Clinical Trial Protocol

	Document Number:	**c18323506-09**
EudraCT No.: **EU Trial No:**	2017-003131-11	
BI Trial No.:	1280-0022	
BI Investigational Product:	Xentuzumab (BI 836845)	
Title:	Xenera™ 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease	
Lay Title:	The Xenera™ 1 study tests xentuzumab in combination with everolimus and exemestane in women with hormone receptor positive and HER2-negative breast cancer that has spread	
Clinical Phase:	II	
Clinical Trial Leader:	[redacted] Phone: [redacted], Fax: [redacted]	
Coordinating Investigators:	[redacted] Phone: [redacted], Fax: [redacted] [redacted] Phone: [redacted], Fax: [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 5))	
Version and Date:	**Version: 6.0**	**Date: 25 Nov 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	N/A
Active ingredient name:	Xentuzumab (BI 836845)
Protocol date	03 Jan 2018
Revision date	25 Nov 2021
Trial number	1280-0022
Title of trial:	Xenera™ 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease
Coordinating Investigator:	[redacted] Phone: [redacted], Fax: [redacted] [redacted] Phone: [redacted], Fax: [redacted]
Trial site(s):	Multi-centre trial conducted in approximately 80 centres in approximately 15 countries
Clinical phase:	II
Objective(s):	The main objective of the trial is to assess the efficacy of xentuzumab in combination with everolimus and exemestane over everolimus and exemestane in patients with HR+/ HER2- advanced or metastatic breast cancer and non-visceral disease.
Methodology:	Double-blind, randomised, placebo-controlled phase II study with two parallel arms. Eligible patients will be randomised to receive therapy with either xentuzumab/everolimus/exemestane or placebo/everolimus/exemestane at a 1:1 ratio. Randomisation will be stratified by evidence of presence of baseline bone-only metastasis (Yes/No), and prior CDK4/6 inhibitor treatment (Yes/No). Independent assessment of the primary endpoint progression free survival (PFS) according to RECIST 1.1 will be completed in a treatment-blinded manner.

Number of patients entered:	Approximately 80 eligible patients
Number of patients on each treatment:	Xentuzumab in combination with everolimus and exemestane: Approximately 40 eligible patients Placebo in combination with everolimus and exemestane: Approximately 40 eligible patients
Diagnosis:	Female patients with HR+ / HER2- advanced or metastatic breast cancer and non-visceral disease
Main in- and exclusion criteria	Main inclusion criteria 1. Documented histologically confirmed breast cancer with ER- and/or PgR-positive and HER2-negative status 2. Locally advanced or metastatic breast cancer not deemed amenable to curative surgery or curative radiation therapy 3. Archival tumour sample available prior to recruitment. Patients must provide a formalin-fixed paraffin embedded tissue biopsy sample preferably taken at the time of presentation with recurrent or metastatic disease (provision of a biopsy sample taken from the bone is not acceptable). If archival tissue is not available, provision of detailed information from the original histology report may be agreed with the sponsor on a case by case basis. 4. Patients must satisfy the following criteria for prior therapy: • Disease progression during treatment or within 12 months of completion of endocrine adjuvant therapy **OR** • Disease progression while on or within 1 month after the end of endocrine therapy for advanced/metastatic breast cancer (Note: the endocrine therapy does not have to be the treatment immediately prior to trial entry) 5. Patients must be either: • Premenopausal on ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist with FSH and estradiol in postmenopausal range (initiated at least 28 days prior to screening) OR • Post-menopausal, defined as one of the following: • Age ≥ 60 years • Age < 60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and FSH and estradiol in the postmenopausal range. • If taking tamoxifen or toremifene, and age < 60 years, then FSH and estradiol level in post-menopausal range. • Surgical menopause with bilateral oophorectomy 6. Patients must have: • At least one measurable non-visceral lesion according to

RECIST version 1.1 in either lymph nodes, soft tissue, skin
AND/OR
- At least one measurable non-visceral lesion according to RECIST version 1.1 as lytic or mixed (lytic + blastic) in bone
- **AND/OR**
- At least one non-measurable (lytic, mixed lytic + blastic, or blastic) bone lesion according to RECIST version 1.1

7. Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1.
8. Adequate organ function

Main exclusion criteria

1. Previous treatment with agents targeting the IGF pathway, AKT, or mTOR pathways
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. Evidence of visceral metastasis/es (i.e. liver, lung, peritoneal, pleural metastases, malignant pleural effusions, malignant peritoneal effusions) at screening. NOTE: Patients with a past history of visceral metastases are eligible if visceral metastases have completely resolved at least 3 months prior to screening.
4. History or evidence of metastatic disease to the brain
5. Leptomeningeal carcinomatosis
6. More than 1 prior line of chemotherapy for metastatic breast cancer
7. Radiotherapy within 4 weeks prior to the start of study treatment
8. Use of concomitant systemic sex hormone therapy (e.g. Megace) within 2 weeks prior to start of trial treatment. NOTE: Ovarian suppression with GnRH agonists is permitted in premenopausal patients.
9. History or presence of cardiovascular abnormalities
10. Known pre-existing interstitial lung disease
11. More than 1 prior treatment line with a CDK4/6 inhibitor
12. Pregnant or nursing (lactating) women
13. Women of child-bearing potential unless they are using highly effective non-hormonal methods of contraception that achieve a failure rate of less than 1% per year when used consistently and correctly during dosing of study treatment and for at least 1 month after the last dose of exemestane, 8 weeks after the last dose of everolimus and 6 months after the last dose of xentuzumab/placebo (whichever is the longest).

Test product(s):	Xentuzumab (BI 836845)
dose:	1000 mg weekly
mode of administration:	i.v.
Combination product 1:	Everolimus in accordance with the SmPC/PI
dose:	10 mg per day
mode of administration:	p.o.
Combination product 2:	Exemestane in accordance with the SmPC/PI
dose:	25 mg per day
mode of administration:	p.o.
Comparator product:	Placebo
dose:	Not applicable
mode of administration:	i.v.
Duration of treatment:	Treatments will be given continuously in both treatment arms until progression of disease, unacceptable adverse events or other reasons requiring treatment discontinuation. Treatment may continue beyond progression in case of clinical benefit.
Endpoints	Primary endpoint: • PFS* Secondary endpoints: • Overall survival (OS) • Disease control (DC)* • Duration of DC* • Objective response (OR)* • Time to pain progression or intensification of pain palliation **Tumour response will be assessed according to RECIST 1.1, independent assessments will be considered primary with the investigator assessment as supportive.*
Safety criteria:	Incidence and severity of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0)

Statistical methods:	A comparison between the treatment groups with respect to the primary endpoint of PFS (independent assessment) will be made via a log-rank test, stratified by baseline bone-only metastases, prior CDK4/6 inhibitor treatment and menopause status. In addition a stratified Cox proportional hazards model will be used to estimate the hazard ratio and corresponding 95% confidence interval (CI). OS and time to pain progression or intensification of pain palliation will be analysed using a similar methodology. Logistic regression models, adjusted for the presence of baseline bone-only metastases, prior CDK4/6 inhibitor treatment and menopause status will be used to compare the treatment groups with respect to DC and OR. Kaplan-Meier estimates will be used to calculate median duration of DC for each treatment group.
	If at the time-point of the primary PFS analysis for this Phase II trial the hazard ratio is below a pre-defined criterion (to be defined in the DMC charter, prior to study initiation), in favour of the xentuzumab arm, then the trial will be expanded into a confirmatory Phase III trial. No formal hypothesis testing will be performed if the trial is not expanded. However, if the trial is expanded PFS and OS will be formally tested in a hierarchical manner controlling for the overall alpha-error of 2.5% (one-sided).

FLOW CHART -No longer applicable per CTPv6.0

	Screening		Treatment Cycle 1**				Treatment Cycle 2-20**	Treatment Cycle 2	Treatment Cycle 21 and subsequent cycles**	End of Treatment***	End of residual effect period and follow-up 1****	Further Follow-up for progression (FU-PD)****	Follow-up for survival (FU-OS) *****
Visit abbreviation	**SV***		**C1V1**	**C1V2**	**C1V3**	**C1V4**	**$Cx_{(2-20)}V1$[a]**	**C2V3**	**$Cx_{(21+)}V1$[a]**	**EOT**	**EOR/ FU1**	**FUx-PD[b]**	**FUx-OS[c]**
Days	**≤ 28 days**	**≤ 14 days**	**Day 1**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 1 every 28 days (± 2 days)**	**Day 15 (± 2 days)**	**Day 1 every 56 days (± 2 days)**	**0-14 days after permanent trial medication discontinuation**	**42 days after permanent trial medication discontinuation (+ 7 days)**	**FU2-PD 56 or 112 days**** after EOT and then every 56 days (± 7 days)**	**Every 84 days after last follow-up visit (± 15 days)**
Informed Consent (1)	X												
Demographics	X												
Medical History	X												
Provision of archival tumour tissue for HR/HER2 analysis and biomarker analysis (2)	X												
Collection of information on available molecular breast cancer signatures (22)			X										
Full physical exam (3)		X								X			
Limited physical exam (4)			X				X		X		X	X	
Vital Signs (5)		X	X	X	X		X		X	X	X	X	
ECOG performance status		X	X	X	X		X		X	X	X	X	
Questionnaires (6)			X				X		X	X	X	X	
Health care resource use (23)			X				X		X	X	X	X	
ECG (7)	X									X			
Echocardiography or MUGA (8)	X									X			

	Screening		Treatment Cycle 1**				Treatment Cycle 2-20**	Treatment Cycle 2	Treatment Cycle 21 and subsequent cycles**	End of Treatment***	End of residual effect period and follow-up 1****	Further Follow-up for progression (FU-PD)****	Follow-up for survival (FU-OS*****
Visit abbreviation	**SV***		**C1V1**	**C1V2**	**C1V3**	**C1V4**	**$Cx_{(2-20)}V1$[a]**	**C2V3**	**$Cx_{(21+)}V1$[a]**	**EOT**	**EOR/ FU1**	**FUx-PD[b]**	**FUx-OS[c]**
Days	**≤ 28 days**	**≤ 14 days**	**Day 1**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 1 every 28 days (± 2 days)**	**Day 15 (± 2 days)**	**Day 1 every 56 days (± 2 days)**	**0-14 days after permanent trial medication discontinuation**	**42 days after permanent trial medication discontinuation (+ 7 days)**	**FU2-PD 56 or 112 days**** after EOT and then every 56 days (± 7 days)**	**Every 84 days after last follow-up visit (± 15 days)**
Safety lab (9)		X	X				X (9)		X (9)	X	X		
Hormone levels, pregnancy test (if applicable) (25)		X(25)	X(25)				X(25)		X(25)	X(25)	X(25)	X(25)	X(25)
Tumour assessment (10)	X		See schedule below (10)										
Review of In-/Exclusion	X	X											
Randomisation (11)			X										
Dispense xentuzumab/placebo (12)			X	X	X	X	X	X	X				
Dispense everolimus and exemestane (13)			X				X (13)		X (13)				
Issue patient diary (14)			Continuous										
Study treatment (24)			Continuous										
Review study medication compliance (14)				X (14)			X		X	X			
Blood sample for PK analysis (15)			X		X		X (15)		X	X	X		
Blood samples for ADAs and nAbs (15)			X		X		X (15)		X	X	X		
Blood samples for cytokines (15)			X				X (15)						
Blood samples for free and total IGF-1, total IGF-2 (16)			X				X (16)						
Blood samples for cfDNA (17)			X				X (17)			X		X (17)	
Blood and Urine samples for Bone remodelling markers (18)			X				X (18)	X		X			

	Screening		Treatment Cycle 1**				Treatment Cycle 2-20**	Treatment Cycle 2	Treatment Cycle 21 and subsequent cycles**	End of Treatment***	End of residual effect period and follow-up 1****	Further Follow-up for progression (FU-PD)****	Follow-up for survival (FU-OS)*****
Visit abbreviation	**SV***		**C1V1**	**C1V2**	**C1V3**	**C1V4**	**$Cx_{(2-20)}V1$[a]**	**C2V3**	**$Cx_{(21+)}V1$[a]**	**EOT**	**EOR/ FU1**	**FUx-PD[b]**	**FUx-OS[c]**
Days	**≤ 28 days**	**≤ 14 days**	**Day 1**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 1 every 28 days (± 2 days)**	**Day 15 (± 2 days)**	**Day 1 every 56 days (± 2 days)**	**0-14 days after permanent trial medication discontinuation**	**42 days after permanent trial medication discontinuation (+ 7 days)**	**FU2-PD 56 or 112 days **** after EOT and then every 56 days (± 7 days)**	**Every 84 days after last follow-up visit (± 15 days)**
Blood sample for genomic DNA			X										
Adverse events (19)	X		X	X	X	X	X	X	X	X	X	X (19)	X (19)
Concomitant medications (20)	X		X	X	X	X	X	X	X	X	X	X (20)	
Termination of study medication										X			
Collection of vital status information (21)										X	X	X	X (21)

* **Screening**: Documented HR/HER2 analyses results are required for the analysis of HR+ and HER2- status. If HR and HER2 status are unknown the patient is not eligible for screening.

** **Treatment: From Cycle 1 to the end of Cycle 20 treatment cycles are 4 weeks in duration (28 days) with weekly visits for infusions and AE/concomitant medication documentation in addition to the CxV1 visits. From cycle 21 until the end of treatment cycles are 8 weeks in duration (56 days) with weekly visits for infusions and AE/concomitant medication documentation in addition to the CxV1 visits. Everolimus and exemestane should be dispensed every 4 weeks. Pregnancy testing (where applicable) to continue to be performed every 4 weeks (see footnote 25 below).** Patients may continue on treatment for an unlimited number of cycles, until the criteria for stopping medication are met (see Section 3.3.4). Note: from cycle 3 onwards those patients that have discontinued xentuzumab/placebo, but remain on everolimus/exemestane will only be required to attend visits on day 1 (V1) of each cycle until the end of cycle 20 and on day 1 (V1) and day 29 (V5) of each cycle from the start of cycle 21.

*** **End of Treatment**: If the decision to permanently discontinue **all** study medication is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

**** **End of Residual Effect Period/Follow up**: An EOR/FU1 visit must be conducted 42 days (+7 days) after the permanent discontinuation of treatment.
If a patient has not progressed nor started further anti-cancer treatment prior to EOR/ FU1, the patient will continue to have regular follow-up visits for PD. FUx-PD visits will take place (i) every 8 weeks (56 days) after EOT for patients who did not yet reach the end of cycle 20 and (ii) every 16 weeks (112 days) for patients who received treatment past cycle 20. These visits should be aligned with the imaging schedule. The FU-PD period will end at the time point of disease progression or start of further anti-cancer treatment.

***** **Follow-up for Survival**: When a patient has either progressed or started a new anti-cancer treatment, the follow period up for overall survival (FU-OS) starts. FU-OS ends when the patient dies, is lost to follow up or withdraws consent for collection of overall survival data (see Section 6.2.3.3). These visits can be conducted as phone calls.

a x is the number of the treatment cycle

b x is the number of the follow-up visit starting with FU2-PD

c x is the number of the follow-up survival assessment

1 Written informed consent must be obtained before any protocol-specific screening assessments are performed. Informed Consent must include consent to collection of demographic data. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions.

2 Archival tumour tissue (either tissue block or 20 slides) to be provided (preferably from the time point closest to trial entry) at SV for retrospective analysis of HR/HER2 at the central laboratory. Results from central laboratory are not required prior to randomisation. Bone biopsy samples are not acceptable (see Section 5.4.1).

3 Full physical examination (Section 5.2.1): Cardiopulmonary examination, clinical tumour assessment, examination of regional lymph nodes and the abdomen, assessment of mental and neurological status. Post baseline: Additional symptoms which were not previously reported should be clarified. Includes height (only at SV) and weight.

4 Limited physical examination (Section 5.2.1): Cardiopulmonary examination, clinical tumour assessment, examination of regional lymph nodes and the abdomen. Includes weight.

5 Vital signs include respiratory rate, pulse, temperature and blood pressure

6 PRO questionnaires will be completed by the patient as their first activity when attending a study visit at the visits indicated in the flow chart.

7 12-lead resting electrocardiograms (ECG) are recorded locally. ECG will be performed at SV and EOT, and if clinically indicated.

8 Echocardiography or MUGA will be performed at SV and EOT, and if clinically indicated. LVEF assessment does not need to be repeated during screening if there is valid result available from an assessment which was performed as part of routine clinical practice within 28 days prior to start of trial treatment.

9 Includes haematology, biochemistry, and urinalysis (Section 5.2.3). To be performed every 4 weeks for cycles 1-5 (C1V1, C2V1, C3V1, C4V1 and C5V1), and then every 8 weeks from cycle 5 (C7V1, C9V1, C11V1 etc.). Reminder: when cycle duration is extended to 8 weeks, i.e. after completion of cycle 20 (week 80), safety lab will be done at Day 1 of each cycle (every 8 weeks). Patients must be in a fasted state for safety bloods. See Section 5.2.3 for details.

10 Tumour assessments will include CT scans of the chest, abdomen, pelvis and a brain CT/MRI as well as a bone scan at screening. If clinically indicated, imaging of any other known or suspected site of disease (e.g. breast) using an appropriate method (CT scan, MRI etc.) will be performed. Imaging assessments do not need to be repeated during screening if there is valid result available from an assessment which was performed as part of routine clinical practice within 28 days prior to start of trial treatment.

The same radiographic procedure must be used throughout the study. If bone lesions are already known or confirmed at screening, bone scans must be performed together with every other CT scan but with an additional bone scan at week 8 (49-56 days after randomisation). If mammography is additionally conducted during clinical routine, it should also be sent to the central imaging assessment together with any correlative images. Breast- ultrasound and biopsy data, if available, will be provided to the central imaging CRO for independent review (see Appendix 10.4 for more detail). Skin lesions will be documented as photographs as described in Appendix 10.4. All images and photos will be sent to a central imaging CRO.

Assessments will be performed every 8 weeks at following time points until week 80, irrespective of scheduled visits, until progression or start of further treatment for mBC;

SV, images taken within 28 days prior to start of trial treatment (C1V1) and compliant with central imaging requirements
During week 8 (49-56 days after randomisation) (including bone scan if applicable)
During week 16 (105-112 days after randomisation) (including bone scan if applicable)
During week 24 (161-168 days after randomisation)
During week 32 (217-224 days after randomisation) (including bone scan if applicable)
During week 40 (273-280 days after randomisation)

For patients continuing beyond week 80 the imaging schedule will change to q12 weeks (bone scans q24 weeks).

For patients in FU-PD (i) (who came off trial treatment before the end of Cycle 20) imaging every 8 weeks (56 days) and (ii) (who received treatment beyond cycle 20) every 12 weeks (84 days). Imaging procedures will be performed until progression or start of further anti-cancer therapy. For patients starting further anti-cancer therapy without objective progression, imaging should be performed prior to starting the new therapy if no image has been performed within the last 4 weeks. If patients continue treatment beyond progression, imaging must also be continued and sent to a central imaging CRO.

In the event of early discontinuation or an interruption/delay to treatment the tumour assessment schedule should not be changed.

11 Patients will be randomised after all SV procedures have been completed and eligibility is confirmed. Treatment must commence as soon as possible after randomisation, but within 7 days at the latest.

12 Xentuzumab/placebo will be dispensed weekly. Drug holidays of up to 14 calendar days will be allowed for xentuzumab/placebo as described in Section 4.3.1. In case of drug holidays please also refer to footnote 14.

13 From Cycles 1 to 20 everolimus and exemestane will be dispensed at V1 of each cycle. After cycle 20 (week 80), dispensation will take place at V1 and V5 of each cycle.

14 A patient diary will be given to the patient for continuous use through the trial. It should be given to the patient at the start of each cycle. The diary collects information about medication taken at home and provides reminders about fasting bloods and urine samples. After one week on study medication, treatment compliance should be discussed with the patient, to ensure that the medication is being taken correctly (no compliance calculation has to be performed). Then at Visit 1 of each cycle and at EOT treatment compliance needs to be checked including compliance calculations.

15 Pharmacokinetic, ADA/nAb and cytokine sampling will take place as described in Appendix 10.1. If a patient misses xentuzumab/placebo infusions due to drug holidays replacement samples for PK, ADAs, nAbs should be drawn at -0:05 timepoint, before the next infusion.

16 Biomarker blood sampling will take place at pre-dose at C1V1, C2V1. At C2V1 an additional sample will be taken 15 min. (±5 min.) after end of xentuzumab/placebo infusion as described in Appendix 10.1.

17 A blood sample from which the plasma needs to be separated and isolated within approx. 4 hours after blood collection. Plasma will be used for cfDNA isolation and further molecular analysis as described in Section 5.4. Sample collection has to be performed (pre-dose) at baseline on C1V1, C3V1, EoT and at time of disease progression during FU-PD if applicable (Appendix 10.1).

18 Samples for bone remodelling markers in blood and urine will be taken (pre-dose) at C1V1, C2V3, C4V1, and EoT as described in Appendix 10.1. Subsequent specimens for comparison should be collected at the same time of day as C1V1 sample. Urine samples must be provided by patient using second morning void (note: this may occur at home)

19 After the EOR/FU1 visit, only drug-related SAEs and AESIs need to be reported. For details refer to Section 5.2.6.2.

20 Analgesic intake will be assessed and completed using Analgesic Quantification Algorithm (AQA) as part of concomitant medications assessment. During FU-PD only concomitant medications for treatment of a drug-related SAE or AESI will be recorded in the CRF.

21 Collection of information on progression, further anti-cancer treatment, pregnancy (if applicable – see footnote 25) and death. Information should be collected from the patient notes or by telephone contact with the patient. A formal study visit is not required.

22 In the case that prior information regarding the patient's genomic breast cancer signature is available, an anonymized copy of the report will be collected for the trial database and results will also be recorded in the CRF.

23 Information on caregiver support (home care), general practitioner, outpatient and hospital visits (other than scheduled visits) will be collected in the CRF and as part of AE reporting to inform on healthcare resource use required. For details refer to section 5.6.3.

24 Everolimus and exemestane should be taken once a day at approximately the same time of day, following a meal. The tablets may be taken at home or in the clinic.

25 Pre-menopausal women:
Serum pregnancy testing to be performed at screening followed by serum or urine testing on Day 1 of each cycle until the end of Cycle 20. From Cycle 21 onwards, serum or urine pregnancy testing to be performed every 4 weeks (i.e. on Day 1 and Day 29 of 56 day cycle) until the end of treatment. Serum or urine pregnancy testing to be performed at end of treatment visit and then during the follow up phase every 4 weeks until either 1 month after the last dose of exemestane, 8 weeks after the last dose of everolimus, or 6 months after the last dose of xentuzumab/placebo, whichever is longer. During the follow up period urine pregnancy tests may be done at home, in which case multiple tests should be provided at end of treatment period to ensure that patient has enough to cover the follow up phase. Patient should be advised to contact the blinded team immediately on result of a positive test, otherwise results of tests will be collected at either the EOR/FU1, FU-PD or FU-OS visits.

Hormone testing to include Estradiol and FSH to be performed at screening followed by estradiol only on Day 1 of every odd number cycle starting at Cycle 3 and end of treatment. See Section 5.2.3.

Post-menopausal women: If under 60, and not had a bilateral oophorectomy, hormone testing to include Estradiol and FSH at screening. See section 5.2.3.

FLOW CHART- Reduced schedule per CTP v6.0 – Ongoing patients

	Treatment Cycle 2 and subsequent cycles*	**End of Treatment, End of residual period & End of Study** **
Visit abbreviation	**CxV1**[a]	**EOT/ EOR/ EOS**
Days	**Day 1, every 28 days (± 2 days)**	**7-14 days after permanent trial medication discontinuation**
Physical exam and Vital Signs	Per institutional practice	
Safety lab	Per institutional practice	
Tumour assessment (1)	Per institutional practice	
Issue patient diary (2)	X	
Review study medication compliance (2)	X	X
Adverse events (3)	X	X
Dispense everolimus and exemestane (4)	X	
Pregnancy test and hormone testing (if applicable) (5)	Per institutional practice	

* **Treatment cycles are 4 weeks in duration (28 days) with a clinic visit on** day 1 (V1) of each cycle. Patients may continue on treatment for an unlimited number of cycles, until the criteria for stopping medication are met (see Section 3.3.4).

** **End of Treatment, End of Residual Period & End of Study**: This combined visit should be scheduled 7-14 days after all trial medications are permanently stopped, to account for the residual periods for everolimus (7 days) and exemestane (5 days).

a x is the number of the treatment cycle

1. Tumour assessments will be performed according to institutional practices. Based on DBL primary analysis, images no longer need to be sent to central CRO and reviewed independently. The overall response only will be collected in the electronic CRF.

2. A patient diary will be given to the patient for continuous use through the trial. It should be given to the patient at the start of each cycle. The diary collects information about medication taken at home and provides reminders about fasting bloods and urine samples. At Visit 1 of each cycle and at EOT treatment compliance needs to be checked including compliance calculation

3. All serious adverse events, AESI and study drug related adverse events still ongoing at the end of treatment will be followed until resolution/stabilization

4. Everolimus and exemestane should be taken once a day at approximately the same time of day, following a meal. The tablets may be taken at home or in the clinic.

5. Pre-menopausal women:
Serum and/or urine pregnancy testing to be performed on Day 1 of each cycle until the end of treatment and after EOT per institutional practice Hormone testing to include estradiol only on Day 1 of every odd number cycle starting at Cycle 3 and end of treatment. See Section 5.2.3.

