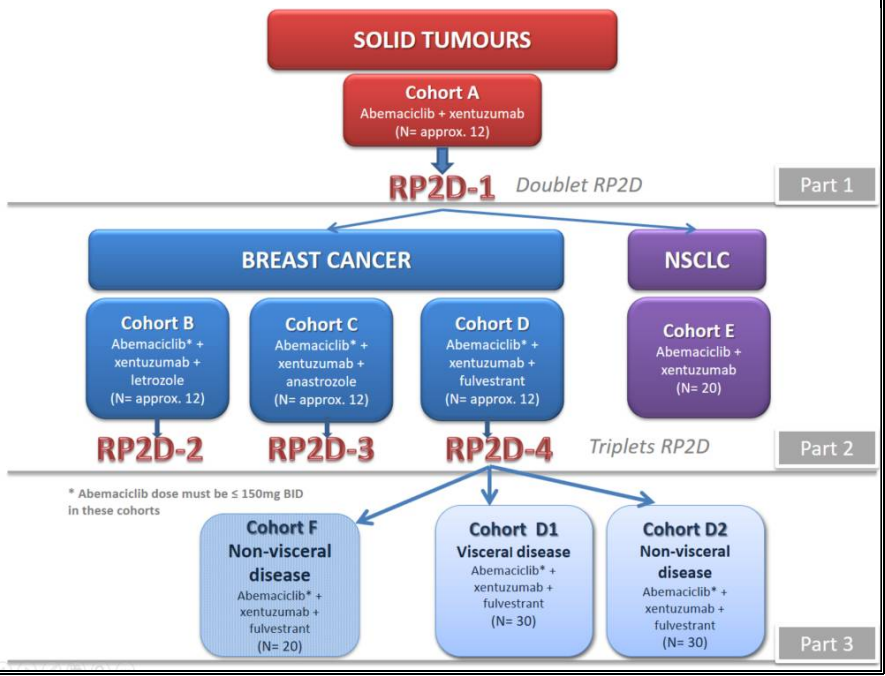
Clinical Trial Protocol

	Document Number:	**c09049566-10**
EudraCT No.: **EU Trial No:**	2016-003142-85	
BI Trial No.:	1280.18	
BI Investigational Product(s):	Xentuzumab (BI 836845)	
Title:	An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts.	
Lay Title:	This study in patients with different types of cancer (solid tumours) aims to find a safe dose of xentuzumab in combination with abemaciclib with or without hormonal therapies. The study also tests how effective these medicines are in patients with lung and breast cancer.	
Clinical Phase:	Phase Ib	
Trial Clinical Monitor:	[redacted] Phone: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted]	
Status:	Final Protocol (Revised Protocol based on global amendment 8)	
Version and Date:	**Version: 9.0**	**Date: 04 Mar 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		Xentuzumab (BI 836845)	
Protocol date: 30 Nov 2016	**Trial number:** 1280.18		**Revision date:** 04 Mar 2022

Title of trial:	An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts.
Coordinating Investigator:	[redacted]
Trial site(s):	Multi-centre trial, international in about 40 sites in US, Europe and Asia including Japan
Clinical phase:	Ib
Trial Design	

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Objective(s):	**Dose finding cohorts A, B, C and D:** To determine the maximum tolerated dose (MTD) / recommended phase II dose (RP2D) of xentuzumab in combination with abemaciclib with or without hormonal therapy (letrozole, anastrozole, fulvestrant). **Expansion cohorts E, F, D1 and D2:** To assess the anti-tumour activity of xentuzumab in combination with abemaciclib in patients with non-small cell lung cancer (cohort E), to assess the anti-tumour activity of the triplet combination xentuzumab, abemaciclib and fulvestrant in patients with locally advanced/ metastatic, HR+ breast cancer who have progressed following prior aromatase inhibitor therapy and prior CDK4/6 inhibitor treatment (cohort F), and to assess anti-tumor activity of the triplet combination xentuzumab, abemaciclib and fulvestrant in patients with locally advanced/metastatic HR+ breast cancer visceral disease (Cohort D1) or non-visceral disease (Cohort D2) who have progressed following endocrine therapy. **Exploratory Objective:** To expand the understanding of the study drug and the disease explorative biomarkers will be measured and analysed. These analyses are hypothesis generating.		
Methodology:	Prospective, open-label, non-randomised, multiple dose finding, phase Ib study, followed by expansion cohorts		

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	Dose finding cohorts: Cohort A: will identify the MTD/RP2D$_1$ of the xentuzumab/abemaciclib combination in patients with solid tumours. Cohorts B, C & D (dose finding): will identify the MTD/RP2D$_{2\text{-}4}$ of the xentuzumab/ abemaciclib combination on a background therapy of letrozole OR anastrozole OR fulvestrant (referred to as "triplets") in postmenopausal women with locally advanced/metastatic hormone receptor positive (HR+) breast cancer. **Expansion cohorts:** Cohort E: will further characterize safety, tolerability, PK, and preliminary efficacy of the xentuzumab/abemaciclib combination in a single-arm dose expansion group of non-small cell lung cancer patients. Cohort F: will investigate the efficacy and PK of the triplet combination xentuzumab/abemaciclib and fulvestrant in a single-arm expansion group of patients with locally advanced/metastatic hormone receptor positive (HR+) breast cancer and only non-visceral disease who have progressed following endocrine therapy (aromatase inhibitor) and prior CDK inhibitor treatment. Cohorts D1 and D2: will explore anti-tumor activity of the triplet combination xentuzumab, abemaciclib and fulvestrant in patients with locally advanced/metastatic HR+ breast cancer visceral disease (Cohort D1) or non-visceral disease (Cohort D2) who have progressed following endocrine therapy (aromatase inhibitor or Selective Estrogen Receptor Modulator).
No. of patients:	N= approximately 148 Dose finding cohorts: Cohort A: approx. 12 evaluable patients Cohort B: approx. 12 evaluable patients

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	Cohort C: approx. 12 evaluable patients Cohort D (dose finding): approx. 12 evaluable patients Expansion cohorts : Cohort E: 20 evaluable patients Cohort F: 20 evaluable patients with non-visceral disease Cohort D1: 30 evaluable patients with visceral disease Cohort D2: 30 evaluable patients with non-visceral disease
total entered:	Approximately 148 evaluable patients
each treatment:	* Dose finding cohorts: o Cohort A (xentuzumab + abemaciclib): ~12 evaluable patients o Cohorts B, C, D (dose finding) (xentuzumab + abemaciclib + hormonal therapy):~ 12 evaluable patients per cohort * Expansion cohorts: o Cohort E (xentuzumab + abemaciclib): ~20 evaluable patients o Cohort F (xentuzumab + abemaciclib + fulvestrant): ~20 evaluable patients with non-visceral disease o Cohort D1: (xentuzumab + abemaciclib + fulvestrant): ~ 30 evaluable patients with visceral disease o Cohort D2: (xentuzumab + abemaciclib + fulvestrant): ~ 30 evaluable patients with non-visceral disease
Diagnosis :	Patients with advanced/metastatic solid tumours in Cohort A; non-small cell lung cancer in Cohort E; pre-/peri-/post- menopausal women with locally advanced/metastatic hormone receptor-positive HER2-negative breast cancer in Cohorts B, C, D (dose finding), and expansion cohorts F (with non-visceral disease), D1(with visceral disease) and D2 (with non-visceral disease).
Main criteria for inclusion:	(see section 3.3 for details)

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Cohort A (Solid Tumours)

- Patient must be able to swallow oral capsules or tablets
- Male or female patients ≥ 18 years (≥20 years for Japan only) at screening willing and able to use highly effective methods of birth control per ICH M3
- Patients with histologically or cytologically confirmed diagnosis of advanced and/or metastatic, measurable or evaluable, non-resectable solid tumours
- Patients must have received and failed, or have been intolerant to, all treatment known to confer clinical benefit, or have no therapeutic options available as deemed appropriate by their treating physician
- Life expectancy ≥ 3 months in the opinion of the investigator

Cohort B, C, D (dose finding), F, D1 and D2 (Breast Cancer):

- Patient must be able to swallow oral capsules or tablets.
- Women ≥ 18 years (≥20 years for Japan only) at screening who have postmenopausal status.
- Histologically or cytologically proven diagnosis of breast cancer with evidence of locally advanced not amenable to curative resection or metastatic disease
- HR+ (local lab results at screening or at the time of diagnosis)
- HER2 negative (local lab results at screening or at the time of diagnosis)
- Previous adjuvant and neoadjuvant chemotherapy is permitted. 0-2 prior lines of chemotherapy for the metastatic setting are allowed **(except Cohorts D1, D2, and F)**.
- At least 1 evaluable lesion (measurable or non-measurable) that can be accurately assessed at baseline with CT or MRI

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	or PET-CT (CT portion of diagnostic quality) and which is suitable for accurate repeated measurement. • Cohort B, C, D (dose finding): Must be eligible for the corresponding hormonal therapy. For Cohorts B and C previous treatment with fulvestrant or exemestane is allowed. For Cohort D (dose finding) prior therapy with non-steroidal aromatase inhibitors (anastrozole, letrozole) or exemestane are permitted. **For Cohorts D1, D2 and F only:** • Have either measurable disease or non-measurable bone only disease. • No more than one prior line of endocrine therapy for metastatic disease is allowed. • Progression on or after endocrine therapy is required (see section 3.3.2) • For cohort F: Patients with resistance to prior therapy with an aromatase inhibitor (AI) and CDK4/6 inhibitor (excluding abemaciclib) for locally advanced or metastatic breast cancer. • For cohort D1 (visceral disease) patient must have at least one documented visceral metastasis (i.e.: lung, liver, pleural, peritoneal, malignant pleural effusion and malignant peritoneal effusion involvement) (see section 3.1.); for cohort D2 and F (non-visceral disease), patient must not have any visceral metastasis (e.g. breast, lymph node, soft tissue, bone allowed). **Cohort E (NSCLC):** • Patient must be able to swallow oral capsules or tablets. • Male or female patients ≥ 18 years (≥20 years for Japan only) at screening willing and able to use highly effective methods of birth control per ICH M3

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- Histologically or cytologically confirmed diagnosis of stage IV NSCLC.
- The participant must have progressed after platinum-based chemotherapy AND immunotherapy (unless deemed inappropriate candidates for immunotherapy by their treating physician) AND have received 1 or a maximum of 2 other prior chemotherapy for advanced and/or metastatic disease OR must be judged by the physician as ineligible for further standard second-line chemotherapy. Prior treatment with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in participants whose tumours have either EGFR-activating mutations or ALK translocations. Prior targeting agents and neoadjuvant/adjuvant therapies are permitted.
- Have measureable disease per RECIST 1.1.

Exclusion Criteria:
All cohorts:

- Any documented active or suspected malignancy or history of malignancy, other than the disease under study, within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix or ductal carcinoma in situ (DCIS) if properly treated in opinion of the investigator.
- Prior anti-cancer chemotherapy, biological or radiation therapy, androgens, thalidomide, other anticancer agents, or any investigational drug within 21 days (14 days for non-myelosuppressive agents); and/or 4 weeks for immunotherapy, before starting any of the trial drugs.
- Prior anti CDK agents (except in cohort F where only prior therapy with abemaciclib is excluded)

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	• Prior radiotherapy to ≥25% of bone marrow regardless of when it was received • Unresolved treatment related toxicity from prior therapy of > CTCAE grade 1at study entry (except for stable sensory neuropathy ≤ CTCAE grade 2 and alopecia). • Previous treatment with IGF-1R targeting compounds. • Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease, as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. History of CNS metastases or cord compression are eligible if they have been definitively treated (e.g. radiotherapy, stereotactic surgery) and are clinically stable, off anticonvulsants and steroids for at least 4 weeks. Patients with brain metastases are eligible if they are asymptomatic, completed radiotherapy for at least 4 weeks, or are on a stable dose of steroids for at least 4 weeks. Patients are not eligible if they have spinal cord compression **(except Cohorts D1, D2 and F).** • Inadequate bone marrow reserve or organ function • Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis • Refractory nausea and vomiting, chronic GI diseases, inability to swallow the product, or previous significant bowel resection that would preclude adequate absorption of abemaciclib or resulting in baseline Grade 2 or higher diarrhoea. • Patients with Diabetes Type I or uncontrolled Type II (defined by HgBA1C > 8%) • Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term including patients with massive uncontrolled

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effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% of liver involvement in metastases.

- Prior hematopoietic stem cell or bone marrow transplant
- Have had major surgery (excluding biopsy) < 28 days of the initial dose of any of the study drugs or planned major surgery during study participation.
- Have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.
- Have active bacterial or fungal (that is, requiring intravenous [IV] antibiotics or therapy at time of initiating study treatment), and/or known viral infection
- Patients with baseline Grade ≥ 2 hyperglycaemia or patients with baseline Grade ≥ 2 diarrhoea
- Patients needing treatment with CYP3A4 inhibitors/inducers cannot be included in the trial. (See Appendix 10.1)

For Cohorts D1, D2 and F only:

- Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, everolimus, alpelisib or abemaciclib. For cohorts D1 and D2 only: prior treatment with palbociclib or ribociclib is also excluded.
- Patients with evidence or history of central nervous system metastasis are excluded.
- Have initiated bisphosphonates or approved RANK ligand (RANK-L) -targeted agents (for example, denosumab) <7 days prior to initiation of any study drug.

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Test product(s):	Xentuzumab (Boehringer Ingelheim): IGF-1/-2 mAb Abemaciclib (LY2835219; [redacted]): CDK 4/6 inhibitor
dose:	**Dose finding cohorts:** * Cohort A: starting dose is 1000 mg iv once weekly for xentuzumab and 150 mg every 12 hours for abemaciclib * Cohorts B, C and D (dose finding): $MTD_1/RP2D_1$ of xentuzumab in combination with abemaciclib as determined in cohort A, plus letrozole (cohort B), anastrozole (Cohort C) or fulvestrant (cohort D). **Expansion cohorts:** * Cohort E: $MTD_1/RP2D_1$ of xentuzumab in combination with abemaciclib as determined in cohort A. * Cohorts F, D1 and D2: $MTD_4/RP2D_4$ of the triplet combination xentuzumab, abemaciclib and fulvestrant as determined in cohort D (dose finding).
mode of administration:	Xentuzumab: intravenously, weekly dosing Abemaciclib: oral, continuous dosing every 12 hours
Background endocrine therapy:	Letrozole, anastrozole, fulvestrant
dose:	Letrozole/anastrozole/fulvestrant at standard doses
mode of administration:	Letrozole, anastrozole, fulvestrant standard mode of administration
Duration of treatment:	Xentuzumab will be given until disease progression, intolerability of the study medication or consent withdrawal. Abemaciclib will be given until disease progression, intolerability of the study medication or consent withdrawal.
Endpoints	**Primary endpoints:**

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	For each dose finding cohorts A, B, C and D: * Maximum tolerated dose (MTD) * Number of patients with DLT during the MTD evaluation period (first 28-day cycle) For expansion cohort E: * Objective response (CR, PR per RECIST 1.1) For cohorts D1 and D2: * PFS rate at 18 month For expansion cohort F: * Disease control (CR, PR, SD lasting at least 24 weeks per RECIST 1.1) **Secondary endpoints:** For each dose finding cohorts A, B, C and D: * No secondary endpoint For each expansion cohorts E, F, D1 and D2: * Disease control (CR, PR, SD lasting at least 24 weeks per RECIST 1.1) (only for Cohorts D1, D2 and E) * Time to objective response * Duration of objective response * Duration of disease control * Progression-free survival (PFS) * Objective response (only for Cohorts D1, D2 and F)
Safety criteria:	Incidence and severity of reported AEs. AEs will be assessed using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 (R10-4848)

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Statistical methods:	All endpoints for each dose finding cohorts and each expansion cohorts will be analysed using descriptive statistics. For dose finding cohorts, inter-patient dose (de-)escalation is guided by a Bayesian Logistic Regression Model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of each dose finding, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD.		

FLOW CHART – COHORT A (SOLID TUMOURS)

Study period	Screening (a)	Treatment Courses (b)								EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards					
Visits (V)	Screening	1	2	3	4	1	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15 ±1	22±1	1 ±2	8 ±2	15 ±2	22 ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria (2)	X (2)	X (2)									
Physical exam (3)	X	X				X				X	X
Height	X										
Body weight	X	X				X				X	X
Vital signs (4)	X	X	X	X	X	X				X	X
ECOG performance status	X	X				X				X	X
12-lead ECG (triplicate) (5)	X	X		X		X		X		X	X
Safety lab (6)	X	X	X	X	X	X		X (7)		X	X
Archival tumour tissue collection (8)	X										
Blood sample for biomarkers (9)	X	X	X			X				X	X
Pharmacokinetics (10)		X	X			X				X	X
Pharmacogenomics and cfDNA (11)		X				X (12)				X	
PGx Plasma -exosomal RNA (13)		X		X		X				X	
DNA banking (14)		X									
Immunogenicity (ADA) (15)		X	X			X				X	X
Tumour assessment and bone scan by RECIST 1.1 (16)	X					X (16)				X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Abemaciclib dispensation (17)		X				X					
Xentuzumab i.v. (17)		X	X	X	X	X	X	X	X		
Compliance check abemaciclib (18)						X				X	
Termination of trial medication										X	
Completion of the study participation											X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 6 cycles is expected.

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

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

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered.
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion.
6. Safety labs: includes haematology (CBC), coagulation, negative serum pregnancy test for women with childbearing potential and biochemistry . Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. Blood soluble biomarkers: for detailed sampling time schedule, refer to Section 5.5 and Appendix 10.2.1
10. Pharmacokinetics: Course 1, Course 2-12, 15, 18, EOTV and FU visits. For detailed PK sampling time schedule, refer to Section 5.4.1 and Appendix 10.2.1 for cohorts A, B, C and D
11. Pharmacogenomics and cfDNA. See Section 5.5 for more details on collection time points. Briefly, one blood sample to isolate genomic DNA will be obtained at C1V1 before treatment. 3 plasma samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at C1V1 before treatment, at C3V1 and at the EOTV.
12. For course 3 only
13. PGx Plasma: blood samples will be collected before treatment on C1V1, C1V3 (Day 15), C2V1, C3V1 and beyond, and at the EOTV. Samples will be used to evaluate exosomal RNA.
14. DNA banking: For details please refer to Section 5.5.1.
15. Immunogenicity (ADA): On days when xentuzumab is dosed and EOTV and FU visit at time points specified in Flow Chart and Appendix 10.2.1, ADA samples are to be collected prior to xentuzumab infusion. ADA samples must be collected at Course 1, Course 2-12, 15, 18, at EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.2.1
16. Tumour assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all pre-specified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans must be performed at screening (see Section 5.2 for more detail).
    Assessment will be performed at the following time points until progression/start of further treatment (tumour assessments after start of xentuzumab should be performed no more than 7 days prior to the scheduled tumour assessment date up to week 48 AND no more than 14 days prior to the scheduled tumour assessment date after week 48):
    - At screening (within 28 days prior to starting of treatment)
    - Every 8 weeks (±7days): during week 8 (49-63 days after start of xentuzumab), during week 16 (105-119 days after start of xentuzumab), during week 24 (161-175 days after start of xentuzumab), during week 32 (217-231 days after start of xentuzumab), during week 40 (273-287 days after start of xentuzumab), during week 48 (329-343 days after start of xentuzumab)
    - Every 12 weeks after week 48 (±7days) (e.g. during week 60 (406-434 days after start of xentuzumab), during week 72 (490-518 days after start of xentuzumab), etc.)
      In the event of an interruption/delay to treatment, the tumour assessment schedule should not be changed.

    Except in case of discontinuation from treatment due to progression, tumour assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
    Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF
17. Abemaciclib and xentuzumab should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
18. Compliance check: on Day 1 of every course starting on course 2 and at EOTV

FLOW CHART – COHORT B (BC TRIPLET WITH LETROZOLE)

Study period	Screening (a)	Treatment Courses (b)								EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards					
Visits (V)	Screening	1	2	3	4	1	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15 ±1	22 ±1	1 ±2	8 ±2	15 ±2	22 ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria (2)	X (2)	X (2)									
Physical exam (3)	X	X				X				X	X
Height	X										
Body weight	X	X				X				X	X
Vital signs (4)	X	X	X	X	X	X				X	X
ECOG performance status	X	X				X				X	X
12-lead ECG (triplicate) (5)	X	X		X		X		X		X	X
Safety lab (6)	X	X	X	X	X	X		X (7)		X	X
Archival tumour tissue collection (8)	X										
Blood sample for biomarkers (9)	X	X	X			X				X	X
Pharmacokinetics (10)		X	X			X				X	X
Pharmacogenomics and cfDNA (11)		X				X (12)				X	
PGx Plasma -exosomal RNA (13)		X		X		X				X	
DNA banking (14)		X									
Immunogenicity (ADA) (15)		X	X			X				X	X
Tumour assessment and bone scan by RECIST 1.1 (16)	X					X (16)				X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Abemaciclib and letrozole dispensation (17)		X				X					
Xentuzumab i.v. (17)		X	X	X	X	X	X	X	X		
Compliance check abemaciclib and letrozole (18)						X				X	
Termination of trial medication										X	
Completion of the study participation											X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 12 cycles is expected.

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

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

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered.
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion.
6. Safety labs: includes haematology (CBC), coagulation, negative serum pregnancy test for women with childbearing potential and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. Blood soluble biomarkers: for detailed sampling time schedule, refer to Section 5.5 and Appendix 10.2.1
10. Pharmacokinetics: Course 1, course 2-12, 15, 18, EOTV and FU visits. For detailed PK sampling time schedule, refer to Section 5.4.1 and Appendix 10.2.1 for cohorts A, B, C and D
11. Pharmacogenomics and cfDNA See Section 5.5 for more details about collection timepoints. Briefly, one blood sample to isolate genomic DNA will be obtained at C1V1 before treatment. 3 plasma samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at C1V1 before treatment, at C3V1 and at the EOTV.
12. For course 3 only
13. PGx Plasma: blood samples will be collected before treatment on C1V1, C1V3 (Day 15), C2V1, C3V1 and beyond and at the EOTV. Samples will be used to evaluate exosomal RNA.
14. DNA banking: For details please refer to Section 5.5.1.
15. Immunogenicity (ADA): On days when xentuzumab is dosed and EOTV and FU visit at time point specified in the Flow Chart and Appendix 10.2.1, ADA samples are to be collected prior to xentuzumab infusion. ADA samples must be collected at Course 1, course 2-12, 15, 18, at EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.2.1
16. Tumour assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans must be performed at screening (see Section 5.2 for more detail).
    Assessment will be performed at the following time points until progression/start of further treatment (tumour assessments after start of xentuzumab should be performed no more than 7 days prior to the scheduled tumour assessment date up to week 48 AND no more than 14 days prior to the scheduled tumour assessment date after week 48):
    - At screening (within 28 days prior to starting of treatment)
    - Every 8 weeks (±7days): during week 8 (49-63 days after start of xentuzumab), during week 16 (105-119 days after start of xentuzumab), during week 24 (161-175 days after start of xentuzumab), during week 32 (217-231 days after start of xentuzumab), during week 40 (273-287 days after start of xentuzumab), during week 48 (329-343 days after start of xentuzumab)
    - Every 12 weeks after week 48 (±7days) (e.g. during week 60 (406-434 days after start of xentuzumab), during week 72 (490-518 days after start of xentuzumab), etc.)
      In the event of an interruption/delay to treatment, the tumour assessment schedule should not be changed.

    Except in case of discontinuation from treatment due to progression, tumour assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
    Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF
17. Abemaciclib, letrozole (in certain countries) and xentuzumab should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
18. Compliance check: on Day 1 of every course starting at course 2 and at EOTV

FLOW CHART – COHORT C (BC TRIPLET WITH ANASTROZOLE)

Study period	Screening (a)	Treatment Courses (b)								EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards					
Visits (V)	Screening	1	2	3	4	1	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15 ±1	22 ±1	1 ±2	8 ±2	15 ±2	22 ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria (2)	X (2)	X (2)									
Physical exam (3)	X	X				X				X	X
Height	X										
Body weight	X	X				X				X	X
Vital signs (4)	X	X	X	X	X	X				X	X
ECOG performance status	X	X				X				X	X
12-lead ECG (triplicate) (5)	X	X		X		X		X		X	X
Safety lab (6)	X	X	X	X	X	X		X (7)		X	X
Archival tumour tissue collection (8)	X										
Blood sample for biomarkers (9)	X	X	X			X				X	X
Pharmacokinetics (10)		X	X			X				X	X
Pharmacogenomics and cfDNA (11)		X				X (12)				X	
PGx Plasma -exosomal RNA (13)		X		X		X				X	
DNA banking (14)		X									
Immunogenicity (ADA) (15)		X	X			X				X	X
Tumour assessment and bone scan by RECIST 1.1 (16)	X					X (16)				X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Abemaciclib and anastrozole dispensation (17)		X				X					
Xentuzumab i.v. (17)		X	X	X	X	X	X	X	X		
Compliance check abemaciclib and anastrozole (18)						X				X	
Termination of trial medication										X	
Completion of the study participation											X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 12 cycles is expected.

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

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

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered.
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion.
6. Safety labs: includes haematology (CBC), coagulation, and negative serum pregnancy test for women with childbearing potential and biochemistry. Urinalysis only at screening and EOTV.Fasting blood test is required for metabolic panels. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. Blood soluble biomarkers: for detailed sampling time schedule, refer to Section 5.5 and Appendix 10.2.1
10. Pharmacokinetics: Course 1, Course 2-12, 15 and 18, EOTV and FU visits. For detailed PK sampling time schedule, refer to Section 5.4.1 and Appendix 10.2.1 for cohorts A, B, C and D
11. Pharmacogenomics and cfDNA See Section 5.5 for more details about collection timepoints. Briefly, one blood sample to isolate genomic DNA will be obtained at C1V1 before treatment. 3 plasma samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at C1V1 before treatment, at C3V1 and at the EOTV.
12. For course 3 only
13. PGx Plasma: blood samples will be collected before treatment on C1V1, C1V3 (Day 15), C2V1, C3V1 and beyond, and at the EOTV. Samples will be used to evaluate exosomal RNA.
14. DNA banking: For details please refer to Section 5.5.1.
15. Immunogenicity (ADA): On days when xentuzumab is dosed and EOTV and FU visit at time points specified in Flow Chart and Appendix 10.2.1, ADA samples are to be collected prior to xentuzumab infusion. ADA samples must be collected at Course 1, Course 2-12, 15 and 18, at EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.2.1
16. Tumour assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans must be performed at screening (see Section 5.2 for more detail).
    Assessment will be performed at the following time points until progression/start of further treatment (tumour assessments after start of xentuzumab should be performed no more than 7 days prior to the scheduled tumour assessment date up to week 48 AND no more than 14 days prior to the scheduled tumour assessment date after week 48):
    - At screening (within 28 days prior to starting of treatment)
    - Every 8 weeks (±7days): during week 8 (49-63 days after start of xentuzumab), during week 16 (105-119 days after start of xentuzumab), during week 24 (161-175 days after start of xentuzumab), during week 32 (217-231 days after start of xentuzumab), during week 40 (273-287 days after start of xentuzumab), during week 48 (329-343 days after start of xentuzumab)
    - Every 12 weeks after week 48 (±7days) (e.g. during week 60 (406-434days after start of xentuzumab), during week 72 (490-518 days after start of xentuzumab), etc.)

    In the event of an interruption/delay to treatment, the tumour assessment schedule should not be changed.
    Except in case of discontinuation from treatment due to progression, tumour assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
    Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF
17. Abemaciclib, anastrozole (in certain countries) and xentuzumab should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
18. Compliance check: on Day 1 of every course starting at course 2 and at EOTV

FLOW CHART – COHORT D – DOSE FINDING (BC TRIPLET WITH FULVESTRANT)

Study period	Screening (a)	Treatment Courses (b)								EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards					
Visits (V)	Screening	1	2	3	4	1	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15 ±1	22 ±1	1 ±2	8 ±2	15 ±2	22 ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria (2)	X (2)	X (2)									
Physical exam (3)	X	X				X				X	X
Height	X										
Body weight	X	X				X				X	X
Vital signs (4)	X	X	X	X	X	X				X	X
ECOG performance status	X	X				X				X	X
12-lead ECG (triplicate) (5)	X	X		X		X		X		X	X
Safety lab (6)	X	X	X	X	X	X		X (7)		X	X
Archival tumour tissue collection (8)	X										
Blood sample for biomarkers (9)	X	X	X			X				X	X
Pharmacokinetics (10)		X	X			X				X	X
Pharmacogenomics and cfDNA (11)		X				X (12)				X	
PGx Plasma -exosomal RNA (13)		X		X		X				X	
DNA banking (14)		X									
Immunogenicity (ADA) (15)		X	X			X				X	X
Tumour assessment and bone scan by RECIST 1.1 (16)	X					X (16)				X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Abemaciclib dispensation (17)		X				X					
Xentuzumab i.v. (17)		X	X	X	X	X	X	X	X		
Fulvestrant i.m. (17)		X		X		X					
Compliance check abemaciclib (18)						X				X	
Termination of trial medication										X	
Completion of the study participation											X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 12 cycles is expected.

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

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

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion.
6. Safety labs: includes haematology (CBC), coagulation, negative serum pregnancy test for women with childbearing potential and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. Baseline Local FSH and estradiol levels should be within 14 days of initial dose of study treatment. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. Blood soluble biomarkers: for detailed sampling time schedule, refer to Section 5.5 and Appendix 10.2.1
10. Pharmacokinetics: Course 1, Course 2-12, 15, 18, EOTV and FU visits. For detailed PK sampling time schedule, refer to Section 5.4.1 and Appendix 10.2.1 for cohorts A, B, C and D
11. Pharmacogenomics and cfDNA See Section 5.5 for more details about collection timepoints. Briefly, one blood sample to isolate genomic DNA will be obtained at C1V1 before treatment. 3 additional blood samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at C1V1 before treatment, at C3V1 and at the EOTV.
12. For course 3 only
13. PGx Plasma: blood samples will be collected before treatment on C1V1, C1V3 (Day 15), C2V1, C3V1 and beyond, and at the EOTV. Samples will be used to evaluate exosomal RNA.
14. DNA banking: For details please refer to Section 5.5.1.
15. Immunogenicity (ADA): On days when xentuzumab is dosed and EOTV and FU visit at time points specified in the Flow Chart and Appendix 10.2.1, ADA samples are to be collected prior to xentuzumab infusion. ADA samples must be collected at Course 1, Course 2-12, 15, 18, at EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.2.1
16. Tumour assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans must be performed at screening (see Section 5.2 for more detail).
    Assessment will be performed at the following time points until progression/start of further treatment (tumour assessments after start of xentuzumab should be performed no more than 7 days prior to the scheduled tumour assessment date up to week 48 AND no more than 14 days prior to the scheduled tumour assessment date after week 48):
    - At screening (within 28 days prior to starting of treatment)
    - Every 8 weeks (±7days): during week 8 (49-63 days after start of xentuzumab), during week 16 (105-119 days after start of xentuzumab), during week 24 (161-175 days after start of xentuzumab), during week 32 (217-231 days after start of xentuzumab), during week 40 (273-287 days after start of xentuzumab), during week 48 (329-343 days after start of xentuzumab)
    - Every 12 weeks after week 48 (±7days) (e.g. during week 60 (406-434 days after start of xentuzumab), during week 72 (490-518 days after start of xentuzumab), etc.)
      In the event of an interruption/delay to treatment, the tumour assessment schedule should not be changed.

    Except in case of discontinuation from treatment due to progression, tumour assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV
    Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF
17. Abemaciclib, xentuzumab and fulvestrant (in certain countries) should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
18. Compliance check: on Day 1 of every course starting at course 2 and at EOTV

FLOW CHART – COHORT E (NSCLC EXPANSION COHORT)

Study period	Screening (a)	Run-in (b)			Treatment Courses (c)									EOTV (d)	FU (e)
	SCR	R			Course 1				Course 2 onwards						
Visits (V)	Screening	1	2	3	1	2	3	4	1	1b	2	3	4		
Days	Within 28d before Run-in V1	-9	-2	-1	1	8 ± 1	15± 1	22± 1	1 ±2	4 ± 1 (f)	8 ±2(g)	15 ± 2	22± 2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X														
Demographics	X														
Medical history	X														
Inclusion/exclusion criteria (2)	X (2)	X (2)													
Physical exam (3)	X	X			X				X					X	X
Height	X														
Body weight	X	X			X				X					X	X
Vital signs (4)	X	X	X	X	X	X	X	X	X					X	X
Dispense Patient Diary (5)		X						X							
ECOG performance status	X	X			X				X					X	X
12-lead ECG (triplicate) (6)	X		X		X		X		X			X		X	X
Safety lab (7)	X	X			X	X	X	X	X			X (8)		X	X
Archival tumour tissue collection (9)	X														
Blood sample for biomarkers (10)	X	X			X	X			X					X	X
Pharmacokinetics (11)		X		X	X	X			X *	X (12)	X (12)			X	X
Pharmacogenomics and cfDNA (13)		X			X				X (14)					X	
PGx Plasma - exosomal RNA (15)		X			X		X		X					X	
DNA banking (16)		X													
Immunogenicity (ADA) (17)		X			X	X			X					X	X
Tumour assessment and bone scan by RECIST 1.1 (18)	X								X (18)					X	
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X			X	X	X	X	X		X	X	X	X	X
Abemaciclib dispensation (19)		X			X				X						
Xentuzumab i.v. (19)					X	X	X	X	X		X	X	X		
Compliance check abemaciclib (20)				X					X					X	

Termination of trial medication														X	
Completion of the study participation															X

* A 24 h sample is also required at C2V1D2 (see Appendix 10.2.2)

a Screening: The screening visit should be performed within 28 days prior to first drug administration (Run-in period). Safety lab at the screening assessment can serve as the Run-in Visit 1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Run in: Consists of 9 days. During the run-in period, patients should take daily abemaciclib treatment. At days with PK sampling, patients have to take their morning dose of abemaciclib in the hospital to allow proper PK sampling.

c Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 6 cycles is expected.

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

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

f On course 2 only for PK purposes

g No time window is applicable for course 2 when PK determinations are scheduled for the visit

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure
5. A patient diary will be handed over to the patient at Run-In Visit 1 and at C1V4. Patients have to fill in this diary up to Run-In V3 and C2V1, respectively (see also Section 4.3 for a short description of the diary)
6. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, Run-in visit 2 Day -2, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion.
7. Safety labs: includes haematology (CBC), coagulation, negative serum pregnancy test for women with childbearing potential and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF
8. For course 2 only
9. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
10. Blood soluble biomarkers: for detailed sampling time schedule, refer to Section 5.5 and Appendix 10.2.2
11. Pharmacokinetics: to be collected at Run-In period as well as in treatment courses 1-12, 15, 18, EOTV and FU visit. For detailed PK sampling time schedule, refer to Section 5.4.1 and Appendix 10.2.2 for cohort E.
    Please note: At days of PK sampling of abemaciclib, patients have to take their morning dose in the hospital in order to allow for proper PK sampling
12. PK sampling at this visit only in course 2
13. Pharmacogenomics and cfDNA See Section 5.5 for more details on collection timepoints. Briefly, one blood sample to isolate genomic DNA will be obtained at Run-in V1 before treatment. 4 plasma samples will be collected to isolate circulating nucleic acids (e.g. cfDNA) from plasma: at Run-in V1, at C1V1 before treatment, at C3V1 and at the EOTV.
14. For course 3 only
15. PGx Plasma: Blood samples will be collected before treatment at run-in V1, on C1V1, C1V3 (Day 15), C2V1, C3V1 onwards and at the EOTV. Samples will be used to evaluate exosomal RNA.
16. DNA banking: For details please refer to Section 5.5.1.
17. Immunogenicity (ADA): On days when xentuzumab is dosed and EOTV and FU visit at time points specified in Flow Chart and Appendix 10.2.2, ADA samples are to be collected prior to xentuzumab infusion. ADA samples must be collected at Run In, in treatment courses 1-12, 15, 18, EOTV and at the FU visit. For detailed sampling schedule, refer to Appendix 10.2.2
18. Tumour assessments should include CT or MRI scans of the chest, abdomen and pelvis, and, if clinically indicated, any other known or suspected sites of disease (e.g. breast, neck, brain etc.) accordingly to RECIST 1.1. After study entry, all lesions identified as target and non-target lesions during the screening should be followed up at all prespecified imaging time points. The same radiographic procedure must be used throughout the study. Bone scans must be performed at screening (see Section 5.2 for more detail).

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

- At screening (within 28 days prior to starting the run-in period)
- Every 8 weeks (±7days): during week 8 (49-63 days after start of xentuzumab), during week 16 (105-119 days after start of xentuzumab), during week 24 (161-175 days after start of xentuzumab), during week 32 (217-231 days after start of xentuzumab), during week 40 (273-287 days after start of xentuzumab), during week 48 (329-343 days after start of xentuzumab)
- Every 12 weeks after week 48 (±7days) (e.g. during week 60 (406-434 days after start of xentuzumab), during week 72 (490-518 days after start of xentuzumab), etc.)

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

Except in case of discontinuation from treatment due to progression, tumour assessment at EOTV is not necessary if the previous evaluation was done within 4 weeks of EOTV

Unscheduled scan based on the investigator's judgement is allowed and should also be documented in eCRF

19. Abemaciclib and xentuzumab should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
20. Compliance check: On Day -1, on Day 1 of every treatment course starting on course 2, and at EOTV

FLOW CHART – COHORT F (BC EXPANSION COHORT)

Study period	Screening(a)	Treatment Courses (b)								EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards					
Visits (V)	Screening	1	2	3	4	1	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15±1	22±1	1 ±2	8* ±2	15* ±2	22* ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria (2)	X (2)	X (2)									
Physical exam (3)	X	X				X				X	X
Height	X										
Body weight	X	X				X				X	X
Vital signs (4)	X	X	X	X	X	X				X	X
ECOG performance status	X	X				X				X	X
12-lead ECG (triplicate) (5)	X	X		X		X		X		X	X
Safety lab (6)	X	X	X	X	X	X		X (7)		X	X
Archival tumour tissue collection (8)	X										
DNA banking (9)		X									
Tumour assessment and bone scan by RECIST 1.1 (10)	Per institutional practice										
Adverse event	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Abemaciclib dispensation (11)		X				X					
Xentuzumab i.v. (11)		X	X	X	X	X	X	X	X		
Fulvestrant i.m. (11)		X		X		X					
Compliance check abemaciclib (12)						X				X	
Termination of trial medication										X	
Completion of the study participation											X

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 24 cycles is expected.

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

d FU: All patients should have a follow-up visit 42 days (+7days) after the permanent discontinuation of the study drugs. Patients who have not progressed and not started further treatment at FU should have additional limited follow-up visits at scheduled tumor assessment until progression, start of further anticancer treatment, consent withdrawal, lost to follow-up or death. See Section 5.2 and Section 6.2.3

* When xentuzumab is discontinued, the visit can be conducted by phone

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status. When xentuzumab is discontinued, physical exam can be done as per institutional practice.
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure. When xentuzumab is discontinued, vital signs assessments can be done as per institutional practice.
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion. When xentuzumab is discontinued, ECGs can be omitted.
6. Safety labs: includes haematology (CBC), coagulation, and negative serum pregnancy test for women with childbearing potential and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. Baseline Local FSH and estradiol levels should be within 14 days of initial dose of study treatment. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF. When xentuzumab is discontinued, safety labs can be done as per institutional practice.
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. DNA banking: For details please refer to Section 5.5.1.
10. Tumour assessments will be performed according to institutional practice. Only the overall response will be collected in the eCRF.
11. Abemaciclib, xentuzumab and fulvestrant (in certain countries) should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
12. Compliance check: On Day -1, on Day 1 of every treatment course starting on course 2, and at EOTV

FLOW CHART – COHORTS D1 AND D2 (BC EXPANSION COHORTS)

Study period	Screening (a)	Treatment Courses (b)									EOTV (c)	FU (d)
	SCR	Course 1				Course 2 onwards						
Visits (V)	Screening	1	2	3	4	1	1b	2	3	4		
Days	Within 28d before C1V1	1	8 ±1	15 ±1	22 ±1	1 ±2	4 ±1 (e)	8* ±2 (f)	15* ±2	22* ±2	Within 7d after last drug intake	42 +7d after last drug intake
Informed consent (1)	X											
Demographics	X											
Medical history	X											
Inclusion/exclusion criteria (2)	X (2)											
Physical exam (3)	X	X				X					X	X
Height	X											
Body weight	X	X				X					X	X
Vital signs (4)	X	X	X	X	X	X					X	X
ECOG performance status	X	X				X					X	X
12-lead ECG (triplicate) (5)	X	X		X		X			X		X	X
Safety lab (6)	X	X	X	X	X	X			X (7)		X	X
Archival tumour tissue collection (8)	X											
DNA banking (9)		X										
Tumour assessment and bone scan by RECIST 1.1 (10)	Per institutional practice											
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X		X	X	X	X	X
Abemaciclib dispensation (11)		X				X						
Xentuzumab i.v. (11)		X	X	X	X	X		X	X	X		
Fulvestrant i.m. (11)		X		X		X						
Compliance check abemaciclib (12)						X					X	
Termination of trial medication											X	
Completion of the study participation												X

* A 24 h sample is also required at C2V1D2 (see Appendix 10.2.4)

a Screening: The screening visit should be performed within 28 days prior to first drug administration (C1V1). Safety lab at the screening assessment can serve as the C1V1 assessment if performed within 72 hours before the first treatment and does not need to be repeated.

b Treatment courses: All courses are 4 weeks in duration (28 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4). A duration of approximately 24 cycles is expected.

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

d FU: All patients should have a follow-up visit 42 days (+7days) after the permanent discontinuation of the study drugs. Patients who have not progressed and not started further treatment at FU should have additional limited follow-up visits at scheduled tumor assessment until progression, start of further anticancer treatment, consent withdrawal, lost to follow-up or death. See Sections 5.2 and 6.2.3

e On course 2 only for PK purposes

f No time window is applicable for course 2 when PK determinations are scheduled for the visit

* When xentuzumab is discontinued, the visit can be conducted by phone

1. Written informed consent must be obtained before any protocol specific screening assessment is performed
2. In/Exclusion criteria must be checked at screening and ensured before study medication has been firstly administered
3. Physical exam: includes a thorough cardiopulmonary, abdominal and lymph node exam and an assessment of the mental and neurological status. When xentuzumab is discontinued, physical exam can be done as per institutional practice.
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure. When xentuzumab is discontinued, vital signs assessments can be done as per institutional practice.
5. 12-lead ECG: 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, EOTV and FU visit. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Course 1, 2, 3; and at Visit 1/Day 1 of Courses 6,9,12, etc. ECG should be performed prior to xentuzumab infusion. . When xentuzumab is discontinued, ECGs can be omitted.
6. Safety labs: includes haematology (CBC), coagulation, and negative serum pregnancy test for women with childbearing potential (within 14 days of first study dose) and biochemistry. Urinalysis only at screening and EOTV. Fasting blood test is required for metabolic panels. Baseline Local FSH and estradiol levels should be within 14 days of initial dose of study treatment. See Section 5.3.3 for detail. Safety lab can be performed one day prior to the scheduled test. Unscheduled safety lab should be performed if clinically indicated and documented in the eCRF. . When xentuzumab is discontinued, safety labs can be done as per institutional practice.
7. For course 2 only
8. Archival tumour tissue collection: the most recent/appropriate archival tumour tissue must be collected prior to the start of trial treatment. Refer to Appendix 10.3 for tissue requirements
9. DNA banking: For details please refer to Section 5.5.1.
10. Tumour assessments will be performed according to institutional practice. Only the overall response will be collected in the eCRF.
11. Abemaciclib, xentuzumab and fulvestrant (in certain countries) should be dispensed through IRT. Patient's screening, all drug dispensation visits and EOTV will be collected in the IRT system
12. Compliance check: on Day 1 of every treatment course starting on course 2, and at EOTV

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the Curve
BC	Breast Cancer
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLRM	Bayesian Logistic Regression Model
CCDS	Company Core Data Sheet
CDK	Cyclin-dependent Kinase
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EOTV	End of Trial Visit
EWOC	Escalation With Overdose Control
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FU	Follow Up
FUV	Follow Up Visit
GCP	Good Clinical Practice
[redacted]	
HR	Hormone Receptor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF	Insulin-like Growth Factor
i.m.	Intramuscular
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
LA	Locally Advanced
LoEE	List of Essential Element
mAB	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities

MST	Medical Sub team
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
OPU	Operative Unit
OS	Overall Survival
PD	Pharmacodynamics
PK	Pharmacokinetics
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PFS	Progression-free survival
pRb	Retinoblastoma protein
q.d.	quaque die (once a day)
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SC	Steering Committee
s.c.	subcutaneous
SmPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
WHO/ECOG	World Health Organization / Eastern Cooperative Oncology Group

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Hormone receptor-positive (HR+) breast cancer (BC)

Breast cancer is one of the most common cancers in women. In 2012, there were approximately 226,870 new cases of breast cancer and 39,510 deaths from the disease among women in the United States (Siegel et al. 2012 R12-2864). 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). The treatment for women diagnosed with hormone receptor positive (HR+) mBC includes endocrine therapy (R16-3983). However, de novo or acquired resistance to endocrine therapy remains an important clinical problem. Many HR+ breast cancers demonstrate overexpression of cyclin D1 (R16-3978), which interacts with cyclin-dependent kinases 4 and 6 (hereafter CDK4/6) in an active protein complex that promotes cell proliferation. Consequently, CDK4/6 represents a potential therapeutic target for HR+ breast cancers, and CDK4/6 inhibitors need to be evaluated for their potential to improve clinical outcomes for women with HR+ mBC.

Despite recent advances, hormone-positive HR+ advanced or metastatic breast cancer still has a dismal prognosis with median progression-free survival (PFS) of less than a year; almost all patients will develop resistance to endocrine treatment and succumb to their disease eventually. Biochemical and genetic characterization of D-type cyclins, their cyclin D–dependent kinases (CDK4 and CDK6), and the polypeptide CDK4/6 inhibitor p16INK4A over two decades ago revealed how mammalian cells regulate entry into the DNA synthetic (S) phase of the cell-division cycle in a retinoblastoma protein (pRb)–dependent manner. These investigations provided proof-of-principle that CDK4/6 inhibitors, such as abemaciclib, particularly when combined with co-inhibition of allied mitogen-dependent signal transduction pathways, might prove valuable in cancer therapy. The recent FDA approval of the CDK4/6 inhibitor palbociclib (Ibrance™), used with the aromatase inhibitor letrozole and fulvestrant for breast cancer treatment, highlights long-sought success by showing unprecedented efficacy in this setting. Moreover, the newest findings herald clinical trials targeting other cancers such as non-small cell lung cancer (NSCLC). Rapidly emerging data with selective inhibitors of CDK4/6 have validated these cell-cycle kinases as anticancer drug targets, corroborating longstanding preclinical predictions (R16-2249; R16-3979).

Non-small cell lung cancer (NSCLC)

Lung cancer is the most common cancer worldwide as well as the leading cause of cancer related deaths in both men and women. Non-small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancers and of these, adenocarcinoma and squamous cell carcinoma (SCC) account for 50% and 30% respectively. Most of these patients present with locally advanced inoperable or metastatic disease, which makes their cancer incurable, and unfortunately almost all of these patients will die from their illness. Despite multiple advances in the staging, diagnostic procedures and therapeutic options, the overall outlook has not greatly changed for the majority of patients with the overall 5-year survival having only marginally increased over the last decade from 15.7% to 17.4% (P15-10237). Smoking remains the major cause of NSCLC, although the identification of driver oncogenes in non-smoking patients represents a critical novel finding during the last decades that fundamentally changed the management of

this disease. The recognition that NSCLC is not a single disease entity today is a well-known reality that has led to divide NSCLC into different sub-types, each one with specific algorithms of treatment, based on histological and molecular features (reviewed in P16-09577 and P15-10237).
Thus, the landscape of NSCLC therapies has rapidly been evolving beyond chemotherapy over the last few years. The discovery of oncogenic driver mutations has led to new ways in classifying NSCLC as well as offered novel therapeutic targets for anticancer therapy. Targets such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements have successfully been targeted with appropriate tyrosine kinase inhibitors (TKIs). Other driver mutations such as ROS, MET, RET, BRAF have also been investigated with targeted agents with some success in the early phase clinical setting. Novel strategies in the field of immune-oncology have also led to the development of inhibitors of cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 receptor (PD-1), which are important pathways in allowing cancer cells to escape detection by the immune system (P15-10237).
Despite this impressive progress, however, there remain many patients that are refractory to immune checkpoint inhibitors (e.g. nivolumab and pembrolizumab) or chemotherapy and who do not benefit from targeted agents against activating -mutations in the EGFR gene or the ALK translocation, such as afatinib or crizotinib, respectively. Clearly, therefore, novel agents against additional molecular targets are desperately needed. In this regard, the insulin growth factor-1 receptor (IGF-1R) is a heterodimeric transmembrane tyrosine kinase receptor that is a mediator of cellular proliferation and frequently overexpressed in NSCLC.

CDK4/6 inhibitors (Abemaciclib)
During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (R16-2249, R16-3704). The cyclin-dependent kinases (CDKs), CDK4 and CDK6 (hereafter designated CDK4/6), participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumour suppressor protein.

Alterations in this pathway occur frequently in human cancers, amongst others HR+ BC, NSCLC and Pancreatic Cancer, and involve 1) loss of CDK inhibitors by mutation or epigenetic silencing, 2) mutation/overexpression of either CDK4/6 or cyclin D, or 3) inactivation of Rb. These alterations render cells less dependent on mitogenic signalling for proliferation. With the possible exception of those tumours with complete inactivation of Rb, which functions downstream of the CDK4/6-cyclinD complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4/6. All of these cancers are potentially sensitive to pharmacologic inhibition of CDK4/6. From a therapeutic standpoint, the goal of inhibiting CDK4/6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumour growth in the cancers investigated in the present trial.

Targeting IGF in cancer (xentuzumab)
The insulin-like growth factor (IGF) signalling system consists of ligands (insulin-like growth factors 1 and 2 (IGF-1, IGF-2), IGF-binding proteins (IGFBPs), and receptors (IGF-1R, IGF-2R and insulin receptor IR)). Evidence that targeting IGF may be useful in cancer treatment was first recognized decades ago. Research in IGF signalling has shown that it controls key cellular activities, including proliferation, growth, and survival and is often deregulated in

neoplasia (R12-4524, P15-00363, P15-10395). There is experimental and clinical evidence that cancer cells express insulin and IGF-1 receptors. Expression of IGF-1R or its ligand is increased in a variety of cancers, including lung, colon, prostate, breast, ovarian, liver cancer and sarcoma (R12-4524, P15-00363, P15-10395). Therefore, the IGF system is an attractive tempting target for anti-cancer drug development.

Pharmacologic targeting strategies include inhibition of receptor function with anti-receptor antibodies or small molecule receptor tyrosine kinase inhibitors (R12-4524, P15-00363, P15-10395). Xentuzumab offers an alternative approach by acting as a ligand specific antibody. Most cancers express IGF-1 receptors, but there is evidence that autocrine and/or paracrine expression of ligands, particularly IGF-2, is deranged in neoplasm (R10-5355). In addition, the IGF-2 gene is an imprinted gene; loss of imprinting is one of several mechanisms leading to IGF-2 overexpression (R10-5694). Further, IGF-2 activates insulin receptor which was not targeted by any of the IGF-1 receptor monoclonal antibodies. Thus, targeting IGF-1 and IGF-2 by neutralization may lead to a higher probability of response to a therapeutic strategy and may confer an advantage over previously attempted approaches. Xentuzumab is a humanized monoclonal antibody directed against insulin-like growth factors 1 and 2 (IGF-1/-2) with the potential of anti-neoplastic activity. Despite encouraging preliminary evidence of clinical activity of several anti-IGF-1R agents, the therapeutic value of targeting the IGF/IGF-1R signalling system remains incompletely tested, given that the development of certain promising agents (e.g., figitumumab, ganitumab, dalotuzumab, R1507) has been discontinued in some indications. Efficacy signals generated by these and other agents warrant further exploration of the potential therapeutic value of targeting the IGF pathway in patients with various cancers.

1.2 DRUG PROFILE

For a more detailed description of the xentuzumab profile and abemaciclib profile please refer to the current Investigator's Brochure (IB) and for letrozole, anastrozole and fulvestrant to the SmPC or US PI.

Xentuzumab
Xentuzumab is a humanized IgG1 monoclonal antibody that binds with high affinity to IGF-1 and IGF-2, and potently neutralizes the proliferative and pro-survival cellular signalling triggered by both proteins. Mode of action differentiation to IGF-1 receptor (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.

At the cut-off date of 18 January 2019, a total of about 494 patients were treated in the xentuzumab clinical program: Eighty-one (81) patients were treated in two xentuzumab Phase I dose-escalation trials, examining a weekly and a three-weekly dosing schedule. Dose escalation to 1800 mg weekly or 3600 mg q3w did not identify a maximum-tolerated dose. A relevant biological dose for xentuzumab monotherapy in solid tumours was determined at 1000 mg weekly, used as the recommended dose for further Phase II trials (RP2D).
Moreover, in a phase Ib / randomized phase II study of xentuzumab in combination with everolimus and exemestane in patients with advanced or metastatic hormone-receptor positive

(HR+) breast cancer (Study 1280.4), 24 patients were treated in the dose escalation part (Ib) of this trial.
The MTD of xentuzumab was 1000 mg/week in combination with exemestane 25 mg/day and everolimus 10 mg/day, which was also determined as the RP2D.
Lastly, a completed phase Ib trial evaluates the safety and anti-tumour activity of xentuzumab in combination with afatinib in patients with non-small cell lung cancer with resistant to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. At the time of the data cut-off (18 January 2019), the safety profile was as expected for monotherapy of afatinib. The RP2D has been determined at 40 mg/day afatinib and 1000 mg/week xentuzumab.

No relevant hyperglycaemia has been observed so far. Xentuzumab was well tolerated, with no relevant side effects reported. The type and pattern of adverse events (AEs) observed to date have generally been of mild to moderate intensity (CTCAE Grades 1 or 2) or consistent with the safety profile of combination backbone treatment or consistent with the underlying neoplastic conditions of patients enrolled on the study. The most frequently reported AEs for xentuzumab monotherapy were fatigue, decreased appetite, nausea, diarrhoea, and vomiting. Infusion-related reaction (IRR) is a listed side effect of xentuzumab treatment.

Promising early efficacy signals in the dose escalation part of the 2 phase I studies have been observed with two confirmed antitumour responses (Partial Responses) according to RECIST criteria in a patient with nasopharyngeal cancer and a patient with a peripheral primitive neuroectodermal tumour (PPNET) or Ewing sarcoma. Moreover, twelve confirmed disease stabilizations (SD) have been observed in heavily pre-treated patients suffering from advanced or metastatic solid tumours. In the expansion cohorts at R2PD, no further objective responses have been observed.
At a planned interim analysis of the randomized phase II part, based on the recommendation of data monitoring committee, recruitment of phase II part was stopped and xentuzumab treatment was discontinued. According to latest analysis, in the overall population, PFS did not improve with the addition of xentuzumab to everolimus plus exemestane. Nevertheless, a favorable signal was observed in the pre-specified subgroup of patients without visceral metastasis (report c22665932-01).
In the aforementioned ongoing trial in HR+ metastatic breast cancer, the safety profile of xentuzumab in combination with everolimus and exemestane is considered favourable and as expected, since the observed safety profile of this triple combination is consistent with previously reported data for the combination doublet everolimus and exemestane (Bolero-2 trial) (Baselga et al. 2011: R12-5635). The same applies for the combination with enzalutamide in CRPC, where the safety profile of this doublet is consistent with previously reported data for enzalutamide (Affirm and Prevail trials) (R13-1229, R15-1307).

Abemaciclib
Abemaciclib (LY2835219) is a small-molecule inhibitor of CDK4 and CDK6 that is structurally distinct from other dual inhibitors (such as palbociclib and ribociclib) and notably exhibits greater selectivity for CDK4 compared with CDK6. Consistent with its activity against CDK4 and CDK6, abemaciclib inhibits Rb phosphorylation and leads to G 1 arrest in RB-proficient cell lines. In a colorectal cancer xenograft model used to develop an integrated pharmacokinetic/pharmacodynamic model, abemaciclib can be dosed orally on a continuous schedule to achieve sustained target inhibition and demonstrates not only durable cell cycle

inhibition but also single-agent antitumour activity. Abemaciclib demonstrates suitable physical and pharmacokinetic (PK) properties, an acceptable toxicity profile in nonclinical species, and antitumour activity in multiple mouse models of human cancer.
Tumour growth inhibition is observed in multiple other human cancer xenograft models, including those derived from non–small cell lung cancer (NSCLC), melanoma, glioblastoma, and mantle cell lymphoma. Abemaciclib distributes across the blood–brain barrier and prolongs survival in an intracranial glioblastoma xenograft model, suggesting potential efficacy against primary and metastatic tumours involving the central nervous system (R16-3982). Importantly, abemaciclib has demonstrated early evidence of activity against HR+ mBC with a confirmed objective response rate (ORR) of 19.7% in the recent Monarch 1 study (R16-5327).
Abemaciclib has been approved by US FDA for the treatment of metastatic breast cancer in three different settings. The approval include combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2− advanced or metastatic breast cancer (Monarch 3), in combination with fulvestrant for the treatment of women with HR+, HER2− advanced or metastatic breast cancer with disease progression following endocrine therapy. (Monarch 2), and as monotherapy for the treatment of HR+, HER2− advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting (Monarch 1).

The approval of abemaciclib plus fulvestrant was based on Monarch 2 study, which is a randomized, placebo-controlled study in women with HR-positive and HER2-negative metastatic breast cancer. A total of 669 patients who had disease progression following endocrine therapy and had not received chemotherapy for metastatic disease were randomized 2:1 to either oral abemaciclib or placebo plus intramuscular fulvestrant injection. Treatment was continued in the absence of disease progression or unmanageable toxicity. The study was positive for primary endpoint investigator-assessed PFS. Abemaciclib plus fulvestrant significantly improved PFS versus placebo plus fulvestrant (median 16.4 v 9.3 months, hazard ratio 0.553) (R17-2796).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

In early-phase clinical studies, abemaciclib has shown encouraging clinical activity in HR-positive breast cancer and NSCLC as well as other solid tumours with a favourable safety profile (Study JPBA and Monarch 1 trial; R16-3982, R16-5327). In September 2017, abemaciclib in combination with fulvestrant was approved by US FDA for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy (R18-2693). Oncogenic activation of the PI3K–mTOR pathway, which is governed by IGF1/IGF-1R, is also capable of stimulating cyclin D1–CDK4/6 activity, due in part to the increased translation of the cyclin D1 mRNA transcript, and to the stabilization of the cyclin D1 protein (see R16-3979). This scenario prompts the implementation of triple combination studies involving the addition of a IGF/IGF-1R signalling inhibitor such as xentuzumab, to the established antihormonal plus CDK4/6 inhibitor regimens in the present trial. It seems likely that CDK4/6 inhibitors will generally prove most effective when used in combination with other agents that either reinforce the cytostatic activity of CDK4/6 inhibitors or convert reversible cytostasis into irreversible growth arrest or cell death (R16-3979). In this regard, preclinical and clinical data indicate that aberrant regulation of the IGF system is attributed to the pathogenesis of breast cancer and also contributes to the resistance to endocrine therapy (R16-3981).
Despite recent progress in the treatment of metastatic NSCLC, these neoplasms basically remain intractable in the metastatic setting, with a median overall survival of less than 12 months in patients with stage IV disease. Hence, new therapeutic approaches are urgently warranted in these areas of high unmet medical need. The IGF/IGF-1R signalling network has also been implicated in the pathogenesis of NSCLC. Specifically, a large body of literature has highlighted the ability of IGF/IGF-1R to mediate resistance to other treatment modalities in NSCLC, and conversely has identified proteins capable of compensating for IGF-1R blockade (P15-00363).

Early evaluations of ongoing clinical trials of anti-IGF/IGF-1R agents including xentuzumab as a single agent, as well as in combination with everolimus and exemestane in HR+ BC (P16-09570), have shown clinical benefit (objective tumour responses or disease stabilizations) in patients with advanced and otherwise incurable cancers.

The insulin-like growth factor receptor (IGF-1R) signalling pathway has been an active area of oncology research for the last decade. IGF-1R is present on most cancer cells, and inhibition of this receptor slowed tumour growth and increased the antitumour activity of chemotherapy, radiation, and biologic agents in xenograft models. In addition, activation of the IGF-1R pathway has been postulated as a mechanism of signalling escape from other anticancer treatments including hormones and targeted agents, including CDK4/6 inhibitors.

In this regard, a drug synergy screen and network modelling in dedifferentiated liposarcoma recently identified CDK4 and IGF-1R as synergistic drug targets (R16-0845). Further experiments confirmed that combined inhibition of CDK4 and IGF-1R cooperatively suppresses the activation of proteins within the AKT pathway. These data suggest that dual

blockade of CDK4 and IGF1R signalling results in cooperativity such that two prosurvival pathways are inhibited.
More recently, Heilman and co-workers found that concurrent targeting of CDK4/6 and IGF-1R resulted in synergistic effects on proliferation of CDKN2A-mutant PaC cell lines in vitro and potent suppression of tumour growth in vivo, suggesting that alterations in these pathways converge to promote the growth of CDKN2A-deleted PaC cells (R16-0844).

This study therefore aims to determine the safety, toxicity and recommended phase II dose (RP2D) as well as potential early efficacy signals for the further development of the combination therapy of xentuzumab and abemaciclib in a variety of cancers with a high unmet medical need, especially NSCLC. In an attempt to further improve outcomes for patients with HR+ BC, the combination of abemaciclib, xentuzumab and hormonal therapy (fulvestrant) is also investigated in this trial in expansion cohorts to determine the RP2D and efficacy for that triple combination. After the US FDA's approval of abemaciclib in combination with fulvestrant and based on the above mentioned potential synergy with supports the triple combination (xentuzumab, abemaciclib, and endocrine therapy), expansion cohorts in patients HR-positive, HER2-negative advanced or metastatic breast cancer will be added to this trial to evaluate the efficacy and safety of triple combination of xentuzumab, abemaciclib, and fulvestrant. Early efficacy signal of addition of xentuzumab to new standard-of-care could be obtained in the expansion cohorts.

2.2 TRIAL OBJECTIVES

For each dose finding cohorts (A, B, C and D):
The primary objective of each dose finding cohort is to determine the maximum tolerated dose (MTD) / recommended phase II dose (RP2D) of xentuzumab in combination with abemaciclib with or without hormonal therapy (letrozole, anastrozole, fulvestrant). Dose limiting toxicities (DLT) will be assessed during the first treatment cycle to assess the MTD/RP2D.

In case that no MTD is reached a RP2D dose will be determined taking into account safety data and other available information. This will be agreed with the Steering Committee.

For each expansion cohorts (E, F, D1 and D2):
The objective of the cohort E is to assess the anti-tumour activity of xentuzumab in combination with abemaciclib in patients with non-small cell lung cancer.

Cohort F will assess the anti-tumour activity of the triplet combination xentuzumab / abemaciclib and fulvestrant in a single-arm expansion group of patients with locally advanced / metastatic hormone receptor positive (HR+) HER2- breast cancer who have progressed following prior therapy with an aromatase inhibitor and a different CDK4/6 inhibitor (excluding abemaciclib).

The primary objective of cohorts D1 and D2 is to assess the anti-tumour activity of the triplet combination xentuzumab, abemaciclib and fulvestrant in patients with locally advanced / metastatic HR+ breast cancer who have progressed on prior endocrine therapy. Cohort D1

will assess the anti-tumos activity for subjects with visceral metastasis and Cohort D2 for subjects with non-visceral metastasis.

[redacted]

2.3 BENEFIT - RISK ASSESSMENT

There is a high unmet medical need for patients with advanced or metastatic HR+ BC and NSCLC, as described in Sections 1.1 and 2.1. Both abemaciclib and xentuzumab have shown encouraging preliminary anti-cancer activity in early-phase clinical trials.

Therefore, and because this trial will enrol patients without curative therapeutic options, it is believed that patients with solid tumours, NSCLCor HR+ BC treated with xentuzumab plus abemaciclib with or without hormonal background therapy at standard doses will have better efficacy (clinical benefit) compared to abemaciclib with or without hormonal background therapy alone.

Abemaciclib
Hematologic toxicities including neutropenia, leukopenia, anaemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Patients will therefore be monitored closely for signs of infection, anaemia, and bleeding.
Gastrointestinal toxicities including diarrhoea, nausea, and vomiting have been observed in patients treated with abemaciclib, and causality has been established. Patients will therefore be monitored closely for gastrointestinal side effects. Patients with these symptoms will be evaluated promptly, treated supportively, and monitored closely for sequelae such as dehydration. Because diarrhoea possibly related to abemaciclib has been manageable with standard antidiarrheal agents such as loperamide, early treatment of diarrhoea is recommended in this trial.

Xentuzumab
As of 18 January 2019, xentuzumab was well tolerated in clinical trials, with no relevant specific side effects reported. The type and pattern of adverse events (AEs) observed to date have generally been of mild to moderate intensity (CTCAE Grades 1 or 2) or consistent with the safety profile of combination backbone treatment or consistent with the underlying neoplastic conditions of patients enrolled on the study. The most frequently reported AEs for xentuzumab monotherapy were fatigue, decreased appetite, nausea, diarrhoea, and vomiting.

Infusion-related reaction (IRR) is a listed side effect of xentuzumab treatment. There have been 3 serious IRRs reported. One event was Grade 3 or higher. All events recovered with management per protocol. Only 1 patient discontinued the study due to an infusion-related reaction. Infusions of xentuzumab should be administered under close supervision of a medically qualified staff member with availability of resuscitation facilities. As mannitol is

used in the formulation of xentuzumab, infusion durations of less than one hour should be avoided. Following each infusion, a one hour observation period is recommended.

Infusion reactions will be graded and treated following standard of care or local guidance in this trial.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.3.6.1.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of abemaciclib and xentuzumab may be found in the Investigators' Brochures (IBs) (see current versions). Information on AEs expected to be related to the investigational product may be found in Section 7 of the IBs. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Sections 6 (Effects in Humans) of the IBs.

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

During the trial, investigators are advised to manage treatment-related side-effects proactively. Suggested supportive care measures for the management of treatment related AEs and instructions for dose reductions for individual patients are provided in Section 4.4
Regular and frequent assessment of clinical benefit throughout the trial will ensure that any patient not deriving clinical benefit will be withdrawn from the trial treatment. The safety of all patients, dose selection and benefit/risk assessment are under frequent surveillance by a Steering Committee (SC) (refer to Section 3.1.1). The SC will carefully assess the observed benefits and adverse events and give advice on potential treatment discontinuation.
Based on the good safety profiles of xentuzumab and abemaciclib, as well as standard hormonal therapy with letrozole, anastrozole or fulvestrant, as single agents, it is expected that the combination treatment can be safely initiated at the doses specified in Section 4.1.2.

As part of the trial, patients are required to provide blood samples and archival tumour tissue to analyse candidate predictive biomarkers, pharmacokinetics and immunogenicity. For blood samples, in some instances this is already becoming standard clinical practice at specialised oncology centres, but for some patients this will be an additional procedure compared to routine clinical practice. Apart from that, there are no invasive procedures in addition to standard oncology practice.

Based on the disease under study, the inclusion of women of childbearing potential, using contraception as described in Section 4.2.2.3, in this study is justified. To minimize the risk of unintentional exposure of an embryo or foetus to the investigational drug, men and women of childbearing potential must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

Based on previous experiences with these drugs, the side effect profile is predictable and manageable for each compound. Safe doses will be established for each set of combination partners during the dose finding parts of the trial. It is expected that those combinations will improve the efficacy of abemaciclib in NSCLC as well as abemaciclib in combination with hormonal therapy in HR+ BC (i.e. letrozole, anastrozole, fulvestrant) by delaying or reversing the resistance mechanisms to these drugs. Additionally, abemaciclib and xentuzumab have exhibited preliminary activity signal in cancers with a high unmet medical need for a new treatment armamentarium.

Based on the pharmacological mechanism and existing non-clinical and clinical data, there is currently no definitive evidence that xentuzumab, either as monotherapy or in combination with abemaciclib/endocrine therapy, will increase the occurrence or worsen the outcomes of a COVID-19 infection. In the target population of patients with advanced or metastatic breast cancer and progression on at least one prior endocrine based regimen, the benefit-risk assessment for xentuzumab remains positive also in the presence of a COVID-19 outbreak.
The decision on whether to continue study drugs if a patient develops COVID-19 will be left to the investigator's benefit/risk assessment on a case-by-case basis. Based on laboratory data and any adverse event that may occur, the clinical trial protocol include guidance for continuation, interruption, dose reduction, and discontinuation of study drugs.

In conclusion, given the good tolerability profile, non-overlapping and manageable toxicities as well as preliminary activity of abemaciclib and xentuzumab as well as the established hormonal therapy (letrozole, anastrozole, fulvestrant) in the aforementioned life-threatening cancers with high unmet medical need, the potential benefits expected from xentuzumab in combination with abemaciclib with or without hormonal background therapy are anticipated to outweigh its risks.

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 of 1280-0022, as of 19 October 2021, Boehringer Ingelheim recommended to immediately discontinue xentuzumab treatment. Sites were also recommended to discontinue associated assessments, including central laboratory sampling.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is an open-label, non-randomised, phase Ib international, multicentre study of the combination of xentuzumab and abemaciclib (doublet) with or without a background of hormonal therapy, such as 2.5 mg letrozole or 1 mg anastrozole or 500 mg fulvestrant (referred to as triplets) .

The study consists of

- 4 dose finding cohorts (A, B, C, D (dose finding)) and
- 4 expansion cohorts (E, F, D1 and D2)

The different dose levels to be used at each cohort are described under Section 4.1.2.
The study will be conducted, chronologically, in 3 parts:

Part 1
Cohort A is a dose finding cohort in approximately 12 evaluable patients to determine the maximum tolerated dose (MTD) or recommended phase 2 dose ($RP2D_1$) of the doublet xentuzumab and abemaciclib in solid tumours. Once the $RP2D_1$ has been established Part 2 of this trial will commence.

Part 2 (all cohorts in part 2 can be conducted in parallel)
Cohort B is a dose finding cohort in approximately 12 evaluable patients to determine the maximum tolerated dose (MTD) or recommended phase 2 dose ($RP2D_2$) of the triplet xentuzumab and abemaciclib and letrozole in breast cancer.
Cohort C is a dose finding cohort in approximately 12 evaluable patients to determine the maximum tolerated dose (MTD) or recommended phase 2 dose ($RP2D_3$) of the triplet xentuzumab and abemaciclib and anastrozole in breast cancer.
Cohort D (dose finding) is a triplet-dose finding investigation in approximately 12 evaluable patients to determine the maximum tolerated dose (MTD) or recommended phase 2 dose ($RP2D_4$) of the triplet xentuzumab and abemaciclib and fulvestrant in breast cancer. Once the $RP2D_4$ has been established Part 3 of this trial will commence.
Cohort E is a single arm expansion in 20 NSCLC patients evaluable for response based on the abemaciclib and xentuzumab doublet $RP2D_1$ as defined in Cohort A.

Part 3
Cohort F will investigate the efficacy of the triplet combination with fulvestrant at the $RP2D_4$ of the abemaciclib and xentuzumab and fulvestrant triplet, as defined by cohort D data, in a single arm expansion cohort in 20 breast cancer patients evaluable for response. Based on the subgroup findings from the previous study 1280.4 (see Section 1.2), cohort F will recruit patients without visceral disease.
Cohort D1 and Cohort D2 will be opened once the $RP2D_4$ of Cohort D (dose finding) has been determined. At least 30 patients will be treated to evaluate anti-tumour activity, safety, and pharmacokinetics of the triplet combination in Cohorts D1 and D2. Cohort D1 will recruit patients with visceral metastasis (at least one visceral metastasis) and Cohort D2 will recruit patients with non-visceral metastasis (absence of visceral metastasis). Visceral metastasis is

defined as lung, liver, pleural, peritoneal, malignant pleural effusion and malignant peritoneal effusion involvement (i.e. an internal organ in the great cavity of the trunk proper) at the time of study entry.

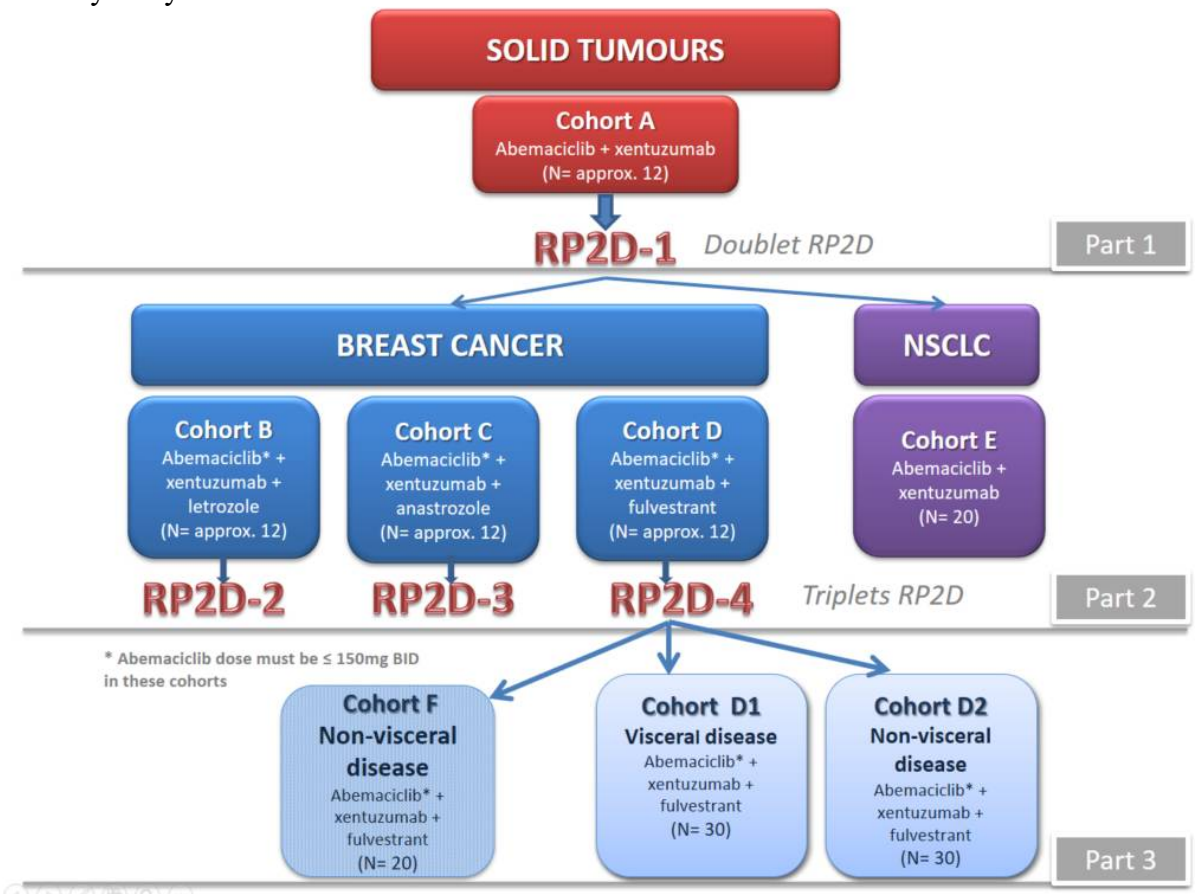


Figure 3.1:1 Trial Design

For dose finding cohorts A, B, C and D:
There are 4 dose-finding cohorts in this trial (i.e. cohorts A, B, C, and D). Each of them may end-up to a different RP2D (i.e. $RP2D_1$, $RP2D_2$, $RP2D_3$ and $RP2D_4$, respectively). For each dose finding cohort, dose (de-)escalation is guided by a Bayesian logistic regression model (BLRM) with overdose control (R13-4803) that will be fitted to binary toxicity outcomes. For further details, please refer to Section 4.1.2 and Section 7.1.

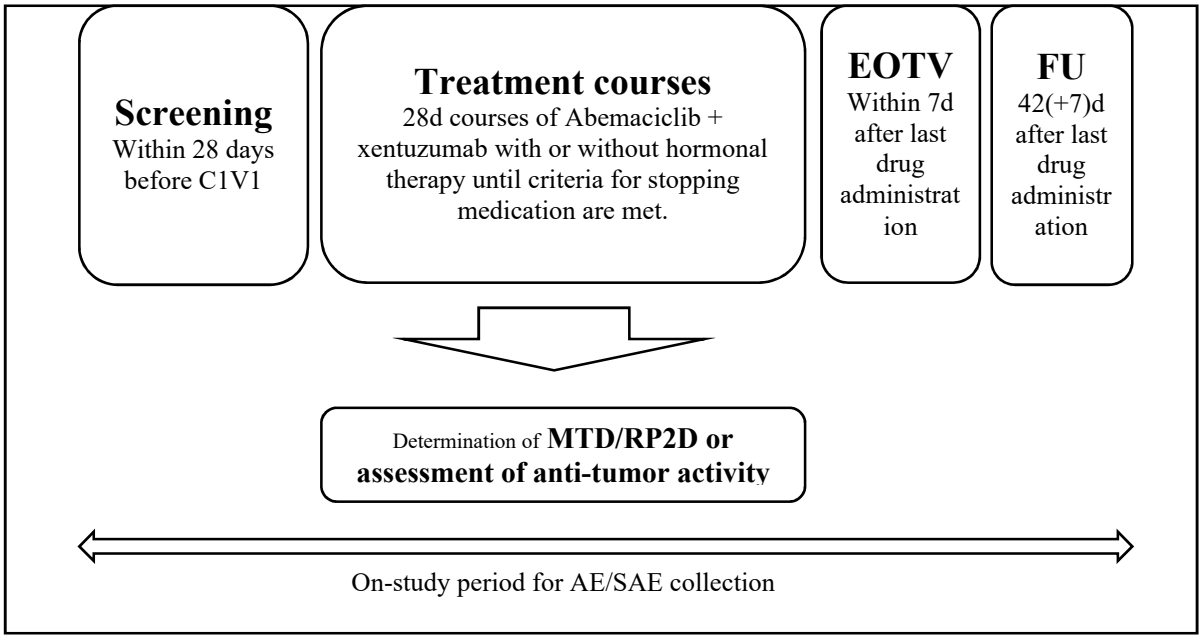


Figure 3.1:2 Trial plan for patients in Cohorts A, B, C, D (dose finding), D1, D2 and F

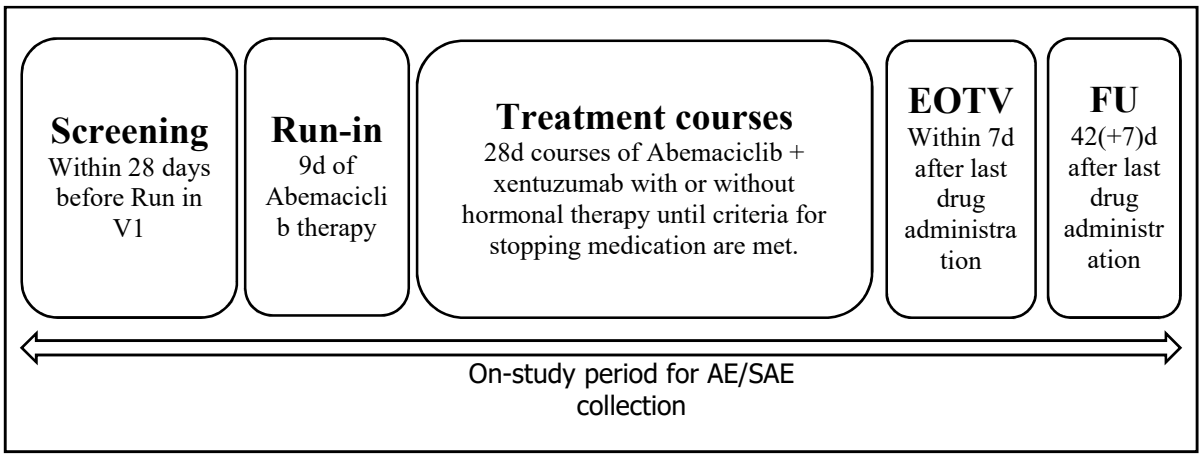


Figure 3.1:3 Trial plan for patients in Cohort E

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, 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 local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to 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.

A Steering Committee (SC) consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigator who will be the chair of the Steering Committee. The composition and the frequency of the meetings 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 an SC-charter filed in the TMF. The Steering Committee will monitor the trial on a regular basis (all operational aspects, recruitment issues, data quality, etc.) and will be responsible for advising on the escalation/de-escalation in the dose finding cohorts and the different RP2D's. The SC can also advice to stop a cohort or the trial based on the emerging clinical trial data.

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

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

All trial relevant documentation will be stored in the (e-) trial master file (e-TMF) at BI. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site.
Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

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

This is an open-label, phase Ib study consisting of 4 dose finding cohorts and 4 expansion cohorts. An open-label design is standard for a dose finding study. Inclusion of a control group is not required for this investigation.

As no data on the optimal dose for the xentuzumab/abemaciclib combination therapy exist so far, the study will first determine the $MTD_1/RP2D_1$ of the double drug regimen (in Part 1 cohort A) prior to further exploring its anti-tumour activity in Part 2.

The dose escalation/de-escalation steps and the dose-level cohort sizes (in each dose finding cohort) will be determined based on the recommendation of the SC, guided by a Bayesian model with overdose control. A potential escalation with overdose control design will increase the flexibility in terms of intermediate dose levels and number of patients in each dose-level cohort. This will increase the chance of treating patients at efficacious doses, while reducing the risk of overdosing. This design is not only an efficient method for dose finding studies, but also for dose confirmation studies due to its flexibility to react to unforeseen toxicity rates (R13-4802). This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802, R13-4804, R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the EMA guideline on small populations (R07- 4856) and by the FDA (R16-2270).

In expansion cohorts, a single arm design is justified as the trial is exploratory in its design to generate safety and efficacy data. If a positive efficacy signal is observed in this trial, a comparative trial may be considered if deemed justified.

The primary endpoint of the expansion cohorts is Objective Response (OR) or PFS rate, which is a well-accepted endpoint for such studies. OR rate defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period is used as primary endpoint for cohort E and F. PFS18 defined as the proportion of patients who were absence of disease progression or death at 18^{th} month is use as primary endpoint for cohorts D1 and D2. A good response of sufficient duration is reasonably likely surrogate for clinical benefit in refractory solid tumour indications or where there is no effective therapy.
PK assessments in the dose escalation cohorts (A, B, C, D (dose finding)) will be limited to the assessment of immunogenicity (anti-drug antibodies ADA) together with a concomitant PK sample for xentuzumab. The basic PK properties of each of the components have been described already.
The potential development of ADAs (immunogenicity against xentuzumab) will be monitored in all patients throughout the trial duration and beyond this (at EOTV and FUV). Regulatory guidelines recommend the monitoring of immunogenicity before, during and beyond treatment. A concomitant PK sample is necessary in order to assess whether an ADA sample result is conclusive or not and to monitor whether any effects of potential ADAs affect the drug concentration.

According to guidelines, combination therapies in oncology should be assessed for their potential effects on the exposure of each other. Therefore, PK investigations of the combination therapies in the trial will be conducted in the expansion cohort E for abemaciclib with xentuzumab and in the expansion cohorts D1 and D2 for fulvestrant with xentuzumab in an exploratory fashion. This approach ensures that a certain number of patients, treated at the same dose, can be evaluated. An intraindividual assessment of the PK of abemaciclib with and without xentuzumab treatment is planned for cohort E. These investigations are performed when the drug to be investigated is at steady state. In order to reach steady state levels with the

mono-treatment abemaciclib, a Run-in phase of 9 days is necessary. The assessment of the PK of the combination is planned to be performed at steady state as well. Xentuzumab reaches steady state after around 30d, therefore, the assessment of the combination treatment will be conducted in the second treatment cycle (that is >28 days after the first xentuzumab infusion). The exposure of xentuzumab will be evaluated descriptively and only a historical comparison to mono-treatment with xentuzumab will be done.

In cohorts D1 and D2 no intraindividual comparison of abemaciclib is planned. Exposure to abemaciclib, fulvestrant and xentuzumab is to be evaluated descriptively and only compared across cohorts or to historical or literature data for fulvestrant.

3.3 SELECTION OF TRIAL POPULATION

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

It is estimated that a total of about 148 evaluable patients will be necessary to determine the MTD or the Recommended Phase II Dose, pharmacokinetics and efficacy of xentuzumab and abemaciclib with or without background hormone treatment.

Part 1 of the trial will be conducted in about 3-6 sites in US, Europe and Japan. Parts 2 and 3 of the trial will be conducted in about 40 sites in US, Europe and Japan. If needed, sites from other regions may also participate. Each site is expected to enrol about one to five patients. If site(s) are unable to recruit patients, additional sites may be opened and underperforming sites may be closed.

3.3.1 Main diagnosis for trial entry

Patients to be included in this trial must have diagnosed and histologically, or cytologically, confirmed advanced and/or metastatic, measurable or evaluable, non-resectable solid tumours (Cohort A), or diagnosed and histologically, or cytologically, confirmed locally advanced and/or metastatic HR+ HER2- breast cancer (Cohorts B, C, D (dose finding), F, D1 and D2), or diagnosis of stage IV NSCLC (Cohort E).

Patients must not have received prior anti CDK agents (except cohort F) or previous treatment with IGF-1R targeting compounds in any setting.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

Cohort A (Solid Tumours)

1. Age ≥ 18 years (≥20 years for Japan only) at screening

2. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
3. WHO/ECOG performance status 0-1 assessed at screening
4. Patient must be able to swallow oral capsules or tablets.
5. Male or female patients ready and able to use highly effective methods of birth control during the study and for 3 weeks following the last dose of abemaciclib per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. Women of childbearing potential[1] must have a negative serum pregnancy test at screening.
6. Patients with histologically or cytologically confirmed diagnosis of advanced and/or metastatic, measurable or evaluable, non-resectable solid tumours
7. Patients must have received and failed, or have been intolerant to, all treatment known to confer clinical benefit or have no therapeutic options available as deemed appropriate by their treating physician
8. Life expectancy ≥ 3 months in the opinion of the investigator assessed at screening;

Cohorts B, C, D (dose finding) (Breast Cancer):

1. Age ≥ 18 years (≥20 years for Japan only) at screening
2. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
3. WHO/ECOG performance status 0-1 assessed at screening
4. Patient must be able to swallow oral capsules or tablets.
5. Women who have postmenopausal status due to either surgical/natural menopause or chemical ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin or radiation-induced ovarian suppression.
    - postmenopausal status due to surgical/natural menopause requires at least one of the following conditions:
        - prior bilateral oophorectomy
        - age ≥ 60 years
        - age < 60 years and amenorrheic (in the absence of tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months; and follicle-stimulating hormone (FSH) and estradiol within the postmenopausal range as per institutional reference ranges.
    - Postmenopausal status due to radiation-induced ovarian suppression must be confirmed by FSH and estradiol level in the postmenopausal range.
6. Histologically or cytologically proven diagnosis of breast cancer with evidence of locally advanced disease not amenable to curative resection or metastatic disease
7. HR+ (local lab results at screening or, if not available, at the time of diagnosis)

[1] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

To fulfil the requirement of HR+ disease, the primary tumour or metastatic lesion of the breast cancer must express at least one of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) by immunohistochemistry (IHC). Estrogen receptor and PgR assays are considered positive 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 (Hammond et al. 2010).

8. HER2 negative (local lab results at screening or, if not available, at the time of diagnosis) as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
9. Previous adjuvant and neoadjuvant chemotherapy is permitted. 0-2 prior lines of chemotherapy for the metastatic setting are allowed.
10. At least 1 lesion (measurable or non-measurable) that can be accurately assessed at baseline with CT or MRI or PET-CT (CT portion of diagnostic quality) and which is suitable for accurate repeated measurement.
11. Cohort B, C, D: Must be eligible for the corresponding hormonal therapy (letrozole, anastrozole or fulvestrant). For Cohorts B and C previous treatment with fulvestrant or exemestane is allowed. For Cohort D prior therapy with non steroidal aromatase inhibitors (anastrozole, letrozole) or exemestane are permitted**.**

Cohort E (NSCLC):

1. Age ≥ 18 years (≥20 years for Japan only) at screening
2. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
3. WHO/ECOG performance status 0-1 assessed at screening
4. Patient must be able to swallow oral capsules or tablets.
5. Male or female patients ready and able to use highly effective methods of birth control during the study and for 3 weeks following the last dose of abemaciclib per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information. Women of childbearing potential[2] must have a negative serum pregnancy test at screening.
6. Histologically or cytologically confirmed diagnosis of stage IV NSCLC.
7. The participant must have progressed after platinum-based chemotherapy AND immunotherapy (unless deemed inappropriate candidates for immunotherapy by their treating physician) AND have received 1 or a maximum of 2 other prior chemotherapy for advanced and/or metastatic disease OR must be judged by the physician as ineligible for further standard second-line chemotherapy. Prior treatment with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) and anaplastic lymphoma kinase (ALK) inhibitors is mandatory in participants whose tumour has EGFR-activating mutations or ALK translocations. Prior targeting agents and neoadjuvant/adjuvant therapies are permitted.
8. Have adequate organ function including haematology, renal, and liver.
9. Have measureable disease per RECIST 1.1.

[2] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

Cohort D1, Cohort D2 and Cohort F (Breast Cancer):

1. Age ≥ 18 years (≥20 years for Japan only) at screening
2. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
3. WHO/ECOG performance status 0-1 assessed at screening
4. Patient must be able to swallow oral capsules or tablets.
5. Women who have postmenopausal status due to either surgical/natural menopause or chemical ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin or radiation-induced ovarian suppression.
    - postmenopausal status due to surgical/natural menopause requires at least one of the following conditions:
        - prior bilateral oophorectomy
        - age ≥ 60 years
        - age < 60 years and amenorrheic (in the absence of tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months; and follicle-stimulating hormone (FSH) and estradiol within the postmenopausal range as per institutional reference ranges.
    - Postmenopausal status due to radiation-induced ovarian suppression must be confirmed by FSH and estradiol level in the postmenopausal range.
6. Histologically or cytologically proven diagnosis of breast cancer with evidence of locally advanced disease not amenable to curative resection or metastatic disease
7. HR+ (local lab results at screening or, if not available, at the time of diagnosis)
   To fulfil the requirement of HR+ disease, the primary tumour or metastatic lesion of the breast cancer must express at least one of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) by immunohistochemistry (IHC). Estrogen receptor and PgR assays are considered positive 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 (Hammond et al. 2010).
8. HER2 negative (local lab results at screening or, if not available, at the time of diagnosis) as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
9. Have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 3 weeks following the last dose of abemaciclib and for at least 6 months after last dose of xentuzumab if postmenopausal status is due to ovarian suppression with a GnRH agonist.
10. Have either measurable disease or non-measurable bone only disease. Measurable and nonmeasurable diseases are defined according to the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1 [v1.1]. Nonmeasurable bone only disease may include any of the following: blastic bone lesions, lytic bone lesions without a measurable soft tissue component, or mixed lytic-blastic bone lesions without a measurable soft tissue component.

Cohort D1 and D2 only:

11. Patients must fulfil 1 of the following criteria:
    a. Relapsed with radiologic evidence of progression while receiving neoadjuvant or adjuvant endocrine therapy, with no subsequent endocrine therapy received following progression.
    b. Relapsed with radiologic evidence of progression within 1 year from completion of adjuvant endocrine therapy, with no subsequent endocrine therapy received following progression.
    c. Relapsed with radiologic evidence of progression more than 1 year from completion of adjuvant endocrine therapy and then subsequently relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Patients may not have received more than 1 line of endocrine therapy or any prior chemotherapy for metastatic disease.
    d. Presented de novo with metastatic disease and then relapsed with radiologic evidence of progression after receiving treatment with either an antiestrogen or an aromatase inhibitor as first-line endocrine therapy for metastatic disease. Patients may not have received more than 1 line of endocrine therapy or any prior chemotherapy for metastatic disease.
12. For cohort D1 (visceral disease) patient must have at least one documented visceral metastasis; for cohort D2 (non-visceral disease), patient must not have any visceral metastasis.

Cohort F only:

13. Patients with resistance to prior therapy with an aromatase inhibitor (AI) and CDK4/6 inhibitor (excluding abemaciclib) for locally advanced or metastatic breast cancer, defined as radiologic evidence of disease progression while on, or within 30 days after last dose of AI and/or CDK4/6 inhibitor (excl. abemaciclib) administered as first-line therapy for locally advanced or metastatic disease. Patients may not have received more than 1 line of prior endocrine based therapy or any prior chemotherapy for advanced/metastatic disease.

14. Patient must not have any visceral metastasis (example of allowed lesions are in breast, lymph nodes, soft tissue, bone).

3.3.3 Exclusion criteria

Cohorts A, B, C, D (dose finding), and E:

1. Any documented active or suspected malignancy or history of malignancy, other than the disease under study, within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix or ductal carcinoma in situ (DCIS) if properly treated in opinion of the investigator.
2. Patients who must 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
3. Previous treatment in this trial

4. Currently enrolled in another investigational device or drug study, or less than 21 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
5. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial
6. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Men who plan to father a child while in the trial.
7. Prior anti-cancer chemotherapy, biological or radiation therapy, androgens, thalidomide, other anticancer agents, or any investigational drug within 21 days (14 days for non-myelosuppressive agents); and/or 4 weeks for immunotherapy, before starting any of the trial drugs.
8. Prior anti CDK agents
9. Prior radiotherapy to ≥ 25% of bone marrow regardless of when it was received
10. Unresolved treatment related toxicity from previous therapy of > CTCAE grade 1 at study entry (except for stable sensory neuropathy ≤ CTCAE grade 2 and alopecia)
11. Previous treatment with IGF-1R targeting compounds
12. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease, as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. History of CNS metastases or cord compression are eligible if they have been definitively treated (e.g. radiotherapy, stereotactic surgery) and are clinically stable, off anticonvulsants and steroids for at least 4 weeks. Patients with brain metastases are eligible if they are asymptomatic, completed radiotherapy for at least 4 weeks or are on a stable dose of steroids for at least 4 weeks. Patients are not eligible if they have spinal cord compression.
13. The patient has serious and/or uncontrolled pre-existing medical condition(s) that, in the judgement of the Investigator, would preclude participation in this study, including interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy.
14. Inadequate bone marrow reserve or organ function as demonstrated by any of the following: ANC < 1.5 x 10^9/L, platelets < 100 x 10^9/L, haemoglobin <90g/L, ALT > 2.5 x ULN or > 5 x ULN in the presence of liver metastases, total bilirubin >1.5 x ULN or >3 x ULN in patients with Gilbert's Syndrome, serum creatinine > 1.5 x ULN concurrent with creatinine clearance ≤ 50 mL/min.
15. Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis
16. Refractory nausea and vomiting, chronic GI diseases, inability to swallow the product, or previous significant bowel resection that would preclude adequate absorption of abemaciclib or resulting in baseline Grade 2 or higher diarrhoea.
17. History of hypersensitivity to active or inactive excipients of xentuzumab, abemaciclib or letrozole/anastrozole/fulvestrant, or loperamide hydrochloride, or drugs with similar chemical structures
18. Patients with Diabetes Type I or uncontrolled Type II (defined by HgBA1C > 8%).
19. Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% of liver involvement in metastases.
20. Prior hematopoietic stem cell or bone marrow transplant

21. Have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.
22. Erythropoietin, G-CSF, and GM-CSF are not allowed within 2 weeks prior to study. The primary prophylactic use of G-CSF is not permitted but it may be used to treat treatment-emergent neutropenia.
23. Have had major surgery (excluding biopsy) < 28 days of the initial dose of any of the study drugs or planned major surgery during study participation.
24. Have active bacterial or fungal infection (that is, requiring IV antibiotics or therapy at time of initiating study treatment), and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen, or hepatitis C antibodies). Screening is not required for enrolment.
25. Patients with baseline Grade ≥2 hyperglycaemia or patients with baseline Grade ≥ 2 diarrhoea
26. Patients needing treatment with CYP3A4 inhibitors/inducers cannot be included in the trial. (See Appendix 10.1)

Cohort D1, Cohort D2 and Cohort F (Breast Cancer):

1. Any documented active or suspected malignancy or history of malignancy (including inflammatory breast cancer), other than the disease under study, within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix or ductal carcinoma in situ (DCIS) if properly treated in opinion of the investigator.
2. Patients who must 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
3. Previous treatment in this trial
4. Currently enrolled in another investigational device or drug study, or less than 21 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
5. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial
6. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
7. Prior anti-cancer chemotherapy, biological or radiation therapy, androgens, thalidomide, other anticancer agents, or any investigational drug within 21 days (14 days for non-myelosuppressive agents); and/or 4 weeks for immunotherapy, before starting any of the trial drugs.For cohort F only: prior palbociclib or ribociclib treatment within 14 days before starting any of the trial drugs.
8. Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, everolimus, alpelisib or abemaciclib. For cohorts D1 and D2 only: prior treatment with palbociclib or ribociclib is also excluded
9. Prior radiotherapy to ≥ 25% of bone marrow regardless of when it was received
10. Unresolved treatment related toxicity from previous therapy of > CTCAE grade 1 at study entry (except for stable sensory neuropathy ≤ CTCAE grade 2 and alopecia)
11. Previous treatment with IGF-1R targeting compounds
12. Have clinical evidence or history of central nervous system metastasis. Screening is not required for enrolment.

13. The patient has serious and/or uncontrolled pre-existing medical condition(s) that, in the judgement of the Investigator, would preclude participation in this study, including interstitial lung disease, severe dyspnoea at rest or requiring oxygen therapy.
14. Inadequate bone marrow reserve or organ function as demonstrated by any of the following: ANC < 1.5 x 10^9/L, platelets < 100 x 10^9/L, haemoglobin <90g/L, ALT > 2.5 x ULN or > 5 x ULN in the presence of liver metastases, total bilirubin >1.5 x ULN or >3 x ULN in patients with Gilbert's Syndrome, serum creatinine > 1.5 x ULN concurrent with creatinine clearance ≤ 50 mL/min.
15. Pre-existing renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome or renal tubular acidosis
16. Refractory nausea and vomiting, chronic GI diseases, inability to swallow the product, or previous significant bowel resection that would preclude adequate absorption of abemaciclib or resulting in baseline Grade 2 or higher diarrhoea.
17. History of hypersensitivity to active or inactive excipients of xentuzumab, abemaciclib or fulvestrant, or loperamide hydrochloride, or drugs with similar chemical structures
18. Patients with Diabetes Type I or uncontrolled Type II (defined by HgBA1C > 8%).
19. Patients with advanced/metastatic, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term including patients with massive uncontrolled effusions (pleural, pericardial, peritoneal), pulmonary lymphangitis, and over 50% of liver involvement in metastases.
20. Prior hematopoietic stem cell or bone marrow transplant
21. Have a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.
22. Erythropoietin, G-CSF, and GM-CSF are not allowed within 2 weeks prior to study. The primary prophylactic use of G-CSF is not permitted but it may be used to treat treatment-emergent neutropenia.
23. Have had major surgery (excluding biopsy) < 28 days of the initial dose of any of the study drugs or planned major surgery during study participation.
24. Have active bacterial or fungal infection (that is, requiring IV antibiotics or therapy at time of initiating study treatment), and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen, or hepatitis C antibodies). Screening is not required for enrolment.
25. Patients with baseline Grade ≥2 hyperglycaemia or patients with baseline Grade ≥ 2 diarrhoea
26. Patients needing treatment with CYP3A4 inhibitors/inducers cannot be included in the trial. (See Appendix 10.1)
27. Have initiated bisphosphonates or approved RANK ligand (RANK-L) targeted agents (for example, denosumab) <7 days prior to initiation of any study drug.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes

careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

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

* The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
* The patient develops unequivocal disease progression, supported by radiological evidence where possible.
* The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication in the opinion of both the investigator and sponsor representative.
* The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
* 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. (See Section 4.3)
* The trial is terminated for any of the reasons listed in Section 3.3.4.2 ” Discontinuation of the trial by the sponsor”.

Given the patient’s agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and Section 6.2.3.
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial

As described in Section 2.3 Benefit-risk assessment, topline results of 1280-0022 showed no added benefit of xentuzumab compared to placebo when treating participants with metastatic breast cancer. Although xentuzumab treatment was recommended to be discontinued in 1280.18, continuation of treatment of patients with xentuzumab was based on an individual assessment by the investigator. Due to the worsening in benefit-risk, the trial will proceed towards termination based on the following 3 steps:

a. For xentuzumab-treated patients, the xentuzumab treatment will not extend past the drug expiration date (May 2023) of the last planned GMP manufacturing batch of IMP xentuzumab (provided that all patients are on xentuzumab for at least 2 years when they are tolerating the drug without tumor progression). Patients that will discontinue xentuzumab can still be eligible for continued treatment with abemaciclib and

fulvestrant (standard of care in this setting) provided they are tolerating the drugs without tumor progression.

b. When all patients have discontinued xentuzumab treatment, if any patient on abemaciclib and fulvestrant is able to continue taking these approved medications off study, then, at the request of the Sponsor, the patient may end such treatment as part of the trial and discontinue study participation (if both the Investigator and patient agree).
c. After all patients end treatment with all study drugs, the trial will be terminated.

3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

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

3.3.5 Replacement of patients

Patients may be replaced for determination of the primary endpoint (MTD) in cases of:

- Patient's withdrawal during the first cycle of treatment for reasons other than DLT, e.g. patient no longer wishes to participate, or lost to follow up during first cycle.
- Patients who do not experience DLT, but miss more than one dose of xentuzumab during the first cycle of treatment, except for dose interruption caused by AE
- Patients who do not experience DLT, but miss 3 or more consecutive doses of abemaciclib during the first cycle of treatment, except for dose interruption caused by AE.
- Patients who miss one complete cycle at any time beyond the first cycle of treatment may be replaced after discussion between the sponsor and the investigator.
- Patients who are non-evaluable with respect to DLT.
- Patients with CTCAE grade ≥3 allergic reaction/hypersensitivity to the study drug(s) within the first cycle may be replaced.
- For cohorts E and F, where objective response or DC is the primary endpoint: if patient doesn't have post-treatment radiological tumor assessment for reason other than worsening of underlying disease

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Patients will receive xentuzumab plus abemaciclib.
Additionally in cohorts B, C, D (dose finding), F, D1 and D2, patients will receive in addition background hormonal therapy with letrozole, anastrozole or fulvestrant.
The sources for each of the products are listed in Section 4.1.1.

As of 19 Oct 2021, based on the primary analysis of top line results of 1280-0022, Boehringer Ingelheim recommended to immediately discontinue xentuzumab in 1280.18 trial. (see Section 2.3)

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Xentuzumab (Investigational product, IMP)

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

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

Table 4.1.1: 2 Abemaciclib (Investigational product, IMP)

Substance:	Abemaciclib. Small molecule CDK4 and CDK6 inhibitor
Pharmaceutical formulation:	Capsules
Source:	[redacted]
Unit strength:	A white hypromellose capsule containing **50 mg** of abemaciclib and the inactive ingredients pregelatinized starch, dimethicone, and colloidal silicon dioxide.
Posology	Treatment/28-day cycle 150 mg p.o. Q12H on Days 1-28 (Starting dose Cohort A) Abbreviations: PO = orally; Q12H = every 12 (± 2) hours
Route of administration:	p.o.
Pharmaceutical formulation:	Tablets
Source:	[redacted]
Unit strength:	Film-coated 50 mg tablets
Posology	Treatment/28-day cycle 150 mg p.o. Q12H on Days 1-28 (Starting dose Cohort A) Abbreviations: PO = orally; Q12H = every 12 (± 2) hours
Route of administration:	p.o.

Table 4.1.1: 3 Fulvestrant. Background endocrine therapy. (Auxiliary Medicinal Product, AMP)

Substance:	Fulvestrant (Faslodex®)
Pharmaceutical formulation:	Solution for injection
Source:	[redacted]
Unit strength:	Prefilled syringes (250 mg fulvestrant in 5mL solution).
Route of administration:	Intramuscular injection

Table 4.1.1: 3 (cont.) Fulvestrant. Background endocrine therapy. (Auxiliary Medicinal Product, AMP):

Substance:	Fulvestrant (Faslodex®)
Posology	500 mg given once a month, with an additional 500-mg dose given two weeks after the first dose. Each dose is given as two slow 250 mg injections lasting one to two minutes, with one injection being given into the muscle of each buttock
Route of administration:	Intramuscular injection

Table 4.1.1: 4 Anastrozole. Background endocrine therapy. (Auxiliary Medicinal Product, AMP)

Substance:	Anastrozole
Pharmaceutical formulation:	Film Coated Tablet
Source:	EU, US or Japan commercial product as applicable
Unit strength:	1 mg
Posology	1 mg tablet once a day
Route of administration:	p.o.

Table 4.1.1: 5 Letrozole. Background endocrine therapy. (Auxiliary Medicinal Product, AMP)

Substance:	Letrozole
Pharmaceutical formulation:	Film coated tablet.
Source:	EU, US or Japan commercial product as applicable
Unit strength:	2.5 mg
Posology	2.5 mg once daily
Route of administration:	p.o.

4.1.2 Selection of doses in the trial

4.1.2.1 Part 1

A semi-mechanistic PK/PD model was developed describing the kinetics of the interaction between xentuzumab and the different PD biomarkers (i.e. IGF-1, IGF-2, and IGFBP3). 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 dose finding cohort A, the starting dose of abemaciclib is 150 mg every 12 (±2) hours. Based on the recommended phase II dose in one dose finding study using combination of a targeted therapy agent with xentuzumab (please refer to the current version of the Investigator's Brochure, c01690707-08), a dose level of 1000 mg with weekly dose schedule is selected as the starting dose for this study. This dose combination has a prior probability of overdosing below 25% (see Section 7.1). Planned dose levels for patients in cohort A are displayed in Table 4.1.2.1: 1 below.

Table 4.1.2.1: 1 Concomitant dosing schedule schemes of Cohort A

Dose level	Xentuzumab (mg weekly)	Abemaciclib (mg/12h)
DL0 (starting dose)	1000	150
DL-1a	750	150
DL-1b	1000	100

Dose escalation beyond the highest dose levels planned as shown above will not be considered. Above dose levels may be modified and/or additional dose levels/administration regimens may be added based on safety profile and other emerging data upon discussion and agreement between the sponsor and the SC.

Intra-patient dose escalation is not permitted. Successive dose-level cohorts of patients will receive doses of xentuzumab in combination with abemaciclib until the $MTD_1/RP2D_1$ is established or until the trial is terminated for other reasons (see Section 3.3.4.2). The trial may be terminated at any time based on emerging safety concerns without establishing the $MTD_1/RP2D_1$.

For any dose-level cohort, at least 3 evaluable patients will be required. However, in the case that only 2 patients are evaluable and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these 2 patients.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that dose-level cohort will be stopped. The BLRM will then be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

After all patients in the initial dose-level cohort have either experienced a DLT or have been observed for at least one course (28 days) without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The SC will then determine the dose regimen for the next dose-level cohort, based on the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post-cycle 1), recommendations from the BLRM, and other data (e.g. anti-tumour activity, pharmacokinetics) if applicable. Details on the Bayesian design are provided in Sections 7.1 and Appendix 10.6.

The overdose risk will be calculated for each further dose combination, and patient enrolment into dose levels will be permitted to all dose combinations which fulfil the escalation with overdose control (EWOC) criterion. Based on the Bayesian model and the additional information as defined above, the SC will decide on the next dose level to be investigated. In the SC meeting, data for each patient in the current dose-level cohort will be described in detail, updated safety data on other ongoing patients, including data in later courses, will be discussed as well.

The SC must reach a consensus on whether to de-escalate, re-escalate and/or expand recruitment into particular cohorts, or to declare the $MTD_1/RP2D_1$. BI will prepare minutes from the SC meetings and circulate them to each Investigator.

To further assess the safety (e.g. specific suspected treatment-related adverse events) of xentuzumab in combination with abemaciclib, one or several doses that are considered acceptably safe, i.e. shown to be lower than or equal to any potential MTD, may be explored to determine the $RP2D_1$. Nevertheless, a minimum of 6 evaluable patients need to be treated at the $MTD_1/RP2D_1$ in the dose finding cohort A prior to starting part 2 (cohorts B, C, D and E) and any dose declared as $MTD_1/RP2D_1$ by the SC needs to fulfil the escalation with overdose control (EWOC) criteria.

The SC may recommend stopping the dose finding cohort A after the criterion for MTD (Section 7.1) is fulfilled. Further patients may be included to confirm the $MTD_1/RP2D_1$ estimate, i.e. to confirm that the EWOC criterion is still fulfilled prior to the start of part 2 (cohorts B, C, D and E).

4.1.2.2 Part 2

The decision on dose escalation/de-escalation, MTD (or Biological Relevant Dose) and RP2D will be determined in discussion with at least BI Trial Clinical Monitor, BI project physician (TMM) and Coordinating Investigator and taking into account patients' safety. This decision will be documented.

Dose finding cohorts B, C and D (dose finding):
For each cohort, starting dose of xentuzumab and abemaciclib will be the $RP2D_1$ determined in cohort A, even if $RP2D_1$ equals the highest dose levels planned (see Table 4.1.2.1: 1). This is because the maximum dose of abemaciclib to be explored in triple combination cohorts is 150mg b.i.d. In that case, the starting dose would then be 1000 mg weekly xentuzumab plus 150 mg / 12h abemaciclib.

In the three cohorts, patients will receive the dose of background hormonal therapy as defined in Tables 4.1.1: 3 to 4.1.1: 5 (i.e. letrozole in cohort B, anastrozole in Cohort C and fulvestrant in cohort D).

Dose escalation/de-escalation of xentuzumab and abemaciclib will be conducted as described in Section 4.1.2.1 for cohort A using a BLRM with a fixed dose of the background hormonal therapy.

Expansion cohort E:
Patients will be treated at the $RP2D_1$ determined in Cohort A.

4.1.2.3 Part 3

Cohorts F, D1 and D2
For Cohort F and Cohorts D1 and D2 patients will be treated at the $RP2D_4$ of abemaciclib and xentuzumab and fulvestrant triplet as determined in Cohort D (dose finding).

4.1.3 Method of assigning patients to treatment groups

For the dose finding cohorts, the treatment slots are assigned by the BI Clinical Monitor (CM) in close communication (email/phone/fax) with the recruiting sites and IRT system and will be assigned on a competitive basis. After the BI Clinical Monitor has been notified by a site about a potential patient, the slot will be reserved to this site for a period of time (approximately a week) until patient signs ICF, otherwise the slot will be opened up again for all recruiting sites. If more than one site notifies potential patients and there are no slots for all proposed candidates, BI Clinical Monitor will allocate the slot prioritizing by planned visits calendar, balanced number of patients per site and other parameters as applicable.

Patients that meet the eligibility criteria and who have given their written informed consent may not be entered into the study depending on the cohort which is being explored at that particular time (for example, but not restricted to, the dose finding cohort A). This needs to be discussed and agreed with BI Trial Team.

Prior to inclusion of a new patient, once the slot has been confirmed, the investigator should also confirm the respective dose with the BI clinical monitor.

4.1.4 Drug assignment and administration of doses for each patient

The treatment medication assignment for xentuzumab and abemaciclib will be managed through IRT system. The treatment medication assignment for anastrozole, letrozole and fulvestrant will be managed through IRT system in certain countries only.
In addition, patient's screening, run-in, all drug dispensation visits and EOTV will be collected in the IRT system.

4.1.4.1 Initial study drug assignment and administration

General information that applies in this study regardless of IRT is described in below sections of individual study drug. The medication kit as well as the treatment will be assigned with the support from IRT.
Before entering patients at the next dose level of the dose finding cohorts, it will be ensured that all patients at the current ongoing dose level have completed at least one course of treatment.

Xentuzumab
Patients will start treatment with their assigned dose tier (see Section 4.1.2) or RP2D of xentuzumab from course 1 day 1. Xentuzumab will be administered at the investigator site intravenously over one hour with a constant infusion rate on the treatment day as specified in the Flow Chart. If scheduled infusion of xentuzumab is not performed within the time window, this treatment will be skipped and will not be made up. Subsequent visits should follow the original visit date schedule. Mannitol is used in the formulation of xentuzumab, 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 specific eCRF. The accuracy of this information is crucial for the proper evaluation and appraisal of the pharmacokinetics – in the relevant cohorts – and other data.

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

Abemaciclib
Abemaciclib will be taken orally every 12 (± 2) hours on days 1 through 28 of a 28-day cycle for a total of 56 doses per cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

No more than 56 doses of abemaciclib should be dispensed for each 28-day cycle.
Abemaciclib dose omissions will be evaluated on a case by case basis and patients may be replaced if dose omissions occur within MTD period of a dose finding cohort or if the number of dose omissions makes the patient non evaluable regardless of the cohort.

4.1.4.2 Temporary treatment interruption and dose reduction

DLT, or those AEs requiring dose adjustment as indicated on the label, should be managed by treatment interruptions and subsequent dose reductions of the presumed causal study drug(s) according to the schedule described in Table 4.1.4.2: 1. Please also refer to Section 4.4 for additional recommendations.

In case of an intolerable adverse event which is suspected to be related to either xentuzumab or abemaciclib in the opinion of investigator, the treatment can be interrupted with subsequent dose reduction for the suspected agent(s) according to Tables 4.1.4.2: 1 (xentuzumab) and 4.1.4.2: 2 (abemaciclib).
In the case of DLT with suspected overlapping toxicities where assigning relatedness to one study drug or the other is difficult, or considered related to both xentuzumab and abemaciclib the dosing with both study drugs should be held until the adequate resolution of AE (CTCAE grade ≤1). Treatment should then be resumed and/or dose reduced as shown in Table 4.1.4.2: 1 for xentuzumab and in Table 4.1.4.2: 2 for abemaciclib.

Recurrent in the context of dose interruptions and delays refers to the same event and severity occurring within 8 weeks (as measured from the stop date of the first event). This does not

include events in the same class (for example, neutropenia followed by anemia 1 month later).

Further to these recommendations, in Part 1, Cohort A, both xentuzumab and abemaciclib must be paused when a DLT occurs during the first treatment course.

The treatment should be paused until patient has recovered from the DLT to grade ≤ 1 or baseline. Baseline is defined as the CTCAE grade at the start of treatment. For patients who develop DLT, treatment may be resumed at reduced dose according to dose reduction scheme of the patient's starting dosage. If a patient has not recovered to Grade ≤ 1 or baseline within 28 days, study treatment must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with study drug(s) will be decided in agreement between the sponsor and the investigator.

If one or more of the study drugs is permanently discontinued, the patient can remain on either abemaciclib or xentuzumab or endocrine therapy only.

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

Abemaciclib dose adjustments are allowed within a cycle and between cycles. Abemaciclib must be reduced sequentially by one dose level. For further instructions as regards dose adjustments of abemaciclib, please refer to Section 4.2.2.

For patients requiring dose reduction(s) of abemaciclib, any re-escalation to a prior dose level is permitted only after discussion and agreement with the sponsor. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table 4.1.4.2: 1 Individual dose reductions schedule

Xentuzumab mg/weekly		Abemaciclib mg/12 h	
Current dose is 1000	Dose reduce to 750	Current dose is 150	Dose reduce to 100
Current dose is 750	Dose reduce to 500	Current dose is 100	Dose reduce to 50
Current dose is 500	No further dose reductions allowed.	Current dose is 50	No further dose reductions allowed.

No dose reduction is allowed below 500 mg/weekly for xentuzumab or 50 mg b.i.d. for abemaciclib.
Alternative dose modification scheme can only be considered after discussion and agreement between the investigator and the BI clinical monitor.

In the event of any unrelated AEs, the study drug(s) may be interrupted for up to 28 days, but no dose reduction should occur. Otherwise, the decision to continue with the study treatment will be made by the BI Clinical Monitor in agreement with the investigator.

Table 4.1.4.2: 2 Dose Adjustments and Delays for Toxicity Possibly Related to Abemaciclib*

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity	Recurrent Grade 3[1]	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: If **patient requires administration of blood cell growth factors.**	Regardless of severity. (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.
Nonhematologic Toxicity[2] (except diarrhoea, ALT increase and ILD/pneumonitis)	Persistent or recurrent[3] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ILD/pneumonitis[5]	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
ILD/pneumonitis	Grade 3 and 4	Dose **MUST** be discontinued	NA
Nonhematologic Toxicity	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhoea	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose MUST be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.

Table 4.1.4.2: 2 (cont.) Dose Adjustments and Delays for Toxicity Possibly Related to Abemaciclib*

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Diarrhoea	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhoea	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Increased ALT	Persistent or Recurrent[3] Grade 2 (>3.0-5.0xULN), or Grade 3 (>5.0-20.0xULN)[4]	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Increased ALT with increased total bilirubin, in the absence of cholestasis	Grade 3 (>5.0xULN) with total bilirubin>2xULN	Abemaciclib **MUST** be discontinued	NA
Increased ALT	Grade 4 (>20.0xULN)	Abemaciclib **MUST** be discontinued	NA

*In case that the Toxicity Profile and Severity qualifies for DLT according to Section 5.3.7, dose suspension and dose reduction will be followed according to the DLT management instructions

[1] Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- shows stable hematological counts (Grade ⩽2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

[2] Additional guidance for renal monitoring is in Section 4.4.1
[3] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).
[4] Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 4.4.4 for additional guidance for hepatic monitoring
[5] For Japan only: refer to local amendment in Japan for ILD guidance

Abbreviation: ASCO = American Society of Clinical Oncology.
Note: MAY = per the investigator's clinical judgment; MUST = mandatory.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial.
The trial will be handled in an open fashion by the Sponsor during the conduct, data cleaning and preparation for analysis.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). 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.

4.1.7 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 for anastrozole, letrozole and fulvestrant. For recommended storage conditions regarding abemaciclib and xentuzumab, please refer to the medication label. A temperature log must be maintained for documentation.

Abemaciclib will be supplied as capsules or tablets for oral administration. The capsules and tablets should be stored at room temperature according to the range provided on the product label and not opened, crushed, or dissolved. Investigators should instruct patients to store the capsules and tablets in the original package and in a location inaccessible to children. Clinical study materials will be labelled according to country regulatory requirements.

Xentuzumab is supplied as a liquid formulation at a concentration of 10 mg/mL in 20 mL single use vials, which contain 200 mg of xentuzumab per vial. All vials containing xentuzumab must be kept refrigerated according to the temperature range provided on the product label prior to dosage preparation.
The vials should not be frozen or shaken and should be kept in the outer carton in order to protect from light. They should not be used beyond the expiration date.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately and product quarantined.

4.1.8 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 trial protocol by the IRB / ethics committee and HA approval,
* Availability of a signed and dated clinical trial contract between the sponsor and the head of 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 Form 1572 (USA specific requirement)

The Investigator and/or Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. 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 investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, 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

There are no special emergency procedures to be followed.

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

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

All medications (other than study drug), including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, and significant non-drug therapies (including physical therapy and blood transfusions) starting or changing after the patient signed informed consent must be listed on the concomitant medication page of eCRF including trade name, start and end dates, indication for use etc. as specified in the Flow Chart.

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

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, including but not limited to immunotherapy, hormonal cancer therapy, radiation, experimental medications, or surgery for cancer will be permitted while patients are on study treatment. Use of megestrol acetate as an appetite stimulant is not permitted.

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) to abemaciclib by 3.4 fold (Study JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study JPBF). Therefore, grapefruit juice should be avoided and inducers and strong inhibitors of CYP3A should be substituted or avoided whenever possible (See Appendix 10.1).

During PK assessments of abemaciclib, the concomitant use of inhibitors or inducers of CYP3A4 should be avoided whenever possible, i.e. during Run-In, course 1 and course 2 of cohort E and during course 1 and 2 of expansion cohorts D1, D2 and F.

Apart from those assessments, patients are recommended to avoid concomitant use of strong CYP3A inhibitors and use caution with coadministered moderate or weak CYP3A inhibitors. Patients who continue to take strong CYP3A inhibitors should reduce the abemaciclib dose. In patients who are taking the starting dose of 150 mg twice daily, reduce the abemaciclib dose to 100 mg twice daily or, specifically in the case of ketoconazole, the abemaciclib dose should be reduced to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. If a patient taking abemaciclib discontinues a strong CYP3A inhibitor, increase the abemaciclib

dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Please refer to current SmPC of Verzenio (abemaciclib).

In case it is unavoidable to treat a patient with a comedication that is a moderate to potent inducer or inhibitor of CYP3A4 dose adaptation of abemaciclib should be done as described above and according to the SmPC of Verzenio (abemaciclib). Furthermore, the patient should be closely monitored and precautions should be taken as described in the SmPC of Verzenio (abemaciclib).

Abemaciclib can be coadministered with drugs which are substrates of CYP enzymes.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin, dofetilide, or dabigatran should be substituted or avoided if possible.

Restrictions regarding concomitant treatment with fulvestrant, letrozole or anastrozole: please refer to the most up to date labelling information of each product, as appropriate (i.e. depending on the treatment cohort).

4.2.2.2 Restrictions on diet and life style

Patients have to show up in fasting condition at the site when blood draw for safety lab is required.

Grapefruit and/or Seville orange juices must be avoided during treatment with abemaciclib.

4.2.2.3 Restrictions regarding men and women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information, and must be used from the screening period until 3 weeks following the last dose of abemaciclib and at least 6 months after the last dose of xentuzumab.

Men should not father a child during treatment with xentuzumab and for at least 70 days after the last dose of xentuzumab.

4.2.2.4 Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care based on the judgment of the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the BI clinical monitor.

Use of any supportive care therapy should be reported on the electronic case report form (eCRF).

4.2.2.5 Growth Factor Therapy

Growth factors may be administered in accordance with American Society of Clinical Oncology guidelines (Smith et al. 2006; Rizzo et al. 2008).

4.2.2.6 Therapy for Diarrhoea

At enrolment, patients should receive instructions on the management of diarrhoea. In the event of diarrhoea, supportive measures should be initiated as early as possible. These include the following:

* At the first sign of loose stools, the patient should initiate anti-diarrheal therapy, if not already receiving such therapy (for example, loperamide), and notify the investigator/site for further instructions and appropriate follow-up.
* Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
* Site personnel should assess response within 24 hours.
* If diarrhoea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, study drug should be suspended until diarrhoea is resolved to baseline or Grade 1.
* When study drug recommences, dosing should be adjusted, refer to the dose adjustment guidelines in Section 4.1.4.2.

In cases of significant diarrhoea, Grade 2 through 4 which has not responded to interventions as outlined above, if the investigators are considering the addition of steroids to treat potential colitis, the sponsor strongly recommends an endoscopic procedure to document colitis prior to initiating steroids.

In severe cases of diarrhoea, the measuring of neutrophil counts and body temperature and proactive management of diarrhoea with antidiarrheal agents should be considered.

If diarrhoea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhoea or any grade of diarrhoea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

4.2.2.7 Ovarian suppression with gonadotropin-releasing hormone agonists

Patients who are postmenopausal due to ovarian suppression should continue GnRH agonist therapy during study treatment.

4.3 TREATMENT COMPLIANCE

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

A patient will be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than 125% the prescribed amount of abemaciclib or less than 75%. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered as noncompliant. Same rules apply to background hormonal therapy.

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on counts, treatment compliance will be calculated as the number of doses taken, divided by the number of doses which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of doses actually taken} \times 100}{\text{Number of doses which should have been taken}}$$

If the number of doses taken is not between 75-125%, site staff will explain the patient the importance of treatment compliance.

The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results.

Xentuzumab 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 is not administered to the patient, it must be documented and explained.
A maximum of three consecutive xentuzumab infusions may be skipped for the recovery from AEs. Missing xentuzumab treatment for any other reasons is considered non-compliant.

Patient diary for cohort E
For the purpose of PK characterisation of abemaciclib, patients of cohort E will be dispensed a patient diary two times during the conduct of the study: at run-in visit 1 and again at Cycle 1 visit 4. These patient diaries will collect information about daily intake of abemaciclib and potential vomiting events. The first patient diary will collect information during the 3 days prior to Run-In Visit 3. The second patient diary will collect information of the 3 days before Cycle 2 Visit 1. Site staff will be required to transfer the data from the patient diary into the corresponding eCRF fields.

4.4 MANAGEMENT OF EXPECTED ADVERSE EVENTS.

4.4.1 Increased Serum Creatinine

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular filtration rate (GFR [as measured by ioxhexol clearance]). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing (remainder elevated but stable through the treatment period), were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function such as blood urea nitrogen, cystatin C, or calculated GFR based on cystatin C.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Section 4.1.4.2).

4.4.2 Management and grading of infusion reactions

The xentuzumab infusion should always be administered under close supervision of a medically qualified staff member with immediate availability of appropriate resuscitation facilities.
Infusion reactions may occur during infusion with xentuzumab and include pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension and hypertension. **A one hour observation period is recommended following each infusion.** If there is no infusion reaction during the first treatment course, the observation period following xentuzumab infusion may be adjusted at the discretion of the investigators. Mild to moderate infusion reactions may be managed with a slower infusion rate and prophylactic antihistamines for subsequent dosing. Severe reactions require immediate and permanent discontinuation of infusion. The hypersensitivity reactions will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R10-4848).

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

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.

Infusion reactions will not be reported on the standard AE page but will be reported on a separate page specifically for infusion reactions in the CRF.

Table 4.4.2: 1 Infusion reaction management

Infusion Reaction Grade	Management
CTCAE Grade 1 or 2	In the event of a CTCAE grade 1 infusion reaction, the infusion rate should be reduced by 50%. A Grade 2 infusion reaction may require symptomatic treatment, as described above (with infusion interruption). Once the event has resolved, the infusion may be restarted at the reduced rate.
CTCAE Grade 3	For patients experiencing a CTCAE grade 3 infusion reaction, 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 hours since the infusion start. The infusion rate should be reduced by half after re-start
CTCAE Grade 4	Patients experiencing CTCAE grade 4 such as anaphylaxis during an infusion should have infusion immediately stopped and receive appropriate treatment, as described above, including use of resuscitation medications If needed. Such patients should NOT receive any further xentuzumab treatment.

4.4.3 Management of Neutropenia

Adverse events of neutropenia have been observed in studies with xentuzumab and causality has been established with abemaciclib. Patients should be monitored closely for signs of infection. Dose adjustment for severe neutropenia (≥ Grade 3) should follow as per Table 4.1.4.2: 1 (xentuzumab) and Table 4.1.4.2: 2 (abemaciclib) in the protocol. Fever or infection in the presence of severe neutropenia should be managed promptly with broad-spectrum antibacterial therapy.

4.4.4 Management of Hepatotoxicity

Grade ≥3 increased ALT was reported in patients receiving abemaciclib in breast cancer studies. Monitor ALT, prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Please refer to Flow Chart for time points. Based on the level of ALT elevations, abemaciclib may require dose modification. (see Table 4.1.4.2:2).

In addition, for hepatic toxicity, additional monitoring should be considered. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (see Section 10.5) and in consultation with the Sponsor. Monitoring of ALT, AST, and total bilirubin should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

4.4.5 Venous Thromboembolism

Venous thromboembolic events were reported in patients receiving abemaciclib plus fulvestrant or aromatase inhibitors in breast cancer studies. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

4.4.6 Guidance for Interstitial lung disease/Pneumonitis

ILD/pneumonitis has been identified as an adverse drug reaction for abemaciclib. Additional information is available in the IB of abemaciclib.
Ask your patients to report any new or worsening respiratory symptoms such as cough, dyspnea, fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging such as high resolution computed tomography (HRCT), broncheoalveolar lavage, and biopsy as clinically indicated. Refer to Table 4.1.4.2:2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis. Discontinue abemaciclib in cases of severe ILD/pneumonitis.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

For dose finding cohorts A, B, C, and D (dose finding):

The primary endpoints for each dose finding cohort are the MTD and the number of patients with dose limiting toxicities (DLT) in the MTD evaluation period.

The MTD evaluation period is defined as the first treatment cycle (28 days). The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 33%. For definition of DLTs, refer to Section 5.3.7

A Bayesian Logistic Regression Model (BLRM) employing the escalation with overdose control (EWOC) principle will be used during each dose finding cohort for a selection of doses to investigate and for estimation of the MTD. Cohorts of patients will receive xentuzumab and abemaciclib (with or without endocrine therapy) until the MTD is reached or until the Steering Committee (SC) decides on stopping the dose finding. Each dose-level cohort will consist of newly enrolled patients. Estimation of the MTD during each dose finding cohort of the study will be based upon the estimation of the probability of a DLT in the MTD evaluation period in the set of evaluable patients for MTD. The corresponding methodology is described in Section 7.

The MTD estimate established during the dose finding cohort will be re-investigated after the corresponding expansion cohort by re-running the BLRM including all data from dose finding cohort and expansion cohort, in particular also considering the DLT information from all treatment cycles.

For expansion cohort E
The primary endpoint for expansion part is objective response (OR) defined as best overall response of complete response (CR) or partial response (PR), where best overall response is determined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 from date of first treatment administration (including run-in for cohort E) until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

For expansion cohorts D1 and D2:
The primary endpoint for expansion part is PFS rate at 18 month defined as the rate of absence of disease progression or death at 18th month, where progression is determined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.

For expansion cohort F
The primary endpoint for expansion part is disease control (DC) defined as best overall response of complete response (CR) or partial response (PR) or confirmed stable disease (SD) (lasting for at least 24 weeks) or Non-CR/ Non-PD (lasting for at least 24 weeks) where best

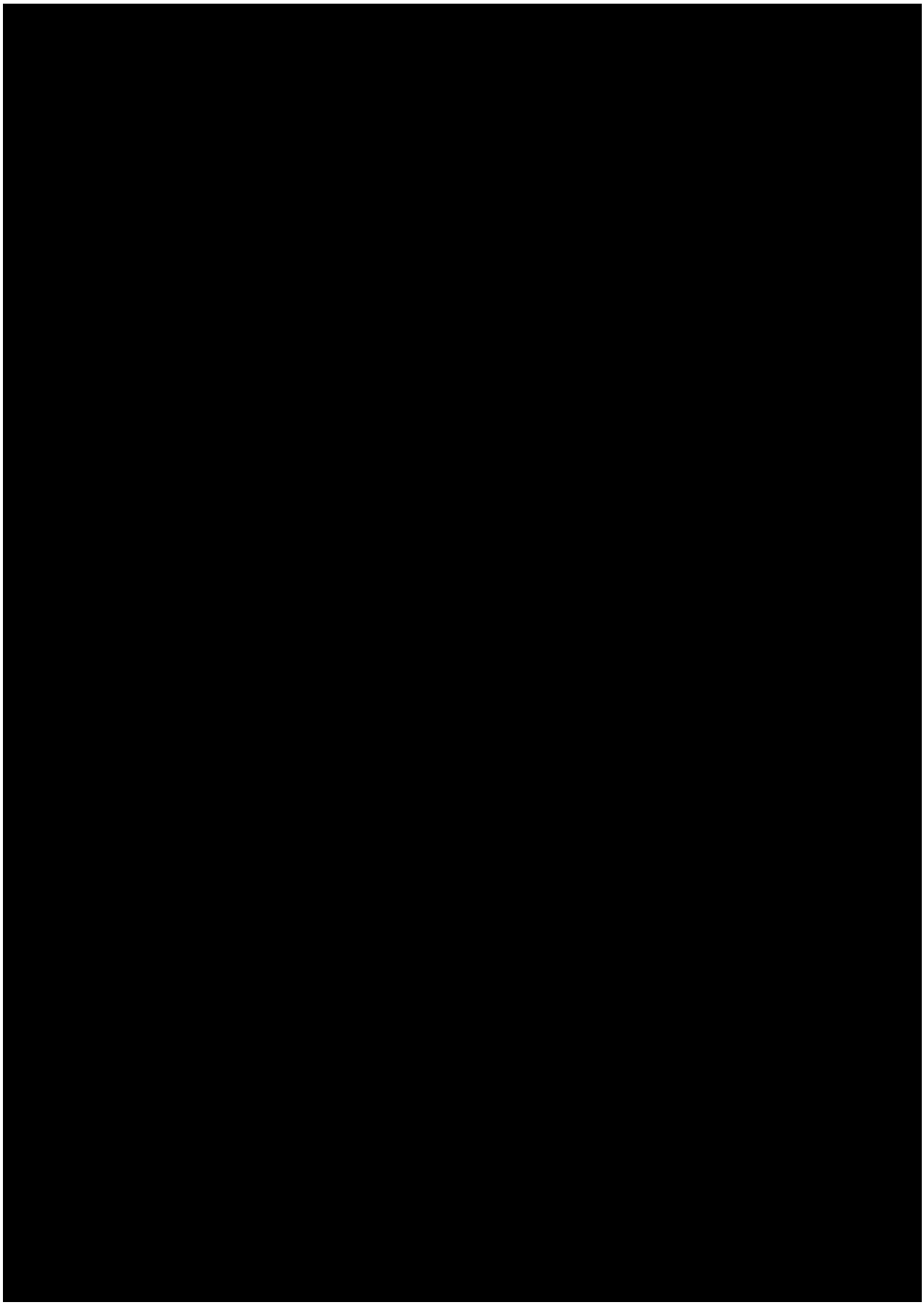
overall response is defined according to RECIST version 1.1 from first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

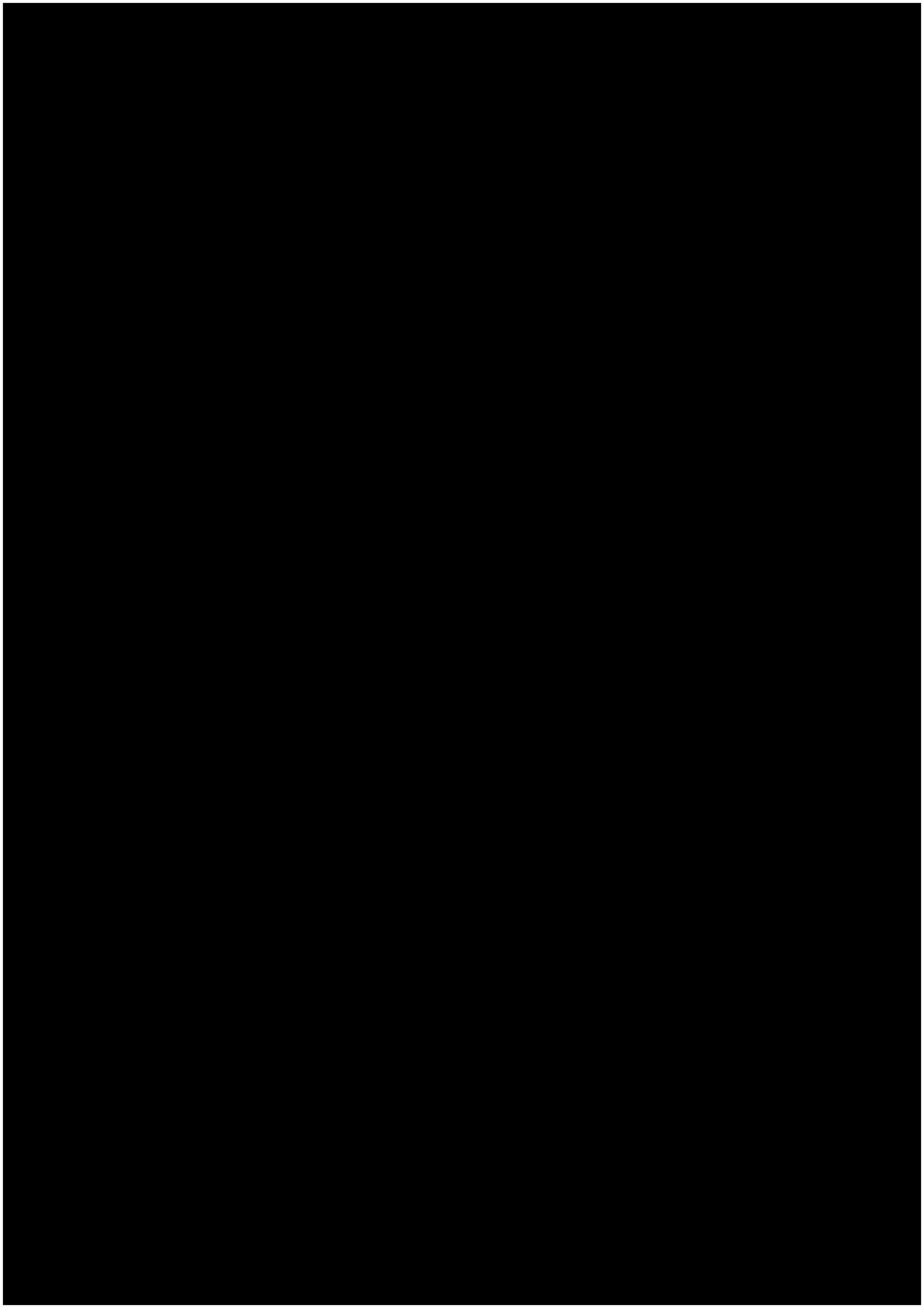
5.1.2 Secondary Endpoint(s)

For dose finding cohorts A, B, C, and D (dose finding)
There are no secondary endpoints.

For expansion cohorts E, F, D1 and D2:
The secondary endpoints are:

* Cohorts D1, D2 and E only: Disease control (DC) defined as best overall response of complete response (CR) or partial response (PR) or confirmed stable disease (SD) (. lasting for at least 24 weeks) where best overall response is defined according to RECIST version 1.1 from first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.
* Time to objective response defined as the time from first treatment administration until first documented complete response (CR) or partial response (PR).
* Duration of objective response defined as the time from first documented complete response (CR) or partial response (PR) until the earliest of disease progression or death among patients with objective response.
* Duration of disease control defined as the time from first treatment administration until the earliest of disease progression or death, among patients with disease control.
* Progression-free survival (PFS) defined as the time from first treatment administration until tumour progression according to RECIST 1.1 or death from any cause, whichever occurs earlier.
* Cohorts D1, D2 and F only: Objective response (OR) defined as best overall response of complete response (CR) or partial response (PR), where best overall response is determined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 from date of first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.





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5.2 ASSESSMENT OF EFFICACY

Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) (R09-0262) will be applied as the primary measure for assessment of tumour response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy). See Appendix 10.4 for details on lesion measurements and response assessment according to RECIST 1.1.

Tumour response will be assessed by Investigator review throughout the study and clinical decisions will be based on Investigator assessment.

Imaging will be performed as indicated in the Flow Chart and in Appendix 10.4.

Tumour assessment will be assessed per institutional practice. Only the overall response will be collected in the eCRF.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at the time points specified in the Flow Chart. A full physical exam must include cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination must be clarified. Wherever possible the same investigator should perform this examination.

When xentuzumab is discontinued, physical examination assessments can be done as per institutional practice.

5.3.2 Vital Signs

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

When xentuzumab is discontinued, vital signs assessments can be done as per institutional practice.

5.3.3 Safety laboratory parameters

Blood samples, including fasting serum samples (fasting state for at least 8 hours) and the fasting lipid profile, can be collected up to one day prior to the scheduled time points as specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations include haematology, coagulation, biochemistry and urine examination. See Table 5.3.3: 1 for details. In case of abnormal findings such as neutropenia or thrombocytopenia, further test may be done if clinically indicated at the discretion of the investigator. All analyses are to be performed by the local clinical laboratory. Unscheduled safety laboratory examinations will be documented in the eCRF along with the results.
Safety laboratory assessment may be performed according to local practice but must include at least all of the following parameters:

Table 5.3.3: 1 Clinical laboratory tests

Category	Parameters
Haematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, white blood cell count (WBC) with differential (neutrophils[1], lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	Blood urea or blood urea nitrogen (BUN), creatinine, cystatin-C (day 1 of every cycle), alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), bilirubin (total and direct), total protein, 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
Pregnancy TEST	Serum (for women of childbearing potential only)
Electrolytes	Sodium, potassium, calcium, magnesium
Lipid profile (fasting)	Total cholesterol, triglycerides, LDL, HDL
Other (fasting)	Glucose, HbA1C and C-peptide
Urinalysis (only at screening and EOTV)	pH, protein, glucose, erythrocytes, leucocytes, ketones and nitrite will be analysed by dipstick (semi-quantitative measurements: -, +, ++, +++); in case of pathological finding further evaluation should be performed and results documented

Table 5.3.3: 1 Clinical laboratory tests (cont.)

Category	Parameters
Post-menopausal status (at screening only for women <60 years old without prior bilateral oophorectomy)	FSH, estradiol

[1] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be reported together

When xentuzumab is discontinued, safety labs can be done as per institutional practice.

5.3.4 Electrocardiogram

As per ICH E 14 large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies, which is not the case for xentuzumab.
Therefore, only local reading of ECG will be conducted in this trial. 12-Lead resting electrocardiograms (ECG) are recorded locally and in triplicate. ECG will be performed at Screening, at Run in visit 2 Day -2 (in cohorts E and F), at EOTV and FUV. ECG will be repeated at Visit 1/Day 1, and Visit 3/Day 15 of Courses 1, 2, 3; and at Visit 1/Day 1 of Courses 6, 9, 12, etc. ECG should be performed prior to xentuzumab infusion.

When xentuzumab is discontinued, ECGs can be omitted.

5.3.5 Other safety parameters

Not applicable.

5.3.6 Assessment of adverse events

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) and includes periodic physical examinations, measurement of vital signs, assessment of performance status, monitoring of laboratory tests (i.e. haematology, chemistry, coagulation, urine, etc.)

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a 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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this 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
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

For Japan only: the following events will be handled as "deemed serious for any other reason". An AE which possibly leads to disability will be reported as an SAE.

AEs considered "Always Serious"
Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
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 given above.

The latest list of "Always Serious AEs" can be found in the EDC system.

These events should always be reported as SAEs as described above.

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

The following are considered as AESIs:

Hepatic injury is defined by the following alterations of hepatic laboratory parameters:
For patients with normal liver function (ALT, AST, and bilirubin within normal limits) at baseline, an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN.

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

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

DLT occurs in the dose finding cohorts. Please refer to Section 5.3.7 for definition of DLTs.

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

Intensity of AEs

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

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 drug class.
- 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 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course 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 study drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patient files.
The following must be collected and documented on the appropriate eCRF(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 (including the REP) until the individual patient's end of trial:
  - All related SAEs and all 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 only report relevant SAEs and relevant AESIs of which the Investigator may become aware of. The rules for Adverse Event Reporting exemptions still apply.

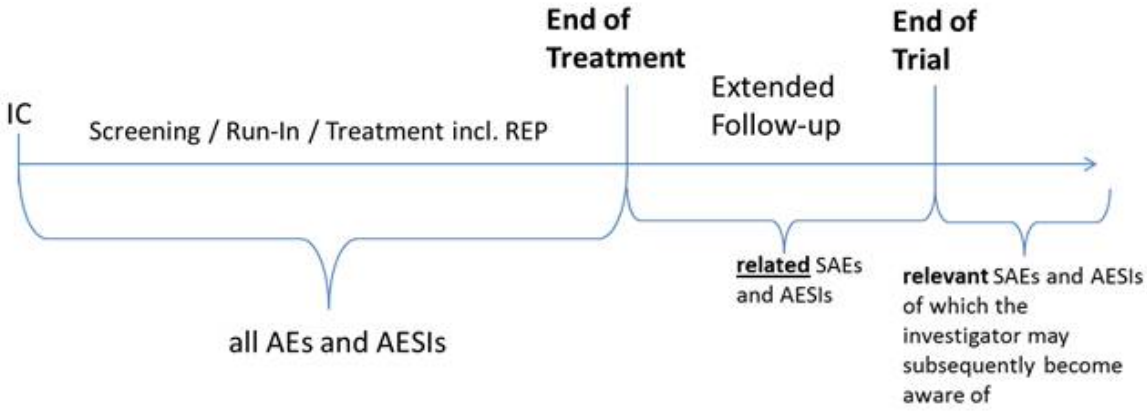

Figure 5.3.6.2: 1 AE collection periods

The REP is defined as 42 days after the last trial medication application. All AEs which occurred through the treatment phase (which includes the run-in period) and throughout the REP will be considered as on treatment; please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF).

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 fax the BI SAE form.

For Japan only: all SAEs must be reported immediately to the head of the trial site.

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. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP)
The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions (see Section 5.3.6.3 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 trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy
In rare cases pregnancy or pregnancy in a female partner of a male participant may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) including drug exposure to female partners of male participants to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (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 Clinical Trials 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.

5.3.6.3 Exemption to (S)AE 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 (e)CRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on the SAE Form.
However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the (e)CRF.

Examples of exempted events of PD may be:

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

Exempted events are collected and tracked following a protocol-specified monitoring plan. Exempted events will be monitored at appropriate intervals by the Steering Committee.

5.3.7 Dose Limiting Toxicities (DLTs)

A dose limiting toxicity (DLT) in this study is defined as an adverse event or laboratory abnormality which 1) is considered related, probably related or possibly related to study drug and 2) meets any of the following criteria, unless that toxicity can be clearly attributed to cancer progression or to another clearly identified etiology:

- CTCAE Grade 3 hyperglycaemia lasting > 48 hours
- CTCAE Grade 4 hyperglycaemia
- CTCAE Grade ≥ 3 pneumonitis
- CTCAE Grade ≥ 3 febrile neutropenia
- CTCAE Grade 4 hematologic toxicity lasting longer than 5 days
- CTCAE Grade 4 thrombocytopenia of any duration and Grade 3 thrombocytopenia associated with bleeding
- AST or ALT > 5x ULN (for baseline AST/ALT ≤ ULN) or > (baseline value + 4x ULN) (for baseline AST/ALT > ULN)
- CTCAE Grade ≥ 3 diarrhoea, nausea, or vomiting lasting more than 2 days despite maximal supportive care
- CTCAE Grade ≥ 3 skin rash despite adequate supportive care measures
- CTCAE Grade ≥ 3 fatigue/asthenia lasting for more than seven days
- Grades 3 to 4 hyperlipidaemia (total cholesterol > 400 mg/dL or triglycerides > 500 mg/dL) not improving despite appropriate treatment for 2 weeks

- Any AE necessitating a 2-week treatment interruption (except for hematologic AEs)
- All other non-hematologic toxicities of CTCAE Grade ≥ 3 (except alopecia, infusion-related reaction and those mentioned above)
- Any other study drug related toxicity considered significant enough to be qualified as DLT in the opinion of the investigators, and confirmed by the safety review with the BI clinical monitor and BI project physician (TMM), will be reported as a DLT

For the purposes of dose finding, only DLT events that occur during the first treatment period of 28 days will be considered. Decisions regarding dose escalation/de-escalation steps will be made only after discussion between the sponsor and the investigators, and in consideration of all the available safety information. Available data of DLTs occurring after first treatment course and all unusual/unexpected AE at any time during treatment will be considered for the purpose of recommending the dose for cohorts B, C, D (dose finding), E, F, D1 and D2.
All DLT events that meet AESI criteria need to be reported immediately to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.3.6.2, and documented in the eCRF.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

As of 22 Oct 2021, samples for PK are no longer collected for ongoing patients.

PK samples will be collected from all patients in this trial at the time points specified in the Flow Chart and in Appendix 10.2 (minimal deviations in the time scheduled will not be considered as protocol violation). The actual sampling date and time for blood samples will be reported in the eCRF and will be used for determination of PK parameters. To allow a valid PK analysis, it is of utmost importance to document the exact clock time of trial medication administration and blood sample collection. Any occurrence of vomiting should be documented as well. The duration of the xentuzumab infusion will be reported with a start and end time in the eCRF. Every attempt should be made to adhere to an infusion time of approximately 1 h for xentuzumab with a constant infusion rate.
At days of PK sampling of abemaciclib (cohorts E, F, D1 and D2) patients should be instructed to take their morning dose of abemaciclib in the hospital (and not at home as usual). This is necessary in order to allow for a valid PK sampling schedule. For details of the PK sampling schedule, please refer to Appendix 10.2.

PK parameters will be evaluated according to Section 5.1.3. Non-compartmental PK analysis will be done in order to calculate PK parameters (Section 5.1.3) using Phoenix WinNonlin (or other validated software) according to BI SOP 001-MCS-36-472 (current version).

5.4.2 Methods of sample collection

As of 22 Oct 2021, samples for PK and ADA are no longer collected for ongoing patients.

Blood samples should be obtained from the arm opposite to the arm used for infusion. In case a central venous access is used for infusion, the blood sample can be collected from either forearm. The actual sampling date and time (24-hour clock time) 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 in the respective cohorts and courses is shown in Appendix 10.2. For details on blood volumes to be collected, sample handling and logistics refer to the ISF (Laboratory Manual).

For quantification of plasma concentrations of abemaciclib and relevant metabolites, blood samples will be taken at the time points listed in the Flow Chart under PK sampling. A detailed sampling schedule in the respective cohorts and courses is shown in Appendix 10.2. For details on blood volumes, sample handling and logistics refer to the ISF (Laboratory Manual).

For quantification of fulvestrant plasma concentrations, blood samples will be taken at the time points listed in the Flow Chart under PK sampling. A detailed sampling schedule in the respective cohorts and courses is shown in Appendix 10.2. For details on blood volumes, sample handling and logistics refer to the ISF (Laboratory Manual).

For ADA assessment, blood will be taken at the time points listed in the Flow Chart under ADA sampling. The exact timing of ADA sampling before, during and beyond the treatment phase is also shown in Appendix 10.2. For details on blood volumes, sample handling and logistics refer to the ISF (Laboratory Manual).

Plasma samples from the study may be used for further methodological investigations, e.g., stability testing. However, only data related to the analyte and/or bioanalytical assay will be generated by these additional investigations. Both PK and ADA 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.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned.
Correlation between drug concentration and any type of response may be made if appropriate. Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modelling techniques, if feasible. For this purpose data may also be combined with those from other trials. Modelling activities will be planned and documented separately.

5.5 ASSESSMENT OF BIOMARKER(S)

As of 22 Oct 2021, samples for biomarkers are no longer collected for ongoing patients.

In this clinical study explorative biomarkers will be measured and analysed. These analyses are hypothesis generating and will be used to expand our understanding of the study drug and the disease. Participation in the biomarker analyses is mandatory for patients from all cohorts.

Evaluation of molecular and biochemical biomarkers in tumour tissue:
Tumour tissue samples will be collected from all patients (except when there is no tumour tissue sample available) to explore the potential influence of molecular and biochemical alterations within the tumour on treatment response and outcome. No biopsies should be done for the only purpose of obtaining tumour tissue for this trial. Tumour tissue samples will be analysed for:

- Mutations and copy number alterations in genes related to the study drugs and involved in tumourigenesis, such as genes of the IGF, PI3K/mTOR, Ras/MAPK, Rb and related signalling pathways (e.g. IGF1R, PIK3CA, PTEN, KRAS, MYC, CCND1, CDK4, CDK6, RB1 and CDKN2A)
- RNA expression of IGF, PI3K/mTOR, Ras/MAPK and cell cycle-related signalling pathways (e.g. IGF1, IGF2, IGFBP-family genes, MYC, CCND1, CDK4, CDK6)
- Expression of Rb and p16 proteins via biochemical methods (e.g. IHC). According to additional knowledge gained from other studies with xentuzumab and/or abemaciclib broader analysis of the samples (including immunohistochemistry/in-situ hybridization/sequencing of e.g. IGF-1/2, PTEN, pAKT, pS6, Ki67) might be conducted to e.g. address predictive biomarkers, exceptional response or resistance mechanisms.

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

Molecular evaluation in blood:
Three kinds of blood samples will be collected for genomic analyses from blood and plasma.

One blood sample will be used to isolate genomic DNA, which will be used as a reference (normal tissue) to distinguish tumour acquired somatic mutations and will be analysed for the indicated panel of genes as in the tumour tissue and/or in the cfDNA (see above).

Secondly, blood samples will be collected and used to isolate circulating nucleic acids such as e.g. cfDNA from plasma. Subsequent analyses of plasma cfDNA may be used for example to detect somatic mutations in cancer genes, e.g. IGF pathway-related and known cancer driver genes. Additionally, changes in nucleic acid concentration over course of treatment may be explored. Analysis of cfDNA 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).

Thirdly, blood samples will be collected and used to evaluate exosomal RNA from plasma. Subsequent analyses of plasma exosomal RNA using standard molecular technology will include, but not be limited to, cell cycle and proliferation related genes, e.g. CCND1, Ki67, RB1, CDK4, CDK6 and CDKN2A.

Methods of sample collection
Formalin fixed paraffin embedded (FFPE) tumour tissue, preferably FFPE blocks, from the most recent time point before entering the study will be collected during screening or at a later timepoint (see Flow Chart, Table 5.5: 1 and Table 5.5: 2 and Appendix 10.3). The FFPE blocks will be used to prepare 25 slides at 5µm thickness. Alternatively, 25 freshly prepared slides at 5µm thickness from FFPE block can be provided but need to be prepared under RNase-free conditions. Isolated nucleic acids (e.g. DNA and RNA) from the tumour tissue will be analysed for genomic alterations such as somatic mutations and copy number alterations as well as RNA expression levels as described above.

In addition, patients will be asked for three kinds of blood samples:

One blood sample will be collected at C1V1 before treatment (see Flow Chart and Table 5.5: 1 and Table 5.5: 2). The isolated DNA will be analysed for genomic alterations in a panel of cancer -related genes as mentioned for the tissue and/or the cfDNA above serving as a reference to allow distinction of tumour-acquired somatic mutations from normal tissue.

For analysis of circulating nucleic acids, blood samples will be collected in plasma preparation tubes at each indicated time point before treatment (Run-in and/or C1V1), at C3V1 and at EOTV (see Flow Chart and Table 5.5: 1 and Table 5.5: 2). The samples will be used to isolate and analyse circulating nucleic acids as described above.

For exosomal RNA analyses, blood samples will be collected in EDTA tubes at each indicated time point before treatment is administered to patient (where applicable): At Run-in and/or C1V1, at C1V3 (Day 15), at C2V1, at C3V1, at C4V1 onwards and at the EOTV, (see Flow Chart and Table 5.5: 1 and Table 5.5: 2). Separation of the plasma from the remaining blood should be performed. The samples will be used to isolate circulating exosomes and analyse exosomal components such as e.g. RNA.

Table 5.5: 1 Overview PGx sample collection timepoints for cohorts A-D (dose finding) and expansion cohorts D1, D2 and F.

Sample	Timepoints						
	Screening	C1V1	C1V3	C2V1	C3V1	C4V1 onwards[1]	EOT
Archival tumour tissue	X						
PGx blood (gDNA)		X					
PGx Plasma (cfDNA)		X			X		X
PGx Plasma (Exosomes)		X	X	X	X	X	X
DNA banking		X					

[1] Refer to the central laboratory manual instructions.

Table 5.5: 2 Overview PGx sample collection timepoints for cohort E

Sample	Timepoints							
	Screening	Run-in V1	C1V1	C1V3	C2V1	C3V1	C4V1 onwards[1]	EOT
Archival tumour tissue	X							
PGx blood (gDNA)		X						
PGx Plasma (cfDNA)		X	X			X		X
PGx Plasma (Exosomes)		X	X	X	X	X	X	X
DNA banking		X						

[1] Refer to the central laboratory manual instructions.

Remaining samples from pharmacogenomic analyses such as tumour tissue, blood or plasma samples (and isolated DNA and RNA) will be destroyed no later than 1 year after the end of the trial if no optional consent for sample biobanking is obtained from the patient (see Section 5.5.1).

Detailed instructions for pharmacogenomic sampling, handling and shipment of samples will be provided in the lab manual.

The biomarker analyses will be performed by Boehringer Ingelheim or a central laboratory authorized by Boehringer Ingelheim.

Protein biomarkers from blood:
The following protein biomarkers are planned to be examined in this trial:

- Free and total IGF-1 in serum (and optionally free and total IGF-2, dissociable IGF-1 and IGF-2, and total IGFBP-3)
- Phosphorylated and total IGF-1R protein in platelet-rich plasma

Serial collection of blood samples for the assessment of these markers is mandatory. As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that come to be known as potentially relevant prognostic/predictive markers of treatment response may also be explored via available tissues/blood or acquisition of additional tumour tissues/blood. Biomarkers that come to be known or emerge as not relevant during the study may be discontinued.

All samples must be adequately labelled by the study site personnel. Details about blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the ISF (laboratory manual).

Biomarker assessments in blood samples
Levels of free and total IGF-1 (optionally IGF-2 and the amount of IGFBP-3) 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 defined as the fraction of total IGF-1 (and total IGF-2) that can be bound by xentuzumab under modified, i.e. more highly diluted in vitro 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. Optionally, total IGFBP-3 will be relatively quantified in serum using a validated immunoassay.

For quantification of free and total IGF-1 (and optionally free and total IGF-2 and IGFBP-3), blood will be taken from a forearm vein at those time points specified in the Flow Chart and Appendix 10.2.

Quantification of IGF-2 and IGFBP-3 will be performed if scientifically justified based on results of ongoing clinical studies with xentuzumab (e.g. 1280.4).

Biomarkers in platelet-rich plasma
In platelet rich plasma, the level of phosphorylated and total IGF-1R will be analysed via immunoassay as an exploratory target engagement biomarker. Based on insights from earlier clinical trials with xentuzumab or abemaciclib, the analysis of other proteins involved in IGF, insulin and/or cyclin-dependent kinase mediated signalling might be added.

For this purpose, blood samples will be taken from a forearm vein at screening and at those time points specified in the Flow Chart and in Appendix 10.2.

All analyses will be performed at Boehringer Ingelheim or a CRO with given authorization by BI.
Remaining samples from protein biomarker analyses such as tumour tissue and blood samples will be destroyed no later than 5 years after the end of the trial if no optional consent for sample biobanking is obtained from the patient (see Section 5.5.1).

5.5.1 Biobanking

If permission for biobanking is obtained from the patient via an optional informed consent, any leftover samples from the study might be stored at Boehringer Ingelheim or contract research organization for up to 30 years unless specified otherwise in the protocol.
These samples may be used to further address scientific questions as new information in regard to the disease or the study drug becomes available.

5.5.1.1 DNA Banking

One blood sample will be used for DNA Banking if participation and the separate informed consent is agreed upon by the patient as noted below. The DNA Banking sample, derived from the original blood sample, will be stored at the sponsor. The stored DNA may retrospectively be analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

Note: Participation in the DNA Banking sampling is voluntary and not a prerequisite for participation in the trial. The DNA Banking sample will be stored for up to 30 years after separate informed consent is given in accordance with local ethical and regulatory requirements.

A blood sample for DNA banking will be collected in a PAXgene Blood DNA tube preferably at C1V1 or at Run-in Visit 1 for cohorts with Run-in period (or at a later time) (see Flow Chart and Table 5.5: 1 and Table 5.5: 2) for those patients who signed a separate PGx informed consent for DNA Banking.

5.6 OTHER ASSESSMENTS

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

1. General demography including sex, birth date and race as allowed by local law, information on smoking and alcohol history. Collection of race and/or ethnic information is necessary in this study because this is a multi-national trial and race and/or ethnicity are known to be associated with biology and outcome of breast cancer and NSCLC. Foreign regulatory agencies may request data or analysis based on race/ethnic information.
2. Medical history/current medical conditions (including history of menopause, prior and concomitant medications and concomitant diagnosis)

3. History and current disease status including date of first histological diagnosis (month and year may be sufficient), type of tumour histology, tumour grade, other diagnosis information such as mutations or receptors overexpression, known tumour genetic alterations, TNM staging, number and locations of metastatic sites (bone, liver, lung, peritoneum, brain, other) at the study entry
4. Previous anticancer treatments: previous surgery, hormonotherapy, chemo-, targeted, or radiation therapy will be reported including setting (neoadjuvant vs. adjuvant vs. therapeutic), start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (chemotherapy), total radiation dose and radiation field (radiotherapy), the best response obtained (complete response, partial response, stable disease/non-CR/non-PD, progressive disease, unknown) and reason for treatment discontinuation

5.6.1 Assessment of Immunogenicity

As of 22 Oct 2021, samples for immunogenicity are no longer collected for ongoing patients.

For the determination of anti-drug antibodies (ADA) against xentuzumab, blood samples will be taken from a forearm vein in an EDTA anticoagulant blood drawing tube at time points specified in the Flow Chart and in Appendix 10.2. Details about blood sample collection, EDTA plasma preparation, storage and shipment will be provided in a laboratory manual.

A qualitative screening for anti-drug antibodies against xentuzumab in the plasma samples will be performed using a validated immunoassay with xentuzumab as capture reagent. The assay enables the sensitive detection of various types of anti-xentuzumab immunoglobulins. ADA samples will be analysed in a multi-tiered approach (Screening, confirmatory and Titration) where screening positive samples will be confirmed and the confirmed positive samples will be tested in titration.

To further characterize the immune response of the ADA, additional analysis may be conducted after the completion of this study. The results will be reported separately. For this purpose samples will be stored beyond end of study for a maximum period of 5 years or until termination of the development project, whichever occurs first.

A detailed description of the assay will be available prior to the start of sample analysis.

5.7 APPROPRIATENESS OF MEASUREMENTS

The RECIST criteria version 1.1 (Appendix 10.4) to be used for evaluation of tumour response are well established and scientifically accepted. The Common Terminology Criteria, CTCAE version 4.03, 14 June 2010 are used in the assessment of adverse events in cancer patients.
All measurements performed during this trial will be to monitor safety and tolerability of xentuzumab in combination with abemaciclib, with or without hormonal therapy, to determine the MTD and /or recommended phase II doses of these combinations.

The scheduled assessments are to monitor drug induced changes in respect to vital signs, standard laboratory values and ECG. Tumour evaluations are necessary for determination of tumour response to treatment and possible PD effects. Pharmacokinetic analysis and biomarker analysis are necessary for correlation with therapeutic outcome. Immunogenicity testing will ensure the detection of any anti-drug antibody reactions as a result of the infusion of xentuzumab.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients must provide written informed consent (ICF) before any study related screening procedures can be performed. Allowable time windows for visits are included in the Flow Chart.

Investigational drugs xentuzumab and abemaciclib will be dispensed at each visit according to the Flow Chart. This also applies to letrozole, anastrozole and fulvestrant in the corresponding cohorts (B, C, D (dose finding), F, D1 and D2)
Patients will receive a new medication kit number through the IRT system on each occasion for medications supplied by the sponsor.

All screening assessment including tumour assessments must be completed within 28 days of start of run-in/C1V1. However, upon clinical assessment, if a patient presents with clinical symptoms of progressive disease, the investigator may use clinical judgement to determine whether to have the patient undergo another scan prior to starting treatment. Tumour assessments required for study participation which are completed as part of Standard of Care before the patient sign the ICF can be used for the screening assessments if they are completed within the allowed timeframe.
All patients are to adhere to the visit schedule as specified in the Flow Chart. In the event of any study drug interruption or delay of treatment, the tumour assessment schedule should not be changed.
Blood samples for pharmacokinetics, biomarkers and immunogenicity will be collected from all patients in all cohorts as per Appendix 10.2. Actual clock time for study drug administration and for each blood draw needs to be documented in the eCRF.

On visit days when safety lab is scheduled, patients should show up in fasting condition, the blood draw can be done up to one day prior to the scheduled date.

In situations where a patient is unable to attend a clinic visit, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period
Refer to the Flow Chart for procedure details. Please review Section 3.3.2 and 3.3.3 for eligibility criteria.
Patients who failed screening may repeat the screening after discussion between investigator and sponsor providing that reasons for screening failure were reversible and have resolved.
All screening assessments including tumour imaging scan and ECG must be completed within 28 days of start of run-in/C1V1.

The provision of tumour tissue is mandatory when available. Please refer to Appendix 10.3 and Table 5.5: 1 and Table 5.5: 2 for details.
Demographics (sex, birth date and race as per each country regulation) and baseline conditions will be collected during the screening visit (See Section 5.6).
Cancer history will also be obtained.

Run-in Period (only applicable to cohort E)
Refer to the Flow Chart, Table 5.5: 2 and Appendix 10.2 for details.

Prior to starting therapy with xentuzumab, patients will receive continuous daily abemaciclib for a 9-days run-in period. Abemaciclib and patient's diary should be dispensed on Day -9 of run-in.
Both, on day -9 and on day -1 of the run-in period, patients must come fasted to the study site and must not take abemaciclib until they have been instructed to do so at the clinic visit.

On Day -9 of run-in, prior to the administration of abemaciclib, blood samples for biomarkers, pharmacokinetics, ADA, etc. will be collected as well as a safety lab blood draw. Please see Appendix 10.2.2.1 and Table 5.5: 2.

On Day -1 of the run-in period, PK samples must be collected before and after the administration of abemaciclib. Please see Appendix 10.2.2.1.

6.2.2 Treatment period(s)

Every treatment course is 28 days. All subsequent visit dates should be calculated based on Course 1 Visit 1 date. If a visit is missed there will be no re-scheduling; if a patient should attend the study site between the "missed" and the next scheduled visit, then the missed visit assessments should be performed except for xentuzumab infusion. The current date and the reason for the delay must be noted in the medical records.
One or more visits can be skipped in case of treatment interruption. However, in the event of any study drug interruption or delay of treatment, the tumour assessment schedule will not be changed.
In this trial, patients may be hospitalized for the day of xentuzumab treatment and PK sampling at the discretion of the investigator; patients may be discharged if tolerated the treatment well and no safety concerns are present as judged by the investigator. Hospitalizations for this purpose should not be recorded as SAEs.

6.2.2.1 Cohort A, B, C, and D (dose finding)

Refer to the Flow Chart and Appendix 10.2.1 for details.

Course 1, Visit 1 (Day 1 of 1st treatment course)
All procedures must be completed on day 1 of Course 1 except for safety labs, which can be performed 1 day prior to the scheduled visit. Patients should come fasted to the study site for safety labs.
Sufficient abemaciclib should be made available for the patient.

ECG will be collected prior to xentuzumab infusion.
Pharmacogenomics blood sample to evaluate exosomal RNA, blood sample to isolate genomic DNA, and a blood sample to analyse circulating nucleic acids will be collected before treatment. Also, blood samples for PK, biomarkers and immunogenicity will be collected during the visit. Please see Appendix 10.2.1.1 and Table 5.5: 1 for details on sampling time points during this visit.

Cohort B: Letrozole will be also dispensed at this visit.
Cohort C: Anastrozole will be also dispensed at this visit.
Cohort D: Fulvestrant will be also administered at this visit.

Course 1, Visit 2 (Day 8±1 of 1st treatment course)
Patients should come fasted to the study site for safety labs.
On Course 1 day 8, **prior** to the administration of xentuzumab infusion, trough PK as well as biomarker and immunogenicity blood samples must be collected. Please see Appendix 10.2.1.1 for details on the sampling schedule for this visit.

Course 1, Visit 3 (15 ±1 days after start of xentuzumab)
Patients should come fasted to the study site for safety labs.
ECG will be collected prior to xentuzumab infusion.
Pharmacogenomics blood sample to evaluate exosomal RNA will be collected before treatment. This sample will be used to evaluate exosomal RNA. Please refer to Table 5.5: 1.
Cohort D: Fulvestrant will be also administered at this visit.

Course 1, Visit 4 (22 ±1 days after start of xentuzumab)
Patients should come fasted to the study site for safety labs.

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

Refer to Flow Chart, Table 5.5: 1and Appendix 10.2.1 for details.

Pharmacogenomics blood sample to evaluate exosomal RNA will be collected before treatment at Course ≥2 day 1.
PK, biomarkers, pharmacogenomics and ADA samples are also applicable to these visits. Please see Table 5.5: 1 and Appendix 10.2.1.2 for details on the samples to be obtained.

Safety labs on day 15±2 are only applicable to course 2.

6.2.2.2 Cohort E

Refer to the Flow Chart, Table 5.5: 2 and Appendix 10.2.2 for details.

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

All procedures must be completed on day 1 of Course 1 except for safety labs, which can be performed 1 day prior to the scheduled visit. For safety labs and PK purposes patients should

come fasted to the study site and must not take abemaciclib until they have been instructed to do so at the clinic visit.
Sufficient abemaciclib should be made available for the patient at this visit.
ECG will be collected prior to xentuzumab infusion.
Pharmacogenomics blood sample to evaluate exosomal RNA will be collected before treatment (Flow Chart and Table 5.5: 2).
Blood samples for PK, biomarkers, pharmacogenomics and immunogenicity will also be collected during this visit. Please see Table 5.5: 2 and Appendix 10.2.2.1 for sampling schedule details.

Course 1, Visit 2 (Day 8±1 of 1st treatment course)
Patients should come fasted to the study site for safety labs.
On Course 1 day 8, **prior** to the administration of xentuzumab infusion, one trough PK as well as biomarker and immunogenicity blood samples must be collected. Please see Appendix 10.2.2.1 for details on sampling schedule for this visit.

Course 1, Visit 3 (15 ±1 days after start of xentuzumab)
Patients should come fasted to the study site for safety labs.
ECG will be collected prior to xentuzumab infusion.
Pharmacogenomics plasma sample will be collected before treatment. This sample will be used to evaluate exosomal RNA (Flow Chart and Table 5.5: 2). Please see Appendix 10.2.2.1 for details on sampling schedule.

Course 1, Visit 4 (22 ±1 days after start of xentuzumab)
Patients should come fasted to the study site for safety labs. Patient's diary will be dispensed to the patient at this visit.

Course 2 (Day 1, 8, 15, 22 ±2 days) and all subsequent courses/visits
Refer to the Flow Chart, Table 5.5: 2 and Appendix 10.2.2.2 for details.

Pharmacogenomics blood sample to evaluate exosomal RNA will be collected before treatment at Course ≥2 day 1 (Flow Chart and Table 5.5: 2).
PK, biomarkers, pharmacogenomics and ADA samples will also be drawn at these visits. Please see Table 5.5: 2 and Appendix 10.2.2.2 for details on the sampling schedule.
At course 2 visit 1, and for PK purposes, patients should come fasted to the study site and must not take abemaciclib until they have been instructed to do so at the clinic visit.
Safety labs on day 15±2 are only applicable to course 2

6.2.2.3 Cohorts D1, D2 and F

Refer to the revised and reduced Flow Chart, for details.

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment visit

End of Treatment Visit (0-7 days after permanent discontinuation of study drugs)
Refer to the Flow Chart for details. The patient must return all study drugs, and the site must document the reason for permanent discontinuation of study medication. If permanent discontinuation of study drug occurs during a scheduled visit, examinations as defined for EOTV should be performed instead of the examinations for the scheduled visit.

6.2.3.2 Follow-up period

All patients must have a follow-up visit 42 days (+7days) after the permanent discontinuation of study drugs.
This follow-up period is aimed for collection of additional AE and PD information. Refer to the Flow Chart for details.

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

Blood samples for soluble biomarkers, PK and ADA must be obtained at this visit. Please refer to Appendix 10.2 for sampling schedule details.

6.2.3.3 Trial Completion

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 period (follow-up visit)
- Lost to follow-up
- Refusal to be followed-up
- Death

The end of the trial is defined in Section 8.6

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will be performed as an open-label study. The primary objective of the dose finding cohorts of this trial is to determine the MTD and the RP2D of:

* Cohort A: xentuzumab in combination with abemaciclib (without endocrine background therapy)
* Cohort B: xentuzumab in combination with abemaciclib on a background therapy of letrozole
* Cohort C: xentuzumab in combination with abemaciclib on a background therapy of anastrozole
* Cohort D (dose finding): xentuzumab in combination with abemaciclib on a background therapy of fulvestrant

To determine the MTD, patients are entered sequentially into escalating or de-escalating dose-level cohorts. For each treatment combination, the dose finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R15-4233, Chapter 6).

This logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of xentuzumab as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner abemaciclib as monotherapy, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

Xentuzumab: $\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

Abemaciclib: $\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

Here, the doses $d_1^* = 1000$ mg i.v. once weekly and $d_2^* = 150$ mg every 12 hours represent the reference doses for xentuzumab and abemaciclib, respectively.

Assuming no toxicity interaction between the two compounds, the probability of a DLT when giving the combination dose d_1, d_2 is obtained as

$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$

with corresponding odds

$\text{odds}(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} / (1 - \pi^0_{12,d1,d2})$.

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between xentuzumab and abemaciclib, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced in the model by the following definition:

$\text{odds}(\pi_{12,d1,d2}) = \text{odds}(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^*\, d_2/d_2^*)$

and $\pi_{12,d1,d2}$ is used in the likelihood

$r_{d1,d2} \sim \text{Binomial}(n_{d1,d2}, \pi_{12,d1,d2})$

where $r_{d1,d2}$ denotes the random variable describing the observed number of DLTs in $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_k will be specified as a mixture of two bivariate normal distributions,
$f(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k)$
with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights ($a_{1,k} + a_{2,k} = 1$), k = 1,2 and
$f_i(\theta_k) = MVN(\mu_{ik}, \sum_{ik})$ a bivariate normal distribution with mean vector μ_{ik} and covariance matrix $\sum_{ik}$ where

$$\Sigma_{ik} = \begin{pmatrix} \sigma^2{}_{ik,11} & \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} \\ \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} & \sigma^2{}_{ik,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

A weakly informative normal prior distribution will be used for η.

The estimated probability of DLT $\pi_{12,d1,d2}$ at each dose combination d_1, d_2 from the model will be summarized using the following intervals:

* Under dosing: [0.00, 0.16)
* Targeted toxicity: [0.16, 0.33)
* Over dosing: [0.33, 1.00]

The BLRM recommended dose combination for the next cohort is the combination with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 100 % for each drug.

The MTD may be considered reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50, or
2. At least 6 patients have been treated at the MTD.

Prior derivation

To determine the prior distributions for θ_1 and θ_2, a meta-analytic predictive (MAP) approach will be used. Toxicity information on xentuzumab and abemaciclib from earlier dose finding studies will be incorporated. Exact details on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix; a brief description is given here.

The historical data for xentuzumab and abemaciclib can be found in Table 7.1:1 and Table 7.1:2, respectively.

Table 7.1: 1 Historical data for xentuzumab

Study	Dose	N of patients with DLTs during MTD evaluation period / N of patients
1280.1 (weekly infusion)	10 mg	0/3
	20 mg	0/3
	40 mg	0/3
	60 mg	0/3
	90 mg	0/3
	135 mg	0/3
	200 mg	0/3
	300 mg	0/3
	450 mg	1/6
	600 mg	0/3
	800 mg	0/3
	1000 mg	0/13
	1050 mg	0/3
	1400 mg	0/3
	1800 mg	0/3
1280.15: Japan (weekly infusion)	750 mg	0/3
	1000 mg	0/9
	1400 mg	0/6

Table 7.1: 2 Historical data for abemaciclib

Study	Dose	N of patients with DLTs during MTD evaluation period / N of patients
Study I3Y-MC-JPBA	75 mg twice-daily	
	100 mg twice-daily	0/3
	150 mg twice-daily	0/4
	200 mg twice-daily (=MTD)	0/3
	275 mg twice-daily	1/7
		2/3

Table 7.1: 2 Historical data for abemaciclib (cont.)

Study	Dose	N of patients with DLTs during MTD evaluation period / N of patients
Study I3Y-JE-JPBC	100 mg twice-daily 150 mg twice-daily 200 mg twice-daily	0/3 0/3 1/6

Study I3Y-MC-JPBA: Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer.
Study I3Y-JE-JPBC: Phase 1 Study of LY2835219 in Japanese patients with Advanced Cancer.

The following steps were used to derive the prior distributions for all parameters:

1. θ_1:
    1. The meta-analytic-predictive prior was derived using the information in Table 7.1:1, allowing for substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    2. A second, weakly-informative component was added with 10% mixture weight.
2. θ_2:
    1. The meta-analytic-predictive prior was derived using the information in Table 7.1:2, allowing for moderate between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    2. A second, weakly-informative component was added with 10% mixture weight.
3. η: based on the a priori assumption of no interaction between the two compounds, a normal distribution with mean 0 and standard deviation 0.707 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an up to 4 fold increase (or decrease) in the odds of a DLT over no interaction.

The prior distribution is given in Table 7.1: 3. The corresponding prior probability of a DLT at different dose combinations and the corresponding probabilities of under-dosing, targeted dosing and overdosing are shown in Table 7.1: 4.

As seen in Table 7.1: 4, the dose combination 1000 mg xentuzumab and 150 mg abemaciclib has prior probabilities of overdosing below 25%. Hence, this dose combination fulfils the overdose criterion and is therefore suitable starting dose combination.

Table 7.1: 3 Prior distributions for the combination of xentuzumab and abemaciclib for Cohort A

Parameter	Means, standard deviations, correlation	Mixture weight
Component 1: $\log(\alpha_1)$, $\log(\beta_1)$	(-3.697, -0.517), (1.031, 0.816), 0.034	0.9
Component 2: $\log(\alpha_1)$, $\log(\beta_1)$	(-4, -0.5), (2, 1), 0	0.1

Table 7.1: 3 Prior distributions for the combination of xentuzumab and abemaciclib for Cohort A (cont.)

Parameter	Means, standard deviations, correlation	Mixture weight
Component 1: $\log(\alpha_2)$, $\log(\beta_2)$	(-2.515, 0.898), (0.829, 0.808), -0.510	0.9
Component 2: $\log(\alpha_2)$, $\log(\beta_2)$	(-3, 0.9), (2, 1), 0	0.1
η	0, 0.707, NA	NA

Table 7.1: 4 Prior probabilities of DLTs for the combination of xentuzumab and abemaciclib for Cohort A

Dose xentuzumab	Dose abemaciclib	Probability of true DLT rate in					Quantiles		
		[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	StD	2.5%	50%	97.5%
750	100	0.873	0.106	0.021	0.083	0.087	0.006	0.056	0.316
750	150	0.706	0.226	0.067	0.137	0.117	0.017	0.102	0.454
1000	100	0.841	0.128	0.032	0.092	0.096	0.007	0.062	0.356
1000	150	0.664	0.238	0.098	0.150	0.134	0.015	0.109	0.517

The prior for cohort A may be updated once the trial has started in case new data that can be used will be available. The priors for cohorts B, C, and D(dose finding) will be additionally based on available data from this trial. The priors that are used for each BLRM analysis for the SC meetings will be documented in the SC minutes. The prior that is used for the final analysis will be documented in the TSAP.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

7.3 PLANNED ANALYSES

No per protocol set will be used in the analysis. However, important protocol violations will be summarised. The TSAP will specify the important protocol violations in detail.

For the determination of the MTD, only MTD evaluable patients will be considered. For the analysis of primary and secondary endpoints of the expansion parts and further endpoints of dose finding and expansion parts, all patients in the treated set (i.e. patients treated with at least one dose of any trial medication, including hormonal therapy) will be included in the analysis. Any other analysis sets will be defined in the TSAP.

The analysis of the primary endpoint of the dose finding cohorts (cohorts A, B, C and D (dose finding) respectively) will be conducted when "last-patient-last-visit-primary-endpoint-dose-finding" has been reached (see Section 8.6).

Primary analysis of expansion cohorts (cohort E, F, D1 and D2) might be done before the end of the study. The further details will be described in TSAP.

The results of each dose finding cohorts (A, B, C, and D (dose finding)) and each expansion cohorts (E, F, D1 and D2) will be analysed separately.

7.3.1 Primary endpoint analyses

For dose finding cohorts A, B, C, and D (dose finding):
In order to identify the MTD, the number of patients with DLTs during the MTD evaluation period at each dose level will be presented. Patients who discontinue during the first treatment course for reasons other than DLT will be excluded from the determination of MTD.

For expansion cohort E:
Objective response will be analysed in terms of objective response rate, defined as the proportion of patients with best overall response of CR or PR (note that no confirmation is required for best overall response).

For cohorts D1 and D2:
PFS rate at 18th month will be derived using Kaplan Meier method. Cohort D1 for visceral vs. cohort D2 for non-visceral will be displayed separately. The details will be described in the TSAP.

For expansion cohort F
DC will be analysed in terms of DC rate, defined as the proportion of patients with best overall response of CR, PR, SD lasting for at least 24 weeks or non-CR/non-PD lasting for at least 24 weeks.

7.3.2 Secondary endpoint analyses

For dose finding cohorts A, B, C, and D (dose finding):
There are no secondary endpoints.

For expansion cohorts E, F, D1 and D2:
The secondary endpoints will be analysed descriptively.

Disease control for Cohorts D1, D2 and E will be analysed in the same way as the primary analysis for Cohort F.

Time to objective response can only be calculated for patients with an objective response:
Time to objective response [days] = date of first documented CR or PR – date of first treatment administration +1.

Duration of objective response can only be calculated for patients with an objective response:

* For patients with disease progression or death:
  Duration of objective response [days] = date of outcome – date of first assessment indicating objective response +1
* For patients without disease progression or death:
  Duration of objective response (censored) [days] = date of outcome – date of first assessment indicating objective response +1

The censoring rules for duration of objective response (i.e. outcome and date of outcome) will be described in the TSAP. Only radiological assessments after first assessment indicating objective response should be taken into account.

Duration of disease control will be derived as follows:

* For patients with disease progression or death:
  Duration of disease control [days] = date of outcome – date of first treatment administration+1
* For patients without disease progression or death:
  Duration of disease control (censored) [days] = date of outcome – date of first treatment administration +1

The censoring rules for duration of disease control (i.e. outcome and date of outcome) will be described in the TSAP.

Progression-free survival will be derived as follows:

* For patients with “event” as an outcome for PFS:
  PFS [days] = date of outcome – date of first treatment administration + 1
* For patients with “censored” as an outcome for PFS:
  PFS (censored) [days] = date of outcome – date of first treatment administration + 1

Censoring rules for PFS will be described in the TSAP.

Objective response for Cohorts D1, D2 and F will be analysed in the same way as the primary analysis for Cohort E.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 42 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.
All treated patients will be included in the safety analysis. 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. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as a period of 42 days after the last dose of trial medication. 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 Medical Dictionary for Drug Regulatory Activities (MedDRA).

DLTs will be tabulated for each dose level in the dose escalation cohorts. The tabulation will be done in two ways:

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

The definition of DLT and determination of MTD are defined in Section 5.3.7 and Appendix 10.6 respectively.

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 highlighted in the listings. 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.

The following analyses will be presented for the laboratory tests:

- Descriptive statistics at each planned assessment,
- Frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment, and
- Frequency of patients with possible clinically significant abnormalities.

Additional more in-depth analyses of AEs and laboratory data will be performed as needed and detailed in the TSAP.

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

7.4 INTERIM ANALYSES

No formal interim analysis is planned for efficacy.

In the dose finding cohorts A, B, C, and D, the SC and BI study team will continuously monitor and assess safety data to ensure patients' safety, as well as to determine the MTD and/or the RP2D of each dose finding cohorts. If considered necessary, as soon as the MTD and/or the RP2D of a particular dose finding cohort is determined, an evaluation of the safety (and potentially efficacy) aspects will be performed via a snapshot of the database. Results of this evaluation will be documented and stored.

Continuous monitoring of safety data for expansion cohorts E, F, D1 and D2 will be done by the SC and BI study team.

Earlier efficacy analyses than those currently planned may be performed to support future decision making and trial planning.

7.5 HANDLING OF MISSING DATA

In general, missing data will not be imputed and all reasonable efforts will be taken during the study to obtain such data.

Missing baseline laboratory values will be imputed by the respective values from the screening visit.

For partial or missing AE onset and/or end dates, BI internal rules will be applied for imputation.

No other imputations will be performed on missing data although every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential DLTs.

Pharmacokinetics:
Drug concentration-time profiles: Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), BLQ (below the limit of quantification) and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (including the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range.

Pharmacokinetic parameters:
In the non-compartmental analysis, concentration data identified with NOS, NOR and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

No randomisation will be performed. In the dose finding cohorts, patients will be assigned sequentially to the dose escalation groups. In the expansion cohorts, patients will be assigned to a cohort based upon previous MTD/RP2D. Medication numbers will be allocated by an IRT system.

7.7 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this study. Approximately 148 patients (including patients at MTD) will be expected for this trial based on the number of dose levels/cohorts that are tested. Fewer or more patients might be needed based on the recommendation of the SC and BI Trial Team and the criteria specified (see Section 7.1).

Dose finding cohorts A, B, C and D:
Approximately 12 patients in cohorts A, B, C and D (dose finding) will be needed to define a MTD. In total, approximately 48 patients will be needed for the dose finding cohorts. However, the actual number of patients will depend on the number of dose levels tested.

Based on the simulation study to evaluate operating characteristics of the BLRM (see Appendix 10.6), approximately 12 patients (in mean) are expected to be treated in the dose finding cohort A for the model to have reasonable operating characteristics relating to its MTD recommendation (see Appendix 10.6).

Considering the toxicity profile of individual compounds, we can assume the same number of patients will be needed in the dose finding cohorts B, C and D (dose finding).

Expansion cohort E:
In expansion cohort E, 20 patients will be treated at the MTD/RP2D.

Assuming a true objective response (OR) rate of 60%, a sample size of 20 patients leads to a probability of 87% of observing at least 10 ORs. If the true OR rate is higher, i.e. 80%, the probability of observing at least 10 ORs is higher than 99%. The probability to observe a false positive signal, i.e. to observe at least 8 ORs if the underlying true OR rate is 20%, is only 3%. Table 7.7: 1 summarizes the probabilities of observing certain OR rates based on different assumptions on underlying OR rates.

Table 7.7: 1 Objective response rates for Cohort E

True OR rate	Patients	Probability to observe at least								
		7 events	8 events	9 events	10 events	11 events	12 events	13 events	14 events	15 events
60%	20	0.99	0.97	0.94	0.87	0.76	0.60	0.42	0.25	0.13
80%	20	>0.99	>0.99	>0.99	>0.99	>0.99	0.99	0.97	0.91	0.80
20%	20	0.09	0.03	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

An OR rate of 60% would be considered clinically relevant in NSCLC patients (cohort E).

These assumed OR rates and the expected ORs are according to the current knowledge and expectations regarding xentuzumab and its combination partners. The calculations were performed using R version 3.2.2.

Expansion cohorts D1 and D2:
For each of cohort, D1 for visceral metastasis and D2 for non-visceral metastasis, 30 patients will be recruited respectively and treated at the $RP2D_4$.

For cohort D1, assuming a true PFS rate of 60% at 18th month, 10 months recruitment period and 20% patient drop rate, a sample size of 30 patients leads to a probability of 62% of observing at least 57% PFS rate at 18th month. If the true PFS rate is higher, i.e. 63%, the probability of observing at least 57% PFS rate is higher than 73%. The probability to observe a false positive signal, i.e. to observe at least 57% PFS rate at 18th month if the underlying true PFS rate is 43%, is only 8%. Table 7.7: 2 summarizes the probabilities of observing certain PFS rates at 18th month based on different assumptions on underlying PFS rates.

Table 7.7: 2 PFS rates at 18th month for cohort D1

True PFS rate at 18 month	Patients	Probability to observe PFS rate at 18th month				
		>0.47	>0.52	>0.57	>0.6	>0.63
43%	30	0.33	0.18	0.08	0.04	0.02
60%	30	0.90	0.79	0.62	0.51	0.39
63 %	30	0.95	0.87	0.73	0.63	0.51

For Cohort D2, assuming a true PFS rate of 69% at 18th month, 10 months recruitment period and 20% patient drop rate, a sample size of 30 patients leads to a probability of 68% of observing at least 65% PFS rate at 18th month. If the true PFS rate is higher, i.e. 75%, the probability of observing at least 65% PFS rate is higher than 87%. The probability to observe a false positive signal, i.e. to observe at least 65% PFS rate at 18th month if the underlying true PFS rate is 52%, is only 10%. Table 7.7: 3 summarizes the probabilities of observing certain PFS rates at 18th month based on different assumptions on underlying PFS rates.

Table 7.7: 3 PFS rates at 18th month for cohort D2

True PFS rate at 18 month	Patients	Probability to observe PFS rate at 18th month				
		>0.56	>0.60	>0.65	>0.69	>0.73
52%	30	0.35	0.22	0.10	0.04	0.02
69%	30	0.92	0.83	0.68	0.52	0.35
75%	30	0.98	0.95	0.87	0.76	0.61

An PFS rate of 60% would be considered clinically relevant in each cohorts: visceral metastasis and non-visceral metastasis.

These assumed PFS rates and the expected PFS rates are based on the current knowledge and expectations regarding xentuzumab and its combination partners. The assumed true PFS rate for each cohort is considered clinically relevant. All calculations were performed using R version 3.2.2.

Cohort F:
In expansion cohort F, 20 patients will be treated at the MTD/RP2D.

Assuming a true DC rate of 60%, a sample size of 20 patients leads to a probability of 87% of observing at least 10 events. If the true DC rate is higher, i.e. 80%, the probability of observing at least 10 events is higher than 99%. The probability to observe a false positive signal, i.e. to observe at least 8 events if the underlying true DC rate is 20%, is only 3%. Table 7.7: 4 summarizes the probabilities of observing certain DC rates based on different assumptions on underlying DC rates.

Table 7.7: 4 Disease Control rates for Cohort F

True DC rate	Patients	Probability to observe at least								
		7 events	8 events	9 events	10 events	11 events	12 events	13 events	14 events	15 events
60%	20	0.99	0.97	0.94	0.87	0.76	0.60	0.42	0.25	0.13
80%	20	>0.99	>0.99	>0.99	>0.99	>0.99	0.99	0.97	0.91	0.80
20%	20	0.09	0.03	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

A DC rate of 60% would be considered clinically relevant in HR+, Her2- locally advanced and/or metastatic breast cancer patients after prior therapy with a different CDK4/6 inhibitor and aromatase inhibitor (cohort F).

These assumed and expected DC rates are according to the current knowledge and expectations regarding xentuzumab and its combination partners. The calculations were performed using R version 3.2.2.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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), the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: 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.

For Japan only: the rights of the Investigator / trial site and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract / trial site's contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

For Japan only: The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents.

For Japan only: The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms (CRF) 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

If defined in the protocol, additional records may need to be requested from the Investigator, e.g. information from any referral physicians on patient history relevant for AE reporting or data required in connection with outcome event collection in outcome studies.
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 subject. 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 subject 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 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, date or 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)
* Medication history
* 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 on-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 CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor 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 ICH 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 the national or 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 with the requirements. Any exemptions from expedited reporting are described under Section 5.3.6.2 and Section 5.3.6.3.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

The rights of the trial patient to privacy and protection of the data / patient notes obtained during the trial have to be ensured in accordance with local laws and regulations. Procedures for data handling and data protection need to be described in the patient information and informed consent form. 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, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

* A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
* The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
* Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment (screening) of the first patient in the whole trial.
The **end of the trial** is defined as the date when the last patient in the whole trial completes the trial as per definition of trial completion in Section 6.2.3.3.

The **"last-patient-last-visit-primary-endpoint-dose-finding"** is defined as the date when all patients in a respective dose finding cohort have completed at least the first treatment course. Thus, this milestone is defined for each dose finding cohorts (A, B, C and D (dose finding)).

The **"last-patient-last-visit-primary-endpoint-expansion" (Cohorts E and F)** is defined as the date when all patients in a respective expansion cohort have completed at least two tumour assessment time points or have permanently discontinued treatment or have completed the trial according to Section 6.2.3. Thus, this milestone is defined for each expansion cohorts (E and F).

The **"last-patient-last-visit-primary-endpoint-expansion"** (Cohorts D1 and D2) is defined as the date when all patients have completed 18 months PFS observation or have permanently discontinued treatment or have completed the trial according to Section 6.2.3. Thus, this milestone is defined for Cohorts D1 and D2.
The "**Last Patient Drug Discontinuation"** (LPDD) 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 LPDD 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 only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
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).

For Japan only: when the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

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

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

For Japan only: in the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

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10. APPENDICES

10.1 INDUCERS AND STRONG INHIBITORS OF CYP3A4

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort
Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl
Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

10.2 PHARMACOKINETICS PLAN

10.2.1 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts A, B, C, and D (dose finding)

10.2.1.1 Flowchart for PK, immunogenicity, and biomarkers for Cohorts A, B, C, and D (dose finding) in treatment course 1

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
SCR	SCR	Within 28d before C1V1	-999:00*	Sampling at screening visit					X
1	1	1	-0:05	Blood sampling prior to xentuzumab infusion	X	X	X	X	X
			0:00	Start of xentuzumab infusion					
			1:00**	Immediately at the end of xentuzumab infusion	X				
	2	8	168:00	Blood sampling ~5 minutes prior to xentuzumab infusion	X	X			X

*Planned time listed at visit SCR is considered to be a dummy planned time to set-up the database, the description in column "Day" defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

10.2.1.2 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts A, B, C, and D (dose finding) in courses 2-12, 15, and 18, EOTV and FU

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
2-12, 15, 18	1	1	-0:05	Blood sampling prior to xentuzumab infusion	X	X	X	X	X
			0:00	Start of xentuzumab infusion					
			1:00**	Immediately at the end of xentuzumab infusion	X				
EOTV	EOTV	Within 7d after last drug intake	998:00*	End of treatment visit	X	X	X	X	X
FU	FU	42 +7d after last drug intake	999:00*	Follow-up	X	X	X	X	X

*Planned times listed at visit EOTV and FU are considered to be dummy planned times to set-up the database, the description in column “Day” defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

10.2.2 FLOW CHART for PK, immunogenicity, and biomarkers for cohort E

10.2.2.1 FLOW CHART for PK, immunogenicity, and biomarkers for cohort E in Run-in phase and treatment course 1

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK***	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
SCR	SCR	Within 28d before Run in V1	-999:00*	Sampling at screening visit						X
Run in	1	-9	-192:05	5 minutes prior to first abemaciclib treatment	X	X	X***	X	X	X
	3	-1	-0:05	Blood sampling 5 minutes prior to abemaciclib administration			X***			
			0:00	abemaciclib administration (morning dose)						
			1:00				X			
			2:30				X			
			4:00				X			
			6:00				X			
			8:00				X			
			12:00 [± 2:00]	Blood sampling **before** intake of evening dose of abemaciclib			X			
1	1	1	-0:05	Blood sampling prior to xentuzumab infusion and abemaciclib administration	X	X	X***	X	X	X
			0:00	Start of xentuzumab infusion						
			0:01	Abemaciclib administration						
			1:00**	Immediately at the end of xentuzumab infusion	X					
	2	8	168:00	Blood sampling prior to xentuzumab infusion	X	X				X

*Planned time listed at visit SCR is considered to be a dummy planned time to set-up the database, the description in column "Day" defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

*** At days of abemaciclib PK sampling, patients have to take their morning dose of abemaciclib in the hospital in order to allow exact timing of PK sampling

10.2.2.2 FLOW CHART for PK, immunogenicity, and biomarkers for cohort E in treatment course 2

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK***	Total IGF-1/2, IGFBP-3	Free dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
2	1	1	-0:05	Blood sampling prior to abemaciclib and xentuzumab administration	X	X	X***	X	X	X
			0:00	Start of xentuzumab infusion						
			0:01	Abemaciclib administration						
			1:00**	Immediately at the end of xentuzumab infusion	X		X			
			2:30		X		X			
			4:00		X		X			
			6:00		X		X			
			8:00		X		X			
			12:00 [± 2:00]	Blood sampling **before** intake of evening dose of abemaciclib	X		X			
	1	2	23:55	Blood sampling prior to abemaciclib administration	X					
			24:00	Abemaciclib administration						
	1b	4±1	72:00	Blood sampling at this visit	X					
	2	8±1	168:00	Blood sampling ~ 5 min prior to abemaciclib administration and xentuzumab infusion	X					

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

*** At days of abemaciclib PK sampling, patients have to take their morning dose of abemaciclib in the hospital in order to allow exact timing of PK sampling

10.2.2.3 FLOW CHART for PK, immunogenicity, and biomarkers for cohort E in treatment courses 3-12, 15, 18 and EOTV and FU visit

Course	Visit	Day	Planned Time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
3-12, 15, 18	1	1	-0:05	Blood sampling prior to abemaciclib administration and xentuzumab infusion	X	X		X	X	X
			0:00	Start of xentuzumab infusion						
			0:01	Abemaciclib administration						
			1:00**	Immediately at the end of xentuzumab infusion	X					
EOTV	EOTV	Within 7d after last drug intake	998:00*	End of treatment visit	X	X		X	X	X
FU	FU	42 +7d after last drug intake	999:00*	Follow-up	X	X		X	X	X

*Planned times listed at visit EOTV and FU are considered to be dummy planned times to set-up the database, the description in column “Day” defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

10.2.3 FLOW CHART for PK, immunogenicity, and biomarkers for cohort F

As of 22 Oct 2021, samples for PK, immunogenicity and biomarkers are no longer collected for ongoing patients.

10.2.3.1 FLOW CHART for PK, immunogenicity, and biomarkers for cohort F in screening and treatment course 1

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK***	Total IGF-1/2, IGFBP-3	Free /dissociable	pIGF-1R/IGF-1R in PBP
SCR	SCR	Within 28d before Run in V1	-999:00	Sampling at screening visit						X
1	1	1	-0:05	Blood sampling prior to abemaciclib administration, xentuzumab infusion and fulvestrant injection	X	X	X***	X	X	X
			0:00	Start of xentuzumab infusion						
			0:01	Abemaciclib administration						
			0:00	Fulvestrant injection up to 15min. after start of xentuzumab infusion						
			1:00**	Immediately at the end of xentuzumab infusion	X					
	2	8	168:00	Blood sampling prior to xentuzumab infusion	X	X				X

*Planned time listed at visit SCR is considered to be a dummy planned time to set-up the database, the description in column "Day" defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

*** At days of abemaciclib PK sampling, patients have to take their morning dose of abemaciclib in the hospital in order to allow exact timing of PK sampling

10.2.3.2 FLOW CHART for PK, Immunogenicity, biomarkers for cohort F in treatment courses 2-12, 15, 18, EOTV and FU

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK	Fulvestrant PK	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
2-12, 15, 18	1	1	-0:05	Blood sampling prior to abemaciclib administration, xentuzumab infusion and fulvestrant injection	X	X	X[1] ***	X[1]	X	X	X
			0:00	Start of xentuzumab infusion							
			0:01	Abemaciclib administration							
			0:00	Fulvestrant injection up to 15min. after start of xentuzumab infusion							
			1:00**	Immediately at the end of xentuzumab infusion	X						
EOTV	EOTV	Within 7d after last drug intake	998:00*	End of treatment visit	X	X			X	X	X
FU	FU	42 +7d after last drug intake	999:00*	Follow-up	X	X			X	X	X

*Planned times listed at visit EOTV and FU are considered to be dummy planned times to set-up the database, the description in column "Day" defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

*** At days of abemaciclib PK sampling, patients have to take their morning dose of abemaciclib in the hospital in order to allow exact timing of PK sampling

[1] this sample needs to be collected in course 2 and 3 only

10.2.4 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts D1 and D2

As of 22 Oct 2021, samples for PK, immunogenicity and biomarkers are no longer collected for ongoing patients.

10.2.4.1 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts D1 and D2 in treatment course 1

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK	Total IGF-1/2, IGFBP-3	Free /dissociable	pIGF-1R/IGF-1R in PBP
SCR	SCR	Within 28d before C1V1	-999:00*	Sampling at screening visit						X
1	1	1	-0:05	Blood sampling prior to abemaciclib administration, xentuzumab infusion and fulvestrant injection	X	X		X	X	X
			0:00	Start of xentuzumab infusion						
			0:01	Abemaciclib administration						
			0:00	Fulvestrant injection up to 15min. after start of xentuzumab infusion						
			1:00**	Immediately at the end of xentuzumab infusion	X					
	2	8	168:00	Blood sampling prior to xentuzumab infusion	X	X				X
	3	15	336:00	Blood sampling prior to xentuzumab infusion	X					
	4	22	504:00	Blood sampling prior to xentuzumab infusion	X					

*Planned time listed at visit SCR is considered to be a dummy planned time to set-up the database, the description in column "Day" defines the timing for these specific samples

** If the infusion duration is different from 1h, please adapt the sampling time accordingly.

10.2.4.2 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts D1 and D2 in treatment course 2

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK***	Fulvestrant PK	Total IGF-1/2, IGFBP-3	Free / dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
2	1	1	-0:05	Blood sampling prior to abemaciclib administration, xentuzumab infusion and fulvestrant injection	X	X	X***	X	X	X	X
			0:00	Start of xentuzumab infusion							
			0:01	Abemaciclib administration							
			0:00	Fulvestrant injection up to 15min. after start of xentuzumab infusion							
			1:00**	Immediately at the end of xentuzumab infusion	X		X[1]	X[1]			
			2:30		X[1]		X[1]				
			4:00		X[1]		X[1]				
			6:00		X[1]		X[1]				
			8:00		X[1]		X[1]				
			12:00 [± 2:00]	Blood sampling ~5 minutes **before** intake of evening dose of abemaciclib	X[1]		X[1]	X[1]			
	1	2	23:55		X[1]			X[1]			
			24:00	Abemaciclib administration							
	1b	4	72:00	Blood sampling prior to abemaciclib administration	X[1]			X[1]			
	2	8	168:00	Blood sampling prior to xentuzumab infusion	X[1]			X[1]			
	3	15	336:00	Blood sampling prior to xentuzumab infusion				X[1]			
	4	22	504:00	Blood sampling prior to xentuzumab infusion				X[1]			

** If the infusion duration is different from 1h, please adapt the planned time accordingly.

*** At days of abemaciclib PK sampling, patients have to take their morning dose of abemaciclib in the hospital in order to allow exact timing of PK sampling

[1] these PK samples will be collected for at least 15 subjects in cohort D1 and at least 15 subjects in cohort D2.

10.2.4.3 FLOW CHART for PK, Immunogenicity, biomarkers for cohorts D1 and D2 in treatment courses 3, 4, 6, 12, 24, EOTV and FU

Course	Visit	Day	Planned time [h:min]	Event and comment	Xentuzumab PK	ADA	Abemaciclib and metabolites PK	Fulvestrant PK	Total IGF-1/2, IGFBP-3	Free /dissociable IGF-1/2	pIGF-1R/IGF-1R in PRP
3, 4, 6, 12, 24	1	1	-0:05	Blood sampling prior to abemaciclib administration, xentuzumab infusion and fulvestrant injection	X	X	X[1]	X[1]	X[2]	X[2]	X
			0:00	Start of xentuzumab infusion							
EOTV	EOTV	Within 7d after last drug intake	998:00*	End of treatment visit	X	X			X	X	X
FU	FU	42 +7d after last drug intake	999:00*	Follow-up	X	X			X	X	X

*Planned times listed at visit EOTV and FU are considered to be dummy planned times to set-up the database, the description in column “Day” defines the timing for these specific samples

[1] this sample needs to be collected in course 3 and course 4 only

[2] this sample needs to be collected in course 3, course 4, and course 6 only

10.3 TUMOUR TISSUE SAMPLE REQUIREMENTS

Marker category	Tissue type	Amount of tissue	Time point of sample taking	Analysis type
PGx	FFPE (RNase-free)	Preferably FFPE tumour tissue block for preparation of 8x 5µm sections	screening	RNA expression
PGx/Protein Biomarkers	FFPE	Preferably FFPE tumour tissue block for preparation of 17x 5µm sections	screening	DNA isolation + mutational/CNA analysis and biochemical protein analysis (e.g. IHC)

10.4 TUMOUR RESPONSE ASSESSMENT ACCORDING TO RECIST 1.1

Response criteria for target lesions

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

Response criteria for non-target lesions

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

Time point response for patients with measurable disease at baseline

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

Time point response for patients with non-measurable disease at baseline

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

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

Best overall response is evaluated from first treatment administration until the earliest of disease progression, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy. When stable disease is believed to be best response, it must also meet a minimum time from first treatment administration of 48 days (i.e. according Flow Chart, the first post−baseline imaging should be performed within 63 days after start of xentuzumab). Note that clinical disease assessment will not be considered for determination of best overall response. No confirmation is required for best overall response

10.5 CLINICAL EVALUATION OF LIVER INJURY

10.5.1 Introduction

Alterations of liver parameters, as described in Section 5.3.6.1 (Protocol-Specified Adverse events of special interest), are to be further evaluated using the following procedures:

10.5.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.
If the alert is confirmed on initial sample, or it is not possible to repeat testing using initial sample, the following must be completed:

1) Evaluate patient within 48 hours and
2) Perform the following laboratory tests:
    1. Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
    2. Haptoglobin
    3. Complete blood count and cell morphology
    4. Reticulocyte count
    5. Creatine Kinase (CK)
    6. Lactate dehydrogenase (LDH)
    7. Alkaline Phosphatase

The results of these laboratory tests must be reported to BI as soon as possible.
If the initial alert values (i.e. AST,ALT, and bilirubin) are confirmed on the second sample described as above, then an abdominal ultrasound or clinically appropriate alternate imaging (to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm) must be completed within 48 hours.
The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process. In the event the etiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), then the “DILI checklist” must be completed. Details of the “DILI checklist” are provided in the ISF. The following assessments need to be performed in order to complete the “DILI checklist” and results will be reported via the eCRF:

obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF;

obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;

obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF;

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

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

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

Hormones, tumour marker
Thyroid-stimulating hormone (TSH)*

Haematology
Thrombocytes, eosinophils

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

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

10.6 STATISTICAL APPENDIX

A Bayesian logistic regression model with overdose control will be used to guide dose escalation/ de-escalation in cohorts A, B, C and D(dose finding). The BLRM is introduced in Section 7.1, which also specifies the prior for the model in cohort A. The priors for other dose finding cohorts (B, C and D(dose finding)) will be documented in the TSAP. After patients in each dose group have completed at least one course of treatment, the prior distributions will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLT will be summarised from BLRM. Selection of the next dose combinations will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.6: 3. In addition, recommendations of the next dose combination by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in

early dose groups to show how it facilitates on-study dose-escalation decisions (see Table 10.6: 1).

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.6: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of target dose and overdose for the current dose combination, as well as the next potential dose combination and related probabilities of under-dosing, target dose, and over-dosing are shown.

For example, scenario 1 shows the example, that at the starting dose combination 150 mg abemaciclib and 1000 mg xentuzumab none of 3 patients experiences a DLT. Then, the BLRM allows treating patients at the same dose which is the maximum combination dose allows by the protocol.

Scenario 4 shows the example, that at the starting dose combination 150 mg abemaciclib and 1000 mg xentuzumab none of 6 patients experiences a DLT. Therefore, the MTD in this case would be the combination of 150 mg / 1000 mg.

Scenario 6 shows the example that at the starting dose combination 150 mg abemaciclib and 1000 mg xentuzumab 2 out of 3 patients experiences a DLT, then none of 3 patients treated at 100 mg / 1000 mg experiences a DLT. The overdose control of the BLRM suggests escalating to 150 mg / 750 mg.

All these scenarios illustrate the adaptive behaviour of the model even in extreme situations.

Table 10.6: 1 Hypothetical data scenarios for cohort A

Scenario	Dose combi-nation (mg/mg)	# patient / # DLT	Current dose combination		Next recommended dose combination*	Next dose combination		
			P(TD)	P(OD)		P(UD)	P(TD)	P(OD)
1	150/1000	3 / 0	0.179	0.027	150/1000	0.794	0.179	0.027
2	150/1000	3 / 1	0.376	0.141	150/1000	0.483	0.376	0.141
3	150/1000	3 / 2	0.397	0.430	100/1000	0.473	0.365	0.162
4	150/1000 150/1000	3 / 0 3 / 0	0.116	0.009	150/1000	0.876	0.116	0.009
5	150/1000 150/1000	3 / 1 3 / 0	0.312	0.048	150/1000	0.640	0.312	0.048
6	150/1000 100/1000	3 / 2 3 / 0	0.309	0.053	150/750	0.324	0.491	0.185

Table 10.6: 1 (cont.) Hypothetical data scenarios for cohort A

Scenario	Dose combi-nation (mg/mg)	# patient / # DLT	Current dose combination		Next recommended dose combination*	Next dose combination		
7	150/1000 100/1000 100/1000	3 / 2 3 / 0 3 / 1	0.428	0.081	100/1000	0.491	0.428	0.081

* Recommended dose combination is the dose combination with the highest target probability. Note that other combinations have similar target toxicity probabilities.

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose combination with true DLT rate in the target interval can be approximated via simulation.

Table 10.6: 2 describes 4 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of this model. These scenarios reflect a wide range of possible cases as follows:

* Scenario 1: aligned with prior means
* Scenario 2: high-toxicity scenario
* Scenario 3: low-toxicity scenario
* Scenario 4: low-high-toxicity scenario

Table 10.6: 2 Assumed true dose-toxicity scenarios for cohort A

Dose combination (mg/mg)		Scenario			
		1: Prior	2: High Tox	3: Low Tox	4: Low-High
100/750	P(DLT)	0.083	0.16	0.03	0.08
150/750		0.137	0.24	0.08	0.16
100/1000		0.092	0.17	0.06	0.10
150/1000		0.150	0.31	0.10	0.20

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients and dose escalation complied with the following rule:

- Escalate to the dose combination which maximises the probability of the targeted toxicity region and satisfies the overdose criterion

The MTD was considered reached if at least 6 patients have been evaluated at a dose combination which is the model's recommendation for the next dose-level cohort and for which the posterior probability of targeted toxicity was at least 50%. Or if in total 6 patients have been evaluated at a dose combination which is the model's recommendation for the next dose-level cohort.

It was then assessed how often a dose combination was declared as MTD with true DLT rate in the under-, targeted or over-dose range.

Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.6: 3 below.

Table 10.6: 3 Simulated operating characteristics for cohort A

Scenario	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	underdose	target dose	overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1: Prior	43.7	54.3	0	2.0	10.86 (3, 21)	2.19 (0, 8)
2: High Tox	0	68.3	23.3	8.4	10.68 (3, 21)	3.10 (1, 9)
3: Low Tox	23.9	73.3	0	2.8	11.94 (3, 21)	1.75 (0, 7)
4: Low-High	3.9	55.1	38.9	2.1	12.10 (3, 21)	2.91 (1, 9)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, almost all of the simulated trials (54%) that have found a MTD declared the MTD with true toxicity rate in the target interval. Few simulated trials (2.0%) have been stopped before declaring a MTD. None of trials declared a MTD with true DLT rate in the overdose interval.

In scenario 2 (high-toxicity scenario) 68% of the simulated trials that have found a MTD declared the MTD with true toxicity rate in the target interval and 23% declared a MTD with true DLT rate in the overdose interval. Few simulated trials (8%) have been stopped before declaring a MTD.

Scenario 3 (low-toxicity scenario) illustrates a behaviour similar to scenario 1.

Scenario 4, a mixture of the high toxicity and the low toxicity scenario, shows characteristics of both of these.

The mean patient numbers range from 10.68 patients (Scenario 2) to 12.10 patients (Scenario 4) and the maximum number of patients was 21. Therefore, the patient numbers are as expected.

By reviewing the metrics presented, it can be seen that the model is not sensitive to different scenarios of truth. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose combination with true P(DLT) ≥ 33% as MTD are much smaller than probabilities of recommending a dose combination with true P(DLT) between 16% and 33% as MTD.

On-study recommendations based on the model are consistent with the clinical decision making process, and should be considered in conjunction with other available clinical information by the SC in deciding the dose levels to be tested in order to determine the MTD estimates.

R version 3.2.2 was used for data scenarios and simulations.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		30 January 2017
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
To be implemented only after approval of the IRB / IEC / Competent Authorities		Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		No
Section to be changed		Clinical Trial Protocol Synopsis – Main Criteria for inclusion – Cohort A (Solid Tumours)
Description of change		Clarification of the inclusion criteria referring to previous treatment for trial disease
Rationale for change		Revision of the wording as per FDA request
Section to be changed		Clinical Trial Protocol Synopsis – Main Criteria for inclusion – Cohort E
Description of change		Additional request to have NSCLC disease confirmed by histology or cytology
Rationale for change		Revision of the criteria as per FDA request
Section to be changed		Clinical Trial Protocol Synopsis – Main Criteria for inclusion – Exclusion criteria

Description of change		Revision of the starting time of trial treatment 3 half-lives after previous immunotherapy instead of 2.
Rationale for change		As per FDA request and in order to minimize overlapping toxicities
Section to be changed		Flow Chart Cohort E and F – Blood sample for Biomarkers
Description of change		Correction of sampling timepoint at Run-In V3
Rationale for change		Revision of the whole protocol and in order to keep consistency between sections. No Biomarker sampling needed at Run-In V3 for Cohorts E and F.
Section to be changed		Flow Chart Cohort F – Footnote #11
Description of change		Change details form Cohort G to Cohort F
Rationale for change		Correction of a typographic error, as no Cohort G planned in the final protocol
Section to be changed		Section 3.3.2. Inclusion Criteria – Cohort A – Criteria #7
Description of change		Clarification of the inclusion criteria referring to previous treatment for trial disease
Rationale for change		Revision of the wording as per FDA request
Section to be changed		Section 3.3.2. Inclusion Criteria – Cohort B, C, D, F (Breast Cancer) – Criteria #8
Description of change		Definition of the HER2 negativity as per ASCO/CAP guidelines
Rationale for change		Inclusion of this references as per FDA request
Section to be changed		Section 3.3.2. Inclusion Criteria – Cohort B, C, D, F (Breast Cancer) – Criteria #10
Description of change		Change from Cohort G to Cohort F
Rationale for change		Correction of a typographic error, as no Cohort G planned in the final protocol
Section to be changed		Section 3.3.2. Inclusion Criteria – Cohort E (NSCLC) – Criteria #6
Description of change		Additional request to have NSCLC disease confirmed by histology or cytology
Rationale for change		Revision of the criteria as per FDA request
Section to be changed		Section 3.3.3. Exclusion Criteria #7

Description of change		Revision of the starting time of trial treatment 3 half-lives after previous immunotherapy instead of 2.
Rationale for change		As per FDA request and in order to minimize overlapping toxicities
Section to be changed		Section 4.1.2.2 Part 2 – Dose finding cohorts B, C, D
Description of change		Clarification of the text referring to starting dose of the study drugs
Rationale for change		Wording error corrected, in order to add clarity to the text
Section to be changed		Section 4.1.4.2 Temporary treatment interruption and dose reduction
Description of change		Clarification of the dose interruption recommendations, with special clarification for potential overlapping toxicities.
Rationale for change		As per FDA request and in order to minimize overlapping toxicities
Section to be changed		Section 4.4.1 Increased serum creatinine
Description of change		Inclusion of the need to perform serum cystatin-C testing to identify true renal function beyond monitoring creatinine
Rationale for change		As per FDA request and in order to give more detailed guidelines in case of renal dysfunction
Section to be changed		Section 5.3.7. Dose Limiting Toxicities (DLTs)
Description of change		Revision of the DLT definition and protocol defined DLTs
Rationale for change		As per FDA request and in order to give more details to this section.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		22 September 2017
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
To be implemented only after approval of the IRB / IEC / Competent Authorities		Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		No
Section to be changed		Clinical Trial Protocol Synopsis – Main Criteria for inclusion – Cohort E
Description of change		Clarification on number of prior lines that participants must have received
Rationale for change		To make text consistent with inclusion criteria in section 3.3.2.
Section to be changed		Clinical Trial Protocol Synopsis – Main Criteria for exclusion
Description of change		Clarification on prior therapies and unresolved toxicities
Rationale for change		To make text consistent with exclusion criteria in section 3.3.3.
Section to be changed		Flow Chart Cohort E – Footnote #6
Description of change		Change detail for Run-in visit 2

Rationale for change		Correction according to the Flow Chart
Section to be changed		Flow Chart Cohort F
Description of change		Added footnote reference for Fulvestrant
Rationale for change		Correction of typographic error
Section to be changed		Section 3.3.3. Exclusion Criteria #3
Description of change		Change the word *enrolment* for *treatment*
Rationale for change		To avoid confusing terminology
Section to be changed		Section 3.3.3. Exclusion Criteria #7
Description of change		Exclusion of prior corticosteroids is deleted
Rationale for change		To keep consistency with section 4.2.2.
Section to be changed		Section 3.3.3. Exclusion Criteria #10
Description of change		Clarification of the exclusion criteria referring to unresolved toxicities from prior treatment
Rationale for change		To add clarity to the criteria
Section to be changed		Section 3.3.3. Exclusion Criteria #18
Description of change		Threshold added for diabetes
Rationale for change		To keep consistency with the synopsis
Section to be changed		4.1.4.1 Initial study drug assignment and administration
Description of change		Change of term referring to dose finding cohorts
Rationale for change		Correct wording error
Section to be changed		4.1.4.2 Temporary treatment interruption and dose reduction
Description of change		Clarification on re-escalation possibilities
Rationale for change		To improve wording clarity
Section to be changed		4.1.4.2 Temporary treatment interruption and dose reduction
Description of change		Clarification on dose reduction requirements
Rationale for change		To keep consistency within the section
Section to be changed		4.1.4.2 Temporary treatment interruption and dose
Description of change		Footnote added referring to toxicity management
Rationale for change		To clarify instructions for toxicity management
Section to be changed		4.4.2 Management and grading of infusion reactions
Description of change		Clarification on CRF page reporting
Rationale for change		To be consistent with CRF design

Section to be changed		5.3.4 Electrocardiogram
Description of change		Correction of cohorts with run-in visits
Rationale for change		To correct the typo error
Section to be changed		5.3.6.1 Definitions of AEs
Description of change		The requirement specific for Japan about the reason of the decision about causality is deleted
Rationale for change		The requirement is no longer applicable in Japan,
Section to be changed		5.3.7 Dose Limiting Toxicities
Description of change		The list of DLTs definitions is revised
Rationale for change		To make the text consistent with the study drugs toxicity profile
Section to be changed		5.4.1 Assessment of Pharmacokinetics
Description of change		Clarification is added about sample timepoints
Rationale for change		To add some flexibility in the sample time schedule
Section to be changed		5.5 Assessment of biomarker(s)
Description of change		Biomarker name corrected and dissociable IGF added
Rationale for change		To correct a typo error and introduce the dissociable IGF definition
Section to be changed		5.6.1 Assessment of Immunogenicity
Description of change		Appendix reference corrected
Rationale for change		To correct a typo error
Section to be changed		8.1 Trial approval, patient information, informed consent.
Description of change		A clause is added to identify the text that is only applicable to Japan
Rationale for change		To clarify that the text is not applicable to all participant countries
Section to be changed		10.1 Inducers and Strong Inhibitors of CYP3A4
Description of change		Topical medication considerations
Rationale for change		For clarification purposes
Section to be changed		10.2 Pharmacokinetics plan
Description of change		Dissociable IGF is mentioned in the flowcharts for the different cohorts
Rationale for change		To be consistent with section 5.5

11.3 GLOBAL AMENDMENT 3

Number of global amendment		3
Date of CTP revision		11 Dec 2018
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
To be implemented only after approval of the IRB / IEC / Competent Authorities		Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		No
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Different sections updated
Rationale for change		To match with the updates in the different protocol sections.
Section to be changed		Clinical Trial Protocol Synopsis-Flow Chart for Cohorts A, B, C and D (dose finding)
Description of change		Footnote #16 corrected
Rationale for change		To clarify an bone scan requirement and correct on day windows for week 60 and week 72
Section to be changed		Clinical Trial Protocol Synopsis-Flow Chart for Cohort D (dose finding)
Description of change		Footnote #6 modified
Rationale for change		To reduce the screening window for local FSH and estradiol
Section to be changed		Clinical Trial Protocol Synopsis-Flow Chart Cohort E and F

Description of change		Footnote #18 corrected
Rationale for change		To clarify an bone scan requirement and correct on day windows for week 60 and week 72
Section to be changed		Clinical Trial Protocol Synopsis-Flow Chart Cohort F
Description of change		Footnote #7 modified
Rationale for change		To reduce the screening window for local FSH and estradiol
Section to be changed		Clinical Trial Protocol Synopsis-Flow Chart Expansion cohorts D1 and D2
Description of change		New Flow Chart added
Rationale for change		To describe the schedule of activities for BC expansion cohorts D1 and D2
Section to be changed		1.2 Drug Profile
Description of change		Text added in the IMPs profile information
Rationale for change		To update with available information
Section to be changed		2.1 Rationale for performing the trial
Description of change		Text added
Rationale for change		Updated information and added rationale for expansion cohorts D1 and D2
Section to be changed		2.2 Trial Objectives
Description of change		Text added
Rationale for change		Primary objective for expansion cohorts D1 and D2 is described
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		Part 3 design update
Rationale for change		To include and describe expansion cohorts D1 and D2
Section to be changed		3.2 Discussion of Trial Design
Description of change		Section updated
Rationale for change		For expansion cohorts D1 and D2 description
Section to be changed		3.3 Selection of Trial Population
Description of change		Change the total number of subjects and sites
Rationale for change		To update the figures needed as per the new cohorts addition
Section to be changed		3.3.2 Inclusion criteria-Cohort A and E: #5

Description of change		Required contraception methods timelines updated
Rationale for change		According to the updated abemaciclib risk profile
Section to be changed		3.3.2 Inclusion criteria-B, C, D(dose finding) and F Cohorts: #5
Description of change		Postmenopausal status requirements wording revision
Rationale for change		To improve specificity and clarity in the criteria
Section to be changed		3.3.2 Inclusion criteria- cohorts D1 and D2
Description of change		Cohorts D1 and D2 inclusion criteria added
Rationale for change		To describe inclusion criteria for expansion cohorts D1 and D2
Section to be changed		3.3.3 Exclusion criteria(cohorts A, B, C, D(dose finding), E and F: #7
Description of change		Text modified
Rationale for change		To relax washout required periods
Section to be changed		3.3.3 Exclusion criteria (cohorts A, B, C, D(dose finding), E and F: #12
Description of change		Clarifications on central nervous system disease
Rationale for change		To further clarify
Section to be changed		3.3.3 Exclusion criteria (cohorts A, B, C, D(dose finding), E and F: #24
Description of change		Clarification added on active infections
Rationale for change		To be more specific on active infection definition
Section to be changed		3.3.3 Exclusion criteria:#27
Description of change		New criteria
Rationale for change		To exclude prior everolimus treatment for cohort F
Section to be changed		3.3.3 Exclusion criteria- cohorts D1 and D2
Description of change		Cohorts D1 and D2 exclusion criteria added
Rationale for change		To describe exclusion criteria for expansion cohorts D1 and D2
Section to be changed		3.3.5 Replacement of patients
Description of change		Text added for dose interruption both for xentuzumab and abemaciclib. Also replacement for cohorts E and F is added.
Rationale for change		For clarification purposes for dose interruption and provide new instruction for cohort E and F

Section to be changed		4.1.2 Selection of doses in the trial
Description of change		Updated information for Part 3
Rationale for change		To include the information for cohorts D1 and D2
Section to be changed		4.1.4.2 Temporary treatment interruption and dose reduction
Description of change		Text revised for overlapping toxicities and DLT management
Rationale for change		Clarification on the management of overlapping toxicities and DLTs
Section to be changed		4.1.4.2:2 Table
Description of change		Header changed
Rationale for change		To clarify that the table is about abemaciclib possibly related toxicity.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Paragraph deleted as per restrictions for abemaciclib.
Rationale for change		Revise the text about CYP3A4 restrictions
Section to be changed		4.2.2.3 Restrictions regarding men and women of childbearing potential
Description of change		Required contraception methods timelines updated
Rationale for change		According to the updated abemaciclib risk profile
Section to be changed		4.2.2.7 Restrictions regarding ovarian suppression
Description of change		New section added
Rationale for change		Requirement added to ensure the postmenopausal status is maintained
Section to be changed		4.4.2 Management and grading of infusion reactions
Description of change		IRR Management instructions revised
Rationale for change		To be in alignment with other xentuzumab trials
Section to be changed		4.4.3 Management on neutropenia
Description of change		New section added
Rationale for change		To reinforce and ensure the monitoring of neutropenia as expected adverse event.
Section to be changed		4.4.4 Management of hepatotoxicity
Description of change		New section added

Rationale for change		To provide guidance on the management of hepatotoxicity as expected adverse event.
Section to be changed		5.1.1 Primary endpoint(s)
Description of change		Section updated for expansion cohorts D1 and D2
Rationale for change		To describe primary endpoint for expansion cohorts D1 and D 2
Section to be changed		5.1.2 Secondary endpoint(s)
Description of change		Section updated for expansion cohorts D1 and D2
Rationale for change		Secondary endpoint added for expansion cohorts D1 and D2
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		5.2 Assessment of efficacy
Description of change		Text added for bone scans requirements
Rationale for change		To clarify on the follow up requirements for bone metastasis assessments
Section to be changed		5.3.6.2 Adverse event collection and reporting
Description of change		Instructions added for female partner in the pregnancy section
Rationale for change		To extend the requirements of DEDP reporting to the female partner of a male participant
Section to be changed		5.3.7 Dose limiting toxicities (DLTs)
Description of change		Revision of DLT definitions
Rationale for change		To excluded some hematologic toxicities and IRR
Section to be changed		5.4.2 Methods of sample collection
Description of change		Clarification on plasma samples use
Rationale for change		No needed to wait until completion of the study to use them.
Section to be changed		5.5 Assessment of biomarker(s)
Description of change		Addition of sample retention plan
Rationale for change		To clarify on remaining sample retention timelines
Section to be changed		6.2. Details of trial procedures at selected visits

Description of change		Description added for cohorts D1 and D2 procedures (6.2.2.3)
Rationale for change		To describe the procedures required for expansion cohorts D1 and D2
Section to be changed		7.3 Planned analysis
Description of change		Description added for the possibility of primary analysis for the expansion cohorts
Rationale for change		To clarify on the primary analyses planned
Section to be changed		7.3.1 Primary endpoints analysis
Description of change		Addition of planned analysis for expansion cohorts D1 and D2
Rationale for change		To update for cohorts D1 and D2 addition
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		Addition of secondary endpoint analyses for cohorts D1 and D2
Rationale for change		To update for cohorts D1 and D2 addition
Section to be changed		7.3.5 Pharmacokinetic and pharmacodynamics analyses
Description of change		Addition of a clarification on the NCA
Rationale for change		To clarify that only applies to the expansion cohorts
Section to be changed		7.4 Interim analyses
Description of change		Added an statement about earlier efficacy analyses
Rationale for change		To clarify that other efficacy analyses may be performed
Section to be changed		7.7 Determination of sample size
Description of change		Descriptions added for cohorts D1 and D2
Rationale for change		To update for cohorts D1 and D2 addition
Section to be changed		8.6 Trial milestones
Description of change		Addition of description of LPLVPE-expansion for cohorts D1 and D2
Rationale for change		To specify different milestone for different expansion cohorts
Section to be changed		10.2.3.2 Flow chart for PK, immunogenicity, and biomarkers for Cohort F in treatment course 2
Description of change		Updates on the events

Rationale for change		Clarifications on the requirements about the sampling related to the abemaciclib intake
Section to be changed		10.2.4 Flow chart for PK, immunogenicity, and biomarkers for cohorts D1 and D2
Description of change		New flow charts
Rationale for change		To describe the required sampling for cohorts D1 and D2

11.4 GLOBAL AMENDMENT 4

Number of global amendment		4
Date of CTP revision		09 Apr 2019
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
To be implemented only after approval of the IRB / IEC / Competent Authorities		Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		No
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Main criteria for inclusion for diagnosis of breast cancer corrected
Rationale for change		To be consistent with section 3.3.2
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Correction of flowchart for cohorts C and D for baseline tumour assessment timepoint
Rationale for change		For consistency
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Footnote #16 in Flowchart for Cohorts D1 and D2 corrected
Rationale for change		To be consistent with 10.2.4.3 flowchart
Section to be changed		1.2 Drug profile
Description of change		Safety profile for xentuzumab updated
Rationale for change		Updated data as per cut off of 2019

Section to be changed		2.1 Rationales for performing the trial
Description of change		Correction made when describing expansion cohorts
Rationale for change		Letrozole and anastrozole are not used
Section to be changed		2.3 Benefit-Risk Assessment
Description of change		Data for xentuzumab updated
Rationale for change		To keep the information up to date
Section to be changed		3.3.2 Inclusion criteria
Description of change		In #9 for cohorts D1 and D2 corrected
Rationale for change		To be consistent with abemaciclib risk profile
Section to be changed		3.3.3 Exclusion criteria
Description of change		Ex #17 for Cohorts D1 and D2 corrected
Rationale for change		Letrozole and anastrozole do not apply for those cohorts
Section to be changed		4.1.4.2 temporary treatment interruption and dose reduction
Description of change		Guidelines for abemaciclib toxicity management update
Rationale for change		To be aligned with the most recent abemaciclib safety information
Section to be changed		4.2.2 Restrictions
Description of change		Updated instructions and guidelines as per inducers and inhibitors of CYP3A
Rationale for change		To be aligned with the most recent abemaciclib safety information
Section to be changed		4.4.4 Management of Hepatotoxicity
Description of change		Updated information and guidelines
Rationale for change		To be aligned with the most recent abemaciclib safety information
Section to be changed		4.4.5 Venous Thromboembolism
Description of change		New section added
Rationale for change		To provide information ad instructions to manage the adverse event
Section to be changed		10.1 Inducers and strong inhibitors of CYP3A4
Description of change		The lists of the strong inhibitors and substrates are updated

Rationale for change		To be aligned with the most recent abemaciclib safety information
Section to be changed		10.2.4.1 Flowchart for PK, AD and biomarkers for cohorts D1 and D2 in course 1
Description of change		Footnote deleted
Rationale for change		For consistency
Section to be changed		10.2.4.2 Flowchart for PK, AD and biomarkers for cohorts D1 and D2 in course 2
Description of change		Fulvestrant PK sample correction
Rationale for change		For consistency
Section to be changed		10.2.4.3 Flowchart for PK, AD and biomarkers for cohorts D1 and D2 in courses 3, 4, 6, 12 and 24
Description of change		Header and footnotes corrected
Rationale for change		For consistency

11.5 GLOBAL AMENDMENT 5

Number of global amendment		5
Date of CTP revision		03 Jul 2019
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
To be implemented only after approval of the IRB / IEC / Competent Authorities		Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		No
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria #13 was updated to exclude subjects with ILD and other respiratory disorders
Rationale for change		To be in accordance with updated abemaciclib safety information
Section to be changed		4.4.6 Guidance for ILD/Pneumonitis
Description of change		New section added
Rationale for change		To be in accordance with updated abemaciclib safety information

11.6 GLOBAL AMENDMENT 6

Date of amendment		23 Dec 2019
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
Global Amendment due to urgent safety reasons:		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Asia region included for trial sites
Rationale for change		To extend to other Asian sites participation
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Tablets mentioned in the eligibility criteria
Rationale for change		To be consistent with section 3.3.2
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Alpelisib added as prior treatment in the exclusion criteria for cohorts D1 and D2
Rationale for change		For a better definition of trial population in reaction to a newly approved treatment
Section to be changed		3.3.2 Inclusion criteria
Description of change		Tablets added to inclusion criteria #4 for all cohorts
Rationale for change		To be consistent with the possibility of tablets intake
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion criteria #9 for cohorts D1 and D2 updated as per the contraception period required for xentuzumab
Rationale for change		Re-assessment of contraception requirements for xentuzumab for WOCBP, including PK variability and normalization of PD effects.
Section to be changed		3.3.3 Exclusion criteria

Description of change		Alpelisib added as prior treatment excluded for cohorts D1 and D2
Rationale for change		For a better definition of trial population in reaction to a newly approved treatment
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		Information added about abemaciclib tablets formulation
Rationale for change		Abemaciclib tablets can be administered to the study subjects
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		The possibility to reduce the abemaciclib dose to 50 mg BID was added
Rationale for change		To facilitate abemaciclib AE management
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Guidelines for abemaciclib dose adjustment to manage ILD/pneumonitis were added
Rationale for change		To be consistent with the abemaciclib IB information
Section to be changed		4.1.7 Storage conditions
Description of change		Abemaciclib tablets added
Rationale for change		To provide instruction on tablets storage requirements
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Instructions updated
Rationale for change		To include the options to reduced abemaciclib dose to 50 mg twice daily.
Section to be changed		4.2.2.3 Restrictions regarding men and women of childbearing potential
Description of change		Update on the contraception period required for xentuzumab
Rationale for change		Re-assessment of contraception requirements for xentuzumab for WOCBP, including PK variability and normalization of PD effects.
Section to be changed		4.4.6 Guidance for Interstitial lung disease/Pneumonitis

Description of change		Text updated
Rationale for change		To be consistent with table 4.1.4.2:2

11.7 GLOBAL AMENDMENT 7

Date of amendment		02 Jul 2020
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
Global Amendment due to urgent safety reasons:		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Text amended in different sections of the synopsis
Rationale for change		To update the synopsis according to the changes made in different sections of the protocol
Section to be changed		Flow Chart-Cohort F
Description of change		Run-in visits and corresponding procedures were removed
Rationale for change		The run-in data from cohort F is no longer required for analysis
Section to be changed		Flow Chart-Cohort F
Description of change		A number PK samples in cycle 2 were removed
Rationale for change		Those PK samples in cohort F no longer required for analysis were removed to simplify the study procedures
Section to be changed		Flow Chart-Cohort F
Description of change		Tumour assessment requirements in follow up period were highlighted
Rationale for change		To clarify the instructions to follow up for progression of disease
Section to be changed		Flow Chart Cohorts D1 and D2
Description of change		Tumour assessment requirements in follow up period were highlighted
Rationale for change		To clarify the instructions to follow up for progression of disease

Section to be changed		2.2 Trial Objectives
Description of change		Trial objectives reworded for cohort F
Rationale for change		To accurately describe primary and secondary objectives for cohort F
Section to be changed		2.3 Benefit-Risk Assessment
Description of change		Language was added about Covid-19 infection
Rationale for change		To provide information and guidance on Covid-19 considerations for the trial
Section to be changed		3.1 Overall Trial Design Plan
Description of change		Section updated for cohort F information
Rationale for change		To accurately describe the design of cohort F
Section to be changed		3.2 Discussion of Trial Design, including the choice of control Group(s)
Description of change		Section updated for cohort F
Rationale for change		To amend the PK plan for cohort F
Section to be changed		3.3.2 Inclusion criteria
Description of change		Modified for cohort F
Rationale for change		To provide a detailed definition of the inclusion criteria for cohort F
Section to be changed		3.3.3 Exclusion criteria
Description of change		Modified for cohort F
Rationale for change		To provide a detailed definition of the exclusion criteria for cohort F
Section to be changed		3.3.5 Replacement of patients
Description of change		Amended for cohort F
Rationale for change		To be consistent with the endpoints updates for cohort F
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Abemaciclib related information was updated
Rationale for change		Modified according to the most current information in the abemaciclib SmPC
Section to be changed		4.3 Treatment compliance
Description of change		Patient diary requirement for cohort F was removed
Rationale for change		To be consistent with the run-in visits removed
Section to be changed		4.4.1 Increased Serum Creatinine

Description of change		Language was updated
Rationale for change		According to the latest abemaciclib information available
Section to be changed		5.1 Trial Endpoints
Description of change		Specific endpoints for cohort F were revised
Rationale for change		To accurately describe the primary and secondary endpoints for cohort F
Section to be changed		5.5 Assessment of Biomarker(s)
Description of change		Headers and footnotes of tables 5.5: 1 and 5.5:2 were corrected
Rationale for change		Correction needed to resolve an inconsistency with the biomarker sampling plan
Section to be changed		6.1 Visit Schedule
Description of change		Language added about the possibility to visit the patient remotely
Rationale for change		That is to mitigate the difficulties to visit the patient at the site under extraordinary circumstances such as relevant infection outbreaks or similar.
Section to be changed		6.2 Details of Trial Procedures at Selected Visits
Description of change		The procedures description were corrected
Rationale for change		To be consistent with the flow charts
Section to be changed		6.2.3.2 Follow up period
Description of change		Details added for follow up period for progression of disease
Rationale for change		To improve the description of the procedures required during the follow up period
Section to be changed		7.3. Planned Analyses
Description of change		Information added for cohort F
Rationale for change		To describe the analyses planned for cohort F endpoints
Section to be changed		7.7 Determination of sample size
Description of change		Specific description for cohort F was added
Rationale for change		Accurately describe the assumptions for cohort F
Section to be changed		10.1 Inducers and strong inhibitors of CYP3A4
Description of change		The list of drugs was revised
Rationale for change		According to the most updated abemaciclib information

Section to be changed		10.2.3 Flow chart for PK, immunogenicity, and biomarkers for cohort F
Description of change		The PK profile for cohort F was reduced
Rationale for change		To simplify the PK profile removing samples no longer required

11.8 GLOBAL AMENDMENT 8

Date of amendment		04 Mar 2022
EudraCT number		2016-003142-85
BI Trial number		1280.18
BI Investigational Product(s)		Xentuzumab (BI 836845)
Title of protocol		An open label, phase Ib, dose-escalation study evaluating the safety and tolerability of xentuzumab and abemaciclib in patients with locally advanced or metastatic solid tumours and in combination with endocrine therapy in patients with locally advanced or metastatic hormone receptor-positive, HER2-, breast cancer, followed by expansion cohorts
Global Amendment due to urgent safety reasons:		☐
Global Amendment		☒
Section to be changed		Flow Chart-Cohort F
Description of change		Schedule of activities revised. Some procedures removed
Rationale for change		To reflect reduced procedures and assessments to support ongoing patients because of 1280-0022 primary endpoint analysis results
Section to be changed		Flow Chart-Cohorts D1 and D2
Description of change		Schedule of activities revised. Some procedures removed
Rationale for change		To reflect reduced procedures and assessments to support ongoing patients because of 1280-0022 primary endpoint analysis results
Section to be changed		2.3 Benefit-Risk assessment
Description of change		New text added
Rationale for change		Based on the 1280-0022 study results of primary endpoint analysis
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		New text added
Rationale for change		To refer to the trial termination possibilities
Section to be changed		3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		New text added
Rationale for change		To describe trial termination possibilities
Section to be changed		4.1 Investigation treatments

Description of change		Xentuzumab treatment discontinuation recommendation added
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.2 Assessment of efficacy
Description of change		Requirements for response assessments reduced
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.3 Assessment of safety
Description of change		Requirements for safety assessments reduced
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.4.1 Assessment of Pharmacokinetics
Description of change		PK samples are no longer collected
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.4.2 Methods of sample collection
Description of change		Blood for PK and ADA is no longer collected
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.5 Assessment of biomarker(s)
Description of change		biomarkers samples are no longer collected
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		5.6.1 Assessment of Immunogenicity
Description of change		blood samples for immunogenicity assessments are no longer collected
Rationale for change		Based on benefit-risk change after 1280-022 primary endpoint analysis results
Section to be changed		6.2.2.3 Cohorts D1, D2 and F
Description of change		Reference to reduced flow chart
Rationale for change		To be consistent with the revised flowcharts for cohorts D1, D2 and F
Section to be changed		6.2.3.1 End of treatment visit
Description of change		Sample collection details removed
Rationale for change		To be consistent with flowchart revision
Section to be changed		7.3 Planned analysis

Description of change		Final analysis timepoint description removed
Rationale for change		To conduct final analyses before last patient out
Section to be changed		10.2.3 FLOW CHART for PK, immunogenicity, and biomarkers for cohort F
Description of change		Blood samples no longer collected
Rationale for change		To be consistent with the revised flowchart for cohort F
Section to be changed		10.2.4 FLOW CHART for PK, immunogenicity, and biomarkers for cohorts D1 and D2
Description of change		Blood samples no longer collected
Rationale for change		To be consistent with the revised flowchart for cohorts D1 and D2