CLINICAL TRIAL PROTOCOL

CONFIDENTIAL

Protocol No:	POL6326-009
IND No:	118.448
EudraCT No:	2018-004211-42
Title:	An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixa**fort**ide in combination with Eribulin versus Eribulin alone in Patients with HER2 negative, Locally **Re**current or Meta**s**tatic Brea**s**t Cancer (FORTRESS)
Development Phase:	Phase 3
Sponsor:	Polyphor Ltd Hegenheimermattweg 125, CH-4123 Allschwil, Switzerland
Co-ordinating Investigators:	Javier Cortés Castán, MD, PhD IOB Institute of Oncology, Madrid & Barcelona Ruber International Hospital Calle de La Maso 38 28034 Madrid, Spain Peter A. Kaufmann, MD Breast Oncology, Division of Hematology/Oncology University of Vermont Cancer Center 05405 Burlington, VT, USA
Protocol Version and Date:	Final Protocol Version 3.0 Date: 15 July 2019

PROTOCOL VERSIONS HISTORY

The table below is intended to capture study protocol versions history, including a description of the change and rationale.

Version	Date	Amend-ment Number	Description of Change	Brief Rationale/Comment
Draft 1.0	28 September 2018		This is the first version.	Not signed by Sponsor and not submitted to regulatory authorities
Draft 1.1	11 October 2018		Frequency of bone scans changed. Some assessments for 30-Day Safety Follow-up removed. Further information added to Section 3.2 on justification for dose of balixafortide. Editorial amendments made.	Improving clarity and practicality of information/Sent to FDA for type B meeting
Final 2.0	29 November 2018		Additional assessments for End-of-Treatment evaluation. Primary Objective, efficacy endpoints, and statistical section amended. Nomenclature for populations to be studied amended. Guidance on contraception amended for inclusion criteria and elsewhere in protocol. Exclusion criteria for drugs that prolong the QT interval or cause torsades de pointes amended. A table of drugs known to cause torsades de pointes added to Appendix 1. Formulation, packaging and storage information amended.	Changes made post discussion at FDA meeting/final and signed version to be submitted to regulatory authorities

Version	Date	Amend-ment Number	Description of Change	Brief Rationale/Comment
			Guidance provided on management of AESIs and AEPIs.	
			Editorial amendments.	
			Changes to administration of the trial.	
Final 3.0	15 July 2019	1	Number of study visits reduced for eribulin monotherapy treatment arm. PK and immunogenicity assessments no longer required for these patients.	To reduce the burden of unnecessary assessments and visits for these patients.
			Separate schedules provided for each treatment arm.	Number of study visits reduced for eribulin monotherapy treatment arm.
			Assessments for tumor biopsy, PK, exploratory biomarkers, and immunogenicity testing integrated with other assessments in Schedules.	To allow all assessments to be displayed together for each treatment arm.
			Number of footnotes reduced and cross-references provided to relevant sections of protocol.	To improve presentation of schedules and to reduce duplication of information.
			Section 2.4 updated to provide information from new studies including a 13-week repeat dose toxicity study in cynomolgus monkeys, studies investigating the immunogenicity and phototoxicity of balixafortide, and studies investigating the effects of balixafortide on cardiac ion channels.	To provide the latest information from non-clinical studies.
			Included updated survival data from POL6326-007 study in Section 2.5.1.	To provide up-to-date survival information.
			Included information on effects of balixafortide on	To explain whether there is potential for a

Version	Date	Amend-ment Number	Description of Change	Brief Rationale/Comment
			eribulin pharmacokinetics and vice versa in Section 2.5.1.	drug interaction between eribulin and balixafortide.
			New Subsection 2.5.2 included.	To summarise balixafortide population pharmacokinetics.
			Additional information added to Section 3.2.	To provide justification for the balixafortide + eribulin dose regimen in terms of disruption of the tumor microenvironment.
			Included statement on hormonal contraception in Section 5.4.5.	To clarify which women can take hormonal contraception.
			Provided additional information on dosing delays and interruptions in Section 6.1.2.1.	To provide practical information on action to take in these situations.
			Treatment Period in Section 7 separated by treatment arm.	Number of study visits reduced for eribulin monotherapy treatment arm.
			Assessments in Section 7 arranged in relation to timing of study medication administration.	To allow information to be used in a practical way.
			Rationalized visits for exploratory biomarkers in all patients.	To accommodate the reduced visits in the eribulin monotherapy treatment arm.
			Tabulated information on visits and timepoints for assessments of ECG (Section 9.8), PK (Section 10), and Exploratory Biomarkers (Section 11.2.2).	To improve presentation and usability.
			Changes to administration of the trial	New Chief Medical Officer and Development Officer from Polyphor Ltd.

PROTOCOL SIGNATURE PAGE

Protocol Number: POL6326-009

Version 3.0 Date: 15 July 2019

Protocol Title: An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixafortide in combination with Eribulin versus Eribulin alone in Patients with HER2 negative, Locally Recurrent or Metastatic Breast Cancer (FORTRESS)

Sponsor Approval

PP Jabe S Barlow MD — 15-7-19

Signature — Date

Name, academic degree: Frank Weber, MD

Function: Chief Medical and Development Officer

Institution: Polyphor Ltd

Address: Hegenheimermattweg 125,
CH-4123 Allschwil,
Switzerland

Telephone number: +41 61 567 1600

Fax number: +41 61 567 1601

Co-ordinating Investigators

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Signature

16 Jul 19

Date:

Name, academic degree: Javier Cortés Castán, MD, PhD

Institution: IOB Institute of Oncology, Madrid & Barcelona, Ruber International Hospital

Address: Calle de La Maso 38
28034 Madrid, Spain

Telephone number: +34 91 336 82 63

Co-ordinating Investigators

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Signature

8/6/19

Date:

Name, academic degree: Peter A. Kaufmann, MD

Institution: University of Vermont Cancer Center

Address: 05405 Burlington, VT, USA

Telephone number: 802 847-8400

DECLARATION OF INVESTIGATORS

POLYPHOR Ltd

Protocol Number: POL6326-009

EudraCT No: 2018-004211-42

Version 3.0 Date: 15 July 2019

Protocol Title: An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixa**fort**ide in combination with Eribulin versus Eribulin alone in Patients with HER2 negative, Locally **Re**current or Meta**s**tatic Brea**s**t Cancer (FORTRESS)

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the well-being of the patients), any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP(R2)) and all applicable Health Authority requirements and national laws.

- I will not deviate from the clinical trial protocol, except where necessary to prevent immediate danger to the subject.

- I explicitly agree to provide direct access to all source document pertinent to subject enrolled in the study to the Sponsor, its designee, Institutional Review Board or Independent Ethics Committee (IEC/IRB) member and competent authorities.

- I have been adequately informed about the development of the investigational product to date. I confirm the receipt of updated Investigator's Brochure. I have read this study protocol and agree that it contains all the information required to conduct the study.

- I will not enroll the first subject in the study until I have received approval from the appropriate IRB/IEC and until all legal and regulatory requirements in my country have been fulfilled.

- The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and its amendments (1), the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws.

- I agree to obtain, in the manner described in this protocol, written informed consent or surrogate informed consent to participate for all subjects enrolled in this study.

- I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol.

- I am aware of the requirements for the correct reporting of serious adverse events, and I commit to document and to report such events as required by Polyphor and in accordance with Health Authority Regulatory requirements.

- I agree to supply – upon request – the Sponsor or Sponsor`s designee with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges.

- I agree with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.

- I agree to keep all source documents and case report forms as specified in the relevant sections of this protocol.

- I will provide all required Regulatory Authority forms, curriculum vitae of myself and sub-investigators before the study starts, which may be submitted to regulatory authorities.

- Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

- I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary to the Sponsor which will use any such information that is collected solely for the purpose for complying with the regulatory requirements

Investigator Signature Date

Print Name and Title

Name and Address of Institution

SPONSOR AND TRIAL ADMINISTRATIVE STRUCTURE

Name and Address of the Sponsor

Polyphor Ltd
Hegenheimermattweg 125
4123 Allschwil, Switzerland

Contract Research Organization

PPD Global Ltd
Granta Park, Great Abington
Cambridge, CB21 6GQ
United Kingdom

Medical Monitoring by CRO

PPD Global Ltd
Granta Park, Great Abington
Cambridge, CB21 6GQ
United Kingdom

Drug Safety Officer

PPD PVG EMEA fax: +44 1223 374 102
PPD PVG EMEA email: EMEAAsiaSafetyCentral.SM@ppdi.com
PPD PVG EMEA hotline: +44 1223 374 240

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ABBREVIATIONS AND DEFINITIONS

ADL	Activities of Daily Living
AE	Adverse Event
AEPI	AE of Particular Interest
AESI	AE of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATC	Anatomical, Therapeutic, or Chemical
AUC	Area Under the Curve
BC	Breast Cancer
β-HCG	Beta Human Chorionic Gonadotropin
BMA	Bone-Modifying Agent
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Ca	Calcium
CBR	Clinical Benefit Rate
CD34+	Cluster of Differentiation 34+
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
CK	Creatine Kinase
CL	Clearance
C_{max}	Maximum Concentration
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Colony Stimulating Factor
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXCR4	C-X-C Chemokine Receptor Type 4

CYP	Cytochrome P
D	Day
DCR	Disease Control Rate
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDISH	evaluation of Drug-induced Serious Hepatotoxicity
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EoT	End-of-Treatment
EQ-5D	EuroQol-5D
EQ VAS	EQ Visual Analogue Scale
ER	Estrogen Receptor
ER+	Estrogenic-receptor Positive
ER-	Estrogenic-receptor Negative
EU	European Union
EudraCT	European Clinical Trials Database
FACT-B	Functional Assessment of Cancer Therapy Breast
FDA	Food and Drug Administration (US)
FDG-PET	18-fluoro-deoxyglucose Positron Emission Tomography
FISH	Fluorescence in Situ Hybridization
FU	Follow-Up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
hERG	Human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor

Ht	Hematocrit
iBOR	Immune Best Overall Response
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IFN	Interferon
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
iPR	Immune Partial Response
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
iSD	Immune Stable Disease
ISF	Investigator Site File
ITT	Intention-To-Treat
IUD	Intrauterine Device
iUPD	Immune Unconfirmed Progressive Disease
IWRS	Interactive Web Response System
IV	Intravenous(ly)
K	Potassium
KIM-1	Kidney Injury Molecule-1
KR	Known Risk
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
MRGPRX2	mas-related gene X2 receptor
MRI	Magnetic Resonance Imaging
msec	Milliseconds
Na	Sodium
NCI	National Cancer Institute
NE	Not Evaluable

NGAL	Neutrophil Gelatinase-associated Lipocalin
NOAEL	No-observed Adverse-effect Level
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PgR	Progesterone Receptor
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcome
PT	Preferred Term
QA	Quality Assurance
QoL	Quality of Life
QTc	Corrected QT Interval
QTcF	QT Interval corrected with Fridericia's formula
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Stable Disease
SDF-1	Stromal Cell-Derived Factor-1
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Terminal Half-life
TdP	Torsades de Pointes
TEAE	Treatment Emergent Adverse Event
UK	United Kingdom
US	United States

ULN	Upper Limit of Normal
V_z	Total Volume of Distribution
WBC	White Blood Cell
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Protocol number: POL6326-009	**Trial drug:** Balixafortide
Title of the trial: An International, Phase 3, Multicenter, Randomized, Open-Label Trial Comparing Balixa**fort**ide in combination with Eribulin versus Eribulin alone in Patients with HER2 negative, Locally **Re**current or Meta**s**tatic Brea**s**t Cancer (FORTRESS)	
Sponsor: Polyphor Ltd	
Development Phase: Phase 3	
Study centers: This study will be performed in at least 95 centers and 14 countries globally.	
Study period (planned): To generate the required number of progression free survival (PFS) events for the main analysis, a 12-month recruitment period is anticipated with an expected follow-up period of 12-months after the last patient is randomized. Patients will then be followed for one additional year for overall survival (OS). The study is planned to begin during the first quarter of 2019.	
Patient Population: Patients with human epidermal growth factor receptor 2 (HER2) negative, locally recurrent or metastatic breast cancer (BC) that has previously been treated with 1−4 chemotherapeutic regimens for locally recurrent or metastatic BC. Unless contra-indicated for safety reasons, patients will have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting. In this protocol, locally recurrent BC is defined as unresectable locoregionally recurrent BC. Two populations of patients will be studied, the: • Overall Population, who receive study medication as 2nd to 5th line of therapy, which will constitute the primary population for regulatory submissions in the European Union (EU) and jurisdictions in which the 2nd line + eribulin label applies. • 3rd line + population, who receive study medication as 3rd to 5th line of therapy (3rd line +), which will constitute the primary population for regulatory submissions in the United States (US) and jurisdictions in which the 3rd line + eribulin label applies.	
Study Design: In this international, multicenter, open-label, randomized, two-arm, pivotal Phase 3 study, eligible patients will be randomly assigned in a 1:1 ratio to one of the following treatment regimens: Balixafortide + eribulin treatment arm *or* Eribulin treatment arm Cross-over will not be allowed at any time after randomization. Patients will be stratified according to: • Line of therapy (2nd line versus 3rd line +) for locally recurrent or metastatic BC. • Hormone receptor (HR) status (positive versus negative) based on estrogen receptor (ER) or progesterone receptor (PgR) status. • Cyclin-dependent kinase (CDK) 4/6 inhibitor treatment received previously (received a CDK 4/6 inhibitor previously versus not received a CDK 4/6 inhibitor previously).	

- Visceral versus non-visceral disease. Visceral metastases will include brain, pulmonary, pleural, hepatic and peritoneal involvement (including pleural effusions and ascites). Any other sites of metastases (e.g. bone, lymph nodes, and skin) will be considered to be non-visceral. Patients with visceral metastases, irrespective of the presence of any other metastatic sites (e.g. bone), will be categorized as visceral. All other patients without visceral metastases will be categorized as non-visceral.

Patients will undergo assessment for efficacy, safety and tolerability, pharmacokinetics (PK; including metabolites), immunogenicity, Quality of Life (QoL), and exploratory biomarkers (including interferon [IFN]-gamma and other circulating cytokines). At selected sites, the study will include assessment of additional exploratory blood and tissue biomarkers.

The Study Schedule of Assessments and sampling are outlined in Section 1.1.

The study will consist of the following:

- **Screening Assessments:** To be obtained ≤21 days prior to randomization.
- **Randomization:** Patients will be randomized within 21 days of starting screening and after having completed the required screening assessments. Patients will be randomized either to the balixafortide + eribulin treatment arm or to the eribulin treatment arm. All patients must begin treatment within 3 days after randomization.
- **Treatment Phase:** Patients will receive 21-day cycles of treatment. All patients will receive eribulin on Days 2 and 9 of each cycle (the rational for this frequency is explained in Section 3.2). In addition, patients randomized to the balixafortide + eribulin arm will receive balixafortide on Days 1−3 and Days 8−10 of each cycle.

  Response Assessments During Treatment: From the date of randomization, patients will be evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 for complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on computed tomography/magnetic resonance imaging (CT/MRI) scans performed every 6 weeks (±7 days) during the first year, and then performed every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression.

  From the date of randomization, additional bone scans will be performed at the discretion of the Investigator (e.g. to confirm CR or if [based on signs and symptoms] new bone metastases are suspected).

  Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.

  Patients will continue treatment as assigned at randomization, until objective PD (according to RECIST v1.1) is documented, there is unacceptable toxicity, death occurs, the patient withdraws consent, or the patient is lost to follow-up (whichever occurs first). Patients discontinued from treatment, for reasons other than PD, will enter the PD Follow-up (as described in PD Follow-up below) unless death occurs, the patient withdraws consent to efficacy follow-up, or the patient is lost to follow-up.

- **End-of-Treatment (EoT) Evaluation:** This will occur as soon as possible, within 7 days after discontinuation of study medication and prior to initiation of any new anti-cancer therapy, regardless of the reason for discontinuation. A targeted physical examination

will be conducted. Weight, Eastern Cooperative Oncology Group (ECOG) performance status, adverse events (AEs), vital signs, clinical laboratory tests, 12-lead electrocardiogram (ECG) and concomitant medications will be assessed and recorded for all patients at this visit. Patients who are discontinued from study medication for any reason, in the absence of objective PD (according to RECIST v1.1), will undergo tumor response assessment. For patients at selected sites, an optional tumor biopsy will be performed. Patients will complete QoL questionnaires.

- **30-Day Safety Follow-up:** This will occur 30 days (and no later than 37 days) from the last dose of study drug. AEs will be assessed and recorded for all patients at this visit. Concomitant medications will also be recorded for patients with unresolved AEs.

- **Long-term Follow-up:**
  (i) *PD Follow-up*: Regardless of treatment arm, patients who are discontinued from study medication for any reason in the absence of PD, will undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient has been on the study for ≥1 year) until PD is documented as per RECIST v1.1, or death occurs, or patient is lost to follow-up, or the patient withdraws consent (whichever occurs first). If a patient stops study medication and begins other anti-cancer therapy before PD is documented, every effort should be made to perform tumor evaluation in these patients until disease progression.
  (ii) *Survival Follow-up*: The Investigator will monitor the patient for OS status every 6 months (or more frequently) until death, until the patient withdraws consent to follow-up for survival, or until the patient is lost to follow-up (whichever occurs first).
  (iii) Every effort should be made to collect and record all anti-cancer medicines that the patient receives during Long-term Follow-up in the patient's source data and electronic case report form (eCRF) until the end of study.

Objectives:

Primary Objective

- To evaluate the efficacy of balixafortide + eribulin versus eribulin monotherapy on (i) PFS in the Overall Population and (ii) PFS and objective response rate (ORR) in the 3rd line + population.

Secondary Objectives

- To compare the OS between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.
- To compare measures of tumor response between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.
- To evaluate the safety and tolerability of balixafortide + eribulin versus eribulin monotherapy.

Exploratory Objectives

- To determine whether the treatment outcome correlates with baseline ER, PgR, or C-X-C chemokine receptor type 4 (CXCR4) expression level.
- To assess tumor tissue and circulating biomarkers and possible association with patient treatment outcome.
- To explore immune response as assessed by iRECIST (2017).
- Measurement of plasma concentration of balixafortide and potential metabolites to integrate in a population PK model.
- To assess the QoL as reported by patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm using standard QoL assessments.

Number of patients (total and for each treatment arm):

In the Overall Population, three hundred and eighty-four patients will be enrolled (192 patients in the balixafortide + eribulin treatment arm, and 192 patients in the eribulin treatment arm), including three hundred and twenty 3rd line + patients with locally recurrent or metastatic BC.

Enrolment Criteria:

Inclusion Criteria

Patients with measurable and non-measurable disease will be eligible for inclusion in this study only if all the following criteria are met:

1. Patients at least 18 years of age (or according to local regulation).
2. Documented histologically confirmed BC.
3. Metastatic BC currently of stage IV disease by American Joint Committee on Cancer criteria or unresectable locoregionally recurrent BC.
4. Molecular status and prior therapies:
    a) Molecular Status

       Eligible patients are, by their patient records and prior therapy, HER2 negative with any ER or PgR status. If a previous record of the HR status is not available, the HR status should be tested locally.

       HER2 negative (immunohistochemistry [IHC] 0,1 or fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH] HER2:CEP17 ratio < 2.0); HER2 2+ patients should be FISH/CISH negative.

    b) Prior Therapies

       Patients with locally recurrent or metastatic BC who have previously received 1−4 chemotherapeutic regimens for the treatment of locally recurrent or metastatic BC. Unless contra-indicated for safety reasons, prior therapy will have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

       Patients with HR positive status (ER+ and/or PgR+) must have been treated with at least one line of endocrine therapy and considered by the treating physician not to be a candidate for further endocrine therapy.
5. At least 14 days from the completion of any previous cytotoxic chemotherapy, biological therapy, or any other investigational agent at time of initiation of study medication. Resolution of chemotherapy and radiation therapy related toxicities to Grade 1 or lower severity, except for stable sensory neuropathy Grade 2 or lower and alopecia.
6. Patients must have proved refractory to the most recent chemotherapy, documented by progression on or within six (6) months of therapy.
7. Females of child bearing potential must be willing and able to use highly effective contraception (as described in the protocol) whilst they or their male partners are on this study from randomization until 3 months after the last dose of study medication (Section 5.4.5). Male patients must commit to using an approved form of birth control (including double-barrier contraception [e.g. consistent and correct use of male condom with diaphragm or male condom with cervical cap] or sterilization method) whilst on treatment and for 3 months after the last dose of study medication (Section 5.4.5).
8. ECOG performance status of 0-2.
9. Life expectancy of 3 months or more as per Investigator assessment.
10. Adequate organ function defined at Screening as:
    a) White blood cell (WBC) ≥3000/mm^3.
    b) Absolute neutrophil count (ANC) ≥1500/mm^3.
    c) Platelets ≥75000/mm^3*.

d) Creatinine Clearance ≥30 mL/minute as calculated by the Cockcroft-Gault equation or serum creatinine <1.5x institutional upper limit of normal (ULN) (2).
e) Total bilirubin ≤1.5x institutional ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤3x institutional ULN (for patients with liver metastases, ≤5x ULN).
f) Hemoglobin ≥10 g/dL.

11. Patients who have central nervous system involvement if metastases have been treated and are stable for at least 4 weeks after completion of radiation therapy and/or surgery. Stable is defined as the absence of the need for dexamethasone or other corticosteroid therapy, and radiographic confirmation of SD.
12. Patients receiving bone-modifying agents (BMA [bisphosphonates or denosumab]) if BMA was initiated at least 4 weeks prior to the start of study medication.
13. Must be willing and able to comply with the protocol and mustunderstand and sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent document.
14. Affiliation with a National Health Insurance plan (applicable to patients in France only).

* ≥100000/mm^3 in France

Patient Exclusion Criteria

Patients will be ineligible if one or more of the following statements are applicable:

1. Previously received eribulin.
2. Peripheral neuropathy Grade ≥3.
3. Receipt of prior CXCR4 therapy.
4. Receipt of colony stimulating factors (CSFs) filgrastim, pegfilgrastim, or sargramostim within 14 days prior to time of initiation of study medication.
5. Radiation therapy within 14 days prior to time of initiation of study medication.
6. Severe concurrent illness or psycho-social situation that would limit compliance with study requirements or that, in the Investigator's opinion, would preclude enrolment.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to balixafortide or eribulin, or known intolerance to balixafortide or eribulin.
8. Breast feeding or pregnant, as determined by a serum pregnancy test beta human chorionic gonadotrophin (β-HCG) at Screening and prior to the administration of study medication.
9. Patients with congestive heart failure, electrolyte abnormalities, bradyarrhythmias, known congenital long QT syndrome, QT interval corrected with Fridericia's formula (QTcF) ≥470 milliseconds (msec) at baseline in the absence of bundle branch block, or currently taking drugs at known risk of prolonging the QT interval or causing torsades de pointes (TdP) (including Class Ia and III anti-arrhythmic drugs; see also Appendix 1 Prohibited Medications). Patients with hypokalemia or hypomagnesemia should not be randomized until the hypokalemia or hypomagnesemia is corrected.
10. Patients with a concurrent malignancy or malignancy 2 years prior to randomization with the exception of adequately treated basal and squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
11. Persons who have been housed in an institution due to a government or judicial order (applicable to Germany only).

Study Medication

The investigational medicinal product (IMP; as defined by EU regulation) in this study is balixafortide. The other drug to be used in this study is eribulin.

Dose and route of administration:

Patients will receive 21-day cycles of treatment. Patients will be randomized to one of the following treatment regimens:

Balixafortide + eribulin treatment arm

Eribulin will be administered, at a dose of 1.4 mg/m^2 on Days 2 and 9 and balixafortide will be administered at a dose of 5.5 mg/kg on Days 1−3 and Days 8−10 of each 21-day cycle.

Cycle Scheme:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
POL6326	1	2	3	treatment break				8	9	10	treatment break										
Eribulin		2	treatment break						9	treatment break											

Eribulin monotherapy treatment arm

Eribulin will be administered at a dose of 1.4 mg/m^2 on Days 2 and 9 of each 21-day cycle.

Cycle Scheme:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Eribulin		2	treatment break						9	treatment break											

Balixafortide will be administered intravenously (IV) over a minimum of 2 hours ±10 minutes; however, the infusion time of balixafortide can be increased to a maximum of 3 hours at the discretion of the treating physician, for reasons of patient tolerability (i.e. to manage infusion-related reactions [IRRs]).

Eribulin will be administered IV over 2 to 5 minutes. In the balixafortide + eribulin treatment arm, eribulin will be administered within 45 minutes after the end of the balixafortide infusion.

Efficacy Assessments:

All patients will be evaluated for disease response and OS. Response assessments will be conducted according to RECIST v1.1 guidelines and include:

- PFS and objective response (as assessed by the Independent Review Committee [IRC].
- PFS and objective response (as assessed by the local Investigator's review).

Follow-up for OS: The Investigator will monitor the patient for OS status until death, until the patient withdraws consent for survival follow-up, or until the patient is lost to follow-up (whichever occurs first).

Safety Assessments:

Safety Assessments will include evaluation of AEs, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), renal function, liver function, ECOG performance status, ECG and clinical laboratory evaluations (chemistry, hematology).

AEs of special interest (AESI), based on the emerging AE profile of balixafortide or established risks with eribulin therapy, will be followed closely. Safety monitoring for serious adverse event (SAEs) will begin after informed consent is given and will continue until 30 days after the last dose of study drug. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Type, incidence,

severity, timing, seriousness, and relatedness of AEs, and laboratory abnormalities will be recorded and reported.

Patients stopping randomized treatment early because of unacceptable AEs will be followed until resolution or stabilization of the AEs in question.

Pharmacokinetic Assessments:

Blood samples will be collected only for the balixafortide+ eribulin treatment arm to:

- Evaluate the PK of balixafortide and its metabolite levels in patients on the balixafortide + eribulin treatment arm.
- Support the data from the immunogenicity assessment by evaluating the PK of balixafortide.

The plasma concentration of balixafortide will be integrated into the population PK model generated using PK data from previous clinical studies.

Additional PK samples, taken up to 48 hours after the last dose in approximately 15 patients, will allow monitoring of drug clearance after dosing has ceased.

General Statistical Considerations:

The data from this study will serve a dual purpose:

(i) To provide efficacy and safety data in the Overall Population for regulatory submissions in the EU and jurisdictions in which the 2nd line + eribulin label applies.

(ii) To provide efficacy and safety data in the 3rd line + population for regulatory submissions in the US and jurisdictions in which the 3rd line + eribulin label applies.

For the Overall Population, the critical efficacy endpoints shall be PFS and OS. For the 3rd line + population, the critical efficacy endpoints shall be ORR, PFS and OS.

In the Overall Population, the formal analysis of PFS is event driven and is expected to be conducted when all patients have been followed for a minimum of 12 months. An interim analysis of OS will be performed at the same time as the analysis of PFS and a final analysis of OS will take place once all patients have been followed for a minimum of 24 months.

In the 3rd line + population, the analysis of objective response is planned once all such patients have been randomized and followed for a minimum of 6 months. The formal analysis of PFS is event driven and planned when all 3rd line + patients have been followed for a minimum of 12 months. An interim analysis of OS will be performed at the same time as the analysis of PFS, and a final analysis of OS will take place once all 3rd line + patients have been followed for a minimum of 24 months.

Alpha allocation and recycling will ensure control of the overall Type I error rate for (i) the Overall Population and (ii) 3rd line + population separately.

Overall Population Efficacy Plan relevant to the EU and other jurisdictions in which the 2nd line + Eribulin Label applies:

Sample Size

Assuming a median PFS on eribulin of 3.9 months, to test for a hazard ratio versus balixafortide + eribulin of 0.699 (corresponding to a median PFS of 5.6 months), a total of 346 PFS events are required to provide 90% power at the 1-sided 2.0% alpha level. Equally, 346 PFS events provides 94.6% power for a hazard ratio of 0.674, corresponding to a PFS of 5.8 months. Assuming a 12-month, non-linear recruitment period (η=2; Carroll, 2009) and a minimum 12-

month follow-up period after the last patient is randomized, a total of 384 patients will be recruited.

Statistical Methods

Patient demographics and clinical characteristics will be summarized using descriptive statistics.

Efficacy Analysis

Primary Endpoint: PFS time (defined as the time from randomization to the first progression or death, as judged by an IRC) is the primary endpoint in the Overall Population. PFS will be analyzed via Cox regression modelling in the intent-to-treat (ITT) population. Patients free from progression and death will be censored at their last follow-up visit. The analysis will be stratified for randomization stratification factors and a fixed effect term will be included for randomized treatment. The hazard ratio will be estimated from the model along with the associated confidence interval (CI) and 2-sided p value. The data will also be displayed using Kaplan-Meier curves and median PFS times will be estimated.

Key Secondary Endpoints: OS will be the key secondary efficacy endpoint in the Overall Population. OS will be analyzed in a fashion similar to that described for PFS.

The statistical design in the 2nd line + population, with pre-defined alpha allocation and recycling, is such that if PFS does not meet statistical significance at its allocated alpha level, then the design still allows OS to be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Type I error Control for Primary and Key Secondary Efficacy Endpoints: The formal analysis of PFS will take place once 346 PFS events have accrued and is expected when all randomized patients have been followed for a minimum of 12 months. The alpha allocation for this analysis will be 0.040 2-sided. At the time of the planned PFS analysis, an interim analysis of OS will be performed with an alpha allocation of 0.002 2-sided. A final analysis of OS will take place once all randomized patients have been followed for a minimum of 24 months. The alpha allocation for this analysis will be between 0.008 and 0.05 2-sided depending on the results of previous analyses. Thus, for the Overall Population, there will be a total of 3 formal efficacy analyses (PFS, interim OS and final OS). The overall Type I error rate will be controlled at 0.05 by means of alpha allocation and recycling.

Other Secondary Endpoints:

Analysis of the other secondary endpoints of objective response rate (ORR), clinical benefit rate (CBR), disease control rate (DCR), time to response, and duration of response will not be subject to Type I error control. Statistical tests will be 2-sided with a nominal Type I error rate of 0.05.

Exploratory Endpoints: The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), EuroQoL-5D (EQ-5D) and Functional Assessment of Cancer Therapy Breast (FACT-B) will be compared between randomized treatments over time. The relationship between baseline biomarkers (including ER status, PgR status, CXCR4 expression levels, cytokines [eg IFN-gamma], immune cells profile and ribonucleic acid [RNA] expression) and ORR, PFS and OS will be explored using a variety of exploratory data analysis.