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ABBREVIATIONS

ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Aromatase inhibitor
AKT	Protein kinase B-alpha
ALT	Alanine amino transferase
AMP	Auxiliary medicinal product
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
aPTT	Activated Partial Thromboplastin Time
AQA	Analgesic Quantification Algorithm
ASCO	American Society of Clinical Oncology
AST	Aspartate amino transferase
BI	Boehringer Ingelheim
BOLERO	Breast cancer trials of OraL EveROlimus
BPI-SF	Brief Pain Inventory– Short Form
BRS	Bone-only metastases randomized set
BUN	Blood urea nitrogen
C	Cycle x
CAP	College of American Pathologists
CCND1	Cyclin D1
CDK	Cyclin-dependent kinases
cf	Cell-free
CI	Confidence Interval
CPK	Creatine phosphokinase
C_{pre}	Pre-dose plasma concentration
CR	Complete response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract research organisation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DC	Disease control
DCR	Disease control rate
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eDC	Electronic Data Capturing
e.g.	Exempli gratia (for example)
ELISA	Enzyme Linked Immunosorbent Assay

EOR	End of residual effect period
EOT	End of treatment
EQ-5D-5L	EuroQoL 5-dimension health status self-assessment questionnaire
ER	Estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron-emission tomography
FFPE	Formalin fixed paraffin embedded
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence *in situ* hybridisation
FSH	Follicle-stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GGT	γ-glutamyltransferase
GMP	Good Manufacturing Practice
HbA1c	Glycated haemoglobin
HCRU	Health care resource utilisation
HDL	High-density lipoprotein
Hep	Hepatitis
HER2	Human epidermal growth factor receptor 2
Hgb	Haemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HR	Hormone receptor
HRQOL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
i.e.	Id est (that is)
IEC	Independent Ethics Committee
IGF	Insulin-like growth factor
IGF-1R	IGF1 receptor
IGFBP3	IGF-binding protein 3
IgG1	Immunoglobulin 1
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International Normalised Ratio
IR-A	Insulin receptor A
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
Ki-67	Antigen KI67
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LSLT	Last Subject Last Treatment
LSLVPE	Last Subject Last Visit Primary Endpoint

LSLVSE	Last Subject Last Visit Secondary Endpoint
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal antibody
mBC	Metastatic breast cancer
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
mTORC1	mTOR complex 1
MUGA	MUltiGated Acquisition scan
nAb	Neutralising antibody
NCI	National Cancer Institute
NE	Not evaluable
NFBSI-16	Network Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index
NIMP	Non-investigational medicinal product
NSAID	Nonsteroidal anti-inflammatory drugs
NTX	N-terminal cross-linked telopeptide of type I collagen
NYHA	New York Heart Association
OME	Oral morphine equivalent
OPU	Operative Unit
OR	Objective response
ORR	Objective response rate
OS	Overall survival
p	Probability
P1NP	N-terminal propeptide of procollagen type 1
PFS	Progression-free survival
PgR	Progesterone receptor
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PD	Pharmacodynamics
PD	Progressive disease
PI	Prescribing information
PK	Pharmacokinetics
p.o.	Per os (oral)
PR	Partial response
PRO	Patient Reported Outcome
PTEN	Phosphatase and tensin homolog
Ras	Rat sarcome
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RNA	Ribonucleic acid
RS	Randomised set
SAE	Serious Adverse Event
sAg	Surface antigen
SC	Steering Committee
SD	Stable disease

SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SS	Skeletal scintigraphy
SUSAR	Suspected Unexpected Serious Adverse Reactions
SV	Screening visit
TNM	Tumour-lymph nodes-metastases; classification of malignant tumours
T_{max}	Time from dosing to the maximum plasma concentration
TMF	Trial Master File
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of institutional normal
V	Visit
VAS	Visual analogue scale
VEGF-C	Vascular endothelial growth factor C
vs.	Versus
WBC	White blood cell
WHO	World Health Organization
XR	Radiography

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Breast cancer is one of the most common cancers in women. More than 180,000 estimated deaths due to breast cancer are expected annually in the United States and Europe combined (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). The traditional separation of breast cancers into HR-positive and -negative cases helps to guide patient management. The only markers with an associated targeted therapy are currently the estrogen receptor (ER) and the human epidermal growth factor receptor 2 (HER2).

Approximately 15% of patients with breast cancer have HER2 overexpressing and/or amplified tumours; these patients are treated with a combination of trastuzumab+/-pertuzumab, monoclonal antibodies targeting HER2, and chemotherapy. For the two-thirds of breast cancers which are positive for ER and/or progesterone receptor (PgR), endocrine therapy with tamoxifen or aromatase inhibitors is generally indicated. However, a subgroup of ER+ patients relapses irrespective of standard hormonal therapy. While early stage disease is curable, patients with metastatic breast cancer (mBC) have a median overall survival (OS) of only 2 to 3 years (R16-3983). *De novo* or acquired resistance to endocrine therapy remains an important clinical problem. HR+ advanced or metastatic breast cancer still has a dismal prognosis. Until recently, progression-free survival (PFS) was less than one year for HR+/HER2- mBC patients when diagnosed with metastatic disease. Only after combinations of the mechanistic target of rapamycin (mTOR) inhibitor everolimus and exemestane median PFS increased from 3.2 to 7.8 months (R16-4906) and cyclin-dependent kinases (CDK) 4/6 inhibitors further improved median PFS to 20-25 months in 1st line setting and 9.5-16 months in 2nd line setting (R16-4899, R17-2796, R17-2798, R17-2979, R17-2980). None of the latter trials to date showed overall survival benefit (R17-2892). Eventually patients relapse and /or develop resistance to endocrine or other follow-up treatment and succumb to their disease.

Combination of mTOR inhibition and hormone treatment:

BOLERO-2 (Breast cancer trials of OraL EveROlimus-2) examined the safety and efficacy of everolimus (10 mg/day orally) in combination with exemestane (25 mg/day p.o.) versus exemestane alone in post-menopausal women with ER+/HER2- advanced breast cancer who recurred or progressed while on or following previous treatment with hormonal therapies letrozole or anastrozole (R12-5635). At a pre-planned analysis, the trial met its primary endpoint of PFS by local investigator assessment and treatment with everolimus and exemestane improved median PFS to 7.8 months from 3.2 months for exemestane alone (hazard ratio 0.45 [95% confidence interval (CI): 0.38, 0.54]; p<0.0001). PFS results by independent central review were consistent with investigator assessment. PFS results were consistent across subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy in the primary analysis (R12-5635), while a later subgroup analysis revealed a longer median PFS of 9.9 months for patients without visceral metastases (R16-0802). Objective response rate was 12.6% (95% CI: 9.8, 15.9) in the everolimus plus exemestane arm vs. 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the everolimus plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm. In BOLERO-2, adding everolimus

to exemestane did not confer a statistically significant improvement in the secondary endpoint OS despite producing a clinically meaningful and statistically significant improvement in the primary endpoint, PFS (4.6 months prolongation in median PFS; P <0.0001): Median OS in patients receiving everolimus and exemestane was 31.0 months [95% CI 28.0-34.6 months] compared with 26.6 months (95% CI 22.6-33.1 months) in patients receiving placebo and exemestane (hazard ratio = 0.89; 95% CI 0.73-1.10; log-rank P = 0.14) (R16-4900).

Most common grade 3/4 adverse events (AEs) were stomatitis (8% vs 1%), anemia (5% vs <1%), dyspnea (4% vs 1%), hyperglycemia (4% vs <1%), fatigue (3% vs 1%), and pneumonitis (3% vs 0%) for the everolimus and exemestane and exemestane groups, respectively.

Data from a correlative exploratory analysis of genetic alterations (next generation sequencing) and everolimus benefit suggest that the efficacy of everolimus was largely independent of the most commonly altered genes or pathways of which they are components (PIK3CA, FGFR1, and CCND1) in HR+/HER2- breast cancer (R16-4905).

Cyclin-dependent kinase (CDK) 4/6 inhibitors:

Cell cycle and gene transcription are under the control of CDKs, whose activity depends on binding to cyclins. Deregulated CDK activities have been reported in a variety of human cancers, representing potential for therapeutic targets (R16-2249; R16-3979) especially, but not exclusively, HR+ breast cancer. Several selective CDK4/6 inhibitors were developed in HR+ mBC and based on significant PFS benefit palbociclib received FDA (Food and Drug Administration) accelerated approval in 2015 in combination with letrozole (R17-2798, R17-2980) and, in 2016 in combination with fulvestrant (R17-2979). As of July 2019, three CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) are approved for treatment of HR+ breast cancer when added to endocrine therapies in both first- and subsequent treatment lines (R16-4899, R17-2796). Approvals were based on significant PFS benefit. OS data are still immature, with the exception of the Paloma-3 study where an increased median survival was observed with the addition of palbociclib to fulvestrant.

Current treatment standards:

For post-menopausal women, aromatase inhibitors (AIs, e.g. letrozole or anastrozole) and fulvestrant are the preferred first-line endocrine therapy. CDK4/6 inhibitors palbociclib, ribociclib may be added to first-line therapy. As second-line therapy fulvestrant may be administered alone or in combination with palbociclib or abemaciclib, alternatively exemestane plus mTOR inhibitor everolimus may be given to post-menopausal women with HR+ mBC whose disease progresses while receiving nonsteroidal AIs alone or in combination with CDK4/6 inhibitors. Single- agent endocrine therapy or abemaciclib can also be considered. It is not uncommon for patients to alternate between endocrine therapy and chemotherapy over the course of their disease based of the extent of cancer burden, adverse profile of treatment regimens and disease-related symptoms. A variety of sequences for endocrine therapy alone or in combination can be appropriate.

Premenopausal women with hormone-receptor positive metastatic breast cancer should be offered ovarian suppression or ablation. Thereafter, endocrine treatment of premenopausal women parallels that of postmenopausal women. (R17-2894) Guidelines

recommend a combination of a different endocrine therapy than used previously with a CDK 4/6 inhibitor or everolimus for premenopausal women on ovarian suppression.

Chemotherapy is usually given to patients with immediately life-threatening disease, endocrine refractory disease, or to patients with symptomatic visceral disease.

Despite evidence that patients with non- visceral involvement in general have less aggressive disease, treatment algorithms are used for all HR+/HER2- mBC patients alike without accounting for presence of visceral or non-visceral disease (P17-09321; R17-2894; R17-2948).

Combination of mTOR inhibitor and exemestane with insulin-like growth factor (IGF) pathway inhibition:

At ASCO 2010, Di Cosimo *et al.* presented initial data that the combination of the oral mTOR inhibitor ridaforolimus with the IGF-1 receptor (IGF-1R) antibody dalotozumab was tolerable and had promising antitumor activity in heavily pre-treated advanced cancer, particularly in ER+/high proliferation breast cancer. Of 23 breast cancer patients enrolled at the time of analysis, 5 ER+ (4 of these with high Ki67) breast tumours had efficacy signals (2 partial responses [PRs], 1 stable disease [SD] for 9 months, and 2 partial metabolic responses on FDG-PET scan) (R13-2056; R17-3094).

Preclinical data on xentuzumab, which is an IGF-ligand blocking monoclonal antibody (mAb) support a combination of xentuzumab, with rapalogs (P16-16103) particularly in patients with non-visceral HR+/HER2- mBC who frequently have (i) bone metastases and/or (ii) lymph node metastases.

(i) There is a clear rationale for a biological role of bone-derived IGF-1 in osteolytic bone metastases, which are predominant in HR+/HER2- mBC patients. IGF-1 which is stored in large amounts in the bone matrix is released by excessive bone destruction in metastatic lesions and promotes proliferation of tumour cells, thereby contributing to the vicious cycle that increases both bone destruction and tumour burden. Published experimental evidence suggests that bone-derived IGF-1 may also promote homing of cancer cells to the bone ('seed-and-soil' hypothesis). Suppression of IGF signaling was shown to inhibit bone metastases in breast cancer models (P04-04292; R17-2113; R17-2114; R17-2115; R17-2116; R17-2118; R17-2119) and may be facilitated by xentuzumab, an IGF-ligand blocking monoclonal antibody.

(ii) Published clinical data also suggest a significant correlation between high circulating levels of IGF-1, IGF-binding protein 3 (IGFBP3), and VEGF-C and lymph node metastasis in ER+ mBC patients. Preclinical studies indicate that IGF-1 may promote lymph node metastasis by increasing VEGF-C expression in tumour cells, thereby inducing lymphangiogenesis. Further, IGF-1 secreted by lymph node stromal cells was found to promote breast cancer cell proliferation and anchorage-independent growth (R17-2300; R17-2303; R17-2306). As such inhibition of IGF via a ligand blocking monoclonal antibody like xentuzumab may provide a rationale treatment option.

1.2 DRUG PROFILE

For a more detailed description of the xentuzumab profile please refer to the current Investigator's Brochure (IB; c01690707) and for everolimus and exemestane to the current Summary of Product Characteristics (SmPC) or the US Prescribing Information (PI).

1.2.1 Xentuzumab

Xentuzumab is a humanised IgG1 monoclonal antibody that binds with high affinity to IGF-1 and IGF-2, and potently neutralises the proliferative and pro-survival cellular signaling triggered by both proteins.

Mode of action differentiation to IGF-1R targeted antibodies was demonstrated, in particular through inhibition of IGF-2 stimulated insulin receptor-A (IR-A) activation, an additional proliferative and pro-survival pathway not inhibited by IGF-1R targeted mAbs.

As of January 2018, xentuzumab is in Phase II of clinical development and has been investigated in a total of 7 clinical studies. Overall, 146 patients with cancer have received xentuzumab in monotherapy studies, 333 patients have been treated in combination therapy studies.

The recommended xentuzumab dose for Phase II clinical development is 1000 mg weekly. In the absence of a maximum tolerated dose in the dose escalation trials (up to 1800 mg weekly or 3600 mg every 3 weeks), this dose was selected based on the integration of preclinical and clinical (safety, anti-tumour activity) data as well as pharmacokinetic (PK)/pharmcodynamic (PD) relationship (IGF-1 saturation, inhibition of IGF bioactivity).

Maximum plasma concentrations of xentuzumab were observed at or shortly after the end of the intravenous infusion. Thereafter, plasma concentrations declined, at least biphasic, with a terminal half-life in the order of 6 days. No deviation from dose-proportional pharmacokinetics has been observed. Repeated weekly dosing resulted in about 1.5fold accumulation of xentuzumab plasma concentrations at steady state.

The AEs observed during xentuzumab treatment to date have generally been of mild to moderate intensity (National Cancer Institute [NCI]) Common Terminology Criteria for Adverse Events [CTCAE] grades 1 or 2) or consistent with the safety profile of combination backbone treatment or the underlying neoplastic conditions of patients enrolled into the studies. The most frequently reported AEs for xentuzumab monotherapy were fatigue, decreased appetite, nausea, diarrhoea, and vomiting. Abnormal liver enzyme elevation tests were observed at low frequencies and were generally of low grade (CTCAE grades 1 and 2) in all monotherapy studies. No cases of drug-induced liver injury were reported. There were no signs of cardiac toxicity, and no laboratory findings that would indicate kidney damage in patients treated with xentuzumab. No clinically relevant hyperglycaemia has been observed so far.

The most frequently reported serious adverse events (SAE) for xentuzumab monotherapy were dyspnoea and pneumonia. AEs leading to death were reported for 3 patients (acute respiratory failure, dyspnoea, and malignant neoplasm progression); none of these events was considered by the investigator to be related to xentuzumab.

To date the only expected serious adverse reactions identified for xentuzumab are

infusion- related reactions observed in patients who received xentuzumab treatment (c01690707).

Anti-tumour activity has been observed in the Phase I monotherapy study 1280.1, with 2 partial responses according to Response Evaluation Criteria In Solid Tumors (RECIST, R09-0262) criteria in a patient with nasopharyngeal cancer and a patient with a peripheral primitive neuroectodermal tumor/Ewing sarcoma and 2 patients with partial response in the Phase I monotherapy study 1280.15. In addition, considerable proportions (12% to 45%) of heavily pre-treated patients in the Phase I monotherapy studies were reported with stable disease when treated with xentuzumab.

Lately a marked improvement in PFS was observed in a pre-specified subgroup of HR+/HER- mBC patients with non-visceral disease (also a stratification factor) who received xentuzumab in addition to everolimus and exemestane (n=33 out of 140 patients, 17 in the xentuzumab and 16 in the control arm, HR=0.21, 95% CI: 0.05-0.98, interaction p- value=0.014). In this subgroup, two PFS events occurred in the xentuzumab treatment arm compared to nine PFS events in the control arm. Similar improvement in PFS was observed in the nested “bone-only” metastasis subgroup (n=16, HR=<0.01 (no events observed in the xentuzumab arm compared to 4 in the control arm), interaction p-value=0.0159).

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 KBP12, 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 I study conducted in solid tumour 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 T_{max} 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 P-glycoprotein (PgP). *In vitro*, everolimus is a competitive inhibitor of cytochrome P450 (CYP) 3A4 and a mixed inhibitor of CYP 2D6 (R12-5281).

Everolimus is approved for various conditions: advanced hormone receptor-positive, HER2- negative breast cancer (in the European Union (EU): with the restriction “for patients without symptomatic visceral disease”), advanced neuroendocrine tumours 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 tumours, including gastric cancer, hepatocellular carcinoma and lymphoma and Phase III trials are under way.

The approved treatment dose of everolimus in advanced HR+ breast cancer is 10 mg daily (please refer to the most current drug prescribing 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 post-menopausal 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 post-menopausal women, exemestane is rapidly absorbed with a mean T_{max} 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). 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 use 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 pre-treatment values. Compared with tamoxifen, there is a reduced incidence of endometrial changes, thromboembolic events, and hot flashes. Limited evidence shows non-adherence 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 non-steroidal aromatase inhibitors remains to be established (R13-1990).

Exemestane is indicated for the treatment of advanced breast cancer in post-menopausal 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 prescribing information for update).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Despite the introduction of everolimus and lately CDK4/6 inhibitors to overcome endocrine resistance, there is still an unmet need in women with advanced or metastatic HR+/HER2- breast cancer and eventually patients succumb to their disease. Dysregulation of both insulin-like growth factor signaling and the phosphatidylinositol 3-kinase (PI3K) - protein kinase B-alpha (AKT) - mTOR signaling pathways are linked to the acquired

resistance to hormonal therapy in breast cancer (R13-1977, R13-1980). Targeting the IGF pathway using xentuzumab, a ligand blocking antibody, in combination with everolimus and exemestane showed promising results in a subgroup of 33/140 HR+/HER2- mBC patients with non-visceral disease in the Phase Ib/II trial 1280.4. Of the 17 non-visceral patients on the xentuzumab arm 2 had a PFS event compared to 9 of the 16 patients on the control arm, leading to a hazard ratio (HR) of 0.21 with a corresponding 95% confidence interval (CI) of 0.05, 0.98 (p-value of 0.029, c22665932-01).

The effect was even more pronounced in 16 patients with bone metastases only, with no PFS events observed in any of the 7 patients on the xentuzumab arm compared to 4 of the 9 patients on the control arm. Based on these results, demonstrating increased efficacy in HR-positive, HER2-negative mBC patients without visceral disease who were treated with a combination of xentuzumab with standard of care everolimus/exemestane, trial 1280-0022, a double blind, randomized, Phase II trial will be initiated in female patients with HR+/HER2- advanced or metastatic breast cancer with non-visceral disease.

1.4 BENEFIT - RISK ASSESSMENT

Trial 1280.4, a Phase Ib/II open-label, randomised study of xentuzumab in combination with exemestane and everolimus versus exemestane and everolimus alone in women with locally advanced or metastatic breast cancer (HR+/HER2- mBC) was terminated early in October 2016 due to a Data Monitoring Committee (DMC) recommendation and an observed preliminary HR for PFS of 1.38 (95% CI: 0.687-2.778). Although this indicated low probability to achieve the desired HR at the time of primary analysis, a subgroup analysis of PFS in the pre-specified subgroup of patients with non-visceral disease derived clear benefit as described in section 1.3.

The safety profile of xentuzumab monotherapy is tolerable. In combination with everolimus and exemestane the safety profile of the combination is largely dominated by side effects observed for the backbone therapy. To date the only expected serious adverse reaction identified for xentuzumab are infusion-related reactions mostly CTCAE grade 1 and 2 (c01690707).

Addition of xentuzumab 1000 mg to established backbone treatment in Phase Ib/II trial 1280.4 did not add any safety concerns, however provided increased efficacy to a subgroup of female HR+/HER2- metastatic breast cancer patients with non-visceral disease. These patients frequently suffer from bone and lymph node metastases and there is a sound scientific rationale supporting the antitumour activity of xentuzumab in this patient population (see Section 1.1). Therefore further assessment of the observed preliminary treatment effect in patients with HR+/HER2- mBC without visceral disease is warranted in a large confirmatory trial. To safeguard patients in this proposed Phase II, a DMC will continuously monitor patients' safety as outlined in Section 8.7. The benefit risk is considered positive.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.6, adverse events of special interest.

The 1280-0022 phase II trial recently completed primary endpoint analysis and showed no added benefit of xentuzumab compared to placebo, in patients with everolimus and exemestane backbone therapy, when treating trial participants with metastatic breast cancer, HR+, HER2- and non-visceral disease. No new safety signals were observed with the addition of xentuzumab to the everolimus and exemestane combination.

In consideration of these top line results and in accordance with clinical trial protocol, as of 29 September 2021, Boehringer Ingelheim recommended to immediately discontinue xentuzumab and placebo administrations. Sites were also recommended to discontinue associated assessments related to primary endpoint assessments, including central imaging, central laboratory sampling and shipments and PRO questionnaires. Lastly, sites were advised that patients no longer needed to be followed for overall survival after they had completed the required safety follow up visits.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This double-blind, placebo-controlled, randomised Phase II trial will be performed in female patients with HR+/HER2- advanced or metastatic breast cancer and non- visceral disease. The main objective of the trial is to assess the efficacy of xentuzumab in combination with everolimus and exemestane over everolimus and exemestane in this patient population. Efficacy will be assessed by determining whether or not the criterion for expanding the trial seamlessly into a Phase III trial is met. If the seamless option is met the trial will be expanded into a confirmatory Phase III trial with formal superiority hypothesis testing. If the seamless option is not met, the observed results will be evaluated in an explorative manner to see if they are sufficient for further development of this compound in this indication.

All imaging-related endpoints will be both independently assessed (in a blinded fashion) and investigator assessed according to RECIST 1.1 (see Appendix 10.4). The data from the independent assessments will be considered primary, with investigator assessment data as supportive.

2.1.2 Primary endpoint

The primary endpoint to determine efficacy of xentuzumab is progression-free survival (PFS) which is defined as time from randomisation until disease progression according to Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1) or death from any cause, whichever occurs earlier.

2.1.3 Secondary endpoints

- Overall survival (OS) is defined as the time from randomisation until death from

any cause.

- Disease control (DC) is defined as a best overall response of complete response (CR), partial response (PR), stable disease (SD) or Non-CR/Non-Progressive Disease (Non-CR/Non-PD). SD and Non-CR/Non-PD must have a minimum duration of 24 weeks from randomisation. Best overall response is defined according to RECIST version 1.1 and will consider all tumour assessments from randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti- cancer therapy, loss to follow-up or withdrawal of consent.
- Duration of DC is defined as the time from randomisation until the earliest of disease progression or death, among patients with DC.
- Objective response (OR) is defined as a best overall response of CR or PR. Best overall response is defined according to RECIST version 1.1 and will consider all tumour assessments from randomisation until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up or withdrawal of consent.
- Time to pain progression or intensification of pain palliation defined as the time from randomisation until the earliest of a clinically significant increase in pain (≥2-point increase from baseline in the Brief Pain Inventory– Short Form [BPI-SF] Item 3) without a decrease in analgesics use, or intensification in pain palliation (≥2-point increase in the 8-point Analgesic Quantification Algorithm [AQA]), or death.

** Note if the trial is expanded the secondary endpoint of OS is included in the statistical testing strategy in a hierarchical manner subsequent to significance being observed in the primary endpoint, for further details refer to Section 7.2.*

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This double-blind, placebo-controlled, randomised Phase II trial is designed to assess the efficacy of xentuzumab in combination with everolimus and exemestane compared to everolimus and exemestane alone in female patients with HR+/HER2- locally advanced or metastatic breast cancer and non-visceral disease.

If the criterion for the seamless option (to be defined in the DMC charter, prior to trial initiation) is met then the trial will be expanded into a confirmatory Phase III trial and remain double-blind. If the seamless option is not met, the observed results will be evaluated in an explorative manner to see if they are sufficient for further development of this compound in this indication (e.g. via a separate Phase III trial).

The trial will be performed by investigators specialised in the treatment of breast cancer. Patient inclusion will be based on locally confirmed HR+ and HER2-status. Archival tissue biopsies (most recent biopsy from initial diagnosis or metastatic setting) will be provided to retrospectively confirm HR+ and HER2-status by central assessment if possible. Provision of biopsy samples from the bone is not acceptable. Receptor status should be assessed by ASCO/CAP guidelines (R15-6055, R17-4255). Patients must not have visceral metastases, i.e. metastases to lung, liver, pleura or peritoneum, malignant pleural or peritoneal effusions. Patients must not have evidence of brain metastases. Patients meeting all eligibility criteria will be randomised 1:1 to the experimental treatment arm containing xentuzumab or to the placebo control arm of the trial (Figure 3.1: 1). Patients will be treated in 28-day cycles until the end of cycle 20 (week 80) and in 56-day cycles from Cycle 21 (week 80) until they have PD, occurrence of intolerable AEs or withdraw consent. Patients will be randomised in blocks, treatment will be double blinded and randomisation will be stratified by the presence of bone-only metastases (Yes/No), and prior CDK4/6 inhibitor treatment (i.e. palbociclib, ribociclib, abemaciclib) (Yes/No). Use of xentuzumab or placebo beyond radiological progression will be allowed if deemed beneficial by the investigator and agreed with the patient. PFS as assessed by an independent blinded review according to RECIST 1.1 will be the primary endpoint. Safety and tolerability will be assessed by incidence and severity of adverse events according to CTCAE version 5.0 (R18- 1357). PK sampling and monitoring of anti-drug antibodies (ADAs) and neutralising antibodies (nAb) will be conducted throughout the trial in both treatment arms. Patients' safety, pattern of their disease progression and post progression information will be monitored throughout the trial by an independent DMC (see Section 8.7).

The end of treatment (EOT) information has to be obtained when the trial treatment is permanently discontinued. EOT is defined as permanent discontinuation of all trial drugs. All patients who end the trial treatment for any reason other than progression of disease or start of further anti-cancer therapy will be followed for tumour assessment. All patients will be followed for drug-related serious adverse events/adverse events of special interest as described in the Flow Chart and Section 6.2.3.

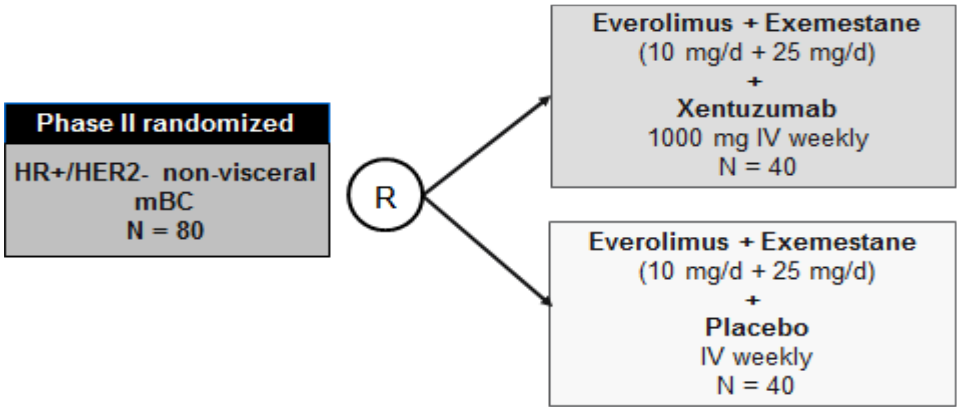


Figure 3.1: 1 Trial design

The primary PFS analysis for this Phase II trial will take place after approximately 40 patients have had an event of disease progression (independent assessment) or death; this is defined as the "Last Subject Last Visit Primary Endpoint" (LSLVPE). Patients will be followed up for OS (FU-OS) until all patients have completed treatment and attended the first follow-up visit (FU1). This time point is defined as the "Last Subject Last Visit Secondary Endpoint" (LSLVSE).

Note if at the time of LSLVPE the trial meets a pre-defined criterion (to be defined in the DMC charter) the trial will be expanded seamlessly into a confirmatory Phase III trial, changes to the LSLVPE and LSLVSE will be provided in a protocol amendment.

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

The trial is designed with two parallel arms in order to assess the efficacy and safety of xentuzumab in combination with everolimus and exemestane when compared to placebo in combination with everolimus and exemestane.

The trial will be conducted in a double-blind fashion as information about treatment assignment can consciously or unconsciously influence the behaviour and decisions of patients, investigators, care-givers and third-party evaluators. By blinding patients and investigators to treatment introduction of bias will be limited. This is particularly important as not only weekly i.v. infusions of blinded trial treatment, but also regular blood collection for assessment of PK, ADAs and biomarkers will be performed. If the trial would be conducted in an unblinded fashion the latter could lead to non-compliance, bias, affect accrual and data integrity and eventually trial outcome.

The backbone therapy for trial 1280-0022, everolimus and exemestane, is standard of care therapy for women with advanced HR+/HER2- advanced or metastatic breast cancer who failed/had recurrent disease after or on treatment with a non-steroidal aromatase inhibitor e.g letrozole or anastrazole. It is used according to its approved label or as recommended by guidelines (P17-09321, R17-2948).

Patients with non-visceral disease constituted 41.5% of the population included into the confirmatory trial for everolimus (BOLERO-2 trial) and with 9.9 months had a

better median PFS compared to patients with visceral metastases who showed 6.8 months median PFS (R16-0802).

Patients should have archival tumour tissue available and a sample of this will be provided for analysis of HR/HER2 status by a central lab (biopsy sample from the bone is not acceptable). It is well documented in the scientific literature that there are discrepancies in biomarker analyses between local and central labs e.g. up to 23% discordance rate for HER2 immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) (R09-6008; R09-6009; R09-6011). HR/HER2 tests will be performed by a central laboratory based on ASCO/CAP guidelines (R15-6055, R17-4255) but results are not required to confirm eligibility.

A Steering Committee (SC) will be established for this trial. The SC will monitor the trial on a regular basis (see Section 8.7).

An independent DMC will be appointed to periodically assess the trial data, including the aggregated data at the treatment level to ensure overall safety and integrity of the trial. A decision as to whether or not the trial is expanded into a Phase III trial will be made by the DMC at the time-point of the primary PFS analysis for this Phase II trial. The criterion for expansion will be pre-defined in the DMC charter, prior to trial initiation. For further details refer to Sections 7.4 and 8.7.

3.3 SELECTION OF TRIAL POPULATION

It is estimated that approximately 180 patients will be screened for the trial in order to enrol approximately 80 eligible patients (see section 7.7). The trial will run at approximately 80 sites globally in approximately 15 countries. The rate of randomisation will vary by trial site, but is expected to be approximately 1 to 2 patients per site. Additional countries may be added if necessary.

Enrolment 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 be recruited for this trial. 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 trial.

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

3.3.1 Main diagnosis for trial entry

All patients that will be included into the trial must be female patients diagnosed with histologically confirmed HR+/HER2- advanced or metastatic breast cancer and non-visceral disease. Male breast cancer patients will be excluded from participation in this trial as breast cancer in male and female patients has different biology and little is known about tolerability and efficacy of hormone treatments in male patients (R17-4300; R17-4303).

3.3.2 Inclusion criteria

1. Histologically confirmed breast cancer with documented ER-positive and/or PgR-positive and HER2-negative status if there are at least 1% positive tumour nuclei in the sample as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (R15-6055, R17-4255)
2. Locally advanced or mBC not deemed amenable to curative surgery or curative radiation therapy
3. Archival tumour sample available at the time of informed consent and provided to the central laboratory around the time of randomisation. Patients must provide a formalin-fixed paraffin embedded (FFPE) tissue biopsy sample preferably taken at the time of presentation with recurrent or metastatic disease (provision of a biopsy sample taken from the bone is not acceptable). If archival tissue is not available, provision of detailed information from the original histology report may be agreed with the sponsor on a case by case basis.
4. Patients must satisfy the following criteria for prior therapy:
   - Disease progression during treatment or within 12 months of completion of endocrine adjuvant therapy

   OR
   - Disease progression while on or within 1 month after the end of prior endocrine therapy for advanced/metastatic breast cancer (Note: the endocrine therapy does not have to be the treatment immediately prior to trial entry).
5. Inclusion criteria 5 is not applicable for patients enrolled after protocol version 4 is approved.
6. Inclusion criteria 6 is not applicable for patients enrolled after protocol version 4 is approved.
7. Female patients ≥18 years old or over the legal age of consent in countries where that is greater than 18 years at the time of informed consent. Patients must be either:
   - Premenopausal on ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist with FSH and estradiol in postmenopausal range (initiated at least 28 days prior screening) OR
   - Post-menopausal, defined as one of the following:
     - Age ≥ 60 years
     - Age < 60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and FSH and estradiol in the postmenopausal range.
     - If taking tamoxifen or toremifene, and age < 60 years, then FSH and estradiol level in post-menopausal range.
     - Surgical menopause with bilateral oophorectomy
8. Patients must have an indication for combination treatment with everolimus and exemestane.
9. Patients must have
   - At least one measurable non-visceral lesion according to RECIST version 1.1 in either lymph nodes, soft tissue, skin

   AND/OR
   - At least one measurable non-visceral lesion according to RECIST version 1.1 as lytic or mixed (lytic + blastic) in bone

   AND/OR

- At least one non-measurable (lytic, mixed lytic + blastic, or blastic) bone lesion according to RECIST version 1.1

10. Eastern Cooperative Oncology Group (ECOG) performance score 0 or1 (R04-1314)
11. Fasting glucose <8.9 mmol/L (<160 mg/dL) and HbA1c <8.0%
12. Adequate organ function, defined as all of the following:
    a) Absolute neutrophil count (ANC) ≥1500/mm3
    b) Platelet count ≥100,000/mm3
    c) International Normalised Ratio (INR)[1] ≤2.0
    d) Serum creatinine ≤1.5 times upper limit of institutional normal (ULN) or creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft and Gault formula).
    e.) Total Bilirubin ≤1.5 times ULN (patients with Gilbert syndrome total bilirubin must be <4 times ULN)
    f) Aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤2.5 times the ULN
    g) Fasting triglycerides ≤300 mg/dL or 3.42 mmol/L h) Haemoglobin (Hgb) ≥9.0 g/dL
13. Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia)

3.3.3 Exclusion criteria

1. Previous treatment with agents targeting the IGF pathway, AKT, or 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. Evidence of visceral metastasis/es (i.e. liver, lung, peritoneal, pleural metastases, malignant pleural effusions, malignant peritoneal effusions) at screening. NOTE: Patients with a past history of visceral metastases are eligible if visceral metastases have completely resolved at least 3 months prior to screening.
4. History or evidence of metastatic disease to the brain
5. Leptomeningeal carcinomatosis
6. Known hypersensitivity to any of the study drugs or their excipients
7. Any contraindication to treatment with everolimus or exemestane
8. More than 1 prior line of chemotherapy for HR+ HER2- metastatic breast cancer
9. Radiotherapy within 4 weeks prior to the start of study treatment, except in case of localised radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within two weeks prior to study treatment
10. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to randomisation or planned after screening
11. Use of concomitant systemic sex hormone therapy (e.g. Megace) within 2 weeks prior to start of trial treatment. NOTE: Ovarian suppression with GnRH agonists is permitted in premenopausal patients.
12. History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥3, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator. Myocardial infarction within 6 months prior to randomisation.
13. Any history of or concomitant condition that, in the opinion of the Investigator, would

compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the study medications.

1. To avoid inclusion of patients with active bleeding, bleeding diathesis

14. Previous or concomitant malignancies at other sites, except effectively treated
    a) Non-melanoma skin cancers
    b) Carcinoma *in situ* of the cervix
    c) Ductal carcinoma *in situ*
    d) Other malignancy that has been in remission for more than 3 years and is considered to be cured.
15. Known pre-existing interstitial lung disease (ILD).
16. Known active hepatitis B infection (defined as presence of Hep B sAg and/or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known Human immunodeficiency virus (HIV) carrier
17. Active infectious disease which puts the patient at increased risk in the opinion of the investigator
18. Any history or presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the study drug (e.g. nausea, uncontrolled vomiting, Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) in the opinion of the investigator
19. Previous randomisation in this trial
20. Concurrent participation in another clinical trial with an investigational device or drug.
21. Patients receiving concomitant immunosuppressive agents or chronic corticosteroid use except in cases outlined below:
    - Topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops, mouth washes or local injections (e.g. intra-articular) are allowed
    - Patients on stable low dose of corticosteroids for at least two weeks before study entry are allowed
22. Patients who have taken or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial must have stopped them at least 2 weeks before C1V1. Treatment with denosumab/bisphosphonates is allowed.
23. Growth hormones or growth hormone inhibitors
24. More than 1 prior treatment line with a CDK4/6 inhibitor
25. Pregnant or nursing (lactating) women.
26. Women of child-bearing potential* unless they are using highly effective non-hormonal methods of contraception that achieve a failure rate of less than 1% per year when used consistently and correctly during dosing of study treatment and for at least 1 month after the last dose of exemestane, 8 weeks after the last dose of everolimus and 6 months after the last dose of xentuzumab/placebo (whichever is the longest). Highly effective contraception methods include:
    - True abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP and withdrawal are not acceptable methods of contraception.
    - Total hysterectomy or tubal ligation at least six weeks before taking study treatment.

- Sterilisation of male partner (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Combination of the following:
    - Placement of an intrauterine device (IUD)** or intrauterine system (IUS)**
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

*A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
** Non-hormone releasing only

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomisation, as well as the explanation of the consequences of withdrawal. The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and case report form (CRF).

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient requires palliative radiotherapy or needs to take concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, secondary malignancy or pregnancy).
- Has radiologic documentation of progressive disease per RECIST version 1.1 (Section 5.1) unless the investigator documents that the patient, after discussion with the investigator, will continue treatment beyond progression due to clinical benefit (Section 6.2.2.1).
- The patient is diagnosed with ILD and meets the criteria for discontinuation in section 4.4.3
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.
- The patient violates eligibility criteria which would affect the safety of the patient (after discussion between the sponsor and the investigator).

- The patient entered the trial as premenopausal on ovarian suppression and estradiol increases above postmenopausal levels for more than 4 weeks (exceptions to this must be discussed with sponsor and patient may be able to stay treatment if they are clinically benefitting from treatment and reestablishment of ovarian suppression, e.g. by oophorectomy, is expected).

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation (EOT and end of residual effect [EOR]/FU1 visit) and further follow up as outlined in the Flow Chart and Section 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

Patients in whom visceral disease is detected by central review of baseline scan will have the possibility to continue treatment on trial after discussion of individual benefit/risk with their investigator.

After completion of the final analyses (see Section 7.3), the Sponsor may remove patients from the trial if the patient has access to the trial medication via an alternative source, e.g. clinical trial, marketed product, an expanded access program, named patient use program, compassionate use protocol or other means based on local regulation. The cost of any ongoing supply of the trial treatment will be incurred by the Sponsor until disease progression occurs.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur. The EOT visit should be performed after permanent discontinuation of study medication. Wherever possible patients should be encouraged to return for the EOR/FU1 visit to ensure patient's safety and that all AEs are followed.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 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 invalidating the earlier positive benefit- risk-assessment that could significantly affect the continuation of the trial
3. Violation of Good Clinical Practice (GCP), the trial protocol, or the contract

impairing the appropriate conduct of the trial

4. All efficacy analyses (see Section 7.3) are complete and all patients have either ended study medication or are eligible to receive trial medication under the conditions described in Section 3.3.4.1.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Patients will either receive xentuzumab in combination with everolimus and exemestane or placebo in combination with everolimus and exemestane (see Tables 4.1.1: 1, 4.1.1: 2, 4.1.2: 1 and 4.1.2: 2).

As of 29 Sept 2021, based on the primary analysis of top line results, Boehringer Ingelheim recommended to immediately discontinue xentuzumab and placebo administrations.

4.1.1 Identity of the Investigational Medicinal Product (IMP) and Comparator

Table 4.1.1: 1 Xentuzumab

Substance:	Xentuzumab (BI 836845)
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL supplied in 20 mL vials (200 mg/vial)
Posology:	Weekly infusions of 1000 mg for one hour administered on Day 1, 8, 15, and 22 of 28-day cycles and on Day 1, 8, 15, 22, 29, 36, 43, and 50 of 56-day cycles (infusion solution is diluted to a total of 250 mL of 0.9% isotonic sodium chloride solution to a concentration of 4 mg/mL). Infusion duration may be extended up to a maximum of three hours in cases of grade ≥2 infusion reactions.
Route of administration:	Intravenous infusion

Table 4.1.1: 2 Placebo

Substance:	Placebo
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	N/A
Posology:	Weekly infusions for one hour administered on the same days as defined in Table 4.1.1: 1.
Route of administration:	Intravenous infusion

Detailed instructions for preparing and handling the infusions, including information on infusion equipment, infusion procedure and disposal of unused medication, will be given in the pharmacist manual/ISF.

4.1.2 Background medication

The background medication consists of everolimus and exemestane (Tables 4.1.2: 1 and 4.1.2: 2) which must be taken in combination with xentuzumab or placebo, respectively. Everolimus and exemestane are not considered as investigational in this trial. However if mandated by local requirements can be regarded as investigational e.g IMP.

Table 4.1.2: 1 Everolimus

Substance:	Everolimus (Afinitor®)
Pharmaceutical formulation:	Tablets
Source:	[redacted]
Unit strength:	2.5 mg and 5 mg
Dose:	10 mg daily in accordance with the current SmPC for EU or the PI of the respective country
Posology:	Once per day, at approximately the same time of day, after a meal
Route of administration:	Oral

Everolimus is a registered commercially available drug. It will be supplied by the Sponsor, either via a local supplier not managed through the IRT system, or via the central depot managed through IRT system.

Table 4.1.2: 2 Exemestane

Substance:	Exemestane (Aromasin®)
Pharmaceutical formulation:	Tablets
Source:	[redacted] or other companies with therapeutic equivalents
Unit strength:	25 mg
Dose:	25 mg daily in accordance with the current SmPC for EU or the PI of the respective country
Posology	Once per day, at approximately the same time of day, after a meal
Route of administration:	Oral

Exemestane is a registered commercially available drug and generic versions are available. It will be supplied by the Sponsor, either via a local supplier not managed through the IRT system, or via the central depot managed through IRT system.

4.1.3 Selection of doses in the trial

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

In the Phase Ib part of BI trial 1280.4 of everolimus/exemestane and xentuzumab in patients with advanced or metastatic breast cancer, the recommended Phase II dose was determined as 10 mg daily everolimus and 25 mg daily exemestane in combination with 1000mg xentuzumab weekly (c03569433-01).

The approval of 10 mg daily dose of everolimus in breast cancer patients is based on BOLERO-2 study in which, 50% patients reported grade 3 or 4 AEs (R12-5281) with 67% patients requiring dose reduction or treatment interruption (R13-1647). The first dose reduction step in BOLERO-2 was 50% or 5 mg daily dose. The mean dose intensity of everolimus was 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.

A semi-mechanistic PK/PD model was developed describing the kinetics of the interaction between xentuzumab and the different PD biomarkers (i.e. free IGF-1 and

free IGF-2). Simulations using this model indicate that a weekly dosing of 1000 mg xentuzumab reduces free IGF-1 concentration by more than 90% and in addition free IGF-2 by 64% at trough steady-state relative to pre-treatment; this is considered a relevant biological effect. Therefore, a weekly dose of 1000 mg xentuzumab is considered a suitable dose in HR+/HER2- breast cancer patients.

4.1.4 Method of assigning patients to treatment groups

Eligible patients will be randomised to receive either xentuzumab in combination with everolimus and exemestane or placebo in combination with everolimus and exemestane in a 1:1 ratio according to a randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

4.1.5 Drug assignment and administration of doses for each patient

The treatment medication assignment for xentuzumab and placebo will be managed through an IRT system.

Everolimus and exemestane will be supplied to all investigator sites by the Sponsor, either via a local supplier not managed through the IRT system, or via the central depot along with the xentuzumab/placebo and managed through the IRT system.

4.1.5.1 Drug assignment and administration

Treatment will commence within 7 days of randomisation. Any exceptions to this must be discussed and agreed with the Sponsor.

Xentuzumab/Placebo
Patients will be treated with 1000 mg xentuzumab/placebo starting at C1V1. Xentuzumab/placebo 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 the scheduled infusion of xentuzumab/placebo is not performed within the time window, this treatment will be skipped. Subsequent visits will follow the original visit date schedule. Mannitol is used in the formulation of xentuzumab/placebo, so infusion duration of less than one hour must be avoided. The infusion time may be extended to over one hour and up to a maximum of three hours in cases of CTCAE grade ≥2 infusion reactions. In case of a delay or an interruption of infusion, the reason and the exact time of deviation must be recorded in the CRF. The accuracy of this information is crucial for the proper evaluation of PK and other data.

Detailed information of dispensation, preparation, and handling of xentuzumab/placebo will be described in the pharmacy manual/ISF.

Drug holidays for up to 14 calendar days (i.e. one missed xentuzumab infusion) e.g. vacation, are allowed, if previously agreed with the investigator. This is not considered non-compliance (for further details also refer to Section 4.3). Missed infusions due to recovery from AEs are not considered “Drug holidays”. Duration of drug holidays beyond

14 calendar days has to be agreed with the sponsor.

Everolimus
The recommended treatment dose for everolimus is 10 mg once daily. Complete guidelines for management and administration of everolimus can be found in the EU SmPC or the PI of the respective country. Please always refer to the current SmPC/PI for instructions. Treatment interruptions and dose adjustments should follow the SmPC/PI.

Everolimus will be prescribed by the investigator. Everolimus is supplied by the Sponsor and will be dispensed at visits described in the Flow Chart either by the investigator, site staff or the affiliated pharmacy through IRT. During the trial, patients may be administered a combination of different dose strengths of everolimus. For example, 10 mg everolimus can be given as one tablet of 10mg, two tablets of 5 mg or one tablet of 5 mg plus two tablets of 2.5 mg.

Per CTP version 6, the revised and reduced flow chart should be referenced.

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 the EU SmPC or the PI of the respective country. Please always refer to the current SmPC/PI for instructions. Treatment interruptions should follow the SmPC/PI.

Exemestane will be prescribed by the investigator. Exemestane is supplied by the Sponsor and will be dispensed at visits described in the Flow Chart either by the investigator, site staff or the affiliated pharmacy through IRT.

Per CTP version 6, the revised and reduced flow chart should be referenced.

4.1.5.2 Temporary treatment pauses and dose reduction

Treatment pauses for each of the combination partners, i.e. xentuzumab/placebo, everolimus and exemestane are possible when AEs occur. For everolimus and exemestane, please refer to the current SmPC/PI. Dose reductions for treatment-related AEs are only recommended for everolimus. For details refer to the current SmPC/PI.

Xentuzumab/Placebo: For xentuzumab/placebo no dose reductions are allowed. In the event of an AE ≥CTCAE grade 3 considered to be related to xentuzumab, treatment should be paused until the 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.

If a patient has not recovered to CTCAE grade ≤1 or baseline within 14 days, continuation of treatment should be discussed with the sponsor. If the patient is deriving obvious clinical benefit according to the investigator's judgement, continuation of treatment with xentuzumab/placebo will be decided by the Sponsor and the investigator.

During temporary treatment pauses of xentuzumab/placebo, the scheduled drug infusion will be missed. Upon restart of xentuzumab/placebo treatment, infusions should be resumed according to regular visit schedule.

If grade 2 AEs persist for ≥7 days despite treatment and are poorly tolerated by the patient, the investigator may choose to pause but must resume treatment within 14 days. For recovery and continuation of treatment refer to previous paragraphs.

Xentuzumab/placebo, everolimus/exemestane: In case all treatment drugs need to be paused for recovery from treatment-related AEs, patients must resume treatment within 14 days. If the patient is not able to restart treatment within 14 days but is deriving obvious clinical benefit according to the investigator's judgement, continuation of treatment will be decided following agreement between the Sponsor and the investigator.

In the case of adverse events not considered related to xentuzumab, everolimus or exemestane, the study drug(s) may be interrupted for up to 14 days, but no dose reduction should occur. If the patient is not able to restart treatment within 14 days but is deriving obvious clinical benefit according to the investigator's judgement, continuation of treatment will be decided following agreement between the Sponsor and the investigator

4.1.6 Blinding and procedures for unblinding

4.1.6.1 Blinding

The trial will be performed according to a parallel-group, double-blind, placebo-controlled design. How long patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments will be dependent upon whether or not the criterion for the seamless option is met. If the criterion for the seamless option is met then the trial will be expanded into a confirmatory Phase III trial and will remain double-blinded until the database lock for the primary PFS analysis time-point of the expanded trial. If the criterion is not met then the trial will be fully unblinded at the time of the database lock for the primary PFS time-point of the unexpanded Phase II trial. The randomisation code will be kept secret by Clinical Trial Support up to database lock for whichever primary analysis time point is applicable.
As no added benefit of xentuzumab compared to placebo was observed at the Phase II primary PFS analysis time-point, blinding of the trial in anyway is no longer necessary.

The independent DMC will have access to the unblinded treatment codes in order to allow them to periodically assess the trial data to ensure the overall safety and integrity of the trial, as well as to conduct the pre-specified Phase II primary PFS analysis detailed in Section 7.4. For further details refer to Section 8.7 as well as the DMC charter.

Due to a visible difference in xentuzumab versus placebo the pharmacy/dispensing team will be unblinded to treatment arm and an unblinded CRA will be employed to monitor compliance within the pharmacy department. Procedures to ensure blinding of the investigator and the trial team are documented in a separate blinding plan and filed in the TMF.

4.1.6.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the

investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.7 Packaging, labelling, and re-supply

The investigational product and the AMPs, if applicable, will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.8 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified range, the unblinded CRA or appropriate back-up (as provided in the list of contacts) must be contacted immediately.

4.1.9 Drug accountability

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

- Approval of the clinical trial protocol by the institutional review board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the investigational site,
- 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,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

The background treatment will be supplied by the Sponsor.

The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the IMP/AMP's delivery to the trial site, the inventory at the site, the

use by each patient, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products at site. If applicable, the Sponsor or warehouse/drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the IMP/AMP 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 clinical trial protocol (CTP) and reconcile all IMPs/AMPs received from the sponsor and/or provided by the investigational site. At the time of return to the sponsor and/or appointed contract research organisation (CRO)/destruction at site, 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 and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Rescue medication

Rescue medications to reverse the effects of xentuzumab/placebo are not available. Side effects of these treatments should be treated symptomatically. There is no specific antidote to overdosage of xentuzumab/placebo. For details regarding everolimus and exemestane refer to the current SmPC/PI.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed that are specific for this protocol.

Precaution should be taken to avoid extravasation of xentuzumab/placebo. 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.

To date the only expected serious adverse reactions identified for xentuzumab are infusion- related reactions observed in patients who received xentuzumab treatment (c01690707).

Xentuzumab/placebo 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 xentuzumab/placebo infusions 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 cycle, the observation period following xentuzumab/placebo infusions may be adjusted at the discretion of the investigator. 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 (see Table 4.2.1.2: 1).

The infusion reactions should be treated symptomatically as judged clinically relevant by the investigator. For symptomatic treatment of infusion reactions: hydrocortisone, antihistamines such as chlorphenamine accompanied by an antipyretic/analgesic and/or a bronchodilator is recommended. The infusion duration may be extended to over one hour and up to a maximum of three hours, see Section 4.1.4.

Table 4.2.1.2: 1 Infusion reaction management

Infusion reaction grade	**Description of event**	**Management**
CTCAE grade 1 or 2	Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	In the event of CTCAE grade 1 infusion reactions, the infusion rate should be reduced by 50%. Grade 2 infusion reactions may require symptomatic treatment, as described to the left (with infusion interruption). Once the event has resolved, the infusion may be restarted at the reduced rate.
CTCAE grade 3	Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	For patients experiencing CTCAE grade 3 infusion reactions, infusion should be interrupted immediately and patients should receive aggressive symptomatic treatment, as described above. Only after all the symptoms have disappeared, the infusion may be re-started if it is within 3 h since the infusion start. The infusion rate should be reduced by 50% after re-start.
CTCAE grade 4	Grade 4: Life-threatening consequences; urgent intervention indicated	Patients experiencing CTCAE grade 4 infusion reactions, such as anaphylaxis during an infusion, should have the infusion immediately stopped and receive appropriate treatment, as described above, including use of resuscitation if needed. Such patients should NOT receive any further xentuzumab/placebo treatment.

4.2.1.3 Concomitant treatments

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

After study enrolment, palliative radiotherapy is not allowed (see also Section 3.3.4.1).

See Section 4.4.1.1 for recommendations on supportive treatments whilst on trial treatment.

Premenopausal women must be treated with concomitant ovarian suppression with GnRH agonists, e.g. goserelin acetate. Estradiol and FSH need to be in the postmenopausal range on ovarian suppression at the time of screening, and monitoring of estradiol to document that it remains in the postmenopausal range during trial treatment is mandatory. If the estradiol level increases above the postmenopausal range during treatment a repeat test should be performed within 4 weeks. If still outside of desired range see Section 3.3.4.1.

Use of denosumab for symptomatic treatment of skeletal-related events in adults with bone metastases (see Section 4.2.2.1) and/or bisphosphonate therapy for the treatment of osteoporosis are permitted during the study according to guidelines and as per SmPC/PI. If bisphosphonate/denosumab therapy is initiated after enrolment, the reason for its use must be clearly documented in the CRF and progression of disease must be excluded.

All medications (other than study drugs), including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements starting from the date of signature of informed consent and ending at the EOR/FU1 visit must be listed on the concomitant medication page of CRF including trade name, start and end dates, indication for use etc. as specified in the Flow Chart. Indicating “parenteral nutrition” or “anesthesia” without specifying details will be sufficient.

Hematopoietic growth factors should be reserved to cases of severe neutropenia and anemia as per the labelling of these agents following ASCO guidelines (R16-1540).

In case of major surgery no modifications for xentuzumab/placebo treatment are needed. For everolimus and exemestane please refer to current SmPC/PI

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

No experimental anti-cancer treatment and/or standard chemotherapy, immunotherapy, endocrine therapy (except for ovarian suppression in premenopausal women as described in section 4.2.1.3), or radiotherapy (other than described in Section 4.2.1.3) is allowed concomitantly with the administration of study treatments.

No hormone replacement therapy, topical oestrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g.

raloxifene) is allowed concomitant with the administration of study treatments.

The use of megestrol acetate to improve appetite and to increase weight in cancer-associated anorexia is **not** allowed.

Restrictions regarding concomitant medications during everolimus and exemestane treatment should follow the current SmPC/PI.

4.2.2.2 Restrictions on diet and life style

Patients need to be fasted for blood draws for safety labs (fasting in this protocol is defined as no food or fluid intake with the exception of water for at least 8 hours).

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 trial drugs exactly as described.

The patient will be provided with a Patient Diary to record administration of both everolimus and exemestane as well as any observations during their treatment period, for example any occurrence of a missed or delayed dose and/or vomiting.

4.3.1 Xentuzumab/Placebo

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

Drug holidays, if previously agreed with the investigator and Sponsor, e.g. vacation, will not be considered as non-compliance. For details see Section 4.1.5. A minimum number of 10 doses of xentuzumab/placebo should be applied per 12 weeks (>80%) but not more than 4 doses per year are allowed to be missed. Treatment pauses due to AEs are not considered non-compliances either.

4.3.2 Everolimus and exemestane

Patients should be given an appropriate number of everolimus and exemestane tablets to be self-administered.

Patients will be asked to bring any remaining trial medication and empty packaging to the investigator site for a compliance check at the end of each treatment cycle. The remaining tablets will be counted by the investigator/site staff and documented. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. Any remaining medication will be collected. If the patient is eligible for further treatment, new trial medication must be provided.

The investigator and/or the Sponsor can terminate a patient's further trial treatment in

the event of serious and persistent non-compliance which jeopardizes the patient's safety or renders trial results for this patient unacceptable.

Drug holidays, if previously agreed with the investigator, e.g. vacation, will not be considered as non-compliance. For details see Section 4.1.5. Treatment pauses due to AEs are not considered non-compliances either.

4.4 MANAGEMENT OF EXPECTED ADVERSE EVENTS

To date the only expected adverse events for xentuzumab are infusion related reactions, which will be graded according to CTCAE version 5.0 (R18-1357) and treated following standard of care or local guidance. Guidance is also provided in Table 4.2.1.2: 1. Immune responses to the xentuzumab mAb will be assessed measuring anti-drug antibody levels during the trial.

However, in trial 1280.4 which was utilizing combination treatment with xentuzumab/everolimus and exemestane, the following AEs were reported in >20% of the patients: Diarrhoea, stomatitis, mucosal inflammation, rash, asthenia, nausea, cough, decreased appetite, fatigue, hyperglycemia, anaemia, neutropenia, vomiting, thrombocytopenia and increased ALT.

Proactive side effect management is crucial to maintain patients on long-term therapy and supportive measures for management of adverse events should be started as early as possible after onset of symptoms. Patients should be advised to report AEs promptly so that appropriate treatment can be initiated.

The following recommendations (as well as those in Appendix 10.2) should be followed unless institutional guidelines are available and are implemented based on the investigator's judgement. Side effects observed with everolimus and /or exemestane treatment should be managed in accordance with their current SmPC/PI.

4.4.1 Management of stomatitis/mucosal inflammation

Routine and systematic oral hygiene is extremely important to reduce the incidence and severity of the side effects of cancer treatment so it is recommended that all patients initiate prophylactic hygiene measures.

Stomatitis most often occurs within the first eight weeks of treatment. Initiating a dexamethasone alcohol-free oral solution as a swish and spit mouthwash has been shown to reduce the incidence and severity of stomatitis (R17-1688).

4.4.1.1 Treatment recommendations for the prophylaxis of stomatitis

- **Mouthwashes should be used from C1V1.** Mouthwashes eliminate food particles that can accumulate and favour bacterial growth. The preferred solutions are dexamethasone oral solution (SWISH guidelines – see R17-1688), normal saline, sodium bicarbonate, or a mixture of normal saline and sodium bicarbonate. These should 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, hydrogen peroxide solution should not be used as this will interfere with the formation of granulation tissue and healing of the ulcer.

- **For sites with access to dexamethasone containing mouthwashes:** Patients should use dexamethasone containing mouth washes from C1V1 (R17-1688**)** as prescribed/provided by investigator/trial site personnel (10 mL of alcohol-free dexamethasone 0.5 mg per 5 mL oral solution). The mouthwash should be swished for 2 min (a timer should be set) and spit four times daily for 8 weeks. Following each mouth wash, patients should not to take anything by mouth for 1 h for a total of 4 h per day. After the initial 8 week period, the dexamethasone mouthwash can be continued for up to 8 additional weeks at the discretion of the investigator and patient.

- Products containing glycerine or lemon, or toothpastes with an abrasive action should be avoided.
- Correct oral hygiene should be maintained with daily brushing of the teeth, tongue and gums, being 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.
- Dental prostheses should be cleaned and brushed, and at night should be left in 1% sodium hypochlorite solution (if they contain no metal) or in a solution of povidone iodine.
- Lips should be kept hydrated using lip balms (cocoa butter), methylcellulose solutions, moisturising cream or olive oil. Petroleum jelly or glycerine should be avoided because of their dehydrating effects on the lip tissue.
- Chlorhexidine can be used in the form of 15 mL of 0.12% chlorhexidine mouthwash 2-3 times a day. It is an antiseptic with a broad antimicrobial spectrum and has a bacteriostatic action and is particularly active against gram-positive microorganisms; 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.
- Foods that trigger pain e.g. acids, spicy and hot foods should be avoided. Patients should attempt to eat a soft diet and increase their intake of cold and nutritious fluids.

4.4.1.2 Treatment recommendations for established stomatitis/mucositis

General and grade specific recommendations are described in Table 4.4.1.2: 1.

Treatment is supportive and aims at symptom control. Treatment may include:

- Atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours);
- Avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide;
- Dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and
- Avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts

and alcohol.

- If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.4.1.2: 1 include: topical analgesics - viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals - nystatin suspension (adapted from P11-09424).
- 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/stomatitis, 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 CYP 3A4, which may potentially have an impact on metabolism of everolimus and exemestane.
- Systemic antiherpetic therapy (i.e. Famvir 750 mg/d for 7 days otherwise Aciclovir oral or i.v.) at investigator's discretion.

For dose reduction, interruption or discontinuation of everolimus in the management of stomatitis, refer to the current EU SmPC of everolimus or the PI of the respective country.

Table 4.4.1.2: 1 Grade-specific treatment recommendations of mucositis/stomatitis

Severity (CTCAE grading)	**Description**	**Treatment recommendations***
Mild (Grade 1)	Asymptomatic or mild symptoms; intervention not indic ated	For sites with access to dexamethasone containing mouthwashes: Swish 10 mL of a 0·9% saltwater solution and spit, followed by the same regimen of dexamethasone mouthwash as in section 4.4.1.1 10–15 min later. For sites without access to dexamethasone containing mouthwashes: Refer to 4.4.1.1

Severity (CTCAE grading)	**Description**	**Treatment recommendations***
Moderate (Grade 2)	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.
Severe (Grade 3)	Severe pain; interfering with oral intake	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.
Life threatening (Grade 4)	Life-threatening consequences; urgent intervention indicated	Same as for grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.

4.4.2 Management of hyperglycaemia

In case of hyperglycaemia treatment should follow the institutional standard or guidelines (R13-1975). Monitoring of fasting glucose is recommended prior to start of therapy and periodically thereafter. Optimal glycaemic control should be achieved before starting trial treatment. After commencing the study medications, monitoring of blood glucose should be individualized according to baseline glycemic function (normal, prediabetic, risks for diabetes mellitus or diabetes mellitus (may refer to R13-1975 and SmPC f/PI for everolimus)). If fasting glucose values above 200 mg/dL occur, the investigator should evaluate the need to intensify antihyperglycaemic therapy potentially in collaboration with the treating physician responsible for the treatment of the diabetic condition or a specialist. If hyperglycaemia occurs in patients without history of diabetes or hyperglycaemia and without contraindication, oral anti-diabetics, such as metformin 1 g to 2.5 g/d with less hypoglycaemic risk, may be started if necessary.

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

4.4.3 Management of non-infectious pneumonitis/ILD

Non-infectious pneumonitis is a class effect of rapamycin derivatives and has been observed in trial 1280.4. Fatal cases of non-infectious pneumonitis (including interstitial lung disease) have occurred. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude pneumonitis/ILD. Interruption of study medication may be considered pending investigation of these symptoms and appropriate treatment instituted as necessary. If pneumonitis/ILD is suspected the investigator should monitor patients for clinical symptoms and radiological changes. For dose reduction, interruption or discontinuation of the trial drugs, the following guidance should be used:

- Xentuzumab/Placebo: see section 4.1.5.2
- Everolimus/Exemestane: refer to the current EU SmPC of everolimus or the PI of the respective country and section 4.1.5.2

4.4.4 Management of neutropenia

Adverse events of neutropenia have been observed in trials with xentuzumab and causality has been established with everolimus. Patients should be monitored closely for signs of infection. No dose adjustment for xentuzumab is indicated. Dose adjustment for severe neutropenia (≥grade 3) should follow the everolimus SmPC/PI. Fever or infection in the presence of severe neutropenia should be managed promptly as clinically indicated. For management of xentuzumab during an infection, please refer to section 4.1.5.2, for management of everolimus, please follow everolimus SmPC/PI.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Response and progression will be evaluated in this trial using RECIST guideline (version 1.1) in combination with MD Anderson criteria for patients with target and/or non target bone lesions, at the time points specified in the Flow Chart. Adaptions to the MD Anderson criteria include clarifications and modifications to the published criteria and aim to provide more objective and reproducible assessments for the disease under study. A modification to the RECIST 1.1 criteria in regards to target lesion location selection will also be also implemented to properly address the patient population being studied (R17-4024). See Appendix 10.4 for details on lesion measurements and response assessment.

Tumour response will be assessed by the investigator and central independent review throughout the trial. Clinical decisions will be based on investigator assessment of tumour response. The results of the independent assessment will not be communicated to the investigator. Instruction for obtaining images and the shipment/transfer of image data will be provided by the central image review provider.

As of 29 September 2021, tumor assessments will be assessed per local practice. Only the overall response will be collected in the eCRF.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed as indicated by incidence and severity of AEs, graded according to NCI CTCAE version 5.0 (R18-1357).

Effective upon approval of CTPv6.0, Physical examination, Vital signs/ECOG Performance Status, and Safety laboratory parameters will be assessed per local institutional practice.

5.2.1 Physical examination

A physical examination will be performed at screening and at the timepoints specified in the Flow Chart. Of note: Skin lesions have to be properly documented and followed as tumour lesions. For details refer to Appendix 10.4.

- **A full physical examination** serves as a clinical tumour assessment and should include a cardiopulmonary examination, examination of the regional lymph nodes, the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. Wherever possible the same investigator should perform this examination. Includes height (only at SV) and weight.
- **A limited physical examination** should include a cardiopulmonary examination, a clinical tumour assessment, an examination of the regional lymph nodes and an examination of the abdomen. Includes weight. The results must be included in the source documents available at the site.

5.2.2 Vital signs and ECOG Performance Status

Vital sign measurements (blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiratory rate, temperature) and the evaluation of the ECOG performance status (see Appendix 10.3) will be performed at the times specified in the Flow Chart. Blood pressure and pulse will be measured after the patient has been recumbent or seated for about 5 minutes.

2 Baseline images will be assessed for evidence of visceral disease. If visceral disease present refer to Section 3.3.4.1.

5.2.3 Safety laboratory parameters

Safety laboratory samples will be analysed at a local laboratory. Safety laboratory examinations will include tests as presented in Table 5.2.3: 1, and should be obtained at the time points specified in the Flow Chart. Note: the safety lab blood draw may be taken on the day before the xentuzumab infusion so long as it is within the window allowed for the visit. Safety laboratory examinations should be taken with the patient in a fasted state (fasting in this protocol is defined as no food or fluid intake with the exception of water for at least 8 hours).

Table 5.2.3:1 Safety laboratory tests

Category	**Parameters**
Haematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, reticulocytes, white blood cell count (WBC) with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Electrolytes	Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO_3)
Biochemistry incl. liver and renal function tests	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. Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin Blood urea (preferred) or blood urea nitrogen (BUN), creatinine; creatinine clearance (for details refer to Section 3.3.2 and Appendix 10.6)
Pancreatic function parameters	Amylase, Lipase

Lipid profile (fasting)	Total cholesterol, triglycerides, LDL, High-density lipoprotein (HDL)
Hormones (premenopausal women) and postmenopausal women less than 60 years of age only)	Premenopausal women: Estradiol, FSH and Pregnancy testing (serum/urine), see Flowchart *Postmenopausal women less than 60 years of age (in the absence of bilateral oophorectomy): Estradiol and FSH, see Flowchart *Effective 29 Sept 2021, hormone testing for post-menopausal woman is no longer applicable

Table 5.2.3:1 Safety laboratory tests (contd.)

Category	**Parameters**
Other	Phosphorus, lactate dehydrogenase (LDH), total protein, uric acid
Other (fasting)	Glucose (preferably from plasma) and HbA1c
Urinalysis	pH, protein, glucose, blood, leucocytes, nitrite will be analysed by dipstick (semi-quantitative measurements: -, +,++, +++); in case of pathological finding further evaluation should be performed and results documented

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal and clinically relevant findings from these investigations need to be reported as an AE.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed and/or treated as medically appropriate.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Effective after approval of CTPv6.0 ECG no longer required for ongoing patients.

5.2.5 Left Ventricular Ejection Fraction

Effective after approval of CTPv6.0 MUGA is assessment is no longer applicable for ongoing patients.

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or Multiple Gated Acquisition (MUGA) scan will be assessed as specified in the Flow Chart. The same method of measurement must be used throughout the trial. LVEF assessment does not need to be repeated during screening if there is valid result available from an assessment which was performed as part of routine clinical practice within 28 days prior to start of trial treatment.

- Echocardiography will be performed to assess the LVEF according to the standard guidelines of the American Society of Echocardiography (R06-1414).
- MUGA scan is recommended for the assessment of diseases of the heart muscle. It is used for the monitoring of the ejection fraction of the cardiac ventricles, especially the LVEF.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed and/or treated as medically appropriate.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

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

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

Serious adverse event
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:
- Results in death,
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- Requires inpatient hospitalisation or
- Requires prolongation of existing hospitalisation,

- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect,

or

- Is deemed serious for any other reason if it is an important medical event when based on 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.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the duration between discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and **AE reporting to sponsor and timelines**".

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

The latest list of "Always Serious AEs" can be found in the Electronic Data Capturing (eDC) system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

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

The following are considered as AESIs:

Hepatic injury is defined by the following alterations of hepatic laboratory parameters:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC system. 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.

Pneumonitis including interstitial lung disease, non-infectious pneumonitis and other analogous terms.

Intensity (severity) of AEs
The intensity (severity) of adverse events should be classified and recorded in the CRF according to the CTCAE version 5.0 (R18-1357).

Causal relationship of AEs
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.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:
- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drugclass.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre- existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:
- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5half-lives). Of note, this criterion may not be applicable to events whose time cycle is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:
- From signing the informed consent onwards until the end of treatment (including the Residual Effect Period, REP):

- All AEs (non-serious and serious) and all AESIs.

• After the end of treatment until the individual patient's end of trial:

- All drug-related SAEs and all drug-related AESIs.

• After the individual patient's end of the trial:

The investigator does not need to actively monitor the patient for AEs but should report drug-related SAEs and drug-related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

The rules for Adverse Event Reporting exemptions still apply.

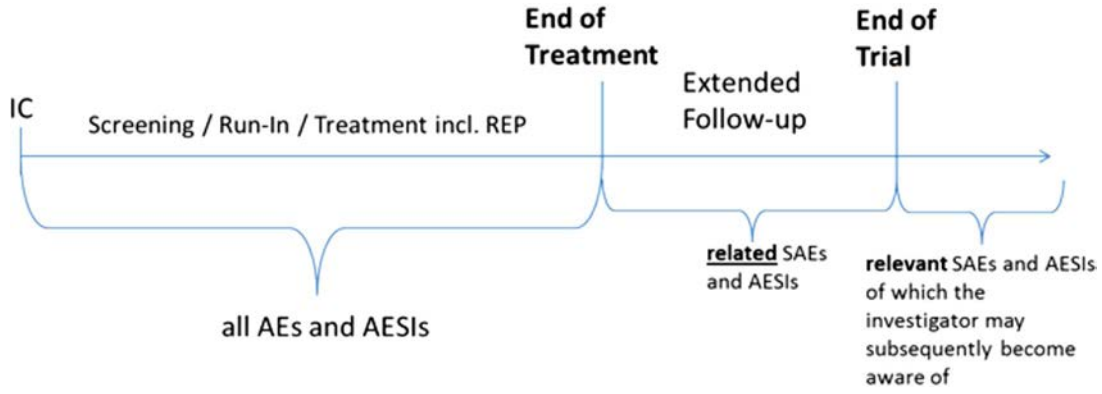


Figure 5.2.6.2: 1 AE collection periods

The REP is defined as 42 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Events which occurred after the REP will be considered as post-treatment events.

5.2.6.2.2 AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the Sponsor's unique entry point (country-specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication and any possible interactions between the trial medication and a NIMP/AMP.

The following should also be recorded as an (S)AE in the CRF and BI SAE form

(if applicable):

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the CRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

Postmenopausal patients are women of non-childbearing potential. Therefore pregnancy is not expected to occur in this patient group.

In rare cases, pregnancy might occur in a premenopausal patient even though she is taking ovarian suppression treatment. Once a premenopausal patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.4 Exemptions to SAE reporting

Exempted outcome events are: Disease progression, Malignant neoplasm progression, Neoplasm progression.

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 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 CRF page and not on the SAE Form.

However, when there is evidence suggesting a causal relationship between the trial drugs and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and in the CRF.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalisation/Procedures solely due 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 will be monitored at appropriate intervals by the DMC.

5.2.6.3 Assessment of healthcare resource use

In case patients would be hospitalised due to AEs, the duration of hospital stay as well as the need to stay and the duration in the intensive care unit will be documented in the CRF. The data collected will be used for a later health economic (cost effectiveness) analysis.

Further HCRU data for use in later health economic (cost effectiveness) analysis will be captured in the CRF, too (see section 5.6.3).

As of 29 September 2021, healthcare resource questionnaire is no longer applicable for ongoing patients.

5.2.7 Safety assessment as of 29 Sept 2021

As of 29 September 2021, all the safety assessments will be done according to local practice.

No follow-up information will be collected after patients discontinue study treatment except all AESIs, SAEs, related AEs still ongoing at the end of treatment, which will be followed until resolution/stabilization.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood for pharmacokinetic analysis of xentuzumab will be collected at visits specified in the Flow Chart at time points as specified in Appendix 10.1.

The following PK parameters will be calculated by means of non-compartmental analysis and evaluated as further endpoints, if calculation is feasible:

- Pre-dose concentration of xentuzumab shortly before the next infusion (C_{pre})
- Concentration of xentuzumab shortly after end of infusion ($C_{1.25}$)

PK sampling scheduled on Day 1 of a cycle should only be performed after the decision has been made to prescribe a new cycle of treatment. However, if the decision to withdraw a patient from treatment is made after the PK sample was already obtained, this PK sample should be registered on the scheduled visit. The sample will be analysed as planned.

As of 29 Sept 2021, PK samples will no longer be collected for ongoing patients.

5.3.2 Methods of sample collection

Blood samples should not be obtained from the arm used for infusion. A central venous access/central port must not be used due to interference of Li- and Na-Heparin with PK assays. The central venous access/central port can only be used when it can be assured that no heparin is contained in the blood sample. Otherwise PK sample collection must occur by i.v. puncture from the forearm. Details will be provided in the ISF. The actual sampling date and time (24 hour time clock) for each sample has to be recorded accurately.

For quantification of xentuzumab plasma concentrations, blood samples will be taken at the time points listed in the Flow Chart under PK sampling. A detailed sampling schedule is shown in Appendix 10.1. For details on blood volumes to be collected, sample handling and logistics refer to the ISF (Laboratory Manual).

After completion of the study, plasma/serum samples may be used for further methodological investigations, e.g., stability testing. However, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Exposure-response relationships will be explored. Formal exposure-response analyses may be omitted in case of a negative trial outcome.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to both exploratory and probable valid biomarkers. The exploratory analyses are hypothesis generating and will be used to expand our understanding of the trial drug and the disease. Participation in the biomarker analyses is mandatory for all patients. If an individual biomarker is assessed as no longer relevant, testing may be discontinued at any time.

Remaining materials from biomarker analyses such as tumour tissue, blood or plasma

samples (and isolated DNA and RNA) will be destroyed no later than 3 years after the end of the trial if no optional consent for sample biobanking is obtained from the patient (see Section 5.4.4).

Detailed instructions for sampling, handling and shipment of samples will be provided in the laboratory manual/ISF.

The biomarker analyses will be performed by the Sponsor or a central laboratory authorised by the Sponsor.

As of 29 Sept 2021, biomarker samples will no longer be collected for ongoing patients.

5.4.1 Evaluation of molecular and biochemical biomarkers in tumour tissue:

Tumour tissue at Screening
Patients will be eligible for enrollment into the trial if their documented tumour status is HR+/HER2-. Archival tumour tissue (preferably from the most recent biopsy prior to entering the study) will be analyzed retrospectively for HR and HER2 status following ASCO/CAP guidelines (R15-6055, R17-4255). (Note: biopsy samples from the bone must not be provided due to not being suitable for HER2 testing). This analysis will be performed by a central laboratory nominated and qualified by the Sponsor. Results will not be required prior to randomisation.

In addition to the mandatory analysis of HR/HER2 status, archival tumour tissue samples may be analysed for:

- Gene expression of e.g., but not limited to, IGF, PI3K/mTOR, Ras/MAPK and breast cancer signalling relevant genes.
- Expression of Ki-67 protein via biochemical methods (e.g. IHC) to measure the proliferative index. This will allow the assessment of luminal A vs. B status. As medical knowledge in this field is constantly evolving, broader analysis of the samples (including immunohistochemistry/in-situ hybridization/sequencing of e.g. IGF-1/2, IGF-1R, pIGF-1R, PTEN, pAKT, pS6, E-Cadherin) might be conducted to e.g. address predictive biomarkers, exceptional response or resistance mechanisms.
- Somatic alterations in genes related to the MoA of the trial drugs and/or involved in breast cancer tumourigenesis, e.g. IGF pathway-related and cancer driver genes.

Individual analyses from tumour tissue will be prioritised based on the availability of sufficient tissue material.

Methods of sample collection
Formalin fixed paraffin embedded (FFPE) tumour tissue, preferably FFPE blocks, from the most recent time point before consent will be collected during Screening (see Flowchart). (Note: biopsy samples from the bone must not be provided). The FFPE blocks will be used to prepare 20 slides at ~5µm thickness. Alternatively, 20 freshly prepared slides at ~5µm thickness from FFPE blocks can be provided but need to be prepared under RNase-free conditions.

5.4.2 Molecular evaluation in blood:

Two kinds of blood samples will be collected for genomic analyses from blood and plasma.

One blood sample will be used to isolate genomic DNA. The isolated genomic DNA will be used as a reference to distinguish somatic alterations in the tumour and will be analysed for the same cancer-related genes as the tumour tissue-derived DNA (if applicable) and the plasma isolated cfDNA.

From the second blood sample plasma needs to be separated within approximately 4 hours. The plasma will be used to isolate cfDNA. Subsequent analyses of the plasma may involve somatic alteration analysis in the IGF pathway and cancer driver genes of plasma isolated cfDNA, potential epigenetic analysis or analysis of plasma derived exosomes. Additionally, changes in nucleic acid concentration over the course of treatment may be explored. Analysis of cfDNA (that includes ctDNA (circulating tumor DNA)) provides a non-invasive technique that might help to find potential biomarkers to predict treatment response or resistance mechanisms to the study drug (R14-1645).

Methods of sample collection
For analysis of cfDNA, blood samples will be collected in plasma preparation tubes before drug administration at each indicated time point (see Flow Chart). If a patient has not progressed at EOT then a blood sample should be collected at the FU-PD visit where progression is documented.

5.4.3 Protein biomarkers from blood and urine

IGF and other proteins involved in IGF signalling
Levels of free and total IGF-1 and total IGF-2 (optionally the amount of IGF-BP3, dissociable IGF-1 or other factors related to IGF signalling) will be relatively quantified in serum using validated immunoassays. Free IGF-1 (and IGF-2) is defined as the fraction of total IGF-1 (and total IGF-2) that can be bound by xentuzumab under *in vitro* assay conditions. Dissociable IGF-1 (and IGF-2) is a different representation of free IGF-1 (and IGF-2) under more diluted assay conditions. Total IGF-1 (and total IGF-2) is quantified in serum samples after splitting the IGF-IGF-binding protein complexes and the IGF- xentuzumab immune complexes.

Bone remodelling markers

Biomarkers for bone resorption and formation (including, but not limited to serum N-terminal propeptide of procollagen type 1(P1NP) and urine N-terminal cross-linked telopeptide of type I collagen (NTX)) will be assessed in blood and urine samples (second morning void – see Flow Chart) at C1V1 prior to the start of therapy, C2V3 and C4V1 and EoT.

Samples for bone biomarkers will be taken prior to administration of trial medication and subsequent specimens for comparison should be collected at the same time of day as the baseline specimen.

Serial collection of blood samples for the assessment of these markers is mandatory. As medical knowledge in this field is constantly evolving, other blood biomarkers that come to be known as potentially relevant prognostic/predictive markers of treatment response may also be explored via available blood. Biomarkers that come to be known

or emerge as not relevant during the trial may be discontinued.

Testing for Cytokine Release

Cytokines are measured to evaluate the influence of xentuzumab on circulating cytokines to judge on the likelihood of cytochrome P450 enzyme regulation and potential drug drug interaction with small molecule drugs.

A panel of cytokines (including, but not limited to IL-1beta, IL6, TNFα, IL2, IFNγ) will be measured in peripheral blood in order to monitor release of cytokines after xentuzumab (or placebo) administration. Cytokine measurements will be performed at the time points specified in the Flow Chart and Appendix 10.1 will be measured in a central lab authorised by Boehringer Ingelheim using immunoassay techniques, such MSD assay.

Methods of sample collection
Blood will be taken from a forearm vein or central line at those time points specified in the Flow Chart or Appendix 10.1. All samples must be adequately labelled by the site personnel.

Urine samples must be provided from the second morning void. When this occurs prior to visiting the clinic, the sample should be collected at the patient's home and brought to the respective visit at those time points specified in the Flow Chart or Appendix 10.1.

5.4.4 Biobanking (Optional)

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies or to gain mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking samples will only be banked after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

The leftovers of the following biomarker samples might be banked:
- Leftover tumour tissue or derivatives (e.g., RNA, DNA) obtained at screening
- Plasma, or the derived nucleic acids (e.g. cfDNA), collected at multiple time points as defined in the Flow Chart
- Serum collected at C1V1 as defined in the Flow Chart

5.4.5 Radiomics

Radiomics investigates the potential for enhanced and improved baseline and on-treatment markers of early efficacy based on comprehensive quantitative CT metrics. Analysis of standard-of-care medical imaging may identify gross or fine imaging features

linked to characteristics of lesions such as tumour neo-vasculature, necrosis, as well as the heterogeneity of the metastatic burden, which may be associated with ongoing intra-tumoural Darwinian dynamics, regional variations in environmental properties, and cellular adaptive strategies. Radiomics thus can be used to build diagnostic, prognostic and predictive models and its features can be trained to identify patterns associated with favourable outcome and thus generate non-invasive clinical decision tools using standard of care CT-scan.

Imaging data used for independent radiological review will be further evaluated using integrated assessment of changes based on e.g. tumour volume(s), shape(s), texture(s). This exploratory analysis will be performed by a CRO nominated by the Sponsor.

5.5 ASSESSMENT OF IMMUNOGENICITY

5.5.1 Assessment of immunogenicity

Anti-drug antibodies will be determined in a tiered approach for all patients before the start of xentuzumab treatment, (baseline immunogenicity assessment), during treatment and at end of treatment and follow up visits. Time points for ADA and neutralising antibody sampling are specified in the Flow Chart and Appendix 10.1.

Immunogenicity of xentuzumab will be assessed using a multi-tiered approach. All samples will first be analysed in the ADA screening assay. Samples found to be putative positive in the ADA screening assay will then be assessed in the confirmatory assay. Titer will be determined for samples that confirmed positive. [redacted]

As of 29 Sept 2021, samples for immunogenicity will no longer be collected for ongoing patients.

5.5.2 Methods of sample collection

Blood samples should be obtained as described for PK samples.

For ADA and nAb assessment, blood will be taken at the time points listed in the

Flow Chart under ADA/nAb sampling. A detailed sampling schedule is shown in Appendix 10.1.

For details on blood volumes to be collected, sample handling and logistics refer to the ISF (Laboratory Manual).

After completion of the study, plasma/serum samples may be used for further methodological investigations, e.g., improving drug tolerance. However, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

[redacted]

5.6 OTHER ASSESSMENTS

5.6.1 Patient-reported outcomes

Patient reported outcomes (PRO) are considered an important contribution to prescribers, patients and health care decision makers when evaluating the clinical utility of a medical intervention. The information collected using PRO instruments can lend supportive arguments to the clinical activity of therapy and refer to the extent of which patients physical, emotional and social well-being are affected by treatment. In this trial the patient perspective will be captured using both symptom and disease specific instruments; in addition information on health related quality of life will be collected using a generic preference based instrument.

PRO will be measured with the following multidimensional questionnaires (see Appendix 10.5):

- Brief Pain Inventory – Short Form (BPI-SF) (R17-2778)
- National Comprehensive Cancer Network Functional Assessment of Cancer Therapy- Breast Cancer Symptom Index (NFBSI-16) (R17-3000).
- EuroQoL 5-dimension health status self-assessment questionnaire (EQ-5D-5L) (R12- 1920).
- Patient reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (R18-2068)

Questionnaires will be completed at the time points specified in the Flow Chart. Paper questionnaires should be completed at the site by patients prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status so that the responses are not influenced (biased).

The questionnaires generally take about 10 minutes to complete. Patients will receive the questionnaire in their native language in countries where validated translations exist. The answered questionnaires will be entered in the CRF by the site personnel.

BPI-SF
The BPI-SF is a 9 item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning (R17-

3500).

The patient is asked to rate their worst, least, average, and current pain intensity in the last 24 h, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10 point scale.

Measurement of pain severity: The BPI-SF assesses pain at its "worst," "least," "average," and "now" (current pain). In clinical trials, the items "worst" and "average" have each been used singly to represent pain severity. In addition a composite of the four pain items (a mean severity score) is sometimes presented as supplemental information. The use of these single items is supported by the IMMPACT recommendations for assessing pain in clinical trials (R07-4358, R09-2344) and by the FDA Draft Guidance for Industry: Patient Reported Outcome Measures (R12-5607). In addition, the BPI-FS's developers recommend that all four severity items be used, because the models for validation of the BPI-FS included all four items.

Measurement of Pain interference: The BPI-FS measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. BPI-FS pain interference is typically scored as the mean of the seven interference items. This mean can be used if more than 50% or four of seven, of the total items have been completed on a given administration.

Other Items: The item, "Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?" is a YES/NO preliminary screening question at the beginning of the BPI-FS. The BPI-FS also asks the patient to indicate the percentage of relief provided by pain treatments or medications.

NFBSI-16

The NFBSI-16 is an updated version of the Functional Assessment of Cancer Therapy – Breast Cancer Symptom Index (FBSI) (R17-3502) which includes all eight items from the original FBSI and eight additional items. It was developed using methods consistent with recent regulatory guidance on patient-reported outcomes as endpoints in clinical trials with emphasis on patient input during the development process Statements are presented and the patients are asked to indicate their response as it applies to the past 7 days with 5 response options, from "not at all" to "very much". A total score can be obtained, and higher scores indicate better outcomes than lower ones. It can be formatted by the subscales: Disease- Related Symptom, Treatment Side-Effect, General Function and Well-Being (R17-3000, R17-3497). The primary aim of the NFBSI-16 is to provide a PRO metric based on breast cancer–specific symptoms identified as high priority by patients and oncology clinicians.
While this can be clinically informative at the level of the overall index, an examination of the specific subscales (e.g., disease-related, treatment side effects, and function and well- being) can yield more specific information about changes in target symptoms over time or in response to intervention.

Minimally clinically important differences have not yet been confirmed for the NFBSI-16, but for the original FBSI minimally important differences (2–3 points) are described (R17-3000).

EQ-5D-5L
The EQ-5D is a disease generic instrument that has been widely used and has been found to capture Health-related quality of life (HRQOL) changes in oncology. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (R12-1920).

- The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. The scores on these five dimensions can be converted to a single summary index number (utility).
- The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

PRO-CTCAE
PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials. It was designed to be used as a companion to the CTCAE criteria, the standard lexicon for adverse event reporting in cancer trials (R18-2068). The PRO-CTCAE Instrument & Form Builder was used to select eight items (difficulty swallowing, skin cracking at corners of the mouth, decreased appetite, vomiting, heartburn, diarrhoea, pain in the abdomen, rash) based on clinical experience and overlap with already included items in the NFBSI-16.

As of 29 Sept 2021, patients reported outcomes will no longer be collected for ongoing patients.

5.6.2 Analgesics use

Pain palliation resulting from antitumor therapy provides direct evidence of treatment benefit when combined with evidence of antitumor activity (R17-3501). Intensification of pain palliation will be defined as a ≥2-point increase in the 8-point Analgesic Quantification Algorithm (AQA, see Table 5.6.2: 1). AQA is a modification of the World Health Organization Analgesic Treatment Ladder that includes additional specificity for patients receiving strong opioids. This algorithm facilitates differentiation between the full ranges of doses of strong opioids used by patients and thus, more accurately enables researchers to determine and control for changes in levels of analgesic medication use over time in clinical trials (R17-2771). It will be completed by the investigator at the same visits as the PROs.

Table 5.6.2: 1 AQA

AQA score	Description
0	No analgesic
1	Non-opioid analgesics
2	Weak opioids
3	Strong opioids ≤75 mg OME per day
4	Strong opioids >75–150 mg OME per day
5	Strong opioids >150–300 mg OME per day
6	Strong opioids >300–600 mg OME per day
7	Strong opioids >600 mg OME per day

5.6.3 Health care resource utilisation

Health care resource utilisation (HCRU) data will allow calculation of direct and indirect costs and will be used for health economic analysis (i.e. cost-effectiveness analysis).

Resource use will be captured at the time points specified in the Flow Chart. Information on caregiver support (home care), general practitioner, outpatient and hospital visits (other than scheduled visits) will be collected in the CRF and as part of AE reporting to inform on healthcare resource use required to treat the trial indication and adverse events observed during the trial.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The NCI CTCAE criteria are used in the assessment of AEs in cancer patients. In the present trial CTCAE version 5.0 (R18-1357) will be used.

The questionnaires used in the present trial have been validated and address the outcome to be evaluated (i.e. symptoms or HRQOL). The BPI-SF has been accepted by multiple national authorities including FDA and EMA, and the NFSBI-16 and the PRO-CTCAE have been developed in accordance with FDA guidance for patient-reported outcome measures.

6 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The visit schedule is in detail described in the Flow Chart for all patients randomised to either the treatment with xentuzumab in combination with everolimus and exemestane or to placebo in combination with everolimus and exemestane. Unscheduled visits can be performed as necessary and assessments will be performed as required at the discretion of the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

See the Flow Chart and Section 5 for details on the procedures performed at each visit. Per Protocol version 6, reference the revised and reduced flow chart and section 5 as appropriate.

6.2.1 Screening

Screening Period
All patients will need to sign the informed consent form (ICF). Only patients who have tested positive for HR and negative for HER2 by prior local analysis according to ASCO/CAP guidelines (R15-6055, R17-4255) are eligible for the trial. Archival tumour tissue sample must be submitted to the central laboratory to retrospectively confirm HR/HER2 status (see Section 5.4). If archival tissue is not available, provision of detailed information from the original histology report may be agreed with the sponsor on a case by case basis. In the case that prior information regarding the patient's genomic breast cancer signature is available, an anonymised copy of the report will be collected for the trial database and specified parameters will also be recorded in the CRF.

Demographic information (sex, date or year of birth (in accordance with local laws and regulations), race) will be obtained, based on information in the patients' medical records. Examinations and assessments per Flow Chart will be conducted and patients' medical history will be collected. Inclusion and exclusion criteria must be assessed (see Sections 3.3.2 and 3.3.3). Baseline images must be available as outlined in the Flow Chart.

Concomitant diagnoses and/or therapies present during trial participation (between first ICF and the first follow-up visit) will be recorded in the CRF. Medical history of mBC will be obtained and reported in the CRF:

- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites (e.g. bone, lymph nodes, skin, subcutaneous, soft-tissue, (contralateral) breast and combinations thereof)
- Tumour stage according to the TNM-classification at diagnosis
- Previous treatment for mBC, including any surgery, radiotherapy, and/or systemic therapy, including start and end dates and the outcome.

Re-screening will be allowed once. Re-screened patients will receive a new

patient number. In case of re-screening any procedures that fall outside the required screening window as defined in Flow Chart must be repeated.

6.2.2 Treatment period

Treatment visits are specified in the Flow Chart and must be conducted as scheduled and outlined there. Treatment cycles are 4 weeks (28 days) in duration until treatment week 80 and then 8 weeks (56 days) in duration.

All planned visit dates are calculated from the start of day 1 (visit 1) of cycle 1. If a visit is missed there will be no re-scheduling; if a patient is required to attend the study site between the "missed" and next scheduled visit, then the missed visit assessments should be performed. The current date and the reason for the delay must be noted in the medical records. All subsequent visits must adhere to the scheduled programme of visits for all cycles of treatment.

Imaging visits must adhere to the schedule provided in the Flow Chart at all times, unless they are scheduled for suspected PD.

6.2.2.1 End of treatment visit and follow-up visit 1

The EOT visit will be performed as soon as possible (within 14 days) after permanent discontinuation of **all** trial medications for any reason or as soon as possible after the investigator became aware that the trial medication had been terminated. Investigators must ensure that PK, ADA and nAB samples are taken as described in the Flow Chart, Section 5.3 and Appendix 10.1.

The follow-up Visit 1 (EOR/FU1) will be performed 42 (+7) days after permanent discontinuation of all trial medications and is primarily to collect follow-up safety information as required by regulatory authorities. For the majority of patients, progression will already be documented at this point.

6.2.2.2 Treatment beyond progression

In case of continued clinical benefit judged by the investigator and based on careful clinical assessment, patients may be allowed to continue trial medications beyond disease progression as defined by RECIST 1.1 criteria. Clinical benefit can include, but will not be restricted to, significant symptom control of originally symptomatic tumours. Patients who continue as described will continue to follow the trial schedule for treatment visits (see Flow Chart) including the imaging and clinical tumour evaluations. Trial medication may be continued as long as judged beneficial by the investigator.

6.2.3 Follow up period and trial completion

Not applicable as per CTP version 6. The end of study is defined as EOR/FUP1

6.2.3.1 Extended follow-up period

For patients without objective disease progression and who have not started a new anti-cancer therapy prior to FU1, additional follow-up visits for progression will be performed every 56 days (8 weeks) ±7 days after the EOT visit for patients who did not yet start cycle 20 and every 16 weeks (112 days) for patients who started cycle 20. The follow-up for progression period will end at the earliest if one of the following events is met:

- Lost to follow-up
- Disease progression
- Start of a new anti-cancer therapy
- Death
- End of whole trial as specified in Section 8.6

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

- For each drug-related SAE/AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Record performance status (ECOG)
- Quality of life questionnaires
- Perform tumour assessment and imaging
- Treatment and start date of any subsequent anti-cancer therapy including the name and type of the anti-cancer drug and/or best supportive care (if applicable)
- Outcome (in case the patient had PD the actual date of PD shall be recorded, date of and reason for death, if applicable)
- Results from pregnancy testing (if applicable) see Flowchart

6.2.3.2 Follow-up for Overall Survival

All patients will be followed up for overall survival at 84 day (12 weeks) intervals until

- Death
- Lost to follow-up or
- Completion of the whole trial (as specified in Section 8.6)

These visits may also be performed by e.g. telephone interview or via written correspondence in case the patient is unable to visit the investigator. The following information will be collected during the follow-up for survival period:

- Date and type of contact
- Post progression information including further anti-cancer treatment: regimen and drug name, start and stop dates, response to further anti-cancer treatment if available
- For each drug-related SAE/AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the

AEs on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Outcome event (record date of and reason for death, if applicable)
- Results from pregnancy testing (if applicable) see Flowchart

6.2.3.3 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:
- Completion of planned follow-up periods
- Lost to follow-up
- Refusal to be followed-up
- Death

If a patient cannot be contacted for vital status, information may also be obtained by other means, e.g. contact with patients' health care providers, public sources, e.g. death registry, obituary listing, etc. when it is available and verifiable.

7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, double-blind, placebo-controlled multi-centre trial in women with HR+/HER2- advanced or metastatic breast cancer with non-visceral disease. The primary objective of the trial is to evaluate whether xentuzumab in combination with everolimus and exemestane prolongs PFS, independently assessed according to RECIST 1.1, in comparison to everolimus and exemestane alone.

Based upon these design considerations, treatment groups will be compared for the primary endpoint via a stratified log-rank test, stratified by the presence of baseline bone-only metastases (Yes/No), prior CDK4/6 inhibitor treatment (Yes/No) and menopause status (pre/post).

If the criterion for the seamless option is met then this Phase II trial will be expanded into a confirmatory Phase III trial, similar to the 2-in-1 design outlined in R18-2061. Pertinent detail regarding hypothesis testing, alpha-spending/control along with increases in sample size in the expansion scenario has been detailed in the following sections. However, prior to expanding the trial additional detail will be provided via a formal protocol amendment.

7.2 NULL AND ALTERNATIVE HYPOTHESES

If at the time-point of the primary PFS analysis for this Phase II trial the hazard ratio (using the model defined in Section 7.3.1) is below a pre-defined criterion (to be defined in the DMC charter, prior to trial initiation), in favour of the xentuzumab arm, then the trial will be expanded into a confirmatory Phase III trial. No formal hypothesis testing will be performed if the trial is not expanded.

However, if the trial is expanded, formally, the null hypothesis for the primary PFS endpoint at the end of Phase III is:

$$H_0 : S_{PFS;\ xentuzumab}(t) <= S_{PFS;\ control}(t), \text{ for all } t > 0,$$

versus the alternative hypothesis:

$$H_1 : S_{PFS;\ xentuzumab}(t) > S_{PFS;\ control}(t), \text{ for any } t > 0,$$

where $S_{PFS}(t)$ is the probability that a patient passes time t without experiencing a PFS event.

The expanded study will be considered positive if the null hypothesis for the primary endpoint can be rejected.

Also in the expanded trial scenario, for the secondary OS endpoint, the null hypothesis is:

$$H_0 : S_{OS;\ xentuzumab}(t) <= S_{OS;\ control}(t), \text{ for all } t > 0,$$

versus the alternative hypothesis:

$$H_1 : S_{OS;\ xentuzumab}(t) > S_{OS;\ control}(t), \text{ for any } t > 0,$$

where $Sos\ (t)$ is the probability that a patient passes time t without experiencing an OS event.

The hypothesis testing will be performed on all randomised patients. The testing strategy includes the endpoints PFS and OS, tested in a hierarchical manner, and will control the overall type-1 error rate at a level of 0.025 (one-sided).

If the trial is expanded then the primary PFS analysis at the end of Phase II will be considered as an interim analysis. Refer to Section 7.4 for further details on this planned interim analysis and the control of the type I error rate in the situation where the trial is expanded.

Superiority, for the endpoint of interest will be declared if the related null hypothesis is rejected in favour of the alternative at the defined significance level and the estimated hazard ratio of xentuzumab vs. control is <1.

The primary objective of this Phase II trial, that xentuzumab in combination with everolimus and exemestane prolongs PFS, will be addressed by assessing whether or not the criterion for the seamless option has been met. If the seamless option is not met, the observed results will be evaluated in an explorative manner to see if they are sufficient for further development of this compound in this indication (e.g. via a separate Phase III trial). If the seamless option is met then expansion into a Phase III trial will allow for formal hypothesis testing via a one- sided test at an alpha level determined by a number of factors (refer to Section 7.4), controlling for the overall type I error rate of 0.025 (one-sided). The hypothesis testing will be supported by the hazard ratio and corresponding 95% CI from a stratified Cox proportional hazards model to describe the magnitude and precision of treatment effects.

7.3 PLANNED ANALYSES

The primary analysis of PFS for this Phase II trial will take place when approximately 40 patients have had disease progression (assessed by independent review) or died. The time point of reaching 40 events will be estimated using investigator assessed events and the discrepancy rates observed between independent and investigator data during the trial. The estimation of this time point is likely to lead to some deviation, though relatively small, from the planned 40 independent assessed events. Based on assumed median PFS times (refer to Section 7.7), the analysis is expected to take place 15 months after the last patient has been randomised. This analysis will be performed by the DMC.

If the criterion for the seamless option is met then the trial will be expanded into a confirmatory Phase III trial and remain double-blind. If the criterion is not met then the database will be unblinded and a clinical trial report (CTR) written, including the evaluations of the primary, secondary and further endpoints. Note that based on these results it is still possible that clinical development in this indication will be continued (e.g. via a separate Phase III trial), in addition patients randomised into this Phase II trial will have further data collected and reported upon, beyond the unblinding time-point. Blinded dummy treatment group assignments will be used in the study database whilst the trial remains blinded. Section 4.1.6 provides further details on the blinding and procedures for unblinding.

An exception to the above plan will occur if the proportion of randomised patients dropping out of the trial without evidence of disease progression, becomes so high that reaching 40 PFS events is either not possible, or has not been met 20 months after the last patient has been randomised. In such an unlikely scenario no DMC analysis will be performed and therefore

the criterion for seamless expansion will not have been met. In this situation the database will be unblinded and a CTR written, including the evaluations of the primary, secondary and further endpoints.

Imaging related endpoints will be both independently assessed and investigator assessed according to RECIST 1.1. The data from the independent assessments will be considered primary, with investigator assessment data as supportive.

The primary efficacy analyses will be performed on the randomised set (RS), consisting of all randomised patients. Patients randomised and not treated will be analysed according to the censoring rules defined in Section 7.5. Randomised patients who receive the wrong treatment will be analysed according to their planned randomised treatment group. No per-protocol analysis is planned.

Stratification (where stated) of analyses will be based on the presence of baseline bone-only metastases (Yes/No), prior CDK4/6 inhibitor treatment (Yes/No) and menopause status (pre/post). Refer to Section 7.6 for further details on the randomisation stratification factors.

The safety analysis will be based on the treated set (TS), consisting of all patients treated with at least one dose of any study treatment. Patients will be analysed according to the actual treatment received.

7.3.1 Primary endpoint analyses

The primary endpoint of this study is PFS defined as the time from the date of randomisation to the date of disease progression, or to the date of death if a patient died earlier. The date of progression will be based on independent assessment according to the RECIST 1.1 criteria.

For patients with ‘event’ as an outcome for PFS:

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

For patients with ‘censored’ as an outcome for PFS:

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

The censoring rules for PFS (i.e. outcome and date of outcome) are described in Table 7.5: 1. The time frame for the primary assessment of PFS will be from randomisation until the earliest of disease progression, death or the time point of the primary PFS analysis (refer to Section 7.3).

A stratified log-rank test will be used to test the primary hypotheses, if the trial is expanded into a Phase III trial.

A stratified Cox proportional hazards model will be used to estimate the hazard ratio and its asymptotic two-sided 95% Wald CI between the two treatment groups. A hazard ratio of less than one will favour the xentuzumab in combination with everolimus and exemestane treatment group.

Kaplan-Meier (KM) estimates will be used to display the distribution of PFS for each treatment group on a KM curve. To support the plot estimated survival probabilities at specific time points of interest (scheduled imaging time-points) will be tabulated along with 95% confidence intervals, using Greenwood’s variance estimate. In addition the survival distribution will be used to provide estimates of the median, 25th and 75th

percentiles.

[redacted]

7.3.2 Secondary endpoint analyses Overall survival

OS will be analysed using the same statistical methods as for PFS. OS will be included in the confirmatory strategy in a hierarchical manner if the trial is expanded into a Phase III trial.

OS is defined as the time from randomisation until death from any cause. For patients with 'event' as an outcome for OS:

- OS [days] = date of outcome – date of randomisation + 1.

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

- OS (censored) [days] = date of outcome – date of randomisation + 1

The censoring rules for OS (i.e. outcome and date of outcome) are given in Table 7.5: 2. The time frame for the primary assessment of OS will be from randomisation until the earliest of death or the time point of the primary OS analysis (refer to Section 7.3).

In addition to the main analysis the following analyses may be performed to examine the pattern of time to death for consistency with the PFS results, while accounting for the extent and influence of post-progression intervention if deemed necessary:

- describe the cumulative proportion of deaths at each scheduled tumour assessment time point
- tabulate the specific anti-cancer treatments after progression
- describe the effect of additional anti-cancer treatment, by separating patients into the following sub-groups:
    - those not eligible for additional treatment
        - patients who did not progress

        - patients who died within one month of progression

    - those eligible for additional treatment (i.e. those who have progressed and not died in the first month after progression)
        - did not take additional treatment
        - did take additional treatment

Disease control

DC will be analysed in terms of DC rate (DCR), defined as the proportion of patients with best overall response of CR, PR, SD or Non-CR/Non-PD. The DCR will be calculated for each treatment group, overall and within each level of the stratification factors. Proportions will be presented with 95% CIs. A logistic regression model adjusting for the stratification factors where appropriate will be used to compare the DCR between the two treatment groups.

For the primary assessment of DC, tumour imaging will be performed every 8 weeks up to week 80 and every 12 weeks thereafter until the earliest of disease progression, death or last evaluable tumour assessment before the start of subsequent anti-cancer therapy or the time point of the primary PFS analysis (refer to Section 7.3).

A best overall response of SD or Non-CR/Non-PD must have a minimum duration of 24 weeks from the date of randomisation.

Duration of disease control

For all patients with DC the duration of DC is defined as the time from randomisation until the earliest of disease progression or death.

For patients with disease progression or death:

- Duration of DC [days] = date of outcome – date of randomisation + 1

For patients without disease progression or death:

- Duration of DC (censored) [days] = date of outcome – date of randomisation + 1

The censoring rules for DC (i.e. outcome and date of outcome) are described in Table 7.5: 1. The time frame for the primary assessment of duration of DC will be from randomisation until the earliest of disease progression, death or the time point of the primary PFS analysis (refer to Section 7.3).

Kaplan-Meier estimates will be used to calculate median duration of DC for each treatment group.

Objective response

OR will be analysed in terms of OR rate (ORR), defined as the proportion of patients with best overall response of CR or PR. The ORR will be calculated for each treatment group, overall and within each level of the stratification factors. Proportions will be presented with 95% CIs. A logistic regression model adjusting for the stratification factors where appropriate will be used to compare the ORR between the two treatment groups.

For the primary assessment of OR, tumour imaging will be performed every 8 weeks up to week 80 and every 12 weeks thereafter until the earliest of disease progression, death or last evaluable tumour assessment before the start of subsequent anti-cancer therapy or the time point of the primary PFS analysis (refer to Section 7.3).

As per RECIST 1.1 guidance confirmation of OR is not a requirement for randomised trials.

Time to pain progression or intensification of pain palliation
Xentuzumab may delay the time to pain worsening. To investigate this, each patient's pain severity and usage of pain palliation will be assessed. Time to pain progression or intensification of pain palliation is defined as the time from randomisation until the earliest of a clinically significant increase in pain (≥2-point increase from baseline in the BPI-SF Item 3) without a decrease in analgesic use, intensification in pain palliation (≥2-point increase in the 8-point AQA) or death.

For patients with 'event' as an outcome for pain progression/intensification of pain palliation:

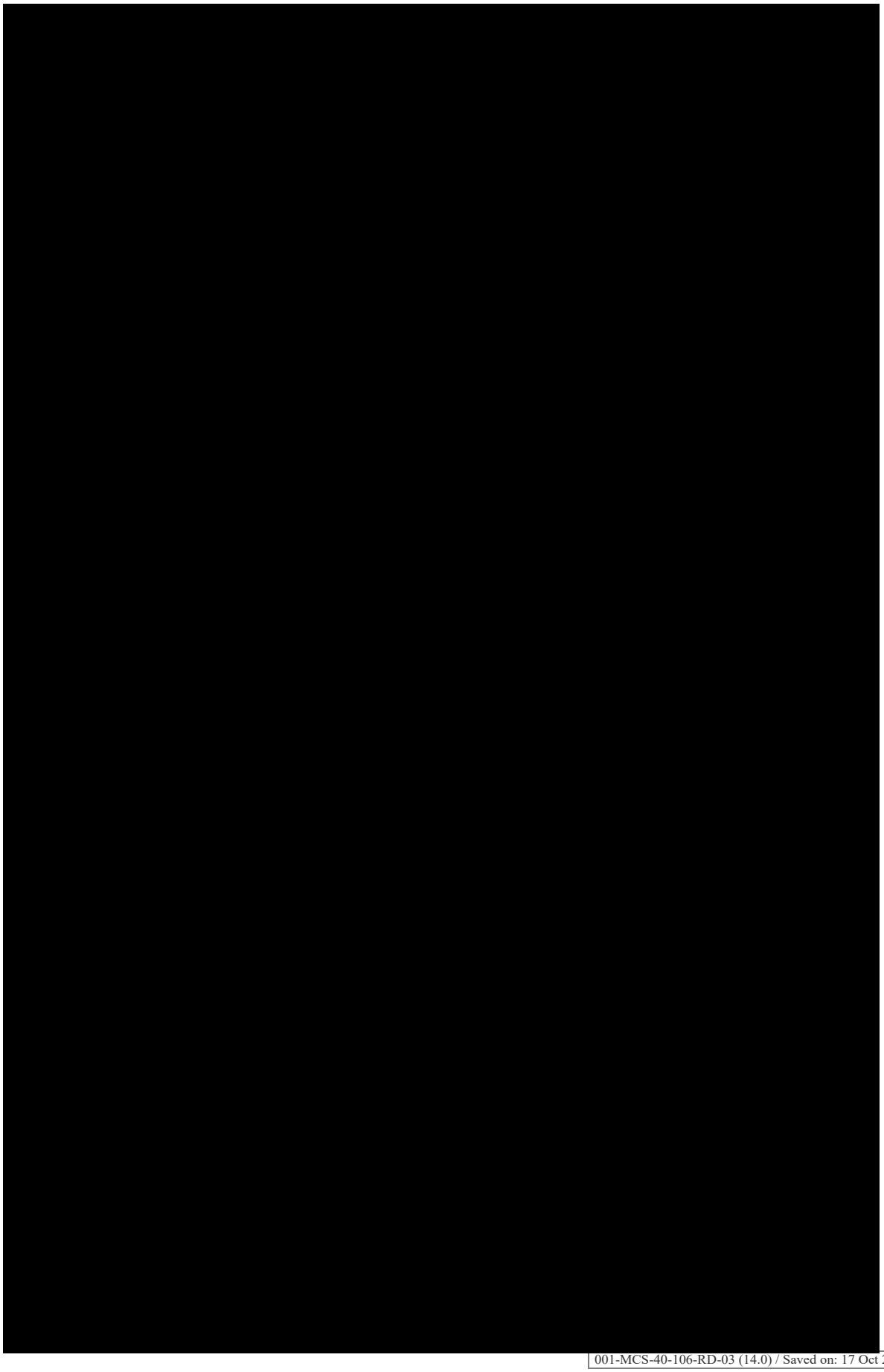
- Progression/intensification [days] = date of outcome – date of randomisation + 1.

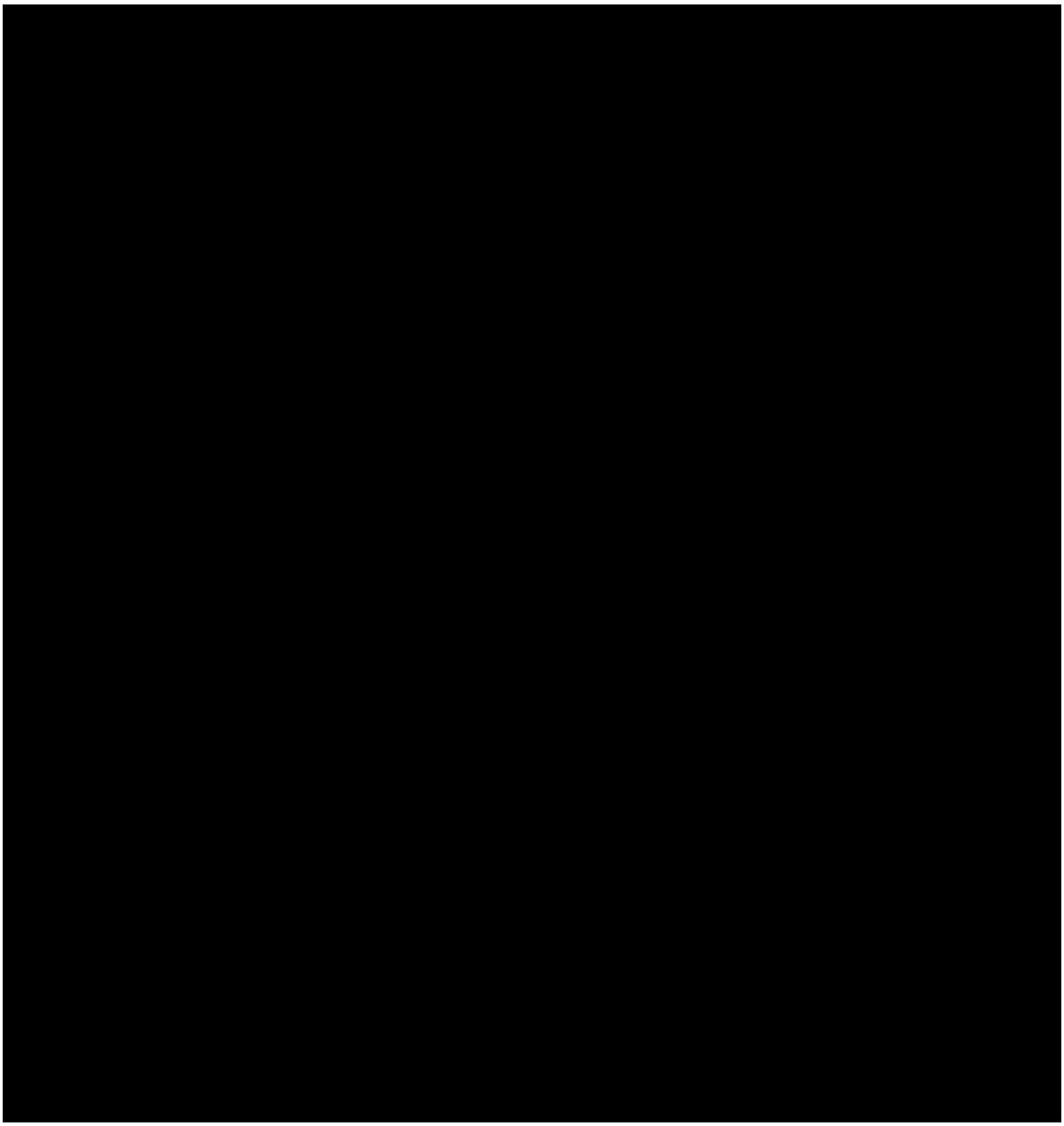
For patients with 'censored' as an outcome for pain progression/intensification of pain palliation:

- Progression/intensification (censored) [days]=date of outcome – date of randomisation + 1

The censoring rules for time to progression/intensification (i.e. outcome and date of outcome) will be described in the TSAP. Time to progression/intensification will be analysed using the same statistical methods as for the primary endpoint.

The time frame for the primary assessment will be from randomisation until the earliest of pain progression, intensification of pain palliation, death or the time point of the primary PFS analysis (refer to Section 7.3).





7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 42 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. As the treatment arms are made up of a combination of individual treatments a patient may have multiple last doses of treatment; therefore the last dose of study medication is defined as the latest of these.

All treated patients will be included in the safety analysis, according to the actual trial medication they received. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.4 INTERIM ANALYSES

As the trial will be conducted as a double-blind trial, an independent external DMC will be established to periodically assess the progress of the clinical trial, including un-blinded safety and efficacy assessments.

A decision as to whether or not the trial is expanded into a Phase III trial will be made by the DMC at the time-point of the primary PFS analysis for this Phase II trial. In order to limit knowledge of the criterion for expansion potentially having an impact on the future conduct of the trial, the criterion for expansion will be pre-defined in the DMC charter (prior to trial initiation) and not this protocol. This analysis will be conducted after approximately 40 PFS events (predicted to occur after 30 months). Note the exception to this as specified in Section 7.3.

If the criterion for the seamless option is met and the trial is expanded into a Phase III trial then formal hypothesis testing (refer to Section 7.2) will be performed with suitable control of the overall type I error rate. In this situation the primary PFS analysis at the end of Phase II will be considered as an interim analysis. Under the null hypothesis the probability of meeting the criterion for seamless expansion and subsequently achieving a one-sided p-value of <0.0249 (see details below) is 0.0028. Analysis time-points along with alpha-spending and control are presented in Figure 7.4: 1 below.

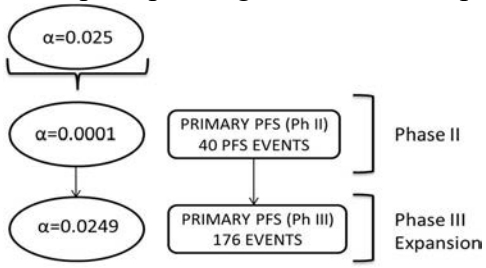


Figure 7.4: 1 Planned testing strategy

If expanded, some (technical) alpha-level of 0.0001 one-sided (see Figure 7.4: 1) will be spent at the time-point of the Phase II primary PFS analysis to adjust for the unblinded interim look by the DMC. If the alpha-boundaries are crossed at this interim analysis time point there are no plans to stop the trial early. A group sequential design user defined alpha-spending function has been used to calculate the final level leading to a nominal level of approximately 0.0249 (ADDPLAN v6.1.1). The nominal level available will be recalculated based on the actual information fraction at the interim, but keeping the alpha spent at 0.0001 for the interim look.

In order to integrate the secondary endpoint of OS into the confirmatory testing strategy in a hierarchical manner, the same alpha-spending function as used for the primary PFS endpoint will be applied. Note that although OS is integrated into the testing strategy it will not be powered for OS and a significant OS benefit is not necessarily expected. The study is considered positive if the primary hypothesis on PFS can be rejected.

Further details will be provided in a protocol amendment if the seamless option is met and the trial is expanded.

7.5 HANDLING OF MISSING DATA

In general missing efficacy data will not be imputed and all reasonable efforts will be taken during the study to obtain such data. Patients with unknown vital status, missing tumour imaging data and missing PRO assessments will be censored for time to event analyses as detailed below.

Table 7.5: 1 describes how patients will be classified for the analysis of PFS. Sensitivity analyses will examine the effect of using alternative rules.

Table 7.5: 1 Derivation rules for PFS

Situation	Outcome	Date of outcome
No baseline radiological assessment		
Death on or before the second planned radiological assessment	Event	Date of death
Alive or death after second radiological assessment	Censored	Date of randomisation
Without post-baseline radiological assessments		
Vital status is unknown or known to be alive	Censored	Date of randomisation
Death prior or on the second planned radiological assessment	Event	Date of death
Death beyond the second planned radiological assessment	Censored	Date of randomisation
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		

Table 7.5: 1 Derivation rules for PFS (cont'd)

Alive and not progressed, no more than one consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, two or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, zero or one missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but two or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessment
Death but no progression, zero or one missed radiological assessment prior to death	Event	Date of death
Death without progression, but two or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to a death	Censored	Date of randomisation

For endpoints related to OR and DC the rules defined above, where applicable, will be followed.

Table 7.5: 2 describes how patients will be classified for the analysis of death. Patients will be censored at the date of last contact if the investigator is no longer able to contact a patient or caregiver, and vital status cannot be determined otherwise, provided that no other information indicates that the patient was near death at that point.

Table 7.5: 2 Derivation rules for OS

Status at time of analysis	Outcome	Date of outcome
Death and the date of death is known	Event	Date of death
Death and date of death is unknown	Event	Date of last contact when the patient is known to be alive + 1 day
Alive	Censored	Date of last contact when the patient is known to be alive
Unknown	Censored	Date of last contact when the patient is known to be alive

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment with a 1:1 ratio (xentuzumab in combination with everolimus and exemestane: everolimus and exemestane alone).
Randomisation will be stratified by the following factors:

- Presence of baseline bone-only metastases (Yes, No)
- Prior CDK4/6 inhibitor treatment (Yes/No)

BI will arrange for the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable.

The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

For the primary endpoint of PFS, it is assumed that xentuzumab in combination with everolimus and exemestane will increase the median from 9.9 months (R16-0802) in the everolimus and exemestane alone group to 19.8 months. Assuming an exponential distribution, this is equivalent to a reduction in the risk for progression of disease or death of 50%, corresponding to an underlying hazard ratio (HR) of 0.50. With 80 eligible patients randomised over a 15 month period, 40 PFS events are predicted to be reached on average around 30 months after the first patient is randomised. This assumes approximately 20% of patients randomised will either drop out of the trial without evidence of disease progression or be assessed as non-PD by independent assessment when the investigator assigned disease progression. If this proportion differs significantly from the 20% assumed then the number of patients randomised may be increased in order to observe 40 PFS events in a timely manner, but the number of patients randomised will not exceed 100 patients.

Table 7.7: 1 shows the probability of observing various HR thresholds for different underlying (true) HR values and accrued PFS events.

Table 7.7: 1 Probability (%) of observed HR for a range of underlying HRs and PFS event numbers

PFS Events	Underlying (True) HR	Probability[1] observing HR			
		≤0.50	**≤0.60**	**≤0.75**	**>0.75**
50	**HR=1.00**	0.7%	3.5%	15.5%	84.5%
40		1.4%	5.3%	18.1%	81.9%
30		2.9%	8.1%	21.5%	78.5%
50	**HR=0.60**	26.0%	50.0%	78.5%	21.5%
40		28.2%	50.0%	76.0%	24.0%
30		30.9%	50.0%	72.9%	27.1%
50	**HR=0.50**	50.0%	74.0%	92.4%	7.6%
40		50.0%	71.8%	90.0%	10.0%
30		50.0%	69.1%	86.7%	13.3%
50	**HR=0.40**	78.5%	92.4%	98.7%	1.3%
40		76.0%	90.0%	97.7%	2.3%
30		72.9%	86.7%	95.7%	4.3%

1 Calculated using the approximate normal distribution of the estimated log HR

With 40 PFS events, if the underlying HR is 0.50, the chance of observing a treatment effect with HR of ≤0.60 is 71.8%, while the chance of observing a treatment effect with HR of ≤0.75 is 90.0%. Also, if the underlying HR is 1.0, the chance of observing a treatment effect with HR of ≤0.60 is 5.3%, while the chance of observing a treatment effect with HR of ≤0.75 is 18.1%. If the PFS events were increased from 40 to 50, the probability of observing a treatment effect with HR of ≤0.60 is increased by 2.2% (from 71.8% to 74.0%) for an underlying HR of 0.50, similarly for a treatment effect with HR of ≤0.75 the increase in probability is 2.4%.

Probabilities of 71.8 or 90%, respectively, based on 40 PFS events and an underlying HR of 0.50 is considered high enough to provide evidence that will allow an informed decision to be made in terms of the next stages of development.

The trial includes a seamless option for the expansion of the ongoing Phase II trial into a Phase III trial provided the predefined criterion (to be defined in the DMC charter) is met after 40 PFS events have been observed.

If the trial meets the criterion for expansion a further 220 patients will be randomised, so 300 patients in total, 150 per treatment arm. Primary analysis would be planned after approximately 176 PFS events, 40 from the primary Phase II analysis time-point plus an additional 136 events after this time-point. With 220 additional patients randomised into the expansion part at a constant rate over a 14 month period, 176 PFS events are predicted to be reached on average around 64 months after the first patient is randomised into the Phase II trial. This includes a 4-month gap between the Phase II results and starting the expanded trial. It is expected that approximately 20% of patients randomised will either drop out of the trial without evidence of disease progression or be assessed as non-PD by independent assessment when the investigator assigned disease progression. This has been accounted for with the planned total of 300 patients to be randomised. Note as for the Phase II part if the drop-out rate differs significantly from 20% the total number of patients randomised may need to be increased from 300, but will not exceed 375.

The patient numbers have been chosen to provide a sufficient amount of efficacy and safety data for submission. A standalone Phase III trial, with an assumed HR of 0.60 and 176 events, would achieve an overall power of at least 90% controlling the overall type I error at 2.5% (one-sided). Also, when considering solely the expansion part with 136 events it is ensured that based on an assumed HR for the expansion part of 0.60 the respective one-sided (second stage) p-value would be less than 0.05 in 90% of the cases. Thereby it is assumed that the event size for the second stage is sufficiently large to allow for informed decision making on homogeneity across the two trial parts in the case of the seamless option being met.

Note that although OS is included in the confirmatory testing strategy, if the trial is expanded, no power calculations have been performed as a significant OS benefit is not anticipated, due to unequal post-progression treatment being expected to obscure the effect of xentuzumab relative to placebo.

8 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), European Directive 2001/20/EC and/or the EU regulation 536/2014 once coming into force, and other relevant regulations.

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

CRFs for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the Sponsor or Sponsor appointed CRO, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)

- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).

- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The Sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in- house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator/institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the clinical research associate (CRA), auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:
The Sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

Exemptions from expedited reporting are described in Section 5.2.6.2, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and

disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers. Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as when the analysis of the LSLVSE (see below) is completed and patients have completed FU1 visit see Section 3.3.4.1.

The **"Last Subject Last Visit Primary Endpoint"** (LSLVPE) is defined as the date when the required number of PFS events has occurred for primary endpoint analysis, see Section 7.3.

The **"Last Subject Last Visit Secondary Endpoint"** (LSLVSE) is defined as the date when patients have completed FU1.

The "**Last Subject Last Treatment"** (LSLT) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LSLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as

specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the Sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written after the LSLVSE, see also Section 7.3. Any data collected in this trial after this will be covered by a revision to the CTR.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The Coordinating Investigators are responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A SC consisting of independent experts and Sponsor representatives will be established to support the Coordinating Investigators. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the Sponsor and also summarised in a SC charter filed in the TMF.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety and efficacy data as well as results of Phase II primary PFS analysis, patients' pattern of progression on trial treatment and post-progression information. The DMC will receive urgent significant safety concerns for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend on continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate authorities, IRBs/IECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain an electronic ISF.

BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,

- ensure appropriate training and information of Clinical Trial Managers, CRAs, and investigators of participating countries.

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

Data Management and Statistical Evaluation may be performed by BI or delegated to a CRO. Delegation of responsibility and details of which SOPs are applicable will be documented.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

Boehringer Ingelheim may appoint additional CROs for specialist services such as central laboratory analyses for retrospective analysis of HR+/HER2- status and logistics of all tissue and blood samples, central collection of HRQOL data, central imaging, radiomic assessments, provision of IRT, and trial medication logistics. Full documentation will be stored in the TMF. In addition each site will have an ISF containing all trial documents relevant for the site. Details will be provided in respective manuals. Trial documents relevant for the site will be available in ISF.

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10 APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD), BIOMARKER (BM) AND ANTI-DRUG-ANTIBODY (ADA) AND NEUTRALIZING ANTIBODY (NAB) SAMPLING

As of 29 Sept 2021, samples will no longer be collected for ongoing patients.

Table 10.1: 1 Time schedule for PK, ADA, nAb, biomarker and cytokine sampling at screening and during treatment, at EOT, and FU

If a patient misses xentuzumab/placebo infusions due to drug holidays replacement samples for **PK, ADAs, nAbs** should be drawn at -0:05 before the next infusion.

Treatment Cycle	Visit	Day	Event + Comment	Planned Time [hh:min]	Event	PK Xentuzumab	ADA	nAB	Free IGF-1	Total IGF-1 Total IGF-2	Bone remodelling markers[3]	Cytokine samples	cfDNA	Genomic DNA
C1	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X	X	X	X	X	X	X
			Start of xentuzumab infusion	0:00	Drug administr.									
			15 (+/- 10) minutes after end of infusion	1:15	Blood sampling	X						X		

[3] Bone remodelling markers are blood and urine samples. Blood samples are taken at sites at the time points indicated in Table 10.1:1. Urine samples must be from the second morning void. When this occurs prior to visiting the clinic, the sample should be collected at the patient's home and brought to the respective visit.

Treatment Cycle	Visit	Day	Event + Comment	Planned Time [hh:min]	Event	PK Xentuzumab	ADA	nAB	Free IGF-1	Total IGF-1 Total IGF-2	Bone remodelling markers [3]	Cytokine samples	cfDNA
C1	V3	15	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X					
C2	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X	X	X		X	
			Start of xentuzumab infusion	0:00	Drug administr.								
			15 (+/- 10) minutes after end of infusion	1:15	Blood sampling	X			X			X	
	V3	15	Up to 1 hour before start of infusion	-0:05	Blood sampling						X		
C3	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X					X
C4	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X			X		
C6	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X				X	

Treatment Cycle	Visit	Day	Event + Comment	Planned Time [hh:min]	Event	PK Xentuzumab	ADA	nAB	Free IGF-1	Total IGF-1 Total IGF-2	Bone remodelling markers[3]	Cytokine samples	cfDNA
C12	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X					
C24	V1	1	Up to 1 hour before start of infusion	-0:05	Blood sampling	X	X	X					
EOT	EOT	0-14	End of Treatment Visit 0-14d after permanent discontinuation of study medication	998:00	Blood sampling	X	X	X			X		X
EOR-FU1	EOR-FU1	42	End of Residual effect period and follow-up 1	999:00	Blood sampling	X	X	X					
FU-PD	FU-PDx		At the time of PD for patients who did not progress at EOT										X

10.2 RECOMMENDATIONS FOR ADVERSE EVENT TREATMENT

10.2.1 Management of Diarrhoea

Diarrhoea may occur and although usually mild to moderate, it may lead to dehydration and require treatment modification or discontinuation, so early management is essential (Table 10.2.1: 1). At the time of treatment initiation patients should be given a supply of anti-diarrhoeal medication such as loperamide to keep with them at all times or access to anti-diarrhoeal medication should be confirmed, and patients should be counselled on the appropriate use.

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

Table 10.2.1: 1 Grade-specific treatment recommendations of diarrhoea

Severity (CTCAE grading)	**Description**	**Treatment recommendations**
Mild (Grade 1)	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; anti-diarrhoeal medication such as loperamide 4 mg (2 tablets) to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 h
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living (ADL)	Continue anti-diarrhoeal medication; assess for dehydration and electrolyte imbalance; consider i.v. fluids and electrolyte replacement
Severe (Grade 3)	Increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared with baseline; limiting self care ADL	See grade 2; plus: An infectious process should be ruled out with stool cultures; aggressive i.v. fluid replacement ≥24 h; hospitalisation to monitor progress; consider prophylactic antibiotics if patient is also neutropenic
Life threatening (Grade 4)	Life-threatening consequences; urgent intervention indicated	See grade 3

[*] If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTCAE grade ≤1 within 14 days, treatment must be permanently discontinued.

In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment will be decided in agreement between the Sponsor and the investigator.

10.2.2 Management of nausea/vomiting

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, it is recommended that patients are treated according to the recommendations given in Table 10.2.2: 1.

Table 10.2.2: 1 Grade-specific treatment recommendations of nausea and vomiting

CTCAE grade	Treatment recommendation
Nausea = Grade 0 and Vomiting = Grade 0	PRN recommended by investigator's discretion[1]
Nausea = Grade 1 and Vomiting = Grade 0	Antiemetic treatment[1] e.g. 5-HT3 antagonist, prochlorperazine, metoclopramide
Nausea = Grade 2 and Vomiting = Grade 0 OR Nausea = Grade 0, 1 or 2 and Vomiting = Grade 1 or 2	Antiemetic treatment[1] e.g. 5-HT3 antagonist, prochlorperazine, metoclopramide Appropriate hydration (1.5 L/m^2/day plus hydration deficit) must be ensured.
Vomiting ≥ Grade 3 or Nausea ≥ Grade 3	Antiemetic treatment[1] e.g. 5-HT3 antagonist, prochlorperazine, metoclopramide Appropriate hydration (1.5 L/m^2/day plus hydration deficit) must be ensured

1. Antiemetic treatment should follow the recommendations given in the National Comprehensive Cancer Network (NCCN) guidelines for antiemesis or the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC) (R06-0986).

10.3 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in R01-0787

10.4 TUMOUR RESPONSE ASSESSMENT ACCORDING TO MODIFIED RECIST 1.1 CRITERIA

The RECIST response evaluation criteria version 1.1 will be adhered to as described in the guidelines published in the European Journal of Cancer (R09-0262) and the accompanying articles. Trial personnel involved in tumour assessment for this trial must be trained and knowledgeable of RECIST criteria version 1.1.

Tumour assessments should include CT scans of the chest, abdomen, pelvis and a brain CT/ MRI as well as a bone scan at screening. If clinically indicated, imaging of any other known or suspected site of disease (e.g. breast) using an appropriate method (CT scan, MRI, etc.) should be performed. The same radiographic procedure must be used throughout the trial. All images acquired and skin lesion photos will be sent to a central imaging CRO. If mammography is additionally conducted during clinical routine, it should also be sent for central imaging assessment together with any correlative images. Breast-ultrasound and biopsy data, if available, will be provided to the central imaging CRO for independent review by Sponsor data management. As of 29 Oct 2021 due to the outcome of the study, images no longer will need to best sent to CRO for independent review.

The preferred method of assessment is a spiral CT scan with i.v. and oral contrast, unless i.v. and/or oral contrast are medically contraindicated. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

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

Bone scans (using 99m-technetium polyphosphonate scintigraphy) must be done at screening. During the trial, bone scans must then be repeated as specified in the Flow Chart with every other CT scan in patients with bone metastasis at baseline. An additional bone scan will be performed at week 8. A bone scan shall always be assessed in correlation with anatomical imaging, CT, MRI, using a combination of modified RECIST 1.1 with MDA criteria (Table 10.4:4), as outlined in detail below in Tables 10.4:1 and 10.4:2 for target and non-target lesions.

For the purposes of this trial, patients should be re-evaluated for response at intervals described in the Flow Chart. In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

Follow-up tumour assessments must utilise the same CT/MRI/photographic method and acquisition technique (including use or non-use of i.v. contrast) as were used for screening assessments to ensure comparability. A chest X-ray or skeletal X-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of CT/MRI/bone scan. Documentation of new visceral disease by ultrasound alone is not sufficient for means of this clinical trial.

Only those patients who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. Patients with disease manifestation in bone only will be evaluated according to RECIST 1.1 with modifications for assessment guidance and clarification following modified MDA criteria, as outlined below in Table 10.4:4.

Measurability of tumour at baseline

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm (by CT scan, MRI, caliper measurement), or if reconstructed slice thickness is >5 mm use double the slice thickness as minimum target lesion measurement, or ≥20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15 mm are also measurable.

Measurable disease

Measurable disease requires the presence of at least one measurable lesion.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement, or if reconstructed slice thickness is >5 mm use double the slice thickness as minimum target lesion measurement, or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques, soft-tissue and skin lesions that are <10 mm or are not documented by imaging and photography, bone lesions that are either <10 mm or are not lytic or mixed.

New lesions in irradiated fields

At baseline, previously irradiated lesions should not be used as indicator lesions unless they have progressed since irradiation. New lesions occurring in previously irradiated fields can be used as target lesions.

Methods of measurement

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

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

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

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Baseline Documentation of Target and Non-target Lesions
Modified RECIST version 1.1: All measurable lesions up to a maximum of five lesions in total can be selected. These five lesions shall be representative of all involved non-visceral anatomical locations. However if a patient presents with target lesions only in bone or in lymph nodes or in soft tissue, five lesions within one anatomical location, bone, nodes, soft tissue, can be identified as target lesions. The longest diameter (LD) will be measured for all lesions except lymph nodes, for which shortest diameter (SD) perpendicular to the LD is used. All target lesions will be recorded and numbered at baseline. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of diameter (SOD) for all target lesions will be calculated (using ShD for lymph nodes and LD for all other lesions) and reported as the baseline SOD. The baseline SOD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.4: 1).

Table 10.4: 1 Evaluation of target lesions with rules for bone lesions according to RECIST 1.1 and modified MDA criteria

Complete Response (CR) For target bone lesions:	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. • Complete sclerotic fill-in of lytic lesions on XR or CT • Normalization of bone density on XR or CT • Normalization of signal intensity on MRI • Normalization of tracer uptake on bone scan
Partial Response (PR) For target bone lesions:	At least a 30% decrease in the SOD of all target lesions taking as reference the baseline SOD. • Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT. • Osteoblastic flare • re - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease • subjective decrease in tracer uptake on bone scan
Stable Disease (SD) For target bone lesions:	Neither sufficient shrinkage to qualify for PR, less than 30% decrease, taking as reference the baseline SOD, nor sufficient increase to qualify for PD, less than 20% increase, taking as reference nadir, the smallest SOD recorded on study (including baseline). No new bone metastases.
Progression (PD) For target bone lesions:	At least a 20% increase in the SOD of all target lesions taking as reference the smallest SOD (nadir) recorded on study (including baseline), together with an absolute increase in the SOD of at least 5 mm. OR The appearance of one or more new unequivocal lesions. • Subjective increase in tracer uptake on bone scan • New bone metastases

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.4: 2).

Table 10.4: 2 Evaluation of non-target lesions and new lesions with rules for bone lesions according to RECIST 1.1 and modified MDA criteria

Complete Response (CR) For non-target bone lesions:	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis) • Complete sclerotic fill-in of lytic lesions on XR or CT • Normalization of bone density on XR or CT • Normalization of signal intensity on MRI • Normalization of tracer uptake on bone scan
Non-CR/Non-PD For non-target bone lesions:	Persistence of one or more non-target lesions • Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT • Osteoblastic flare – • Interval visualization of lesions with sclerotic rims or new sclerotic lesions and absence of progressive bony disease • subjective increase or decrease in the size of ill-defined lesions on XR, CT, or MRI not sufficient for either PD or CR • subjective increase or decrease in tracer uptake on bone scan not sufficient for PD or CR
Progression (PD) For non-target bone lesions:	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. • Subjective substantial increase in the size of ill-defined lesions on XR, CT, or MRI • Subjective substantial increase in tracer uptake on bone scan • New bone metastases

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status if in accordance with standard of care and after consent from patient based on institutional guidelines.

Evaluation of best response to study treatment

The best response to study treatment is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest SOD recorded on study). The tables below are showing the time point response for patients with target (Table 10.4: 3) and non-target only disease (Table 10.4: 4). The time point responses for each patient are used to determine their best response to trial treatment.

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

Table 10.4: 3 Time point response: patients with target disease

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

Table 10.4: 4 Time point response: patients with non-target disease

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

A "Non-CR/non-PD is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Response evaluation rules for bone lesions aligned with the MDA criteria
Target and non-target assessment are adapted in alignment with the MDA criteria (R17-4024; see Table 10.4: 5). Bone lesion measurements will not be performed perpendicular bidimensional, as described in MDA, but unidimensional following RECIST 1.1. The %-changes of target lesion measurements follow RECIST 1.1, at least 30% decrease for PR and at least 20% increase for PD accordingly. Non target lesions' assessment will not be based on quantitative analysis, but according to RECIST 1.1 on qualitative assessment only.

In this patient population with predominantly osteolytic or mixed skeletal metastases from breast cancer, a mere lesion counting on bone scans is not sufficient and would be medical incorrect and inacceptable. Thus a combination of the RECIST-defined assessment of bone lesions in conjunction with the more detailed description of a joined assessment of bone scan and anatomical imaging is scientifically reasonable. 99m-technetium bone scan alone may show metabolic activity with tracer uptake, which could be misinterpreted as a false positive progression for responding and healing lesions, and vice versa non-activity with lack of tracer

uptake could be misinterpreted as false negative implying response, PR or CR, for metabolically inactive lesions. CT or MRI alone may only detect large bone lesions but may not be sensitive enough for small, faint or new lesions. The combined evaluation with both methods and both criteria thus allows for a more detailed, more precise assessment of the skeletal disease and its response to treatment or lack thereof.

Table 10.4: 5 MD Anderson (MDA) criteria*

Response category	**Criteria**
Complete Response	Complete sclerotic fill-in of lytic lesions on XR or CT Normalization of bone density on XR or CT Normalization of signal intensity on MRI Normalization of tracer uptake on BS
Partial Response	Development of a sclerotic rim or partial sclerotic fill-in of lytic lesions on XR or CT. Osteoblastic flare - Interval visualization of lesions with sclerotic rims or new sclerotic lesions in the setting of other signs of PR and absence of progressive bony disease ≥50% decrease in measurable lesions on XR, CT, or MRI ≥50% subjective decrease in the size of ill-defined lesions on XR, CT, or MRI ≥50% subjective decrease in tracer uptake on SS
Progressive Disease	≥25% increase in size of measurable lesions on XR, CT, or MRI ≥25% subjective increase in the size of ill-defined lesions on XR, CT, or MRI ≥25% subjective increase in tracer uptake on SS
Stable Disease	No change <25% increase or <50% decrease in size of measurable lesions <25% subjective increase or <50% subjective decrease in size of ill-defined lesions No new bone metastases

*Measurements are based on the sum of a perpendicular, bidimensional measurement of the greatest diameters of each individual lesion (R17-4024).

10.5 HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRES

10.5.1 BPI-SF

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

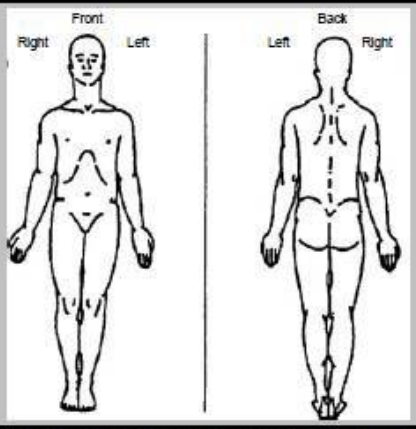
Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/___/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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10.5.2 NFBSI-16

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

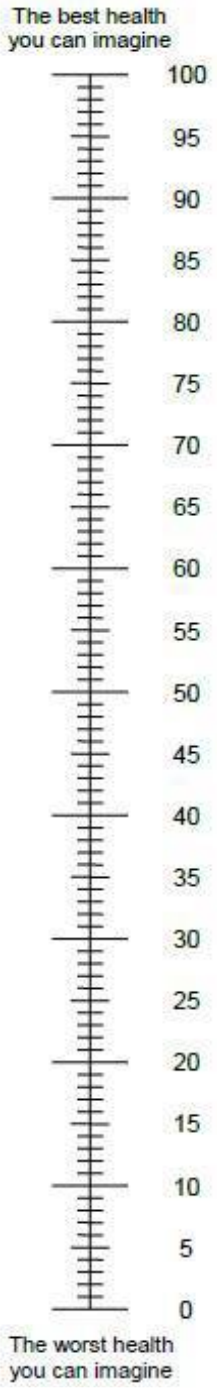
			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy.....	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
	HI7	I feel fatigued.....	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	GF5	I am sleeping well.....	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	N6	I have mouth sores.....	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life.....	0	1	2	3	4
	GF7	I am content with the quality of my life right now.....	0	1	2	3	4

10.5.3 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



I am extremely anxious or depressed ❑

10.5.4 PRO-CTCAE

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

7.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

10.6 COCKCROFT-GAULT FORMULA

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \text{ if } Female]}{72 \cdot \text{SerumCreatinine}(\text{in mg/dL})}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot \text{Constant}}{\text{SerumCreatinine}(\text{in µmol/L})}$$

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 Jun 2018
EudraCT number **EU number**		2017-003131-11
BI Trial number		1280-0022
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		Xenera™ 1: A multi-centre, double-blind, placebo-controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in post-menopausal women with HR+ / HER2- metastatic breast cancer and non-visceral disease
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		All sections
Description of change		Typos and minor corrections
Rationale for change		To provide correct protocol language
Section to be changed		All sections
Description of change		Phase III was changed to Phase II
Rationale for change		To reflect the change of trial design
Section to be changed		Synopsis
Description of change		Number of participating countries and sites was deceased
Rationale for change		Update of number of trial sites and countries
Section to be changed		Synopsis
Description of change		Update of trial objectives
Rationale for change		To reflect the change of trial design
Section to be changed		Synopsis
Description of change		Patient numbers were decreased
Rationale for change		Update of patient numbers for Phase II
Section to be changed		Synopsis
Description of change		Clarification that effusion should be malignant
Rationale for change		More details are provided to exclusion criterion number 3

Section to be changed		Synopsis
Description of change		Statistics part was adapted
Rationale for change		Change from Phase III to Phase II statistics
Section to be changed		Flow Chart
Description of change		Biomarker sampling and biobanking was adjusted
Rationale for change		Biomarker sampling and biobanking was changed to Phase II requirements
Section to be changed		1. Medical background
Description of change		Minor corrections
Rationale for change		Update of recent changes in therapies
Section to be changed		1.2.1 Xentuzumab
Description of change		Minor corrections
Rationale for change		Update with recent IB data
Section to be changed		1.3 Rationale for performing the trial
Description of change		Most current numbers are provided from the analysis of trial 1280.4
Rationale for change		To provide most current data on which this trial is based on
Section to be changed		2.1.1 Main objectives
Description of change		Main objectives were adapted
Rationale for change		Update of Phase III to Phase II objectives of the trial
Section to be changed		3.1 Overall trial design and plan
Description of change		Paragraphs added for the option to expand seamlessly into Phase III if a pre-defined criterion is met Figure for trial design adapted
Rationale for change		Update on the plan to expand this Phase II seamlessly into a Phase III Provision of current figure for Phase II trial design
Section to be changed		3.2 Discussion of trial design, including the choice of control group(s)
Description of change		Wording adapted for the option to expand seamlessly into Phase III and the change of interim analysis
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		3.3 Selection of trial population
Description of change		Update on participating sites and countries
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		3.3.3 Exclusion criteria

Description of change		Clarification that effusion should be malignant
Rationale for change		More details are provided to exclusion criterion number 3
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		Paragraph added for patients with visceral disease:
Rationale for change		Provision of more detail on how to handle mistakenly included patients with visceral disease
Section to be changed		4.1.1 Identity of IMP and comparator
Description of change		Unit strength was updated
Rationale for change		Provision of updated details to IMP because a different formulation is used
Section to be changed		4.1.6.1 Blinding
Description of change		Description of how to handle blinding if the trial seamlessly goes into a Phase III was added
Rationale for change		Update on the plan to expand this Phase II seamlessly into a Phase III
Section to be changed		4.4 Management of expected adverse events
Description of change		Section 4.4.4 Management of neutropenia was added
Rationale for change		Provision of guidance on neutropenia
Section to be changed		5.3.2 Methods of sample collection
Description of change		Wording was added on sampling procedure
Rationale for change		Provision of updated instructions for PK sampling
Section to be changed		5.4 Assessment of biomarkers
Description of change		Update of biomarker sampling for Phase II Further explanation on radiomics was added
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		5.6.1 Patient-reported outcomes
Description of change		An additional questionnaire (PRO-CTCAE) was added
Rationale for change		Introduction of this PRO will address patients assessment of AEs in more detail
Section to be changed		6.2.1 Screening
Description of change		Update on biomarker sampling
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		7. Statistical methods and determination of sample size
Description of change		Section 7 was partly re-written
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		8.6 Trial milestones
Description of change		Adaptation of trial milestones

Rationale for change		Update for change from Phase III to Phase II
Section to be changed		10.1 Time schedule for PK, PD and ADA and nAB blood sampling
Description of change		Update of biomarker sampling for Phase II
Rationale for change		Update for change from Phase III to Phase II
Section to be changed		10.5 Health-related quality of life questionnaires
Description of change		Section 10.5.4 was added
Rationale for change		Provision of PRO-CTCAE questionnaire

11.2 GLOBAL AMENDMENT 2

Date of amendment		14 Feb 2019
EudraCT number **EU number**		2017-003131-11
BI Trial number		1280-0022
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		Xenera™ 1: A multi-centre, double-blind, placebo- controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in post-menopausal women with HR+ / HER2- metastatic breast cancer and non-visceral disease
To be implemented only after approval of the IRB / IEC / Competent Authorities		**X**
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title page
Description of change		Clinical Trial Leader updated; Xenera changed to Xenera TM
Rationale for change		Administrative change

Section to be changed		Protocol synopsis – Main Inclusion and Exclusion Criteria
Description of change		Inclusion 3 and 6, Exclusion 8 updated
Rationale for change		Inclusion 3: Clarification that biopsies cannot be performed after consent for the purpose of the trial. Inclusion 6: Administrative grammar changes Exclusion 8: Updated to match exclusion criteria in section 3.3.3

Section to be changed		Protocol synopsis – Safety Criteria
Description of change		CTCAE version 4.03 updated to version 5.0
Rationale for change		Updated to current CTCAE version

Section to be changed		Flowchart
Description of change		Screening period increased to 28 days; C2V3 added as a column in flowchart; wording to clarify biopsy not performed after consent for purpose of the trial updated; diary card added to flow chart; section on when safety labs should be taken updated; follow up period timepoints updated in table to match footnotes; minor wording changes and additions to clarify procedures to be performed (text added from main body of protocol); number of slides required to be sent to central lab added; confirmation of HER2 changed to analysis of HER2
Rationale for change		To ensure that all protocol assessments are covered in the flowchart; to ensure biopsies not performed after consent for the purpose of the trial; to relax the time window for some of the screening procedures from 14 to 28 days based on feedback from investigative sites

Section to be changed		Section 1.1 Medical Background
Description of change		Number of deaths due to breast cancer in USA and Europe updated
Rationale for change		Corrected to match reference updated in November 2018: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

Section to be changed		1.3 Rationale for performing the trial
Description of change		Additional reference added; grammar changes
Rationale for change		To provide a report on the subgroup analysis in trial 1280.4; administrative change

Section to be changed		Section 2.1.1 Main Objectives
Description of change		Grammar change
Rationale for change		Administrative change

Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Removal of language regarding fresh tissue biopsy after consent; addition of language stating archival bone biopsy samples should not be sent. Grammar changes; changes to the collection of safety data in the follow up period.
Rationale for change		Clarification that biopsies cannot be performed after consent for the purpose of the trial. Administrative changes to make protocol consistent with other sections.

Section to be changed		Section 3.2 Discussion of Trial Design, Including the Choice of Control Group(s)
Description of change		Grammar changes; clarification that only archival biopsy samples should be sent; interim analysis removed
Rationale for change		Clarification that biopsies cannot be performed after consent for the purpose of the trial; early preparations for expanding into a phase III trial will already be put into place so administrative interim analysis is no longer required

Section to be changed		Section 3.3.2 Inclusion Criteria
Description of change		Inclusion 3 updated to clarify that archival tumour sample is accepted and that bone samples should not be sent. Inclusion 6: Grammar change
Rationale for change		Clarification that biopsies cannot be performed after consent for the purpose of the trial.

Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion 22 updated to include a washout period for any restricted medications.
Rationale for change		To include wash out period.

Section to be changed		Section 3.3.4.1 Withdrawal from trial treatment
Description of change		Section updated to add that if patient required palliative radiotherapy they would need to stop trial; pregnancy removed as withdrawal criteria; additional withdrawal criteria added to state that if patient violates eligibility criteria a discussion would need to take place as to whether patient stays on trial Other grammar changes.
Rationale for change		Palliative radiotherapy updated to match section 4.2.1.3; pregnancy removed as not applicable; withdrawal due to violation of eligibility criteria added to cover the situation where it is determined that patient is not eligible after starting the trial treatment and would be better suited to a different treatment regimen e.g. discovered to have visceral disease.

Section to be changed		Section 4.1.1 Identity of the Investigational Medicinal Product (IMP) and comparator
Description of change		Duration of infusion for xentuzumab/placebo updated from about 1 hour to 1 hour
Rationale for change		Duration of infusion updated to match project standard

Section to be changed		Section 4.1.2 Background Medication
Description of change		Language changes regarding the sourcing of background medication; 10mg unit strength added with confirmation that only 2.5 and 5mg are provided centrally; additional language added about when to take background medication; grammar changes
Rationale for change		10mg unit strength added as some sites sourcing own medication will use this strength; language about when to take medication added as the requirement to take at different time on PK sampling days was removed from protocol and clarification needed on when to take treatment.

Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		Grammar changes
Rationale for change		Administrative changes

Section to be changed		Section 4.1.5 Drug assignment and administration
Description of change		Requirement for background medication to be taken after the start of the infusion on the days of PK sampling removed; grammar changes; addition of language for actions required in case of unrelated adverse events.
Rationale for change		PK for everolimus and exemstane is not being performed for this trial so no requirement to take the background medication a set time, language added in case of unrelated adverse events.

Section to be changed		4.1.6.1 Blinding
Description of change		Interim analysis removed; language added to document that there is a visual difference between xentuzumab and placebo vials and the requirement for third party blinding.
Rationale for change		Early preparations for expanding into a phase III trial will already be put into place so administrative interim analysis is no longer required; to ensure that investigators, ethics committees, institutional review boards and health authorities are aware of third party blinding concept.

Section to be changed		Section 4.1.8 Storage conditions
Description of change		Clinical trial manager updated to unblinded CRA or back up
Rationale for change		To clarify that unblinded pharmacies should contact unblinded sponsor team. Clinical trial managers will remain blinded to treatment arm.

Section to be changed		Section 4.1.9 Drug accountability
Description of change		Administrative changes
Rationale for change		Administrative changes

Section to be changed		Section 4.2 Other treatments, emergency procedures, restrictions (including sections 4.2.1.1, 4.2.1.2, table 4.2.1.2:1, 4.2.1.3, 4.2.2.1, 4.2.2.2)
Description of change		Grammar changes; fasting defined in section 4.2.2.1; additional restricted medications added
Rationale for change		Information on fasting added to match lab manual; additional restricted medications added to match exclusion criteria

Section to be changed		Section 4.3 Treatment compliance
Description of change		Information on requirement for patient diary added
Rationale for change		Administrative

Section to be changed		Section 4.4 Management of expected adverse events
Description of change		Text changed to clarify that the sections following are recommendations and should be followed unless institutional standards are available and implemented on investigator judgment; CTCAE version updated to version 5.0
Rationale for change		To ensure that investigator sites are aware that sections are recommendations and not mandated; to use latest CTCAE version

Section to be changed		Section 4.4.1 Management of stomatitis/mucosal inflammation
Description of change		Section updated to provide guidance and recommendations for sites both with and without access to dexamethasone containing mouthwashes.
Rationale for change		Updated to further clarify recommendations as well as acknowledge that dexamethasone containing mouthwashes are not available in all participating countries.

Section to be changed		Section 4.4.1.2 Treatment recommendations for established stomatitis/mucositis
Description of change		Table 4.4.1.2:1 updated; CTCAE version 4.03 updated to version 5.0
Rationale for change		To make table easier to read in cases where dexamethasone mouthwashes are not available; enable use of the most recent CTCAE version

Section to be changed		Section 4.4.2 Management of hyperglycaemia
Description of change		Section updated to clarify recommendation in case of hyperglycaemia
Rationale for change		To provide further clarification

Section to be changed		Section 5.1 Assessment of Efficacy
Description of change		Addition of language that MD Anderson criteria will also be used in selection of target and or non-target lesions in the bone; clarification that tumour response will be assessed by investigator and independent reviewer
Rationale for change		To define modification from Appendix 10.4 in the main part of protocol; clarification that investigator will also assess response

Section to be changed		Section 5.2 Assessment of Safety
Description of change		Version 4.03 CTCAE updated to version 5.0
Rationale for change		To use current version.

.2

Section to be changed		Section 5.2.2 Vital signs and ECOG performance status
Description of change		Title updated to include ECOG performance
Rationale for change		Administrative change

Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		Section updated to include fasting requirements and to clarify that safety labs can be taken on the day before infusion so long as within protocol specified visit windows.
Rationale for change		Updated to match lab manual and to provide further guidance for site staff.

Section to be changed		Section 5.2.5 Left Ventricular Ejection Fraction
Description of change		Paragraph added that clinically relevant findings should be added into CRF
Rationale for change		Administrative change

Section to be changed		Section 5.2.6 Assessment of adverse events
Description of change		CTCAE version 4.03 updated to version 5.0
Rationale for change		Enable use of the most recent CTCAE version

Section to be changed		Section 5.3.1 Assessment of pharmacokinetics
Description of change		Removal of statement regarding sample collection in case of treatment being discontinued early.
Rationale for change		In case of early treatment discontinuation patients would still follow procedures in flow chart as normal

Section to be changed		Section 5.4 (including 5.4.1, 5.4.2 and 5.4.3) Assessment of biomarkers
Description of change		Section and subsections updated to simplify the section, specify required timelines and remove duplication; updated to clarify that only archival biopsy samples should be sent; additional test to be performed (E-cadherin) on the archival tumour tissue collected; clarification that biopsy of the bone must not be provided to sponsor
Rationale for change		Section updated so that it is more easily understandable for sites as well as to clarify that fresh tissue biopsies should not be performed for the purpose of the trial; additional test added to further enhance the results from the trial.

Section to be changed		Section 5.7 Appropriateness of Measurements
Description of change		CTCAE version 4.03 updated to version 5.0
Rationale for change		Enable use of the most recent CTCAE version

Section to be changed		Section 6.2.1 Screening
Description of change		Section updated to clarify that only archival tumour tissue should be sent; that anonymized report of patients genomic breast cancer signature would be collected and entered into CRF where available; option to prolong screening period to 6 weeks removed
Rationale for change		Section updated to clarify procedures required for the trial; prolongation of rescreening period removed as screening up to 28 is allowed instead of 14 days. In case patient cannot start treatment with 28 days then there is option to rescreen patient.

Section to be changed		Section 6.2.2 Treatment period (including 6.2.2.1 and 6.2.2.2_
Description of change		Additional language added to clarify that although visit windows are allowed sites should refer back to C1V1 and ensure that treatment cycles are 28 days in duration; sentence about PK samples etc. at end of treatment simplified.
Rationale for change		Administrative

Section to be changed		Section 6.2.3 Follow up period and trial completion
Description of change		Clarification on which follow up visits are relevant to patients depending on whether or not they have started further anti-cancer therapy
Rationale for change		Administrative

Section to be changed		Section 7.2 Null and Alternative Hypotheses
Description of change		Clarification that null hypothesis for primary analysis PFS is at end of phase III; sentence added that if the trial was seamlessly expanded to phase III then end of phase II would be considered as an interim analysis.
Rationale for change		Updated due to removal of interim analysis

Section to be changed		Section 7.3 Planned Analyses
Description of change		Clarification that it will be just the trial database that is unblinded; interim analysis removed
Rationale for change		Early preparations for expanding into a phase III trial will be put into place so this administrative interim analysis is no longer required

Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		Section 7.4 Interim analysis
Description of change		Interim analysis removed, Figure 7.4.1 updated
Rationale for change		Updated due to removal of interim analysis

Section to be changed		8.7 Administrative structure of the trial
Description of change		Interim analysis removed; Clinical Monitor Local was changed to Clinical Trial Manager and Trial Clinical Monitor was changed to Clinical Trial Leader; confirmation of HER2 was changed to analysis
Rationale for change		Early preparations for expanding into a phase III trial will already be put into place so this administrative interim analysis is no longer required; Update to current role names; HER2 testing will be done but will not overrule sites initial test result

Section to be changed		9.1 Published references
Description of change		Reference for 4.03 CTCAE removed and reference for 5.00 CTCAE added
Rationale for change		References updated

Section to be changed		9.2 Unpublished references
Description of change		Additional reference added
Rationale for change		To provide a report on the subgroup analysis in trial 1280.4.

Section to be changed		Appendix 10.1 Time schedule for PK, PD, BM and ADA and nAB blood sampling
Description of change		Table updated to include genomic DNA sample as well as administrative changes to match up to Flow Chart and other sections of protocol; time window added in for sampling
Rationale for change		Administrative changes

Section to be changed		10.2.1 Management of diarrhoea
Description of change		Update of CTCAE version 4.03 to version 5.0 AE grade definitions
Rationale for change		To enable use of the most recent CTCAE version

Section to be changed		Section 10.4 Tumour response assessment according to modified RECIST 1.1 criteria
Description of change		Updated to remove language about biopsies; addition of language about biopsy after treatment being according to standard of care
Rationale for change		Biopsies should not be performed as part of the trial

11.3 GLOBAL AMENDMENT 3

Date of amendment		19 Sep 2019
EudraCT number **EU number**		2017-003131-11
BI Trial number		1280-0022
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		Xenera™ 1: A multi-centre, double-blind, placebo- controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease
Global amendment due to urgent safety reasons		
Global amendment		X

Section to be changed		Title page
Description of change		Removal of the term post-menopausal from the title of the trial
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		Protocol Synopsis-Title of trial
Description of change		Removal of the term post-menopausal from the title of the trial
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		Protocol Synopsis-Objectives
Description of change		Removal of the term post-menopausal from the objectives section.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		Protocol Synopsis-Diagnosis
Description of change		Removal of term post-menopausal term from the section.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		Protocol synopsis – Main Inclusion Criteria
Description of change		Update of the following inclusion bullets: Inclusion: 3, 4, 5, 6. Removal of two inclusion bullets regarding previous therapies.
Rationale for change		3: Modified to allow for cases where archival tissue is not available. 4: Adapted to account for various endocrine options (including more than 1 line of nsAI in premenopausal and postmenopausal patients, including the use of fulvestrant in postmenopausal patients. 5: Updated to include premenopausal patients on ovarian suppression, updated to bring criteria in line with NCCN definition. 6. Option to enroll patients with blastic lesions only has been added; for non-measurable lesions there is no difference for determination of PD and date of PD, independent of radiographic morphology. Bullets 4 and 5 removed, no longer applicable as criteria updated in section 3.3.2.

Section to be changed		Protocol synopsis – Main Exclusion Criteria
Description of change		Update of the following inclusion/exclusion bullets: Exclusion: 1, 3, 6, 8, 11, 12 and 13 added
Rationale for change		1. Patients may now have received previous PI3K therapy. Based on emerging preclinical evidence. 3. Updated to clarify visceral metastases at screening versus historical evidence of visceral metastases. 6. Updated to allow one line of chemotherapy as chemotherapy is sometimes used in patients where a rapid response is required for palliation of symptoms. 8. Updated as premenopausal women included in the trial will remain on ovarian suppression medications.
		11. Added to confirm only 1 prior line of CDK4/6 inhibitor can be used. Previously covered in inclusion 4, which has been deleted.

		12.To account for rare fetal drug exposure risk in pre-menopausal population on ovarian suppression. 13.Pre-menopausal women cannot be enrolled in trial unless on specified method of birth control, due to rare risk of pregnancy

Section to be changed		Protocol Synopsis-Statistical methods
Description of change		Addition of menopause status as a stratification factor for analysis.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		Protocol Flow Chart
Description of change		Additional line added for pregnancy and hormone level testing Bullet 10 updated to clarify that baseline imaging assessment must be performed 28 days prior to start of trial treatment as opposed to randomisation Bullet 25 added to detail pregnancy and hormone testing
Rationale for change		Administrative changes

Section to be changed		1.1 Medical Background
Description of change		Updated to provide further background on the approvals of CDK4/6 inhibitors and their use in this patient population, further information about the use of these treatments in premenopausal women on ovarian suppression, as well as the use of chemotherapy.
Rationale for change		Updates and clarifications to reflect changes in current therapies and treatment practice.

Section to be changed		1.3 Rationale for performing the trial
Description of change		Removal of the term post-menopausal from the section.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		2.1 Main objectives, primary and secondary endpoints
Description of change		Removal of the term post-menopausal from the section.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to

		adapted inclusion 7.

Section to be changed		3.1 Overall trial design and plan
Description of change		Language regarding provision of archival tissue updated.
Rationale for change		If retrospective provision of archival tissue is not possible, the patient will no longer be excluded.

Section to be changed		3.2 Discussion of trial, design, including the choice of control groups
Description of change		Language regarding provision of archival tissue updated. Use of everolimus and exemstane according to recommendations by guidelines
Rationale for change		To reflect changes in archival tissues collection as per inclusion criteria 3 If retrospective provision of archival tissue is not possible, patient will not be excluded

Section to be changed		3.3.1 Main Diagnosis for Trial Entry
Description of change		Removal of the term post-menopausal from the section.
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		3.3.2 Inclusion Criteria
Description of change		Modification of Inclusion Criteria as listed below.
Rationale for change		Inclusion 3: Modified to allow for cases where archival tissue is not available Inclusion 4: Adapted to account for various endocrine options in premenopausal and postmenopausal patients, including use of fulvestrant in postmenopausal patients. Inclusion 5 and 6: Deleted to account for changes in standard of care for endocrine therapy. The protocol aims at a population with at least 1 line of prior endocrine therapy, but does not now exclude more than 1 line of treatment. Based on a recent trial the median PFS of fulvestrant was less than 6 months and therefore patients who have used fulvestrant for less than 6 months are no longer excluded. Inclusion 7: Updated to allow the inclusion of

		premenopausal patients on ovarian suppression. Definition of post-menopausal status updated as per NCCN guidelines. Inclusion 9. Option to enroll patients with blastic lesions only added. For non-measurable lesions, there is no difference for determination of PD and date of PD, independent of radiographic morphology.

Section to be changed		3.3.3 Exclusion Criteria
Description of change		Modification of Exclusion Criteria
Rationale for change		Exclusion 1: Removal of the requirement for patients not to have received previous PI3K therapy. Based on emerging preclinical evidence. Exclusion 3: Update to define visceral metastases at screening versus historical evidence Exclusion 8: One line of chemotherapy is sometimes used in patients where a rapid response is required for palliation of symptoms Exclusion 11: Updated as hormonal treatments are required for premenopausal patients as per revised inclusion 7 Exclusion 24: Exclusion criteria added. More than one line of CDK4/6i is not considered standard in current practice (was previously included in inclusion criteria 4). Exclusion 25: To account for rare fetal drug exposure risk in pre-menopausal population on ovarian suppression. Exclusion 26: Pre-menopausal women cannot be enrolled in trial unless on specified method of birth control, due to rare risk of pregnancy

Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		Addition of withdrawal criteria regarding women on ovarian suppression remaining in post-menopausal state. Addition of pregnancy as withdrawal criteria.

Rationale for change		Pre-menopausal women on ovarian suppression have been allowed in the trial under protocol version 4 but it is important that they remain in post-menopausal state throughout the trial. Women must not get pregnant whilst on study.

Section to be changed		4.1.2 Background medication
Description of change		Section updated to clarify that everolimus and exemestane are not considered as investigational in this trial but that where local regulatory requirements mandate it then either may be considered as IMP and would be provided as labelled product to the sites. Section update to remove 10mg as a unit strength used in trial as no supplies will be sourced by sites after approval of amendment.
Rationale for change		The use of everolimus in premenopausal women on ovarian suppression may be considered as off-label use in some countries and therefore considered investigational.

Section to be changed		4.1.5 Drug assignment and administration of doses of each patient
Description of change		The section on sourcing of background therapy by sponsor was updated.
Rationale for change		Background therapy will be provided to all sites, either via a local supplier or from the central depot and managed through the IRT system.

Section to be changed		4.1.7 Packaging, labelling, and re-supply
Description of change		Term revised to investigational products
Rationale for change		Everolimus may be considered as investigational in some countries.

Section to be changed		4.1.9 Drug accountability
Description of change		Updated based on new strategy for supplying everolimus and exemestane to the sites.
Rationale for change		As everolimus may be considered as investigational in some countries.

Section to be changed		4.2.1.3 Concomitant treatments
Description of change		Further information added about the requirement for treatments and monitoring for pre-menopausal women included in the trial

Rationale for change		Ovarian suppression requirements for the inclusion of premenopausal women updated

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Further information added about the requirement for treatments and monitoring for pre-menopausal women included in the trial Administrative clarification regarding concomitant treatment
Rationale for change		Ovarian suppression requirements for the inclusion of premenopausal women updated Administrative correction

Section to be changed		4. 4. 4 Management of neutropenia
Description of change		Administrative guidance for infection guidance
Rationale for change		Administrative clarification and reference added for management of xentuzumab and everolimus during infection

Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Inclusion of pregnancy testing, FSH and estradiol hormone lab parameters.
Rationale for change		Addition of pregnancy and hormone lab values due to addition of premenopausal women on ovarian suppression

Section to be changed		5.2.6.2.2 AE reporting to sponsor and timelines
Description of change		Removal of fax as required method to send SAE forms to BI
Rationale for change		Administrative change to allow flexibility in how SAE forms are sent to BI.

Section to be changed		5.2.6.2.3 AE reporting and collection- Pregnancy
Description of change		Addition of pregnancy statement due to inclusion of pre-menopausal
Rationale for change		To define an established reporting and follow up process in the event of pregnancy

Section to be changed		5.4.1 Evaluation of molecular and biochemical biomarkers in tumor tissue
Description of change		Language regarding provision of archival tissue updated.
Rationale for change		To reflect changes in archival tissues collection as per inclusion criteria 3 as no longer mandatory

Section to be changed		6.2.1 Screening
Description of change		Language regarding provision of archival tissue updated.
Rationale for change		To reflect changes in archival tissues collection as per inclusion criteria 3 as no longer mandatory

Section to be changed		7.1 Statistical Design
Description of change		Removal of post-menopausal term from title Addition of menopause status (pre/post) as a stratification factor for analysis
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		7.3 Planned Analyses
Description of change		Change of expected timeframe for PFS analysis from 18 to 15 months. Addition of menopause status (pre/post) as a stratification factor for analysis
Rationale for change		Confirmation of adjusted timelines Inclusion of premenopausal women on ovarian suppression

Section to be changed		7.3.1 Primary endpoint analysis
Description of change		Addition of menopause status (pre/post) as a stratification factor for analysis
Rationale for change		Premenopausal women on ovarian suppression will be included in the trial according to adapted inclusion 7.

Section to be changed		7.4 Interim Analysis
Description of change		Updated predicted timelines for PFS events to 30 months.
Rationale for change		Confirmation of adjusted timelines.

Section to be changed		7.7 Determination of sample size
Description of change		Revised recruitment and event predicted timelines
Rationale for change		Confirmation of adjusted timelines.

11.4 GLOBAL AMENDMENT 4

Date of amendment		05 Feb 2020
EudraCT number **EU number**		2017-003131-11
BI Trial number		1280-0022
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		Xenera™ 1: A multi-centre, double-blind, placebo- controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease
Global amendment due to urgent safety reasons		
Global amendment		X

Section to be changed		Protocol Synopsis-Number of patients entered
Description of change		Approximately added
Rationale for change		Recruitment may be increased up to a maximum of 100 patients in order to ensure the required number of events. Further details are provided in section 7.7 of protocol.

Section to be changed		Protocol Synopsis-Number of patients on each treatment
Description of change		Approximately added
Rationale for change		Recruitment may be increased up to a maximum of 100 patients in order to ensure the required number of events. Further details are provided in section 7.7 of protocol.

Section to be changed		Protocol synopsis – Main Exclusion Criteria
Description of change		Exclusion 13 updated to specify the required follow up period for use of contraception for each of the three therapies.
Rationale for change		Update of contraception requirements for xentuzumab for women of childbearing potential to at least 6 months after the last dose, based on the 98th percentile for normalization of total IGF levels in PK/PD simulations. Update of contraception requirements for backbone therapy according to SmPC.

Section to be changed		Protocol Flow Chart
Description of change		Additional X added for pregnancy testing during follow up phase. Footnote ** updated to include reminder that pregnancy testing should be performed every 4 weeks from Cycle 21 onwards where cycles are 8 weekly in duration. Also updated to allow patients discontinuing xentuzumab/placebo to switch to 4 weekly visits as on everolimus/exemestane alone Footnote 9 updated to remove serum so that any appropriate material can be tested. Footnote 10 updated to include imaging (if no imaging available within 4 weeks) at end of treatment for patients discontinuing trial treatment without objective progression if starting straight away on subsequent anti-cancer therapy and not entering FU-PD Footnote 21 updated to include mention of pregnancy testing during overall survival follow up Footnote 25 updated to clarify when pregnancy testing should be performed for pre-menopausal women as well as the addition of screening hormone testing for post-menopausal women under 60 years of age (in the absence of bilateral oophorectomy) for eligibility purposes.

Rationale for change		Update of contraception requirements for xentuzumab for women of childbearing potential to at least 6 months after the last dose, based on the 98th percentile for normalization of total IGF levels in PK/PD simulations. Flexibility in study visits for patients who discontinue xentuzumab/placebo in order to help patient retention. Imaging for patients without objective progression and starting new anticancer therapy to ensure that a recent image is available for PFS assessment Check of eligibility for post-menopausal women less than 60 years of age. Serum removed to allow more flexibility as

		biochemistry may be analyzed in plasma or serum depending on laboratory test.

Section to be changed		3.2 Discussion of trial, design, including the choice of control groups
Description of change		Post-menopausal removed from paragraph.
Rationale for change		Everolimus and exemestane are considered standard of care to both pre- and post-menopausal women

Section to be changed		3.3. Selection of trial population
Description of change		Word approximately added and a reference to section 7.7 added.
Rationale for change		Recruitment may be increased up to a maximum of 100 patients in order to ensure the required number of events. Further details are provided in section 7.7 of protocol.

Section to be changed		3.3.2 Inclusion Criteria
Description of change		Modification of Inclusion Criteria 11: Word plasma removed
Rationale for change		Although plasma glucose is preferred, glucose may be tested from any appropriate sampling material.

Section to be changed		3.3.3 Exclusion Criteria
Description of change		Modification of Exclusion Criteria 26: addition of specific timelines for which contraception must continue to be used once patient off each treatment type. Footnote for Exclusion Criteria 27: added regarding non hormone releasing intrauterine device (lUD) or intrauterine system (IUS).
Rationale for change		Update of contraception requirements for xentuzumab for women of childbearing potential to at least 6 months after the last dose, based on the 98th percentile for normalization of total IGF levels in PK/PD simulations. Additional footnote added to clarify that only non hormone releasing intrauterine device (lUD) or intrauterine system (IUS) can be used

Section to be changed		3.3.4 Withdrawal of patients from therapy or assessments
Description of change		Update of bullet regarding ILD referring to section 4.4.3
Rationale for change		Patients should only be withdrawn from trial

		treatment for ILD following the guidance in the SmPCs and guidance on dose changes for xentuzumab/placebo in the protocol

Section to be changed		4.1.5.1 Drug assignment and administration
Description of change		Administrative change to remove comparator medications being provided by sites
Rationale for change		Per protocol version 4 all comparator medication will be supplied by sponsor

Section to be changed		4. 4. 2 Management of hyperglycaemia
Description of change		Serum removed
Rationale for change		Although plasma glucose is preferred, glucose may be tested from any appropriate sampling material.

Section to be changed		4. 4. 3 Management of non-infectious pneumonitis/ILD
Description of change		Title of section updated to include ILD Section updated to be consistent with section 4.1.5.2
Rationale for change		To ensure consistency with SmPC and guidance in section 4.1.5.2

Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Table 5.2.3:1 updated: Hormone testing section simplified but with reference to flowchart for details. Hormone testing should be done for premenopausal women but also post-menopausal women less than 60 years of age (in absence of bilateral oophorectomy). Other (fasting) blood tests updated to detail that plasma glucose is preferred but any appropriate sampling material is permitted.
Rationale for change		Update of contraception requirements for xentuzumab for women of childbearing potential to at least 6 months after the last dose, based on the 98th percentile for normalization of total IGF levels in PK/PD simulations. Other administrative changes.

Section to be changed		6.2.3.1 Extended follow up period
Description of change		Additional of collection of pregnancy test results in extended follow up
Rationale for change		Due to increased pregnancy test requirements

Section to be changed		6.2.3.2 Follow up for overall survival
Description of change		Additional of collection of pregnancy test results in overall survival follow up
Rationale for change		Due to increased pregnancy test requirements

Section to be changed		7.3 Planned Analyses
Description of change		Updated to allow for analysis of the phase II trial without 40 PFS events with the condition that the trial will not be considered to have met criteria for seamless transition to phase III
Rationale for change		Updated in the event that a larger number of patients than anticipated withdraw from the trial with symptomatic progression or AEs and start further therapies before objective progression is observed, thereby putting the trial at risk for not meeting primary analysis target of 40 events.

Section to be changed		7.4 Interim Analysis
Description of change		Reference to section 7.3 added with regard to not reaching 40 events
Rationale for change		Administrative

Section to be changed		7.6 Randomisation
Description of change		Paragraph regarding percentage of patients to be recruited into bone only vs non bone only strata removed from section.
Rationale for change		This section has been determined not relevant for phase II trial.

Section to be changed		7.7 Determination of sample size
Description of change		Section updated to describe situation where recruitment may go more than 80 patients but no more than 100 patients for the phase II and 375 for the phase III if this goes ahead.
Rationale for change		Due to higher than expected number of early patients dropping out due to symptomatic progression, additional patients may need to be recruited.

11.5 GLOBAL AMENDMENT 5

Date of amendment		25 Nov 2021
EudraCT number **EU number**		2017-003131-11
BI Trial number		1280-0022
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		Xenera™ 1: A multi-centre, double-blind, placebo- controlled, randomised phase II trial to compare efficacy of xentuzumab in combination with everolimus and exemestane versus everolimus and exemestane in women with HR+ / HER2- metastatic breast cancer and non-visceral disease
Global amendment due to urgent safety reasons		
Global amendment		X

Section to be changed		Title page
Description of change		Revision to clinical trial leader assignment
Rationale for change		New clinical trial leader managing trial

Section to be changed		Protocol Flow Chart
Description of change		New Protocol Flow Chart added
Rationale for change		New flow chart to reflect reduced procedures and assessment to support ongoing patients as a result of top line results

Section to be changed		Section 1.4 Benefit-Risk assessment
Description of change		Updates to benefit risk assessment
Rationale for change		Benefit risk assessment updated to based on database lock endpoint analysis, recommending study discontinuation of xentuzumab infusions

Section to be changed		Section 4.1- Investigational treatments
Description of change		Xentuzumab treatment discontinuation
Rationale for change		Based on the top line results, recommendation to stop xentuzumab infusions

Section to be changed		Section 4.1.5.1- Drug assignment and administration
Description of change		Reference to updated flow chart
Rationale for change		Updated flow chart

Section to be changed		Section 4.1.6.1- Blinding
Description of change		Clarification on unblinding
Rationale for change		Decision to unblind as there was no added benefit based on primary endpoint analysis

Section to be changed		Section 5.1- Assessment of Efficacy
Description of change		Tumor assessments per local practice
Rationale for change		Procedural change as a results of primary endpoint analysis

Section to be changed		Section 5.2- Assessment of Safety
Description of change		Safety assessments per local practice
Rationale for change		Procedural change as a results of primary endpoint analysis

Section to be changed		Section 5.2.3, Table 5.2.3:1- Safety Laboratory tests
Description of change		hormone testing updated for Post-menopausal woman
Rationale for change		Hormone testing is no longer necessary for women less than 60 years of age and in absence of bilateral oophorectomy

Section to be changed		Section 5.2.4 Electrocardiogram
Description of change		Removal of ECG
Rationale for change		Procedural change as a results of primary endpoint analysis

Section to be changed		Section 5.2.5 Left Ventricular Ejection Fractions
Description of change		Removal of MUGA
Rationale for change		Procedural change as a result of primary endpoint analysis

Section to be changed		Section 5.2.6.2.1 AE Collection
Description of change		Updated clarification of safety information after REP
Rationale for change		Administrative change

Section to be changed		Section 5.2.6.3 Assessment of Healthcare resource use
Description of change		Removal of Healthcare resource questionnaire use
Rationale for change		Procedural change as a result of primary endpoint analysis

Section to be changed		Section 5.2.7 Safety Assessment as of 29 Sep 2021
Description of change		Safety Procedure Updates
Rationale for change		Procedural change as a results of primary

		endpoint analysis, As IMP is discontinued safety assessments can be per local practice.

Section to be changed		Section 5.2.7 Safety Assessment as of 29 Sep 2021
Description of change		New text to reflect safety information collection
Rationale for change		Changes to safety information collection due to discontinuation of xentuzumab

Section to be changed		Section 5.3 Drug Concentration Measurement and Pharmacokinetics
Description of change		Removal of PK sampling
Rationale for change		Procedural change as a result of primary endpoint analysis

Section to be changed		Section 5.4-Assesment of Biomarkers
Description of change		Removal of Biomarker sampling
Rationale for change		Procedural change as a result of primary endpoint analysis

Section to be changed		Section 5.5-Assesment of Immunogenicity
Description of change		Removal of Assessment of Immunogenicity
Rationale for change		Procedural change as a results of primary endpoint analysis

Section to be changed		Section 5.6-Other Assessments
Description of change		Removal of Patient Questionnaires
Rationale for change		Procedural change as a result of primary analysis

Section to be changed		Section 6.2 Detail of Trial Procedures at Selected Visits
Description of change		Administrative Change
Rationale for change		Reference to updated flow chart

Section to be changed		Section 6.2.3 Follow up period and trial completion
Description of change		Removal of Follow up for PD and follow up for OS

Rationale for change		Procedural change as a result of primary analysis

Section to be changed		Section 10.4 Tumor Response Assessment according to modified recist 1.1 criteria
Description of change		Independent imaging review removed
Rationale for change		Procedural change as a result of completion of primary analysis

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-06

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-On behalf of First Author	[redacted]	29 Nov 2021 08:50 CET
Author-Statistician		29 Nov 2021 09:04 CET
Approval-Clinical Program[redacted]		29 Nov 2021 10:00 CET
Approval		06 Dec 2021 16:20 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed