulation tissue and healing of the ulcer. Do not use products that contain alcohol, glycerine or lemon, or toothpastes with an abrasive action.
- Dental prostheses should be cleaned and brushed in the same way as the mouth, and at night should be left in 1% sodium hypochlorite solution (if they contain no metal) or in a solution of povidone iodine.
- The lips must be maintained in a perfect state of hydration using lip balms (cocoa butter), methylcellulose solutions, moisturising cream or olive oil. Avoid using petroleum jelly or glycerine because of their dehydrating effects on the lip tissue.
- Chlorhexidine is an antiseptic with a broad antimicrobial spectrum. It has a bacteriostatic action and is particularly active against gram-positive micro-organisms; it is sporostatic and fungistatic (activity against candida). It has a rapid effect and, in addition, presents considerable persistence and residual adherence. Due to its cationic nature, it has the property of binding to the oral mucosa. It has been used in the form of 15 ml of 0.12% chlorhexidine mouthwash 2-3 times a day.

- Avoid foods that trigger pain: acids, spicy and hot foods. Attempt to eat a soft diet and increase the intake of cold and nutritious fluids.
- Avoid irritants such as alcohol and tobacco

4.4.1.2 Treatment of established mucositis

- Lidocaine is an amide-type local anaesthetic that is widely used both topically and parenterally. In the management of mucositis, it can be useful for the treatment of pain. It is administered locally in the form of a gel or solution. Apply 1% lidocaine viscous to ulcers before each meal.
- Nystatin is an antifungal (fungistatic) agent with a broad spectrum. Nystatin suspension has been studied as prophylaxis against candida in patients on treatment with antineoplastic and/or immunosuppressant drugs. Apply after the main meals if there are signs of candidal superinfection of mucositis.

Corticosteroids, in the case of mucositis, reduce the inflammatory reaction that occurs in this condition, probably by inhibiting the production of leukotrienes and prostaglandins.

- Triamcinolone acetonide 0.1% in orabase qsp 30 g or
- Hydrocortisone 1% in orobase qsp 50 g

Applications are performed 2-3 times a day with the recommendation not to eat or drink for 30 minutes after the application to facilitate its adherence to the mucosa.

In case of no improvement of mucositis, additional therapy may be added:

- Fluconazol oral 100 mg daily in case of no improvement with topical antifungal treatment with nystatin.

  Please note that fluconazole is a moderate inhibitor of CYP3A4, which may potentially have an impact on metabolism of everolimus and exemestane.

- Systemic antiherpetic therapy (ie Famvir 750 mg/d for 7 days otherwise Aciclovir oral or iv.) at investigator's discretion.

4.4.2 Management and grading of infusion reactions

The BI 836845 infusion should always be administered under close supervision of a medically qualified staff member with immediate availability of appropriate resuscitation facilities.

Infusion reactions may occur during infusion with BI 836845 and include pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension and hypertension. **A one hour observation period is recommended following each infusion.** If there is no infusion reaction during the first treatment course, the observation period following BI 836845

infusion may be adjusted at the discretion of the investigators. 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 hypersensitivity reactions will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R10-4848).

Table 4.4.2: 1 Infusion reaction management

Infusion Reaction Grade	Management
CTCAE Grade 1 or 2	In the event of a CTCAE grade 1 infusion reaction, the infusion rate should be reduced by 50%. Grade 2 infusion reaction may require symptomatic treatment (e.g., antihistamines, NSAIDs, steroids, narcotics, IV fluids) with infusion interruption. Once the event has resolved, the infusion may be restarted at the reduced rate.
CTCAE Grade 3	For patients experiencing CTCAE grade 3 infusion reaction, infusion should be interrupted immediately and patients should receive aggressive symptomatic treatment. Only after all the symptoms have disappeared, the infusion may be re-started if it is within 3 hours since the infusion start. The infusion rate should be reduced by half if it is restarted.
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 NOT receive any further BI 836845 treatment.

The infusion duration may be extended to over one hour and up to a maximum of three hours, see Section 4.1.4.

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.

4.4.3 Management of hyperglycemia and hyperlipidemia

In case of hyperglycaemia and hyperlipedemia, treatment should follow institutional standard, prescribing information for everolimus and/or guideline (R13-1975). Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting trial therapy. After commencing the study medication, in patients with diabetes, fingerstick glucose values should be monitored daily. If fasting glucose values above 200 mg/dL occur, the investigator should evaluate the need to intensify antihyperglycemic therapy potentially in

collaboration with the treating physician responsible for the treatment of the diabetic condition or a specialist. For hyperglycemia occurs to patients without history of diabetes or hyperglycemia, oral anti-diabetics, such as metformin 1 g to 2.5 g/d with less hypoglycemic risk, may be started if necessary.

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

4.4.4 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Fatal cases of non-infectious pneumonitis (including interstitial lung disease) have occurred. The investigator should monitor patients for clinical symptoms or radiological changes. For dose reduction, interruption or discontinuation of everolimus in the management of non-infectious pneumonitits, refer to everolimus SPC or prescribing information of respective country.

4.4.5 Management of viral hepatitis

Everolimus has immunosuppressive properties and may predispose patients to viral infection including reactivation of hepatitis virus. Please follow the current label of everolimus and local guidance should treatment for viral hepatitis is needed.

Prior to study treatment, patients must be screened for hepatitis risk factors and any past and current illnesses of hepatitis B and hepatitis C. Refer to Flow Chart for lab screening of Hepatitis B and C. Patients with baseline positive HBV-DNA or positive HbsAg, positive HCV-RNA or positive anti-HCV Ab are not eligible for the study.

4.4.6 Management of infection (related to everolimus)

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Opportunistic infections such as pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) have been reported in patients who received everolimus and should be ruled out in the differential diagnosis of non-infectious pneumonitis. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids (e.g. for treatment of non-infectious pneumonitis) or other immunosuppressive agents are required.

Please follow the most current everolimus SPC or local prescribing information for updated recommendations of management.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

5.1.1.1 Primary endpoint

Phase II part: Progression-free survival (PFS).

PFS is defined as the duration of time from the date of randomization until the date of the first objective tumor progression according to RECIST 1.1 or death due to any cause, whichever occurs earlier. If a patient has not had an event, PFS will be censored at the date of last adequate tumor assessment.

5.1.1.2 Secondary endpoints

Phase II part:

1. Time to progression (TTP), defined as the duration of time from the date of randomization until the date of the first objective tumor progression according to RECIST 1.1.

2. Objective response (OR), defined as best overall response of complete response (CR) or partial response (PR) (CR + PR), where best overall response is determined according to RECIST 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy.

3. Time to objective response, defined as the time from randomisation until first documented CR or PR.

4. Duration of objective response, defined as the time from first documented CR or PR until the earliest of disease progression or death among patients with OR.

5. Disease control (DC), defined as best overall response of complete response (CR) or partial response (PR), or stable disease (SD) ≥24 weeks, or Non-CR/Non-PD for ≥24 weeks, where best overall response is defined according to RECIST 1.1 from date of randomisation until the earliest of disease progression, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy.

6. Duration of disease control, defined as the time from randomisation until the earliest of disease progression or death, among patients with disease control.

5.1.2 Assessment of efficacy

5.1.2.1 Tumor response

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (R09-0262). Tumor response will be assessed by local investigator's review.

For the Phase II part of the study, image acquisition will be performed as described in the Imaging Guideline (wich will be filed in the ISF). Images will be collected and stored at a central facility assigned by the sponsor. The sponsor retains the option to perform an independent blinded central review of the study images at a later time.

See APPENDIX 10.4, RECIST 1.1 (R09-0262) for details on lesion measurements and response assessment.

Every effort should be made to objectively evaluate tumor response for all patients who enter into the trial, including those who discontinue prematurely.

RECIST 1.1 will be followed in this study for tumor assessment. Tumor assessments should include scans of the chest, abdomen and pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. breast, neck, brain etc) should be performed using an appropriate method (CT/MRI, etc.). Assessment will be performed at screening and then every 8 weeks after the first dose of BI 836845 (Phase I) or after randomization (Phase II) until week 48 and every 12 weeks thereafter. After screening, for each scheduled tumor assessment -7 days and -14 days windows are allowed, respectively before and after week 48. Tumor assessment does not need to be repeated at the screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment. For the phase II part, these need to also meet the requirements in the Imaging Guideline. Patients who discontinue the trial for any reason other than imaging based progressive disease should have a tumour assessment (RECIST 1.1) performed at EOTV before starting new anti cancer therapies (exception to this are patients who have already had tumor assessment within 28 days of EOT visit)

In case of skin lesions, these should be measured with calliper and photographic documentation should be performed. However, skin lesion should not be considered as target lesion in this study.

A bone scan should be performed at screening. If the patient has known bone metastases or if bone metastases are detected at screening, correlative imaging (X-ray or CT scan with bone windows or MRI) of the respective lesion(s) must be done at screening and subsequent imaging time points. Post screening bone scans should also be performed if clinically indicated. Abnormalities suggestive of progression of existing lesions or new lesions must be confirmed by X-ray, CT scan or MRI. Additional tumor assessments performed prior to starting new anticancer therapy/disease progression must also be documented in eCRF.

If a patient presented with both irradiated and non-irradiated bone lesions, only the non-irradiated lesions should be followed for tumor assessments unless progression is documented after the radiation.

Follow-up tumor assessments must utilize the same CT/MRI method and acquisition technique as were used for screening assessments to ensure comparability. CT and MRI scan with contrast media should be used except for patients who are allergic/ sensitive to the radiographic contrast media. 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.

For patients with only bone lesions at baseline, the evaluation of response will be based solely on non-target lesion responses of RECIST 1.1. Specifically, in the absence of new lesions, the overall response at each assessment will be one of the following: Complete Response, Non-CR/Non-PD, Not Evaluable (not assessable, insufficient data) or Progressive Disease. Non-CR/Non-PD would include all assessments not qualifying for Complete Response, Progressive Disease or Not Evaluable. In the presence of any new lesion, the overall lesion response will be Progressive Disease.

In the event of a delay, interruption or discontinuation of treatment, tumor assessment should continue to follow the original schedule. For patients who prematurely discontinue study medication including those discontinued with only clinical disease progression but without radiographic PD, tumor assessments should continue to be performed every 8 or 12 weeks as if the patient remained on study drug until criteria for end of follow-up period are met (refer to section 6.2.3 for details).

5.1.2.2 Assessment of disease progression

Disease progression will be based on the local investigator's tumor assessment.

For patients with measurable disease at baseline, progression will be determined according to the RECIST 1.1 (R09-0262).

In the absence of measurable disease at baseline, patients with bone lesions, lytic or mixed (lytic + sclerotic), will be allowed to enter the study and the following will be considered disease progression among these patients:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.

5.2 SAFETY

5.2.1 Endpoints of safety

For the phase I part, the primary endpoints are DLT and MTD.

MTD is defined as the highest dose level examined of BI 836845 in combination of everolimus and exemestane, at which no more than 1 out of 6 MTD evaluable patients experienced a dose limiting toxicity during the MTD evaluation period.

The number of MTD evaluable patients per dose level with dose limiting toxicities during the MTD evaluation period will be used for the determination of the maximum tolerated dose.

Safety of BI 836845 when administered together with everolimus and exemestane will be evaluated by intensity and incidence of AEs, graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 (R10-4848).

Other assessments of safety include:

- The incidence and intensity of AEs, as well as seriousness and relatedness of adverse events to treatment
- AE leading to dosage reduction or discontinuation
- Change from baseline in laboratory values
- Other safety-related assessments involving ECG parameters and ECOG score will be described with respect to possible changes compared to baseline values. Further details on the analysis of ECG data will be specified in the TSAP.

5.2.2 Assessment of adverse events

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) and includes periodic physical examinations, measurement of vital signs, assessment of performance status, monitoring of laboratory tests (i.e. haematology, chemistry, coagulation, urine analysis, HBV and HCV) and assessment of cardiac function with periodic ECGs as outlined in the Flow Chart and Section 6.2.

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.

The following hospitalizations are not considered to be serious adverse events (SAEs) because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or PK assessment

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 judgement 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 eCRF.

Exemption to (S)AE Reporting

Disease Progression is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an (S)AE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the (e)CRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (ARISg) and

hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on the SAE Form.

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the (e)CRF.

Examples of exempted events of PD may be:

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

Exempted events are to be monitored by the study Data Monitoring Committee at the intervals defined in the DMC charter for the phase II part of the trial.

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 eCRF, 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 is defined by the following alterations of hepatic laboratory parameters:
  - For patients with normal liver function (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, and/or marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

  - For patients with abnormal liver function tests at baseline (AST and/or ALT >ULN), an elevation of transaminase ≥ (baseline + 4x 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 explain possible deteriorations of baseline conditions.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to Appendix 10.6 of this clinical trial protocol and the "DILI checklist" provided in the ISF.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified adverse event of special interest. 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 phase I part. Please refer to Section 5.2.6 for definition of DLTs.

- Cases of pneumonitis (including interstitial lung disease, non-infectious pneumonitis and other analogous terms) occurring at any cycle in both phases.

These are considered as protocol-specified adverse events of special interest and have to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.2.

If the investigator determines any protocol-specific adverse events of special interest are related to study drug, the administration of the study drug must be managed according to Section 4.1.4 of the protocol.

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 follow up visit will be collected, documented and reported to the sponsor by the investigator on the appropriate 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.

The terminal half-life of BI 836845 is the longest one compared to that of everolimus and exemestane, the residual effect period (REP) for the study, after elimination of BI 836845, is therefore defined as 42 days in this study. All adverse events from the date of signing of informed consent until the last follow-up visit must be reported. All AEs, including those persisting at the end of follow-up visit, must be followed up until resolved or until sufficiently characterised.

Once the patient completed the follow-up, the investigator does not need to actively monitor patients for adverse events. However, if s/he becomes aware of a SAE(s) that occurred after

the patient has completed the follow-up, the event should be reported to the sponsor if considered relevant. Deaths (unless considered drug-related or trial related) will not be reported as SAE when occurring after the follow-up period.

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.

Table 5.2.2.2: 1 AE/SAE reporting requirements

Time period	Reporting requirements
From signing of informed consent until last follow up visit	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 a 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 in the trial, by RDC using the SAE form immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically related to the SAE(s), and protocol-specified adverse events of special interest.

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 these 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 adverse events of special interest becomes available.

Pregnancy

Patients are women of non-childbearing potential. Therefore pregnancy is not expected to occur in this study.

5.2.3 Assessment of safety laboratory parameters

Blood samples, including fasting serum samples (fasting state for at least 8 hours) and the fasting lipid profile, will be collected up to one day 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, further test may be done if 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 all of 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 or blood urea nitrogen (BUN), creatinine, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), bilirubin (total and direct), albumin, 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

Table 5.2.3: 1 Clinical laboratory tests (Cont'd)

Category	Parameters
Electrolytes	Sodium, potassium, calcium, magnesium, phosphorous
Lipid profile (fasting)	Total cholesterol, triglycerides, LDL, HDL
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

Triplicate 12-lead ECGs (3 ECGs taken approximately 2-3 minutes apart) will be performed in all patients in both phases as specified in the Flow Chart.

The ECG timepoints for the **phase I part** is defined as the following:

- Screening
- Day 1, Day 8, Day 15 of Course 1; Day 1, Day 15 of Courses 2 and 3; and Day 1 of Courses 6, 9, 12, etc. at pre-dose (-60 min. to -5 min. of administration of BI 836845) and immediately after the end of infusion
- EOTV
- Follow-up Visit

The ECG timepoints for the **phase II part** is defined as the following:

- Screening
- Day 1, Day 8, Day 15 of Course 1; Day 1 of Course 2; and Day 1 of Courses 3, 6, 9, 12, etc. at pre-dose (-60 min. to -5 min. of administration of BI 836845 and/or everolimus + exemestane), and immediately after the end of infusion (for patients receiving BI 836845) OR one hour after the administration of everolimus + exemestane (for patients not receiving BI 836845)
- EOTV
- First Follow-up Visit

The ECGs will be digitally recorded using dedicated equipment provided by a CRO. In addition, a centralised evaluation of all recorded 12-lead ECGs will be performed by a CRO in a blinded fashion. It is not mandatory to wait for central evaluation of ECGs to take clinical decisions, but in case of values close to 470ms at screening visit, it's strongly recommended to ask for central lab report to confirm eligibility for patients' safety. The ECG recordings must also be analyzed and checked for abnormality by the investigator. Any ECG finding that meets AE criteria should be reported. Positive findings on QT prolongation must be followed up sufficiently as deemed by the investigator. Additional ECGs should be done whenever the investigator deems necessary.

After the primary analysis of the study, a decision can be made by the sponsor and communicated by the trial clinical monitor to stop the triplicate ECG monitoring and central evaluation if necessary. Thereafter the ECG will be evaluated locally by the investigator using site equipment if clinically indicated.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination

A full physical exam 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.

5.2.5.2 Vital signs, height and weight

Vital sign measurements (blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, temperature and measurement of height (at screening) and body weight and the evaluation of the ECOG performance status will be performed at the times specified in the Flow Chart and Schedule of Procedures/Assessments (Section 6.2). Blood pressure and pulse will be measured after the patient has been recumbent or seated for 5 minutes.

5.2.6 Dose limiting toxicity (DLT)

The primary endpoints of the Phase I part are occurrence of Dose Limiting Toxicity (DLT) and determination of MTD.

A dose limiting toxicity (DLT) in this study is defined as an adverse event or laboratory abnormality which 1) is considered related to study drug and 2) meets any of the following criteria:

- CTCAE Grade 3 hyperglycemia lasting > 48 hours
- CTCAE grade 4 hyperglycemia
- CTCAE Grade ≥ 3 stomatitis (oral mucositis) despite appropriate supportive care
- CTCAE Grade ≥ 3 thrombocytopenia lasting ≥ 7 days or thrombocytopenia associated with active bleeding or requiring platelet transfusion
- CTCAE Grade ≥ 4 decreased platelet count

- CTCAE grade ≥ 3 febrile neutropenia and/or documented infection with ANC <1.0x10^9/L
- CTCAE Grade 4 decreased neutrophil count lasting ≥ 7 days
- AST or ALT > 5x ULN (for baseline AST/ALT ≤ ULN) or > (baseline value + 4x ULN) (for baseline AST/ALT > ULN)
- CTCAE grade ≥ 3 diarrhea, nausea, or vomiting despite adequate supportive care
- CTCAE Grade ≥ 3 skin rash despite adequate supportive care measures
- CTCAE Grade ≥ 3 fatigue/asthenia lasting for more than seven days
- Grades 3 to 4 hyperlipidemia (total cholesterol > 400 mg/dL or triglycerides > 500 mg/dL) not improving despite appropriate treatment for 4 weeks
- Any AE necessitating a 2-week treatment interruption
- All other toxicities of CTCAE Grade ≥ 3 (except alopecia, allergic reaction, infusion reaction and those mentioned above)
- 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 everolimus 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 dose finding, only DLT events that occur during the first treatment period of 28 days will be considered. Decisions regarding dose escalation/de-escalation steps will be made only after discussion between the sponsor and the clinical investigators, and in consideration of all the available safety information. Available data of DLTs occurring after first treatment course and all unusual/unexpected AE at any time during treatment will be considered for the purpose of recommending the dose for phase II part.

All DLT events must be reported immediately to the sponsor and documented in the eCRF.

5.2.7 Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)

The MTD is defined as:

The highest dose level of combination of BI 836845, everolimus, and exemestane, at which no more than 1 out of 6 patients experience a drug related DLT during the first course of treatment. DLTs occurring after the start of the second treatment course will be analyzed separately. DLT will only be investigated in the phase I part of the study.

For the definition of DLT and determination of MTD refer to Sections 5.2.6 and 4.1.3.2.

The MTD or a lower dose level will be chosen as the recommended phase II dose (RP2D) based on the totality of the safety data available by the time that 12 evaluable patients have finished course 1 of treatment at the MTD (or tentative RP2D if MTD not reached); at the earliest. The discussion and agreement on dose selection between the investigator and the sponsor will be documented and communicated to all participating sites.

5.2.8 HBV and HCV testing

The HBV and HCV testing at screening must include HBV-DNA and/or HBsAg, anti-HCV

Ab and/or HCV RNA-PCR. The test will be performed in a laboratory facility at (or close to) the investigational site.

5.3 OTHER

[redacted]

[redacted]

5.3.4 Demographics and medical history

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

1. General demography including sex, birth date, race if allowed by local law, information on smoking and alcohol history. Collection of race and/or ethnic information is necessary in this study because this study is a multi-national and registrational trial and race and/or ethnicity are known to be associated with biology and outcome of breast cancer. Foreign regulatory agency may request data or analysis based on race/ethnic information.

2. Medical history/current medical conditions (including history of menopause, prior and concomitant medications and concomitant diagnosis)

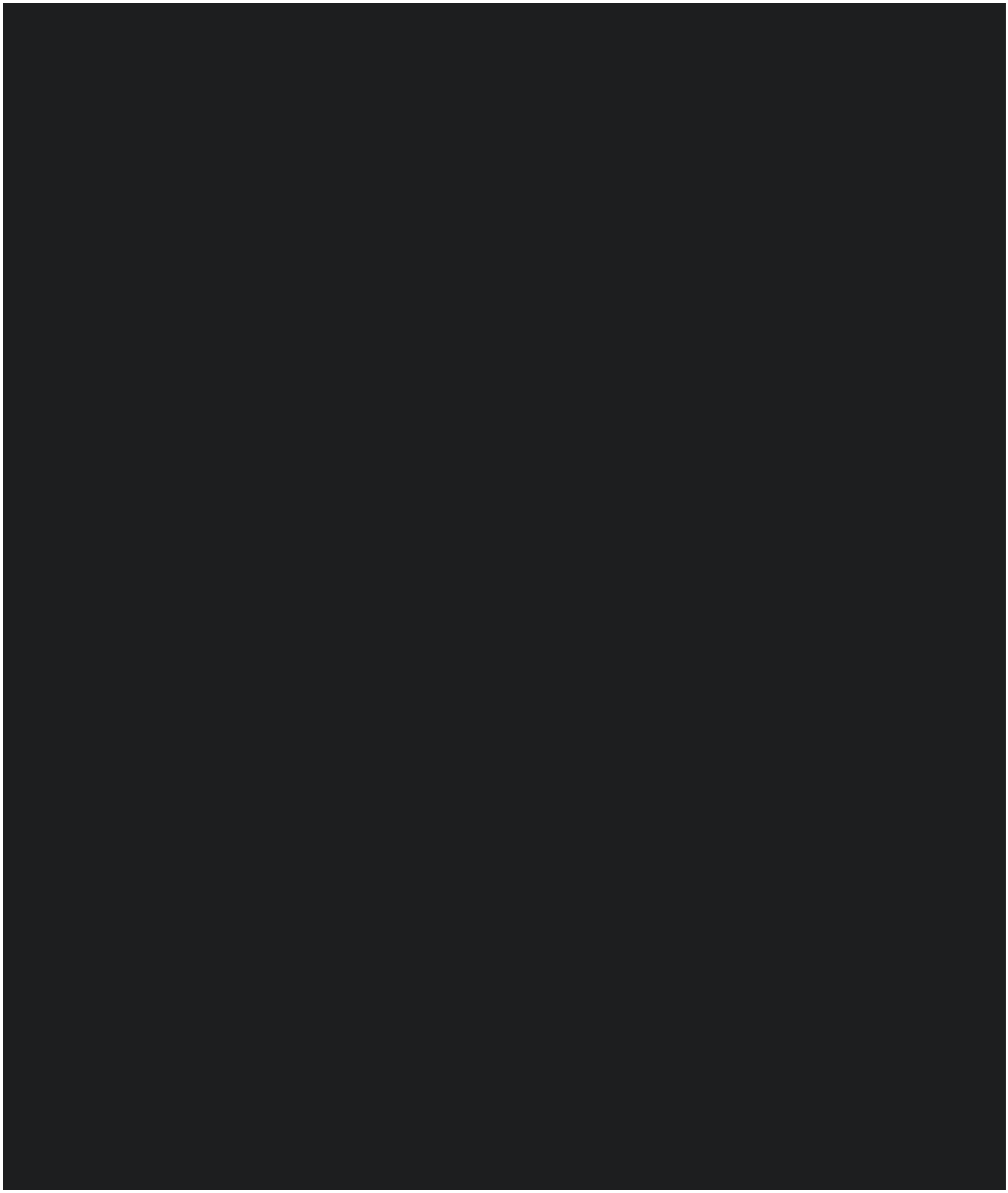
3. History and current disease status including date of first histological diagnosis (month and year may be sufficient), type of tumor histology, tumor grade, other diagnosis information such as Ki-67, ER, PgR (including % cell positive) and HER2 status (FISH and/or IHC, +, ++, etc.), known tumor genetic alterations, TNM staging, number and locations of metastatic sites (bone, liver, lung, peritoneum, brain, other) at the study entry

4. Previous anticancer treatments: previous surgery, hormonotherapy, chemo-, targeted, or radiation therapy will be reported including setting (neoadjuvant vs. adjuvant vs. therapeutic), start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (chemotherapy), total radiation dose and radiation field (radiotherapy), the best response obtained (complete response, partial response, stable disease/ non-CR/non-PD, progressive disease, unknown) and reason for treatment discontinuation

5.4 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumors. Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 are used for assessment of the change in tumor burden. These criteria are well established and well received by the regulatory authorities and scientific community.

The US NCI CTCAE is used in the assessment of adverse events in cancer patients. In the present study CTCAE version 4.03 will be used.



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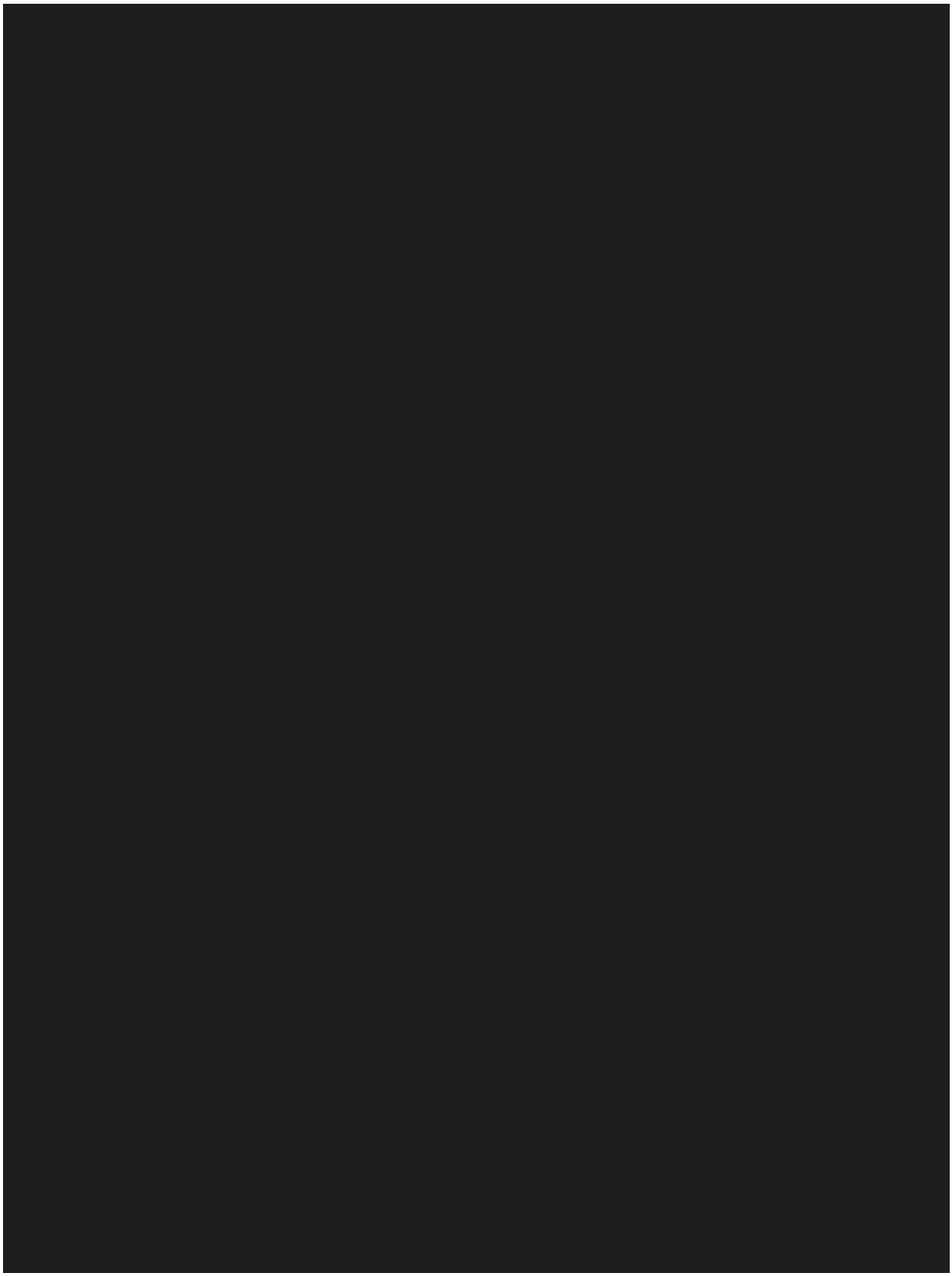

6. INVESTIGATIONAL PLAN

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 BI 836845 and everolimus will be dispensed at each visit according to the Flow Chart. Patients will receive a new medication kit number through the IRT system on each occasion for medications supplied by the sponsor. Exemestane and non-investigational everolimus (if applicable) should be prescribed by the investigator and supplied by pharmacy at study visits according to Flow Chart.

All screening assessment including tumor assessments must be completed within 28 days of start of run-in/C1V1. 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. Tumor assessments required for study participation which are completed as part of Standard of Care before the patient sign the ICF can be used for the screening assessments if they are completed within the allowed timeframe.

All patients are to adhere to the visit schedule as specified in the Flow Chart. In the event of any study drug interruption or delay of treatment, the tumor assessment schedule should not be changed.

Blood samples for pharmacokinetics, biomarkers and immunogenicity will be collected from all patients in the Phase I part. In the Phase II part, tissue and blood samples will be collected for biomarkers from both treatment arms; blood samples for PK and immunogenicity testing will be collected from the patients on arm 2 only (BI 836845 + everolimus + exemestane). For specific PK, biomarker and immunogenicity sampling schedule refer to Appendix 10.5, Tables 10.5.1: 1 to 10.5.2: 2. 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, everolimus and exemestane should be administered during the clinical visit. On visit days when safety lab is scheduled, patients should show up in fasting condition, the blood draw can be done up to one day prior to the scheduled date.

Adverse events and concomitant medication must be collected starting from Day -7 of run-in until the (last) follow-up visit.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

6.2.1.1 Screening period

Refer to the Flow Chart for procedure details. Please review Section 3.3.2 and 3.3.3 for eligibility criteria.

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.

All screening assessments including tumor imaging scan and ECG must be completed within 28 days of start of run-in/C1V1.

The provision of tumor tissue is mandatory. An archival tumor tissue must be collected prior to the start of study treatment [redacted] Please refer to Appendix 10.7 for details.

6.2.1.2 Phase I part run-in period (from Day -7 to -1).

Refer to the Flow Chart and Appendix 10.5 Table 10.5.1: 1 for details. Prior to starting of triple-drug combination therapy with BI 836845, everolimus and exemestane, patients will receive continuous daily everolimus and exemestane doublet therapy for a 7-day run-in period. Everolimus and exemestane should be dispensed/filled on Day -7 of run-in.

On Day -7 of run-in, prior to the administration of everolimus and exemestane, blood samples for biomarkers will be collected.

On Day -1 of the run-in period, patients must come fasted to the study site and must not take everolimus or exemestane until they have been instructed to do so at the clinic visit (refer to 4.1.4.1.2 and 4.2.2.2 for details). PK samples must be collected before (-0.05h) and after the administration of everolimus and exemestane at 1:15h, 2h, 4h, 7h.

Patients must show up at fasting condition for a safety lab blood draw.

6.2.2 Treatment periods

Every treatment course is 28 days. All subsequent visit dates should be calculated based on Course 1 Visit 1 date. If a visit is missed there will be no re-scheduling; if a patient should attend the study site between the "missed" and the next scheduled visit, then the missed visit assessments should be performed except for BI 836845 infusion (if applicable), in which case, the infusion should be skipped on the delayed visit. The current date and the reason for the delay must be noted in the medical records.

One or more visits can be skipped in case of treatment interruption. However, in the event of any study drug interruption or delay of treatment, the tumor assessment schedule will not be changed.

In this trial, patients may be hospitalized for the day of BI 836845 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.

6.2.2.1 Phase I part

Refer to the Flow Chart and Appendix 10.5 Tables 10.5.1: 1 – 10.5.1: 2 for details.

Course 1, Visit 1 (Day 1 of 1st treatment course)

All procedures must be completed on Day 1 of Course 1. Compliance regarding everolimus and exemestane intake during the run-in period will be assessed. Sufficient everolimus and exemestane should be made available for the patient. Patients should come fasted to the study site and should not take everolimus and exemestane until they have been instructed to do so at the clinic visit (refer to 4.1.4.1.2 and 4.2.2.2 for details). Blood samples for PK, biomarkers and immunogenicity will be collected before (-0.05h) and 1:15h, 2h, 4h, 7h after the administration of BI 836845, everolimus and exemestane. ECG will be collected prior to trough PK sampling and BI 836845 infusion, and immediately after BI 836845 infusion.

Course 1, Visit 2 (Day 2 of 1st treatment course, consecutive to course 1 Day 1 visit)

Patients should come fasted to the study site and should not take everolimus and exemestane until they have been instructed to do so at the clinic visit (refer to 4.1.4.1.2 and 4.2.2.2 for details). On Course 1 Day 2, **prior** to the administration of everolimus and exemestane, one trough PK as well as biomarker blood samples must be collected 24h after the first administration of BI 836845, everolimus and exemestane on Course 1 Day 1.

Course 1, Visit 3 (8 ±1 days after start of BI 836845)

Blood samples for safety lab, PK and biomarker must be collected. PK and biomarker samples must be collected before and after drug administration of BI 836845, everolimus and exemestane. ECG will be collected prior to trough PK sampling and BI 836845 infusion, and immediately after BI 836845 infusion.

Course 1, Visit 4 (15 ±1 days after start of BI 836845)

Blood samples for safety lab, PK and biomarker must be collected. PK and biomarker samples must be collected before and after drug administration of BI 836845, everolimus and exemestane. ECG will be collected prior to trough PK sampling and BI 836845 infusion, and immediately after BI 836845 infusion.

Course 1, Visit 5 (22 ±1 days after start of BI 836845)

Blood samples for PK and biomarker must be collected before and after drug administration of BI 836845, everolimus and exemestane.

Course 2 (Day 1, 8, 15, 22 ±2 days) and all subsequent visits

Refer to Flow Chart and Appendix 10.5 Tables 10.5.1: 1 – 10.5.1: 2 for details.

6.2.2.2 Phase II part

Refer to the Flow Chart and Appendix 10.5 Tables 10.5.2: 1 – 10.5.2: 2 for details including timing on ECG, PK and drug administration.

If extremely necessary, for arm 2 patients receiving BI 836845 infussion at a subsequent visit, the transaction with the IVRS/IWRS system can be done up to one day before the actual visit date. Please refer to BI 836845 Preparation Storage and Administration instructions for more information about BI 836845 stability and storage conditions once diluted in the infusion bag

Course 1, Visit 1 (Day 1 of 1st treatment course)

All procedures must be completed on Day 1 of Course 1. However, the randomization may take place up to 3 days prior to the C1V1 if site procedures require advance randomization to accommodate the logistics of dispensing study medication to patients. Sites that use this option must include a copy of the policy or a documented justification in the ISF and submit a copy to the sponsor. The patient must take the first oral dose of study medications and receive BI 836845 infusion (if randomized to BI 836845 containing arm), while she is still at the investigative site, and to record this in the site source document. Sufficient drugs (everolimus and exemestane) should be made available for the patient. Blood samples for biomarkers (for all patients), immunogenicity and PK (for arm 2 patients only) will be collected before (-0.05h) and after (form arm 2 patients only) the administration of everolimus and exemestane with or without BI 836845. ECG will be collected from all patients, prior to trough PK sampling and administration of any study drug, and immediately after the end of BI 836845 infusion (for patients receiving BI 836845) OR one hour after the administration of everolimus + exemestane (for patients not receiving BI 836845).

Course 1, Visit 2 (8 ±2 Day after C1V1)

BI 836845 should be administrated with PK blood samples taken before and after the infusion for patients on arm 2 only. ECG, vital signs, adverse events and concomitant medication will be collected from all patients.

Course 1, Visit 3 (15 ±2 Days after C1V1)

Blood samples for biomarkers, PK and immunogenicity (for patients on arm 2 only) will be collected before (-0.05h) the administration of BI 836845 and/or everolimus plus exemestane. Furthermore, for patients having a biopsy, in addition to fresh tumor biopsy, blood samples for biomarkers (for all patients) and PK (for arm 2 patients only) should also be collected before the biopsy tumor sample is obtained (but not earlier than one hour before the biopsy). ECG will be collected from all patients, prior to trough PK sampling and administration of any study drug, and immediately after the end of BI 836845 infusion (for patients receiving

BI 836845) OR one hour after the administration of everolimus + exemestane (for patients not receiving BI 836845).

