CLINICAL STUDY PROTOCOL

Protocol no.: AL-2001
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Title:
Phase II, open label, single arm study to investigate anti-tumor effect of ixabepilone in patients with locally recurrent or metastatic breast cancer (mBC) selected by the ixabepilone Drug Response Prediction (DRP) after failure of an anthracycline and a taxane.

Investigational medicinal product:
Ixabepilone

Indication:
Locally Recurrent and Metastatic Breast Cancer

Development phase:
Phase 2

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CONFIDENTIALITY STATEMENT

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1 PROTOCOL OUTLINE

Working title		Phase II, open label, single arm study to investigate anti-tumor effect of ixabepilone in patients with locally recurrent or metastatic breast cancer (mBC) selected by the ixabepilone Drug Response Prediction (DRP) after failure of an anthracycline and a taxane
Objectives		Primary: • To evaluate the clinical benefit rate (CBR) of ixabepilone Secondary: • To evaluated progression free survival (PFS) • To evaluate overall survival (OS) • To evaluate objective response rate (ORR) defined as Complete Response (CR) and Partial Response (PR) • To evaluate the safety profile of ixabepilone in patient with locally recurrent or metastatic breast cancer • To further establish the clinical validation of the use of the DRP-Ixabepilone-Breast in selecting patients with locally recurrent or metastatic breast cancer • Assess difference in prediction based on archival and fresh biopsy from same patient (percent agreement in binary prediction, and difference in primary and secondary endpoints with archival versus fresh biopsies)
Efficacy variables	Primary	• Clinical Benefit Rate (CBR) will be defined as the proportion of patients having a Complete Response (CR), Partial Response (PR), or Stable Disease (SD) for at least 24 weeks
	Secondary	• PFS defined as time from randomisation until progressive disease(PD) according to RECIST v 1.1 or death, whichever occurs first • OS defined as the time from randomization until death from any cause • ORR defined as the proportion of patients with complete response (CR) + partial response (PR) according to RECIST v 1.1 • Duration of response (DOR) defined as time of first documented CR or PR response until documented tumor progression (RECIST v 1.1)
Safety variables		• An elicited toxicity in target organs based on the Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0) • A description of the frequency and severity of adverse events based on CTCAE v.5.0 • Hematology and clinical biochemistry • Vital signs

Selection criteria	Inclusion	1. Signed informed consent form 2. Age 18 years or older 3. Patients with histologically or cytological confirmed adenocarcinoma of the breast and with confirmed locally recurrent or metastatic disease 4. Patients with hormone receptor positive and HER2 negative or triple negative primary tumor. 5. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated. 6. Maximum of three (3) prior chemotherapies in the metastatic setting in addition to any number of prior lines of endocrine therapy 7. Measurable disease by RECIST v 1.1 criteria 8. Performance status of ECOG ≤ 1 9. Ixabepilone DRP - score of >67%. 10. Adequate conditions as evidenced by the following clinical laboratory values: a. Absolute neutrophils count (ANC) ≥ 1.5 x 10^9/L b. Hemoglobin > 10 g/dL (6.2 mmol/L) c. Platelets ≥ 100 x 10^9 /L d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN e. Serum bilirubin ≤ 1.0 ULN f. Creatinine ≤ 1.5 ULN g. Alkaline phosphatase ≤ 2.5 x ULN or ≤5x ULN if documented liver/bone metastases. h. Blood urea within normal limits 11. Because of possible interference of cytochrome P450 3A4 activity by ixabepilone, patients will be excluded from receiving the following medications at enrollment and while enrolled onto the study: amiodarone, clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, and saquinavir 12. Negative pregnancy test at baseline 13. Women of childbearing age and potential must be willing to use highly effective contraception during the study and at least until 30 days after last dose of study drug. Male patients or male patients who have female partners of childbearing age and potential must be willing to use effective contraception during the study and at least until 90 days after last dose of study drug. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

	Exclusion	1. HER2 positive tumor 2. Concurrent chemotherapy, radiotherapy, hormonal therapy, or other investigational drug except non-disease related conditions (e.g. insulin for diabetes) during study period 3. Patients with intracranial disease 4. Other malignancies with exception of curative treated non-melanoma skin cancer or cervical carcinoma in situ within 5 years prior to entering the study 5. Any active infection requiring parenteral or oral antibiotic treatment. 6. Patients with grade 2, in case of diabetes grade 1 or greater neuropathy 7. Clinically significant (i.e. active) cardiovascular disease: a. Stroke within ≤ 6 months prior to day 1 b. Transient ischemic attach (TIA) within ≤ 6 months prior to day 1 c. Myocardial infarction within ≤ 6 months prior to day 1 d. Unstable angina e. New York Hart Association (NYHA) Class II or greater congestive heart failure (CHF) f. Serious cardiac arrhythmia requiring medication 8. Other medications or conditions, including surgery, that in the Investigator's opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results 9. Requiring immediate palliative treatment of any kind including surgery and/or radiotherapy 10. Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry) 11. Known prior severe hypersensitivity reactions to agents containing polyoxyethylated castor oil (Cremophor EL) 12. Patients must not continue treatment with the following strong inhibitors of CYP3A4: ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine and voriconazole. These therapies should be discontinued 72 hours prior to initiation of study drug therapy. Similarly, patients must not continue treatment with the following strong inducers of CYP3A4: phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital. (20 mg dexamethasone can be used for pre-treatment if required). These therapies should be discontinued 72 hours prior to initiation of study drug therapy 13. Positive HIV and hepatitis B and C status, assessed from medical records only
Methods & procedures		This study is a multi-center, open-label, non-randomized, phase II study of ixabepilone as treatment in patients with locally recurrent or metastatic breast cancer. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated. The patients should have received a maximum of three (3) prior chemotherapies in the metastatic setting. Patients will be screened with the ixabepilone DRP. If the DRP score is above >67% the patient can be included in the clinical study, if all the other eligibility criteria are fulfilled. The biopsy should be taken after the last anticancer treatment has been stopped. If such biopsy is not available it has to be done during the screening (first 2 weeks,

		if possible). The biopsy can be taken from any lesion, and the sample will be used to obtain the DRP score. Patients will receive ixabepilone every 3 weeks until the occurrence of: • disease progression, or • unacceptable toxicity, or • patient refusal/withdrawing of consent, or • non-compliance to the protocol, or • physician decision to discontinue treatment, or • treatment delay > 2 weeks (except in the case of perceived patient benefit)
Medication (dose, route, duration)	Test	Ixabepilone is classified as a microtubule inhibitor and is a semisynthetic analog of the natural product epothilone B. The dose of ixabepilone is 40 mg/m^2 infused intravenously over 3 hours every 3 weeks. Doses for patients with body surface area (BSA) greater than 2.2 m^2 should be calculated based on 2.2 m^2. To minimize the chance of occurrence of a hypersensitivity reaction, all patients must be premedicated approximately 1 hour before the infusion of ixabepilone with: • An H1 antagonist (e.g., diphenhydramine 50 mg orally or equivalent) and • An H2 antagonist (e.g., famotidine 20 -40 mg orally, cimetidine 200 - 400 mg orally or equivalent) Patients who experienced a hypersensitivity reaction to ixabepilone require premedication with corticosteroids (e.g., dexamethasone 20 mg intravenously, 30 minutes before infusion or orally, 60 minutes before infusion) in addition to pretreatment with H1 and H2 antagonists. Neuropathy will be closely monitored in order to adjust or delay dosing of ixabepilone (according to US IXEMPRA package insert; instruction for use).
	Comparator	None
Statistics	Sample size	Up to 200 patients with sufficient tumor tissue material will be screened to include 60 patients (53 patients evaluable for response), who consent to participate in the study. Patients for whom a biopsy after last anticancer treatment is not available or has a DRP below 67 % will not count towards the 200 patients screened, and 60 patients treated, and will not be included in the primary analysis.

	Methods	Simon's two-stage design (Simon, 1989, Minimax) will be used. The null hypothesis that the true clinical benefit rate is 25% will be tested against a one-sided alternative. In the first stage, 30 patients will be accrued, and 28 patients are expected to be evaluable. If there are 7 or fewer with clinical benefit in these 28 patients, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 60, of which 53 are expected to be evaluable. The null hypothesis will be rejected if 19 or more with clinical benefit are observed in 53 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true response rate is 41%. The clinical benefit rates may differ in the actual population, but the difference between unselected historical control and selected population should remain constant. One-sided comparisons of CBR between treatment and historic control will be performed, and will be repeated for subgroups defined by ER status.

2 LIST OF ABBREVIATIONS

ADC	Analog-to-Digital Converter
ADL	Activities of Daily Living
AE	Adverse Event
Allarity	Allarity Therapeutics
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophils Count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CHF	Congestive Heart Failure
CI	Confidence Interval
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
DM	Data Manager
DOR	Duration of Response
DPD	Dihydropyrimidine Dehydrogenase Deficiency
DPO	Data Protection Officer
DRP	Drug Response Prediction
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group Performance
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	The European Medicines Agency
EOT	End of Treatment
ER	Estrogen Receptor
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-stimulating Factor
GM-CSF	Granulocyte-macrophage Colony-stimulating Factor
HCG	Human Chorionic Gonadotropin
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Viruses
HSR	Hyper Sensitivity Reaction
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	Independent Committee Review
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention-To-Treat
IV	Intravenous

L	Litre
mBC	Metastatic Breast Cancer
mg	Milligram
mL	Millilitre
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRP1	Multidrug Resistance-related Protein 1
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Hart Association
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over the Counter
pCR	Pathological Complete Remission
pCRB	Pathologic Complete Response in the Breast at surgery
pCRBL	Pathologic Complete Response in the Breast and Lymph nodes at surgery
PD	Progressive Disease
PI	Principal Investigator
PIS	Patient Information Sheet
PR	Partial Response
PSF	Progression Free Survival
Q3	Every 3 weeks
RECIST	Response evaluation criteria in solid tumors
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD	Stable Disease
SDV	Source Data Verification
SmPC	Summary of product characteristics
SOP	Standard Operating System
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emerging Adverse Events
TIA	Transient Ischemic Attach
ULN	Upper Limit Normal

3 INTRODUCTION

3.1 Breast Cancer and standard treatment

Breast cancer is the leading cancer disease and the leading cause of cancer related deaths in women. A large proportion of patients with primary breast cancer are categorized as having high risk disease based on tumor histology grade, estrogen receptor measurements, lymph node involvement, and age and tumor size. These high-risk breast cancer patients are offered adjuvant chemotherapy which often includes anthracyclines, cyclophosphamide and taxanes. Despite adjuvant treatment approximately 20% of all breast cancer patients will experience disease recurrence with local or distant recurrences, some of which will be metastasis to the brain. Treatment for metastatic breast cancer includes endocrine treatment and/or chemotherapy in combination with biological treatment in HER2 positive patients.

The outcome after chemotherapy and endocrine therapy for metastatic breast cancer becomes poorer and poorer at each time a new treatment is introduced due to progression on the former treatment. With first line treatment, the expected objective response rate is approximately 50% declining to less than 25% at 3-4th line treatment (1). Worldwide about 500,000, in Europe about 189.000 and in Denmark about 1100 breast cancer patients die annually (2,3).

Anthracyclines and taxanes are generally considered the most active cytotoxic drug classes in breast cancer. As a result, both classes of agents are commonly used in the metastatic as well as the adjuvant setting. However, some patients demonstrate primary resistance to anthracyclines and taxanes and some patients fail to respond to taxanes in the first-line setting.

Capecitabine is approved to treat patients with metastatic breast cancer who have received prior anthracycline- and taxane-based chemotherapy for early or late-stage breast cancer (4) and FDA have approved capecitabine in combination with ixabepilone for this indication. However, this treatment regime was not approved by EMA in EU as they concluded, that combination with ixabepilone did not substantially improve the effect of capecitabine alone (5). Patient selection with the ixabepilone DRP is expected to enrich the trial population with likely responders.

3.2 Drug Class

The IMP ixabepilone is FDA approved as IXEMPRA® for the treatment of Breast Cancer (https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022065s002lbl.pdf) and is a semisynthetic analog of the natural product epothilone B. The epothilones and their analogs are a novel class of non-taxane microtubule-stabilizing agents obtained from the fermentation of Sorangium cellulosum. Ixabepilone was developed by Bristol-Myers Squibb (BMS) for its potential use in the treatment of cancer.

Ixabepilone is a novel antineoplastic agent that stabilizes microtubule dynamics, resulting in blockade of cancer cells in mitosis during cell division, leading to cell death (6). Ixabepilone induces a distinct pathway of cellular apoptosis via activation of caspase-2, whereas other tubulin agents, such as the taxanes, act via caspase-9 (7). Ixabepilone is a poor substrate for efflux transporters such as the multidrug resistance-related protein (MRP1) and P-glycoprotein (P-gp) that are involved in drug-resistance mechanisms (8). Epothilones have a tubulin-binding mode distinct from that of other microtubulestabilizing agents 1(9). Ixabepilone's tubulin-binding mode affects the microtubule dynamics of multiple β-tubulin isoforms, including the class III isoform of β-tubulin (β-III tubulin) (8, 10, 11) the expression of which has been implicated in clinical taxanes resistance (12-15).

3.3 Previous Clinical Studies with ixabepilone in Metastatic Breast Cancer

Ixabepilone has been evaluated in 13 BMS-sponsored clinical studies hereof 8 in Metastatic Breast Cancer.
In Phase 1 studies of ixabepilone as monotherapy, objective responses were demonstrated in 9 various tumor types (16, 17). Dose-limiting toxicities observed in ixabepilone as monotherapy included sensory neuropathy, neutropenia, myalgia, and fatigue. Adverse events (AEs) in patients where ixabepilone was used in combination with other chemotherapy agents were similar qualitatively, no toxicities unique to combination therapies were reported.
Pharmacokinetics results indicate that exposure to ixabepilone is increased by 22%, 30%, and 81% in patients with mild, moderate, or severe hepatic dysfunction, respectively (18). After coadministration of ixabepilone and capecitabine, PK differences are minor and are not expected to affect the safety profile or efficacy of either ixabepilone or capecitabine.

Phase 2 studies demonstrated the activity of ixabepilone in advanced breast cancer (19-24), and other malignancies, the most notable toxicities reported of ixabepilone as monotherapy are peripheral neuropathy, neutropenia, myalgia, arthralgia, alopecia, and fatigue. The peripheral neuropathy has been predominantly sensory, cumulative in nature, and reversible upon discontinuation of ixabepilone.

Five studies of ixabepilone monotherapy (40 mg/m^2/3 hours) have shown effect in breast cancer as neoadjuvant treatment and 4 in advanced, locally recurrent or metastatic, breast cancer (see Table 1).

Table 1. Survey of Phase 2 Studies, Monotherapy (40 mg/m2/3 h) in Breast Cancer [(25)]

Study No.	Setting/Population	N	Treatment	Efficacy end-point
CA163009	Advanced breast cancer Taxane resistant	49	Ixabepilone 40 mg/m2 Q3 week	ORR[1]
CA163010	Advanced breast cancer Anthracycline pretreated	65	Ixabepilone 40 mg/m2 Q3 week	ORR[1]
CA163081	Advanced breast cancer - resistant to anthracycline, taxane, and capecitabine	126	Ixabepilone 40 mg/m2 Q3 week	ORR[1]
CA163080	Neoadjuvant therapy Invasive breast adenocarcinoma ≥ 3 cm not amenable to breast conservation surgery	164	Ixabepilone 40 mg/m2 Q3 week (max 4 cycles)	1° Best ORR[1] (CR[2] or PR[3]) Co-2°: pCRB[4] and pCRBL[5]
CA163107	Metastatic breast cancer Anthracycline pretreated, taxane resistant	54	Ixabepilone 40 mg/m2 Q3 week (max 9 cycles)	1° RR[6] (by IRC[7]) 2°:duration of response time to progression

[1]ORR=Objective Response Rate, [2]CR=Complete Response, [3]PR=Partial Response, [4]pCRB = pathologic complete response in the breast at surgery, [5]pCRBL= pathologic complete response in the breast and lymph nodes at surgery, [6]RR=Response Rate, [7]IRC= Independent Review Committee; Q3=every 3 weeks

3.3.1 Efficacy

In advanced breast cancer the ORR of ixabepilone monotherapy varies from 11.5 to 42 % depending on the lines of chemotherapy and resistancy (26). In the large phase 2 study (CA163081) in patients resistant to anthracycline, taxane and capecitabine, ORR was 11.5% (CI-

95% 6.3 to 18.9%) and with SD ≥24 weeks in 14.3%. Furthermore, the median PFS and duration of response was 3.1 months and 5.7 months respectively (24).

3.3.2 Safety

3.3.2.1 General safety concerns

The most common Treatment-emerging Adverse Events (TEAE) of ixabepilone monotherapy in advanced breast cancer (Studies CA163081, CA163009, CA163010 and CA163080) were alopecia (59%), fatigue (53%), myalgia (50%), peripheral sensory neuropathy (49%), nausea (48%), arthralgia (31%), vomiting (30%), stomatitis (28%), and diarrhea (26%). Treatment-related cardiac events were rare in patients who received ixabepilone as monotherapy.
The most frequently reported grade 3/4 TEAEs appear from Table 2.

Table 2. Grade 3/4 treatment-emerging adverse events most frequently reported in patients with advanced breast cancer (monotherapy)(Studies CA163081, CA163009, CA163010 and CA163080).

	Number (%) of Patients				
	CA163081	CA163009	CA163010	CA163 081/009/010	CA163080
N	126	49	65	240	161
Peripheral sensory neuropathy	17 (13)	7 (14)	14 (22)	38 (16)	4 (2)
Fatigue/asthenia	16 (13)	13 (27)	4 (6)	33 (14)	3 (2)
Arthralgia/myalgia	10 (8)	5 (10)	7 (11)	22 (9)	3 (2)
Stomatitis/mucositis	8 (6)	2(4)	3 (5)	13 (5)	3 (2)

Table 3 presents both the nonhematologic and hematological most commonly reported treatment related adverse events occurring in patients with metastatic or locally advanced breast cancer treated with ixabepilone as monotherapy in the published study CA163081.

Table 3. Most common treatment-emerging adverse events in CA163081,(24)

Table 4. Overall Treatment-Related Nonhematologic Adverse Events Occurring in ≥ 5% Patients and Hematology (worst on-study CTC grade; n = 126)

Adverse Event	Total (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Treatment-related nonhematologic adverse event				
Peripheral sensory neuropathy	60	30	13	1
Fatigue/asthenia	50	21	13	1
Myalgia/arthralgia	49	26	8	0
Alopecia	48	39	0	0
Nausea	42	11	2	0
Stomatitis/mucositis	29	7	6	1
Vomiting	29	9	1	0
Diarrhea	22	5	1	0
Musculoskeletal pain	20	9	3	0
Anorexia	19	3	2	0
Constipation	16	6	2	0
Abdominal pain	13	3	2	0
Headache	11	6	0	0
Peripheral motor neuropathy	10	7	1	0
Dyspnea	9	2	1	0
Nail disorder	9	4	0	0
Pain	8	2	3	0
Palmar-plantar erythrodysesthesia syndrome	8	3	2	0
Pyrexia	8	2	1	0
Dizziness	7	2	0	0
Dysgeusia	6	1	0	0
Gastroesophageal reflux	6	2	0	0
Hot flush	6	2	0	0
Hypersensitivity	5	2	1	0
Hematology (worst on-study CTC grade)				
Leukopenia	90	23	36	13
Anemia	84	26	6	2
Neutropenia	79	17	31	23
Thrombocytopenia	44	4	6	2

Abbreviation: CTC, National Cancer Institute Common Toxicity Criteria.

3.3.3 Specific safety concerns

3.3.3.1 Peripheral neuropathy

Peripheral neuropathy is the main non-hematologic toxicity of ixabepilone. Peripheral neuropathy was reported in 62% of patients in study CA163081 (64% across the 3 monotherapy studies). Painful neuropathies, as defined by the occurrence of neuropathic pain, dysesthesia or neuralgia, were reported in 6% of patients in the 3 monotherapy studies. Peripheral motor neuropathy was reported in 7% of patients in the 3 monotherapy studies and usually occurred in patients with sensory neuropathy. Autonomic neuropathy was rare, occurring in 1% of patients in the 3 monotherapy studies. The ixabepilone studies focused on patients who were resistant to prior therapies, including taxanes. As such, a proportion of patients had baseline peripheral sensory neuropathy (27% in CA163081), though patients with Grade 2 or higher peripheral neuropathy (sensory or motor) at study entry were excluded from studies with ixabepilone.

The neuropathy is cumulative with the time of treatment and partly reversible after dose-reduction. In CA163081 the median number of cycles to onset of grade 3/4 neuropathy was 4 and the median time to improvement and resolution of grade 3/4 neuropathy was 4.6 and 5.4 weeks respectively (from 'Withdrawal assessment report for Ixempra', European Medicines Agency (EMA) London, 23 April 2009) (5).

3.3.3.2 Myelosuppression

Myelosuppression was summarized across studies CA163081, CA163009, CA163010 and CA163080. In this population Grade 3 or 4 neutropenia was reported in 55% of all patients treated with monotherapy in advanced breast cancer. Furthermore, thrombocytopenia was mostly

Grade 1 (35%) and Grades 3 or 4 thrombocytopenia was reported in 6% of patients. The majority of cases of anemia were Grade 1 or 2 and Grades 3 or 4 anemia was reported in 8% of all patients.

3.3.3.3 Hypersensitivity Reactions

The diluent used with BMS-247550 is a BMS-purified polyoxyethylated castor oil (CremophorEL) and has the potential for inducing a hypersensitivity reaction. In clinical trials of BMS-247550, anaphylaxis and severe hypersensitivity reactions (dyspnea requiring bronchodilators, hypotension requiring treatment, syncope, and bradycardia) that were reported as serious adverse events have occurred in less than 1% of patients. Routine premedication, including H1 and H2 blockers (e.g., diphenhydramine and ranitidine) was instituted after 2 patients developed severe hypersensitivity adverse events (dyspnea and bronchospasm) in the weekly Phase I monotherapy trial. Since the institution of premedication the incidence of CTC term: hypersensitivity of any grade is < 1% in 439 patients treated in all BMS sponsored Phase II trials. Additionally, 17% of patients had CTC terms of allergy/immunology: Other, (of any grade) reported; the majority of incidents consisted of skin rash. Steroids were not required as premedication, unless prior hypersensitivity reaction (HSR) had been reported. Patients with a prior history of HSR to polyoxyethylated castor oil were excluded from the studies.

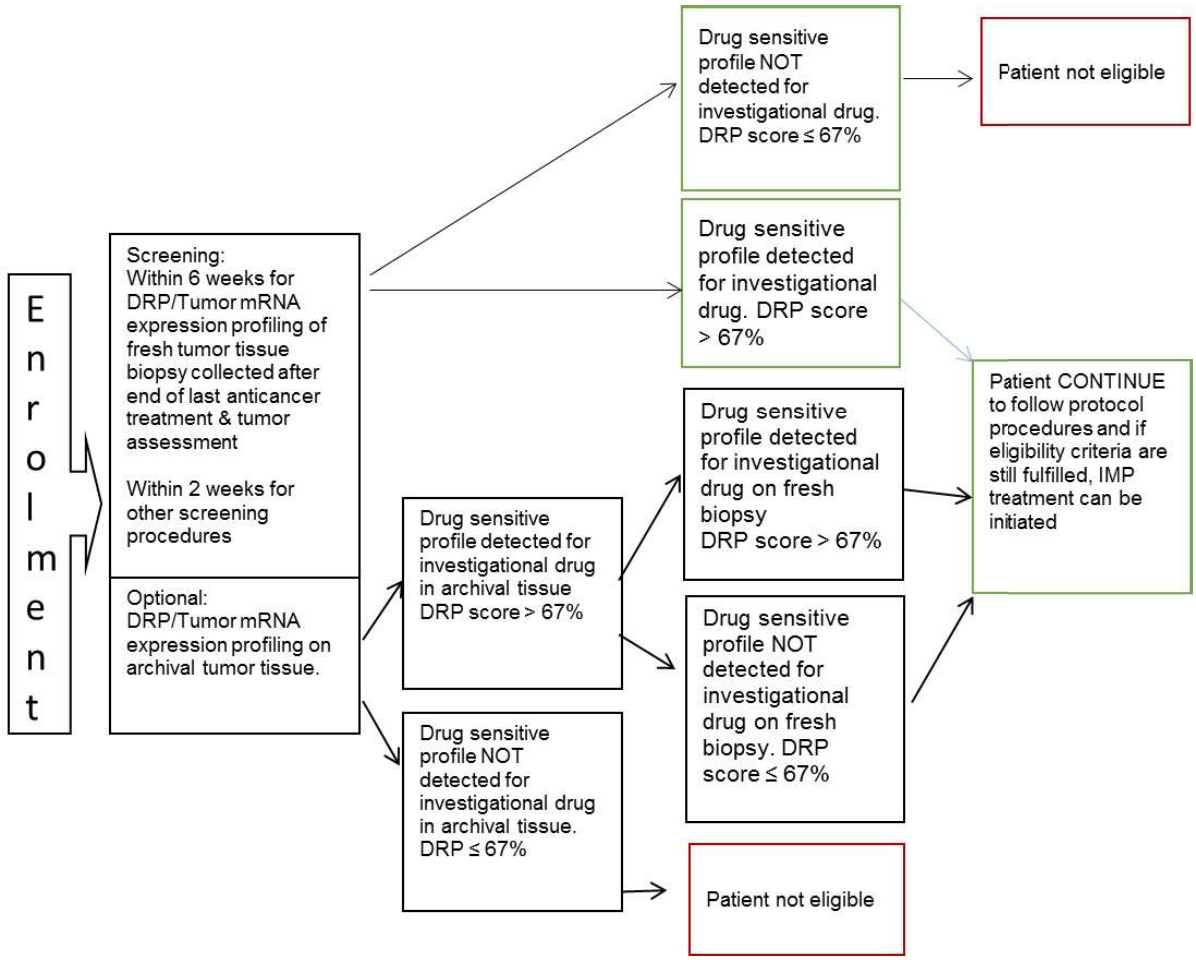
Hypersensitivity reactions were reported in 79 (6%) of the 1323 patients who received any ixabepilone in the Phase II and III studies. Most HSR occurred in Cycles 1 (32/79; 41%) and 2 (36/79; 46%). Grade 3/4 hypersensitivity reactions, including anaphylaxis, were rare and were reported in 9 (1%) patients (all but 1 in the first 2 cycles), 3 of whom subsequently received additional cycles of ixabepilone. HSRs rarely led to discontinuation (< 1% of patients). There were no deaths due to hypersensitivity reactions.

3.4 Rationale for study design

Ixabepilone is approved by FDA for use in patients with with metastatic or locally advanced breast cancer. Ixabepilone has documented treatment effect both in combination with capecitabine and as monotherapy (see current SmPC for Ixempra). Since there are few treatment options for patients resistant to antracylines, taxanes and capecitabine, ixabepilone is an alternative treatment option for these late stage breast cancer patients. Ixabepilone given as monotherapy has a documented ORR that varies between 11.5 to 42% (26). With this relatively low response rate a relatively high amount of patients will be exposed to treatment without having an effect, and thereby also exposed to the side effects of the product. Therefore, a Drug Response Prediction methodology (see below) has been introduced in the current study. Patients expected to respond to treatment will be selected according to a tumor biopsy mRNA expression profiling, leading to a DRP score (see section 3.5) and only patients having a DRP score > 67% will be considered as possible positive responders and included in the study. About half of patients are expected to have a positive DRP score (above > 67%) and can be offered therapy with ixabepilone.

This is a clinical study with an enrichment design to facilitate precision medicine. The DRP profile is used to allocate the patients with high likelihood of response to therapy with ixabepilone (Figure 1).

Figure 1. Schematic diagram of trial design and procedures for patient selection



3.5 DRP® – General Description

Allarity Therapeutics (Allarity) in Hoersholm, Denmark, is developing the Drug Response Prediction (DRP®) for individual systemic anti-cancer treatments. A DRP® is an assay that is based on samples from a tumor that can estimate the likelihood of whether the tumor will respond to a specific drug. The DRP® method builds on the comparison of sensitive and resistant cell lines including genomic information from the NCI (USA) NCI60 cell lines, clinical tumor biology and clinical correlates in a systems biology network. Allarity uses messenger RNA (mRNA) to make such a drug specific estimate. Analytical validation is established. Clinical validation has been investigated and established in several study settings and have been published (27-33). The further clinical validity of the ixabepilone DRP® in advanced breast cancer is one of the objectives of this phase 2 study.

Each drug for which Allarity Therapeutics develops a DRP® based on in vitro data and big data from patients, has a unique signature of 200 to 400 genes. This signature is matched to the corresponding genes in the universal microarray (which contains all genes) in order to make prediction for a specific drug for a specific patient. Even drugs, for which a signature is developed in the future, can be matched to the existing microarray data for a specific patient.

3.6 Ixabepilone DRP®

The procedure for developing ixabepilone DRP® is based on mRNA expression data on data from growth inhibition studies in 60 cancer cell lines (NCI60). The prediction has been tested in a cross-validation on the cell line data. The correlation between measured and predicted sensitivity was 0.28 which points to an ability to predict in a clinical setting. The genes that differed in expression between sensitive and resistant cell lines were analyzed for clues to resistant mechanisms. In an analysis of 26 different cancer indications, it was predicted that in addition to hematological malignancies, breast cancer, renal cancer, melanoma, glioma and others were sensitive to ixabepilone.

Evaluation of ixabepilone DRP in neoadjuvant breast cancer.

The ixabepilone DRP, an mRNA-based predictor of responsiveness to ixabepilone was developed and applied to gene expression data prepared using clinical samples from breast cancer patients treated neoadjuvantly with ixabepilone (34). The samples were diagnostic biopsies analyzed with Affymetrix GeneChips. Using the ixabepilone DRP, patients with pathological complete remission (pCR) were predicted to be more sensitive to ixabepilone than patients with no pCR (Figure 2).

Figure 2. Sensitivity to ixabepilone predicted by the ixabepilone DRP.

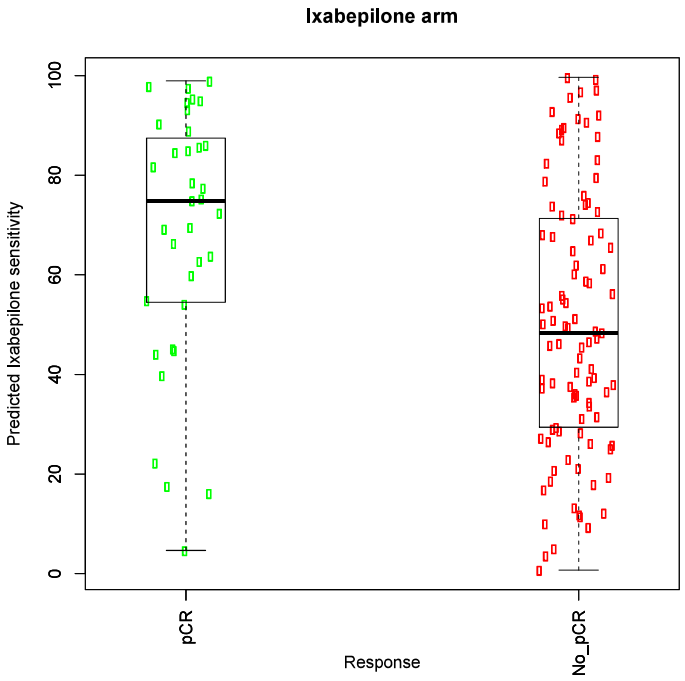


Table 4 shows the number of responders correctly predicted at a cutoff of 67, demonstrating an increased response rate for breast cancer patients having DRP scores above the cutoff.

Table 4. Number of predicted responders at a cutoff of 67

	Responders (pCR)	Non responders (no pCR)
DRP positive (>67)	21	29
DRP negative (<=67)	14	68

Response rate above cutoff: 42%

Response rate below cutoff: 17%

3.7 Benefit/Risk Assessment

Locally advanced or metastatic breast cancer is a life-threatening disease. The outcome after chemotherapy and endocrine therapy for metastatic breast cancer becomes poorer and poorer each time a new treatment is introduced due to progression on the former treatment. The management of metastatic breast cancer continuous to evolve and improve towards a chronic disease model with sequential use of lines of therapy. Therefore there is a need for alternative treatment options, for patients who progress on various taxanes, anthracyclines, and capecitabine; that can be supported by a methodology (Drug Response Prediction) for selecting the most efficient drug for the patient.

If DRP selection identifies those patients who have a high likelihood of responding to ixabepilone, we can select those patients who will benefit while excluding those patients that will not. The toxicity profile of ixabepilone is generally manageable and predictable. The potential benefit of treatment would then most likely outweigh the expected risks.

4 OBJECTIVES

4.1 Primary objective:

- To evaluate the clinical benefit rate (CBR) ixabepilone.

4.2 Secondary objective:

- To evaluated progression free survival (PFS).
- To evaluate overall survival (OS).
- To evaluate objective response rate (ORR) defined as Complete Response (CR) and Partial Response (PR).
- To evaluate the safety profile of treatment with in locally recurrent or metastatic breast cancer.
- To further establish the clinical validation of the use of the DRP-Ixabepilone-Breast in selecting patients locally recurrent or with metastatic breast cancer.
- Assess difference in prediction based on archival and fresh biopsy from same patient (percent agreement in binary prediction, and difference in primary and secondary endpoints with archival versus fresh biopsies)

5 PATIENT SELECTION

The target study population is patients with locally recurrent or metastatic breast adenocarcinoma, with hormone positive and HER2 negative or triple negative primary tumors, who have received a maximum of 3 prior chemotherapies in the advanced setting.

5.1 Inclusion Criteria

In order to participate in this study the patients must meet all of the following inclusion criteria:

1. Signed informed consent form
2. Age 18 years or older
3. Patients with histologically or cytological confirmed adenocarcinoma of the breast and with confirmed locally recurrent or metastatic disease
4. Patients with hormone receptor positive and HER2 negative or triple negative primary tumor
5. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated
6. Maximum of three (3) prior chemotherapies in the metastatic setting in addition to any number of prior lines of endocrine therapy
7. Measurable disease by RECIST v 1.1 criteria
8. Performance status of ECOG ≤ 1
9. DRP®-Ixabepilone score of >67%.
10. Adequate conditions as evidenced by the following clinical laboratory values:
    a. Absolute neutrophils count (ANC) ≥ 1.5 x 10^9/L
    b. Hemoglobin ≥ 10 g/dL (6.2 mmol/L)
    c. Platelets ≥ 100 x 10^9 /L
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN
    e. Serum bilirubin ≤ 1.0 ULN
    f. Creatinine ≤ 1.5 ULN
    g. Alkaline phosphatase ≤ 2.5 x ULN or ≤5x ULN if documented liver/bone metastases
    h. Blood urea within normal limits
11. Because of possible interference of cytochrome P450 3A4 activity by ixabepilone, patients will be excluded from receiving the following medications at enrollment and while enrolled onto the study: amiodarone, clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, and saquinavir
12. Negative pregnancy test before study entry
13. Women of childbearing age and potential must be willing to use highly effective contraception during the study and at least until 90 days after last dose of study drug. Male patients or male patients who have female partners of childbearing age and potential must be willing to use effective contraception during the study and at least until 90 days after last dose of study drug. Highly effective methods of birth control are defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

5.2 Exclusion Criteria

In order to participate in the study the patients must not meet any of the following exclusion criteria:

1. HER2 positive tumors
2. Concurrent chemotherapy, radiotherapy, hormonal therapy, or other investigational drug except non-disease related conditions (e.g. insulin for diabetes) during study period and terminated within 4 weeks prior to entering the study
3. Patients with intracranial disease
4. Other malignancy with exception of curative treated non-melanoma skin cancer or cervical carcinoma in situ within 5 years prior to entering the study
5. Any active infection requiring parenteral or oral antibiotic treatment.

6. Patients with grade 2, in case of diabetes grade 1 or greater neuropathy
7. Clinically significant (i.e. active) cardiovascular disease:
    a. Stroke within ≤ 6 months prior to day 1
    b. Transient ischemic attach (TIA) within ≤ 6 months prior to day 1
    c. Myocardial infarction within ≤ 6 months prior to day 1
    d. Unstable angina
    e. New York Hart Association (NYHA) Class II or greater congestive heart failure (CHF)
    f. Serious cardiac arrhythmia requiring medication
8. Other medications or conditions, including surgery, that in the Investigator's opinion would contraindicate study participation for safety reasons or interfere with the interpretation of study results
9. Requiring immediate palliative treatment of any kind including surgery and/or radiotherapy
10. Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry)
11. Known prior severe hypersensitivity reactions to agents containing polyoxyethylated castor oil (Cremophor EL)
12. Patients must not continue treatment with the following strong inhibitors of CYP3A4: ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine and voriconazole. These therapies should be discontinued 72 hours prior to initiation of study drug therapy
    Similarly, patients must not continue treatment with the following strong inducers of CYP3A4: phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital (20 mg dexamethasone can be used for pre-treatment if required). These therapies should be discontinued 72 hours prior to initiation of study drug therapy
13. Positive HIV and hepatitis B and C status, assessed from medical records only

5.3 Recruitment

Eligible patients will have the study explained to them and will receive the written patient information sheet (PIS). After having had the time to review the nature of the study, they will have the opportunity to ask questions to the investigational team. If, after this, the patients agree to participate, they will be asked to sign and date one original of the written informed consent form (ICF). The patients will then receive a copy of the signed and dated patient information/informed consent form. The original signed ICF will be filed in the Investigator Site File (ISF). The PIS will contain site contact information in case of any questions or medical emergency.

Any written information given to potential patients will be submitted to, and approved by, the respective Ethics Committee(s) prior to implementation.

The Investigator will maintain a Patient Screening Log to collect information on all patients who sign an ICF regardless of whether or not they meet the study eligibility criteria following completion of the screening evaluations. After completion of Screening, all patients deemed eligible to take part in this study will be entered onto a Patient Identification Log.

5.4 Methods for Assigning Patients to Treatment

All patients signing the ICF and who enter the formal screening process will be assigned a unique screening number automatically via the eCRF system. This number will consist of two letters and 5 digits. The letters identifying the country, the first two digits being the site number (e.g., 01) and the last three digits consisting of the sequence number in which the patient was screened at the site (e.g., the third patient screened would be 003).
Following successful compltion of the screening/baseline evaluations and confirmation that the patient is eligible for participation, the patient will be assigned to treatment.

5.5 Formalin-Fixed Paraffin-Embedded (FFPE) tumor tissue for DRP analysis

A biopsy should be taken after the last anticancer treatment has been stopped. If such biopsy is not available it may be done during the screening (first 2 weeks, if possible). This sample will be used for DRP assessment.
The biopsy can be taken from any lesion, most likely the most accessible lesion, but this will be the physician's decision. Formalin-Fixed Paraffin-Embedded (FFPE) tissue specimens should be prepared (see the Standard Guidelines for FFPE Tissue Collection for DRP analysis).
Patients can be included based on an archival biopsy, but a new biopsy should be obtained wherever possible before treatment start. If included on archival biopsy and the new biopsy is negative or not possible, patients can continue treatment.

Tumor tissue will be obtained from the local pathology department in accordance with "Standard Guidelines for FFPE Tissue Collection for DRP analysis" and relevant tissue section (2-6 sections of 10-20µm for a total of 40-60µm) will be cut at the pathological department. Tissue collection kits are produced for participating sites. The collection kits are produced as single unique, serialized and pseudonymized kits ensuring confidentiality for the patient. All data is stored secured and all data transfers are encrypted.

Allarity Therapeutics will receive the samples. RNA is isolated from the tumor biopsy, amplified, labelled and hybridized to microarray gene chips to obtain gene expression data of the tumor tissue. The gene expression data is patented to Allarity Therapeutics's DRP analysis algorithm for generation of a DRP score ranging from 0 to 100. Investigator sites will get binary DRP result reported, i.e. 1 for a DRP positive score and 0 for a DRP negative score.
Analyses of the tumor tissue will be performed Allarity Therapeutics, Hoersholm, Denmark. They will calculate the DRP score and report back to the site within approximately 2 weeks. The samples will be destroyed at the end of study.

6 TREATMENT PROCEDURES

6.1 Overall Study Design

This study is a multi-center, open-label, non-randomized, phase II study of ixabepilone as treatment in patients with locally recurrent or metastatic breast cancer. Previous chemotherapies (neoadjuvant, adjuvant or in the metastatic setting) must have included a taxane and an anthracycline unless anthracycline therapy is not indicated. The patients should have received a maximum of three (3) prior chemotherapies in the metastatic setting.

A biopsy should be taken after the last anticancer treatment has been stopped. If such biopsy is not available it may be done during the screening (first 2 weeks, if possible). This sample will be used for DRP assessment. The patient mRNA expression profiling will lead to a DRP score selected by the Ixabepilone DRP methodology.

Up to 200 patients with sufficient tumor tissue material will be screened to include 60 patients (53 patients evaluable for response) with a DRP score of > 67%. The study will be performed in accordance with the Simon two-stage design. In the first stage, 30 patients will be accrued, and 28 patients are expected to be evaluable. If there are 7 or fewer with clinical benefit in these 28 patients, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 60, of which 53 are expected to be evaluable. Patients for whom a biopsy after last anticancer treatment is not available or has a DRP below 67% will not count towards the 200 patients screened, and 60 patients treated, and will not be included in the primary analysis.

The patients will come to the screening visits within 6 weeks prior to the first possible administration of IMP. Patients will receive ixabepilone 40 mg/m^2 as a 3-h intravenous infusion on day 1 in a 21 days cycle.
Patients will continue the treatment until the occurrence of:

- disease progression, or
- unacceptable toxicity, or
- patient refusal/withdrawing of consent, or
- non-compliance to the protocol, or
- physician’s decision to discontinue treatment, or
- treatment delay > 2 weeks (except in the case of perceived patient benefit).

An End of Treatment visit will be conducted 4 weeks after administration of ixabepilone is stopped. Patients with CR, PR or SD where treatment have been stopped will continue to be follow-up and tumour assessment will be performed until disease progression.
All study related visits will be conducted within the period approved by the Regulatory Authorities and Ethics Committees. Any delay in the study that will affect the overall approved period will be amended to the authorities.

6.2 Study Flow-chart

Procedures	Pre-treatment		All Treatment Cycles		End of Treatment[19]	Post treatment follow-up (~every 3 months)
	Screening ≤ 6 weeks	Baseline ≤ 2 weeks	Day 1	Day 8 ±3 days and Day 15±3 days		
Informed Consent[1]	X					
Inclusion/Exclusion Criteria[2]	X[a]	X[b]				
Tumor biopsy - DRP/Tumor mRNA expression profiling[3]	X					
DRP results[4]		X				
Medical history[5]		X				
Physical examination and vital signs[6]		X	X		X	
Neurotoxicity questionnaire[7]			X		X	
Complete Blood Count (CBC)[8]		X	X	X[c]	X	
Blood chemistry[9]		X	X		X	
Pregnancy test[10]		X	X			
Tumor assessments/Scans[11]	X		At Week 6 and thereafter every 9 Weeks for 24 weeks; thereafter every 3 months			X (every 3 months until progression)
12-lead ECG[12]		X			X	
Pre- Medication[13]			X			
IMP (ixabepilone)[14]			X			
Follow up during infusion of ixabepilone[15]			X			
Adverse events / Baseline Conditions / Toxicity assessments[16]		X	X	X[d]	X	X
Concomitant medication/therapies[17]		X	X	X[e]	X	
Survival follow-up[18]						X

1. Acquire a signed Written Informed Consent prior to conducting any study related procedures.
2. Verify and confirm eligibility a. Verify inclusion criteria 1-9 and all exclusion criteria. b. Verify and confirm all eligibility prior assigning a patient to the study treatment.
3. Tumor biopsy DRP/Tumor mRNA expression profiling; A biopsy should be taken after the last anticancer treatment has been stopped. If such biopsy is not available an archival biopsy can be used as primary screening. If score is >67% patient will continue screening. If eligible an additional biopsy should be obtained prior to treatment initiation if possible.
4. Only patient with an ixabepilone DRP - score of >67% will continue screening.
5. Prior to Cycle 1 (Day 1) complete medical history/Baseline conditions, including breast cancer history, its previous therapy, and current medication will be recorded.
6. Physical examination, in addition the patients should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain), vital signs (including heart rate, blood pressure, respiratory rate and temperature), measurements of height (only at baseline), weight and Performance status (ECOG). All assessments will be performed within 14 days prior to Day 1 and within 24 hours prior to treatment start, prior to each cycle (drug administration) thereafter and at patient's end of treatment visit, when study discontinuation.
7. Patients to fulfil the questionnaire before each ixabepilone infusion and at end of treatment visit
8. Complete Blood Count (CBC) including absolute neutrophil, lymphocyte, monocyte, basophil, eosinophil count, and platelets. CBC will be performed prior to and weekly at day 8 and 15 in each cycle, at end of treatment and, if applicable, post treatment every 4 weeks until all related toxicities resolved, stabilized or

returned to baseline or are able deemed irreversible. c Day 8 and day 15 Complete Blood Count can be carried out at a local hospital or in primary care after 1st cycle, if required .

9. Blood Chemistry assessments (sodium, potassium, chloride, urea, creatinine, glucose (non-fasting), total protein, albumin, free calcium, total bilirubin, alkaline phosphatase, magnesium, phosphate, ALT, AST, INR, APTT and prothrombin time will be performed prior to each cycle and at end of treatment and, if applicable, post treatment every 4 weeks until all related toxicities resolved, stabilized or returned to baseline or are able deemed irreversible.
10. Pregnancy test will be performed prior to day 1 cycle 1 and before each drug administration in the following cycles by all female patients with reproductive potential.
11. Tumor measurements (e.g. CT or MRI etc.) will be performed within 4 weeks prior to day 1 cycle 1, at Week 6, prior Day 1 cycle 3 and then approximately every 9 weeks for 24 weeks and then every 3 months until progression. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks. Patients who discontinue protocol treatment for other reason than progression will have tumor assessments every 9 weeks until week 24 and then every 3 month until disease progression.
12. A 12-lead ECG will be performed prior first cycle and at any other time if clinically indicated.
13. All patients will receive premedication prior to each infusion of ixabepilone (see section 6.1)
14. Infusion to start after all safety measurements have been done and pre-medication given.
15. Follow-up subjects for symptoms during infusion, as applicable (e.g. observed by a study nurse for approximately 30 min for the 2 first cycles, if no reactions observed).
16. Patients will be monitored for adverse events (AEs)/Baseline conditions prior to the study start and continuously throughout the study until end of treatment. After that only events related to IMP should be reported. Only related AEs and all SAEs will be followed until returned to the baseline grade or ≤ Grade 1 or stability is reached.d May be performed by telephone call after 1st cycle.
17. Concomitant medication/therapies will be recorded prior to the study start and continuously throughout the study until end of treatment. After that, only anticancer related medications/therapies will be collected during the post treatment follow up period. e May be performed by telephone call after 1st cycle.
18. Survival will be followed until death or until last patient have been in the study for 2 years.
19. Approximately 28 days after end of last cycle

6.3 Assessments and Procedures

6.3.1 Clinic visits

After signing the Informed Consent the patient will visit the clinic for the screening procedures that may start up to 6 weeks prior to treatment start. While on treatment the patient will visit clinic at Day 1 (±3 days window) and Day 8 (±3 days window) and Day 15 (±3 days window) for all cycles and at end of treatment and post treatment follow-up. Please see flowchart section 4.2.

6.3.2 Demographics

At screening/baseline the date of birth, sex, and ethnicity will be recorded in the eCRF for all enrolled patients.

6.3.3 Urinary pregnancy test

A urine pregnancy test (or serum blood test, see section 6.3.4) will be performed at all visits for participating female patients of child-bearing potential.

Note: Female patients participating in the study:

- will be considered to be of child-bearing potential after the onset of their first menstrual period.
- who are documented as being of non-child-bearing potential (infertile, surgically sterile or post-menopausal) are to be exempt from pregnancy testing and the contraceptive requirements.
- will be considered post-menopausal if they have had 12 months of consecutive spontaneous amenorrhea, without an alternative medical cause. In case of doubt, a urine pregnancy test should be performed.
- will be considered surgically sterile if they are post-hysterectomy, 6 months post-surgical bilateral oophorectomy or 6 months post tubal ligation.
- who become pregnant during the study must immediately discontinue study medication and undergo an Early Termination visit according to the procedures described for end of treatment visit (Section 6.4.6).

A positive urine pregnancy test (or serum blood test, see section 6.3.4) at Screening or Randomisation Visits would result in exclusion of the patient from study participation (see exclusion criteria in Section 5.2)
A diagnosed pregnancy at later visits must be recorded on the Pregnancy Report Form. In addition, the patient must immediately stop IMP intake, be withdrawn from study participation and the pregnancy must be followed up until termination and/or birth. If the pregnancy does not reach full term, the reasons must be provided. Details concerning the health of the new-born must also be collected, if the pregnancy leads to a birth.

6.3.4 Laboratory tests

If an unexpected, clinically significant change from baseline occurs in a laboratory value or other measurement, the Investigator should repeat the test, if appropriate, to verify the result. The Investigator must comment on all clinically significant changes in laboratory values. All clinically significant adverse events must, if not resolved at end of study, be followed-up and this follow-up documented until the event returns to Grade 1 or becomes stabilized.

Laboratory tests will be assessed according to the hospital clinical practice. The samples will be analyzed at the local laboratory. Upon review of the results the Investigator should assess the clinical significance of all results. All clinically significant findings should be recorded as medical history at baseline or as an Adverse Event (AE) at later visits.

Hematology: Complete Blood Count (CBC) including absolute neutrophil, lymphocyte, monocyte, basophil, eosinophil count and platelets. CBC will be performed at predefined time points, see study flow chart, section 6.2.

Biochemistry: Blood Chemistry assessments (sodium, potassium, chloride, urea, creatinine, glucose (non-fasting), total protein, albumin, free calcium, total bilirubin, alkaline phosphatase, magnesium, phosphate, ALT, AST, INR, APTT and prothrombin will be performed at predefined time points, see study flow chart, section 6.2.

All women of reproductive potential must be screened for pregnancy by serum hCG test (if urine pregnancy test is not performed, see section above) at baseline (performed within 14 days prior to Cycle 1, Day 1 all cycles). If a female patient becomes pregnant during the study, she will need to discontinue the study treatment.

HIV and hepatitis B and C: status will be assessed at screening from medical records only. Patients infected with HIV or hepatitis are not eligible for inclusion in this study unless the disease is deemed under control by the investigator.

6.3.5 Medical history

A complete review of the patient's medical history will be undertaken by the Investigator to check that no exclusion criteria have been met. New MRI/CT scans will not be taken at screening if recent scanning information is available for tumor assessment (baseline). The baseline scans must have been done within 4 weeks prior Day 1 Cycle 1; first drug administration.

6.3.5.1 Previous cancer history and anti-cancer treatment

A complete review of the subject's past cancer history and anti-cancer treatment will be conducted with no time limitation.

6.3.6 Vital signs

The following vital sign evaluations will be performed prior to each drug administration for all cycles during the study and at end of treatment and recorded as applicable in the Case Report Form.

- Blood pressure (systolic and diastolic): Will be performed as seated after at least 5 minutes of rest) (in mmHg)
- Heart rate: Taken after at least 5 minutes of rest (in beats per minute (bpm))
- Respiratory rate: Taken after at least 5 minutes of rest (in breaths per minute (bpm))
- Temperature:Tympanic temperatures will be measured(in ºC)

All new findings or changes to previous findings considered clinically significant are to be recorded in the eCRF, either as Medical history if the finding is made prior to administration of the IMP, or as an adverse event if the finding is made subsequent to the first IMP administration.

6.3.7 Physical examination

A complete physical evaluation will include a thorough review of all organ systems, by the Investigator. The complete physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes and nervous system. Any findings made during the physical examination must be noted regardless of if they are part of the participant's medical history.

Symptom-directed evaluations on the other hand, will only be performed on the organ systems which are warranted, e.g., when the patient has indicated any problems with the affected system or for which the Investigator or study nurse has reason to believe there may be a problem with the affected organ system.

In addition, the patients will be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. The patients will also be asked to fulfil a Neurotoxicity Questionnaire (see Appendix 2) before each ixabepilone infusion and at end of the treatment visit (Day 1).

All new findings, or changes to previous findings, considered clinically significant are to be recorded on the eCRF either as medical history if the finding is made prior to IMP administration, or as an adverse event (Section 8.3), if the finding is made subsequent to first IMP administration.

6.3.8 ECG

A 12-lead ECG will be recorded within 14 days prior to treatment start and at any time it is clinically needed.

6.3.9 Concomitant diseases

Any concomitant disease, whether considered relevant for the study or not by the Investigator, must be reported in the eCRF. The duration of diagnosis should be noted. See also above (medical history).

6.3.10 Concomitant medication

All concomitant medication will be reported from 4 weeks prior to the first dosing visit (Day 1) and until approximately 4 weeks after last cycle (End of Treatment visit).

6.3.11 Tumor assessment

Clinical efficacy will be assessed by RECIST 1.1(35). Tumor response will be assessed by CT/MRI using RECIST 1.1 at Week 6 (before infusion) and then approximately every 9 weeks until 6 months and then approximately every 3 months until progression, withdrawal or death, which ever comes first. Every attempt should be made to use whichever imaging technique(s) used initially for repeat evaluations throughout the study.The hospitals imaging procedure for diagnostic CT or MRI of chest, abdomen and pelvis should be followed. The images should be evaluated by a dedicated radiologist at site.

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria (35).

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with callipers by clinical exam. All tumor measurements must be recorded in millimetres (or decimal fractions of centimetres).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator believes it is appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

6.3.12 Baseline documentation

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 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.

Non-target lesions. All other lesions (or sites of disease) including any non-measureable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.13 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 the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

6.3.14 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.15 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started (Table 5 (35)).

Table 5. Evaluation of Best Overall Response for Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No.	PD	

Any	Any	Yes	PD	

*See RECIST 1.1. (35) for further details on what is evidence of a new lesion.
**Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

6.3.16 Adverse events

Documentation of AEs will start as soon as the patient has signed the Informed Consent and will last until patient's final visit. Further details are provided in Section 10.3.

6.4 Description of Individual Visits

All patients will perform the screening and baseline visits before receiving the IMP. Day 1, Day 8 and Day 15 will be repeated for each cycle (~3 weeks between each drug administration).
When the subject discontinue from the study, an end of treatment visit will be performed approximately 4 weeks after last treatment cycle.

6.4.1 Screening visit (within 6 weeks prior to treatment start):

- Signed and dated written informed consent (must be obtained before any study related procedures are initiated)
- Patient demographic information will be collected
- Verify and confirm inclusion criteria 1 to 9 are meet
- Verify and confirm all exclusion criteria
- Tumor biopsy for DRP/Tumor mRNA expression profiling. The biopsy should be taken after the last anticancer treatment stopped.

6.4.2 Baseline visit (within 2 weeks prior to treatment start):

- Review ixabepilone Drug Response Predictor (DRP®) - must have a score >67% for the patient to continue the baseline screening.
- Review of all inclusion/exclusion criteria
- Medical/Surgical history/concomitant diseases, including breast cancer history
- Review concomitant medication and previous anti-cancer therapies
- Evaluation of performance status using the ECOG scale
- Physical examination, vital signs, height and weight
- 12-lead ECG
- Laboratory measurements including: Hematology and Biochemistry (see section 6.3.3)
- Urine or Serum Pregnancy test
- Adverse events

6.4.3 Day 1 of each cycle (within 24 hours before dosing):

- Physical examination, vital signs and weight
- Evaluation of performance status using the ECOG scale
- Laboratory measurements including: Hematology and Biochemistry (see section 6.3.3). Hematology results to be evaluated before infusion.
- Urine or Serum Pregnancy test
- Neurological examination and patient's to fulfil neurotoxicity questionnaire before drug administration
- Review concomitant medication and therapies
- Administer pre-medication approximately 60 minutes before IMP infusion
- Dispensing of IMP and follow-up subject's for symptoms during infusion, as applicable (e.g. observed by a study nurse for approximately 30 min for the 2 first cycles, if no reactions observed).
- Adverse events
- Neurological examination and patient's to fulfil neurotoxicity questionnaire before discharged.

6.4.4 Day 8±3 and Day 15±3 of each cycle

- Laboratory measurements including: Hematology (see section 4.3.3) (Complete Blood Count can be carried out at a local hospital or in primary care after 1st cycle, if required)
- Adverse events (may be reviewed by telephone call at day 8 and day 15 after 1st cycle)
- Review concomitant medication and therapies (may be reviewed by telephone call at day 8 and day 15, after 1st cycle)

6.4.5 Imaging

- Tumor assessment according to RECIST criteria version 1.1 (35) by MRI or CT scan of thoracic, abdominal and pelvic region, and other imaging studies which might be required to determine the extent of disease. Scans will be performed within 4 weeks of screening, at Week 6, and then approximately every 9 weeks up to 24 weeks and then every three months until progression or death.

6.4.6 End of treatment (EOT); approximately 28 days after end of last cycle

- Physical examination (including tumor evaluation by clinical examination), vital signs and weight
- Laboratory measurements: Hematology and Biochemistry (see section 6.3.4)
- Adverse events
- 12-lead ECG
- Review concomitant medication and therapies
- Evaluation of performance status using the ECOG scale
- Neurological examination and patients to complete neurotoxicity questionnaire

6.4.7 Consecutive follow-up:

Patients who discontinue protocol treatment for other reason than progression will have tumor assessments every 9 weeks until week 24 and then every 3 month until disease progression and thereafter followed for survival every 3 months until death.
For patients stopping treatment with ixabepilone due to progression, survival follow up to be performed approximately every 3 months until death. All patients are to be followed until death or until last patient has been in the study for 2 years, whichever comes first. Death certificates or other official proof of date of death to be obtained. Treatment related adverse events and anticancer medication will be reported.

7 INVESTIGATIONAL MEDICINAL PRODUCT

7.1 Investigational Medicinal Product (IMP)

The following medication supplies will be used in the study:
The IMP vial contains the active substance ixabepilone as a single-use, sterile lyophilised powder for concentrate for solution for infusion. Two strengths 15 and 45 mg/vial will be available. The medicinal product contains two vials; one for the powder and one for the constituting solvent for IV administration supplied by the Sponsor.

7.2 Supply, Packaging, Labelling, Handling and Storage

The IMP ixabepilone for Injection and its Vehicle for Constitution (diluent) will be supplied by the Sponsor via a Vendor (Klifo). The IMP will be labelled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.
The IMP should be stored refrigerated at 2°C to 8°C (36 to 46°F) and should be protected from light.
The IMP for injection must be constituted with supplied DILUENT. The IMP concentration in constituted solution is 2 mg/mL. Constituted solution must be diluted with one of the specified fluids (see current SmPC for Ixempra and the Study Specific Pharmacy Manual), to a final IMP concentration of 0.2 mg/mL to 0.6 mg/mL.
The infusion must be administered through an appropriate in-line filter with a microporous membrane of 0.20 to 5.0 microns. Administration of the entire infusion volume must be completed within the 6 hour time period. For further information see the study specific Pharmacy Manual.

7.3 Dosage and Administration

Ixabepilone 40 mg/m2 will be administrated as a continuous 3-hour intravenous infusion Day 1 in a 3-week cycle. BSA should be calculated using DuBois formula (BSA = 0.007184 * Height $^{0.725}$ * Weight $^{0.425}$) for each cycle. Dose reduction is required in certain patients See section 7.5.1

7.4 Toxicity Grading

All toxicities observed will be graded according to the NCI-CTCAE, Version 5.0 (34) and recorded as adverse events.

For those toxicities not graded in the NCI-CTCAE, grade of the adverse experience shall be recorded as adverse events as mild, moderate, severe or life-threatening, based on the following definitions:

- Mild: Sign or symptom noticeable but does not interfere with normal daily activities.
- Moderate: Sign or symptom sufficient to interfere with normal daily activities.
- Severe: Sign or symptom is incapacitating with inability to perform daily activities.
- Life-Threatening: Sign or symptom significantly increases risk of death.

If an unexpected, clinically significant change from baseline occurs in a laboratory value or other measurement, the Investigator should repeat the test if appropriate, to verify the result. The Investigator must comment on all clinically significant changes in laboratory values. All clinically significant adverse events must be followed-up and this follow-up documented until the events return to normal or become stabilized.

7.5 Dose Modifications

7.5.1 Dose Adjustments during Treatment

Patients should be evaluated during treatment by periodic clinical observation and laboratory tests including complete blood cell counts. If toxicities are present, treatment should be delayed to allow recovery. Dosing adjustment guidelines for monotherapy is shown in Section 7.5.2, Table 7. If toxicities recur, an additional 20% dose reduction should be made.

The dose of the IMP will be reduced as described in Table 6.

Table 6. Dose Levels of IMP

Dose Level	**IMP**
Starting dose	40 mg/m2
Dose after 1st dose reduction (20% dose reduction)	32 mg/m2
Dose after 2nd dose reduction (additional 20% dose reduction)	25 mg/m2

Patients requiring dose reductions after the second dose reduction must discontinue IMP.No dose re-escalation will be allowed after dose reduction.

7.5.2 Dose modification - according to toxicity

Table 7 Dose Adjustment Guidelines

Nonhematologic:	
Grade 2 neuropathy (moderate) lasting ≥7 days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting <7 days	Decrease the dose by 20%
Grade 3 neuropathy (severe) lasting ≥7 days or disabling neuropathy	Discontinue treatment
Any grade 3 toxicity (severe) other than neuropathy	Decrease the dose by 20%
Transient grade 3 arthralgia/myalgia or fatigue	No change in dose of IXEMPRA
Grade 3 hand-foot syndrome (palmar-plantar erythrodysesthesia)	
Any grade 4 toxicity (disabling)	Discontinue treatment
Hematologic:	
Neutrophil <500 cells/mm^3 for ≥7 days	Decrease the dose by 20%
Febrile neutropenia	Decrease the dose by 20%
Platelets <25,000/mm^3 or platelets <50,000/mm^3 with bleeding	Decrease the dose by 20%

Patients with hepatic impairment should be dosed based on the guidelines in Table 8.

Table 8 Dose Adjustments in Patients with Hepatic Impairment

	Transaminase Levels		BilirubinLevels[a]	Ixabepilone[b](mg/m2)
Mild	AST and ALT ≤2.5 x ULN	and	≤1 x ULN	40
	AST and ALT ≤10 x ULN	and	≤1.5 x ULN	32
Moderate	AST and ALT ≤10 x ULN	and	>1.5 x ULN - ≤3 x ULN	20 – 30

a Excluding patients whose total bilirubin is elevated due to Gilbert's disease.
b Dosage recommendations are for first course of therapy; further decreases in subsequent courses should be based on individual tolerance.

7.5.3 Retreatment Criteria

Patients may be retreated with a new cycle of study therapy if ANC is at least 1,500/mm^3, platelet count is at least > 100,000/mm^3 and treatment-related non-hematologic toxicity has resolved to baseline or Grade 1 (excluding Grade 2 alopecia and Grade 2 fatigue, for which resolution is not required) (according to the SmPC). Patients with Grade 2 neuropathy will not be retreated until resolution to Grade 1. Refer to Tables 6 and 7, for specific instructions on dose interruption and retreatment.

If a patient fails to meet criteria for retreatment on Day 21, then retreatment should be delayed and the patient should be re-evaluated at least weekly.

Initiation of subsequent cycles may be delayed for a maximum of three weeks. Any patient who fails to recover from a treatment related toxicity to baseline or Grade 1 (except Grade 2 alopecia and Grade 2 fatigue) within three weeks of scheduled retreatment (i.e., beyond Day 42) will be removed from the study. Patients who are clinically benefiting may continue treatment on study after consultation with and approval by the Sponsor.

7.6 Prohibited and Restricted Therapies during the Study

7.6.1 Prohibited Therapies

No other chemotherapy, hormonal therapy, immunotherapy, radiation therapy or experimental anticancer medications will be permitted while the patient is on treatment. Patients may continue to receive hormonal replacement therapy. Substances that inhibit CYP3A4 activity may decrease metabolism and increase ixabepilone concentrations. There is a significant increase in exposure to ixabepilone when ixabepilone is co-administered with ketoconazole. It is recommended that ixabepilone not be co-administered with the following strong inhibitors of CYP3A4: ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, nelfinavir, delavirdine and voriconazole. Caution should be used when considering the use of other CYP3A4 inhibitors with ixabepilone. Patients who receive drugs that are known to inhibit 3A4 other than those described above should be monitored closely for safety.

Conversely, inducers of CYP3A4 may decrease plasma concentrations of ixabepilone. The use of concomitant strong CYP3A4 inducers should be avoided (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital). (20mg dexamethasone can be used as premedication if required). Selection of an alternative concomitant medication with no or minimal enzyme induction potential should be considered.

7.6.2 Restricted Therapies

Palliative and supportive care for disease-related symptoms will be offered to all patients on this trial. The use of bisphosphonates for palliation of bone metastases will be allowed if initiated prior to study entry. Although, colony-stimulating factors (i.e., G-CSF, GM-CSF, etc.) are allowed, their prophylactic use should not replace the dose reduction schema. Growth factor use must be consistent with product label. Growth factor may not be given for 24 hours before or after ixabepilone. Prophylactic or therapeutic use of erythropoietin will be permitted.

7.6.3 Other Restriction

The patients will be instructed to abstain from grapefruit or products containing grapefruit for 24 hours prior to first dose administration and throughout the study until the end of treatment visit.
The inhibitory interaction of grapefruit juice on CYP3A4 may decrease metabolism and increase ixabepilone concentrations in blood.

7.7 Concomitant Medication

Any medication (prescription as well as over the counter (OTC) drugs) or therapeutic intervention deemed necessary for the patient, and which, in the opinion of the Investigator, do not interfere with the safety and efficacy evaluations, may be continued unless they are included in the list of 'medications and therapeutic regimens excluded from the study' outlined above. However, the Investigator should be cautious in evaluating the need for change in dosage and should carefully assess if any concomitant medication is necessary. If possible, all unnecessary concomitant medication should be stopped before entering the patient into this study.
Any new medications or changes to the dose or regimen of pre-existing medications will be updated on a routine basis during the study.

7.8 Duration of Treatment

Patients will continue the treatment until one or more of the following:

- Disease progression
- Unacceptable toxicity
- Patient refusal
- Physician decision
- Non-compliance to the protocol
- Treatment delay of > 2 weeks (except in cases of potential or perceived benefit)

7.9 Drug Accountability

All IMP supplies for this study must be retained in a safe place at all times of the study. Only personnel authorized by the PI at each site should dispense the IMP, and the accountability is the responsibility of the Investigator. The Investigator or pharmacist must complete and return the IMP supply form to the monitor, verifying the receipt of the IMP.

8 PREMEDICATION AND HYPERSENSITIVITY REACTIONS

8.1 Premedication before treatment with IMP

All patients must be premedicated before each treatment with ixabepilone to prevent a hypersensitivity reaction, Regimen 1 described below is the premedication regimen recommended for routine use.

Regimen 1) Premedicate approximately one hour prior to the infusion of ixabepilone with:

- An H1 antagonist (e.g., diphenhydramine 50 mg orally or equivalent)

and

- An H2 antagonist (e.g., famotidine 20 -40 mg orally, cimetidine 200 - 400 mg orally or equivalent)

Note that, in the event of patient intolerability to the antihistamines specified, alternatives may be substituted at the Investigator's discretion. In addition, if the specified antihistamine is not available, alternate antihistamines may be substituted (including intravenous formulations at equivalent doses).

8.2 Hypersensitivity Reactions

The IMP is formulated in polyoxyethylated castor oil (Cremophor EL), thus, hypersensitivity reactions may occur. Therefore, patients should be monitored closely for any signs or symptoms of hypersensitivity. Appropriate emergency equipment and medications (e.g., epinephrine, corticosteroids, antihistamines) should be made available in the event of an HSR. Refer to Section 8.3 for additional recommended premedication regimens (Regimen 2 and 3) to prevent hypersensitivity reactions in patients who developed hypersensitivity reactions despite premedication with Regimen 1.

A hypersensitivity reaction will generally occur within seconds or minutes of drug administration. Reactions may include urticaria, dyspnea, bronchospasm, angiodema, hypotension, tachycardia or occasionally cardio-respiratory arrest. In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate.

8.3 Additional Recommended Pre-medication to Prevent Hypersensitivity Reactions if Oral Medication Fails

If a patient experiences a hypersensitivity reaction with oral H_1 and H_2 blockers (Regimen 1) then the patient, if re-treated, should be premedicated according to the recommended regimen below:

Regimen 2) Premedicate approximately 30 - 45 minutes prior to each infusion of ixabepilone with:

a) Dexamethasone 20 mg IV (or equivalent),
b) Diphenhydramine 50 mg IV (or equivalent), and
c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent).

If a patient continues to experience a hypersensitivity reaction with Regimen 2 then the patient, if retreated, should be premedicated according to the recommended regimen below:

Regimen 3) Premedicate with:

a) Dexamethasone 20 mg po administered, approximately 12 and 6 hours prior to the infusion of ixabepilone
b) Diphenhydramine 50 mg IV, approximately 30 - 45 minutes prior to each infusion of ixabepilone,
c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent), approximately 30 - 45 minutes prior to each infusion of ixabepilone.

9 PATIENT WITHDRAWAL AND REPLACEMENT OF PATIENTS

In accordance with the Declaration of Helsinki, the Investigator must explain to the patient that they have the right to withdraw from the study at any time, and that this will in no way prejudice

their future treatment. However, unless safety issues occur, we plan to follow the patients for the entire duration of the study in order to analyse efficacy and safety variables also for those patients withdrawing from the study. The reason for any kind of withdrawal must be recorded on the appropriate CRF.
There will be two main categories for withdrawals from the study:

9.1 Complete withdrawal

Stopping ixabepilone and also continued efficacy and safety evaluations.
Standard reasons for withdrawing from further participation in the study and from the follow-up visits may be:

- Patient's decision (withdrawal of consent to participate)
- Patient lost to follow-up

9.2 Withdrawal from the study:

Stopping ixabepilone but continuing follow-up visits, including efficacy and safety evaluations.
Standard reasons for withdrawing from taking further ixabepilone, but continuing follow-up visits and safety evaluations may be:

- Unacceptable adverse events
- Patient request
- Investigator's discretion
- Patient lost to follow-up/non-attendance
- Intercurrent illness

However, whenever a patient is withdrawn from a study, or for whatever reason is not coming to any further visits, a final study evaluation must be completed for that patient (End of treatment visit) - stating the reason(s) why the patient was withdrawn from the study. All documentation concerning the patient must be as complete as possible.
Withdrawals due to non-attendance must be followed up by the Investigator to obtain the reason for non-attendance. Withdrawals due to intercurrent illnesses or adverse events must be fully documented in the case record form, with the addition of supplementary information if available and/or appropriate.

9.3 Replacement of Patients

Replacement of patients will be permitted under the following circumstances:
If the patient was properly screened and enrolled into the study, and started taking the IP, but then subsequently had to withdraw from the study, and did not complete 2 full cycles of treatment, this patient can be replaced.

9.4 IMP Accountability

All IMPs supplies for this study must be retained in a safe place at all times of the study. Only personnel authorised by the PI at each site should dispense the IMP, and the accountability is the responsibility of Investigator. The Investigator or pharmacist must complete and return the IMP supply form to the CRO-monitor, verifying the receipt of IMP.

10 RESPONSE VARIABLES AND ENDPOINTS

10.1 Assessment of Efficacy

10.1.1 Primary Efficacy Variable

- Clinical Benefit Rate will be defined as the proportion of patients having a Complete Response (CR), Partial Response (PR), or Stable Disease (SD) for at least 24 weeks, according to RECIST v 1.1

10.1.2 Secondary Efficacy Variables

- PFS defined as time from randomisation until progressive disease (PD) according to RECIST v 1.1 or death, whichever occur first.
- OS defined as the time from randomisation until death from any cause.
- ORR defined as the proportion of patients with complete response (CR) + partial response (PR) according to RECIST v 1.1
- Duration of response (DOR) defined as time of first documented CR or PR response until documented tumor progression (RECIST v 1.1)

10.2 Assessment of Safety

Safety evaluation will include assessments of adverse events, medical history, physical examinations, vital signs, concomitant medications, performance status and laboratory assessments at baseline and throughout the study period.

- A description of the extent, duration and reversibility of ixabepilone elicited toxicity in target organs based on the Common Terminology Criteria for Adverse Events (NCI-CTCAE v.5.0).
- A description of the frequency and severity of adverse events based on CTCAE v.5.0.
- Changes of Hematology and clinical biochemistry over time from baseline.
- Changes in Vital signs over time from baseline.
- Changes in ECOG over time.

10.2.1 Study-specific Safety Variables

The safety profile will be analysed by assessing clinical and laboratory adverse events.
If an unexpected, clinically significant change from baseline occurs in a laboratory value or other measurement, the Investigator should repeat the test if appropriate, to verify the result. The Investigator must comment on all clinically significant changes in laboratory values. All clinically significant adverse events must be followed-up and this follow-up documented until the events return to normal or become stabilised.
Myelosuppression, primarily neutropenia, is common. To monitor for myelosuppression, frequent peripheral blood cell counts will be performed on all patients receiving ixabepilone. Patients who experience severe neutropenia or thrombocytopenia should have their dose reduced (see section 7.5).

Further safety variables will be based on vital signs (blood pressure, heart rate) and physical examinations,

In addition special focus will be on peripheral neuropathy which is a common reported adverse event. Patients treated with ixabepilone should be monitored for symptoms of neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain. Neuropathy occurred early during treatment; ~75% of new onset or worsening neuropathy occurred during the first 3 cycles. Patients experiencing new or worsening symptoms may require a reduction or delay in the dose of ixabepilone (see Section 7.5). Peripheral neuropathy will be managed through dose reductions, dose delays, and treatment discontinuation.

10.3 Adverse Events and Serious Adverse Events

10.3.1 Definitions of Adverse Events

10.3.1.1 Adverse Events (AE):

An AE is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.

A baseline symptom is any medical event in a clinical study subject that occurs after the subject signed the ICF up until the first administration of IMP.

A treatment emergent AE (TEAE) is any AE not present prior to the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.

Only TEAEs are collected in this study (i.e. events occurring between screening and the first IMP administration are regarded as baseline symptoms and should not be recorded in the AE log in the CRF).

10.3.1.2 Serious Adverse Events (SAE):

An SAE is any AE that:

- results in death
- is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the subject signed the ICF and that did not change in grade are not SAEs.

Events **not** considered SAEs in this study:

The following events will ***not*** be considered ***nor*** recorded as SAEs in this study:

- Progressive disease
- Elective hospital admission including planned treatment for progressive disease.
- Admission to hospital for socio-economic reasons
- Admission to hospital due to progressive disease
- Death from progressive disease

10.3.1.3 Unexpected Adverse Event:

An experience not previously reported in the current SmPC for for ixabepilone (IXEMPRA).

10.3.1.4 Serious Adverse Drug Reaction

The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as possibly, probably or definitely related to the IMP.

10.3.1.5 Suspected unexpected serious adverse reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any SADR whose nature or grade is not consistent with the current version of the SmPC for ixabepilone (IXEMPRA).

10.3.2 Adverse Event assessment definitions

10.3.2.1 Severity

The grading of the AEs will follow the CTCAE v5.0 (36). Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the severity/intensity of an AE using the following definitions, and record it on the Adverse Event Form in the CRF:

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)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.3.2.2 Causality of AEs

All available evidence for the cause of the AE should be considered, such as, the pharmacology of the IMP, the nature of the event, timing with respect to IMP administration, dechallenge, and other causes. Possible other causes could include:

- The subject's medical history.
- Lack of efficacy or worsening of the treated condition.
- Other treatment, concomitant or previous.
- Withdrawal of study treatment.
- Treatment error.
- Protocol-related procedure.
- Other factors.

10.3.2.3 Relationship to IMP

The causal relationship between the IMP and the AE should be indicated, such as:

Unrelated: No evidence of a relationship with IMP use.

Unlikely: There is a temporal relationship only with IMP use; there is little or no pharmacological plausibility to suggest a relationship; there is at least one other more likely cause for the AE.

Possible: There is a temporal relationship with IMP use; it is pharmacologically plausible that the IMP is the cause of the AE; there may be one or more other possible causes for the AE.

Probable: There is a strong temporal relationship with IMP use; it is pharmacologically likely that the IMP is the cause of the AE; other causes of the AE are unlikely.

Definite: All available evidence indicates that the IMP is the cause of the AE.

For data analysis and SAE reporting purposes, AEs classified as 'unrelated' and 'unlikely' will be regarded as 'not related'; AEs classified as 'possible', 'probable' and 'definite' will be regarded as 'related'.

10.3.3 Follow-up of unresolved AEs

All ongoing (S)AEs will be followed-up at least until at least 30 days after last IMP administration, resolved or returned to baseline value.

10.3.4 Reporting of adverse events

All Adverse Events must be recorded in the case report form, defining relationship to study medication and severity.

As soon as the Investigator is aware of a potential Serious Adverse Event (SAE), he/she should contact the local SMERUD monitor by phone, fax or e-mail, and in any case no later than 24 hours after the knowledge of such a case.

If identification of the event occurs outside of office hours, the emergency phone number described in the Investigator Site File may be used. At the time of the call, the Investigator must

provide as a minimum requirement, the subject number, birth date, nature of the SAE, and a preliminary assessment of causality. The Investigator should follow-up the initial notification of the potential SAE by faxing a copy of the SAE reporting form to SMERUD at the number provided in the Investigator Site File. The faxed SAE reporting form should be received at SMERUD within 24 hours after knowledge of such a case.

Smerud medical Research International AS
E-mail: pharmacovigilance@smerud.com
Fax: +47 23 27 20 01
Tel: +47 23 27 20 00

Follow-up information on an existing SAE that is fatal or life-threatening should be reported by the Investigator to SMERUD within 5 days after the initial report. Where appropriate, hospitalization or autopsy reports should be made available. All Serious Adverse Events will be followed up until resolution (i.e., asymptomatic, stabilization or death).

10.4 Serious Adverse Reactions and Unexpected Adverse Reactions

10.4.1 Definitions

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

For marketed medicinal products, an adverse reaction is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Unexpected Adverse Reaction:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (the Summary of Products Characteristics (SmPC)).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

Any serious adverse reaction that might be related to the study medication and are unexpected according to the definition above.

10.4.2 Reporting of suspected unexpected serious adverse reactions by SMERUD

Suspected unexpected serious adverse reactions (SUSARs) will be reported by SMERUD according to appropriate Competent Authority and Ethics Committee requirements. SMERUD will report SUSARs to Investigators twice yearly according to ICH Good Clinical Practice and to local regulations. SUSAR reporting to the Competent Authorities and Ethics Committees will be performed according to local regulations in an unblinded manner. The Competent Authorities will be notified of all SUSARs through the Eudravigilance database.

Fatal and life-threatening SUSARs should be reported by SMERUD as soon as possible to the Competent Authorities and Ethics Committees according to local regulations, and in any case no

later than seven calendar days, after knowledge by SMERUD of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the Competent Authorities concerned and to the Ethics Committee concerned according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by SMERUD.

11 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

11.1 Study Statistical Design

Simon's two-stage design will be used (37). The null hypothesis that the true overall objective response rate is 25% will be tested against a one-sided alternative. In the first stage, 30 patients will be accrued, and 28 patients are expected to be evaluable. If there are 7 or fewer with clinical benefit in these 28 patients, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 60 of which 53 are expected to be evaluable. The null hypothesis will be rejected if 19 or more objective responses are observed in 53 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true clinical benefit rate is 41%. The null hypothesis that the true overall objective response rate is 25% will be tested against the alternative hypothesis of true response rate 41%
The objective response rates may differ in the actual population, but the difference between unselected historical control and selected population should remain constant. One-sided comparisons of ORR between treatment and historic control will be performed, and will be repeated for subgroups defined by ER.

11.2 Estimation of Sample Size

Up to 53 evaluable patients can be included to give a power of 80% in the Simon two-stage design.

11.3 Statistical Analysis Plan

A separate document, Statistical Analysis Plan (SAP) will be developed and will detail all analysis to be performed in this study.

11.4 Study Populations

11.4.1 Intention-to-treat population (ITT):

Patients will be included in the primary intention-to-treat population for analysis of efficacy if they receive treatment for at least 1 dose of ixabepilone and have measurable disease at baseline. The ITT population will be used as the primary analysis population.

Patients for whom a biopsy after last anticancer treatment is not available or has a DRP score below 67% will not count towards the 200 patients screened, and 60 patients treated, and will not be included in the primary analysis.

11.4.2 Safety population:

Patients will be included in the safety population if they receive treatment for at least 1 dose of ixabepilone.

11.4.3 Per protocol population:

In order to qualify for the stringent per protocol population, the patients must have followed the study protocol without any major violations and they should have received at least 2 cycles of treatment. Any examinations missed will be substituted with the last observation carried forward, but examinations from not more than 1 visit may be lost. The per protocol population will be identified prior to database lock.

11.4.4 Total population:

Any patient who withdraws from the study will be included in the safety analysis (adverse events and laboratory parameters). Data for all patients will be listed, and a list of withdrawn patients, with all reasons for withdrawal, will be given.

This also applies to data for those patients who - after having consented to participate - underwent screening examinations required for inclusion into the study but whom - because a criterion for exclusion was met or for other reasons - were not included in the study.

11.5 Data Collection / Case Report Forms

Data will be collected using an electronic data capture (EDC) solution. Electronic Case report forms (eCRFs) will be utilised for recording data from each patient meeting the eligibility criteria and being included in the study. The eCRF system, Viedoc™, will be available on an internet portal accessible through any standard computer with internet access. All study staff responsible for entering data into the eCRF system will be trained by the Clinical Research Associate (CRA) prior to the start-up of the study. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained. No clinical trial information will be transferred via the eCRF system until the site has been qualified through completion of a validation eCRF.

All evaluations performed shall be entered in a timely manner into the eCRF by a member of the site staff delegated responsibility for this specific task by the Principal Investigator (PI) of the clinical site. It is the responsibility of the Investigator to ensure that the eCRFs are properly completed. The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF data entry screens to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data protection regulations.

Captured data will be monitored electronically and Source Data Verification (SDV) will take place at the site, i.e. relevant information (as outlined in the monitoring plan) will be verified against the individual patient records unless the eCRF is considered source data.

Any inconsistencies will be presented as queries; either as automatically generated queries if raised by the logical data checks of the eCRF system, or by manually generated queries if raised

by the data validation checks or the SDV performed by the Data Manager (DM) or the CRA, respectively. Queries shall be resolved in a timely member by a trained member of the site staff.

11.6 Data Management

Data will be transmitted electronically into the web based EDC system. Upon receipt, data will be coded according to pre-specified dictionaries and in accordance with CRO Standard Operating Procedures (SOP). The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

12 REGULATORY AND ADMINISTRATIVE PROCEDURES

12.1 Institutional Review

The study will be conducted in accordance with the Fortaleza, 2013 amendment to the Declaration of Helsinki 1964.

The Protocol and the Patient Information Sheet / Informed Consent Form will be approved by the relevant Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements before commencement. If a protocol amendment is necessary, this will be prepared with the agreement of the Principal Investigator and signed by the relevant parties. If the amendment is considered to be substantial, it will be submitted to the Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before the required approvals are obtained. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) will not be submitted to Competent Authorities or Ethics Committees.

SUSAR reports and Periodic Safety Reports will be sent to Competent Authorities and Ethics Committees according to local regulations.

12.2 Patient Information / Informed Consent

The Investigator is responsible for giving the study patient full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. Study patients must also be notified that they are free to withdraw from the study at any time. The patients should have reasonable time to read and understand the information before signing. The Investigator is responsible for obtaining signed informed consent from all patients before including the patient in any study related procedures.

A signed copy of the patient information and of the Informed Consent Form in local language, will be given to the patients.

12.3 Patient Confidentiality

The Investigator must ensure that patient's confidentiality will be maintained. eCRF or other documents submitted to the sponsor should only identify patients by their initials and study number. The Investigator should keep a separate log of patient codes and names. Documents not for submission to the Sponsor, e.g., patient's completed Consent Forms, should be retained by the Investigator in strict confidence.

The Investigator is required to record primary efficacy and safety data, concomitant medication and patient progress in the patient's file/notes/medical record.

The patient's medical records will be reviewed by the CRO monitor and possibly by other sponsor personnel or regulatory authorities, to verify adequate source documentation, accuracy and completeness of eCRFs. The review will be conducted with strict adherence to professional standards of confidentiality. No patient identifiable data will be taken out of the investigator site.

All patients screened for the study will have their initials and birth date entered chronologically on the Patient Screening Log at the initial visit. An explanation for exclusion from admission to the protocol is to be provided on the Patient Screening Log.

12.4 Data Protection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the potential effects of ixabepilone. Collection, handling and storage of personal data from the clinical trial will only take place as described in the PIS/ICF as well as in section 9.5 (Data Collection) and in accordance with the General Data Protection Regulation (EU 2016/679), current EU clinical trial regulations (currently Directive 2001/20/EC and 2005/28/EC; to be replaced by regulation 536/2014) and any applicable local regulations.

A dedicated Data Protection Officer (DPO) employed by SMERUD is registered at the Data Protection Authority. The DPO will at all times supervise that the subjects' data protection is maintained by auditing and approving the electronic data capture (EDC) provider, ensuring data protection procedures are in place and ensuring that the annual audit programs include also checks of subject data protection.

12.5 Patient Treatment Plan

Patients will continue treatment until disease progression or unacceptable toxicity or patient refusal/withdrawing of consent, or non-compliance to the protocol, or physician decision to discontinue treatment, or treatment delay > 2 weeks (except in the case of perceived patient benefit). Further treatment will be given on the discretion of the investigator.

12.6 GCP

The study will be managed and conducted according to the latest International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP). A copy of these guidelines can be found in the Investigator Site File (ISF).

12.7 Essential Documents

The ICH guideline for GCP lists a number of essential GCP documents required prior to, during and after the conduct of the study. It is the responsibility of the monitor to ensure that the Investigator is always provided with a copy of such documents prepared by the study management, and it is likewise the responsibility of the Investigator to provide the monitor with essential documents prepared by the Investigator or the local Ethics Committee. A complete list of essential GCP documents can be found in the Investigator Site File.

12.8 Record Retention

The investigator site file, eCRFs and all medical records upon which the eCRFs are based (source data) must be kept for at least 15 years or according to local legislation whichever is the longest after completion of the study. Image carriers or other data carriers may be used for this purpose. The documentation should be easily retrievable and readable during the entire archiving duration.

12.9 Monitoring / Quality Control

Prior to the start of the study, the CRO monitor will review the protocol and eCRFs with the Investigator and his/her staff. The Investigator will be visited on a regular basis by the CRO monitor, who will check study procedures, including safety assessments, IMP handling, data recording and perform source data verification (SDV). The CRO monitor must be allowed to review patient records to confirm that required protocol procedures are being followed and check consistency between patient record and eCRF data. Incorrect or missing entries in the CRFs will be queried and must be corrected immediately.

Risk based monitoring of source data verification will be done.

The monitor will record dates of the visits in a monitoring visit log that will be kept at the site. The first monitoring visit at each site will be scheduled after the first patient has been enrolled.

12.10 Quality Assurance

During or after the study is completed, sponsor representatives or regulatory authorities may wish to carry out an audit or an inspection. These representatives must have the same access to study data and patient source data as the CRO monitor.

12.11 Insurance and Liability

Subject insurances will be issued according to local requirements. Liability for IMP-induced injury will be according to local requirements. The sponsor will indemnify the Investigator in accordance to national regulations.

12.12 End of Trial

Regular Trial Termination

The end of the trial is defined as the last visit of the last patient included in the trial. Within 90 days of the end of the trial, the Sponsor/CRO will notify Competent Authorities and Ethics Committees the regular termination of the of the study as required according to national law and regulations.

Premature Trial Termination

For safety reasons, this trial may be terminated prematurely at any time by the sponsor, or competent authorities. If the sponsor decides to terminate the trial for any other reason, the investigator, ethics committee and competent authority will be informed about the reason(s) for stopping the study.

12.13 Study Report

A clinical study report (CSR) will be prepared covering clinical and statistical aspects and summarising all findings of the clinical study. The content has to be treated as strictly confidential. The study report will be sent to the Investigators, the Competent Authorities and Ethics Committees according to local requirements.

12.14 Publication and Data Rights

It is envisaged that the findings of the study will, in due course and by mutual agreement, be published in a scientific journal and/or presented at a scientific meeting. The final determination of authorship of this publication will be decided by the sponsor, Inc.; all participating Investigators will be mentioned and listed as members of the study group.

The information developed during the conduct of this clinical study is confidential and may only be disclosed as authorized in writing by the sponsor.

The published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to; i.e. 'All persons designed as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit will therefore be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1), 2) and 3) must all be met. Participation solely in acquisition of funding or the collation of data does not justify authorship. General supervision of the research group is not sufficient for authorship. It is intended that information on what each author has contributed will be published.
It is emphasized however, that only those who entirely meet the above-mentioned criteria will be listed as authors.

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14 SIGNATURES

The protocol has been approved by:

Name and function	Signature	Date
Peter Gimsing Medial Monitor	DocuSigned by: Peter Gimsing 1A765E3F62974A5...	3/29/2022
Marie Foegh Sponsor's representative	DocuSigned by: Marie Foegh 1E35DB20BE11483...	3/29/2022
Nils Meland Statistician CRO, Smerud Medical Research International	DocuSigned by: Nils Meland 70EE65EBAA4947A...	3/29/2022

15 SIGNATURE PAGE FOR INVESTIGATOR

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Allarity Therapeutics
- Not to implement any changes to the protocol without the agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or the Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the patents, or for purely administrative aspects of the study where all applicable regulatory requirements are permissive.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor in writing including, but not limited to, the following:
    - The current protocol and the current Summary of product characteristics for IXEMPRA
- That I am aware of and will fully comply with Good Clinical Practices (GCP) as outlined in 21 CFR Parts 50, 54, 56 and 312 and 45 CFR Part 46 and all other applicable regulatory requirements.
- To insure that all persons assisting me with this study are adequately informed about the Allarity Therapeutics investigational product and of their study-related duties and functions as described in this protocol.
- That I have been informed that certain regulatory authorities require Allarity Therapeutics to obtain and supply, as necessary, details about Investigators' ownership interest in Allarity Therapeutics, its investigational product, and more generally about the Investigator's financial ties to Allarity Therapeutics. For this reason,

I further agree:

- To supply Allarity Therapeutics with any requested information regarding ownership interest and financial ties, including those of my spouse and dependent children;
- To promptly update this information if any relevant changes occur during the course of the study and for one (1) year following completion of the study; and
- That Allarity Therapeutics will maintain this information in a confidential matter, but that it may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

_____

Investigator Name

_____ Date:_____

Investigator Signature

16 APPENDICES

Appendix 1. Eastern Cooperative Oncology Group Performance Status

Scale	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Adapted from Oken MM et al. Am J Clin Oncol. 1982;5:649-55. [13]

Appendix 2. Neuropathy Assessment Patient evaluation form

Neurotoxicity Questionnaire

The patients are asked to fulfill the questionnaire before each ixabepilone infusion as a tool for identifying patients with neurologic AEs.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

Concerns	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hand	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning buttons	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Appendix 3. Version tracker

Protocol version	Revisions
Version 2.0	• The following text was added to exclusion criteria no. 14: . *Similarly, patients must not continue treatment with the following strong inducers of CYP3A4: phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital. (20 mg dexamethasone can be used for pre-treatment if required)*. • Screening period has been increased from 4 to 6 weeks. • It has been added that: *Complete blood count at day 8 and 15 may be done at local hospital or in primary care after 1st cycle is completed.* • It has been added that: *Follow-up on AEs and concomitant medication at day 8 and 15 may be done by phone after the 1st cycle.* • Dose Adjustments in Patients with Hepatic Impairment have been added in section 7.5.2 Table 8. • The following text has been added to section 7.6.1: *Conversely, inducers of CYP3A4 may decrease plasma concentrations of ixabepilone. The use of concomitant strong CYP3A4 inducers should be avoided (eg, phenytoin, carbamazepine, rifampin, rifabutin, dexamethasone, and phenobarbital). (20mg dexamethasone can be used as premedication if required). Selection of an alternative concomitant medication with no or minimal enzyme induction potential should be considered.*
Version 3.0	Sponsor has been changed from Allarity Therapeutic AS to Allarity Therapeutics Europe ApS It has been added to the protocol that patients can be included based DRP conducted on archival tisse (section 5.5). DRP shoud be repeated on a biopsy taken after last cancer tratemnt if possible. Exclusion criteria 12 and 13 have been

	deleted. A secondary endpoint was added: • *Assess difference in prediction based on archival and fresh biopsy from same patient (percent agreement in binary prediction, and difference in primary and secondary endpoints with archival versus fresh biopsies)*

DocuSign

Certificate Of Completion

Envelope Id: FFBCF822173B45F4BCED32EE905C02C8
Status: Completed
Subject: Please DocuSign: Ixabepilone mBC_Final Protocol v 3.0_23.02.2022 _final new CI.pdf
Source Envelope:
Document Pages: 62
Signatures: 3
Certificate Pages: 2
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

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Record Tracking

Status: Original
3/28/2022 11:27:53 PM
Holder: Charlotte Kleiveland
charlotte.kleiveland@smerud.com
Location: DocuSign

Signer Events	Signature	Timestamp
Marie Foegh mfoegh@allarity.com Chief Medical Officer Security Level: Email, Account Authentication (None)	DocuSigned by: Marie Foegh 1E35DB20BE11483... Signature Adoption: Pre-selected Style Using IP Address: 98.7.68.224	Sent: 3/28/2022 11:30:50 PM Viewed: 3/29/2022 4:14:07 AM Signed: 3/29/2022 4:15:00 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Peter Gimsing pgimsing@allarity.com Security Level: Email, Account Authentication (None)	DocuSigned by: Peter Gimsing 1A765E3F62974A5... Signature Adoption: Pre-selected Style Using IP Address: 83.94.33.24	Sent: 3/29/2022 4:15:05 AM Viewed: 3/29/2022 4:22:40 AM Signed: 3/29/2022 4:23:33 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Nils Meland nils.meland@smerud.com Security Level: Email, Account Authentication (None)	DocuSigned by: Nils Meland 70EE65EBAA4947A... Signature Adoption: Pre-selected Style Using IP Address: 109.74.178.98	Sent: 3/29/2022 4:23:38 AM Resent: 3/29/2022 6:46:57 AM Viewed: 3/29/2022 6:51:08 AM Signed: 3/29/2022 6:57:29 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/28/2022 11:30:50 PM
Certified Delivered	Security Checked	3/29/2022 6:51:08 AM
Signing Complete	Security Checked	3/29/2022 6:57:29 AM
Completed	Security Checked	3/29/2022 6:57:29 AM

Payment Events	Status	Timestamps