3rd line + Population Efficacy Plan relevant to the US and other jurisdictions in which the 3rd line + Eribulin Label applies:

Sample Size

Assuming a median PFS on eribulin of 3.9 months, to test for a hazard ratio versus balixafortide + eribulin of 0.674 (corresponding to a median PFS of 5.8 months), a total of 286 PFS events are required to provide 90% power at the 1-sided 2.0% alpha level. Assuming a 12-month, non-linear recruitment period (η=2; Carroll, 2009(3)) and a minimum 12-month follow-up period after the last patient is randomized, a total of 320 3rd line + patients will be recruited.

Statistical Methods

Patient demographics and clinical characteristics will be summarized using descriptive statistics.

Efficacy Analysis

Co-Primary Endpoints: In the 3rd line+ population ORR (CR + PR) and PFS are co-primary endpoints population.

ORR (CR + PR) will be analyzed by exact logistic regression and will be stratified for randomization stratification factors. The odds ratio will be estimated from the model along with the associated CI and 2-sided p-value.

PFS will be analyzed using the same methodology as described for the 2nd line + population.

Key Secondary Endpoints: OS is the key secondary efficacy endpoint. OS will be analyzed using the same methodology as described for the 2nd line + population.

The statistical design in the 3rd line + population, with pre-defined alpha allocation and recycling, is such that even if ORR does not meet statistical significance at its allocated alpha level, then PFS can still be tested and, if it meets statistical significance at its allocated alpha level, the study can still meet its primary objective. Further, if PFS does not meet statistical significance at its allocated alpha level, then OS can still be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Type I error Control for Co-Primary and Key Secondary Efficacy Endpoints: The formal analysis of ORR is planned for the 3rd line + population once all such patients have been randomized and followed for a minimum of 6 months. The alpha allocation for this analysis will be 0.001 2-sided. The formal analysis of PFS will take place once 286 PFS events have accrued, being expected when all randomized patients have been followed for a minimum of 12 months (this analysis is anticipated to coincide with the planned analysis of PFS in the 2nd line + population). The alpha allocation for this analysis will be 0.040 2-sided; if the PFS in the 3rd line + population meets the allocated alpha level, PFS in the Overall Population will also be formally tested at the same alpha level; further, at the time of the PFS analysis an interim analysis of OS will be performed with an alpha allocation of 0.001 to 0.002 2-sided, depending on the result of the previous ORR analysis. The final analysis of OS will take place once all randomized patients have been followed for a minimum of 24 months at which time 226 events are expected (again, this analysis is anticipated to coincide with the planned analysis of OS in the 2nd line + population). The alpha allocation for this analysis will be between 0.008 and 0.05 2-sided depending on the results of previous analyses. Thus, there will be a total of 5 formal efficacy analyses in the 3rd line + population (ORR, PFS, PFS in the Overall Population if PFS is met in the 3rd line+ population, interim OS and final OS). The overall Type I error rate will be controlled at 0.05 by means of alpha allocation and recycling.

Other Secondary Endpoints: Analysis of the other secondary endpoints of CBR, DCR, time to response, and duration of response will be conducted in the same manner as described for the 2nd line + population.

Exploratory Endpoints: EORTC-QLQ-C30, EQ-5D, FACT-B the relationship between baseline biomarkers and efficacy outcomes will be analyzed in the same manner as described for the 2nd line + population.

Safety Analysis

The Safety Population is defined as all randomized patients who received at least 1 dose (or partial dose) of study medication regardless of line of therapy. Summaries of AEs and other safety parameters will be provided by treatment arm received, based on the first dose of study drug.

AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity will be graded according to the NCI CTCAE v5.0 whenever possible. All AEs reported from the first dose of study drug until 30 days after the last dose of study drug will be considered as treatment-emergent AEs (TEAEs) and will be summarized descriptively by treatment, and by the frequency of patients experiencing TEAEs corresponding to body systems and MedDRA preferred term. Patients with multiple occurrences of events will only be counted once at the maximum severity/grade to study drug for each Preferred Term, System Organ Class (SOC), and overall. Any AEs with missing severity or relationship to study drug will be classified as severe and treatment-related, respectively. Deaths that occur within 30 days after the last dose of study drug are defined as on-study deaths.

All AEs will be summarized by relatedness to study medication and may be summarized by cycle as warranted. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, severity, relationship to study drug, action taken, and clinical outcome.

Any AEs leading to death or discontinuation of study medication, events classified as NCI CTCAE v5.0 Grade 3 or higher, AESIs (Section 9.2.6), study drug-related events, and SAEs will be monitored with special attention.

The format and content of summary tables and individual patient listings is described in the Statistical Analysis Plan (SAP).

Scheduled physical examination, vital signs, and hematology and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTCAE v5.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study medication. Shift tables will be provided to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE v5.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

Data Safety Monitoring Committee: An independent Data Safety Monitoring Committee (DSMC) will be established with the responsibility of safeguarding the safety of study participants. The DSMC will review accumulating safety data during the conduct of this open label study and the interim analyses. The DSMC will provide ongoing review and recommendations to the Sponsor as necessary in relation to study conduct and patient management. The composition and operation of the DSMC is described in the DSMC charter.

1.1 Study Schedule

1.1.1 Schedule of Assessments for Balixafortide + Eribulin Treatment Arm

1.1.1.1 Screening, Cycle 1, and Cycle 2

Table 1 Schedule of Assessments for Balixafortide + Eribulin Treatment Arm: Screening, Cycle 1, and Cycle 2

Visits (Visit Window days) / Assessment	Section number	Screening (-21 to -1)	Active treatment phase (21 Days per cycle)												
			Cycle 1						Cycle 2						
			D1	D2	D3	D8	D9	D10	D1	D2	D3	D8	D9	D10	D21
Informed consent	15.2	X													
IWRS/IRT		X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria	5.1 & 5.2	X													
Demographics (gender, date of birth, race, ethnicity) and baseline data	–	X													
Medical history	7.1	X													
Patient reported health outcomes	11.3	X	X						X						
Physical examination[1]	9.6	X[2]	X[3]						X[3]						
Vital signs (body temperature, resting blood pressure, respiratory rate, pulse rate)[1]	9.7	X	X						X						
Weight, height[4]	9.6	X	X						X						
ECOG performance status	9.6	X	X						X						
Adverse events	9.1 & 9.2	X[5]	X----------												----------X
Prior/Concomitant medications	5.4.1	X	X----------												----------X
Clinical Laboratory tests[1]	9.9	X[6]	X[7]			X[7]			X[7]			X[7]			
Pregnancy test	5.4.5.1	X[8]	X[9]						X[9]						

Visits (Visit Window days) / Assessment	Section number	Screening (-21 to -1)	Active treatment phase (21 Days per cycle)												
			Cycle 1						Cycle 2						
			D1	D2	D3	D8	D9	D10	D1	D2	D3	D8	D9	D10	D21
Contraceptive advice	5.4.5	X													
CT/MRI scan[10, 11]	8.2	X[12]													X[10]
Bone scan	8.2	X[12, 13]													
12-lead ECG[1]	9.8	X	X	X			X			X[14]			X[14]		
Document date and results of last tumor biopsy/fresh tumor biopsy	11.2.1	X													
Blood for PK	10.1			X		X	X			X		X	X		
Blood for immunogenicity testing	11.1		X			X			X			X			
Blood for exploratory biomarkers in all patients[15]	11.2.2		X	X	X	X	X								
Confirmation of eligibility and randomization	5.1 & 5.2		X												
Balixafortide treatment[16]	6.1		X	X	X	X	X	X	X	X	X	X	X	X	
Eribulin treatment	6.1			X			X			X			X		
For patients at selected sites															
Optional tumor biopsy[17]	11.2.1	X											X[18]		
Blood for other exploratory biomarkers	11.2.2		X	X		X							X[19]		

MRI: magnetic resonance imaging; RECIST: Response Evaluation Criteria In Solid Tumors; SAE: serious adverse event. **Footnotes:**

1. Additional assessments to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled examination should be recorded in the patient's source data and eCRF.
2. Standard, complete physical examination.
3. Targeted physical examination.
4. Height will be measured at Screening only.
5. SAEs will be recorded from the date that the informed consent form is signed.
6. Screening blood tests should be taken within 7 days prior to randomization.

7. Blood test results must be available within 24 hours prior to study medication administration.
8. Serum pregnancy test for women of child bearing potential only, no more than 7 days prior to Randomization. More frequent assessments can be performed if medically indicated as determined by the Investigator, and these evaluations will be recorded in the patient's source data and eCRF.
9. Urine pregnancy test for women of child bearing potential only.
10. CT/MRI scan will be performed at Screening, then from the date of randomization every 6 weeks (±7 days) during the first year, and then every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. It is critical that tumor assessments are performed according to the Study Schedule in a timely and complete manner regardless of any dosing delay or interruption. Imaging assessments will be scheduled using the randomization date as the reference date for all timepoints and NOT scheduled according to the date of the previous timepoint. A delay in the imaging assessment to accommodate a treatment delay is not permitted. Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.
11. At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression; the results of the unscheduled scan should be recorded in the patient's source data and eCRF.
12. Record date and results of last scan on the patient's source data and eCRF. If no scan has been performed in the 30 days prior to Randomization a scan should be performed during Screening.
13. From the date of randomization, additional bone scans will be performed at the discretion of the Investigator.
14. After Cycle 2, the frequency of ECGs can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
15. Blood will be collected from all patients to assess plasma levels of interferon gamma and additional cytokine markers.
16. Patients will start study medication within 3 days from randomization.
17. Patients at selected sites can optionally consent to fresh tumor biopsy at Screening and subsequent timepoints. If a biopsy has already been performed within 30 days prior to Randomization and tumor tissue is still available, then the fresh tumor biopsy is not required during Screening.
18. Alternatively, can be performed on Day 10 if preferred.
19. A blood sample will be taken only in patients at selected sites who are scheduled to have an optional, fresh tumor biopsy; the blood sample can be taken before or after the biopsy.

1.1.1.2 Cycle 3, Subsequent Cycles, and Post-treatment Phase

Table 2 Schedule of Assessments for Balixafortide + Eribulin Treatment Arm: Cycle 3, Subsequent Cycles, and Post-treatment Phase

Visits (Visit Window days)	Section number	Active treatment phase (21 Days per cycle)															Post-treatment phase		
		Cycle 3								Subsequent Cycles							EoT (+7)	30-day safety FU (+7)	Long-term FU (±7)[1]
Assessment		D1	D2	D3	D4	D5	D8	D9	D10	D1	D2	D3	D8	D9	D10	D21			
IWRS/IRT	-	X	X	X			X	X	X	X	X	X	X	X	X		X		
Patient reported health outcomes	11.3	X								X							X		
Targeted physical examination[2]	9.6	X								X							X		
Vital signs (body temperature, resting blood pressure, respiratory rate, pulse rate)[2]	9.7	X								X							X		
Weight	9.6	X								X							X		
ECOG performance status	9.6	X								X							X		
Adverse events	9.1 & 9.2	X----------															----------X		
Prior/Concomitant medications	5.4.1	X----------															----------X	X[3]	
Clinical Laboratory tests[2]	9.9	X[4]					X[4]			X[4]			X[4]				X		
Pregnancy test	5.4.5.1	X[5]								X[5]							X[5]		
CT/MRI scan[6, 7]	8.2															X[6]	X[8]		X[1]
Bone scan[9]	8.2																		

Visits (Visit Window days)	Section number	Active treatment phase (21 Days per cycle)															Post-treatment phase		
		Cycle 3								Subsequent Cycles							EoT (+7)	30-day safety FU (+7)	Long-term FU (±7)[1]
Assessment		D1	D2	D3	D4	D5	D8	D9	D10	D1	D2	D3	D8	D9	D10	D21			
12-lead ECG[2]	9.8		X[10]					X[10]			X[10]			X[10]			X		
Blood for PK	10.1		X		X[11]	X[11]					X[12]	X[12]							
Blood for immunogenicity testing	11.1	X								X[13]							X		
Blood for exploratory biomarkers in all patients[14]	11.2.2	X	X	X	X[15]	X[15]	X	X											
Balixafortide treatment	6.1	X	X	X			X	X	X	X	X	X	X	X	X				
Eribulin treatment	6.1		X					X			X			X					
Document reason for treatment discontinuation	–																X		
Survival status, PD monitoring, all anticancer medicines received	7.8																		X
For patients at selected sites																			
Optional tumor biopsy	11.2.1																X		
Blood for other exploratory biomarkers	11.2.2	X	X														X		

AE: adverse event; MRI: magnetic resonance imaging; RECIST: Response Evaluation Criteria In Solid Tumors. **Footnotes:**

1. Regardless of treatment arm, patients discontinued from study medication for any reason, in the absence of PD, will undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient has been on the study for ≥1 year) until PD is documented as per RECIST v1.1, or death occurs, or the patient is lost to follow-up, or the patient withdraws consent (whichever occurs first). Once PD is recorded, the patient will be

followed every 6 months (or more frequently) for Survival Follow-up only, until the patient dies, withdraws consent, or is lost to follow-up (whichever occurs first). Survival follow-up can be conducted by telephone.

2. Additional assessments to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled examination should be recorded in the patient's source data and eCRF.
3. Concomitant therapy/medications taken since previous visit to be recorded for patients with unresolved AEs.
4. Blood test results must be available within 24 hours prior to study medication administration.
5. Urine pregnancy test for women of child bearing potential only.
6. CT/MRI scan will be performed at Screening, then from the date of randomization every 6 weeks (±7 days) during the first year, and then every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. It is critical that tumor assessments are performed according to the Study Schedule in a timely and complete manner regardless of any dosing delay or interruption. Imaging assessments will be scheduled using the randomization date as the reference date for all timepoints and NOT scheduled according to the date of the previous timepoint. A delay in the imaging assessment to accommodate a treatment delay is not permitted. Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.
7. At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression; the results of the unscheduled scan should be recorded in the patient's source data and eCRF.
8. CT/MRI scans will be performed in patients who are discontinued from study medication in the absence of PD; however, patients who have already demonstrated objective PD (according to RECIST v 1.1) do not need to have scans repeated at the EoT visit.
9. From the date of randomization, additional bone scans will be performed at the discretion of the Investigator.
10. After Cycle 2, the frequency of ECGs can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
11. For patients at selected sites only.
12. Cycle 5 and Cycle 7 only.
13. After Cycle 3, blood samples are taken on Day 1 of every alternate cycle (e.g. Cycle 5, Cycle 7, Cycle 9 etc).
14. Blood will be collected from all patients to assess plasma levels of interferon gamma and additional cytokine markers.
15. Only in patients at selected sites scheduled to have PK sampling.

1.1.2 Schedule of Assessments for Eribulin Monotherapy Treatment Arm

Table 3 Schedule of Assessments for Eribulin Monotherapy Treatment Arm

	Section number	Screening (-21 to -1)	Active treatment phase (21 Days per cycle)										Post-treatment phase		
			Cycle 1		Cycle 2			Cycle 3		Subsequent Cycles			EOT (+7)	30-day safety FU (+7)	Long-term FU (±7)[1]
Assessment			D2	D9	D2	D9	D21	D2	D9	D2	D9	D21			
Informed consent	15.2	X													
IWRS/IRT	-	X	X	X	X	X		X	X	X	X		X		
Inclusion/exclusion criteria	5.1 & 5.2	X													
Demographics (gender, date of birth, race, ethnicity) and baseline data	–	X													
Medical history	7.1	X													
Patient reported health outcomes	11.3	X	X		X			X		X			X		
Physical examination[2]	9.6	X[3]	X[4]		X[4]			X[4]		X[4]			X[4]		
Vital signs (body temperature, resting blood pressure, respiratory rate, pulse rate)[2]	9.7	X	X		X			X		X			X		
Weight, height[5]	9.6	X	X		X			X		X			X		
ECOG performance status	9.6	X	X		X			X		X			X		
Adverse events	9.1 & 9.2	X[6]	X----------									----------X			
Prior/Concomitant medications	5.4.1	X	X----------									----------X		X[7]	
Clinical laboratory tests[2]	9.9	X[8]	X[9]	X[9]	X[9]	X[9]		X[9]	X[9]	X[9]	X[9]		X		
Pregnancy test	5.4.5.1	X[10]	X[11]		X[11]			X[11]		X[11]			X[11]		
Contraceptive advice	5.4.5	X													

	Section number	Screening (-21 to -1)	Active treatment phase (21 Days per cycle)										Post-treatment phase		
			Cycle 1		Cycle 2			Cycle 3		Subsequent Cycles			EOT (+7)	30-day safety FU (+7)	Long-term FU (±7)[1]
Assessment			D2	D9	D2	D9	D21	D2	D9	D2	D9	D21			
CT/MRI scan[12,13]	8.2	X[14]					X[12]					X[12]	X[15]		X[1]
Bone scan	8.2	X[14, 16]													
12-lead ECG[2]	9.8	X	X	X	X[17]	X[17]		X[17]	X[17]	X[17]	X[17]		X		
Document date and results of last tumor biopsy/fresh tumor biopsy	11.2.1	X													
Blood for exploratory biomarkers in all patients[18]	11.2.2		X	X				X	X						
Confirmation of eligibility and randomization	5.1 & 5.2		X												
Eribulin treatment[19]	6.1		X	X	X	X		X	X	X	X				
Document reason for treatment discontinuation	–												X		
Survival status, PD monitoring, all anticancer medicines received	7.8														X
For patients at selected sites															
Optional tumor biopsy[20]	11.2.1	X				X							X		
Blood for other exploratory biomarkers	11.2.2		X			X[21]		X					X		

AE: adverse event; RI: magnetic resonance imaging; RECIST: Response Evaluation Criteria In Solid Tumors; SAE: serious adverse event. **Footnotes:**

1. Regardless of treatment arm, patients discontinued from study medication for any reason, in the absence of PD, will undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient has been on the study for ≥1 year) until PD is documented as per RECIST v1.1, or death occurs, or the patient is lost to follow-up, or the patient withdraws consent (whichever occurs first). Once PD is recorded, the patient will be followed every 6 months (or more frequently) for Survival Follow-up only, until the patient dies, withdraws consent, or is lost to follow-up (whichever occurs first). Survival follow-up can be conducted by telephone.

2. Additional assessments to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled examination should be recorded in the patient's source data and eCRF.
3. Standard, complete physical examination.
4. Targeted physical examination.
5. Height will be measured at Screening only.
6. SAEs will be recorded from the date that the informed consent form is signed.
7. Concomitant therapy/medications taken since previous visit to be recorded for patients with unresolved AEs.
8. Screening blood tests should be taken within 7 days prior to randomization.
9. Blood test results must be available within 24 hours prior to study medication administration.
10. Serum pregnancy test for women of child bearing potential only, no more than 7 days prior to Randomization. More frequent assessments can be performed if medically indicated as determined by the Investigator, and these evaluations will be recorded in the patient's source data and eCRF.
11. Urine pregnancy test for women of child bearing potential only.
12. CT/MRI scan will be performed at Screening, then from the date of randomization every 6 weeks (±7 days) during the first year, and then every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. It is critical that tumor assessments are performed according to the Study Schedule in a timely and complete manner regardless of any dosing delay or interruption. Imaging assessments will be scheduled using the randomization date as the reference date for all timepoints and NOT scheduled according to the date of the previous timepoint. A delay in the imaging assessment to accommodate a treatment delay is not permitted. Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.
13. At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression; the results of the unscheduled scan should be recorded in the patient's source data and eCRF.
14. Record date and results of last scan on the patient's source data and eCRF. If no scan has been performed in the 30 days prior to Randomization a scan should be performed during Screening.
15. CT/MRI scans will be performed in patients who are discontinued from study medication in the absence of PD; however, patients who have already demonstrated objective PD (according to RECIST v 1.1) do not need to have scans repeated at the EoT visit.
16. From the date of randomization, additional bone scans will be performed at the discretion of the Investigator.
17. After Cycle 2, the frequency of ECGs can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
18. Blood will be collected from all patients to assess plasma levels of interferon gamma and additional cytokine markers.
19. Patients will start study medication within 3 days from randomization.
20. Patients at selected sites can optionally consent to fresh tumor biopsy at Screening and subsequent timepoints. If a biopsy has already been performed within 30 days prior to Randomization and tumor tissue is still available, then the fresh tumor biopsy is not required during Screening.
21. A blood sample will be taken only in patients at selected sites who are scheduled to have an optional, fresh tumor biopsy; the blood sample can be taken before or after the biopsy.

2. INTRODUCTION

2.1 Background on the Disease to be Treated

Breast cancer (BC) is the most common cancer in women worldwide with nearly 1.7 million new cases diagnosed in 2012, representing 25% of all cancers in women (4). In Europe, there were an estimated 464000 new cases of BC (female) in 2012 and an estimated 131000 deaths from the disease (5). Deaths from BC among women accounted for 16.2% of all deaths from cancer (6) and metastatic BC has a 5-year relative survival rate of about 22% (7).

Hormonal therapy is the initial course of treatment for those BCs that are estrogenic-receptor positive (ER+) whereas chemotherapy is the initial treatment course for patients who are estrogenic-receptor negative (ER-). Unfortunately, hormone therapy often leads to drug resistance requiring ER+ patients to also rely on chemotherapy to control their disease. However, there is no single preferred first-line chemotherapy; after failure of initial chemotherapy, treatment options are few and cumulative toxicity from previous therapy can also be a problem. Therefore, there remains a need for more and better therapeutics to treat metastatic BC that improve clinical outcomes (including the response rate and time to progression) and safety profile (8, 9).

C-X-C chemokine receptor type 4 (CXCR4) is principally expressed by hematopoietic stem cells and immune cells, and its main physiological role is to regulate their function and trafficking. It is also overexpressed in over 20 human tumor types (including primary and metastatic BC). Its natural ligand, stromal cell-derived factor-1 (SDF-1), is highly expressed at prevalent sites of BC metastases: lymph nodes, bone marrow, bone, lung and liver (10-13). The CXCR4/SDF-1 axis promotes cancer growth by allowing tumor immune evasion and creating a pro-tumor microenvironment within the metastatic niche; it may also protect BC cells from cytotoxic therapy (14-19). CXCR4 expression correlates with aggressive metastatic phenotypes and poor prognosis in BC (14, 20, 21). The increased risk appears to be independent of any particular BC subtype, stage, or type of adjuvant therapy (20).

After failure of initial chemotherapy, there is no clinical standard of care for human epidermal growth factor receptor 2 (HER2) negative patients with metastatic BC. Eribulin is indicated for the treatment of adult patients with locally advanced or metastatic BC who have progressed after at least one chemotherapeutic regimen for advanced disease (prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments). The eribulin approvals were based on the Phase 3, EMBRACE study in women with locally recurrent or metastatic BC. Most women in this study were HER2 negative and all received 3rd line therapy, or beyond, with either eribulin or treatment of physician's choice. The EMBRACE study provided a median overall survival (OS) of 13.1 versus 10.6 months respectively (22).

In another Phase 3 study of patients with locally advanced or metastatic BC, previously treated with an anthracycline or taxane, and most of whom were HER2 negative, eribulin showed a similar median OS to capecitabine (15.9 versus 14.5 months) (23). A pooled analysis of patients with metastatic BC (who met the criteria in the European Union [EU] Summary of Product Characteristics [SmPC] to receive eribulin, and most of whom were HER2 negative) suggested that eribulin was associated with a longer median OS than capecitabine (15.1 versus 12.0 months) (24).

Despite the advent of new therapies, metastatic BC remains an essentially incurable disease. There is a huge need for treatments that improve OS for women with recurrent or advanced metastatic BC, particularly those patients who have received multiple prior therapies. Many patients either do not respond to available treatments or develop resistance to approved agents such as anthracyclines and taxanes.

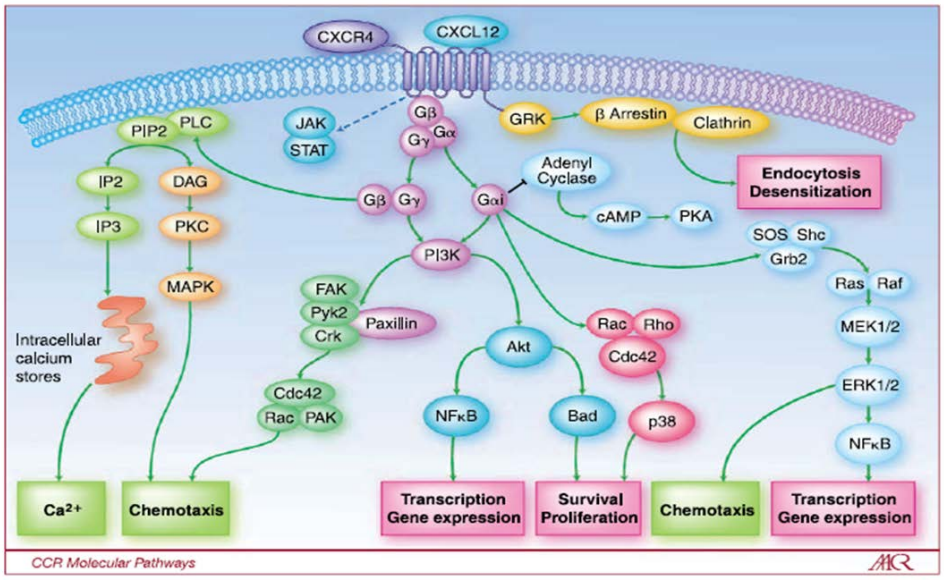
2.2 Balixafortide

Balixafortide (POL6326) is a potent, selective antagonist of the highly conserved human CXCR4 receptor as demonstrated by *in vitro* receptor binding studies. Balixafortide is a cyclic synthetic peptide consisting of 16 amino acids with a disulfide bridge between the two Cysteines: Cys4 and Cys11. All amino acid residues except for D-Pro7 and D-Pro15 are in the L-configuration. Acetic acid is present in a non-stoichiometric ratio.

Product code name:	POL6326
INN	Balixafortide
Chemical Name:	Cyclo(-L-tyrosyl-L-histidyl-L-alanyl-L-cysteinyl-L-seryl-L-alanyl-D-prolyl-L-2,4-diaminobutyryl-L-arginyl-L-tyrosyl-L-cysteinyl-L-tyrosyl-L-glutaminyl-L-lysyl-D-prolyl-L-prolyl) (4 →11) disulfide, acetate salt
Chemical Name (Abbreviated):	Cyclo(-Tyr-His-Ala-Cys-Ser-Ala-D-Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-D-Pro-Pro), disulfide bond between Cys4 and Cys11, acetate salt or Cyclo(-Tyr-His-Ala-Cys-Ser-Ala-D-Pro-Dab-Arg-Tyr-Cys-Tyr-Gln-Lys-D-Pro-Pro) Cys4 → Cys11 disulfide, acetate salt
Molecular Weight:	1864.1 g/mol (net)
Molecular Formula:	C84H118N24O21S2 (net)

As summarized by Teicher et al, 2010 (25), interference with the CXCR4/SDF-1 axis may directly suppress tumor growth through disruption of survival signaling pathways driven by CXCR4 (Figure 1).

Figure 1 Downstream signaling pathways linked with SDF-1/CXCR4 signaling



Source: Teicher et al 2010 (25)

Preclinical evidence suggests that disrupting this pathway may prevent the development of distant BC metastases (26-29).

Furthermore, it has been shown that high levels of CXCR4 expression in primary tumors and metastases are associated with aggressive metastatic phenotypes, a negative prognosis, and poor survival in BC (14, 20, 21, 30).

Recent strategies have focused on the potential of CXCR4 antagonists to enhance the cytotoxic effect of chemotherapy, both directly and via regulation of the tumor microenvironment to enhance endogenous anti-tumor responses (15, 17, 28, 31). In addition, recent evidence in both preclinical models (32) and in the clinical setting (33), suggests that antagonism of CXCR4 might counteract tumor cells immune-evasion by altering immune cell distribution and/or activity in the tumor microenvironment.

Besides published data on the potential modes of action of CXCR4 antagonists, preclinical data indicate that POL5551 (an analogue of balixafortide) and eribulin showed an enhanced cytotoxic effect, as well as inhibition of metastases, in triple-negative BC models (34). In addition, in preclinical models POL5551 has been demonstrated to enhance sensitivity to chemotherapy in pediatric acute lymphoblastic leukemia (35), target glioblastoma stem cells (36), and disrupt anti-vascular endothelial growth factor therapy-induced glioma dissemination (37).

The clinical effect in the form of cluster of differentiation 34+ (CD34+) stem cell and white blood cell (WBC) release, as demonstrated with balixafortide and described above in completed and ongoing Phase 1 trials (38), confirms that balixafortide effectively interacts and blocks the CXCR4 receptor in these clinical settings. This clinical activity might be considered a surrogate marker for use in oncology indications, where the focus is less on actual release of cells but rather on general interference with the SDF-1/CXCR4 signaling. Disrupting this interaction, by administering balixafortide to patients with metastatic BC, is expected to enhance the cytotoxic effect of chemotherapy both directly and via regulation of the tumor microenvironment to enhance endogenous anti-tumor responses.

In an ongoing Phase 1 clinical trial sponsored by Polyphor (study POL6326-007), the combination of balixafortide and eribulin is being studied in HER2 negative metastatic BC patients with evidence of CXCR4 tumor cell expression in historical tissue samples. At the interim analysis in patients who received 2nd to 5th line treatment, safety, tolerability and activity data were encouraging. The Phase 1 data indicate that the objective response rate (ORR) and clinical benefit rate (CBR) achieved with the combination of balixafortide and eribulin are considerably higher numerically than those reported for eribulin monotherapy in the literature. These observations are most pronounced for the Expanded Cohort of patients receiving eribulin + 5.5 mg/kg balixafortide where ORR was 38%, CBR was 63%, the median progression free survival (PFS) was 6.2 months, and 12-month OS was 75%. In contrast, the figures reported for eribulin monotherapy in the literature are ORR 9-12%, CBR 17%, median PFS of 2.6−4.1 months and 12-month OS of 54%) (22, 23, 39-41). In the Phase 1 trial, the safety and tolerability of balixafortide + eribulin appear comparable to published data on either eribulin or balixafortide monotherapy (41).

Thus, Polyphor is developing balixafortide as an intravenous (IV) therapy for metastatic BC, in combination with eribulin. Balixafortide's novel mechanism of action and its combination with an established approved therapy is intended to improve disease control (reduce tumor burden and/or provide a period of disease stabilization) in patients with HER2 negative metastatic BC.

The dosing schedule used in the Expanded Cohort of the Phase 1 trial is the same as the dosing schedule that is proposed for this pivotal trial. This regimen allows for maximum

disruption of the protective tumor microenvironment (e.g. blockade of pro-survival SDF-1 signaling, change in distribution and activation of immunosuppressive cells) by balixafortide in combination with eribulin.

2.3 Eribulin

Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage (42).

Eribulin was first approved in the United States (US) in 2010 and in the EU in 2011. The most common adverse reactions (≥25%) in metastatic BC are neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions are febrile neutropenia and neutropenia. The most common adverse reaction resulting in discontinuation of eribulin is peripheral neuropathy. The complete information supporting the safe and effective use of eribulin is found in the current version of the US Prescribing Information (43) which represents the reference information for this study, as described in the Investigator's Brochure (44).

2.4 Balixafortide Non-Clinical Development Overview

In vitro, receptor binding studies demonstrated a high affinity of balixafortide for the human CXCR4 receptor, as well as a general lack of significant binding to other potential target receptors (44). Balixafortide is not cytotoxic and does not elicit any hemolytic activity in human blood *in vitro* (up to a concentration of 100 µM).

In vitro plasma protein binding of balixafortide is low with averages of 32% (human), 35% (mouse) and 32% (rat) (44). Balixafortide is stable in rat, mouse and human plasma *in vitro*. When administered IV to mouse, dog, or monkey, the terminal half-life ($t_{1/2}$) ranged from 0.3−1.7 hours. When balixafortide was infused in humans, the $t_{1/2}$ ranged from 5−9 hours in healthy volunteers, and from 7−15 hours in female patients with metastatic BC. Balixafortide is not, or only to a very minor extent, metabolized by enzymes present in liver microsomal extracts. The average amount of compound that remained after 60 minutes in *in vitro* assays using liver microsomal extracts from humans, mouse, and rats was 93%, 93%, and 94%, respectively. An *in vitro* assessment of the potential of balixafortide to inhibit the major human cytochrome P (CYP) 450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5) showed no significant inhibition with any of the substrates tested, using a recombinant human enzyme for each reaction.

Following IV bolus administration of balixafortide, no significant cardiovascular or respiratory effects were observed in cynomolgus monkeys except for transient reduction in blood pressure (BP) (for approximately 30 minutes) in 1 animal at the high dose level (1.25 mg); tachycardia was observed with reduced RR, QT, and corrected QT (QTc) intervals. In some toxicity studies, histaminergic-like responses were observed. In addition, no cardiac effect was observed in the electrocardiogram (ECG) recordings in the 28-day repeat-dose toxicity study in monkeys with balixafortide doses up to 200 mg/kg subcutaneously (SC), nor in the 13-week repeat-dose toxicity study in cynomolgus monkeys, where doses up to 135 mg/kg were administered by 2-hour IV infusion.

Key toxicological findings included changes in hematology endpoints (i.e. increased leukocyte counts); these events were expected based on the pharmacology of balixafortide (44). The kidney was identified as the target organ in the 28-day and 13-week repeat-dose toxicity studies in monkeys. A dose of 200 mg/kg/day SC produced marked tubular vacuolation associated with minimal to slight degeneration/necrosis of the renal tubules. The no-observed-adverse-effect level (NOAEL) in the 28-day monkey study, was considered to be 50 mg/kg/day, with a corresponding mean plasma maximum concentration (C_{max}) of 60.7 mg/L and area under the curve (AUC) of 317.8 mg·h/L, corresponding to safety margins of 4-5 fold at a human dose level of 5.5 mg/kg. In the 13-week study in cynomolgus monkeys, where balixafortide was administered by 2-hour IV infusion for 3 consecutive days per week to approximate the clinical dosing regimen, there was a lower frequency of adverse microscopic kidney findings than in the 28-day study. The NOAEL was considered to be 45 mg/kg/day, due to the presence of adverse moderate renal tubular degeneration/necrosis with evidence of ongoing regeneration in a single female who received high-dose balixafortide (135 mg/kg/day) in the main phase and who also had high plasma urea and creatinine. The mean C_{max} at this dose level was 89.3 mg/L and mean AUC was 378 mg·h/L, corresponding to safety margins of 7.5- and 5-fold respectively at a human dose level of 5.5 mg/kg. Nephrotoxicity biomarker analyses revealed balixafortide-related increased urinary clusterin levels, following the 3-day dosing cycles at 135 mg/kg/day, that were reversible following the non-dosing period. There were no balixafortide effects on the kidney injury molecule-1 (KIM-1) urine concentration, and there was high intra-animal variability in cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) urine concentrations.

Balixafortide was not mutagenic in *in vitro* tests, is not phototoxic, does not block the cardiac channels human ether-a-go-go-related gene (hERG), voltage gated sodium channel ($Na_V1.5$) or voltage gated sodium channel ($Ca_V1.2$) at concentrations in excess of 18-fold the mean free plasma concentrations in the clinic, and has been assessed to have a low immunogenic potential. Toxicity studies in the mouse and the monkey showed no effects of balixafortide on reproductive organs (44).

No specific local tolerance studies have been performed. Local tolerance was assessed as part of the 13-week study in monkey (44). The same infusion rate of 0.5 mL/kg/hour was used for all groups. The concentration of balixafortide formulation infused in the high-dose group was 13.5 mg/mL. Similar microscopic findings were present in animals in the control and in the balixafortide-treated groups, with no relationship to the dose level, and were considered infusion procedure-related findings, and not related to balixafortide.

Overall, balixafortide was well tolerated in toxicity studies and showed minimal to marked tubular vacuolation in the kidney at high doses (200 mg/kg) in monkeys. No other target organ toxicity was observed in the nonclinical test species. Other study findings were confined to hypoactivity in the mouse and transient skin reddening (face and scrotum), swelling of the lips and genital area and scratching/biting of the face, tail and body in the monkey, effects considered to be due, at least in part, to a histamine response which may be mediated through activation of mas-related gene X2 receptor (MRGPRX2). In the 13-week study in monkey, some animals exhibited signs of dehydration and emesis at 135 mg/kg/day.

2.5 Balixafortide Overview of Clinical Studies

Balixafortide has been investigated in 6 clinical studies that enrolled a total of 330 subjects, of which 235 subjects received at least one dose of balixafortide, in doses ranging from 0.01 to 5.5 mg/kg. There were 3 completed Phase 1 studies exploring the safety, tolerability, and pharmacokinetics (PK) of balixafortide (POL-001, POL-003, POL-004) and two completed Phase 2 studies to explore safety, tolerability, efficacy and PK/pharmacodynamics in patients with multiple myeloma (POL-002) and acute myocardial infarction (POL-006). Additionally, a

Phase 1 study with eribulin in metastatic BC has been conducted and interim results are described in Section 2.5.1.

2.5.1 Phase 1 Study (POL6326-007 – Ongoing at the time of Protocol development)

POL6326-007 is a Phase 1, open-label, non-randomized, dose escalation study of balixafortide + eribulin in 56 female patients aged ≥18 years with Stage IV histologically confirmed invasive BC and evidence of tumor cell CXCR4 expression, at least one measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1) criteria, who previously received at least one chemotherapy regimen for metastatic BC, and were eligible to receive eribulin as 2nd to 5th line of chemotherapy for metastatic BC treatment. Patients with hormone receptor (HR) positive status must have failed at least one endocrine therapy or be considered unsuitable for endocrine therapy.

In the interim analysis for this study, the ORR and CBR in the patients who received the highest dose of balixafortide (5.5 mg/kg) + eribulin (1.4 mg/m^2), was 38% and 63%, respectively, with a corresponding median duration of 4.4 months and 8.1 months, respectively. In the Overall Efficacy Population, the ORR and CBR were lower at 30% and 44%, respectively, with a correspondingly lower median duration of 3.2 months and 7 months, respectively, potentially suggesting a dose response. The Kaplan-Meier analysis showed a median PFS of 6.2 months (95% CI, 2.9–8.1) and 4.5 months (95% CI, 3.1–5.7) in the Expanded Cohort and Overall Efficacy Populations respectively.

On 4 October 2017, the date on which all patients had reached 12 months post enrolment, the 1-year survival rate was 62% (95% CI 47−74) for the Overall Efficacy Population and 75% (95% CI 53−88) in the Expanded Cohort. On 4 April 2019, the 18-month survival rate was 42% in the Overall Efficacy Population and 50% in the Expanded Cohort; the 24-month survival rate was 25% in the Overall Efficacy Population and 33% in the Expanded Cohort (45).

The median mature OS on 4 September 2018 was 16.8 months for the Overall Efficacy Population and 18 months for the Expanded Cohort (46).

Eribulin + balixafortide was shown to be well tolerated, allowing for a long duration of treatment in this study. The median duration of treatment for all patients was 105 days (3−504).

The incidence of most adverse events (AEs) in this study, even at the highest dose of balixafortide (5.5 mg/kg), were similar to those reported in other studies for eribulin alone (22, 23, 47-49): Grade 3/4 neutropenia 41% for balixafortide + eribulin (45−64% reported for eribulin alone in the literature), Grade 3/4 leukopenia 9% for balixafortide + eribulin (14−18% reported for eribulin alone in the literature), Grade 3/4 peripheral neuropathy 3.6% for balixafortide + eribulin (5−8% reported for eribulin alone in the literature), neuropathy of any grade 39% for balixafortide + eribulin (27−35% reported for eribulin alone in the literature), and no suggestion that these were associated with increasing balixafortide doses.

AEs leading to treatment discontinuation were reported in 2 (3.6%) patients: fatigue (2.5 mg/kg balixafortide + 1.4 mg/m^2 eribulin) and peripheral neuropathy (3.5 mg/kg balixafortide + 1.4 mg/m^2 eribulin). Two patients (3.6%) had treatment emergent adverse events (TEAEs) reported to have a fatal outcome: septic shock following neutropenia and streptococcal pneumonia in a 55 year old patient receiving 1 mg/kg balixafortide + 1.4 mg/m^2 eribulin, and neutropenia (Grade 4) and infiltration of both lungs, suggestive of bilateral pneumonia, in a 48 year old patient receiving 5.5 mg/kg balixafortide + 1.4 mg/m^2 eribulin.

The combination of balixafortide + eribulin demonstrated encouraging signs of activity in patients with HER2 negative metastatic BC; the results showed that the safety and tolerability

of balixafortide + eribulin was similar to that of eribulin monotherapy in BC or to balixafortide monotherapy in studies of healthy volunteers or patients with other malignancies (41).

The PK profile of balixafortide was not affected by eribulin. Over the entire dose range tested for balixafortide, the C_{max} and AUC for eribulin were within published ranges (50). Therefore, a drug interaction between eribulin and balixafortide is unlikely (51).

2.5.2 Balixafortide Population Pharmacokinetics

The population PK of balixafortide was established using data from 6 clinical studies (POL-001, POL-002, POL-003, POL-004, POL-006, and POL6326-007) with a total of 229 subjects to whom doses ranging from 0.01−5.5 mg/kg were administered as 1-, 2-, or 3-hour IV infusions as single or repeated daily doses.

Using data from all 6 clinical studies, the population PK analysis of balixafortide estimated a clearance (CL) of 6.5 L/h, a total volume of distribution (V_z) of 45 L, and a $t_{1/2}$ of 6.6 h for a typical healthy individual. In the metastatic BC patient population, CL was lower (4.4 L/h), V_z larger (49 L), and terminal $t_{1/2}$ longer (16 h). Balixafortide PK was non-linear with a faster CL at low doses. The between patient variability was moderate with a coefficient of variation for balixafortide CL of 20%. Estimated glomerular filtration rate (GFR) was a statistically significant covariate of CL, with slower CL in individuals with a reduced estimated GFR. There was a larger V_z and a faster CL in heavier individuals. There was a larger peripheral volume and a faster inter-compartmental exchange in older individuals.

2.6 Balixafortide Current Benefit/Risk Ratio

Balixafortide is being developed in combination with eribulin for the treatment of HER2 negative, locally recurrent metastatic BC, in adult patients who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane unless contra-indicated for safety reasons. In this protocol, locally recurrent BC is defined as unresectable locoregionally recurrent BC.

The safety profile of balixafortide is derived from 6 clinical studies (three Phase 1, one Phase 1/2 and two Phase 2 studies) that enrolled a total of 330 subjects, of which 235 subjects received at least one dose of balixafortide, either as a single agent or in combination with other drugs (44). The IV formulation was investigated in a broad range of doses from 0.01−5.5 mg/kg, with IV infusion times between 1 and 3 hours, and treatment duration up to 16 months. The accumulated safety data for balixafortide and the known safety profile of eribulin indicates that the following AEs of special interest (AESIs) should be evaluated and managed in accordance with established guidelines (e.g. American Society of Clinical Oncology [ASCO] guidelines for minimizing the incidence of febrile neutropenia): hypersensitivity/infusion-related reaction (IRRs), neutropenia, febrile neutropenia, infections associated with neutropenia, and renal impairment. The following AEs of particular interest (AEPIs) should be evaluated and managed: thrombocytopenia, QTc interval prolongation, peripheral neuropathy and hepatic impairment. Detailed information is provided in this protocol and the accompanying Investigator's Brochure.

In the Phase 1 study POL6326-007 (Section 2.5.1), the combination of balixafortide + eribulin demonstrated encouraging signs of activity in patients with HER2 negative metastatic BC, and the results showed that the safety and tolerability of balixafortide + eribulin was similar to that of eribulin or balixafortide monotherapy (41). This supports a positive benefit-risk balance in the target population, which is designed to reasonably reflect the target population in clinical practice.

Based on the available efficacy and safety data for balixafortide, the benefit risk profile remains unchanged and favorable. Further development of balixafortide in combination with eribulin, is justified by the anticipated benefits expected for patients with HER2 negative, locally recurrent or metastatic BC, who have progressed after at least one chemotherapeutic regimen for advanced disease.

2.7 Conduct of Study

This clinical study will be conducted in compliance with this Protocol, the Good Clinical Practice (GCP) guidelines of International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56, and 312 as appropriate, EU Directive 2001/20/EC and Commission Directive 2005/28/EC and EC ENTR/CT2, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, 2013), the General Data Protection Regulation (EU) 2016/679, designated Standard Operating Procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

In this study, the Investigator can delegate his/her tasks to an appropriately qualified designee. In this study, the use of the term Sponsor also refers to the Sponsor's designee.

3. STUDY DESIGN

3.1 Scientific Rationale for Study Design

Current treatment options for patients with locally recurrent and metastatic BC who have failed at least one chemotherapeutic regimen for advanced BC are modestly effective, strengthening the medical need for more therapeutic options with demonstrable improvement in clinical outcomes while not adding significantly to cumulative toxicity for patients with metastatic, HER2 negative BC.

Balixafortide is a potent, selective antagonist of the CXCR4 which has a central role in the progression of metastatic BC (13). Eribulin has regulatory approval in the US and in a number of other countries for treatment of patients with advanced BC who have failed at least two chemotherapeutic regimens for metastatic disease and in the EU for treatment of patients with advanced BC who have failed at least one chemotherapeutic regimen for metastatic disease.

The novel combination of balixafortide with eribulin is intended to improve disease control (reduce tumor burden and/or provide a period of disease stabilization) in patients with HER2 negative, locally recurrent or metastatic BC.

Phase 1 clinical data (Study POL6326-007), as well as nonclinical data, have provided meaningful information to support the pharmacology, safety profile and dose of balixafortide, and eligibility for enrolment, choice of reference therapy, and objectives for this Phase 3 trial.

The interim results of the Phase 1 trial (POL6326-007) in patients with relapsed metastatic BC provide highly promising results with regard to the efficacy and the overall safety profile of balixafortide in combination with eribulin. This supports a positive benefit-risk balance in the target population, which is designed to reasonably reflect the target population in clinical practice.

To address concerns of potential bias in assigning subjects to study drugs (selection bias), a central randomization procedure will be used. To address concerns of potential bias in the evaluation of patients (assessment bias), blinded centralized review of computed tomography (CT)/magnetic resonance imaging (MRI) scans have been included in the design of this

Phase 3 study to allow an unbiased estimate of the size of effect to be obtained. The study endpoints for this pivotal Phase 3 study are well recognized and accepted standards for evaluating the efficacy of oncology treatments.

In order to protect the integrity of the trial and the robustness of the results, project team members (both Polyphor Ltd and Contract Research Organization [CRO] personnel) will not evaluate, formally or informally, data grouped by randomized treatment arm as data are accruing over time; the exception to this will be the pre-planned interim efficacy analyses and safety reviews. Procedures relating to the execution of pre-planned interim efficacy analyses and safety reviews by the Data Safety Monitoring Committee (DSMC) are described in the DSMC charter. Procedures for the coding/blinding of the patient's name/identity for the Independent Review Committee (IRC) is provided in the imaging plan.

Regular monitoring of Investigators by Sponsor-designated personnel, instruction manuals, and data verification (including cross-checking and data audits) will be performed to ensure the quality of all data.

3.2 Justification for Dose

The dose of balixafortide to be used in this study (5.5 mg/kg) and the frequency of its administration have shown promising results with regard to efficacy, safety and tolerability in study POL6326-007 (Section 2.5.1). In study POL6326-007, no dose-limiting toxicities were confirmed and, therefore, the maximum tolerated dose was not reached. The highest balixafortide dose evaluated in this study was 5.5 mg/kg. Dosing to maximum tolerated dose was not continued because, based on PK evaluation, further dose increments by 1 mg/kg balixafortide (the maximum increment allowed in the protocol) would not have provided a sufficient increase in exposure; in addition, the ORR observed in Part II of this study was 3-fold greater than that published for eribulin alone. This suggested that anti-tumor activity was worthy of further exploration at the 5.5 mg/kg dose which was selected as the recommended Phase 2 dose.

Patients will receive eribulin mesylate at the dose approved in both the US and the EU (1.4 mg/m^2), with the appropriate dose reductions as described in Section 6.1.2. Eribulin is approved for use on Days 1 and 8 of each treatment cycle; however, in this study eribulin will be administered on Days 2 and 9 of each treatment cycle to allow balixafortide treatment to begin before eribulin. This cycle scheme was also used in study POL6326-007, and the schedule was designed to maximize exposure to balixafortide in relation to eribulin, while minimizing the number and burden of balixafortide administrations for the patient. In addition, this regimen allows for significant disruption of the protective tumor microenvironment (e.g. blockade of pro-survival SDF-1 signalling, change in the distribution and activation of immunosuppressive cells) by balixafortide in combination with eribulin. Bracketing the administration of balixafortide with chemotherapy is deemed appropriate regardless of whether a synergistic or immune-stimulant effect is the pharmacodynamic driver of balixafortide.

3.3 Overall Design

This international, multicenter, open-label, randomized, parallel, two-arm, pivotal Phase 3 trial has been designed to investigate the efficacy and safety of balixafortide in combination with an established, approved therapy (eribulin) relative to eribulin monotherapy in patients with HER2 negative, locally recurrent or metastatic BC who have previously been treated with 1−4 chemotherapeutic regimens for locally recurrent or metastatic BC. Unless contra-indicated for safety reasons, patients will have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting. In this protocol, locally recurrent BC is defined as unresectable locoregionally recurrent BC.

Two populations of patients will be studied, the:

- Overall Population, who receive study medication as 2nd to 5th line of therapy, which will constitute the primary population for regulatory submissions in the EU and jurisdictions in which the 2nd line + eribulin label applies.

- 3rd line + population, who receive study medication as 3rd to 5th line of therapy (3rd line +), which will constitute the primary population for regulatory submissions in the US and jurisdictions in which the 3rd line + eribulin label applies.

Patients will be stratified according to:

- Line of therapy (2nd line versus 3rd line +) for locally recurrent or metastatic BC.

- HR status (positive versus negative) based on ER or progesterone receptor (PgR) status.

- Cyclin-dependent kinase (CDK) 4/6 inhibitor treatment received previously (received a CDK 4/6 inhibitor previously versus not received a CDK 4/6 inhibitor previously).

- Visceral versus non-visceral disease. Visceral metastases will include brain, pulmonary, pleural, hepatic and peritoneal involvement (including pleural effusions and ascites). Any other sites of metastases (e.g. bone, lymph nodes, and skin) will be considered to be non-visceral. Patients with visceral metastases, irrespective of the presence of any other metastatic sites (e.g. bone), will be categorized as visceral. All other patients without visceral metastases will be categorized as non-visceral.

The study will consist of the following:

- **Screening Assessments:** To be obtained ≤21 days prior to randomization.

- **Randomization:** Patients will be randomized within 21 days of starting screening and after having completed the required screening assessments. Patients will be randomized either to the balixafortide + eribulin treatment arm or to the eribulin treatment arm. All patients must begin treatment within 3 days after randomization.

- **Treatment Phase:** The treatment regimens for the study are described in Section 6.1.1. Patients will receive 21-day cycles of treatment. All patients will receive eribulin on Days 2 and 9 of each cycle (the rational for this frequency is explained in Section 3.2). In addition, patients randomized to the balixafortide + eribulin arm will receive balixafortide on Days 1−3 and Days 8−10 of each cycle.

  Response Assessments During Treatment: From the date of randomization, patients will be evaluated according to RECIST v1.1 for complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on CT/MRI scans performed every 6 weeks (±7 days) during the first year, and then performed every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression. The decision about the patient's disease status and progression during the study will be taken based on the local radiologist's/Investigator's assessment.

From the date of randomization, additional bone scans will be performed at the discretion of the Investigator (e.g. to confirm CR, to follow up existing metastases, or if [based on signs and symptoms] new bone metastases are suspected).

It is critical that tumor assessments are performed according to the Study Schedule in a timely and complete manner to allow full comparability of the two treatment arms. To prevent the introduction of any bias into the efficacy results, the assessment must be performed according to the calendar regardless of any dosing delay or interruption. Imaging assessments will be scheduled using the randomization date as the reference date for all timepoints and NOT scheduled according to the date of the previous imaging timepoint. A delay in the imaging assessment to accommodate a treatment delay is not permitted. Incomplete assessment and/or wrong timing (out of Schedule) will result in the inability to accurately assess disease status for that timepoint. For a given patient/tumor lesion, the same technique for tumor assessment MUST be used throughout the study.

Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.

Patients will continue treatment as assigned at randomization, until objective PD (according to RECIST v1.1) is documented, there is unacceptable toxicity, death occurs, the patient withdraws consent, or the patient is lost to follow-up (whichever occurs first).

Patients who progress radiologically according to RECIST v1.1, but who are deemed by the Investigator to be clinically benefiting from study medication, may continue that study medication at the discretion of the Investigator; a PD confirmatory scan will be done at least 6 weeks after the last scan to identify potential pseudo-progression.

Patients discontinued from treatment, for reasons other than PD, will enter the PD Follow-up (as described in PD Follow-up below) unless death occurs, the patient withdraws consent to efficacy follow-up, or the patient is lost to follow-up.

- **End-of-Treatment (EoT) Evaluation:** This will occur as soon as possible, within 7 days after discontinuation of study medication and prior to initiation of any new anti-cancer therapy, regardless of the reason for discontinuation. A targeted physical examination will be conducted. Weight, Eastern Cooperative Oncology Group (ECOG) performance status, AEs, vital signs, clinical laboratory tests, 12-lead ECG and concomitant medications will be assessed and recorded for all patients at this visit. Patients who are discontinued from study medication for any reason, in the absence of objective PD (according to RECIST v1.1), will undergo tumor response assessment. For patients at selected sites, an optional tumor biopsy will be performed. Patients will complete quality of life (QoL) questionnaires.

- **30-Day Safety Follow-up:** This will occur 30 days (and no later than 37 days) from the last dose of study drug. AEs will be assessed and recorded for all patients at this visit. Concomitant medications will also be recorded for patients with unresolved AEs.

- **Long-term Follow-up:**

  (i) *PD Follow-up*: Regardless of treatment arm, patients who are discontinued from study medication for any reason in the absence of PD, will undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient has been on the study for ≥1 year) until PD is documented as per RECIST v1.1, or death occurs, or patient is lost to

follow-up, or the patient withdraws consent (whichever occurs first). If a patient stops study medication and begins other anti-cancer therapy before PD is documented, every effort should be made to perform tumor evaluation in these patients until disease progression.

(ii) *Survival Follow-up*: The Investigator will monitor the patient for OS status every 6 months (or more frequently) until death, until the patient withdraws consent to follow-up for survival, or until the patient is lost to follow-up (whichever occurs first).

(iii) Every effort should be made to collect and record all anti-cancer medicines that the patient receives during Long-term Follow-up in the patient's source data and electronic case report form (eCRF) until the end of study.

In this study, 384 patients will be enrolled (192 patients in the balixafortide + eribulin treatment arm, and 192 patients in the eribulin treatment arm) including 320 patients who will receive study medication as 3rd line +.

Patients will undergo assessment for:

- Efficacy.
- Safety and tolerability.
- PK (including metabolites).
- Immunogenicity.
- QoL.
- Exploratory biomarkers (including interferon [IFN]-gamma and other circulating cytokines).

At selected sites, the study will include assessment of additional exploratory blood and tissue biomarkers.

The Study Schedule of Assessments and sampling are outlined in Section 1.1.

3.4 Randomization and Treatment Allocation

Patients will be randomized in a 1:1 ratio to one of the following treatment regimens:

- Balixafortide + eribulin treatment arm

or

- Eribulin treatment arm.

Patients will be stratified as described in Section 3.3. CXCR4 expression (high versus low; threshold to be determined) is not currently planned as a stratification factor since (i) there is currently no validated test, and (ii) there was no correlation of ORR/CBR with level of CXCR4 expression in the Phase 1 trial. That said, CXCR4 expression level, based on immunohistochemistry (IHC) of historical tumor samples, will be recorded and the correlation

with efficacy will be explored. It should be noted that all BC patients screened for the Phase 1 trial expressed CXCR4 to some degree.

Both the randomization and the stratification will be handled by an Interactive Response System (IRT); refer to the IRT manual for further details.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of balixafortide + eribulin versus eribulin monotherapy on (i) PFS in the Overall Population and (ii) PFS and ORR in the 3rd line + population.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the OS between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.
- To compare measures of tumor response between patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm.
- To evaluate the safety and tolerability of balixafortide + eribulin versus eribulin monotherapy.

4.3 Exploratory Objectives

The exploratory objectives of this study are:

- To determine whether the treatment outcome correlates with baseline ER, PgR, or CXCR4 expression level.
- To assess tumor tissue and circulating biomarkers and possible association with patient treatment outcome.
- To explore immune response as assessed by iRECIST.
- Measurement of plasma concentration of balixafortide and potential metabolites to integrate in a population PK model.
- To assess the QoL as reported by patients in the balixafortide + eribulin treatment arm versus eribulin monotherapy treatment arm using standard QoL assessments.

4.4 Endpoints

4.4.1 Overall Population Efficacy Endpoints

Primary Efficacy Endpoint

In the Overall Population intended for regulatory submissions in the EU and jurisdictions in which the 2nd line + eribulin label applies, the primary endpoint is:

- PFS according to RECIST v1.1 guidelines, as assessed by the IRC.

Key Secondary Efficacy Endpoint

- OS.

The statistical design in the overall, 2nd line+ population, with pre-defined alpha allocation and recycling, is such that if PFS does not meet statistical significance at its allocated alpha level, then the design still allows OS to be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Other Secondary Efficacy Endpoints

- PFS according to RECIST v1.1 guidelines, as assessed by the local Investigator's review.
- ORR [confirmed CR + confirmed PR]) according to RECIST v1.1 guidelines, as assessed by the IRC in the Overall Population.
- ORR (confirmed CR + confirmed PR) according to RECIST v1.1 guidelines, as assessed by the local Investigator's review.
- CBR (proportion of patients with confirmed CR, confirmed PR, or SD ≥6 months) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review.
- Disease control rate (DCR; number of patients with confirmed CR, confirmed PR, or SD) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review.
- Time to response as assessed by the IRC and by the local Investigator's review.
- Duration of response as assessed by the IRC and by the local Investigator's review.

4.4.2 3rd Line + Population Efficacy Endpoints

Co-Primary Endpoints

In the 3rd line + population intended for regulatory submissions in the US and jurisdictions on which the 3rd line + eribulin label applies, the co-primary endpoints are:

- ORR (confirmed CR + confirmed PR) according to RECIST v1.1 guidelines, as assessed by the IRC.
- PFS according to RECIST v1.1 guidelines, as assessed by the IRC.

If PFS in the 3rd line + population is met at the allocated alpha level, PFS in the Overall Population will also be formally tested at the same alpha level.

Key Secondary Efficacy Endpoint

- OS.

The statistical design in the 3rd line + population, with pre-defined alpha allocation and recycling, is such that even if ORR does not meet statistical significance at its allocated alpha level, then PFS can still be tested and, if it meets statistical significance at its allocated alpha level, the study can still meet its primary objective. Further, if PFS does not meet statistical significance at its allocated alpha level, then OS can still be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Other Secondary Efficacy Endpoints

- PFS according to RECIST v1.1 guidelines, as assessed by the local Investigator's review.
- ORR (confirmed CR + confirmed PR) according to RECIST v1.1 guidelines, as assessed by the local Investigator's review.
- CBR (proportion of patients with confirmed CR, confirmed PR, or SD ≥6 months) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review.
- DCR (number of patients with confirmed CR, confirmed PR, or SD) according to RECIST v1.1 guidelines as assessed by the IRC and by the local Investigator's review.
- Time to response as assessed by the IRC and by the local Investigator's review.
- Duration of response as assessed by the IRC and by the local Investigator's review.

4.4.3 Secondary Safety Endpoints

These will include:

- Type, frequency and severity of AEs (including serious adverse events [SAEs], AESIs).
- Laboratory abnormalities.
- Vital signs.

Additionally, signs and symptoms of anaphylaxis will be captured and summarized in accordance with guidance provided by the Second Symposium on the Definition of Anaphylaxis (52). Evaluation of liver parameters will be made according to the evaluation of Drug-induced Serious Hepatotoxicity (eDISH) criteria (53); this requires a log-log plots of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) vs total bilirubin to identify potential cases of concern, followed by time course plots of all the identified potential cases.

4.4.4 Exploratory Endpoints

- Relationship between objective response, PFS, or OS and ER, PgR or CXCR4 expression levels.
- Relationship between objective response, PFS, or OS and exploratory biomarkers (from tumor tissue or blood) including cytokines (e.g. IFN-gamma), immune cells profile, and ribonucleic acid (RNA) expression.

- Response as assessed by iRECIST (2017) in those patients who continue treatment despite progression.
- Plasma concentration of balixafortide and potential metabolites (Population PK).
- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) change from baseline to the end of each treatment cycle.
- The Functional Assessment of Cancer Therapy Breast (FACT-B) and EuroQol-5D (EQ-5D) change from baseline to the end of each treatment cycle.

5. STUDY POPULATION

5.1 Patient Inclusion Criteria

Patients with measurable and non-measurable disease will be eligible for inclusion in this study only if all the following criteria are met:

1. Patients at least 18 years of age (or according to local regulation).
2. Documented histologically confirmed BC.
3. Metastatic BC currently of stage IV disease by American Joint Committee on Cancer criteria or unresectable locoregionally recurrent BC.
4. Molecular status and prior therapies:
    a) Molecular Status
    Eligible patients are, by their patient records and prior therapy, HER2 negative with any ER or PgR status. If a previous record of the HR status is not available, the HR status should be tested locally.
    HER2 negative (IHC 0,1 or fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH] HER2:CEP17 ratio < 2.0); HER2 2+ patients should be FISH/CISH negative.
    b) Prior Therapies
    Patients with locally recurrent or metastatic BC who have previously received 1−4 chemotherapeutic regimens for the treatment of locally recurrent or metastatic BC. Unless contra-indicated for safety reasons, prior therapy will have included an anthracycline and a taxane in either the adjuvant or metastatic setting.
    Patients with HR positive status (ER+ and/or PgR+) must have been treated with at least one line of endocrine therapy and considered by the treating physician not to be a candidate for further endocrine therapy.
5. At least 14 days from the completion of any previous cytotoxic chemotherapy, biological therapy, or any other investigational agent at time of initiation of study medication. Resolution of chemotherapy and radiation therapy related toxicities to Grade 1 or lower severity, except for stable sensory neuropathy Grade 2 or lower and alopecia.
6. Patients must have proved refractory to the most recent chemotherapy, documented by progression on or within six (6) months of therapy.
7. Females of child bearing potential must be willing and able to use highly effective contraception (as described in the protocol) whilst they or their male partners are on this study from randomization until 3 months after the last dose of study medication (Section 5.4.5). Male patients must commit to using an approved form of birth control (including double-barrier contraception [e.g. consistent and correct use of male condom with diaphragm or male condom with cervical cap] or sterilization method) while on treatment and for 3 months after the last dose of study medication (Section 5.4.5).
8. ECOG performance status of 0-2.
9. Life expectancy of 3 months or more as per Investigator assessment.

10. Adequate organ function defined at Screening as:
    a) WBC ≥3000/mm^3
    b) Absolute neutrophil count (ANC) ≥1500/mm^3.
    c) Platelets ≥75000/mm^{3*}.
    d) Creatinine Clearance ≥30 mL/minute as calculated by the Cockcroft-Gault equation or serum creatinine <1.5x institutional upper limit of normal (ULN) (2).
    e) Total bilirubin ≤1.5x institutional ULN; AST, ALT ≤3x institutional ULN (for patients with liver metastases, ≤5x ULN).
    f) Hemoglobin ≥10 g/dL.
11. Patients who have central nervous system involvement if metastases have been treated and are stable for at least 4 weeks after completion of radiation therapy and/or surgery. Stable is defined as the absence of the need for dexamethasone or other corticosteroid therapy, and radiographic confirmation of SD.
12. Patients receiving bone-modifying agents (BMA [bisphosphonates or denosumab]) if BMA was initiated at least 4 weeks prior to the start of study medication.
13. Must be willing and able to comply with the protocol and must understand and sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent document.
14. Affiliation with a National Health Insurance plan (applicable to patients in France only).

* ≥100000/mm^3 in France

5.2 Patient Exclusion Criteria

Patients will be ineligible if one or more of the following statements are applicable:

1. Previously received eribulin.
2. Peripheral neuropathy Grade ≥3.
3. Receipt of prior CXCR4 therapy.
4. Receipt of colony stimulating factors (CSFs) filgrastim, pegfilgrastim, or sargramostim within 14 days prior to time of initiation of study medication.
5. Radiation therapy within 14 days prior to time of initiation of study medication.
6. Severe concurrent illness or psycho-social situation that would limit compliance with study requirements or that, in the Investigator's opinion, would preclude enrolment.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to balixafortide or eribulin, or known intolerance to balixafortide or eribulin.
8. Breast feeding or pregnant, as determined by a serum pregnancy test beta human chorionic gonadotrophin (β-HCG) at Screening and prior to the administration of study medication.
9. Patients with congestive heart failure, electrolyte abnormalities, bradyarrhythmias, known congenital long QT syndrome, QT interval corrected with Fridericia's formula (QTcF) ≥470 milliseconds (msec) at baseline in the absence of bundle branch block, or currently taking drugs at known risk of prolonging the QT interval or causing torsades de pointes (TdP) (including Class Ia and III anti-arrhythmic drugs; see also Appendix 1 Prohibited Medications). Patients with hypokalemia or hypomagnesemia should not be randomized until the hypokalemia or hypomagnesemia is corrected.
10. Patients with a concurrent malignancy or malignancy 2 years prior to randomization with the exception of adequately treated basal and squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
11. Persons who have been housed in an institution due to a government or judicial order (applicable to Germany only).

5.3 Patient Withdrawal Criteria

5.3.1 Discontinuation from Treatment

The term "treatment interruption" refers to a patient stopping the study drug during the course of the study, but then re-starting it at a later time in the study (see Section 6.1). The reason for dosing interruption will be collected on the patient's source data and eCRF.

The term "treatment discontinuation" refers to a patient's withdrawal from the study treatment phase. The reason for discontinuation from treatment will be collected on the patient's source data and eCRF.

Treatment discontinuation should be discussed where possible with the Sponsor before the patient stops treatment with the study medication, and the Study Monitor should be notified before treatment discontinuation.

Patients may be discontinued from treatment in case of:

- Disease progression according to RECIST v1.1. However, patients are allowed to continue on treatment based on medical judgement.
- Deterioration in the general health status of the patient without evidence of disease progression according to RECIST v1.1.
- Unacceptable toxicity or AE.
- Pregnancy (Section 5.3.4).
- Patient withdraws consent to continue treatment.

Patients who discontinue study medication for any reason should not be considered as discontinued from study (Section 5.3.2); these patients should be requested to attend the EoT visit, the 30-day Safety Follow-up visit and the Long-term Follow-up visits as outlined in the Study Schedule (Section 1.1), unless consent to participate in the study and consent to be followed for OS is also withdrawn (Section 5.3.3).

5.3.2 Discontinuation from Study

The term "study discontinuation" refers to a patient's withdrawal from the study, including treatment discontinuation (if the patient is still on treatment) as well as the 30-Day Safety Follow-up and Long-term Follow-up.

Patients are discontinued from study in case of:

- Withdrawal of full consent (Section 5.3.3).
- At the discretion of the Investigator, for instance, for safety reasons.
- Death.
- Lost to follow-up.

Reasonable effort should be made and documented to contact any patient lost to follow-up during the study in order to complete assessments and retrieve any outstanding data. One

documented attempt must include sending a certified letter to the patient's last known address, requesting that they return to the study site for final evaluations. If necessary, the patient's family doctor/general practitioner will be contacted for collection of survival data.

If a patient withdraws consent to continue with the study, no further evaluations will be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent in compliance with local laws and regulations.

5.3.3 Patient Withdrawing Consent

Patients will be advised on the Informed Consent Form (ICF) that at any time, for any reason, without prejudice, they have the right to withdraw consent to:

(i) Treatment only, but still consent to post-treatment study visits and Long-term Follow-up (for PD and survival).

(ii) Treatment and to post-treatment study visits, but consent to Survival Follow-up.

(iii) Treatment, post-treatment study visits and Long-term Follow-up (i.e. discontinuation from study).

5.3.4 Patient Withdrawal in case of Pregnancy

Patients who become pregnant during the study must be withdrawn from treatment immediately.

In the event of a pregnancy, whenever possible, it should be followed to term, any premature terminations reported to the Sponsor, and the status of the mother and child should be reported to the Sponsor after delivery and at important developmental milestones during the first year (Section 9.3).

5.3.5 Patient Replacement

Patients who discontinue from treatment or study will not be replaced.

5.4 Patient Restrictions

5.4.1 Prior or Concomitant Medication

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the Investigator. Any medications, including herbal supplements, vitamins, or treatment taken by the patient, from 28 days prior to the start of study medication and up to 30 days (and no later than 37 days) following the last dose of study drug (as described in Section 7.7) and the reason for their administration must be recorded on the patient's source data and eCRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms can be used and must be recorded in the patient's source data and eCRF.

5.4.2 Permitted Medications

The following are permitted throughout the duration of the treatment:

- **Standard therapies** for pre-existing medical conditions, medical and/or surgical complications, and palliation may be used during this study. Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) may also be used at the Investigator's discretion. All medications must be recorded in the patient's source data and eCRF.

- **Antihistamines (H_1 receptor antagonists) and corticosteroids** can be used to manage IRRs Section 9.2.6.3). At the discretion of the treating physician, H_1 receptor antagonists may be used as premedication for the prevention of IRRs.

- **Hematopoietic growth factors** (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Receipt of CSFs within 14 days prior to study Day 1 (Cycle 1) are not permitted (Section 5.2). However, after study Day 1 (Cycle 1), this study requires adherence to the ASCO guidelines for minimizing the incidence of febrile neutropenia, including the recommended prophylactic use of CSFs, where appropriate at the discretion of the Investigator (Appendix 7 ASCO Guidance on the Use of CSFs) (54). Risk factors for febrile neutropenia in addition to those posed by eribulin and advanced BC are shown in Table 10.

- **Erythropoietin** may be used at the Investigator's discretion for the supportive treatment of anemia.

- **Bisphosphonates** may be continued for the treatment of osteoporosis or management of existing bone metastases for patients who have been receiving them at a stable dose for at least 4 weeks prior to randomization (Section 5.1). If the dose is increased or therapy is initiated during the study, the reason must be documented in the patient source documentation and disease progression according to RECIST v1.1 must be ruled out.

- **Palliative radiotherapy** is permitted if done solely for bone pain relief. If palliative radiotherapy is initiated after start of study medication, the reason for its use must be clearly documented and disease progression according to RECIST v1.1 must be ruled out.

5.4.3 Prohibited Medications

Anti-cancer agents: No additional investigational or commercial anti-cancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than eribulin and balixafortide will be permitted during the study treatment phase. Patients who receive any other drug which is indicated for the treatment of BC during the treatment phase will be withdrawn from treatment and will be requested to attend the EoT visit and the 30-day Safety Follow-up visit. The Investigator will also follow these patients for PD and survival (Long-term Follow-up).

Drugs at known risk of prolonging the QT interval or causing TdP are prohibited during the study treatment phase. A list of prohibited drugs is provided in Appendix 1 Prohibited Medications. If the patient is on treatment with a drug at known risk of prolonging the QTc interval or causing TdP, an alternative medication should be considered. If an alternative is not available or deemed appropriate, the patient should be excluded from participation in the study.

5.4.4 Medications Not Recommended

The following treatments are not recommended throughout the duration of the study treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the Sponsor is required prior to treatment initiation.

Chronic immunosuppressive therapies and/or high dose steroids should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics, or inhaled as well as short course of oral/topical or short acting steroids given for allergic reactions or asthma flares are allowed. Corticosteroids can be used to manage IRRs during the study (Section 9.2.6.3).

The use of **herbal medicines** is not recommended during the study treatment phase.

5.4.5 Women and Men of Child bearing Potential

A woman is considered to be of child bearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- XY genotype, Turner syndrome, uterine agenesis.
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

All women of child bearing potential must be instructed to use adequate, highly effective contraception whilst they or their male partners are taking part in this study from randomization until 3 months after the last dose of study medication. Contraceptive methods should be in compliance with local legislation. Such contraception includes:

- Intrauterine devices (IUD)
- Sterilization method (bilateral tubal occlusion or vasectomized partner),
- True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject.

Note: hormonal contraception is contra-indicated in women patients participating in this study. However, the female partners of male patients participating in this study can use hormonal contraception if medically indicated.

Male patients must be willing to use an approved form of birth-control, including double-barrier contraception (e.g. consistent and correct use of male condom with diaphragm or male condom with cervical cap) or sterilization method, from randomization until 3 months after the last dose of study medication. Male patients are also encouraged to seek advice on conservation of sperm prior to beginning study medication because of the possibility of irreversible infertility due to therapy with eribulin. The study doctor should discuss acceptable birth control options with the patient. The methods of birth control used must be recorded in the source data and eCRF.

5.4.5.1 Pregnancy Test

Analysis of samples for pregnancy tests will be conducted locally. For patients of child bearing potential, a serum β-HCG pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the Screening Visit no more than 7 days prior to Randomization. Before beginning dosing for each Cycle (on Study Day 1 for patients on the balixafortide + eribulin treatment arm and on Study Day 2 for patients on the eribulin monotherapy treatment arm), a urine pregnancy testing will be performed. Any positive urine HCG results will be further confirmed by a serum HCG test. A negative pregnancy result is required before the patient may receive study medication. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period or when potential pregnancy is otherwise suspected, as determined by the Investigator, and these evaluations will be recorded in the patient's source data and eCRF. In the case of a positive HCG test, the patient will be withdrawn from study drugs, but may remain in the study for survival follow-up. A urine pregnancy test will also be conducted at the EoT visit. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

6. STUDY MEDICATION

The investigational medicinal product (IMP; as defined by EU regulation) in this study is balixafortide. The other drug to be used in this study is eribulin.

6.1 Study Drug Administration

6.1.1 Dosing and Administration

Patients will be randomized to one of the following two treatment regimens:

Balixafortide + eribulin treatment arm

Balixafortide will be administered on Days 1−3 and Days 8−10 and eribulin will be administered on Days 2 and 9 of each 21-day cycle.

Cycle Scheme:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
POL6326	1	2	3	treatment break				8	9	10	treatment break										
Eribulin		2	treatment break						9	treatment break											

Eribulin monotherapy treatment arm

Eribulin will be administered on Days 2 and 9 of each 21-day cycle.

Cycle Scheme:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Eribulin		2	treatment break						9	treatment break											

Balixafortide will be administered, at a dose of 5.5 mg/kg, IV over a minimum of 2 hours ±10 minutes; however, the infusion time of balixafortide can be increased to a maximum of 3 hours at the discretion of the treating physician, for reasons of patient tolerability (i.e. to manage IRRs).

Eribulin should be administered IV at a dose of 1.4 mg/m^2 over 2 to 5 minutes on Days 2 and 9 of each 21-day cycle; **note:** this dose is expressed as the salt, eribulin mesylate; however, in some countries this dose is expressed as the base, equivalent to eribulin 1.23 mg/m^2. In the balixafortide + eribulin treatment arm, eribulin will be administered within 45 minutes after the end of the balixafortide infusion. The eribulin dose should be modified in patients with hepatic and/or renal impairment as described in the regulatory label for eribulin in the country where the patient is being treated or as described in Table 4 (Section 6.1.2) for other countries.

Crossover will not be allowed at any time after randomization.

6.1.2 Dose Modifications (including delays and interruptions)

Balixafortide

Balixafortide dosing may be modified for reasons of patient tolerability as described below. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dosing modifications for balixafortide may occur in 2 ways:

- Within a cycle: dosing interruption during a given treatment cycle until there is adequate recovery to Grade 1 or lower.
- Between cycles: administration of the next cycle may be delayed due to persistent toxicity.

Based on currently available data, there are no dose reductions recommended for balixafortide. Investigators should discuss with the Sponsor in a timely manner, any balixafortide dose reduction they feel warranted for that patient due to AEs and possible resumption of balixafortide at the full dose.

In the rare event that patients are discontinued from balixafortide treatment due to treatment-related toxicity, patients should attend the EoT Visit, the 30-day Safety Follow-up visit, and the Long-term Follow-up visits.

Eribulin

The recommended dose reductions for eribulin are presented in Table 4 and based on the US label (43) as reference. In countries where eribulin is approved, guidance on dose modification provided in the local, currently approved eribulin label may be followed. The eribulin dose should not be escalated after it has been reduced.

Table 4 Recommended dose reductions for eribulin

Event description	Recommended dose	
	Expressed as salt (eribulin mesylate)	**Expressed as base (eribulin)**
Mild hepatic impairment (Child-Pugh A)	1.1 mg/m^2	0.97 mg/m^2
Moderate hepatic impairment (Child Pugh B)	0.7 mg/m^2	0.62 mg/m^2
Moderate or severe renal impairment (CrCl 15–49 mL/min)	1.1 mg/m^2	0.97 mg/m^2
Permanently reduce the 1.4 mg/m^2 of eribulin mesylate dose (equivalent to 1.23 mg/m^2 eribulin base) for any of the following		
ANC <500/mm^3 for >7 days	1.1 mg/m^2	0.97 mg/m^2
ANC <1,000/mm^3 with fever or infection	1.1 mg/m^2	0.97 mg/m^2
Platelets <25,000/mm^3	1.1 mg/m^2	0.97 mg/m^2
Platelets <50,000/mm^3 requiring transfusion	1.1 mg/m^2	0.97 mg/m^2
Non-hematological Grade 3 or 4 toxicities	1.1 mg/m^2	0.97 mg/m^2
Omission or delay of Day 9 eribulin dose in previous cycle for toxicity	1.1 mg/m^2	0.97 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2	0.62 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin	Discontinue eribulin

ANC: absolute neutrophil count; CrCl: creatinine clearance.
Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
Source: Eisai Inc. (2017). Full prescription information for HALAVEN® US (43).

6.1.2.1 Dosing Delays or Interruptions

Patients will start study medication within 3 days from randomization as outlined in the Study Schedule (Section 1.1). Subsequent cycles of treatment should be started within 3 days of completing the previous cycle. Any delays beyond this that are being considered to the beginning of a cycle for logistical or scheduling reasons should be discussed with the Sponsor on a case by case basis.

If study medication during a cycle is delayed for <14 days (counted from the beginning of dosing in that cycle), then treatment can be resumed during that cycle. In these circumstances, the total duration of a cycle could potentially be extended up to 27 days.

If study medication during a cycle is delayed for ≥14 days (counted from the beginning of dosing in that cycle), then treatment for that cycle cannot be resumed. Instead, the next cycle will be initiated as planned. If the next cycle cannot be initiated as planned, the patient should be discontinued from treatment unless discussed and agreed otherwise with the Sponsor.

The doses of balixafortide on Days 1, 2 and 3 are interdependent with the eribulin dose on Day 2. Similarly, the doses of balixafortide on Days 8, 9 and 10 are interdependent with the eribulin dose on Day 9. Therefore, if an eribulin dose is delayed by a few days during a cycle, then the adjunctive balixafortide doses must also be delayed accordingly during that cycle. Although delays of <14 days (counted from the beginning of dosing in that cycle) may change the days on which doses are given in relation to the Schedule, the interval between doses in a cycle should remain the same as those shown in Section 6.1.1. If a dose of eribulin is omitted, the corresponding dose/s of balixafortide must also be omitted. Some examples of the circumstances that could arise are given below:

- Example 1, if eribulin is given on Day 3 instead of Day 2, then balixafortide can be given on Days 2, 3 and 4 instead of on Days 1, 2 and 3.
- Example 2, if eribulin is given on Day 12 instead of Day 9, then balixafortide can be given on Days 11, 12 and 13.
- Example 3, if eribulin is omitted on Day 9, then the balixafortide on Days 8, 9, and 10 can also be omitted.

Tumor assessments must continue to be performed according to the Study Schedule regardless of any dosing delay (Section 8.2).

Recommended Dose Delays for Eribulin

Do not administer eribulin on Day 2 or Day 9, if any of the following occur:

- ANC <1000/mm^3.
- Platelets <75000/mm^3.
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 non-hematological toxicities.

The Day 9 eribulin dose may be delayed for a maximum of 1 week. If toxicities:

- Do not resolve or improve to CTCAE Grade ≤ 2 severity by Day 16, omit the dose.
- Resolve or improve to CTCAE Grade ≤ 2 severity by Day 16, administer the eribulin at a reduced dose (Table 4) and initiate the next cycle no sooner than 2 weeks later.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator. This study requires adherence to the ASCO guidelines for minimizing the incidence of febrile neutropenia, including the recommended prophylactic use

of CSFs, where appropriate at the discretion of the Investigator (Appendix 7 ASCO Guidance on the Use of CSFs) (54).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Accountability

The Investigator, or an approved designee, must maintain records of the product's delivery to the study site, the inventory at the site, the use for each patient, and will ensure that all study drugs are stored in a secure, limited access area. These records must include dates, quantities, batch/serial numbers, expiry dates (if applicable), and the unique code numbers assigned to the study drug(s) and study patients. A temperature log of the medication storage refrigerator must also be kept. Investigators must maintain records that document adequately that the patients were provided with the doses specified by the Protocol and reconcile all study drug(s) received from the Sponsor.

To ensure adequate records, all study medications will be accounted for on an on-going basis throughout the study in drug accountability forms at the study site. Records will be kept in accordance with the applicable regulatory requirements and the Investigator will ensure that study medication is dispensed only by qualified site staff. These records will be independently monitored by a Study monitor.

6.2.2 Formulation, Appearance, Packaging, and Labelling

Balixafortide is provided in 15R (15 mL) single-use glass vials (European Pharmacopoeia [Ph. Eur.] hydrolytic class I) with serum stoppers, aluminum seal and plastic flip-off caps as a clear, colorless, aqueous concentrate for solution for infusion in phosphate buffered, isotonic sodium chloride. Each vial contains 11 mL extractable volume (385 mg/vial) of balixafortide. Vials are provided at 2-8°C in boxes (as secondary package). Vials are individually labelled and new vial(s) will be used for each dose administration.

Balixafortide is labelled in local language. Labelling is performed according to Annex 13 of the Good Manufacturing Practice (GMP) guidelines of the European Commission, ICH GCP guidelines, and local laws.

Eribulin is provided as a clear, colorless aqueous solution for injection, in type I glass vials with Teflon-coated, butyl rubber stoppers and flip-off aluminum over seals. Each vial contains 2 mL of eribulin solution with ethanol anhydrous, water for injections, hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment) as excipients. Vials are provided at 15-25°C in boxes. Vials are individually labelled and new vial(s) will be used for each dose administration.

6.2.3 Product Storage and Stability

Study medication must be stored in securely locked areas not generally accessible until administered to the patients. The key to the storage area is to be kept by the Investigator (or delegated person responsible for the study drug). The store will be accessible only to those persons authorized by the Investigator to dispense/administer study medication under this protocol.

Further details on drug handling will be provided in a separate pharmacy manual.

Balixafortide and eribulin supplied by the Sponsor, are to be used exclusively in this clinical trial according to the instructions of this protocol.

Unopened vials of balixafortide can be stored at 2-8°C for at least 2 years when protected from light.

Unopened vials of eribulin can be stored at 15-25°C for 5 years. In countries where eribulin is approved, the local label should be consulted for storage instructions.

6.2.4 Preparation

To minimize the risk of microbial contamination, balixafortide and eribulin should be used immediately after opening. If this is not feasible, the in-use storage times apply as specified below. Please refer to the pharmacy manual for additional information.

Balixafortide

The dose will be adjusted per mg/kg body weight. The concentrate for solution for infusion will be diluted with isotonic saline (0.9%) solution for infusion (pharmacopeial grade) to obtain a final infusion solution with a concentration of 0.5 mg/mL balixafortide.

The in-use storage time of the final solution for infusion should not exceed 24 hours at 2-8°C or 6 hours at room temperature.

Eribulin

The Investigator (or designee) will aseptically withdraw the required amount of eribulin from the single-use vial and administer either undiluted or after dilution in up to 100 mL with isotonic saline (0.9%) solution.

Undiluted eribulin can be stored in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (2-8°C). Diluted solutions of eribulin can be stored for up to 4 hours at room temperature or up to 24 hours under refrigeration.

Eribulin must not be mixed with other medicinal products and should not be diluted in glucose 5% infusion solution. Eribulin should only be prepared and administered by personnel appropriately trained in handling of cytotoxic agents. Pregnant staff should not handle eribulin.

6.3 Assessment of Compliance

Study drugs must be used only as directed in the Protocol. As the study drugs will be administered at the study site by the Investigator or trained study site staff, it is not considered necessary to assess subject compliance in this study.

7. STUDY ASSESSMENTS AND PROCEDURES

All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable visit time windows are presented in the Study Schedules (Section 1.1). For the purposes of this study, one cycle is 21 days. For dose interruptions, see Section 6.1.2.1.

Every effort should be made to ensure that the protocol-required activities and procedures are completed as described. However, there may be circumstances, outside of the control of the Investigator, which may make it unfeasible to perform the activity. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required activity cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure

that normal processes are adhered to as soon as possible. The Sponsor will be informed of these incidents in a timely fashion.

7.1 Screening Visit (Day –21 to –1)

On the day of the Screening, the Investigator or designee must obtain the patient's consent before performing any protocol-related procedure and assessment (see Section 15.2 for further details).

Once the consent is obtained, the following procedures and assessments will be performed and recorded in the patient's source data and CRF:

All patients:

- Informed consent.
- Interactive Web Response System (IWRS)/IRT registration–the patient number will be allocated.
- Patient eligibility (inclusion/exclusion criteria).
- Demographics (gender, date of birth, race and ethnicity) and baseline data.
- Medical history (e.g. important medical, surgical, and allergic conditions from the patient's medical history that could have an impact on the patient's evaluation, all cancer history, all previous cancer therapy, and all relevant, current medical conditions that are present at the time of signing informed consent). Any pre-planned intervention or procedure to occur during the study will also be recorded.
- Stratification factors for the trial i.e. whether HR status positive or negative (based on ER or PgR status), previous lines of chemotherapy received for locally recurrent or metastatic BC, whether CDK 4/6 inhibitor treatment was received previously, whether visceral or non-visceral disease is present. Visceral metastases will include brain, pulmonary, pleural, hepatic and peritoneal involvement (including pleural effusions and ascites). Any other sites of metastases (e.g. bone, lymph nodes, and skin) will be considered to be non-visceral. Patients with visceral metastases, irrespective of the presence of any other metastatic sites (e.g. bone), will be categorized as visceral. All other patients without visceral metastases will be categorized as non-visceral.
- Prior/concomitant therapy/medications taken up to 28 days before the start of study medication (see Section 5.4.1).
- Patient reported health outcome QoL questionnaires (see Section 11.3).
- Standard, complete physical examination (see Section 9.6).
- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight and height.
- ECOG performance status (see Section 9.6).
- SAEs will be recorded from the time that the ICF is signed (see Section 9.2).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9). Screening blood tests should be taken within 7 days prior to randomization.
- Serum pregnancy test (β-HCG) for women of child bearing potential (see Section 5.4.5) only, no more than 7 days prior to Randomization.
- Females of child bearing potential must be instructed to use adequate, highly effective contraception whilst they or their male partners are on this study from randomization until 3 months after the last dose of study medication (Section 5.4.5). Male patients must commit to using an approved form of birth control, including double-barrier method of contraception (e.g. consistent and correct use of male condom with diaphragm or male

condom with cervical cap) or sterilization method from randomization until 3 months after the last dose of study medication (Section 5.4.5). Male patients are also encouraged to seek advice on conservation of sperm prior to beginning study medication because of the possibility of irreversible infertility due to therapy with eribulin.

- Date and results of last CT/MRI scan. If no scan has been performed in the 30 days prior to Randomization a scan should be performed (see Section 8.2.1).
- Date and results of last bone scan. If no scan has been performed in the 30 days prior to Randomization a scan should be performed (see Section 8.2.1).
- 12-lead ECG (see Section 9.8).
- Date and results of last tumor biopsy (see Section 11.2.1).
- For patients who have had a previous tumor biopsy at any time, consent will be required to donate this tissue for biomarker assessment. If multiple biopsies are available, it is recommended to collect a sample of each. If such tumor tissue is not available, then the patient will be requested to provide a fresh tumor biopsy (see Section 11.2.1). If a fresh tumor biopsy is not available, the patient's refusal to provide a tumor biopsy or the lack of lesions from which a biopsy can be collected will be documented in the patient's source data and eCRF.

Patients at Selected Sites Only

For patients at selected sites, the following additional assessments will be performed:

- Patients can optionally consent to fresh tumor biopsy at Screening and subsequent timepoints as defined in the Study Schedules (Section 1.1) for exploratory biomarkers. If a biopsy has already been performed within 30 days prior to randomization and tumor tissue is still available, then the fresh tumor biopsy is not required during Screening (see Section 11.2.1).

7.2 Randomization

The Investigator will review the patient's laboratory test results and confirm that the patient is eligible for the study. If the patient is eligible, the Investigator will randomize the patient to the study via the IRT. The IRT will allocate the patient to the respective treatment arm. Further details are provided in the IRT manual.

No patient should be randomized into the study more than once. If a patient is randomized in error (e.g. randomization number is allocated incorrectly) and/or receives the wrong treatment, the Sponsor should be notified as soon as the error is discovered (Section 9.4).

7.3 Treatment Period–Balixafortide + Eribulin Treatment Arm Only

7.3.1 Cycle 1

7.3.1.1 Cycle 1 Day 1

Patients will start study medication within 3 days from randomization as outlined in the Study Schedule (Section 1.1).

The following procedures and assessments will be performed following randomization:

Before Balixafortide Administration:

- Patient reported health outcome QoL questionnaires (see Section 11.3).
- Targeted physical examination (see Section 9.6).

- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight
- ECOG performance status (see Section 9.6).
- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the Screening Visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration.
- Urine pregnancy test for women of child bearing potential (see Section 5.4.5.1).
- 12-lead ECGs, 2 baseline ECG recordings taken within 1 hour prior to administration of balixafortide (see Section 9.8).
- Blood samples for immunogenicity taken immediately before starting balixafortide infusion (see Section 11.1).
- Blood samples for exploratory biomarkers in all patients taken immediately before starting balixafortide infusion (see Section 11.2.2).
- IWRS/IRT registration.

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Infusion:

- Blood samples for exploratory biomarkers in all patients (see Section 11.2.2).

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.3.1.2 Cycle 1 Day 2

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- IWRS/IRT registration.
- 12-lead ECG before starting balixafortide infusion (see Section 9.8).
- Blood sample for PK taken immediately before starting balixafortide infusion, see Section 10.1.

Balixafortide Administration (see Section 6.1).

After Balixafortide Administration, but Before Administration of Eribulin:

- Blood samples for exploratory biomarkers in all patients taken immediately after completing balixafortide infusion, but before administration of eribulin (see Section 11.2.2).
- Blood sample for PK taken immediately after completing balixafortide infusion, see Section 10.1.

Eribulin Administration (see Section 6.1).

After Study Medication Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8).
- One additional blood sample scheduled flexibly with precise recording, at 1−20 hours after completing the infusion of balixafortide on Day 2, see Section 10.1.

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- Blood sample for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.3.1.3 Cycle 1 Day 3

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- IWRS/IRT registration.

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Administration:

- Blood samples for exploratory biomarkers in all patients taken immediately after completing balixafortide infusion (see Section 11.2.2).

7.3.1.4 Cycle 1 Day 8

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration.
- IWRS/IRT registration.
- Blood samples for immunogenicity taken immediately before starting balixafortide infusion (see Section 11.1).
- Blood samples for exploratory biomarkers in all patients taken immediately before starting balixafortide infusion (see Section 11.2.2).

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Infusion:

- Blood sample for PK, see Section 10.1.

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.3.1.5 Cycle 1 Day 9

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- 12-lead ECG before starting balixafortide infusion (see Section 9.8).
- IWRS/IRT registration.
- Blood sample for PK taken immediately before starting balixafortide infusion, see Section 10.1.
- Blood samples for exploratory biomarkers in all patients taken immediately before starting balixafortide infusion (see Section 11.2.2).

Balixafortide Administration (see Section 6.1).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8).

7.3.1.6 Cycle 1 Day 10

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- IWRS/IRT registration.

Balixafortide Administration (see Section 6.1).

7.3.2 Subsequent Cycles

7.3.2.1 Day 1

Before Balixafortide Administration:

- Patient reported health outcome QoL questionnaire (see Section 11.3).
- Targeted physical examination (see Section 9.6).
- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight.
- ECOG performance status (see Section 9.6).
- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9; blood test results must be available within 24 hours prior to study drug administration).
- Urine pregnancy test for women of child bearing potential (see Section 5.4.5.1).
- IWRS/IRT registration.

Cycles 2, 3, 5, 7 and then every alternate cycle only:

- Blood samples for immunogenicity taken immediately before starting balixafortide infusion (see Section 11.1).

Cycles 3 only:

- Blood samples for exploratory biomarkers in all patients taken immediately before starting balixafortide infusion (see Section 11.2.2).

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Infusion:

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients (see Section 11.2.2).

Patients at Selected Sites Only:

Cycle 3 only:

For patients at selected sites, the following additional assessments will be performed:

- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.3.2.2 Day 2

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- 12-lead ECG before starting balixafortide infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
- IWRS/IRT registration.

Cycle 3 only:

- Blood sample for PK taken immediately before starting balixafortide infusion (see Section 10.1).

Balixafortide Administration (see Section 6.1).

After Balixafortide Administration, but Before Administration of Eribulin:

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients taken immediately after completing balixafortide infusion, but before administration of eribulin (see Section 11.2.2).

Cycles 2, 3, 5, and 7 only:

- Blood sample for PK in all patients taken immediately after completing balixafortide infusion, see Section 10.1.

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8). After Cycle 2 the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).

Patients at Selected Sites Only:

Cycle 3 only:

For patients at selected sites, the following additional assessments will be performed:

- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.3.2.3 Day 3

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- IWRS/IRT registration.

Cycle 5 and 7 only:

- Blood sample for PK taken immediately before starting balixafortide infusion, see Section 10.1.

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Administration:

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients taken immediately after completing balixafortide infusion (see Section 11.2.2).

7.3.2.4 Day 4 (Cycle 3 only)

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Blood sample for PK at 24 hours (±4 hours) after completing the balixafortide infusion on Day 3 (see Section 10.1).
- Blood samples for exploratory biomarkers taken 24 hours (±4 hours) after completing the balixafortide infusion on Day 3, only in those patients scheduled to have blood samples for PK on Cycle 3, Day 4 (see Section 11.2.2).

7.3.2.5 Day 5 (Cycle 3 only)

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Blood sample for PK at 44 hours (±4 hours) after completing the balixafortide infusion on Day 3 (see Section 10.1).

- Blood samples for exploratory biomarkers taken 44 hours (±4 hours) after completing the balixafortide infusion on Day 3, only in those patients scheduled to have blood samples for PK on Cycle 3, Day 5 (see Section 11.2.2).

7.3.2.6 Day 8

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9) blood test results must be available within 24 hours prior to study drug administration.
- IWRS/IRT registration.

Cycle 2 only:

- Blood sample for immunogenicity taken immediately before starting balixafortide infusion (see Section 11.1).

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients taken immediately before starting balixafortide infusion (see Section 11.2.2).

Balixafortide Administration (see Section 6.1).

Immediately After Completing Balixafortide Infusion:

Cycle 2 only:

- Blood sample for PK, see Section 10.1.

7.3.2.7 Day 9

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- 12 lead ECGs before starting balixafortide infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
- IWRS/IRT registration.

Cycle 2 only:

- Blood sample for PK taken immediately before starting balixafortide infusion (see Section 10.1).

Cycles 3 only:

- Blood samples for exploratory biomarkers taken immediately before starting balixafortide infusion (see Section 11.2.2).

Balixafortide Administration (see Section 6.1).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).

Patients at Selected Sites Only:

Cycle 2 only:

For patients at selected sites, the following additional assessments will be performed:

- Optional tumor biopsy (see Section 11.2.1); alternatively, biopsy can be performed on Day 10 if preferred.
- Blood samples for other exploratory biomarkers in patients at selected sites who are scheduled to have an optional, fresh tumor biopsy (see Section 11.2.2); the blood sample can be taken before or after the biopsy.

7.3.2.8 Day 10

Before Balixafortide Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- IWRS/IRT registration.

Balixafortide Administration (see Section 6.1).

7.3.2.9 Day 21

All patients (from the date of randomization every 6 weeks [±7 days] during the first year, and then every 12 weeks [±7 days] thereafter until PD is documented):

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- CT/MRI scan (see Section 8.2.2). Scans performed to assess progression or response must match the baseline scan (i.e. if CT scan at baseline then CT scan for all other scans).

7.4 Treatment Period—Eribulin Monotherapy Treatment Arm Only

7.4.1 Cycle 1

Patients will start study medication within 3 days from randomization as outlined in the Study Schedule (Section 1.1).

The following procedures and assessments will be performed following randomization.

7.4.1.1 Cycle 1 Day 2

Before Eribulin Administration:

- Patient reported health outcome QoL questionnaires (see Section 11.3).
- Targeted physical examination (see Section 9.6).
- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight.
- ECOG performance status (see Section 9.6).

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration.
- Urine pregnancy test for women of child bearing potential (see Section 5.4.5.1).
- 12-lead ECG before starting eribulin infusion (see Section 9.8).
- IWRS/IRT registration.
- Blood samples for exploratory biomarkers in all patients taken immediately before starting eribulin infusion (see Section 11.2.2).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8).

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- Blood sample for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.4.1.2 Cycle 1 Day 9

Before Eribulin Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration.
- 12-lead ECGs before starting eribulin infusion (see Section 9.8).
- IWRS/IRT registration.
- Blood samples for exploratory biomarkers in all patients taken immediately before starting eribulin infusion (see Section 11.2.2).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8).

7.4.2 Subsequent Cycles

7.4.2.1 Day 2

Before Eribulin Administration:

- Patient reported health outcome QoL questionnaires (see Section 11.3).
- Targeted physical examination (see Section 9.6).
- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight.

- ECOG performance status (see Section 9.6).
- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration).
- Urine pregnancy test for women of child bearing potential (see Section 5.4.5.1).
- 12-lead ECG before starting eribulin infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
- IWRS/IRT registration.

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients to be taken immediately before starting the eribulin infusion (see Section 11.2.2).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).

Patients at Selected Sites Only:

Cycle 3 only:

For patients at selected sites, the following additional assessments will be performed:

- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.4.2.2 Day 9

Before Eribulin Administration:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9); blood test results must be available within 24 hours prior to study drug administration.
- 12-lead ECG before starting eribulin infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).
- IWRS/IRT registration.

Cycle 3 only:

- Blood samples for exploratory biomarkers in all patients to be taken immediately before starting eribulin infusion (see Section 11.2.2).

Eribulin Administration (see Section 6.1).

After Eribulin Administration:

- 12-lead ECG within 1 hour after completing eribulin infusion (see Section 9.8). After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).

Patients at Selected Sites Only:

Cycle 2 only:

For patients at selected sites, the following additional assessments will be performed:

- Optional tumor biopsy (see Section 11.2.1).
- Blood samples for other exploratory biomarkers in patients at selected sites who are scheduled to have an optional, fresh tumor biopsy (see Section 11.2.2); the blood sample can be taken before or after the biopsy.

7.4.2.3 Day 21

All patients (from the date of randomization every 6 weeks [±7 days] during the first year, and then every 12 weeks [±7 days] thereafter until PD is documented):

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1)
- CT/MRI scan (see Section 8.2.2). Scans performed to assess progression or response must match the baseline scan (i.e. if CT scan at baseline then CT scan for all other scans).

7.5 Unscheduled Visit

Additional assessments to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status, or if additional radiographic tumor assessments are required because there is clinical suspicion of disease progression); the findings of an unscheduled examination should be recorded in the patient's source data and eCRF.

7.6 End of Treatment Visit

Patients who discontinue treatment will attend the EoT Visit (i.e. withdrawal) as soon as possible, within 7 days after discontinuation and prior to initiation of any new anti-cancer therapy, regardless of the reason for discontinuation.

All patients:

- Patient reported health outcome QoL questionnaires (see Section 11.3).
- Targeted physical examination (see Section 9.6).
- Vital signs (resting BP, respiratory rate, pulse rate, and body temperature; see Section 9.7).
- Weight.
- ECOG performance status (see Section 9.6).
- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit (see Section 5.4.1).
- 12-lead ECG (see Section 9.8).
- Clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.9).
- Urine pregnancy test for women of child bearing potential (see Section 5.4.5.1).
- CT/MRI scan (see Section 8.2.2) in patients who are discontinued from study medication in the absence of PD; however, patients who have already demonstrated objective PD (according to RECIST v 1.1) do not need to have scans repeated at the EoT visit.

- Blood samples for immunogenicity only for patients from the balixafortide + eribulin treatment arm (see Section 11.1).
- Document reason for treatment discontinuation.
- IWRS/IRT registration.

Patients at Selected Sites Only:

For patients at selected sites, the following additional assessments will be performed:

- Optional tumor biopsy (see Section 11.2.1).
- Blood samples for other exploratory biomarkers in patients at selected sites (see Section 11.2.2).

7.7 30-Day Safety Follow-up

The 30-day safety follow-up visit will be scheduled 30 days (and no later than 37 days) after the last dose of study drug and can be conducted over the telephone. If for any reason the safety follow-up occurs earlier than scheduled (e.g. initiation of new anticancer therapy, withdrawal of consent), the time of the visit should be documented along with the reasons for the early follow-up; the data from these visits will be evaluated separately.

All Patients:

- AE reporting (see Section 9.2).
- Concomitant therapy/medications taken since the previous visit to be recorded for patients with unresolved AEs (see Section 5.4.1).

7.8 Long-term Follow-up

Every effort should be made to collect and record all anti-cancer medicines that the patient receives during Long-term Follow-up in the patient's source data and eCRF until the end of study.

7.8.1 PD Follow-up

Regardless of treatment arm, patients who are discontinued from study medication for any reason, in the absence of PD, will undergo repeat imaging and tumor response assessments (including CT/MRI scans, see Section 8.2.2) every 8 weeks ±7 days (every 12 weeks ±7 days if the patient has been on the study for ≥1 year) until PD is documented as per RECIST v1.1, or death occurs, or patient is lost to follow-up, or the patient withdraws consent (whichever occurs first). If a patient stops study medication and begins other anti-cancer therapy before PD is documented, every effort should be made to perform tumor evaluation in these patients until disease progression. CT/MRI scan (see Section 8.2.2) performed to assess progression must match the baseline scan (i.e. if CT scan at baseline then CT scan for all other scans).

7.8.2 Survival Follow-up

The Investigator will monitor the patient for OS status every 6 months (or more frequently) until death, until the patient withdraws consent to follow-up for survival, or until the patient is lost to follow-up (whichever occurs first). Survival follow-up can be conducted by telephone.

7.9 Duration of Study Participation

Patients will attend the study site for the Screening Visits between Day -21 to -1 and then as outlined in the Study Schedule Section 1.1.

Patients will initiate treatment and will continue, as assigned at randomization, until PD by RECIST v1.1 criteria is met or until one of the treatment discontinuation or study withdrawal criteria, outlined in Section 5.3 is met.

Patients who discontinue randomized treatment for any of these reasons will be required to attend an EoT Visit (Section 7.4) and a 30-Day Safety Follow-up (Section 7.7). Patients who have not withdrawn from the study will be entered into the Long-term Follow-up phase (Section 7.8) for the determination of PFS and OS, until the first occurrence of any of the below:

- Death.
- Loss to follow-up.
- Withdrawal of consent.

To generate the required number of PFS events for the main analysis, a 12-month recruitment period is anticipated with an expected follow-up period of 12-months after the last patient is randomized. Patients are expected to be followed for one additional year for OS. The study is planned to begin during the first quarter of 2019.

7.10 End of Study Definition

The end of the active treatment phase of the study is defined as the date the last patient completes the safety follow-up period (i.e. 30 days [±7 days] after the last study drug administration).

The end of the study (study completion) is defined as the date on which all patients have completed the 30-day Safety Follow-up and when the final OS analysis is completed, this is expected to be 2 years after the last patient is enrolled on study.

In the opinion of the Investigator, those patients who continue to derive benefit from study medication, at the end of the study, will be able to continue receiving study medication on an individual basis (e.g. separate protocol, or Polyphor providing study medication to the Investigator as per local regulations).

8. ASSESSMENT OF EFFICACY

The Study Schedule of Assessments and sampling are outlined in Section 1.1.

Tumor response will be assessed locally and centrally.

8.1 Independent Review of Disease Response

A blinded IRC will perform a retrospective review of radiographic images and clinical information collected on-study to verify the protocol defined endpoints of disease response and progression as assessed by the Investigator.

It is important that all specified imaging studies and clinical information (including photographs) are forwarded to the IRC as each patient enrolls and progresses through the study.

Information on materials to be forwarded to the IRC, correct procedures for the coding/blinding of the patient's name/identity, and the return of the source data/documents to the site is provided in the imaging plan.

8.2 Tumor Assessments

The Study Schedule of Assessments and sampling are outlined in Section 1.1. Since the primary endpoint of the study is PFS, it is critical that tumor assessments are performed according to the Study Schedule in a timely and complete manner to allow full comparability of the two treatment arms. To prevent the introduction of any bias into the efficacy results, the assessment must be performed according to the calendar regardless of any dosing delay or interruption. Imaging assessments will be scheduled using the randomization date as the reference date for all timepoints and NOT scheduled according to the date of the previous imaging timepoint. A delay in the imaging assessment to accommodate a treatment delay is not permitted. Incomplete assessment and/or wrong timing (out of Schedule) will result in the inability to accurately assess disease status for that timepoint. CT/MRI scan will be used to measure target lesions that are selected for response assessment. For a given patient/tumor lesion, the same technique for tumor assessment MUST be used throughout the study.

8.2.1 Screening or Baseline Tumor Assessment

The date and results of the patient's last CT/MRI scan and bone scan will be recorded in the patient's source data and eCRF. If no CT/MRI scan has been performed in the 30 days prior to Randomization a CT/MRI scan must be performed during Screening. Similarly, if no bone scan has been performed in the 30 days prior to Randomization a bone scan must be performed during Screening.

CT/MRI scan will be used to measure target lesions that are selected for response assessment. For a given patient/tumor lesion, the same technique for tumor assessment MUST be used throughout the study. Guidance on measurability of tumors at baseline and documentation at baseline is provided in Appendix 3 Summary of RECIST v1.1 Guidelines.

The following scans must be available for all patients at Screening/Baseline:

- CT/MRI scan of the chest, abdomen, and pelvis.
- CT/MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the eCRF.
- Bone scans in order to detect bony sites of disease. Any suspicious abnormalities (i.e. hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan or MRI scan.
- Baseline brain CT/MRI is only required if signs and symptoms suggest the presence of metastatic brain disease or if the patient has a history of stable metastatic brain disease (Section 5.1).

8.2.2 Post-baseline Tumor Assessments

Tumor assessments are to be scheduled using the randomization date as the reference date for all timepoints; tumor assessments are NOT to be scheduled according to the timepoint of the previous tumor assessment.

From the date of randomization, patients will be evaluated according to RECIST v1.1 for CR, PR, SD, or PD based on CT/MRI scans performed every 6 weeks (±7 days) during the first year, and then every 12 weeks (±7 days), thereafter, until PD is documented by RECIST v1.1. The RECIST v1.1 definitions of the criteria used to determine tumor response for target lesions are provided in Table 5 and for non-target lesions in Table 6. Table 7 provides a summary of the overall response calculation that is to be used at each response assessment timepoint specified in the Study Schedule for patients who have measurable disease at baseline. When patients have non-measurable disease only, Table 8 is to be used. Further information is summarized in Appendix 3 Summary of RECIST v1.1 Guidelines.

Table 5 Determination of Objective Tumor Response for Target Lesions

Tumor Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum of diameters of target lesions recorded on stud*y (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 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Source: (55)

Further details can be found in Appendix 3 Summary of RECIST v1.1 Guidelines.

Table 6 Determination of Tumor Response for Non-target Lesions

Tumor Response	Evaluation of Non-target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Progressive Disease (PD)	Unequivocal progression (see Appendix 3 Summary of RECIST v1.1 Guidelines) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Source: (55)

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the timepoints specified in the Study Schedule. Further details can be found in Appendix 3 Summary of RECIST v1.1 Guidelines.

Table 7 Determination of Overall Response at each Timepoint specified in the Study Schedule 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	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.
Source: (55)

Further details can be found in Appendix 3 Summary of RECIST v1.1 Guidelines.

Table 8 Determination of Overall Response at each Timepoint specified in the Study Schedule 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[a]
Not all evaluated	No	Not evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR: complete response; PD: progressive disease; SD: stable disease

Source: (55)

a. `Non-CR/Non-PD' is preferred over `stable disease' for non-target disease because SD is used as an endpoint for assessment of efficacy so to assign this category when no lesions can be measured is not advised.

Further details can be found in Appendix 3 Summary of RECIST v1.1 Guidelines.

At the discretion of the Investigator, additional radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression; the results of an unscheduled scan must be recorded in the patient's source data and eCRF. The methodology used for scans to assess progression or response must be the same as those used for the baseline scan (i.e. if CT scan at baseline then CT scan for all other scans).

The local Investigator will assess the presence of disease following CT/MRI scan performed at Screening, and those performed subsequently, and record the details in the patient's source data and eCRF relative to the previous assessment of disease status/metastatic burden.

Following initial documentation of an objective response, a confirmatory CT/MRI scan will be performed at least 4 weeks later.

Patients will continue treatment as assigned at randomization until objective PD (according to RECIST v1.1) is documented, there is unacceptable toxicity, death occurs, the patient withdraws consent, or the patient is lost to follow-up (whichever occurs first).

CT/MRI will be performed at the EoT visit in patients who are discontinued from study medication in the absence of PD; however, patients who have already demonstrated objective PD according to RECIST v 1.1 do not need to have scans repeated at the EoT visit.

Regardless of regimen, patients who are discontinued from study medication for any reason in the absence of PD, will also undergo repeat imaging and tumor response assessments (including CT/MRI scans) every 8 weeks ±7 days (every 12 weeks [±7 days] if the patient has been on the study for ≥1 year), until PD is documented as per RECIST v1.1, or death occurs, or patient is lost to follow-up, or the patient withdraws consent (whichever occurs first). If a patient stops study medication and begins another anti-cancer therapy before PD is documented, every effort should be made to perform tumor evaluation in these patients until disease progression. Every effort should be made to collect and record all anti-cancer medicines that the patient receives during Long-term Follow-up in the patient's source data and eCRF until the end of the study.

Patients who progress radiologically according to RECIST v1.1, but who are deemed by the Investigator to be clinically benefiting from study medication may continue that study medication at the discretion of the Investigator; a PD confirmatory scan will be done at least 6 weeks after the last scan to identify potential pseudo-progression according to iRECIST (56) (Appendix 4 Summary of iRECIST Guidelines). If progression is not confirmed, tumor reassessment should continue as originally planned according to the Study Schedule.

Post-baseline scans will include:

- CT/MRI scan of the chest, abdomen, and pelvis.
- CT/MRI scan of any other sites of disease as identified at Baseline.
- Clinical assessment of sites of superficial disease identified at Baseline. Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the eCRF.
- Bone scans will be performed at the discretion of the Investigator (e.g. to confirm CR, to follow up existing metastases, or if [based on signs and symptoms] new bone metastases are suspected). Any suspicious abnormalities (i.e. hotspots) will be confirmed by X-ray, CT scan or MRI (if applicable, using the same method used to confirm the bone lesions at Baseline).
- Brain CT/MRI is only required if signs and symptoms suggest the presence of metastatic brain disease or if the patient has a history of stable metastatic brain disease (Section 5.1).

8.2.3 Further Information for CT/MRI Scans

CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contra-indicated for medical reasons. If IV contrast is medically contra-indicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the Investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contra-indicated. In such cases, CT will be performed without contrast. If MRI is used to follow-up bone lesion(s), it must be performed a few days before any treatment that may affect bone-marrow cellularity (e.g. G-CSF).

The same method and technique should be used to characterize each lesion identified and reported at Baseline, during the study treatment phase, and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays) is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

For patients having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment eCRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion CRF.

8.3 Efficacy Parameters

The evaluation of disease response will be conducted according to RECIST v1.1 guidelines.

8.3.1 Progression Free Survival

The primary efficacy variable for this study is time to PFS, based on an assessment by the IRC. A supportive analysis of PFS will be performed based on the local Investigator's review.

PFS is defined as the time from the date of randomization to the earliest evidence of documented PD or death from any cause.

8.3.2 Overall Survival

OS is defined as the time from date of randomization in this study to date of death due to any cause. Patients without a death date will be censored at the date the patient was last known to be alive.

The Investigator will monitor the patient for OS status, for the remainder of the study period, as described in Section 7.

8.3.3 Objective Response Rate

ORR is defined as the proportion of patients with a confirmed CR + confirmed PR. The ORR will be assessed according to RECIST v1.1 guidelines by the IRC and by the local Investigator's review and will be based on the best response assessed.

8.3.4 Time to Response

Time to response is defined as the time from date of randomization to the time of first documented CR or PR as assessed by the IRC and by the local Investigator's review.

8.3.5 Duration of Response

Duration of response is defined as the time from first documented CR or PR until the earliest evidence of disease progression or death from any cause based on the IRC review and the local Investigator's review.

8.3.6 Clinical Benefit Rate

CBR is defined as the proportion of patients with confirmed CR, confirmed PR, or SD for ≥6 months. The CBR will be assessed according to RECIST v1.1 guidelines by the IRC and by the local Investigator's review. CBR will be compared between the treatment arms using logistic regression as described for ORR. Exact Clopper Pearson 2-sided 95% confidence limits will be calculated for the CBR of each treatment arm.

8.3.7 Disease Control Rate

DCR is defined as the number of patients with confirmed CR, confirmed PR, or SD. The DCR will be assessed according to RECIST v1.1 guidelines by the IRC and by the local Investigator's review.

9. ASSESSMENT OF SAFETY

9.1 Safety Assessments

Safety assessments will consist of monitoring all AEs, including SAEs (Section 9.2), regular monitoring of hematology, serum chemistry (Section 9.9), renal function, liver function, ECGs

(Section 9.8), physical examinations (Section 9.6), vital signs (Section 9.7), and ECOG performance status (Section 9.6).

Comprehensive assessment of any apparent AE experienced by the patient will be performed throughout the course of the study, from the time that the patient receives the first dose of study medication until 30 days after the last study drug administration; SAEs will be recorded from the date that the ICF is signed.

Study site personnel will report any AE, whether observed by the Investigator or reported by the patient.

AE assessment will include type, incidence, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5.0, see Section 9.2.3, Severity Assessment), timing, seriousness, and relatedness.

Adverse Events of Particular Interest and Adverse Events of Special Interest

AEPIs include all events of special interest and additionally, all events for which a separate analysis will be performed (Table 9).

AEPIs are based on the emerging AE profile of balixafortide or on the established risks associated with eribulin.

All grade events of thrombocytopenia, peripheral neuropathy, hepatic impairment and QTc interval prolongation have been identified as AEPIs.

Serious events of IRRs, neutropenia and infection, and all cases of renal impairment will be considered AESIs, as well as being AEPIs.

AESIs are to be reported by the Investigator to the Sponsor within **24 hours** of learning of the event.

AESIs must be reported using the same form as for SAEs and notified to the Sponsor within **24 hours** of the Investigator becoming aware of the event, irrespective of causality with the study drug.

Table 9 AEs of Particular Interest and AEs of Special Interest

Adverse Events of Particular Interest	Definition
Thrombocytopenia	Defined using SMQ "Haematopoietic Thrombocytopenia narrow". SMQ code 20000031
Peripheral neuropathy	Defined using SMQ "Peripheral neuropathy narrow" SMQ code 20000034
Hepatic impairment	Defined using SMQ "Liver related investigations, signs and symptoms (SMQ) narrow" SMQ code 20000008
QTc prolongation	Defined using SMQ "Torsade de pointes/QT prolongation "SMQ code 20000001
Hypersensitivity/IRRs	IRRs are defined as AEs that are deemed related to any study treatment by the Investigator, which occurred during infusion or within 24 hours from the end of infusion. Note: IRRs encompass AEs reported as the MedDRA PT "Infusion related reaction" (within the SOC "Injury, Poisoning and Procedural Complications") together with reported signs and symptoms of IRRs
Neutropenia (serious)	Based on reported AEs rather than laboratory values. Defined using SMQ "Haematopoietic Cytopenia" SMQ code 20000027
Neutropenic infections	Defined by PT neutropenic infection
Febrile neutropenia	Defined by the PT febrile neutropenia
Renal impairment	Defined using SMQ "Acute renal failure" SMQ code 20000003
Adverse Event of Special Interest	**Definition**
Hypersensitivity/IRRs (serious)	IRRs are defined as AEs that are deemed related to any study treatment by the Investigator, which occurred during infusion or within 24 hours from the end of infusion. Note: IRRs encompass AEs reported as the MedDRA PT "Infusion related reaction" (within the SOC "Injury, Poisoning and Procedural Complications") together with reported signs and symptoms of IRRs
Neutropenia (serious)	Based on reported AEs rather than laboratory values
Neutropenic infections	Defined by PT neutropenic infection
Febrile neutropenia	Defined by the PT febrile neutropenia
Renal impairment	Defined using SMQ "Acute renal failure" SMQ code 20000003

AE: adverse event; IRR: infusion-related reaction; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QTc: corrected QT interval; SMQ: Standardized MedDRA query; SOC: system order class.

Baseline tumor-related signs and symptoms will be recorded at the Cycle 1, Day 1 visit and then reported as AEs (Section 9.2.5) during the study if they worsen in severity or increase in frequency.

9.2 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study drug(s) must be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE, and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and the Sponsor concurs with that assessment.

If a patient opts to discontinue from the treatment phase because of an unacceptable AE, "Withdrawal of Consent" must not be the reason for discontinuation, rather, the reason for discontinuation must be recorded as "Unacceptable Toxicity". Details of the AE leading to the patient's withdrawal of consent and the action taken must be completed on the AE CRF. AEs must be reported in accordance with the reporting requirements defined in Section 9.2.5.

9.2.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation of a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered the AE rather than the procedure itself.

Examples of AEs include but are not limited to:

- Clinically significant signs and symptoms.
- Changes in physical examination findings.
- Abnormal test results.
- Signs and symptoms resulting from circumstances such as drug overdose, misuse, interaction, exposure during pregnancy, medication errors or occupational exposure.
- Hypersensitivity.

Pre-existing conditions
Medical conditions that present at Screening, and do not worsen in severity or frequency during the study, are defined as Baseline Medical Conditions and are NOT to be considered AEs. Findings discovered during Screening must be recorded as part of Medical History and any pre-planned intervention or procedure to occur during the study recorded in the patient's source data and eCRF.

Malignancy under study
Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the patient's source data and eCRF; tumor assessments may be

done at any time if there is clinical suspicion of disease progression (Section 8.2.2). Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings
Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are clinically meaningful or associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfils these criteria, the identified medical condition (e.g. anemia, hepatitis) must be reported as the AE rather than the abnormal value itself.

9.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).
- Results in congenital anomaly/birth defect.
- Is otherwise considered as medically important.

The term “life-threatening” in this definition refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization
Hospitalization is defined as initial admission in a hospital or similar healthcare facility, or any prolongation of an existing hospitalization. Hospitalization (or prolongation of hospitalization) in the absence of a precipitating, clinical AE is not in itself an SAE. An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance. Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient.

Progression of malignancy under study
Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period (see Section 9.2.5.1). Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or

within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with NCI CTCAE Grade 5 in the patient's source data and eCRF (see Section 9.2.3).

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

9.2.3 Severity Assessment

The Investigator will report AEs using concise medical terminology (verbatim) as well as the appropriate severity graded according to NCI CTCAE version 5.0 on the patient's source data and eCRF and will use the following definitions of severity to describe the maximum intensity of the AE:

- **Grade 1 Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 Moderate**; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1].
- **Grade 3 Severe or medically significant but not immediately life-threatening**; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- **Grade 4 Life-threatening consequences**; urgent intervention indicated.
- **Grade 5 Death related to AE**.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function), but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

9.2.4 Causality Assessment

Investigators must also systematically assess the causal relationship of AEs to the study drugs using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study medications include, but may not be limited to, temporal relationship between the AE and the study medications, known side effects of trial treatments, medical history, concomitant medication, course of the underlying disease, study procedures.

- **Not related:** Not suspected to be reasonably related to the study medications. AE could not medically (pharmacologically/clinically) be attributed to the study medications under study in this clinical trial protocol. A reasonable alternative explanation must be available.

[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

- **Related:** Suspected to be reasonably related to the study medications. AE could medically (pharmacologically/clinically) be attributed to the study drug under trial in this clinical study.

If the Investigator's causality assessment is unknown but not related, this must be clearly documented on study records, including the patient's source data and eCRF. If the Investigator does not know whether or not the study drug caused the event, then the event will be conservatively handled as "related" to the study drug.

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and the patient's source data and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

9.2.5 Reporting Requirements

9.2.5.1 Serious Adverse Event Reporting

For SAEs, the active reporting period to Sponsor begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study (i.e. prior to undergoing any study-related procedure and/or receiving study drug) through and including 30 calendar days after the last administration of the study drug.

If an SAE occurs, the Sponsor is to be notified within **24 hours** of the Investigator becoming aware of the event. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports, as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the patient's AE source data and eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor.

SAEs occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

9.2.5.2 Non-Serious Adverse Event Reporting

AEs must be recorded on the patient's source data and eCRF from the time the patient has taken at least one dose of study drug through to the patient's safety follow-up visit at 30 days (±7 days) after the last dose of study drug. AEs should be reported using concise medical terminology. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually.

All events should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first. If a patient begins a new systemic anti-cancer therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.2.5.3 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will conduct appropriate safety reporting to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her patients to the IEC/IRB that approved the study.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could adversely affect the safety of patients, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study." In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator must place copies of Safety Reports in the Investigator Site File (ISF). National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor and of filing copies of all related correspondence in the ISF.

For studies covered by the European Commission legislation the Sponsor responsibilities will be carried out in accordance with the applicable legislation.

9.2.6 Monitoring and Management of AESIs and AEPIs

9.2.6.1 Potential Cases of Drug-induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

- Patients with baseline AST or ALT and total bilirubin values within the normal range who subsequently present with AST or ALT values ≥3x ULN concurrent with a total bilirubin value ≥2x ULN with no evidence of hemolysis and an alkaline phosphatase (ALP) value ≤2x ULN or not available.

- For patients with pre-existing ALT or AST or total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with pre-existing baseline AST or ALT values above the normal range: AST or ALT values ≥2x the baseline values and ≥3x ULN, or ≥8x ULN (whichever is smaller).
- For patients with pre-existing values of total bilirubin above the normal range:

- Total bilirubin level increased from baseline by an amount of at least 1x ULN or if the value reaches ≥3x ULN (whichever is smaller).

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase (CK), total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time/international normalized ratio (INR), and ALP. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected.

Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases must be reported as SAEs (see Section 9.2.5.1).

9.2.6.2 QT Prolongation

In the event of a QT prolongation, possible alternative reversible causes such as serum electrolyte abnormalities, or concomitant medications with the potential to prolong the QT interval (Appendix 1 Prohibited Medications) should be evaluated. If such reversible causes are identified, they should be corrected accordingly (i.e. correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation of concomitant medications known to prolong the QT interval).

At the first occurrence of a QTc interval >480 msec and ≤500 msec (Grade 2), Investigators should identify and treat alternative reversible causes and initiate more frequent ECG monitoring according to the Investigator's best medical judgement until QTc ≤480 msec. Dosing of the study drug can continue. However, if the QTc interval remains >480 msec or reoccurs in the absence of alternative causes or despite their correction, specialist cardiologist consultation should be arranged, and treatment continuation discussed with the cardiologist and Medical Monitor.

If at any time the mean QTcF is prolonged (≥501 msec on at least two separate ECGs, [i.e. CTCAE Grade ≥3]), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading confirms a QTc of ≥501 msec, immediate search for reversible causes (including electrolyte abnormalities, and concomitant medications for drugs with the potential to prolong the QT interval [see Appendix 1 Prohibited Medications]) must be performed.

If QTc interval reverts to <501 msec, and, in the judgment of the Investigator(s) in consultation with the Sponsor, the cause is determined to be due to cause(s) other than study drugs, treatment may be continued with appropriate ECG monitoring.

If a prolonged QTcF interval ≥501 msec is confirmed, study drug will be held until the QTc interval decreases to <501 msec.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (e.g. change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

Events of QT prolongation >480 msec, or otherwise considered clinically significant, must be reported as AEs.

9.2.6.3 Infusion-Related Reactions

Acute IRRs and hypersensitivity events due to histamine release, such as rash, pruritus, erythema and flushing may occur. The majority of hypersensitivity events in the earlier studies occurred during first administration and were generally dose dependent.

All patients should be observed during the infusion of balixafortide and recommended dosage and infusion duration closely adhered to. An antihistamine kit must be kept available for immediate intervention in case of IRRs. Prophylactic use of H_1 receptor antagonists may be used for premedication at the discretion of the treating physician.

For management of IRRs:

- The balixafortide infusion should be interrupted and vital signs monitored until the IRR resolves to Grade ≤1 and then the infusion can be restarted at a slower rate.
- Treatment with antihistamines and methylprednisolone can be initiated, or other treatments can be given as necessary in line with the patient's condition and local standard of care.
- The patient can be pre-treated with antihistamines prior to the next balixafortide infusion.
- If the IRR continues, the balixafortide infusion rate can be slowed down to 3 hours and if not resolved, the Sponsor contacted.

When anaphylaxis is suspected and/or confirmed, treatment with epinephrine must be initiated immediately. In case of severe reactions, the infusion of balixafortide should be stopped immediately and treatment discontinued permanently.

AEs of IRRs and hypersensitivity must be captured on the patient's source data and AE eCRF page, along with their signs and symptoms. If dosing is interrupted, discontinued or the patient is withdrawn from the study as a result of an infusion site reaction, this must be recorded in the patient's source data and eCRF.

9.2.6.4 Neutropenia

Risk factors for febrile neutropenia in addition to those posed by eribulin and advanced BC are shown in Table 10. From Day 2, Cycle 1, this study requires adherence to the ASCO guidelines for minimizing the incidence of febrile neutropenia, including the recommended prophylactic use of CSFs, where appropriate at the discretion of the Investigator (Appendix 7 ASCO Guidance on the Use of CSFs) (54).

Table 10 Patient Risk Factors for Febrile Neutropenia

Risk Factor[a]
Age ≥65 years
Advanced disease
Previous chemotherapy or radiation therapy
Pre-existing neutropenia or bone marrow involvement with tumor infection
Open wounds or recent surgery
Poor performance status or poor nutritional status
Poor renal function
Liver dysfunction, most notably elevated bilirubin
Cardiovascular disease
Multiple comorbid conditions
HIV infection

HIV: human immunodeficiency virus

Source: (54)

a: When estimating a patient's overall risk of febrile neutropenia, consider these risk factors in addition to those posed by eribulin and advanced breast cancer.

Severe neutropenia (ANC<500/mm^3) lasting more than 1 week occurred in 12% of patients who received eribulin in the EMBRACE study, leading to discontinuation in <1% of patients (43). The mean time to nadir was 13 days and the mean time to recovery from severe neutropenia with eribulin was 8 days. Febrile neutropenia occurred in 5% of patients treated with eribulin.

Patients with ALT or AST >3x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia with eribulin than patients with normal aminotransferase levels. Patients with bilirubin >1.5x ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia with eribulin.

If the ANC is <1000/mm^3, refer to guidance on dose modifications and interruptions with eribulin in Section 6.1.2.

Local guidance on management of neutropenic infections should be consulted. Guidance on outpatient management of fever and neutropenia in patients treated for malignancy is provided by ASCO (57).

9.2.6.5 Thrombocytopenia

Guidance on platelet transfusions in patients with cancer is provided by ASCO (58).

9.2.6.6 Peripheral Neuropathy

Grade 3 and Grade 4 peripheral neuropathy occurred in 8% and 0.4% of patients who received eribulin respectively (43). Peripheral neuropathy led to discontinuation of eribulin in 5% of patients and neuropathy lasting more than 1 year occurred in 5% of patients.

Patients should be monitored closely for signs of peripheral motor and sensory neuropathy. If Grade 3 or 4 peripheral neuropathy develops, refer to guidance on dose modifications and interruptions with eribulin in Section 6.1.2.

9.2.6.7 Renal Impairment

If renal function changes or worsens under treatment with balixafortide, a review of all medication and medical conditions potentially contributing to renal impairment should be done. Standard medical care principals should be applied to stabilize kidney function (e.g. fluid management and the use of diuretics if appropriate).

9.3 Exposure During Pregnancy

An exposure during pregnancy occurs if a female becomes, or is found to be, pregnant either while receiving or having been exposed (e.g. because of treatment or environmental exposure) to the study drugs; or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the study drugs. An example of environmental exposure would be a case involving direct contact with a study product in a pregnant woman (e.g. a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

If a study patient or study patient's partner becomes, or is found to be, pregnant during the study patient's treatment with the study drugs, the Investigator must submit this information to the Sponsor on the Pregnancy Reporting Form, regardless of whether an AE or SAE has occurred. In addition, the Investigator must submit information regarding environmental exposure to a study product in a pregnant woman (e.g. a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the designated Pregnancy Reporting Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all in utero exposure reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor of the outcome as a follow-up to the initial pregnancy report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e. ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator must follow the procedures for reporting SAEs.

In the event of a pregnancy in a patient occurring during the course of the study, the patient must be discontinued from study medication immediately. The Sponsor must be notified without delay and the patient must be followed up as mentioned above.

9.4 Medication Errors

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Medication errors may result from administration or consumption of the study drug(s) by the wrong patient, wrong time or at the wrong strength. Medication errors include medication errors involving patient exposure to the study drug, as well as potential medication errors or uses outside what is foreseen in the protocol that do, or do not involve the study patient.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is captured on the medication error version of the patient's source data and eCRF page and, if applicable, any associated AE(s) are captured on the patient's source data and eCRF. In the event of an SAE resulting from a medication error, the Sponsor must be notified immediately in alignment with the SAE reporting process (see Section 9.2.5.1).

9.5 Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the study product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the Medical Monitor within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a Case Report Form (CRF); however, a copy of the completed SAE Report form must be maintained in the ISF.

9.6 Physical Examination

A standard, complete physical examination will include an examination of all major body systems (including general appearance, head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at Screening only), weight, BP, and pulse rate; it may be performed by a physician, registered nurse or other qualified health care provider (as delegated in the Study Site Log).

A targeted physical examination will include an examination of general appearance, skin (including presence of rash), lungs and heart, extremity examination for the presence of peripheral edema, abdominal if relevant, neurologic (particularly motor and sensory function, coordination), and lymph nodes in addition to specific areas of interest based on sites of disease.

A standard, complete physical examination will be performed in all patients at Screening.

A targeted physical examination will be performed on Day 1 of each cycle for patients on the balixafortide + eribulin treatment arm and on Day 2 of each cycle for patients on the eribulin monotherapy treatment arm. The assessment should be done prior to administration of study medication.

A targeted physical examination will also be performed in all patients at the EoT visit.

Additional physical examinations to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled physical examination should be recorded in the patient's source data and eCRF.

Height will be assessed and recorded in all patients at Screening only.

Weight will be assessed in all patients at Screening and at the EoT visit. Weight will also be assessed on Day 1 of each cycle for patients on the balixafortide + eribulin treatment arm and on Day 2 of each cycle for patients on the eribulin monotherapy treatment arm. The assessment should be done prior to administration of study medication.

Furthermore, during physical examinations, special attention should be paid to the development of any signs of peripheral neuropathy that could warrant eribulin dose modifications or delays as described in Sections 6.1.2 and 6.1.2.1.

ECOG Performance Status Assessment

To be eligible for entry into this study, patients must have an ECOG Performance Status of 0-2 at Screening. The ECOG Performance Status will be recorded in all patients at the Screening Visit and at the EoT visit.

The ECOG Performance Status will also be recorded on Day 1 of each treatment cycle in patients on the balixafortide + eribulin treatment arm and on Day 2 of each cycle for patients on the eribulin monotherapy treatment arm. (The assessment should be done prior to administration of study medication).

The ECOG Performance Status assessment is provided in Appendix 2 ECOG Performance Status.

9.7 Vital Signs

Body temperature, resting BP, respiratory rate, and pulse rate will be measured and recorded as vital signs.

Vital signs will be assessed in all patients at Screening, and at the EoT visit.

Vital signs will also be assessed on Day 1 of each cycle for patients on the balixafortide + eribulin treatment arm and on Day 2 of each cycle for patients on the eribulin monotherapy treatment arm. The assessment will be done prior to administration of study medication. Additional measures of vital signs to those scheduled for this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled assessment should be recorded in the patient's source data and eCRF.

Vital signs measured in the event of an infusion reaction should also be recorded in the patient's source data and eCRF.

BP will be measured in the patient's arm and recorded to the nearest mmHg. The same arm and position should be used throughout the study, using an appropriate cuff size. All BP readings should be measured in the supine position after resting for at least 5 minutes. When the timing of these measurements coincides with blood collection, the BP and heart rate should be obtained first.

Any clinically relevant abnormalities in vital signs at Screening must be handled as Pre-existing Conditions as outlined in Section 9.2.1.

9.8 12 Lead Electrocardiogram

An ECG will be performed at the clinical site during the visits and timepoints shown in Table 11.

Table 11 ECG Schedule

Treatment Arm	Visit	Day	ECG Timepoint	ECG Type
All	Screening	-21 to -1	Anytime	12-lead
Balixafortide + eribulin	Cycle 1	1	Within 1 hour prior to administration of balixafortide	Duplicate 12-lead
Balixafortide + eribulin	Cycle 1	2	Immediately before starting the balixafortide infusion	12-lead
Eribulin monotherapy	Cycle 1	2	Immediately before starting the eribulin infusion	12-lead
All	Cycle 1	2	Within 1 hour after completing the eribulin infusion	12-lead
Balixafortide + eribulin	Cycle 1	9	Immediately before starting the balixafortide infusion	12-lead
Eribulin monotherapy	Cycle 1	9	Immediately before starting the eribulin infusion	12-lead
All	Cycle 1	9	Within 1 hour after completing the eribulin infusion	12-lead
Balixafortide + eribulin	Cycle 2 & subsequent cycles[a]	2	Immediately before starting the balixafortide infusion	12-lead
Eribulin monotherapy	Cycle 2 & subsequent cycles[a]	2	Immediately before starting the eribulin infusion	12-lead
All	Cycle 2 & subsequent cycles[a]	2	Within 1 hour after completing the eribulin infusion	12-lead
Balixafortide + eribulin	Cycle 2 & subsequent cycles[a]	9	Immediately before starting the balixafortide infusion	12-lead
Eribulin monotherapy	Cycle 2 & subsequent cycles[a]	9	Immediately before starting the eribulin infusion	12-lead
All	Cycle 2 & subsequent cycles[a]	9	Within 1 hour after completing the eribulin infusion	12-lead
All	EoT	-	Anytime	12-lead

a: After Cycle 2, the frequency of ECG recordings can be reduced to every 2 cycles if deemed clinically appropriate (i.e. absence of ECG findings in earlier assessments).

Additional ECGs can be performed as clinically indicated at any time and the results recorded in the source data and eCRF.

All ECGs will be performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG measurements will include PR interval, QT interval, QTcF interval, RR interval, and QRS complex. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Patients should be supinely resting for at least 10 minutes before and 5 minutes after timepoints for ECG recordings. When the timing of the ECG coincides with blood collection, the ECG should be obtained first. During treatment, ECGs will be compared to Screening or most recent ECG and any clinically significant changes will be recorded as AEs and evaluated further, as clinically warranted. Episodes of QT prolongation should be managed as described in Section 9.2.6.2.

9.9 Clinical Laboratory Evaluations

Analysis of clinical laboratory samples will be conducted locally. The following parameters will be analyzed for the clinical laboratory tests:

- **Hematology** – WBC count with differential, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Ht), platelet count.
- **Chemistry** – albumin, total protein, ALT, AST, total bilirubin, GGT, ALP, glucose, creatinine, blood urea nitrogen (BUN), CK, calcium (Ca), potassium (K), sodium (Na), and magnesium (Mg).
- **Urinalysis** – appearance, color, dipstick (pH, gravity, ketones, protein, glucose, blood, bilirubin, nitrite, leukocytes). Microscopic analysis if warranted by Dipstick results.

Abnormal laboratory test results considered to be clinically significant shall be recorded as an AE in the patient's source data and eCRF (Section 9.2.1) and the patient will be followed-up until the laboratory value has returned to normal range or stabilized at a non-clinically significant value.

Any additional blood tests to those scheduled in this study should be performed as indicated at the Investigator's discretion (e.g. due to concerns about patient safety, patient's clinical status); the findings of an unscheduled test should be recorded in the patient's source data and eCRF.

10. PHARMACOKINETIC ASSESSMENT

Blood samples will be collected only for the balixafortide + eribulin treatment arm to:

- Evaluate the PK of balixafortide and its metabolite levels in patients on the balixafortide + eribulin treatment arm.

- Support the data from the immunogenicity assessment by evaluating the PK of balixafortide.

Details on sample collection, processing and shipment to Central Laboratories will be provided in a separate laboratory manual.

10.1 Balixafortide + Eribulin treatment arm

For patients who receive eribulin + balixafortide, the blood samples will be taken in relation to the timing of the balixafortide infusion. Blood samples that are to be taken:

- Immediately before starting the balixafortide infusion will ideally be taken within 0−30 minutes before starting the balixafortide infusion.

- Immediately after completing the balixafortide infusion will ideally be taken within 0−15 minutes after completing the balixafortide infusion.

The times at which all blood samples are taken should be documented precisely; this is mandatory for the samples taken during the 1−20 hours timeframe and also the pre and post-dose balixafortide samples.

Blood samples will be collected from *all* patients on the balixafortide + eribulin treatment arm at the visits and timepoints shown in Table 12.

Table 12 Schedule for Pharmacokinetic Assessments of All Patients in the Balixafortide + Eribulin Treatment Arm

Visit Cycle	Day	Timepoint
1	2	Immediately before starting the infusion of balixafortide
1	2	Immediately after completing the infusion of balixafortide
1	2	One additional sample scheduled flexibly with precise recording, at 1−20 hours after completing the infusion of balixafortide on Day 2
1	8[a]	Immediately after completing the infusion of balixafortide
1	9[a]	Immediately before starting the infusion of balixafortide
2	2[a]	Immediately after completing the infusion of balixafortide
2	8[a]	Immediately after completing the infusion of balixafortide
2	9[a]	Immediately before starting the infusion of balixafortide
3	2	Immediately before starting the infusion of balixafortide
3	2	Immediately after completing the infusion of balixafortide
5	2[a]	Immediately after completing the infusion of balixafortide
5	3[a]	Immediately before starting the infusion of balixafortide
7	2[a]	Immediately after completing the infusion of balixafortide

7	3[a]	Immediately before starting the infusion of balixafortide

a: Primarily to support the data from the immunogenicity assessment and used to evaluate the PK of balixafortide and its metabolites.

Additional PK samples, taken up to 48 hours after the last dose in approximately 15 patients, will allow monitoring of drug clearance after dosing has ceased. Therefore, blood samples will be collected from patients at *selected* sites at the visits and timepoints shown in Table 13.

Table 13 Schedule for Pharmacokinetic Assessments of Patients at Selected Sites in the Balixafortide + Eribulin Treatment Arm

Visit Cycle	Day	Timepoint
3	4	24 hours (±4 hours) after completing the balixafortide infusion on Day 3
3	5	44 hours (±4 hours) after completing the balixafortide infusion on Day 3

The plasma concentration of balixafortide will be integrated into the population PK model generated using PK data from previous clinical studies.

11. EXPLORATORY ASSESSMENTS

11.1 Immunogenicity Assessment

To evaluate **immunogenicity** and analyze for anti-drug antibodies, blood samples will be taken from *all* patients on the balixafortide + eribulin treatment arm at the visits and timepoints shown in Table 14. Sampling for immunogenicity is not required for patients in the eribulin monotherapy treatment arm.

Table 14 Schedule for Immunogenicity Assessments for Patients on the Balixafortide + Eribulin Treatment Arm

Visit Cycle	Day	Timepoint
1	1	Immediately before starting the infusion of balixafortide
1	8	Immediately before starting the infusion of balixafortide
2	1	Immediately before starting the infusion of balixafortide
2	8	Immediately before starting the infusion of balixafortide
3	1	Immediately before starting the infusion of balixafortide
Every alternate cycle after Cycle 3	1	Immediately before starting the infusion of balixafortide

EoT	-	Anytime

EoT: end of treatment

To support the immunogenicity evaluation, corresponding PK samples will also be analyzed (Section 10).

Details on sample collection, processing and shipment to Central Laboratories will be provided in a separate laboratory manual.

11.2 Exploratory Biomarkers Assessment

Samples will be tested at laboratories designated by Polyphor. However, all samples will be stored at the PPD laboratories facility. PPD laboratories will be responsible for custody of all samples during the study and after the study, until their destruction.

PPD laboratories will manage sample transfer for testing at third party laboratories (when PPD is not also responsible for testing). After the testing is completed, samples will be returned to PPD for storage. These samples will not be shared with any other party except the laboratories that will perform the testing, and the samples and the data from the testing will only be available to Polyphor and its delegates, IRB representatives, auditors and inspectors.

These samples will be stored until a maximum of 5 years after study termination. Samples will be destroyed after this period. However, the samples may be destroyed at any time if requested by the patient, and in this case no further testing will be done. However, any data collected up to the point that the patient requests sample destruction will still be used for future analysis as defined in this protocol.

11.2.1 Tumor Tissue

All Patients

For patients who have had a previous tumor biopsy at any time, consent will be required to donate this tissue for biomarker assessment. The date of the last tumor biopsy will be documented in the patient's source data and eCRF at Screening. If multiple biopsies are available, it is recommended to collect a sample of each.

If such tumor tissue is not available, then the patient will be requested to provide a fresh tumor biopsy. If a fresh tumor biopsy is not available, the patient's refusal to provide a tumor biopsy or the lack of lesions from which a biopsy can be collected will be documented in the patient's source data and eCRF. Patient refusal to provide fresh tumor biopsy or lack of lesions from which a biopsy can be collected will not limit a patient's participation in this study.

Patients at Selected Sites

Patients can optionally consent to fresh tumor biopsy at Screening and subsequent timepoints (Cycle 2 [Day 9; alternatively, for patients in the balixafortide + eribulin treatment arm, biopsy can be performed on Day 10 if preferred] and at the EoT Visit) as defined in the Study Schedules (Section 1.1). If a biopsy has already been performed within 30 days prior to Randomization and tumor tissue is still available, then the fresh tumor biopsy is not required during Screening.

The patient will not be excluded from the study if they do not grant this consent.

Any trauma and clinical sequelae related to the mechanics of the tumor biopsy should be reported as related to the study procedure.

Tumor tissues will be analyzed for exploratory biomarkers. CXCR4 expression level, based on IHC of archival or fresh biopsy tumor samples, will be assessed and the correlation with efficacy parameters will be explored. In addition, tumor-infiltrating lymphocytes, the ratio of immune-suppressive and immune response stimulating cells, and expression of immune-related markers such as granzyme B may be determined by validated standardized microscopic procedures. RNA expression of such markers may be measured (e.g. by Nanostring technologies). It is recommended that archival formalin-fixed paraffin-embedded tumor samples are provided, ideally from the metastatic lesion, however, a very recent biopsy can be sent if archival specimen is unavailable. Blocks are preferred, however, if this is not possible, then at least 15−20 unstained slides should be prepared for the biomarker analysis.

Details on sample collection, processing, testing procedures and shipment (if required) to Central Laboratories will be provided in a separate laboratory manual.

11.2.2 Biomarkers in Blood or Plasma

All Patients

Blood will be collected from all patients to assess plasma levels of IFN gamma and additional cytokine markers at the visits and timepoints shown in Table 15 for patients in the balixafortide + eribulin treatment arm and in Table 16 for patients in the eribulin monotherapy treatment arm.

Table 15 Schedule for Blood Exploratory Biomarker Assessment of All Patients in the Balixafortide + Eribulin Treatment Arm

Visit Cycle	Day	Timepoint
1	1	Immediately before starting the infusion of balixafortide
1	1	Immediately after completing the infusion of balixafortide
1	2	Immediately after completing the balixafortide infusion, but before administration of eribulin
1	3	Immediately after completing the infusion of balixafortide
1	8	Immediately before starting the infusion of balixafortide
1	9	Immediately before starting the infusion of balixafortide
3	1	Immediately before starting the infusion of balixafortide
3	1	Immediately after completing the infusion of balixafortide
3	2	Immediately after completing the balixafortide infusion, but before administration of eribulin
3	3	Immediately after completing the infusion of balixafortide
3	4	24 hours (±4 hours) after completing the balixafortide infusion on Day 3 only in those patients scheduled to have PK sampling at these times (Section 10.1)

Visit Cycle	Day	Timepoint
3	5	44 hours (±4 hours) after completing the balixafortide infusion on Day 3 only in those patients scheduled to have PK sampling at these times (Section 10.1)
3	8	Immediately before starting the infusion of balixafortide
3	9	Immediately before starting the infusion of balixafortide

PK: pharmacokinetic

Table 16 Schedule for Blood Exploratory Biomarker Assessment of All Patients in the Eribulin Monotherapy Treatment Arm

Visit Cycle	Day	Timepoint
1	2	Immediately before starting the infusion of eribulin
1	9	Immediately before starting the infusion of eribulin
3	2	Immediately before starting the infusion of eribulin
3	9	Immediately before starting the infusion of eribulin

A re-evaluation of the sampling schedule may take place based on the initial evaluation of biomarker levels.

Patients at Selected Sites

Additional blood will be collected to assess other exploratory biomarkers from patients at selected sites as described in the Study Schedule (Section 1.1). For patients on the balixafortide + eribulin treatment arm samples will be taken during:

- Cycle 1 (Days 1, 2, and 8).
- Cycle 2 (Day 9, only in patients who are scheduled to have an optional, fresh tumor biopsy; the blood sample can be taken before or after the biopsy).
- Cycle 3 (Days 1 and 2).
- EoT visit.

For patients on the eribulin monotherapy treatment arm samples will be taken during:

- Cycle 1 (Day 2).
- Cycle 2 (Day 9, only in patients who are scheduled to have an optional, fresh tumor biopsy; the blood sample can be taken before or after the biopsy).
- Cycle 3 (Day 2).
- EoT visit.

Sampling schedule may change according to the technical requirements of the methods which are in place at the selected sites. The blood biomarker analyses may include, but is not limited to, enumerating surface marker characterization, RNA expression (e.g. by Nanostring), and genomic profiling of circulating tumor cells and cells of the leukocyte fraction (including cells participating in immune responses). In addition, receptor occupancy of balixafortide on circulating cells by flow cytometric methods may be performed. Further biomarker

assessments may include typology and quantification of circulating deoxyribonucleic acid (DNA) and miRNA. Blood samples can be treated post collection, *ex vivo*, with immunostimulants to determine the immune competence (e.g. by the True Culture system) followed by determination of released factors.

This study may include additional, optional biomarker components which must be supported by an exploratory objective. Such studies are hypothesis generating (e.g. from current and future research) and are optional to the patient.

Details on sample collection, processing and shipment (if required) to Central Laboratories will be provided in a separate laboratory manual.

11.3 Patient Reported Outcomes

Patient reported outcomes (PROs) of health-related QoL and health status will be assessed using the EORTC-QLQ-C30, FACT-B and EQ-5D instruments. Patients will complete each instrument at the Screening Visit and at the EoT visit. Patients on the balixafortide + eribulin treatment arm will also complete each instrument pre-dose on Day 1 of each cycle. Patients on the eribulin monotherapy treatment arm will also complete each instrument pre-dose on Day 2 of each cycle. These instruments should be completed in the same sequence at each scheduled assessment.

During the study treatment phase, patients must complete these instruments in clinic (cannot be taken home) and prior to having any clinical assessments, drug dosing, diagnostic testing, and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic may be used under special circumstances (e.g. patient forgot their glasses or feels too ill).

The EORTC-QLQ-C30 is a validated instrument to measure QoL and assess symptoms and side effects of treatment and their impact on everyday life. The instrument is composed of 5 multi-item functional scales (physical, role, social, emotional and cognitive functioning), a global health status/QoL scale, 3 symptom scales (fatigue, nausea/vomiting and pain), and 6 single items (financial difficulties, appetite loss, diarrhea, constipation, insomnia and dyspnea).

PROs of health-related QoL and health status will be assessed using the FACT-B and EQ-5D instruments. The FACT-B and EQ-5D will be given to the patient in the appropriate language.

The EQ-5D consists of two parts, the EQ-5D descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

FACT-B is a self-administered questionnaire designed for patient suffering from BC. It consists of 5 subscales (physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing, breast subscale)

This data will be collected via electronic diaries or electronic data capture. Completed questionnaires are always considered source document and must be filed accordingly.

12. STATISTICS

12.1 General Statistical Methods

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

All statistical analyses will be carried out using Statistical Analysis System (SAS) version 9.3 (or later). The SAP will be written and finalized prior to the first patient randomized. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

The data from this study will serve a dual purpose:

(i) To provide efficacy and safety data in the Overall Population, who receive study medication as 2nd to 5th line of therapy, for regulatory submissions in the EU and jurisdictions in which the 2nd line + eribulin label applies.

(ii) To provide efficacy and safety data in the 3rd line + population who receive study medication as 3rd to 5th line of therapy, for regulatory submissions in the US and jurisdictions in which the 3rd line + eribulin label applies.

For the Overall Population, the critical efficacy endpoints shall be PFS and OS. The formal analysis of PFS is planned once 346 PFS events have accrued and is expected to be conducted when all randomized patients have been followed for a minimum of 12 months. At the time of the PFS analysis, an interim analysis of OS will be performed, and a final analysis of OS will take place once all randomized patients have been followed for a minimum of 24 months.

For the 3rd line + population, the critical efficacy endpoints shall be ORR, PFS, with ORR and PFS being co-primary efficacy endpoints. The formal analysis of ORR is planned when all such patients have been randomized and followed for a minimum of 6 months. The formal analysis of PFS will take place once 286 PFS events have accrued and is expected when all randomized patients have been followed for a minimum of 12 months; if the PFS in the 3rd line + population meets the allocated alpha level, PFS in the Overall Population will also be formally tested at the same alpha level; further, at the time of the PFS analysis an interim analysis of OS will be performed. The final analysis of OS will take place once all randomized patients have been followed for a minimum of 24 months.

In this study, the statistical design in the overall, 2nd line + population, with pre-defined alpha allocation and recycling, is such that if PFS does not meet statistical significance at its allocated alpha level, then the design still allows OS to be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Similarly, the statistical design in the overall, 3rd line + population, even if ORR does not meet statistical significance at its allocated alpha level then PFS can still be tested and, if it meets

statistical significance at its allocated alpha level, the study can still meet its primary objective. Further, if PFS does not meet statistical significance at its allocated alpha level, then OS can still be tested and, if it meets statistical significance at its allocated alpha level, then the study can still be formally positive for efficacy.

Alpha allocation and recycling will ensure control of the overall Type I error rate within each of (i) the Overall Population and (ii) 3rd line + population.

Analyses of biomarkers will be addressed in a separate analysis plan.

12.2 Overall Population Efficacy Analysis Plan relevant to the EU and other jurisdictions in which the 2nd line + Eribulin Label applies

12.2.1 Sample Size

Assuming a median PFS on eribulin of 3.9 months, to test for a hazard ratio versus balixafortide + eribulin of 0.699 (corresponding to a median PFS of 5.6 months), a total of 346 PFS events are required to provide 90% power at the 1-sided 2.0% alpha level. Equally, 346 PFS events provides 94.6% power for a hazard ratio of 0.674, corresponding to a PFS of 5.8 months. Assuming a 12-month recruitment period (η=2; Carroll, 2009(3)) and a minimum 12-month follow-up period after the last patient is randomized, a total of 384 patients will be recruited. Patients who discontinue from the study will not be replaced.

12.2.2 Analysis Sets

The following analysis sets are defined for the Overall Population:

- **Intention-to-treat (ITT) Population** is defined as all randomized patients. Efficacy data in this population will be summarized by randomized treatment. The co-primary endpoint PFS and key secondary efficacy endpoint OS will use the ITT population. Patients will be analyzed by the treatment arm to which they are randomized.

- **Safety Population** is defined as all randomized patients who receive at least one dose (or partial dose) of study medication. Patients will be analyzed by the treatment arm received, based on the first dose of study drug.

- **Response Evaluable Population** will be used to evaluate disease response. The Response Evaluable Population includes all patients who are randomized in the study with measurable disease by RECIST v1.1 (as determined by the Investigator). The co-primary endpoint analysis of ORR and other secondary endpoint analyses of CBR and duration of response will be conducted using the Response Evaluable Population. Patients will be analyzed by the treatment arm to which they are randomized.

- **Patient Reported Outcome (PRO) Population** is defined as all patients in the ITT Population where the patient has at least one post randomization PRO value. Patients will be analyzed by the treatment arm to which they are randomized.

12.2.3 Demographics and other Baseline Characteristics

The following demographic and baseline disease characteristic data for all analysis populations will be summarized: age (years), sex, race, ethnicity, ECOG performance status, reproductive status, smoking history, height (cm), weight (kg), body surface area (m^2), systolic BP (mmHg), and diastolic BP (mmHg). Key laboratory parameters will also be summarized.

12.2.3.1 Medical History

Medical history of BC will be summarized for the ITT population. Medical history will include time since initial diagnosis (years), time since diagnosis of locally recurrent or metastatic disease (years), stage at initial diagnosis, TNM staging, receptor data, receptor status, and pathological diagnosis.

Medical conditions collected at Screening will be mapped by the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by System Organ Class (SOC) and preferred term (PT) for the ITT population. For summary tables, a patient will be counted only once per body system and PT.

Patients will be stratified according to:

- Line of therapy (2nd line versus 3rd line +) for locally recurrent or metastatic BC.
- HR status (positive versus negative) based on ER or PgR status.
- CDK 4/6 inhibitor treatment received previously (received a CDK 4/6 inhibitor previously versus not received a CDK 4/6 inhibitor previously).
- Visceral versus non-visceral disease. Visceral metastases will include brain, pulmonary, pleural, hepatic and peritoneal involvement (including pleural effusions and ascites). Any other sites of metastases (e.g. bone, lymph nodes, and skin) will be considered to be non-visceral. Patients with visceral metastases, irrespective of the presence of any other metastatic sites (e.g. bone), will be categorized as visceral. All other patients without visceral metastases will be categorized as non-visceral.

12.2.3.2 Medical History of Prior Systemic Cancer/Oncology Therapies

The number and percent of patients receiving prior anthracycline and/or a taxane will be summarized. The number of prior hormonal therapies, cytotoxic chemotherapy regimens for BC, neoadjuvant regimens, adjuvant regimens, cytotoxic regimens for locally recurrent, and cytotoxic regimens for metastatic disease will be calculated based on prior cancer therapies reported on eCRFs and summarized for the ITT population.

Duration of prior anthracycline and/or taxane use will be summarized descriptively. If a patient received multiple treatments of a therapy, the sum of duration will be calculated.

Prior systemic cancer/oncology therapies will be tabulated for the ITT population using the latest version of World Health Organization Drug Dictionary Enhanced (WHO-DDE) and Anatomical, Therapeutic, or Chemical (ATC) level 2 classifications and PT.

12.2.3.3 Previous Radiotherapy and Surgical History

Previous radiotherapy and surgical history related to BC will be listed for the ITT population.

Surgical history related to BC and the percentage of patients receiving prior radiotherapy will be summarized for the ITT population.

12.2.4 Patient Disposition

A summary of patient disposition will display the number of patients who were randomized and who comprised each analysis population by treatment arm. In addition, the number of patients who discontinued study medication, and the number of patients who discontinued

from study, both overall and by reason, will be presented by randomized treatment arm. Disposition data, including populations to/from which patients are included/excluded, will be presented graphically.

The three randomization stratification factors, HR status, previous CDK 4/6 inhibitor treatment, and visceral disease, will be listed and tabulated as documented on the eCRF and as recorded by randomized treatment arm. Any discrepancies between those two sources will be identified and summarized.

12.2.5 Protocol Deviations

Details on the handling of protocol deviations will be described in a separate Deviations Plan.

Patients with important protocol deviations will be listed and summarized by treatment arm as randomized and for each study site. Important protocol deviations will include, but is not limited to, the following:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who developed withdrawal criteria during the study, but who were not withdrawn from the study medication.
- Those who received the wrong study medication or incorrect dose.
- Those who received a concomitant treatment that is prohibited or not recommended.

These important protocol deviations will be captured by searching relevant data fields reported in the clinical database. Final determination of important deviations will be made by the joint Polyphor/CRO study team prior to the first planned interim analysis and associated database lock. All protocol deviations that are captured will be summarized by category and type and will be presented in a data listing.

12.2.6 Treatments and Medication

12.2.6.1 Prior and Concomitant Medication

Prior and concomitant medications will be recorded on the source data and eCRF and coded to ATC code and preferred drug name using the latest version of WHO-DDE. Concomitant medications will be tabulated for the Safety Population by WHO-DDE ATC.

12.2.6.2 Subsequent Anti-cancer Therapy

Subsequent anti-cancer therapy will be summarized for the ITT Population. Subsequent anti-cancer therapy will be tabulated using the latest version of WHO-DDE and ATC Level-2 classifications and PT.

12.2.6.3 Exposure/Study Medication

Overall exposure to study medications, and study medication administration for each cycle and all cycles combined will be summarized for the Safety Population. Overall exposure to study medication will be summarized in terms of exposure duration and cumulative number of cycles.

12.2.7 Efficacy Analyses

12.2.7.1 Primary Endpoint: Progression Free Survival

PFS time (defined as the time from randomization to the first progression or death, as judged by an IRC) is the primary endpoint. The alpha allocation will be 0.040 2-sided. PFS will be analyzed via Cox regression modelling in the ITT population. Patients free from progression and death will be censored at their last follow-up visit. The analysis will be stratified for randomization stratification factors and a fixed effect term will be included for randomized treatment. The hazard ratio will be estimated from the model along with the associated 96% confidence interval (CI) and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and median PFS times will be estimated.

Supportive analyses for PFS will be conducted using:

(i) A stratified log rank test on PFS as determined by IRC; strata will be the randomization stratification factors. The 2-sided p-value will be extracted and presented alongside the results of the Cox analysis; and

(ii) Cox regression analysis on PFS as determined by the local Investigator's review.

12.2.7.2 Key Secondary Endpoint: Overall survival

OS will be analyzed using the same Cox model as for PFS. The CI coverage for OS at the planned interim and at the final analysis will be determined by the allocated alpha level. A sensitivity analysis using a stratified log rank test will be performed, again as per the analysis of PFS.

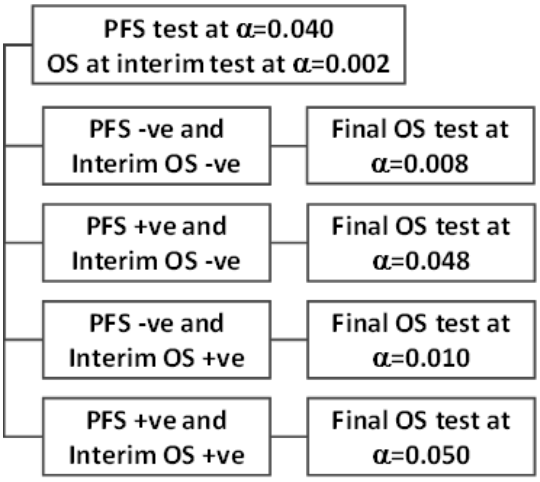
The OS proportion at 6, 12 and 18 months, including 95% CIs, will also be presented.

12.2.7.3 Type I Error Control

The formal analysis of PFS is planned for the Overall Population once 346 PFS events have accrued and is expected when all randomized patients have been followed for a minimum of 12 months. An interim analysis of OS will take place at the same time, and the final analysis of OS will take place once all randomized patients have been followed for a further 12 months (i.e. a minimum of 24 months).

The overall Type I error rate will be controlled at 5% across the primary and key secondary endpoint analyses by means of alpha allocation and recycling as described in Figure 2.

Figure 2 Type I Error Control for Primary and Secondary Efficacy Analyses in the Overall Population



OS: overall survival; PFS: progression free survival.

12.2.7.4 Other Secondary Endpoints

Analysis of the other secondary endpoints in the overall, 2nd line + population, i.e. ORR, CBR, DCR, time to response, and duration of response will not be subject to Type I error control. Statistical tests will be 2-sided with a nominal Type I error rate of 0.05.

ORR will be analyzed by exact logistic regression and be stratified for randomization stratification factors. The odds ratio will be estimated from the model along with the associated 95% CI and 2-sided p-value. Exact Clopper-Pearson 2-sided 95% CI limits will be calculated for the proportion of patients with ORR in each arm.

ORR analyses will be performed for the Response Evaluable Population. Patients who do not have measurable disease at baseline will be excluded from the population. In addition to presenting ORR, the best response using response categories CR, PR, SD, PD, and not evaluable (NE) will be tabulated. The proportion of the response in each response category will be calculated. Patients who do not have any post-baseline tumor assessment will be counted under the category NE. SD requires at least one post-baseline scan performed at 6 weeks (42 days) or later. Patients who did not have any post baseline scans for the 6 week assessment or later, and who also do not have a documented PD will be counted as NE.

Duration of response will be analyzed in the Response Evaluable Population, and CBR will be analyzed in both the Response Evaluable Population and ITT population.

CBR will be compared between the treatment arms using exact logistic regression as described for ORR. Exact Clopper Pearson 2-sided 95% confidence limits will be calculated for the CBR of each treatment arm.

Duration of response will be analyzed via Cox regression modelling with a fixed effect term for randomized treatment. The hazard ratio will be estimated from the model along with the associated 95% CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves; median duration of response and the 95% CIs will be estimated from the Kaplan-Meier

by treatment arm. A supportive analysis will be performed based on the expected duration of response as per Ellis et al (2008) (59).

12.2.7.5 Exploratory Efficacy Endpoints

Analysis of exploratory efficacy endpoints will not be subject to Type I error control. Statistical tests will be 2-sided with a nominal type I error rate of 0.05.

EORTC-QLQ-C30-QoL: As per the user's manual, raw scores for the EORTC-QLQ-C30 will be transformed using a linear transformation to standardize the results so that scores range from 0 to 100. At each assessment point, summary statistics of absolute scores and changes from baseline will be calculated by treatment group for each scale for both the raw score and the linear transformed score. Scores will be compared between treatments over time using mixed model repeated measures.

EQ-5D: The EQ-5D data will be scored and handled as recommended in its user's manual, and analyzed in a similar way to the EORTC-QLQ-C30.

FACT-B: The FACT-B data will be scored and handled as recommended in its user's manual, including handling of missing data both within the subscales and overall. The scores will be summarized by randomized treatment group at each assessment point. The scores will also be analyzed over time using mixed model repeated measures analysis in a similar way to the EORTC-QLQ-C30 and EQ-5D.

The analysis of the EORTC-QLQ-C30, EQ-5D and FACT-B will be performed in the PRO Population.

Relationship between biomarkers and clinical outcome: The relationship between baseline biomarkers (including ER status, PgR status, CXCR4 expression levels, cytokines [e.g. IFN-gamma], immune cells profile and RNA expression) and ORR, PFS and OS will be explored using a variety of exploratory data analysis methods including Cox and logistic regression models, time dependent covariate analysis (for biomarker measured longitudinally) and multivariate stepwise model selection methods. All such analyses will be essentially descriptive and hypothesis generating in nature.

12.3 3rd line + Population Efficacy Analysis Plan relevant to the US and other jurisdictions in which the 3rd line + Eribulin Label applies

12.3.1 Sample Size

Assuming a median PFS on eribulin of 3.9 months, to test for a hazard ratio versus balixafortide + eribulin of 0.674 (corresponding to a median PFS of 5.8 months), a total of 286 PFS events are required to provide 90% power at the 1-sided 2.0% alpha level. Assuming a 12-month, non-linear recruitment period (η=2; Carroll, 2009(3)) and a minimum 12-month follow-up period after the last patient is randomized, a total of 320 3rd line + patients will be recruited.

12.3.2 Analyses Sets

12.3.2.1 3rd line + Population

The following analysis sets are defined for the 3rd line + population:

- **ITT Population (3rd line +)** is defined as all randomized patients in the 3rd line + population. Efficacy data in this population will be summarized by randomized

treatment. The co-primary endpoint PFS and key secondary efficacy endpoint OS will use the ITT population. Patients will be analyzed by the treatment arm to which they are randomized.

- **Response Evaluable Population (3rd line +)** will be used to evaluate disease response. The Response Evaluable Population includes all patients in the 3rd line + population who are randomized in the study with measurable disease by RECIST v1.1 (as determined by the Investigator). The co-primary endpoint analysis of ORR and other secondary endpoint analyses of CBR and duration of response will be conducted using the Response Evaluable Population. Patients will be analyzed by the treatment arm to which they are randomized.

- **PRO Population (3rd line +)** is defined as all patients in the 3rd line + population where the patient has at least one post randomization PRO value. Patients will be analyzed by the treatment arm to which they are randomized.

- **Safety Population** is the same as that defined for the overall, 2nd line + population.

12.3.3 Demographics and Other Baseline Characteristics

Will be summarized in the 3rd line+ population in the same fashion as for the overall, 2nd line + population.

12.3.3.1 Medical History

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.3.2 Medical History of Prior Systemic Cancer/Oncology Therapies

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.3.3 Previous Radiotherapy and Surgical History

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.4 Patient disposition

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.5 Protocol Deviations

Will be handled in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.6 Treatments and Medication

12.3.6.1 Prior and Concomitant Medication

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.6.2 Subsequent Anti-cancer Therapy

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.6.3 Exposure/Study Medication

Will be summarized in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.7 Efficacy Analyses

12.3.7.1 Co-Primary Endpoints: Objective Response Rate and Progression Free Survival

Objective Response Rate

Will be analyzed in the 3rd line + population in the same fashion as for the overall, 2nd line + population. The alpha allocation will be 0.001 2-sided.

Progression Free Survival

Will be analyzed in the 3rd line+ population in the same fashion as for the overall, 2nd line + population. The alpha allocation will be 0.040 2-sided. If PFS in the 3rd line + population is met at the allocated alpha level, PFS in the overall population will also be formally tested at the same alpha level.

12.3.7.2 Key Secondary Endpoint: Overall survival

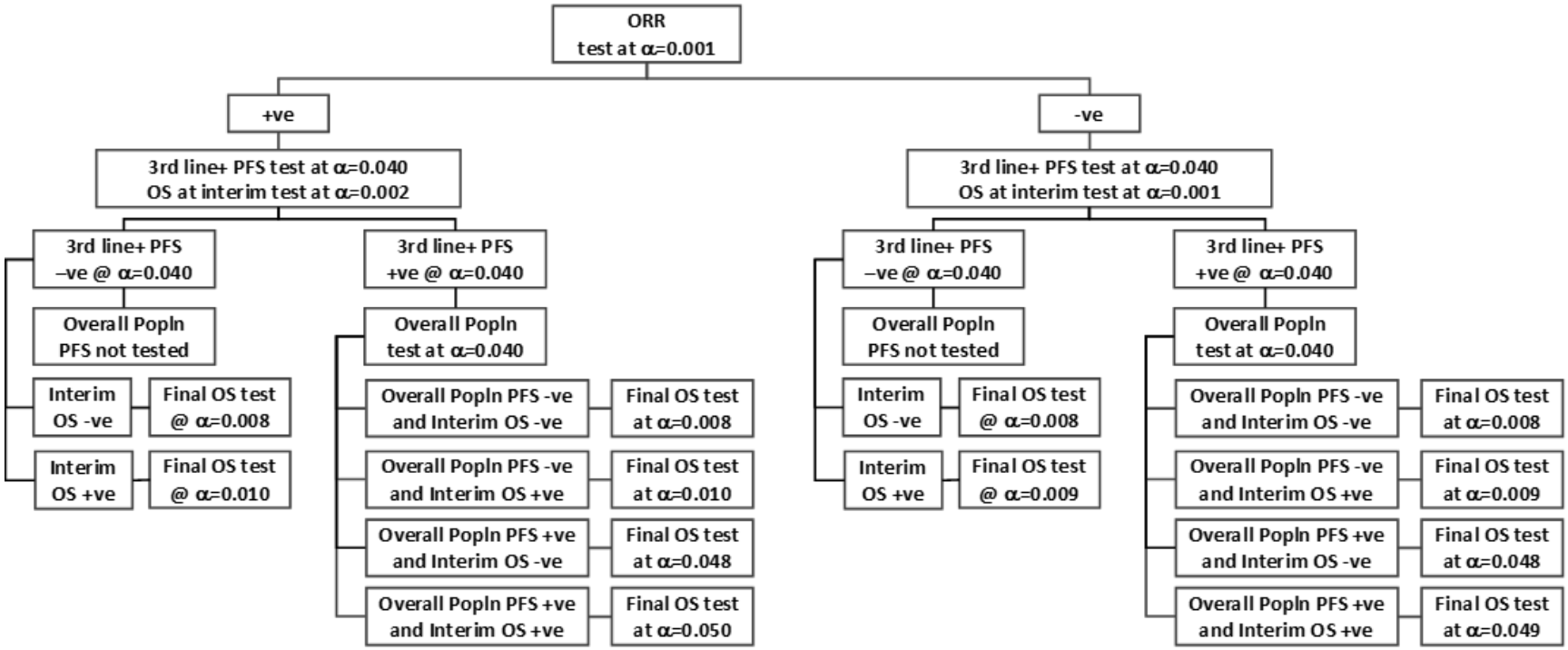
Will be analyzed in the 3rd line + population in the same fashion as for the overall, 2nd line + population. The alpha allocation will be between 0.001 and 0.002 2-sided at the interim and between 0.008 and 0.050 at the final analysis depending on the results of previous analyses.

12.3.7.3 Type I Error Control

The formal analysis of ORR is planned for the 3rd line + population once all such patients have been randomized and followed for a minimum of 6 months. The formal analysis of PFS will take place once 286 PFS events have accrued and is expected when all randomized patients have been followed for a minimum of 12 months; if the PFS in the 3rd line + population meets the allocated alpha level, PFS in the Overall Population will also be formally tested at the same alpha level. At the time of the PFS analysis, an interim analysis of OS will be performed and the final analysis of OS will take place once all randomized patients have been followed for a minimum of 24 months at which time 226 OS events are expected. The overall Type I error

rate will be controlled at 5% across the primary and secondary endpoints by means of alpha allocation and recycling as described in Figure 3.

Figure 3 Type I Error Control for Primary and Secondary Efficacy Analyses in the 3rd line + (3rd to 5th line of therapy) Population



ORR: objective response rate; OS: overall survival; PFS: progression free survival; Popln: population.

12.3.7.4 Other Secondary Endpoints

Analysis of the other secondary endpoints of CBR, DCR, time to response, and duration of response will not be subject to Type I error control. Statistical tests will be 2-sided with a nominal Type I error rate of 0.05. These endpoints will be analyzed in the 3rd line + population in the same fashion as for the overall, 2nd line + population.

12.3.7.5 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints EORTC-QLQ-C30, EQ-5D, FACT-B and the relationship between baseline biomarkers and efficacy outcomes will be analyzed in the 3rd line + population in the same manner as described for the overall, 2nd line + population. Analysis of the other exploratory efficacy endpoints will not be subject to Type I error control. Statistical tests will be 2-sided with a nominal type I error rate of 0.05.

12.4 Safety Analysis

The Safety Population is defined as all patients who received at least 1 dose (or partial dose) of study medication regardless of line of prior therapy. Summaries of AEs and other safety parameters will be provided by treatment arm received, based on the first dose of study drug.

12.4.1 Adverse Events

AEs will be classified using the latest version of MedDRA classification system. The severity will be graded according to the NCI CTCAE v5.0 whenever possible. All AEs reported from the first dose of study drug until 30 days (+7 days) after the last dose of study drug will be considered as TEAEs and will be summarized descriptively by treatment, and by the frequency of patients experiencing TEAEs corresponding to body systems and MedDRA PT. Patients with multiple occurrences of events will only be counted once at the maximum severity/grade to study drug for each PT, SOC, and overall.

All AEs will be summarized by relatedness to study medication and may be summarized by cycle as warranted. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, severity, relationship to study drug, action taken, and clinical outcome. AEs that are reported as possibly, probably, or definitely related to study drug will be counted as related to study drug. AEs with a missing relationship will be considered as “related” for this summary.

Any AEs leading to death or discontinuation of study medication, events classified as NCI CTCAE v5.0 Grade 3 or higher, AESIs (see Section 9.1), study drug-related events, and SAEs will be monitored with special attention.

The format and content of summary tables and individual patient listings is described in the SAP.

12.4.2 Laboratory Results

Hematology and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTCAE v5.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study medication. Shift tables will be provided to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE v5.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

12.4.3 Analysis of Vital Signs

Each vital sign (temperature, BP [systolic and diastolic], respiration rate, and heart rate) and respective change from baseline will be summarized and presented by treatment arm and study visit. Patients with clinically significant abnormalities in vital signs as compared to baseline will be listed.

12.4.4 Physical Examination

A summary table for the shift from baseline to post-baseline timepoints for physical examination will be provided for the Safety population. All physical examination results will be presented in a data listing.

12.4.5 12-Lead Electrocardiogram

ECG data will be summarized by study medication arm and by cycle using descriptive statistics for change-from-baseline values and categorical outliers. Any clinically significant changes will be recorded as AEs.

QTc intervals between >480 msec and ≤500 msec (Grade 2) and or between ≥501 msec from baseline (Grade 3) will be identified and summarized by study medication arm.

12.4.6 Exposure During Pregnancy

Patients who become, or are found to be, pregnant during exposure to study medication, will be summarized by treatment arm. The outcome of the pregnancy will be summarized in accordance with the Pregnancy Reporting Form including termination, still birth and live birth. In the event of a termination, the reasons for termination will be summarized and the structural integrity of the terminated fetus will also be summarized where possible. For live birth, the presence of any congenital anomalies will be summarized.

12.5 Deviations from the Original Statistical Plan

Any deviations from the original statistical plan as described in this Protocol will be agreed by the Sponsor and documented and justified in a Protocol Amendment, the final SAP or the clinical trial report, as appropriate.

12.6 Data Management

An eCRF and trial database will be created to capture and store trial data. All trial data will be processed and stored in a secure database.

The Investigator, or designee, will be responsible for entering data directly into the trial database via a secure internet connection, according to instructions provided for data entry. During data entry, range checks, plausibility checks, and consistency checks will be performed to ensure accuracy and completeness of the data being collected. Data queries will also be generated and resolved according to the pre-prepared data management plan. At pre-determined time points, SAS datasets will be generated from the trial database ready for analysis. A complete audit trail of all corrections will be available for inspection.

When data have been entered, reviewed and edited, the Investigator will be notified to review and sign the eCRF electronically as per the agreed project process, data will be locked to

prevent further editing, and a copy of the eCRF and data query sheets will be archived at the Investigator's site.

12.7 Data Safety Monitoring Committee

An independent DSMC will be established with the responsibility of safeguarding the safety of study participants by ongoing review of accumulating safety data during the conduct of this open label study. The DSMC will provide ongoing review of study conduct and patient management and make appropriate recommendations to the Sponsor based on the reported data. The final responsibility for acting upon DSMC recommendations lies with the Sponsor. The DSMC will be operational prior to enrolment of the first subject into the study. The composition and operation of the DSMC is described in the DSMC charter. The DSMC will also provide oversight and governance of the planned interim analyses of ORR and OS.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical monitor(s) should be given direct access to primary patient data (i.e., source data) which supports the data on the eCRFs for the study, i.e., hospital notes, appointment books, original laboratory records, etc. Because this enters the realm of patient confidentiality, this fact must be included in the ICF that the patient signs. Other authorized persons such as auditors and inspectors from regulatory authorities may need to have direct access to this source data.

13.1 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

All key data must be recorded in the patient's medical records.

13.2 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, any patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, records kept at the pharmacy, at the laboratories and at medico technical departments involved in the clinical trial).

13.3 Direct Access

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g. Regulatory Authorities, Polyphor Ltd, or CRO monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Polyphor Ltd proprietary information.

14. QUALITY CONTROL AND QUALITY ASSURANCE

An independent audit at the study site may take place at any time during or after the study. The independent audit can be carried by the Quality Assurance (QA) department of Polyphor Ltd, or the QA department of a CRO. In addition, an inspection may be carried out by a regulatory authority.

14.1 Quality Control

Quality Control is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Quality Assurance

QA is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

14.2.1 Inspection

An Inspection is defined as the act by a Regulatory Authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical trial and that may be located at the site of the study, or at Polyphor Ltd's facilities or at any other establishments deemed appropriate by the Regulatory Authorities.

14.2.2 Audit

An Audit is a systematic and independent review of study-related activities and documents to determine whether the validated study-related activities will be conducted, and the data will be recorded, analyzed and accurately reported according to the Protocol, designated SOPs, GCP and the applicable regulatory requirements.

15. ETHICS

This clinical trial will be conducted in compliance with this Protocol, the GCP guidelines of ICH, EU Directive 2001/20/EC, and Commission Directive 2005/28/EC, and EC ENTR/CT2, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, 2013), the General Data Protection Regulation (EU) 2016/679, designated SOPs, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

The IECs and IRBs must be constituted according to the local laws/guidelines.

15.1 Independent Ethics Committee/Institutional Review Board Approval

Polyphor Ltd will be responsible for preparing and submitting the regulatory approval in each country in which the study is to be conducted. In addition, Polyphor Ltd will be responsible for

informing the Regulatory Authorities of relevant changes to the Protocol. Approval must be received from the Regulatory Authority in each country prior to release of study drugs and patient recruitment.

Before initiating a study, the Investigator should have received written and dated approval/favorable opinion from the relevant IECs/IRBs for the Protocol (and any amendments), written ICF, consent form updates, patient recruitment procedures (e.g. advertisements), and any other written information to be provided to patients. Approval will be indicated in writing with reference to the final Protocol number and date. Details of the IECs/IRB's constitution including names of its members and what function they perform on the committee (e.g. chairman, specialist, lay-member) should be made available to Polyphor Ltd

During the study, the Investigator should provide all documents that are subject to review to the IECs/IRBs.

Each participating center will submit the Protocol to the local hospital/university/independent IEC/IRB, and their written unconditional approval obtained and submitted to Polyphor Ltd before the start of the study. Those with potential conflicts of interest (e.g. Investigators of this study, Polyphor board members) should not partake in the IEC/IRB decision process.

Polyphor Ltd will ensure an up-to-date Investigator's Brochure is available and will supply the Investigator with the Investigator's Brochure and Protocol for the Investigator to submit to the IECs/IRB for the Protocol's review and approval. Verification of the IECs/IRB unconditional approval of the Protocol will be transmitted to Polyphor Ltd prior to the start of the study. This approval must refer to the study by exact Protocol title and number, identify the documents reviewed and state the date of review.

The IEC/IRB must be informed by the Investigator of all subsequent Protocol amendments and of unexpected SAEs occurring during the study, which are likely to affect the safety of the patients or the conduct of the study.

The Investigator should provide the IEC/IRB with all relevant amendments or updates of the Protocol and Investigator's Brochure. Also, the Investigator should provide written reports to the IEC/IRB annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted by the Investigator to the IEC/IRB.

15.2 Informed Consent

Before beginning any study procedure on a patient, it is the responsibility of the Investigator to obtain voluntary written Informed Consent from all patients or their legal representatives. The principles of Informed Consent in the Declaration of Helsinki should be implemented in this clinical trial before any Protocol specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC/IRB. The information must be expressed in a way that can be comprehended by lay people. Patients, their relatives, or if necessary, their legal representatives must be given ample opportunity to enquire about details of the study.

The Investigator will explain the nature, purpose and risks of the study and provide the patient or his/her legal representative with a copy of the study information sheet. The patient or his/her legal representative will be given sufficient time to consider the study's implications before deciding whether to participate. The Investigator must notify the patient or his/her legal representative about the option to withdraw consent at any time.

Consent forms must be in a language fully comprehensible to the prospective patient or his/her legal representative. Informed Consent will be documented by using a written ICF approved by the IEC/IRB and signed by the patient or his/her legal representative, and the Investigator obtaining the consent. The ICF will also be annotated with the study patient number.

The written Informed Consent document will comply with ICH guidelines, embody the elements of Informed Consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the patient's (or his/her legal representative's) dated signature. The signature confirms the Consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the Investigator for possible inspection by Regulatory Authorities and Polyphor Ltd

The patient or his/her legal representative will be given an original hardcopy of the signed ICF.

Should there be any amendments to the final Protocol that would directly affect the patient's participation in the study (e.g. a change in any procedure), the ICF must be amended to incorporate this modification and the patients or their legal representatives must agree to sign this amended ICF indicating that they re-consent to participate in the study.

15.3 Modification of Protocol

The Investigator(s) must adhere to this Protocol and will be responsible for enrolling only those patients who have met the eligibility criteria. The Investigator(s) will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the Protocol.

The Investigator must not implement any deviation from, or changes of, the Protocol without agreement by Polyphor Ltd, and prior review and documented approval/favorable opinion from the IEC/IRB of an amendment. The only exceptions are where it is necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor[s], change of telephone number[s]).

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed Protocol amendment(s) should be submitted:

- To the IEC/IRB for review and approval/favorable opinion
- To the Regulatory Authority(ies) according to local laws/guidelines.

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by Polyphor Ltd and the Principal Investigator. Polyphor Ltd (or its designated CRO) will ensure that the Investigators submit necessary Protocol amendments to the appropriate IEC/IRB.

All agreed Protocol amendments must be clearly documented using standard procedures as defined by Polyphor Ltd, and must be signed and dated by Polyphor Ltd, and the Investigator.

15.4 Safety Reporting

The Sponsor and its authorized designees are responsible for clinical trial and safety reporting to Regulatory Authorities and ethics committees in each country in which the study is conducted (see Section 9.2.5.3).

15.5 Trial Termination

Polyphor Ltd reserves the right to terminate the study at any time. Study termination may also be requested by a competent authority/ies.

15.6 End of Trial Notification and Submission of Summary Report

Polyphor Ltd is responsible for preparing and submitting the end of trial notification to the Ethics Committees and Regulatory Authorities in the EU Member States in which the study has been conducted. This must be submitted within 90 days of the end of the trial (15 days if the trial is terminated early). Notification of the end of trial will be provided to the FDA in the Annual Report.

For this purpose, the end of the trial (trial completion) is defined in Section 7.10. Any change to this definition is considered a significant amendment and MUST be notified to (and approval sought from) the Ethics Committees and the Regulatory Authorities concerned.

Polyphor Ltd will be responsible for preparing and submitting a summary of the CSR to the Regulatory Authorities in each country in which the study was conducted within 12 months of the end of the study.

Polyphor Ltd will be responsible for uploading the End of Trial summary results to the European Clinical Trials Database (EudraCT) as per the current European legislation. Polyphor Ltd will also report the end of trial information in the US clinical trial register.

16. DATA HANDLING AND RECORD KEEPING

16.1 Completion of Electronic Case Report Forms

Data will be collected and recorded in an eCRF. Data entered in the eCRF are stored in a centralized database on a remote server. Data will be entered directly into the eCRF via a single data entry process. The data entry activities are regulated and described in the eCRF manual.

Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies should be explained.

16.2 Confidentiality

In order to maintain patient confidentiality, only a site number and an anonymized patient number will identify all study patients on eCRFs and other documentation submitted to the Sponsor. Additional patient confidentiality issues (if applicable) are covered in the Clinical Trial Agreement.

Data collected during this study may be used to support the development, registration or marketing of balixafortide. Polyphor Ltd will control all data collected during the study and will abide by the General Data Protection Regulation (EU) 2016/679 concerning the processing and use of patients' personal data. For the purpose of data privacy legislation, Polyphor Ltd will be the data controller.

After patients have consented to take part in the study their medical records and the data collected during the study will be reviewed by the Sponsor. These records and data may, in addition, be reviewed by the following: independent auditors who verify the data on behalf of

Polyphor Ltd; third parties with whom Polyphor Ltd may develop, register or market balixafortide; national or local regulatory authorities and the IRB/IECs that gave approval for this study to proceed.

All US-based investigational sites and laboratories or entities providing support for this trial, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. An investigational site that is not a Covered Entity as defined by HIPAA, must provide documentation of this fact to Polyphor Ltd.

The results of this study may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions in other countries.

16.3 Archiving and Retention of Investigational Records

All 'essential documents' (as described in the ICH GCP Guidelines) must be retained by Polyphor Ltd and the Investigator for at least 15 years after the completion of the clinical trial. These documents may be retained for a longer period, however, if required by the applicable regulatory requirements (e.g. ICH GCP) or by an agreement with Polyphor Ltd. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. The Investigator must obtain written permission from Polyphor Ltd prior to the destruction of any study document.

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

To enable evaluations and/or audits from Regulatory Authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development.

If the Investigator becomes unable, for any reason, to continue to retain study records for the required period (e.g. retirement, relocation), the Sponsor should be prospectively notified.

The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution. The Investigator must obtain the Sponsor’s written permission before disposing of any records, even if retention requirements have been met.

17. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with the Investigator and will be documented in a separate financial agreement that will be signed by the Investigator, Sponsor, and other relevant parties as applicable, in advance of the study commencing.

Polyphor Ltd has insurance coverage for study-related medicine-induced injury and other liabilities incurred during clinical studies which will provide compensation for any trial related injury according to local laws and regulations.

18. PUBLICATION POLICY

Publication of study results is discussed in the Clinical Trial Agreement.

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to Regulatory Authorities. The following conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning balixafortide (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Polyphor Ltd and not previously published) is considered confidential by Polyphor Ltd and shall remain the sole property of Polyphor Ltd. The Investigator agrees not to use it for other purposes without Polyphor Ltd's written consent.

It is understood by the Investigator that Polyphor Ltd will use the information developed in this clinical trial in connection with the development of balixafortide and therefore may be disclosed as required to Polyphor Ltd's Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical trial, the Investigator understands that he/she has an obligation to provide Polyphor Ltd with complete test results and all data developed during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Polyphor Ltd 30 days in which to review and comment upon the publication manuscript. Polyphor Ltd agrees that before it publishes any results of this study, it shall provide the Investigators at least 30 days for full review of the publication manuscript. In accordance with generally recognized principles of scientific collaboration, co-authorship with any Polyphor Ltd personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Polyphor Ltd in advance of submission. The review is aimed at protecting Polyphor Ltd proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data shall be set out in the agreement between each Investigator and Polyphor Ltd.

19. REFERENCES

1. World Medical Association Declaration of Helsinki. Ethical Principles for Medical research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. Last Amendment at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
2. Lichtman SM, Harvey D, Smitt MD, Rahman A, Thompson MA, Roach N, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(33):3753-9.
3. Carroll KJ. Back to basics: explaining sample size in outcome trials, are statisticians doing a thorough job? Pharm Stat. 2009;8(4):333-45.
4. World Cancer Research Fund International. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Breast Cancer.; 2017.
5. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
6. Eurostat. Cancer statistics - specific cancers 2017 [updated 25 Oct 2017. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cancer_statistics_-_specific_cancers#Breast_cancer.
7. American Cancer Society. Breast Cancer 2017 [Available from: https://www.cancer.org/cancer/breast-cancer/
8. GLOBOCAN. Cancer Fact Sheets: Breast Cancer [Available from: http://globocan.iarc.fr/old/FactSheets/cancers/breast-new.asp.
9. Wan L, Pantel K, Kang Y. Tumor metastasis: moving new biological insights into the clinic. Nat Med. 2013;19(11):1450-64.
10. Cojoc M, Peitzsch C, Trautmann F, Polishchuk L, Telegeev GD, Dubrovska A. Emerging targets in cancer management: role of the CXCL12/CXCR4 axis. Onco Targets Ther. 2013;6:1347-61.
11. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell. 2005;121(3):335-48.
12. Zhao S, Chang SL, Linderman JJ, Feng FY, Luker GD. A Comprehensive Analysis of CXCL12 Isoforms in Breast Cancer(1,2.). Transl Oncol. 2014.
13. Domanska UM, Kruizinga RC, Nagengast WB, Timmer-Bosscha H, Huls G, de Vries EG, et al. A review on CXCR4/CXCL12 axis in oncology: no place to hide. Eur J Cancer. 2013;49(1):219-30.
14. Allinen M, Beroukhim R, Cai L, Brennan C, Lahiti-Domenici J, Huang H, et al. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004;6(1):17-32.
15. Hassan S, Buchanan M, Jahan K, Aguilar-Mahecha A, Gaboury L, Muller WJ, et al. CXCR4 peptide antagonist inhibits primary breast tumor growth, metastasis and enhances the efficacy of anti-VEGF treatment or docetaxel in a transgenic mouse model. Int J Cancer. 2011;129:225-32.
16. Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer. 2009;9(4):274-84.
17. Price TT, Burness ML, Sivan A, Warner MJ, Cheng R, Lee CH, et al. Dormant breast cancer micrometastases reside in specific bone marrow niches that regulate their transit to and from bone. Sci Transl Med. 2016;8(340):340ra73.

18. Scala S. Molecular Pathways: targeting the CXCR4–CXCL12 axis—untapped potential in the tumor microenvironment. Clin Cancer Res. 2015;21(19):4278-85.
19. Zhang XH, Wang Q, Gerald W, Hudis CA, Norton L, Smid M, et al. Latent bone metastasis in breast cancer tied to Src-dependent survival signals. Cancer Cell. 2009;16(1):67-78.
20. Rhodes LV, Short SP, Neel NF, Salvo VA, Zhu Y, Elliott S, et al. Cytokine receptor CXCR4 mediates estrogen-independent tumorigenesis, metastasis, and resistance to endocrine therapy in human breast cancer. Cancer Res. 2011;71(2):603-13.
21. Xu TP, Shen H, Liu LX, Shu YQ. The impact of chemokine receptor CXCR4 on breast cancer prognosis: a meta-analysis. Cancer Epidemiol. 2013;37(5):725-31.
22. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-23.
23. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(6):594-601.
24. Pivot X, Marmé F, Koenigsberg R, Guo M, Berrak E, Wolfer A. Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Annals of Oncology. 2016;27(8):1525-31.
25. Teicher BA, Fricker SP. CXCL12 (SDF-1)/CXCR4 pathway in cancer. Clin Cancer Res. 2010;16(11):2927-31.
26. Ali S, Lazennec G. Chemokines: novel targets for breast cancer metastasis. Cancer Metastasis Rev. 2007;26(3-4):401-20.
27. Galsky MD, Vogelzang NJ, Conkling P, Raddad E, Polzer J, Roberson S, et al. A phase I trial of LY2510924, a CXCR4 peptide antagonist, in patients with advanced cancer. Clin Cancer Res. 2014;20(13):3581-8.
28. Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature. 2001;410(6824):50-6.
29. Xu C, Zhao H, Chen H, Yao Q. CXCR4 in breast cancer: oncogenic role and therapeutic targeting. Drug design, development and therapy. 2015;9:4953-64.
30. Liang Z, Wu T, Lou H, Yu X, Taichman RS, Lau SK, et al. Inhibition of breast cancer metastasis by selective synthetic polypeptide against CXCR4. Cancer Res. 2004;64:4302-8.
31. Hiller D, Chu QD. CXCR4 and axillary lymph nodes: review of a potential biomarker for breast cancer metastasis. Int J Breast Cancer. 2011;2011:420981.
32. Feig C, Jones JO, Kraman M, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti–PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci U S A. 2013;110(50):20212-7.
33. Andtbacka RHI, Yushak M, Ross M, Grossmann K, Pierce R, Tsiroyannis E, et al. X4P-001, an Orally Bioavailable CXCR4 Antagonist, Increases T Cell Infiltration in Human Metastatic Melanoma. Poster presented at The Society for Immunotherapy of Cancer Annual Meeting , November 8–12, 2017 ·; National Harbor, Maryland2017.
34. Xiang J, Hurchla MA, Fontana F, Su X, Amend SR, Esser AK, et al. CXCR4 Protein Epitope Mimetic Antagonist POL5551 Disrupts Metastasis and Enhances Chemotherapy Effect in Triple-Negative Breast Cancer. Mol Cancer Ther. 2015;14(11):2473-85.
35. Sison EA, Magoon D, Li L, Annesley CE, Romagnoli B, Douglas GJ, et al. POL5551, a novel and potent CXCR4 antagonist, enhances sensitivity to chemotherapy in pediatric ALL. Oncotarget. 2015;6(31):30902-18.

36. Barone A, Sengupta R, Warrington NM, Smith E, Wen PY, Brekken RA, et al. Combined VEGF and CXCR4 antagonism targets the GBM stem cell population and synergistically improves survival in an intracranial mouse model of glioblastoma. Oncotarget. 2014;5(20):9811-22.
37. Gagner JP, Sarfraz Y, Ortenzi V, Alotaibi FM, Chiriboga LA, Tayyib AT, et al. Multifaceted C-X-C Chemokine Receptor 4 (CXCR4) Inhibition Interferes with Anti-Vascular Endothelial Growth Factor Therapy-Induced Glioma Dissemination. Am J Pathol. 2017;187(9):2080-94.
38. Karpova D, Bräuninger S, Wiercinska E, Krämer A, Stock B, Graff J, et al. Mobilization of hematopoietic stem cells with the novel CXCR4 antagonist POL6326 (balixafortide) in healthy volunteers-results of a dose escalation trial. J Transl Med. 2017;15(2):DOI:10.1186/s12967-016-1107-2.
39. Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roche H, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(25):3922-8.
40. Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(18):2954-61.
41. Pernas S, Martin M, Kaufman PA, et al. Balixafortide plus eribulin in HER2-negative metastatic breast cancer: a phase I, single-arm, dose-escalation trial. Lancet Oncol. 2018;19(6):812-24.
42. Eisai. HALAVEN(R) (Eribilun) SmPC. 2016.
43. Eisai. Full prescription information for Halaven®. 2017.
44. Polyphor. Investigator's Brochure: Balixafortide. 2019;Version 11.0.
45. Kaufman PA, Pernas Simon S, Martin M, et al. Balixafortide (a CXCR4 antagonist) + eribulin in HER2-negative metastatic breast cancer (MBC): survival outcomes of the phase I trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2019;37(Suppl 2606).
46. Cortes Castan J, Martín M, Pernas S, et al. Balixafortide (a novel CXCR4 inhibitor) and eribulin in HER2-neg metastatic breast cancer (MBC) patients (pts): a Phase I trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2018;29(Suppl 8):viii90-viii121.10.1093/annonc/mdy272.
47. Pivot X, Marme F, Koenigsberg R, Guo M, Berrak E, Wolfer A. Pooled analyses of erubilin in metastatic breast cancer patients with at least one prior chemotherapy. Annals of Oncology. 2016;27:1525-31.
48. Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roche H, et al. Phase II study of the halichondrin B anolog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane and capecitabine. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(25):3922-8.
49. Vahdat LT, Pruitt B, Fabian CJ, et al. Phase II study of eribulin mesylate, a halichondrin B anolog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(18):2954-61.
50. Devriese LA, Witteveen PO, Wanders J, et al. Pharmacokinetics of eribulin mesylate in patients with solid tumours receiving repeated oral rifampicin. British journal of clinical pharmacology. 2012;75(2):507-15.
51. Polyphor (data on file). Report no: RPT04501: Bioanalytical sample analysis report in support of the study entitled, “A phase I dose escalation study of POL6326 with eribulin

in patients with relapsed, triple negative and hormone refractory ER positive metastatic breast cancer. 2018.
52. Sampson HA. Second Symposium on the Definition and Management of Anaphylaxis: Summary Report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine. 2006;47(4):373-80.
53. FDA 2009. Guidance for industry. Drug-induced livery injury: premarketing clinical evaluation.http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
54. Smith TJ, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update Journal of Clinical Oncology. 2015;33(28):3199-214.
55. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J Cancer. 2009;45:228-74.
56. Seymour L, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncology. 2017;18(3):e143-e52.
57. Taplitz RA. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(14):1443-53.
58. Schiffer CA. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update Journal of Clinical Oncology. 2018;36(3):283-99.
59. Ellis S, Carroll KJ, Pemberton K. Analysis of Duration of Response in Oncology Trials Contemporary Clinical Trials. 2008;29:456-65.
60. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

20. APPENDICES

Appendix 1 Prohibited Medications

CredibleMeds® has reviewed available evidence for the drugs on the following list and categorized them as drugs of Known Risk (KR) of torsades de pointes (TdP). The full description of these categories can be found on the CredibleMeds.org website. For a complete and most up-to-date drug list, please check the website at: https://www.crediblemeds.org/healthcare-providers/drug-list

Generic Name	Brand Name
Aclarubicin (KR)	Aclacin and others
Amiodarone (KR)	Cordarone® and others
Anagrelide (KR)	Agrylin® and others
Arsenic trioxide (KR)	Trisenox®
Astemizole (KR)	Hismanal®
Azithromycin (KR)	Zithromax® and others
Bepridil (KR)	Vascor®
Chloroquine (KR)	Aralen®
Chlorpromazine (KR)	Thorazine® and others
Cilostazol (KR)	Pletal®
Ciprofloxacin (KR)	Cipro® and others
Cisapride (KR)	Propulsid®
Citalopram (KR)	Celexa® and others
Clarithromycin (KR)	Biaxin® and others
Cocaine (KR)	Cocaine
Disopyramide (KR)	Norpace®
Dofetilide (KR)	Tikosyn®
Domperidone (KR)	Motilium® and others
Donepezil (KR)	Aricept®
Dronedarone (KR)	Multaq®
Droperidol (KR)	Inapsine® and others
Erythromycin (KR)	E.E.S.® and others
Escitalopram (KR)	Cipralex® and others
Flecainide (KR)	Tambocor® and others
Fluconazole (KR)	Diflucan® and others
Gatifloxacin (KR)	Tequin®
Grepafloxacin (KR)	Raxar®
Halofantrine (KR)	Halfan®

Generic Name	Brand Name
Haloperidol (KR)	Haldol® [US & UK] and others
Hydroxyquinidine, dihydroxyquinidine (KR)	Serecor®
Ibogaine (KR)	None
Ibutilide (KR)	Corvert®
Levofloxacin (KR)	Levaquin® and others
Levomepromazine (methotrimeprazine) (KR)	Nosinan® and others
Levomethadyl acetate (KR)	Orlaam®
Levosulpiride (KR)	Lesuride® and others
Mesoridazine (KR)	Serentil®
Methadone (KR)	Dolophine® and others
Moxifloxacin (KR)	Avelox® and others
Ondansetron (KR)	Zofran® and others
Oxaliplatin (KR)	Eloxatin®
Papaverine HCl (Intracoronary) (KR)	none
Pentamidine (KR)	Pentam®
Pimozide (KR)	Orap®
Probucol (KR)	Lorelco®
Procainamide (KR)	Pronestyl® and others
Propofol (KR)	Diprivan® and others
Quinidine (KR)	Quinaglute® and others
Roxithromycin (KR)	Rulide® and others
Sevoflurane (KR)	Ultane® and others
Sotalol (KR)	Betapace® and others
Sparfloxacin (KR)	Zagam®
Sulpiride (KR)	Dogmatil® and others
Sultopride (KR)	Barnetil® and others
Terfenadine (KR)	Seldane®
Terlipressin (KR)	Teripress® and others
Terodiline (KR)	Micturin® and others
Thioridazine (KR)	Mellaril® and others
Vandetanib (KR)	Caprelsa®

KR: known risk of torsades de pointes; UK: United Kingdom; US: United States

Appendix 2 ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG Performance Status*

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

Source: (60)

Appendix 3 Summary of RECIST v1.1 Guidelines

This summary is based on the RECIST v1.1 guidelines which should be consulted for further details (55).

Measurability of Tumors at Baseline

All measurements should be recorded in metric notation using calipers if clinically assessed.

Measurable Tumor Lesions

Tumor lesions must be measured accurately in at least 1 dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical examination (lesions which cannot be measured accurately with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Measurable Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in the *short axis* when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and during follow-up, only the *short axis* will be measured and followed.

Non-measurable Tumor Lesions or Lymph Nodes

These are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Baseline Documentation of 'Target' and 'Non-target' Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as *target lesions,* and will be recorded and measured at baseline. This means that in patients who have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions will be recorded respectively.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to *reproducible repeated measurements*. In cases where the largest lesion does not lend itself to reproducible measurement, the next largest lesion that can be measured reproducibly should be selected.

Lymph Nodes

Pathological lymph nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The *baseline sum diameters* will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response Criteria

Assessment of Target Lesions

The RECIST v1.1 definitions of the criteria used to determine tumor response for target lesions are provided in Table 5, Section 8.2.2.

(i) *Lymph nodes*: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. CRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

(ii) *Target lesions that become 'too small to measure':* While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value is recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly

seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

(iii) *Lesions that split or coalesce on treatment:* When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Assessment of Non-target Lesions

The RECIST v1.1 definitions of the criteria used to determine tumor response for non-target lesions are provided in Table 6, Section 8.2.2.

While some non-target lesions may be measurable, they need not be measured and instead should be assessed qualitatively only at the time points specified in the protocol.

Assessing progression of non-target disease is described below:

(i) *When the patient also has measurable disease:* In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will, therefore, be extremely rare.

(ii) *When the patient has only non-measurable disease:* This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore, the increase must be substantial.

(iii) *New Lesions:* The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up:

  If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

  If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

  If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[I] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target

disease and will also take into consideration the appearance of new lesions. Furthermore, it will require confirmation as outlined in Section 8.2.2.

Timepoint Response

Table 7 (Section 8.2.2) provides a summary of the overall response calculation that is to be used at each response assessment timepoint specified in the Study Schedule for patients who have measurable disease at baseline. When patients have non-measurable (i.e. non-target) disease only, Table 8 (Section 8.2.2) is to be used.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response where Confirmation of CR or PR Required

The best overall response is determined once all the data for the patient is known.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (i.e. at least 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in Table 17.

Table 17 Best overall response when confirmation of CR and PR required

Overall Response at first timepoint	Overall Response at subsequent timepoint (i.e. at least 4 weeks after first timepoint)	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR

Overall Response at first timepoint	Overall Response at subsequent timepoint (i.e. at least 4 weeks after first timepoint)	Best Overall Response
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR: complete response; PD: progressive disease; NE: not evaluable; PR: partial response; SD: stable disease

Source: (55)

a: If a CR is *truly* met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes `CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on an increase in size of the nodes. This means that patients with CR may not have a total sum of 'zero' on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 7, Table 8 and Table 17.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. Both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled

assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Appendix 4 Summary of iRECIST Guidelines

This summary is based on the iRECIST guidelines (56).

iRECIST is based on RECIST v1.1. Responses assigned using iRECIST have a prefix of "i" (i.e. immune)—e.g. "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorized into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

The continued use of RECIST v1.1 is recommended to define whether tumor lesions (including lymph nodes) are measurable or non-measurable, as well as for the management of bone lesions, cystic lesions, and lesions with previous local treatment. The principles for establishing objective tumor response are similar to RECIST v1.1, but the main change for iRECIST is the action to be taken if RECIST v1.1 progression is followed at the next assessment by tumor shrinkage.

iRECIST defines iUPD in a similar way to RECIST v1.1 guidance, however, iUPD requires confirmation, by observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified (i.e. target or non-target disease), or progression (defined by RECIST v1.1) in lesion categories that had not previously met RECIST v1.1 progression criteria. However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria for iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumor size or extent occurs from iUPD, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified.

Assessment of Target, Non-target, and New Lesions

Most RECIST v1.1 recommendations are unchanged for timepoint response, including the management of lymph nodes, lesions that become too small to measure, lesions that split or coalesce, and the definition of CR, PR, SD, and PD. Each timepoint response is based on the assessment of target lesions, non-target lesions, and new lesions.

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed. iUPD is defined by RECIST v1.1 criteria for PD; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (at least 6 weeks later in this study) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if CR, PR, or SD criteria (compared with baseline and as defined by RECIST v1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST v1.1, in which any progression precludes later CR, PR, or SD). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can be documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as

iCPD was not confirmed. iUPD is defined by RECIST v1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment.

PD in the non-target lesion category is confirmed if subsequent imaging, done at least 6 weeks after iUPD in this study, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST v1.1 criteria for CR or non-iCR/non- iUPD are met after a previous iUPD. The status is reset (unlike RECIST v1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

RECIST v1.1 defines the appearance of new malignant lesions as denoting true disease progression, providing that other lesions (artefacts or benign intercurrent disease) are assessed appropriately and discounted if not malignant. These principles of RECIST v1.1 remain useful and clearly identify the management of new lesions that are considered to be potentially artefactual: “If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up assessment will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan”.

However, many aspects of new lesion assessment are unique to iRECIST. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorized as measurable or non-measurable using RECIST v1.1 principles. Five lesions (no more than 2 per organ) should be measured and recorded as a new lesion target, but should not be included in the sum of measures of the original target lesions identified at baseline. Other measurable and non-measurable lesions are recorded as new lesion non-target. New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD. iCPD is assigned to the new lesion category if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target).

Notably, if iUPD criteria were met on the basis of progression in the target or non-target disease, or the appearance of new lesions, then RECIST v1.1-assigned progression in another lesion category in the confirmatory scan also confirms iCPD.

Continued Treatment after iUPD

The existing literature describes pseudoprogression as an increase in the size of lesions, or the visualization of new lesions, followed by a response, which might be durable. Differentiating transient pseudoprogression from true progression can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective salvage therapy.

An assignment of clinical stability requires that there is no worsening of performance status, that there are no clinically relevant increases in disease-related symptoms (e.g. pain or dyspnea) that are thought to be associated with disease progression (generally understood to mean a requirement for increased palliative intervention), and that there is no requirement for intensive management of disease-related symptoms (including increased analgesia, radiotherapy, or other palliative care).

The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether to continue therapy.

Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the eCRF. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of PFS.

If the confirmatory scan confirms iCPD, but the Investigator or patient believes that continued treatment is appropriate, imaging should continue, and data should be collected to allow further elucidation of tumor growth dynamics with immune modulators. For the same reason, and if feasible, even patients who discontinue therapy for iCPD are recommended to continue to have disease assessments until they start other systemic or local therapies.

Timepoint and Best Overall Response

Although the principles of assigning the timepoint response and best overall response closely follow RECIST v1.1, and reflect assessment of target and non-target lesions as well as the presence of new lesions, the possibility of pseudoprogression adds complexity. The timepoint response is calculated using the response assigned for each category of lesion (as for RECIST v1.1), but takes into account the last timepoint response (Table 18).

Table 18 Key Principles to Consider

Have criteria for iUPD been met?	Principles to consider
No	Follow RECIST V1.1 guidance
Yes	Next timepoint response could be: • iUPD (no change noted in any category of lesion) • iSD, iPR, or iCR, Here, iUPD (followed by iCPD) should occur again • iCPD (if the category in which iUPD was met at the last timepoint response shows a further increase in tumor burden as evidenced [as applicable] by a ≥5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions

iCPD: immune confirmed progression; iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progression; RECIST: Response Evaluation Criteria In Solid Tumors.

The algorithm for patients with no previous iUPD is identical to RECIST v1.1.

For patients with iUPD at the last timepoint response, the next timepoint response is dependent on the status of all lesions (including target, non-target, new lesion target, and new lesion non-target), on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met), or the appearance of additional new lesions.

For iRECIST, the immune best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR (Table 19), this means that iPR or iSD can be assigned (timepoint response

or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met.

Table 19 Assignment of Timepoint Response Using iRECIST

	Timepoint Response	
	No previous iUPD in any category	**Previous iUPD in any category***
Target lesions: iCR Non-target lesions: iCR New lesions: no	iCR	iCR
Target lesions: iCR Non-target lesions: non-iCR/non-iUPD New lesions: no	iPR	iPR
Target lesions: iPR Non-target lesions: non-iCR/non-iUPD New lesions: no	iPR	iPR
Target lesions: iSD Non-target lesions: non-iCR/non-iUPD New lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint Non-target lesions: iUPD with no change, or decrease from last timepoint New lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR Non-target lesions: iUPD New lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST v1.1 criteria for unequivocal progression)
Target lesions: iUPD	IUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD

	Timepoint Response	
	No previous iUPD in any category	**Previous iUPD in any category***
Non-target lesions: non-iCR/non-iUPD, or iCR New lesions: no		
Target lesions: iUPD Non-target lesions: iUPD New lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD Non-target lesions: iUPD New lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression Non-target lesions: non-iUPD or progression New lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

iCPD: immune confirmed progression; iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progression; non-iCR/non-iUPD: criteria for neither immune CR nor PD have been met; RECIST: Response Evaluation Criteria In Solid Tumors.

Target lesions, non-target lesions, and new lesions defined according to RECIST v1.1 principles; if no pseudoprogression occurs, RECIST v1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint.

"i" indicates immune responses assigned using iRECIST.

The duration of iCR and iPR is calculated from the timepoint when the criteria for iCR or iPR are first met, whereas the duration of iSD is calculated from baseline.

Assessments that are not done or are NE should be disregarded. For example, an iUPD followed by an assessment that was not done or NE, and then another unconfirmed progressive disease, would be indicative of iCPD.

Progression Free Survival

The event date to be used for calculation of iPFS should be the first date at which progression criteria are met (i.e. the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol non-compliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer. The eCRF collects the reason why confirmatory response assessment was not done at any timepoint, such as not clinically stable, center error, patient refusal, or patient death.

Appendix 5 Scales and Assessments

Body surface area will be calculated according to the following formula:

$$\text{Body surface area } \{m^2\} = ([\text{Height } \{cm\} \times \text{Weight } \{kg\}]/3600)^{1/2}$$

Appendix 6 Prescribing Information and Labels for Eribulin

See separate attachments

Appendix 7 ASCO Guidance on the Use of CSFs

See separate attachment and also reference (54).

Appendix 8 ASCO Guidance on Outpatient Management of Fever and Neutropenia in Patients Treated for Malignancy

See separate attachments and reference (57).

Appendix 9 ASCO Guidance on Platelet Transfusions for Patients with Cancer

See separate attachments and reference (58).

Appendix 10 Any Additional Study Information that the Patient will Receive

See separate attachments

Appendix 11 Quality of Life Patient Questionnaires

See separate attachments