Course 1, Visit 4 (22 ± 2 Days after C1V1)

BI 836845 should be administrated for patients on arm 2. Vital signs, adverse events and concomitant medication should be collected from all patients.

Course 2 (Day 1, 8, 15, 22 ±2 Days) and all subsequent visits

Refer to Flow Chart and Appendix 10.5 Tables 10.5.1: 1 – 10.5.1: 2 for details.

For patients on arm 1 (everolimus + exemestane) of the Phase II part, the study visits on Visits 2 and 4 of Courses 3 through 6, and on Visits 2, 3, 4 from Course 7 onwards can be conducted via phone for the collection of adverse events and concomitant medication.

6.2.3 End of trial and follow-up period

6.2.3.1 End of treatment visit

End of Treatment Visit (0-7 days after permanent discontinuation of study drugs)

Refer to the Flow Chart for details. The patient must return all study drugs, and the site must document the reason for permanent discontinuation of study medication. If permanent discontinuation of study drug occurs during a scheduled visit, examinations as defined for EOTV should be performed instead of the examinations for the scheduled visit.

Blood samples for soluble biomarkers (for all patients), PK and immunogenicity (for patients on BI 836845 regimen) must be obtained.

In patients who are experiencing disease progression at EOTV of the phase II part, a fresh tumor biopsy should be performed from those with appropriate informed consent.

6.2.3.2 Follow-up

This follow-up period is aimed for collection of additional AE and PD information. Refer to the Flow Chart and Appendix 10.5 for details.

Blood samples for soluble biomarkers, PK and immunogenicity (for patients on BI 836845 regimen) must be obtained at FU1.

Phase I part

All patients should have a follow-up visit 42 days (+7days) after the permanent discontinuation of study drugs.

Phase II part

Follow-up 1 (42 +7 days after permanent discontinuation of study drug)
Every patient should complete the first follow-up visit. Refer to the Flow Chart for details.

Additional follow-up visits
Additional follow-up visits should be performed at scheduled tumor assessment according to the Flow chart.

The follow-up period for every Phase II patient will end at the earliest of the following events:

- Disease progression
- Start of a new anti-cancer therapy
- Lost to follow-up
- Withdrawal of consent
- Death

6.2.3.3 Observation period

Phase I part

There is no observation period in the phase I part.

Phase II part

All patients will be followed-up for Overall Survival every 90 days after the last follow-up visit (as specified in Section 6.2.2.2) until death or completion of the whole trial (as specified in Section 6.2.3.4) whichever occurs earlier. During this period only information on patient vital status and subsequent anti-cancer treatment(s) will be collected. The investigator may report SAE if s/he becomes aware of it.

The following information should be collected from patient's notes or by telephone contact (a formal visit is not required). The investigator/site staff should make at least three tries to obtain the information if a phone contact is conducted.

- Date of contact and method of contact
- Further anticancer treatment
- Death
- Lost to follow-up
- Withdrawal of consent

A snapshot of observation period data may be requested at any time. Following the primary analysis, the collection of observation period data may be reduced in frequency or stopped as appropriate, as decided and communicated by the Trial Clinical Monitor.

6.2.3.4 End of Trial

Phase I part

The end of the phase I part of the trial will be when the last patient has completed the follow-up visit.

Phase II part

The end of the phase II part of the trial will be when the last patient has completed the first follow-up visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

Only descriptive and exploratory analyses are planned and no formal statistical testing is planned.

7.2 NULL AND ALTERNATIVE HYPOTHESES

As an exploratory Phase II trial, inferences about the efficacy of BI 836845 in combination with exemestane and everolimus will be based on the magnitude of the observed difference in PFS and other efficacy endpoints, e.g. objective response, overall survival, rather than a formal hypothesis testing.

7.3 PLANNED ANALYSES

During the Phase I part, cohorts of patients treated with BI 836845 in combination with exemestane and everolimus will be evaluated continuously based on the totality of the safety data available in order to determine the recommended phase II dose.

Efficacy analysis will include all randomised patients in the Phase II part. For the Phase I dose finding stage, PFS and objective tumor response will be summarized descriptively by cohort. No comparison will be done between cohorts.

Safety analysis will be summarized separately for patients treated in the Phase I and Phase II part of the trial. The safety profile of the Phase II part will be compared in a descriptive manner between the experimental and the control arm.

7.3.1 Primary analyses

The primary analysis of PFS will be conducted and reported when approximately 90 patients (out of 150 randomized patients) have progressed or died. However, it may be performed with fewer events within approximately 30 months after the first patient is randomized in the Phase II part. Any additional information collected after the data cut-off for the primary analysis will be reported in a revised clinical trial report.

The stratified Cox proportional hazards model will be applied to derive the estimate and confidence interval of the hazard ratio between the two treatment arms, stratified by visceral involvement (yes vs. no). Median PFS and PFS rate at certain time points, e.g. 2, 4, 6 months after randomization will be calculated from Kaplan-Meier curves with 95% confidence interval using the Greenwood variance estimate. Nominal p-value of a two-sided log-rank test on PFS will also be provided.

Response and disease progression is assessed according to RECIST 1.1. Refer to Section 5.1.1.2 for PFS definition. Clinical deterioration without image-based progression

will be censored from the primary analysis, but will be examined as part of a sensitivity analysis.

Derivation of PFS:

For patients with 'event' as an outcome for PFS:

- PFS [days] = date of outcome – date of randomization + 1.

For patients with 'censored' as an outcome for PFS:

- PFS (censored) [days] = date of outcome –date of randomization + 1.

Detailed censoring rules will be specified in the Trial Statistical Analysis Plan (TSAP).

7.3.2 Secondary analyses

The objective tumor response and the disease control for at least 24 weeks between the two treatment groups will also be compared using logistic regression with exact inferences providing nominal p-value. The confidence interval for the difference in rates between the two treatment arms will also be provided.

Kaplan-Meier curves and estimates with 95% confidence intervals will be calculated for time to progression. The progression free survival of Phase I patients will be summarized descriptively. Duration of objective response and duration of disease control will be summarized by their medians and quartiles derived using the Kaplan-Meier estimation procedure. Descriptive statistics will be calculated for time to objective response.

7.3.2.1 Other analyses

Stratified Cox proportional hazards model will be used to compute the hazard ratio of overall survival (OS) for BI 836845 in combination with exemestane and everolimus vs. exemestane and everolimus alone. Kaplan-Meier curves of OS will be calculated. Stratified log-rank test with nominal p-value will also be performed to compare the survival curves. OS will be analyzed twice. The first analysis will be performed at the time of primary PFS analysis. The second analysis will take place at the time of trial completion when all patients permanently discontinued the study drug and when the last patient completed the first follow up (FU1) visit.

For all patients (Phase I and Phase II, separately) with measurable target lesions, the maximum percent decrease since baseline in sum of the longest diameters of all target lesions and the percent change over time will be explored descriptively and graphically. Other further endpoints will be analysed descriptively.

[redacted]

7.3.3 Safety analyses

DLTs will be tabulated for each dose cohort in the Phase I part. The tabulation will be done in two ways:

- DLTs with onset in the first treatment course, and
- All DLTs regardless of treatment course at onset

The definition of DLT and determination of MTD are defined in Section 4.1.3 and Section 5.2.6 respectively.

Adverse events will be graded according to CTCAE, Version 4.03 (R10-4848). Key safety measures will include:

- The overall incidence and intensity of AEs, as well as seriousness and relatedness of adverse events to treatment
- Events leading to dosage reduction
- Events leading to permanent treatment discontinuation

Other safety-relevant assessments including those involving ECG, and ECOG score, will be described with respect to possible changes compared to baseline values. Further details on the analysis of ECG data will be specified in the statistical analysis plan.

The safety profile will be summarized after the determination of RP2D.

7.3.4 Interim analyses

No formal interim analysis is planned during this trial.

A continuous monitoring of safety data of the Phase II part will be done by a DMC to ensure a benefit risk assessment at any time. During regular meetings, the committee may examine the efficacy data in order to completely assess the benefit risk of BI 836845 in combination with exemestane and everolimus.

Additionally to the continuous monitoring, the DMC will examine the efficacy data at two pre-specified time-points, after 30 and 45 PFS events are observed according to investigator's assessment. The objective of these meetings is to facilitate further drug substance development and project planning based upon evaluation of the primary endpoint.

In case some pre-specified thresholds are met, the DMC can give the recommendation to start the preparation of a phase III trial or to start discussion of results with authorities, depending on the strength of this signal. All details of the methodology as well as the thresholds used for the signal detection will be described in an appendix to the DMC charter. This appendix will be kept confidential. Only a limited number of persons from BI, who are independent from the trial and project team, will have access to this appendix to avoid the potential introduction of operational bias. The people will be named in the DMC charter.

The trial or project team will remain blinded and will not be involved in any operation requested by the DMC. An independent team will be designated to perform any actions the DMC deems necessary. The composition of this team will be pre-specified and documented in an interim analysis logistics plan, which will also describe how data protection will be ensured and define which functions and individuals will have access to the unblinded results. Anyone included in the aforementioned groups will sign a confidentiality agreement for these tasks, and is not allowed to discuss any unblinded results with people who are not authorized to know about them.

Regardless of whether the efficacy signal is observed and the above actions initiated, the trial will continue until its final analysis.

[redacted]

7.4 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

For PFS, every effort will be made to obtain date of progression for patients known to have progressed.

Missing or incomplete AE onset and end dates are imputed according to BI standards on handling of missing and incomplete AE dates.

[redacted]

[redacted]

[redacted]

7.5 RANDOMISATION

No randomisation is needed for the Phase I part. Patients will be assigned sequentially to the dose cohort at the time.

In the Phase II part, patients will be randomised in a 1:1 ratio to one of the two treatment groups. Randomisation will be stratified based on visceral involvement (yes vs. no). Within each stratum, a central randomisation will be performed across all study centres. The method of permuted blocks will be used.

An Interactive Response Technology (IRT) will be used to perform the randomisation centrally. Boehringer Ingelheim will arrange for the randomisation. A randomisation list will be generated using a validated pseudo-random number generator, yielding reproducible and non-predictable results.

7.6 DETERMINATION OF SAMPLE SIZE

The Phase I part follows a 3+3 design to determine the MTD and RP2D of BI 836845 in combination with exemestane and everolimus. A total of 12 patients will be treated at the RP2D level before commencing the Phase II part. Assuming two cohorts are needed with 3 patients treated in the first cohort, at least 15 evaluable patients will be needed to determine the RP2D in the Phase I part.

Once the RP2D is determined, the Phase II part of the study will start.

In parallel with the commencing Phase II part, an additional 6 patients will be treated in the setting of the Phase I part of the study on the RP2D (leading to a total number of 18 fully evaluable patients at that level), to investigate [redacted]. These additional patients are needed to allow for an estimation of a potential impact of BI 836845 on the [redacted]

The phase II part of the study is intended to provide evidence that will allow informed decision making in terms of the next stages of development. It is therefore sized such that, if the true effect of BI 836845 in combination with exemestane and everolimus relative to exemestane and everolimus alone had a hazard ratio of 0.72 (median PFS 10.8 months of triple combination vs. 7.8 months exemestane and everolimus alone), the probability of observing a small hazard ratio is sufficiently large. If the true hazard ratio is 1, the probability of observing a small hazard ratio is small enough.

Table 7.6: 2 summarizes different numbers of PFS events and associated probabilities for observing hazard ratio less than some thresholds under different assumptions of true hazard ratio value. With 90 PFS events, if the true HR is 0.72, the chance of observing a treatment effect with HR of ≤ 0.8 is 69%, while the chance of observing a treatment effect with HR of ≤ 0.9 is 86%. With 90 PFS events, if the true HR is 1.0, the chance of observing a treatment effect with HR of ≤ 0.8 is 14%, while the chance of observing a treatment effect with HR of ≤ 0.9 is 31%. In this phase II exploratory study, the sample size is calculated to make an informed decision instead of confirmatory hypothesis testing.

If the PFS events are to be increased from 90 to 100, the probability of observing a treatment effect with HR of ≤ 0.85 is increased by 2% (from 78% to 80%) if true HR is 0.72. The same probability is increased by 1% (from 61% to 62%) if true HR is 0.8. Increasing the sample size will benefit more if the true HR is smaller. However, the probability of 78% when true HR is 0.72 is considered high enough for 90 PFS events in this exploratory setting.

Table 7.6: 2 Number of PFS events and corresponding probability of making observing HR below thresholds

		Probability[1] observing HR of ≤			
PFS Events	**True HR**	**0.8**	**0.85**	**0.9**	**1.0**
80	0.72	68%	77%	84%	93%
90		69%	78%	86%	94%
100		70%	80%	87%	95%
		Probability[1] observing HR of ≤			
PFS Events	**True HR**	**0.8**	**0.85**	**0.9**	**1.0**
80	0.80	50%	61%	70%	84%
90		50%	61%	71%	86%
100		50%	62%	72%	87%
		Probability[1] observing HR of ≤			
PFS Events	**True HR**	**0.7**	**0.8**	**0.85**	**0.9**
80	1.0	6%	16%	23%	32%
90		5%	14%	22%	31%
100		4%	13%	21%	30%

[1] Calculated based on the approximate normal distribution of the estimated log HR.

Ninety PFS events is considered sufficient in this phase II trial to show positive efficacy signal if the experimental treatment is superior to the control.

Assuming constant recruitment rate of 12.5 patients per month for a period of A months, the percentage of observed PFS events relative to sample size is a function of study duration T:

$$\frac{1}{2}\left[\left(1-\frac{e^{-\lambda_1(T-A)}-e^{-\lambda_1 T}}{A\lambda_1}\right)+\left(1-\frac{e^{-\lambda_2(T-A)}-e^{-\lambda_2 T}}{A\lambda_2}\right)\right],$$

where λ_1=0.064 and λ_2=0.089 are the parameters of exponential distribution assuming median PFS 10.8 months for BI 836845 in combination with exemestane and everolimus and 7.8 months for exemestane and everolimus alone. Assuming rates of permanently censored patients between 20 to 30%, the study duration of observing 90 PFS events is estimated to be between 24.9 and 32.5 months (Table 7.6: 3). Permanently censored patients are those patients that leave the trial without having a PFS event. For the duration of a trial that is event driven it is a concern if patients leave the study without such an event before the primary evaluation, as it will take longer until the primary analysis can be performed.

Therefore, the primary analysis is targeted when 90 PFS events are observed or 30 months after first patient was randomized in the phase II part.

According to these considerations, a total of 150 patients will be randomised in the Phase II part of the trial.

Table 7.6: 3 Study duration until targeted number of PFS events for different rates of permanently censored patients

Patients randomised	Accrual period [months]	Rate of permanently censored patients	Number of PFS events expected at primary readout	Expected trial duration to reach expected number of PFS events[1] [months]
150	12	20%	90	24.9
150	12	25%	90	27.9
150	12	30%	90	32.5

[1]Assuming a true HR of 0.72 (median PFS 10.8 vs 7.8 months) and a recruitment rate of 12.5 patients per month

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.

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.

If a patient has withdrawn consent to continue trial medication and trial procedures, the informed consent form must specifically indicate that the patient has given permission to collect informatin on his/her vital status and further treatment for those who participated in the Phase II part of the study.

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

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. For drug accountability, refer to Section 4.1.8.

Coding of the data obtained will be done by using the medical dictionary for regulatory activities (MedDRA) and the world health organisation drug dictionary (WHO-DD).

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.

8.3.3 Storage of records

Trial sites:
The trial sites must retain the source documents and essential documents for a period defined by GCP regulations or other Guidelines as applicable per country (i.e.
European Commission Directive, Japanese GCP regulation and FDA Guidelines).

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 836845, this is the current version of the Investigator's Brochure (U10-2830). For everolimus and exemestane, this is the latest version of EU SPC. 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.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial. The sponsor needs to notify the IEC and CA within 90 days of regular completion of the trial and within 15 days in case of early termination in accordance with Directive 2001/20/EC. In case of early termination, a detailed written explanation of the reasons for the termination needs to be given. A summary of the trial results (tabulated summary of the CTR) needs to be provided to the IEC and CA within 1 year of the end of the trial.

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10. APPENDICES

10.1 NYHA CLASSIFICATION OF HEART FAILURE

Class	Patient Symptoms
Class I (Mild)	No limitation 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.

10.2 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

10.3 LIST OF CYP3A4 INHIBITORS, INDUCERS AND LIST OF INHIBITORS OF P-GLYCOPROTEIN

10.3.1 Examples of CYP 3A4 inhibitors and inducers

CYP3A4 Inhibitors	CYP3A4 Inducers
Strong inhibitors: atazanavir, boceprevir, ciclosporin, clarithromycin, conivaptan, darunavir, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, osaconazole, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole Moderate inhibitors: amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice*, imatinib, ritonavir, verapamil * The effect of grapefruit juice varies widely and is preparation-dependent.	**Strong inducers:** carbamazepine, phenytoin, rifampin/rifampicin, rifabutin, rifapentine, phenobarbital, St. John's wort** ** The effect of St. John's wort varies widely and is preparation-dependent. Moderate inducers: bosentan, corticosteroids (e.g. dexamethasone, prednisone, prednisolone), phenobarbital, efavirenz, etravirine, modafinil, nafcillin, nevirapine

As the information may evolve, it is important for the investigator to assess such status on concomitant therapies and contact BI clinical monitor in case of questions.

10.3.2 List of inhibitors of P-glycoprotein (MDR1)

Pgp Inhibitors
Amiodarone
Azithromycin
Captopril
Carvedilol
Ciclosporin
Clarithromycin
Conivaptan
Diltiazem
Dronedarone
Erythromycin
Felodipine
Itraconazole
Ketoconazole
Lopinavir
Nelfinavir
Ritonavir
Quercitin
Quinidine
Ranolazine
Saquinavir
Tacrolimus
Ticagrelor
Verapamil

As the information may evolve, it is important for the investigator to assess the status of each concomittant therapies. In case of questions, please contact BI clinical monitor.

10.4 TUMOR RESPONSE ASSESSMENT ACCORDING TO RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of a least 5mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

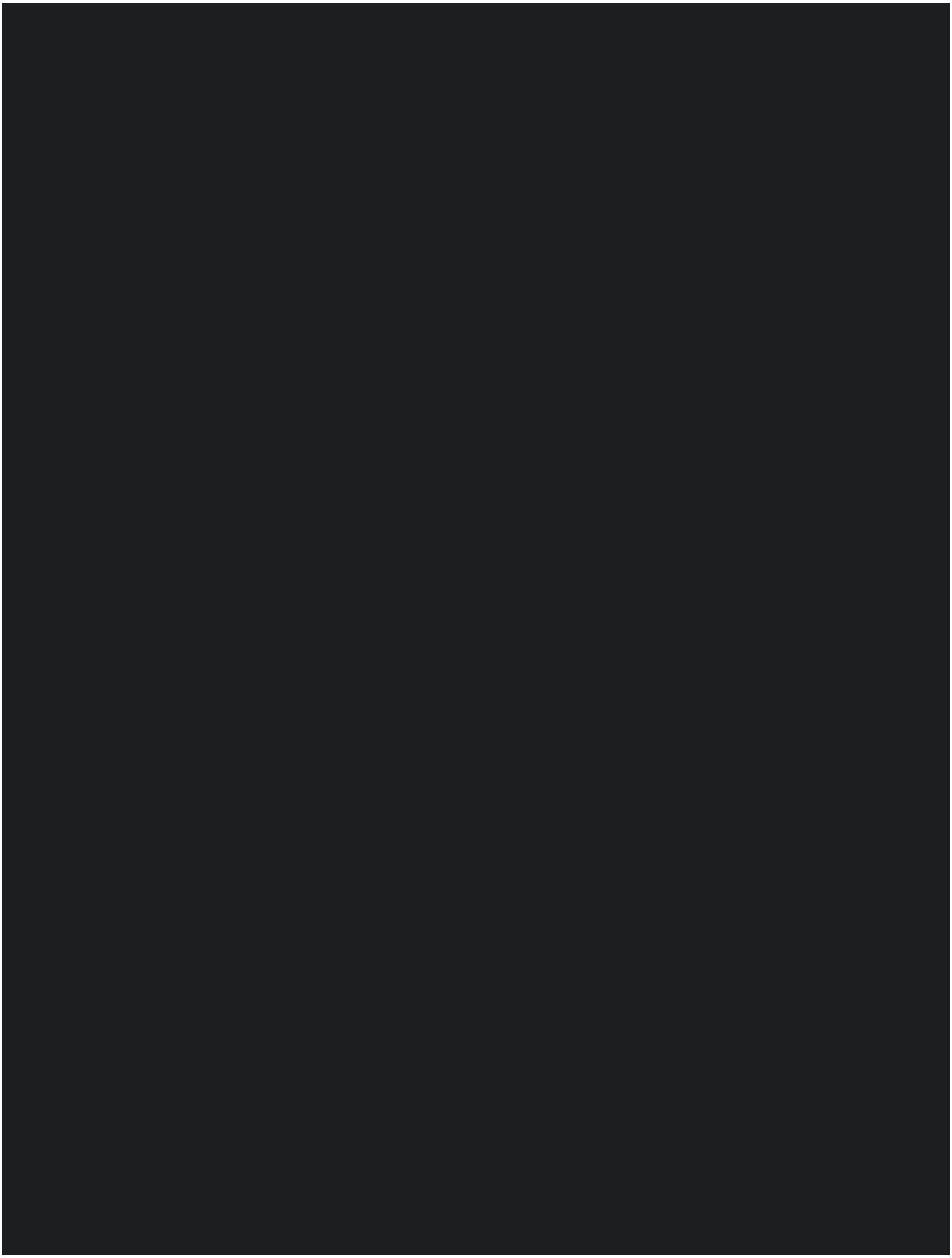
Timepoint response for patients with measurable disease at baseline

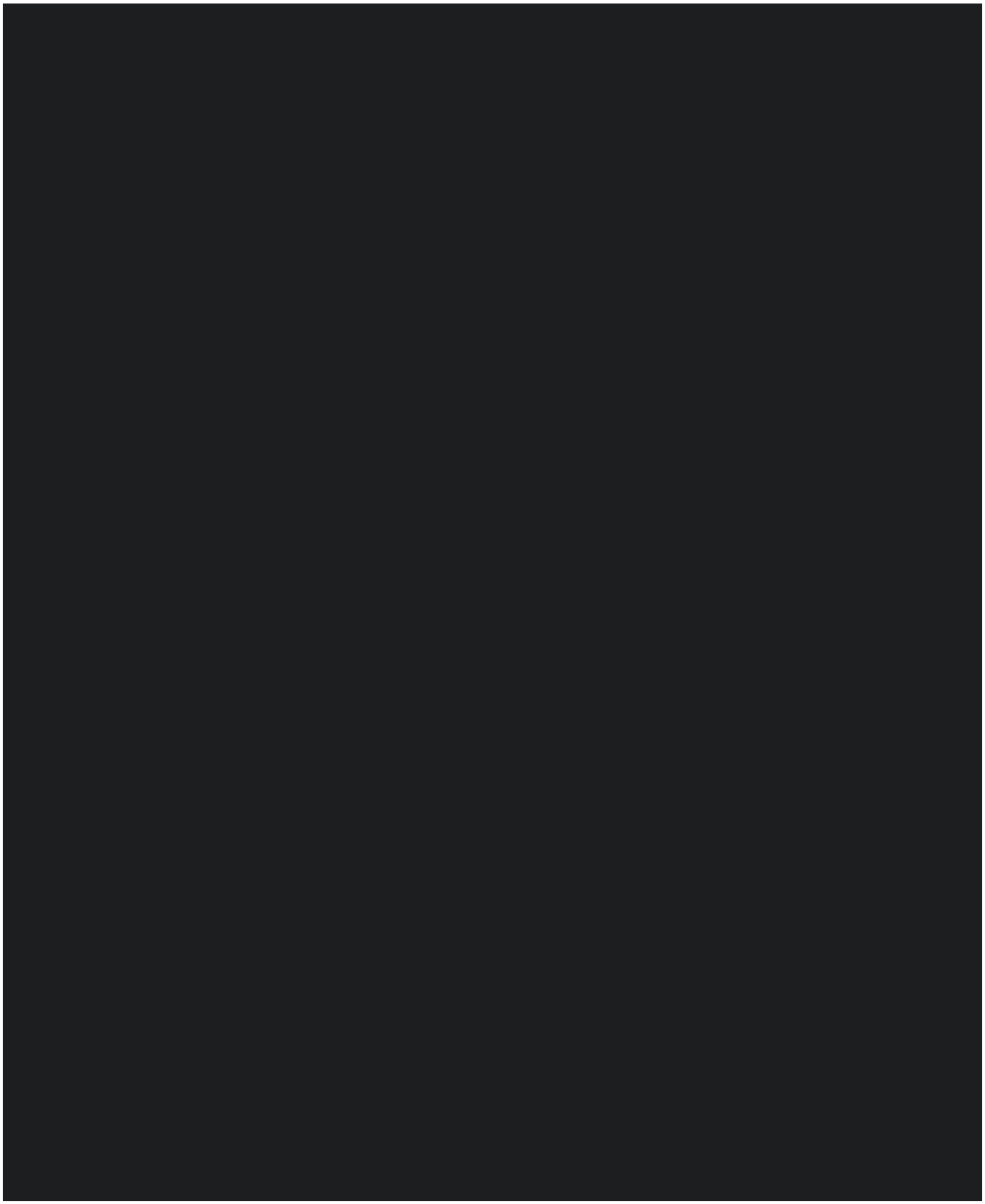
Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

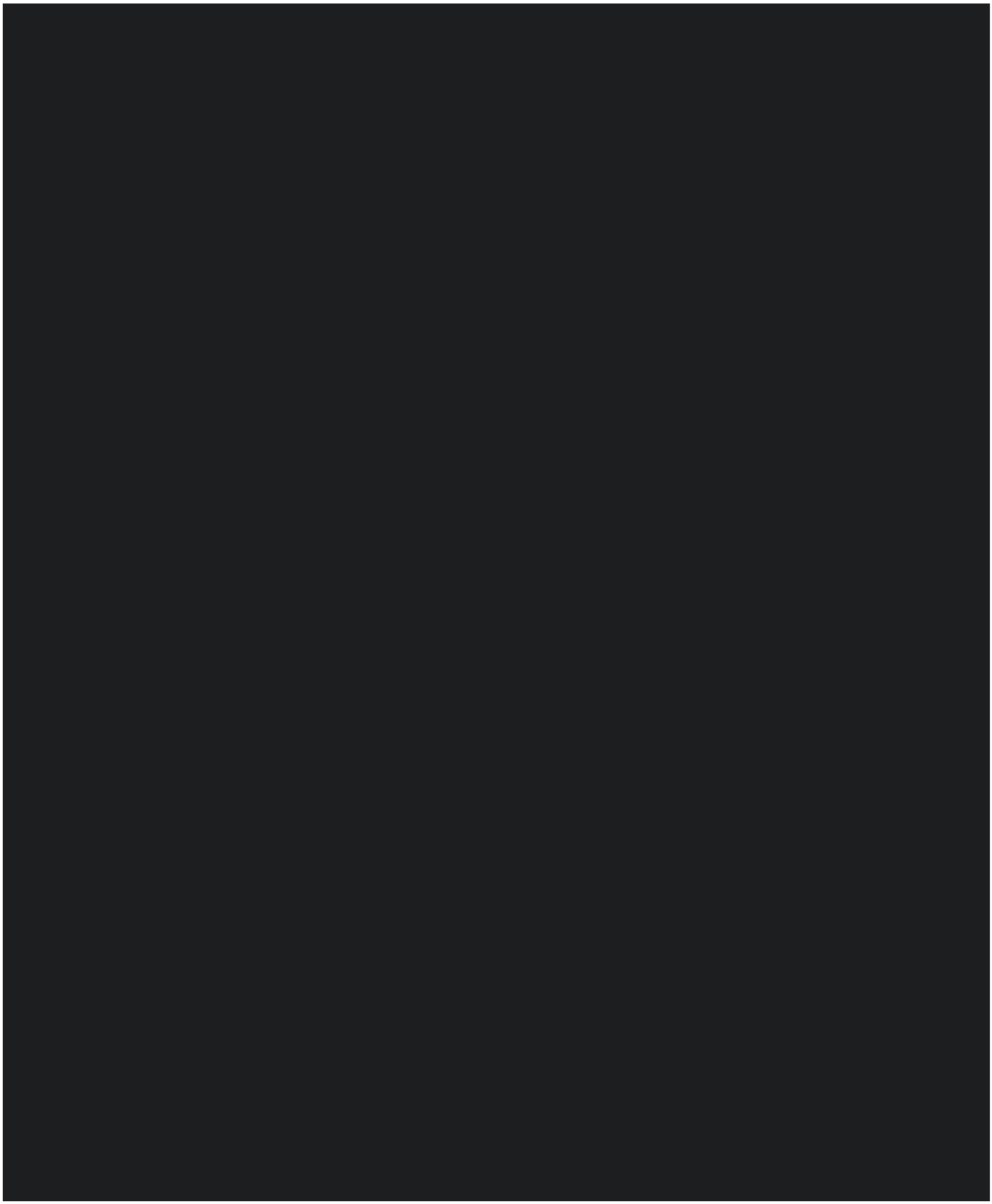
Timepoint response for patients with non-measurable disease at baseline

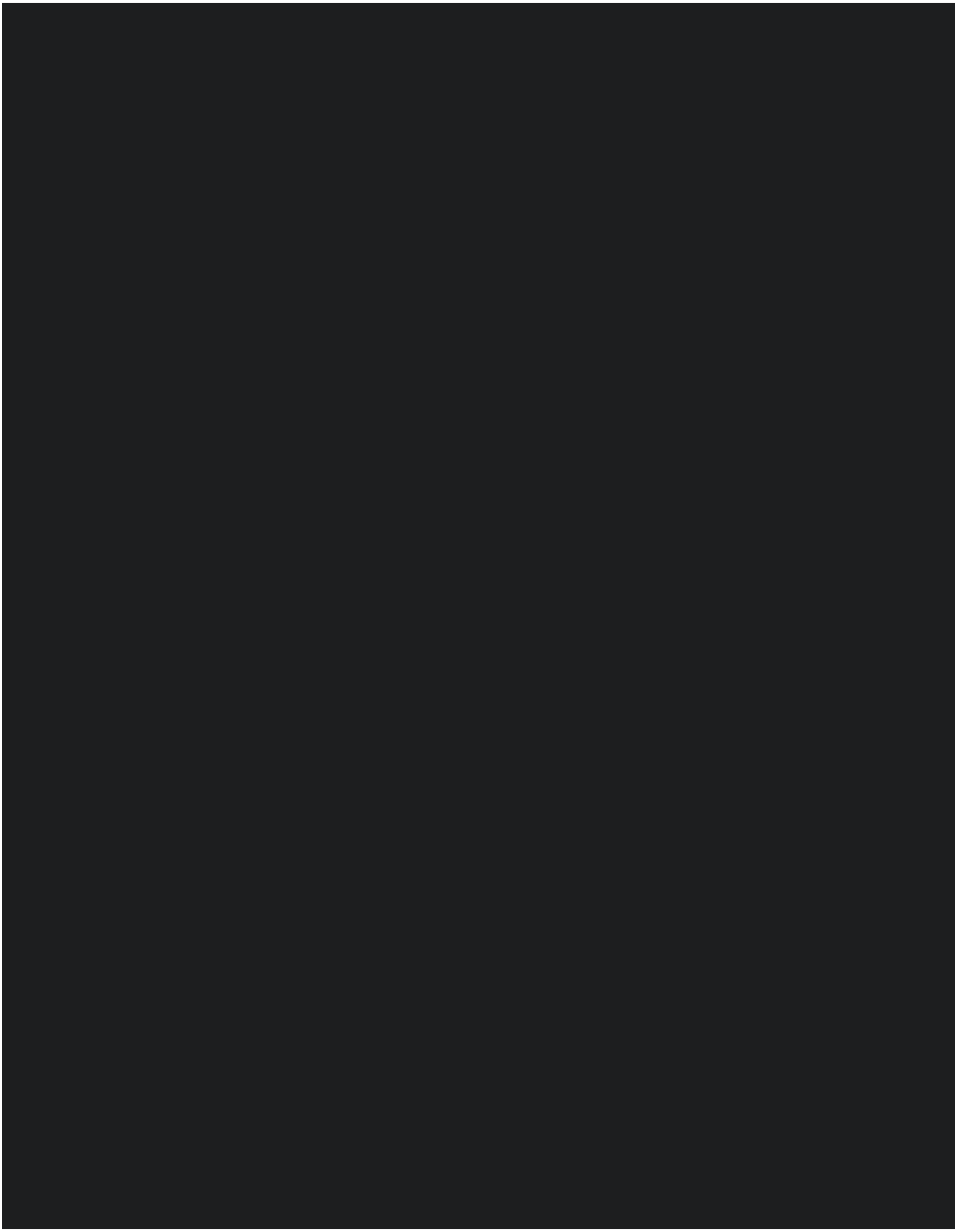
Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/ Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

RECIST 1.1 is as published in Eur. J. Cancer R09-0262









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 intial 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, tumor 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).

and report these via the eCRF.

10.7 TUMOR TISSUE SAMPLE REQUIREMENTS

Marker category	Tissue type	Amount of tissue	Time point of sample taking	Analysis type
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGx	FFPE	Section of >=40 µm at least*	screening	mutational status
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 8 to 10 sections of 5µm each are also acceptable.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		07 May 2015
EudraCT number		2013-001110-15
BI Trial number		1280.4
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer
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		**Clinical Trial Protocol Synopsis**
Description of change		The sentence: "Patients must have a measurable lesion according to RECIST version 1.1 or bone lesion only: lytic or mixed (lytic + sclerotic) in the absence of measurable lesion" **Has been updated to** "Patients must have a measurable lesion according to RECIST version 1.1 or bone lesion: lytic or mixed (lytic + sclerotic) in the absence of measurable lesion"
Rationale for change		Clarification
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Criteria for efficacy section **has been updated** by replacing "6m" by "24w"
Rationale for change		Accuracy
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Criteria for efficacy section **has been updated** by replacing "Clinical benefit" by "Disease control"
Rationale for change		Terminology update
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		cfDNA tests and CTC tests **have been added** in the criteria for efficacy section.
Rationale for change		Additional tests.
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Objectives for Phase I part. A "coma**" has been replaced**

Number of global amendment		1
		by "and"
Rationale for change		Clarification
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Criteria for safety **has been updated from** "The primary endpoint of the phase I part of this study is occurrence of dose limiting toxicity." **to** "The primary endpoints of the phase I part of this study are occurrence of dose limiting toxicity and determination of MTD."
Rationale for change		Update for accuracy
Section to be changed		**Flow Chart - Phase I Part**
Description of change		Footnote 7: "(local lab)" **has been added.**
Rationale for change		Clarification.
Section to be changed		**Flow Chart - Phase I Part**
Description of change		Footnote 12 **has been reworded**
Rationale for change		To clarify that PK samples have to be taken after ECG recording, both before and at the end of BI 836845 infusion.
Section to be changed		**Flow Chart - Phase I Part**
Description of change		Footnote 15: RECSIT **corrected to** RECIST
Rationale for change		Typographic error correction
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Sample for future companion diagnostics development **has been included** in the flowchart.
Rationale for change		Procedure was already described in section 5.6.3.1 but was not included in the flowchart.
Section to be changed		**Flow Chart - Phase II Part**
Description of change		The text "(visit or phone contact allowed)" **has been added** in footnote g
Rationale for change		Clarification added for consistency
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 2: "or documented justification" **has been added**.
Rationale for change		To clarify that this can be a document other than a formal hospital policy.
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 7: "(local lab)" **has been added.**
Rationale for change		Clarification.
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 09 **has been reworded**
Rationale for change		To clarify that pre-treatment fresh tumour sample can be [redacted]
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 12 **has been reworded**
Rationale for change		[redacted].
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 15. The following sentence **has been added**: "and during the phase II part of the trial imaging guidelines should be observed."
Rationale for change		Central reading of tumour imaging may be conducted if needed

Number of global amendment		1
Section to be changed		**Flow Chart - Phase II Part**
Description of change		Footnote 23 **has been added:** "23. If extremely necessary, for arm 2 patients receiving BI 836845 infussion at a subsequent visit, the transaction with the IVRS/IWRS system can be done up to one day before the actual visit date. Please refer to BI 836845 Preparation Storage and Administration instructions for more information about BI 836845 stability and storage conditions once diluted in the infusion bag."
Rationale for change		It may be needed to be able to start BI 836845 early enough to perform all required procedures during the visit
Section to be changed		**Flow Chart - Phase II Part**
Description of change		[redacted]
Rationale for change		Abbreviations section needs to be updated as a result of the changes implemented by this amendment
Section to be changed		**Abbreviatons**
Description of change		AESI Adeverse Event of Special Interest **has been added**
Rationale for change		Abbreviations section needs to be updated as a result of the changes implemented by this amendment
Section to be changed		**Abbreviatons**
Description of change		[redacted]
Rationale for change		Abbreviations section needs to be updated as a result of the changes implemented by this amendment
Section to be changed		**Abbreviatons**
Description of change		[redacted]
Rationale for change		Abbreviations section needs to be updated as a result of the changes implemented by this amendment
Section to be changed		**Abbreviatons**
Description of change		DC Disease control **has been added**
Rationale for change		Abbreviations section needs to be updated as a result of the changes implemented by this amendment
Section to be changed		**2.3 Benefit – Risk assessment**
Description of change		The whole section **has been reviewed**
Rationale for change		Improve the benefit-risk assessment by providing more detailed information.
Section to be changed		**3.1 Overall trial design and plan**
Description of change		"additonal" **corrected to** "additional"
Rationale for change		Typographic error correction
Section to be changed		**3.1.1 Administrative structure of the trial**
Description of change		The following CRO service description **has been added**: "storage and potential central analysis of tumour images"
Rationale for change		If needed, a central independent review of tumour images may be conducted.
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		Criterion 4: "aged ≥18 years old" **has been added** to the criterion, and "women" has been changed to "female patients"
Rationale for change		Clarification
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		Criterion 7b: the word "only" **has been deleted** to avoid misunderstandings

Number of global amendment		1
Rationale for change		Clarification
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Criterion 2 has been **updated from**: "Prior treatment with exemestane" **To** "Prior treatment with exemestane (except adjuvant exemestane stopped > 12 months prior to start of study treatment as long as patient did not recur during or within 12 months after the end of adjuvant exemestane)"
Rationale for change		Consistency with clinical practice.
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		On criterion 6, "run-in treatment" **has been updated to** "the start of study treatment"
Rationale for change		A synonym expression is preferred because fits better in the Phase II part of the trial, where treatment starts at C1V1 because there's no run-in period.
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		On criterion 7, the sentence "(This criterion concerns anti-cancer therapy only)" **has been added.**
Rationale for change		Clarification
Section to be changed		**3.3.4 Removal of patients from therapy or assessments**
Description of change		The sentence "The sponsor may remove patients from the study after completion of the primary efficacy analysis and the patient has access to BI 836845 through an expanded-access program, named patient use program, or compassionate use protocol." **has been deleted**.
Rationale for change		The procedure is not applicable in this trial
Section to be changed		**4.1.2 Method of assigning patients to treatment groups**
Description of change		The sentence "If more than one site notifies potential patients and there are no slots for all proposed candidates, BI Clinical Monitor will allocate the slot prioritizing by planned calendar, balanced number of patients per site and other parameters as needed." **has been added.** **AND** The sentence "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." **has been updated to** "for a reasonable period of time until patient signs IC"
Rationale for change		Better describe the actual procedure to assign available slots to the sites participating in the Phase Ib part of the trial.
Section to be changed		**4.1.4.3 Temporary treatment interruption and dose reduction**
Description of change		"No dose reduction is allowed below 500 mg for BI 836845 or 2.5 mg for everolimus." **Has been corrected to:** "No dose reduction is allowed below 500 mg for BI 836845 or 2.5 mg every other day for everolimus."
Rationale for change		Correction made for consistency throughout the protocol.
Section to be changed		**4.2.1.3 Concomitant treatments**
Description of change		The following paragraph has been moved from section 4.2.2.1 Restrictions to this section:

Number of global amendment		1
		"The acute use of bisphosphonates for symptomatic treatment of bone metastases is permitted during the study, but chronic use for the prevention of bone metastases is prohibited (see Section 4.2.2.1). Bisphosphonate therapy for the treatment of osteoporosis, at the doses indicated under prescribing information, is permitted during the study. If bisphosphonate therapy is initiated after enrollment, the reason for its use must be clearly documented clearly documented in the eCRF."
Rationale for change		For consistency, since the use of bisphosphonates is allowed in certain conditions it should be included in the concomitant treatments section
Section to be changed		**4.2.2.1 Restrictions regarding concomitant treatment**
Description of change		The paragraphs: "For everolimus: Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Concomitant strong CYP3A4 inhibitors should not be used with everolimus. Exercise caution when everolimus is used in combination with moderate CYP3A4 and/or strong and moderate PgP inhibitors. If alternative treatment cannot be administered, reduce the dose of everolimus. Consider a dose increase of everolimus when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St.John's Wort may decrease everolimus exposure unpredictably and therefore should be avoided. For exemestane: Exemestane is a substrate of CYP3A4. Pharmacokinetic study showed that co-medications that induce CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's wort) may significantly decrease exposure to exemestane. Hence, dose modification is recommended for patients who are also receiving a potent CYP 3A4-inducer." **Has been updated to:** "For everolimus: Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Systemic concomitant strong CYP3A4 inhibitors and PgP inhibitors should not be used with everolimus. (refer to Appendix 3 for a list of examples). Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided (refer to Appendix 3 for a list of examples). If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued,

Number of global amendment		1
		consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the everolimus dose is returned to the dose used prior to initiation of the co-administration. Avoid the use of concomitant potent CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, dexamethasone or St. John's wort). If patients require co-administration of a potent CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the co-administration. St.John's Wort may decrease everolimus exposure unpredictably and therefore should be avoided. For exemestane: Exemestane is a substrate of CYP3A4. Pharmacokinetic study showed that co-medications that induce CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, dexamethasone or St. John's wort) may significantly decrease exposure to exemestane. Since the clinical relevance of this interaction has not been evaluated, the co-administration of drugs known to induce CYP3A4 may reduce the efficacy of exemestane Exemestane does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Nevertheless, exemestane should be used cautiously with drugs that are metabolised via CYP3A4 and have a narrow therapeutic window."
Rationale for change		Update information as per Afinitor SmPC new version, dated 16 December, 2014 Update dose modification recommendations for Exemestane according to EU label (US label information has been taken out), as per Swedish authorities request.
Section to be changed		**4.2.2.1 Restrictions regarding concomitant treatment**
Description of change		The paragraph: "In addition, the following concomitant treatments are not allowed during the study: 1) Chronic concomitant bisphosphonate therapy for the prevention of bone metastases Bisphosphonate therapy for the treatment of osteoporosis is permitted during the study. Bisphosphonate therapy for the management of bone metastases is recommended as standard of care. Please refer to prescribing information for

Number of global amendment		1
		details of administration. If bisphosphonate therapy is initiated after enrollment, the reason for its use must be clearly documented" **Has been updated to:** "In addition, the following concomitant treatments are not allowed during the study: 1) Chronic concomitant bisphosphonate therapy for the prevention of bone metastases (the use of any other agent for the prevention of bone metastasis is not allowed during the study)."
Rationale for change		Clarification
Section to be changed		**4.2.2.1 Restrictions regarding concomitant treatment**
Description of change		The paragraph: 7) The use of concomitant medications that prolong the QT/QTc interval (refer to website crediblemeds.org for the list of medications) **Has been updated to:** 7) The use of concomitant medications that prolong the QT/QTc interval (refer to website crediblemeds.org for the list of medications) should be avoided, except in those cases where treatment is necessary after a risk-benefit evaluation by the investigator and provided that the drug in question cannot be substituted by any other agent.
Rationale for change		Consistency with clinical practice and patient needs.
Section to be changed		**Section 4.4 Management of expected adverse events**
Description of change		The following paragraph **has been added**: "In everolimus SPC, non-infectious pneumonitis, infections, hypersensitivity reactions, concomitant use of angiotensin-converting enzyme inhibitors, oral ulceration, renal failure events, and some lab tests and monitoring are described under "Special warnings and precautions for use". For updated information regarding warning and precautions of everolimus and exemestane, please refer to the most current version."
Rationale for change		Update information as per Afinitor SmPC new version, dated 16 December, 2014
Section to be changed		**Section 4.4.6 Management of infection (related to Everolimus)**
Description of change		**Section created** with the following wording: "Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan

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		infections, including infections with opportunistic pathogens. Opportunistic infections such as pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) have been reported in patients who received everolimus and should be ruled out in the differential diagnosis of non-infectious pneumonitis. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids (e.g. for treatment of non-infectious pneumonitis) or other immunosuppressive agents are required. Please follow the most current everolimus SPC or local prescribing information for updated recommendations of management."
Rationale for change		Update information as per Afinitor SmPC new version, dated 16 December, 2014
Section to be changed		**Section 5**
Description of change		Correct the definition of PFS using randomization instead of C1V1
Rationale for change		Use BI standard PFS and most widely accepted definition
Section to be changed		**5.1.1.2 Secondary endpoints**
Description of change		"Phase II part" **has been added**
Rationale for change		Clarification
Section to be changed		**5.1.1.2 Secondary endpoints**
Description of change		"clinical benefit" **has been updated to** "disease control"
Rationale for change		Terminology update
Section to be changed		**5.1.1.2 Secondary endpoints**
Description of change		"6m" **has been updated to** "24w"
Rationale for change		Accuracy
Section to be changed		**5.1.2.1 Tumor Response**
Description of change		The following sentences **have been added:** "For the Phase II part of the study, image acquisition will be performed as described in the Imaging Guideline (wich will be filed in the ISF). Images will be collected and stored at a central facility assigned by the sponsor. The sponsor retains the option to perform an independent blinded central review of the study images at a later time." "For the phase II part, these need to also meet the requirements in the Imaging Guideline."
Rationale for change		If needed, a central independent review of tumor images may be conducted at a later time.
Section to be changed		**5.1.2.3 Assessment of disease progression**
Description of change		"patients with bone only lesions" **has been updated to** "patients with bone lesions"
Rationale for change		Clarification
Section to be changed		**5.2.1 Endpoints of safety**
Description of change		The sentence: "For the phase I part, the primary endpoints are DLT and MTD" **has been added**
Rationale for change		Clarification
Section to be changed		**5.2.1 Endpoints of safety**
Description of change		The sentence: "Dose limiting toxicities (primary endpoint for Phase I part only)" **has been deleted**
Rationale for change		DLT is a formal endpoint and should not be listed here.

Number of global amendment		1
Section to be changed		**5.2.1 Endpoints of safety**
Description of change		"Safety endpoints" has been replaced by "Other assessments of safety"
Rationale for change		To be more accurate and clarify that the list does not correspond to formal endpoints
Section to be changed		**5.2.1 Endpoints of safety**
Description of change		"Other safety-related assessments involving ECG parameters and ECOG score" **Has been updated to** "Other safety-related assessments involving ECG parameters and ECOG score will be described with respect to possible changes compared to baseline values. Further details on the analysis of ECG data will be specified in the TSAP."
Rationale for change		To provide more precise information
Section to be changed		**5.2.2.1. Definitions of adverse events**
Description of change		The term "Significant adverse events" **Has been updated to** "Adverse events of special interest"
Rationale for change		Terminology consistency through the protocol and the BI standards.
Section to be changed		**5.2.2.1. Definitions of adverse events**
Description of change		DILI definition includes now marked peak aminotransferase (ALT, and/or AST) elevations equal or above 10 fold ULN. Other wording in the section **has been refined** to fit the new company templates.
Rationale for change		Consistency with BI standards.
Section to be changed		**5.2.5.2. Vital signs, height and weight**
Description of change		The sentence "Blood pressure and pulse will be measured after the patient has been recumbent for 5 minutes" **Has been updated to** "Blood pressure and pulse will be measured after the patient has been recumbent or seated for 5 minutes"
Rationale for change		It's also allowed to measure blood pressure and pulse if the patient has not been recumbent but seated.
Section to be changed		**5.2.6 Dose limiting toxicity (DLT)**
Description of change		**"**The primary endpoint of the Phase I part is occurrence of Dose Limiting Toxicity (DLT)." **has been updated to** "The primary endpoint of the Phase I part are occurrence of Dose Limiting Toxicity (DLT) and determination of MTD." **AND** Oral mucositis **has been added** as a synonym term for stomatitis **AND** "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 phase II part." **has been updated to** "Available data of DLTs occurring after first treatment course and all unusual/unexpected AE at any time during treatment will be

Number of global amendment		1
		considered for the purpose of recommending the dose for phase II part."
Rationale for change		Update for accuracy
Section to be changed		**5.2.7 Maximum Tolerated Dose (MTD) and Recommended Phase II Dose (RP2D)**
Description of change		The sentence "by the time that 12 evaluable patients have finished course 1 of treatment at the MTD (or tentative RP2D if MTD not reached); at the earliest." **has been added.**
Rationale for change		Clarification
Section to be changed		**5.3.1 Other endpoints**
Description of change		The following endpoint: [redacted] **Has been added** for the phase II part.
Rationale for change		Clarification
Section to be changed		[redacted]
Description of change		The following paragraph **has been added**: [redacted]
Rationale for change		Include additional analysis
Section to be changed		[redacted]
Description of change		

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		[redacted]
Rationale for change		To be more accurate.
Section to be changed		**5.3.4 Demographics and medical history**
Description of change		The following explanation **has been added:** "Collection of race and/or ethnic information is necessary in this study because this study is a multi-national and registrational trial and race and/or ethnicity are known to be associated with biology and outcome of breast cancer. Foreign regulatory agency may request data or analysis based on race/ethnic information."
Rationale for change		Provide the rationale for capturing race information in this trial.
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		Rewording for correctness
Section to be changed		[redacted]
Description of change		[redacted].
Rationale for change		Additional tests.
Section to be changed		**5.6.1 Endpoints based on biomarker(s)**
Description of change		The following text **has been added:** [redacted]
Rationale for change		Add additional tests
Section to be changed		[redacted]
Description of change		

Number of global amendment		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		**6.1 Visit Schedule**
Description of change		"filled" **corrected to** "supplied"
Rationale for change		Clarification.
Section to be changed		**6.1 Visit Schedule**
Description of change		"tmor" **corrected to** "tumor"
Rationale for change		Correct misspelled word.
Section to be changed		**6.2.1.2 Phase I part run-in period (from Day -7 to -1).**
Description of change		A mistake in the description of a PK sample timepoint has been **corrected from** "45 minutes" **to** "1:15h"
Rationale for change		Consistency throughout the protocol.
Section to be changed		**6.2.2.1 Phase I part**
Description of change		Course 1, visit 3 (8±1 days after start of BI 836845) "[redacted]
Rationale for change		Re-worded for clarification.
Section to be changed		**6.2.2.2 Phase II part**
Description of change		The following paragraph **has been added** "If extremely necessary, for arm 2 patients receiving BI 836845 infussion at a subsequent visit, the transaction with the IVRS/IWRS system can be done up to one day before the actual visit date. Please refer to BI 836845 Preparation Storage and Administration instructions for more information about BI 836845 stability and storage conditions once diluted in the infusion bag"
Rationale for change		It may be needed to be able to start BI 836845 early enough to perform all required procedures during the visit
Section to be changed		**6.2.2.2 Phase II part**

Number of global amendment		1
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		**6.2.2.2 Phase II part**
Description of change		Course 1, visit 1 (Day 1 of 1st treatment course) "for arm 2 patients only" **Has been added**
Rationale for change		[redacted]
Section to be changed		**6.2.2.2 Phase II part**
Description of change		Course 1, visit 1 (Day 1 of 1st treatment course) "or a documented justification" **Has been added**
Rationale for change		To clarify that this can be a document other than a formal hospital policy.
Section to be changed		**6.2.3.3. Observation period**
Description of change		Link updated
Rationale for change		Correction
Section to be changed		**6.2.3.3. Observation period**
Description of change		"Further treatment" **has been updated to** "Further anticancer treatment"
Rationale for change		Clarification
Section to be changed		**Section 7**
Description of change		Correct the definition of PFS using randomization instead of C1V1
Rationale for change		Use BI standard PFS and most widely accepted definition
Section to be changed		**7.3.2 Secondary analyses**
Description of change		"clinical benefit" **has been replaced by** "disease control"
Rationale for change		Terminology update
Section to be changed		**7.3.2 Secondary analyses**
Description of change		"6m" **has been replaced by** "24w"
Rationale for change		Accuracy
Section to be changed		**Table 7.3.2.1 Other analyses**
Description of change		[redacted] statistics will be computed" **has been added**
Rationale for change		Additional tests.
Section to be changed		**Table 7.3.4. Interim analyses**
Description of change		"an internal DMC" **has been updated to** "a DMC"
Rationale for change		Clarification
Section to be changed		**7.3.5 Pharmacokinetic analyses**
Description of change		"P10, Q1, Q3, P90" descriptive statistics **have been added**
Rationale for change		Completeness of the list of descriptive statistics.
Section to be changed		**Table 7.6: 2 Number of PFS events and**

Number of global amendment		1
		corresponding probability of making observing HR below thresholds
Description of change		"paitent" **has been corrected to** "patient"
Rationale for change		Typographic error
Section to be changed		**Table 7.6: 2 Number of PFS events and corresponding probability of making observing HR below thresholds**
Description of change		The sentence "According to these considerations, a total of 150 patients will be randomised in the Phase II part of the trial." **has been added**.
Rationale for change		Clarification
Section to be changed		**8.3 Records.**
Description of change		The sentence "Coding of the data obtained will be done by using the medical dictionary for regulatory activities (MedDRA) and the world health organisation drug dictionary (WHO-DD)." **has been added**
Rationale for change		Correct omission in the previous version.
Section to be changed		**8.3.3 Storage of records.**
Description of change		Section added with the following text: "Trial sites: The trial sites must retain the source documents and essential documents for a period defined by GCP regulations or other Guidelines as applicable per country (i.e.European Commission Directive, Japanese GCP regulation and FDA Guidelines). Sponsor: The sponsor must retain the essential documents according to the sponsor's SOPs. When it is no longer necessary for the trial site to retain the source documents and essential documents, the sponsor must notify the trial site."
Rationale for change		Correct omission in the previous version of the protocol.
Section to be changed		**9. References**
Description of change		References R14-1645 and R15-0261 have been added.
Rationale for change		New reference added in section 5.3.3
Section to be changed		**10.3 LIST OF CYP3A4 INHIBITORS, INDUCERS AND LIST OF INHIBITORS OF P-GLYCOPROTEIN**
Description of change		Ciclosporin, rifabutin, rifapentine and phenobarbital **have been added.**
Rationale for change		Update information as per Afinitor SmPC new version, dated 16 December, 2014
Section to be changed		**Various sections throughout the trial**
Description of change		Follow-up visit window **has been updated from** 42±7 days **to** 42+7 days
Rationale for change		Consistency with the predefined residual effect of 42 days.
Section to be changed		**10.5 PHARMACOKINETIC AND BIOMARKER SAMPLING TIME POINTS**
Description of change		The following footnote **has been added**: 

Number of global amendment		1
Rationale for change		Consistency with protocol and flowchart.
Section to be changed		**Table 10.5.1: 1 Blood sampling scheme in Run-in phase and course 1 of the Phase I part**
Description of change		At visit 5 day 22 the text " and ECG recording" **has been deleted.**
Rationale for change		There's no ECG scheduled at this visit
Section to be changed		**Table 10.5.1: 2 Blood sampling scheme in courses 2 through 12 of the Phase I part**
Description of change		The following footnote **has been added**: [redacted]
Rationale for change		Clarification

[redacted]

[redacted]

Section to be changed		**10.7 Tumor tissue sample requirements.**
Description of change		Footnote “8 to 10 sections of 5µm each are also acceptable” **and** “at least” **have been added**.
Rationale for change		Clarification

[redacted]

Number of global amendment		2
Date of CTP revision		30 March 2016
EudraCT number		2013-001110-15
BI Trial number		1280.4
BI Investigational Product(s)		BI 836845
Title of protocol		A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer
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		**Flowchart (all phases)**
Description of change		Bone scan reference added
Rationale for change		Reminder of procedure added to flowchart.
Section to be changed		**Flowchart (phase II part)**
Description of change		Footnote # 9 has been refined
Rationale for change		Consistency with Appendix 10.5
Section to be changed		**Abbreviations**
Description of change		PTM = Planned Time has been added.
Rationale for change		Omission in previous versions
Section to be changed		**3.3.2. Inclusion criteria**
Description of change		Inc. criterion #7 added wording: "Both, a) and b) above must fulfil the condition described in Section 5.1.2 for irradiated tumors Both, a) and b) above must fulfil the condition described in Section 5.1.2 for irradiated tumors"
Rationale for change		Clarification
Section to be changed		**3.3.2. Inclusion criteria**
Description of change		Inc. criterion #4 has been reworded
Rationale for change		Consistency with current postmenopausal status definition at participating investigational sites.
Section to be changed		**3.3.3. Exclusion criteria**
Description of change		"or current presence" added in excl. criterion #14 Reference to relevant section added to excl. criterion #12 "(in lung)" added to excl. criterion #15
Rationale for change		Clarification
Section to be changed		**2.3 Benefit-Risk Assessment**
Description of change		Recommendation to monitor weight loss has been added added
Rationale for change		Patients well-being
Section to be changed		**5.1.2 Assessment of efficacy - Flowchart footnote 15 also**

Number of global amendment		2
		adapted accordingly
Description of change		The following wording has been added "Patients who discontinue the trial for any reason other than imaging based progressive disease should have a tumour assessment (RECIST 1.1) performed at EOTV (exception to this are patients who have already had tumor assessment within 28 days of EOT visit)"
Rationale for change		Improve accuracy of assessment of efficacy for these particular cases
Section to be changed		**5.2.2.1 Definitions of adverse events**
Description of change		Prenumonitis has been added as AE of special interest
Rationale for change		Decision has been made to closely monitor these AEs. Pneumonitis cases will be reported as AESI from the time this amendment is approved by Authorities, and in no case a retrospective reporting will be mandated.
Section to be changed		**5.2.3 Assessment of safety laboratory parameters**
Description of change		Phosphorus to be determined
Rationale for change		Patients safety, based on Everolimus SmPC
Section to be changed		**5.2.4 Electrocardiogram**
Description of change		Clarification added "It is not mandatory to wait for central evaluation of ECGs to take clinical decisions, but in case of values close to 470ms at screenint visit, it's strongly recommended to ask for central lab report to confirm eligibility for patients' safety."
Rationale for change		Clarification
Section to be changed		3.1.1 Administrative structure of the trial
Description of change		Clarification of the DMC tasks (2 pre-defined analysis)
Rationale for change		It has been decided on project level that the DMC performs two additional pre-specified looks for efficacy.
Section to be changed		4.1.5.1 Blinding
Description of change		Clarification of the process to keep the trial team blinded while the DMC is looking at unblended data
Rationale for change		Following the decision to add two interim looks by the DMC, blinding process has been clarified
Section to be changed		5.1.1.1 Primary endpoint and 5.1.1.2 Secondary endpoints
Description of change		Definitions of the endpoints have been updated
Rationale for change		Follow the Reference document to the CTP SOP, for oncology trials (001-MCS-40-106_RD-22) There is no change regarding the content, but the wording is now harmonised with the RD
Section to be changed		5.2.1 Endpoints of safety
Description of change		Definitions of the endpoints have been updated
Rationale for change		Follow the Reference document to the CTP SOP, for oncology trials (001-MCS-40-106_RD-22) There is no change regarding the content, but the wording is now harmonised with the Reference Document
Section to be changed		5.2.2.1 Definitions of adverse events
Description of change		Wording regarding "Exemption to (S)AE reporting" has been added
Rationale for change		PD is already reported as clinical trial endpoint and therefore does not need to be reported as an (S)AE. This is common procedure in most oncology trials.
Section to be changed		5.3.1 Other endpoints

Number of global amendment		2
Description of change		Definitions of the endpoints have been updated
Rationale for change		Follow the Reference document to the CTP SOP, for oncology trials (001-MCS-40-106_RD-22) There is no change regarding the content, but the wording is now harmonised with the reference document Further endpoints for phase I part have been added.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		7.3.1 Primary analyses
Description of change		Derivation of PFS and censoring rules have been added
Rationale for change		Follow the Reference document to the CTP SOP, for oncology trials (001-MCS-40-106_RD-22)
Section to be changed		7.3.2 Secondary analyses
Description of change		Analyses of some secondary endpoints has been adapted
Rationale for change		Follow the Reference document to the CTP SOP, for oncology trials (001-MCS-40-106_RD-22)
Section to be changed		7.3.4 Interim analyses
Description of change		More detailed description of the two prespecified analyses performed by the DMC has been added
Rationale for change		It has been decided on project level that the DMC performs two additional predefined looks for efficacy.
Section to be changed		Section 7.6.2 and Table 7.6.3
Description of change		Refine wording and renaming “drop outs” as “permanently censored patients”
Rationale for change		Accuracy
Section to be changed		Appendix 10.5
Description of change		Clarifications added and timepoints for sampling reduced
Rationale for change		Reduce sampling timepoints and clarify analysis as knowledge in the field evolves

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-revision-02

Title: A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	31 Mar 2016 16:19 CEST
Approval-Translational Medicine Expert		31 Mar 2016 16:24 CEST
Approval-Team Member Medicine		31 Mar 2016 16:46 CEST
Approval-Team Member Medicine		31 Mar 2016 23:42 CEST
Approval-Clinical Program Leaders		01 Apr 2016 09:24 CEST
Author-Trial Statistician		01 Apr 2016 12:01 CEST
Author-Trial Clinical Pharmacokineticist		01 Apr 2016 12:38 CEST
Verification-Paper Signature Completion		04 Apr 2016 13:41 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed