CLINICAL STUDY PROTOCOL

Study Title:	ALERT: A phase II study of **al**ternating **er**ibulin and hormonal **t**herapy in pre-treated ER+ve breast cancer.
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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	Adverse event
AI	Aromatase Inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve
CBR	Clinical Benefit Rate
cfDNA	Circulating free deoxyribonucleic acid
CI	Chief investigator
CNS	Central Nervous System
CNV	Copy Number Variation
CR	Complete response (RECIST)
CRUK	Cancer Research UK
CRF	Case report form
CSR	Clinical study report
CT	Computerised tomography
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Averse Events
CYP34A	Cytochrome P34A
DNA	Deoxyribonucleic acid
DTCs	Disseminated Tumour Cells
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ER+ve	Oestrogen Receptor Positive
ECG	Electrocardiogram
FFPE	Formalin Fixed Paraffin Embedded
HER2	Human Epidermal Growth Factor Receptor 2
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICH GCP	International Conference on Harmonisation – Good Clinical Practice
ICHTB	Imperial College Healthcare NHS Tissue Bank
CCTS	Cancer Clinical Trials Section
IEC	Independent Ethics Committee
IES	Intergroup Exemestane Study
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITTS	Intention to treat analysis set
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
mm	Millimetre
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Non-evaluable (RECIST)
NTL	Non-Target Lesion
ORR	Objective response rate

OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PR	Partial response
PgR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease (RECIST)
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SPC	Summary Product Characteristics
SSPM	Study Specific Procedure Manual
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TL	Target Lesion
TMG	Trial Management Group
TPC	Treatment of Physician's Choice
TSC	Trial Steering Committee
ULN	Upper Limit of Normal

TRIAL SUMMARY

Title:	A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer.
Objectives:	**Primary:** • To assess the efficacy of eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) based on progression free survival (PFS) **Secondary:** • To assess the efficacy of eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) based on clinical benefit rate (CBR) • To assess the safety and tolerability of eribulin when prescribed in alternating cycles with an AI **Translational:** • To observe whether circulating tumour cells (CTCs) and the tumour derived fraction of circulating free DNA (cfDNA) termed ctDNA, increase during hormonal therapy suggesting relapse off chemotherapy
Endpoints:	**Primary:** • PFS rate at the following fixed time points: at 3, 6 and 9 months(as estimated by Kaplan-Meier curve). **Secondary:** • CBR defined as the proportion of patients whose best overall response, according to RECIST v1.1 is either a complete response (CR), partial response (PR) or stable disease (SD) for at least 6 months. • Safety and tolerability as assessed by adverse events (AEs) and serious adverse events (SAEs) according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.03) **Translational:** • To measure alterations in CTCs and cfDNAs from baseline and at 9, 18 and 36 weeks after start of treatment and associate these with clinical outcomes
Design:	A single centre, single arm phase II study of alternating eribulin and hormonal therapy in 12 patients with locally advanced or metastatic breast cancer who have received at least one chemotherapy in the metastatic setting.
Sample size:	12 patients
Main inclusion criteria:	1. Written informed consent prior to admission to this study 2. Aged 18≥over 3. Histologically confirmed ER+ve metastatic breast cancer according to local criteria 4. ECOG performance status 0 – 2 5. Have progressed after at least one chemotherapy regime for advanced/metastatic disease

	6. Patients must have had at least one prior line of chemotherapy treatment in the metastatic setting prior to enrollment in the study. 7. At least one measurable site of locally advanced and/or metastatic disease that can be accurately assessed by CT/MRI scan at baseline (RECIST v1.1)[1] 8. Life expectancy of ≥6 months 9. Adequate organ function 10. Postmenopausal as defined by age >50, no menstruation for >2 years, previous oophorectomy or lab results confirming this status 11. Premenopausal if has been subject to ovarian ablation/ suppression at least 3 weeks prior to commencing AI therapy[2] [1]RECIST v1.1 updated and now considers bone metastasis with an identifiable soft tissue mass to be measurable disease. Therefore, patients with bone metastasis are eligible, provided they have evaluable disease. [2] A pregnancy test is required if patient is premenopausal and has been subject to ovarian ablation/ suppression at least 3 weeks prior to commencing AI therapy.
Main exclusion criteria:	1. Triple negative or HER2 positive cancer 2. Hypersensitivity to the active substance or to any of its excipients 3. History of another primary malignancy within 5 years prior to starting study treatment, except adequately treated basal or squamous cell carcinoma of the skin, carcinoma in site and the disease under study 4. Evidence of uncontrolled active infection 5. Severe hepatic impairment (Child-Pugh C) 6. Evidence of significant medical condition or laboratory finding which, in the opinion of the Investigator, makes it undesirable for the patient to participate in the trial 7. Concurrent therapy with any other investigational agent or everolimus 8. Concomitant use within 14 days prior to commencement of study treatment of any investigational agent 9. Uncontrolled abnormalities of serum potassium, sodium, calcium (corrected) phosphate or magnesium levels 10. Pregnant or lactating women. Effective non-hormonal contraception is mandatory for all patients of reproductive potential 11. Evidence of ovarian activity 12. Prior eribulin therapy

1. BACKGROUND AND RATIONALE

1.1. Breast Cancer

Breast cancer is one of the most common causes of morbidity and mortality in women. In 2007, in the UK alone, 45,972 new cases were diagnosed with 12,047 deaths in 2008 (CRUK, 2010). Breast cancer mortality has been steadily decreasing over the last twenty years as a result of screening and improvements in treatment. The majority of breast cancer patients are diagnosed with early stage disease and treated with curative intent by surgery, followed by various combinations of adjuvant chemotherapy, radiotherapy, hormonal therapy and trastuzumab depending on tumoural expression of oestrogen receptor alpha (ERα), progesterone receptor (PgR) and HER2. Despite these improvements, approximately 6% of patients have metastatic disease at diagnosis and a further 30% of patients will suffer relapse and eventually die of their disease. While there has been improvement in the long term survival rate from metastatic breast cancer (MBC), it remains incurable and the current median overall survival remains approximately 24 months (Giordano, et al., 2004). The goals of treatment in MBC are to treat symptoms, improve quality of life and prolong survival.

Over 70% of breast cancers are oestrogen receptor positive (ER+ve) and endocrine therapy is the treatment of choice, except in the presence of rapidly progressive visceral disease or where disease is known to be insensitive or resistant to endocrine therapy. Current endocrine therapy for postmenopausal women with HER2 negative breast cancer includes tamoxifen, anastrozole, letrozole, exemestane and fulvestrant.

1.2. Investigational Agent

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

Eribulin is licenced for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least one chemotherapeutic regimen for the treatment of advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.

1.3. Clinical Studies

The efficacy of eribulin in breast cancer is primarily supported by two randomised phase 3 trials.

In the EMBRACE study (NCT00388726) 762 women with locally recurrent or metastatic breast cancer were randomly allocated to treatment groups (508 eribulin, 254 treatment of physician's choice (TPC)). Overall survival was significantly improved in women assigned to eribulin (median 13.1 months, 95% CI 11·8–14·3) compared with TPC (10.6 months, 9·3–12·5; hazard ratio 0·81, 95% CI 0·66–0·99; p=0·041). The most common adverse events in both groups were asthenia or fatigue (270 [54%] of 503 patients on eribulin and 98 [40%] of 247 patients on TPC at all grades) and neutropenia (260 [52%] patients receiving eribulin and 73 [30%] of those on TPC at all grades). Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin, occurring in 24 (5%) of 503 patients (Cortes , et al., 2011; Twelves, et al., 2010).

In the second study (NCT00337103) 1102 women with locally advanced or metastatic breast cancer were randomised to receive either eribulin monotherapy or capecitabine monotherapy. The primary analysis for OS was based on 905 (82%) events or deaths in the trial. The median OS among patients receiving Eribulin was 15.9 months and 14.5 months in the capecitabine group. The hazard ratio (HR) for OS (Eribulin vs Capecitabine) was 0.879 (95% CI, 0.770 to 1.003), and a p-value of 0.0560 (Kaufman PA, et al., 2012). Progression free survival was similar between eribulin and capecitabine with medians of 4.1 months vs 4.2 months (HR 1.08; [95% CI: 0.932, 1.250]) respectively. Objective response rate was also similar between eribulin and capecitabine; 11.0% (95% CI: 8.5, 13.9) in the eribulin group and 11.5% (95% CI: 8.9, 14.5) in the capecitabine group (Twelves, et al., 2010).

Eribulin is a standard of care in many women with advanced breast cancer.

1.4. Aromatase Inhibitors (AI)

In contrast to premenopausal women, in whom most of the oestrogen is produced in the ovaries, in postmenopausal women oestrogen is mainly produced in peripheral tissues of the body. Because some breast cancers respond to oestrogen, lowering oestrogen production at the site of the cancer (i.e. the adipose tissue of the breast) with aromatase inhibitors has been proven to be an effective treatment for hormone-sensitive breast cancer in postmenopausal women. We have performed many of the large studies of aromatase inhibitors, such as the IES trial, at Charing Cross Hospital and Imperial College, London.

Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into oestrogens by a process called aromatization. As oestrogen receptor positive breast cancers are stimulated by oestrogens, decreasing their production is a way of suppressing recurrence of the breast tumour tissue. The main source of oestrogen is the ovaries in premenopausal women, while in post-menopausal women most of the body's oestrogen is produced in peripheral tissues (outside the CNS), and also a few CNS sites in various regions within the brain.

The recent past has witnessed the appearance of substantial data relating to endocrine therapy of breast cancer. In the adjuvant therapy setting in early breast cancer, several large, well-conducted, randomized, double-blind clinical trials have provided evidence for the value of the third-generation aromatase inhibitors (AI) anastrozole, exemestane, and letrozole in postmenopausal women. The three major studies to date [i.e., Arimidex, tamoxifen alone, or in combination (ATAC), Intergroup Exemestane Study (IES), and letrozole after 5 years of tamoxifen (MA.17)] evaluated three different populations of women from the standpoints of duration of prior tamoxifen and thus time since the treatment of the primary breast cancer. A consistent pattern of improvement in disease-free survival was seen whether the control arm was tamoxifen (ATAC and IES) or placebo following tamoxifen (MA.17). From a toxicity standpoint, the major findings with the AIs were a decreased incidence of thromboembolic events and endometrial cancers but an increase in musculoskeletal complaints and potential for decreasing bone density.

1.5. Rationale

The aim of this study is to alternate eribulin and aromatase inhibitors, examining whether there may be breakthrough relapse during the AI therapy or on the other hand we can extend the duration that eribulin may be used for. Importantly, blood based biomarkers, the tumour derived fraction of cfDNA (ctDNA), and circulating tumour cells will be measured. A major aim of this study is to test whether biomarkers fluctuate between chemotherapy and AI treatment in the setting of advanced breast cancer.

1.5.1. Biomarkers

The hypothesis to be tested is that specific circulating biomarkers whether circulating free DNA (cfDNA) or in circulating tumour cells (CTCs) can facilitate the earlier detection of breast cancer potentially improving management. The aim is to demonstrate that a circulating phenotype is an important prognostic and predictive factor for relevant clinical outcomes in breast cancer.

1.5.1.1. Circulating tumour cells

Several groups, including our own, have reported that measuring CTCs by the widely used CellSearch® method and DTCs in bone marrow can help in cancer prognosis and follow-up (Bidard, et al., 2014). Here, we wish to address whether circulating markers have the potential to: (a) predict breast cancer outcome; (b) predict response to therapies; (c) predict relapse; and (d) detect small changes that have clinical consequences.

Patient benefit would also be achieved if our non-invasive test(s) predict disease progression at a time when additional therapy can be given with potential life-prolonging intent, or to decide who would benefit from a change in therapy. Once validated in breast cancer, the markers could be applied to other cancers that are distinguished by resectable primary cancers and micrometastases, such as colorectal cancer.

Studies of CTCs have generally recruited individuals with newly diagnosed metastatic cancer, with recent data also indicating their prognostic value in the adjuvant setting. Their role in advanced patients has not been established so at Imperial, CTCs were measured in 43 individuals with metastatic breast cancer estimated to have less than 6 months to live who had exhausted standard therapeutic options. Remarkably, those with a CTC count of $\leqslant$100 had a median of 182 days to live, compared with those with a CTC count of >100 who had a median of 17 days until death (p = 0.009, Log Rank, HR 3.1, 95% CI 1.4-7.3). We thus found that a CTC count of >100 is associated with imminent death (Stebbing, et al., 2014). Provided external validity is demonstrated, such information would be useful for patients and their families who often request specific prognostic clarity and could improve the quality of end-of-life care.

1.5.1.2. Circulating free DNA (CfDNA)

CfDNA was first described over 60 years ago. Elevated levels of cfDNA are seen in cancer in part due to reduced DNase activity. Elevated levels of cfDNA in plasma were suggested for the diagnosis of breast cancers and qualitative tests showed increased cfDNA integrity/size in breast cancers. However elevated levels of cfDNA are sometimes seen in benign breast disease; therefore levels of cfDNA are not tumour specific markers. Specific patterns in cfDNA (e.g. mutations, loss of heterozygozity, hypermethylation) have the potential to provide tumour specific markers and have been more widely investigated. These and other studies highlight the potential of cfDNA as a circulating biomarker in cancer. In our first study using just 2 circulating markers we showed that cfDNA was more sensitive than either CTCs or disseminated tumour cells (DTCs) for detecting evidence of minimal residual disease in primary breast cancer patients (Shaw, et al., 2000). We then demonstrated amplified *HER2* in cfDNA up to 10 years after treatment in asymptomatic patients, suggesting persistent micrometastases and a dormant state and confirmed persistence of ctDNA using whole genome approaches (Shaw, et al., 2012).

We were the first group to assay the whole genome in cfDNA isolated from breast cancer patients using Affymetrix® SNP 6.0 Array, which features single nucleotide polymorphism (SNP) and non-

polymorphic probes for detection of copy number variation (CNV). These CNVs are amplified or deleted regions of the genome, which are recognised as a major source of normal human genome variability and contribute significantly to phenotypic variation. Our cfDNA results from 65 patients highlight several novel findings of importance for patients with breast cancer. Firstly, we were able to distinguish between patients with primary breast cancer and healthy female controls ($p < 0.0001$) and between pre-operative breast cancer patients and patients on follow-up after surgery and treatment ($p = 0.002$) by concordance of SNP genotype calls. Principal component analysis of SNP and copy number results also separated cfDNA of pre-surgical breast cancer patients from the healthy controls suggesting that the disease status is reflected within these profiles. Secondly, results from 50 patients on follow-up were striking, and demonstrate for the first time that some tumour-specific CNVs remain detectable in cfDNA a decade after treatment and during clinical remission. About one third of cfDNAs had a "normal" cfDNA profile as would be expected if these patients are cured. However, the remainder showed persistence of tumour associated CNVs, again suggesting persistent micrometastases and a dormant state (Shaw, et al., 2011).

Recent parallel sequencing data also indicate that the cancer genome can change with the evolution of metastatic disease. In support of this, our data shows that plasma cfDNA evolves in time and both the frequency and the nature of these changes are indicative of breast cancer evolution: We saw evidence of changes in CNVs detected between paired plasma samples (taken a mean of 6.1 and 9 years after surgery) notably in 8 patients who relapsed. These CNVs were absent in the matched normal leucocyte DNA samples and in cfDNA of healthy controls: this suggests the existence of cancer markers that are long lasting and a better sensitivity of cfDNA. This is one study in which we wish to understand the role of these molecules better. The study strengthens the established collaboration between the Cancer Research UK Centres at Leicester and Imperial College.

1.6. Risk / Benefit Assessment

1.6.1. Potential Benefits

Eribulin and AIs are known to be effective and safe in this patient population, and it is believed that alternating eribulin therapy with an AI may increase duration of response seen when the 2 agents are used sequentially and that exposure to chemotherapy may cause re-sensitization of cancers to endocrine therapy previously thought to have become ineffective .

1.6.2. Potential Risks

Common side effects (≥1/10) of eribulin are standard chemotherapy toxicities such as:

- Bone marrow suppression manifested as neutropenia, leukopenia, anaemia, thrombocytopenia with associated infections
- New onset or worsening of pre-existing peripheral neuropathy
- Gastrointestinal toxicities manifested as anorexia, nausea, vomiting, diarrhoea, constipation and stomatitis
- Fatigue, alopecia, increased liver enzymes, sepsis and musculoskeletal pain syndrome

AIs can cause arthralgias and osteoporosis.

1.6.3. Overall benefit-risk assessment

In the advanced cancer setting that has been chosen for this study, prolonged survival rates are very low and there is a large unmet clinical need for controlling disease progression, indeed in some cases, palliative treatment may be the best that can be offered.

Although there can be no certainty of clinical benefit to patients the non-clinical and clinical safety profile of eribulin has not identified any risks that would preclude investigation in this setting. Thus the risk-benefit assessment for this study supports the inclusion of patients with advanced cancer, according to the proposed study design.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective and endpoint

Objective	Endpoint
To assess the efficacy of eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) based on progression free survival (PFS).	• PFS rate at the following fixed time points: at 3, 6 and 9 months(as estimated by Kaplan-Meier curve).

2.2. Secondary objectives and endpoints

Objective	Endpoint
To assess the efficacy of eribulin when prescribed in alternating cycles with an Aromatase Inhibitor (AI) based on clinical benefit rate (CBR).	CBR defined as the proportion of patients whose best overall response, according to RECIST v1.1, is either a complete response (CR), partial response (PR) or stable disease (SD) for at least 6 months.
To assess the safety and tolerability of eribulin when prescribed in alternating cycles with an AI.	Safety and tolerability as assessed by adverse events (AEs) and serious adverse events (SAEs) according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.03).

2.3. Translational objectives and endpoints

Objective	Endpoint
To observe whether circulating tumour cells (CTCs) and circulating free DNA (cfDNA) levels increase during hormonal therapy suggesting relapse off chemotherapy.	To measure alterations in CTC and cfDNA levels from baseline and at 9, 18 and 36 weeks after start of treatment, and associate these with clinical outcomes.

3. STUDY DESIGN

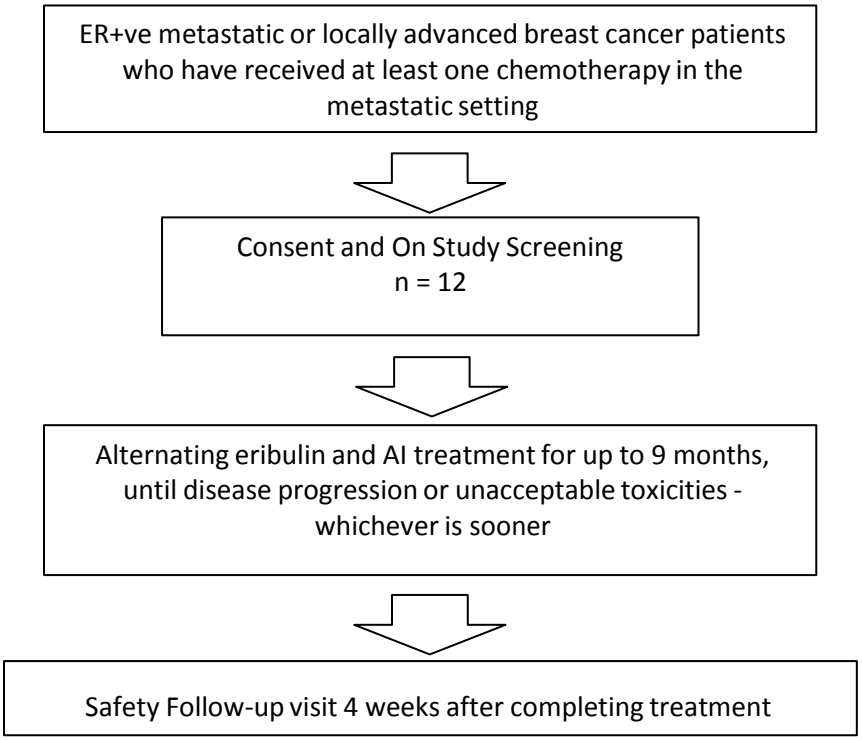
3.1. Overall study design

This is a single centre, single arm phase II study of alternating eribulin and hormonal therapy in 12 patients with locally advanced or metastatic breast cancer who have received at least one chemotherapy in the metastatic setting.

3.2. Treatment regimens

12 patients with locally advanced or metastatic breast cancer who have received at least one chemotherapy in the metastatic setting will be enrolled to receive treatment as per Figure 1.

Figure 1: Study Flow Chart



3.3. Follow-up

Patients will be followed up as described in Table 1 with an end of study safety visit 4 weeks after completion of study treatment.

3.4. Study termination

The study will be terminated when all patients on study treatment have permanently discontinued study medication due to progression or unacceptable toxicities and have completed their 4 week safety follow-up visit.

3.4.1. Treatment after study termination

Following participation in the study, patient care will be decided by their local doctor according to usual practice.

4. PATIENT SELECTION AND RECRUITMENT

4.1. Screening and enrolment

Each patient will undergo screening assessment to confirm eligibility. Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided they comply with the protocol specified timelines. Written informed consent will be obtained before the subject undergoes any study specific procedures.

Each potential patient will be assigned a unique identifier number for use during the trial. A complete record of all patients who enter screening for the study, and also those who go on to be enrolled, must be maintained at each site. The local investigator is responsible for ensuring that this

record includes the allocated trial ID as well as the patient identifiable data including name, hospital number and date of birth.

Eligible patients who take part in the study must meet all of the listed inclusion criteria and none of the exclusion criteria.

4.2. Subject Selection

4.2.1. Inclusion Criteria

Patients who meet all of the following inclusion criteria will be considered eligible for this study:

1. Written informed consent prior to admission to this study
2. Aged 18≥over
3. Histologically confirmed ER positive metastatic breast cancer according to local criteria.
4. ECOG performance status 0 – 2
5. Have progressed after at least one chemotherapy regime for advanced/metastatic disease
6. Patients must have had at least one prior line of chemotherapy treatment in the metastatic setting prior to enrollment in the study.
7. At least one measurable site of locally advanced and/or metastatic disease that can be accurately assessed by CT/MRI scan at baseline (RECIST v1.1)[1]
8. Life expectancy of ≥6 months
9. Adequate organ function, as defined by:
    - Haemoglobin (Hb) ≥ 9 g/dL
    - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count (Plts) $\geq 100 \times 10^9$/L
    - White Blood Cell (WBC) ≥ 3.0 x 10^9/L
    - Serum albumin ≤ 1.5 ULN
    - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3 x ULN if no demonstrable liver metastases or ≤ 5 x ULN in the presence of liver metastases.
    - ALP ≤ 5 x ULN
    - Total bilirubin ≤ 1.5 x ULN if no demonstrable liver metastases or ≤ 3 x ULN in the presence of liver metastases
    - Creatinine ≤ 1.5 x ULN or creatinine clearance >50ml/min
10. Postmenopausal as defined by age >50, no menstruation for >2 years, previous oophorectomy or lab results confirming this status
11. Premenopausal if has been subject to ovarian ablation/ suppression at least 3 weeks prior to commencing AI therapy[2]

[1] RECIST v1.1 updated and now considers bone metastasis with an identifiable soft tissue mass to be measurable disease. Therefore, patients with bone metastasis are eligible, provided they have evaluable disease.

[2] A pregnancy test is required if patient is premenopausal and has been subject to ovarian ablation/ suppression at least 3 weeks prior to commencing AI therapy.

4.2.2. Exclusion criteria

Patients who meet any of the following exclusion criteria will <u>not</u> be considered eligible for this study:

1. Triple negative or HER2 positive cancer
2. Hypersensitivity to the active substance or to any of its excipients

3. History of another primary malignancy within 5 years prior to starting study treatment, except adequately treated basal or squamous cell carcinoma of the skin, carcinoma in site and the disease under study
4. Evidence of uncontrolled active infection
5. Severe hepatic impairment (Child-Pugh C)
6. Evidence of significant medical condition or laboratory finding which, in the opinion of the Investigator, makes it undesirable for the patient to participate in the trial
7. Concurrent therapy with any other investigational agent or everolimus
8. Concomitant use within 14 days prior to commencement of study treatment of any investigational agent
9. Uncontrolled abnormalities of serum potassium, sodium, calcium (corrected) phosphate or magnesium levels
10. Pregnant or lactating women. Effective non-hormonal contraception is mandatory for all patients of reproductive potential
11. Evidence of ovarian activity
12. Prior eribulin therapy

5. STUDY PLAN AND PROCEDURES

5.1. Study schedule

After signing written informed consent, patients will undergo a 28 day screening period. Once confirmed as eligible, patients will remain on treatment for up to nine months or until disease progression, unacceptable toxicities or patient choice, whichever is sooner. While receiving study treatment patients will be reviewed at the time-points scheduled in Table 1. A +/- 1 week window is permitted for the scheduled week 18 study assessments visit. Patients will attend an end of study safety visit 4 weeks after completing study treatment. For assessment details see Table 1.

Table 1: Schedule of Assessments

Time-point → Assessment ↓	Screening	Treatment							FU	
	-4 to 0 weeks	1 week	9 weeks	12 weeks (Month 3)	18 weeks[10]	24 weeks (Month 6)	27 weeks	36 weeks (Month 9)	End of Treatment[5]	Safety FU[6]
Informed Consent	X									
Eligibility checklist	X									
Demographics	X									
Medical History	X									
Physical Examination	X	X	X	X	X	X	X	X	X	X
Height	X									
Vital Signs[1]	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[9]	X									
Haematology[2]	X	X	X	X	X	X	X	X	X	X
Biochemistry[3]	X	X	X	X	X	X	X	X	X	X
ECG	X									
Tumour Evaluation (RECIST v1.1)	X			X		X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Blood Sample CTC	X		X		X			X	X	
Blood Sample cfDNA	X		X		X			X	X	
Start of Eribulin 3x3 weekly Cycles[4]		X			X					
AI Dispensing[4]			X				X			
AI Accountability					X			X	X	
Primary Tumour Sample	X									
Biopsy of Recurrent Disease	X[7]									X[8]

1. *Vital signs include weight, pulse and blood pressure*
2. *Haematology: Haemoglobin, Leukocyte, Neutrophils, Lymphocytes, Platelets*
3. *Biochemistry: ALT, AST, Alkaline phosphatase, Bilirubin (total), Calcium (total), Creatinine (total), Random glucose, Magnesium, Phosphate, Potassium, Sodium, Urea nitrogen, serum albumin*
4. *Refer to Table 2 for details on treatment administration*

5. *Treatment will continue until the 36 week/month 9 visit unless patients permanently discontinue from treatment at an earlier or unscheduled visit. This visit would then be treated as an End of Treatment visit, and the discontinuation scheduled assessments will be performed.*
6. *The safety follow-up visit should occur 4 weeks after the last dose of study treatment.*
7. *This procedure is optional.*
8. *This procedure is optional, and upon disease progression.*
9. *Pregnancy test is required if patient is premenopausal and has been subject to ovarian ablation/ suppression at least 3 weeks prior to commencing AI therapy.*
10. *A +/- 1 week visit window is permitted for the scheduled week 18 study assessments.*

Table 2: Treatment Schedule

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Treatment	Eribulin cycle 1[1]			Eribulin cycle 2[1]			Eribulin cycle 3[1]			AI treatment[2]								
Week	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Treatment	Eribulin cycle 4[1]			Eribulin cycle 5[1]			Eribulin cycle 6[1]			AI treatment[2]								

1. *3 x 3 weekly cycles at the recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesilate), administered intravenously over 2-5 minutes on days 1 and 8 of every 21-day cycle.*
2. *Type of AI to be prescribed at the clinician's discretion.*

5.2. Procedures and measurements

5.2.1. Demographic data and medical history

Demographic data and other characteristics will be recorded and will include date of birth, race/ethnicity, height, weight and smoking history. A standard medical history will be obtained including details of previous and current medication, surgical history and tumour characteristics.

5.2.2. Physical examination and performance status

A complete physical examination will be performed, as per local practice at the scheduled visits indicated in Table 1. The following examinations should be undertaken: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen and neurological. The outcome of the examinations will be assessed as normal or abnormal, and whether clinically significant.

5.2.3. ECOG Performance Status

Performance status will be assessed at the scheduled visits indicated in Table 1 according to ECOG criteria as follows:

Table 3: ECOG Performance Status

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, 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 50% or more of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

5.2.4. Vital signs

Vital signs including weight, pulse and blood pressure will be measured at the scheduled visits indicated in Table 1. Vital signs may be assessed at any time during the visit; however, supine blood pressure and pulse should be measured after 10 minutes rest. Height will be measured at initial screening visit only.

5.2.5. ECG

A 12-lead ECG will be performed at the scheduled visits indicated in Table 1. A standardised ECG machine should be used and where possible, the patient should be examined with the same machine throughout the study. Details of rhythm, ECG intervals and an overall evaluation will be collected

5.2.6. Laboratory Evaluations

5.2.6.1. Routine Evaluations

Blood samples for haematology and clinical chemistry will be taken at scheduled visits and analysed at the local laboratory using standard methods for routine tests.

The following variables will be measured:

- *Clinical Chemistry*: ALT, AST, Alkaline phosphatase, Bilirubin (total), Calcium (total), Creatinine (total), Random glucose, Magnesium, Phosphate, Potassium, Sodium, Urea nitrogen, Serum Albumin
- *Haematology*: Haemoglobin, Leukocyte, Neutrophils, Lymphocytes, Platelets

Laboratory values that have changed significantly from baseline and are considered to be of clinical concern must be recorded as an adverse event and followed up as appropriate.

5.2.6.2. Circulating Tumour Cells (CTC)

10ml peripheral blood, will be collected into CellSave tubes, and sent to the central lab (room temperature, in a padded envelope) for analysis using CellSearch® within 72 hours of blood sampling. Please refer to the Site Laboratory Manual for comprehensive instructions.

5.2.6.3. Circulating free DNA (cfDNA)

20ml venous blood samples will be collected in EDTA tubes centrifuged within 2 hours of collection at 1000g for 10 min, and plasma will be taken from the upper phase and decanted into fresh polypropylene tubes. Tubes will then be spun again at 2000g to remove any contaminating leucocytes, and the resulting supernatant will be aliquoted into sterile tubes and stored at −80 °C. Plasma samples will be allowed to thaw to room temperature and will be re-spun in a bench-top centrifuge to remove any remaining cell debris. Please refer to the Site Laboratory Manual for comprehensive instructions.

5.2.7. Tumour assessments

Tumour assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis; the same method used for assessment at baseline must then be used at all subsequent time points. RECIST v1.1 criteria will be used to assess patient response to treatment by determining tumour size, PFS and ORR. The RECIST v1.1 (January 2009) guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are detailed in Appendix 1.

Baseline assessment should be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment; it should include all areas known for possible breast cancer metastases.

5.2.8. Treatment Compliance (Patient Diary)

Patients will keep a detailed record of all study medication that they take at home (i.e. AI treatment) in their patient diaries. Date and time of administration, drug name and drug dose will be collected.

5.2.9. Concomitant Medications

All medications, with the exception of prohibited medications, that are being taken during screening and those taken whilst on study will be documented as a concomitant medication. The following details will be collected: drug name, reason for therapy, therapy dosage / units, frequency of therapy, route of administration, start and end date of therapy

5.3. Exploratory Research

5.3.1. Exploratory biomarker research

Biological samples e.g. archived and study-specific tumour samples will be collected and may be analysed for exploratory biomarkers to investigate possible relationships with disease status, efficacy of study drug and outcome. These results may be reported separately from the clinical study report (CSR).

5.3.1.1. Collection of archival tumour tissue samples

Where available, an archival tissue sample (either from the diagnostic tumour or a metastatic site) in the form of formalin fixed paraffin embedded (FFPE) tumour block will be collected for each patient. If it is not possible to obtain the tumour block, 10-20 slides of freshly prepared unstained 5 micron sections may be provided instead.

Further details on sample processing, handling and shipment are provided in the Study Manual.

Archival tumour blocks will be returned to source at the end of the study or, upon request, earlier if required.

5.3.1.2. Collection of paired tumour biopsies

This part of the study is optional. Where patients consent to take part, tumour biopsies should be collected. The date and time of collection will be recorded on the case report form (CRF).

These samples are classified as research samples and will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

Further details on sample processing, handling and shipment are provided in the Study Manual.

5.3.2. Chain of custody of biological samples

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle.

The investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal.

Any sample receiver e.g. sub-contracted service provider keeps full traceability of samples from receipt of arrival to further shipment or disposal (as appropriate).

Imperial College keeps overall oversight of the entire lifecycle through internal procedures and monitoring of study sites

Samples retained for further use will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

5.4. Total Blood Volumes

The total volume of blood that will be drawn from each patient in this study is shown in Table 4. The number of samples taken, and the volume required for analysis, may change during the course of the study as new data becomes available.

Table 4: Volume of blood to be drawn from each patient

	Sample volume (mL)	Number of samples	Total volume (mL)
Clinical chemistry [1]	8	10[3]	80
Haematology [1]	6	10[3]	60
CTC	10	5[3]	50
cfDNA	20	5[3]	100
		Total	**290[2]**

1 exact volume of blood for clinical chemistry and haematology may vary depending on local practice
2 this represents the maximum amount of blood that could be drawn during the trial. The actual amount drawn from each patient will depend on the duration the patient remains on treatment for.
3 this represents the maximum number of samples, as end of treatment visit may coincide with one of the other scheduled visits.

6. STUDY TREATMENT

Trial treatment must begin within 1 week of the patient being enrolled into the study. Trial patients will be administered alternating regimes of 3 x 3 weekly cycles of intravenous eribulin over 2-5 minutes on days 1 and 8 of every 21 day cycle, followed by 9 weeks of AI treatment, followed again by 3 x 3 weekly cycles of eribulin and 9 weeks of an AI.

6.1. Non Investigational Medicinal Products

AI treatment (exemestane, anastrazole or letrozole) will be dispensed from site specific hospital stock. Compliance to these treatments will be recorded using Patient Diary cards and all data transferred to the eCRFs.

6.2. Investigational Medicinal Product Details

Eribulin (Halaven®) is manufactured by NerPharma according to Good Manufacturing Practice. The Investigational product is provided to sites, free of charge, by Eisai Ltd. as 2mL vials for injection.

In the EU, Eribulin is licenced for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments. It will be used outside of its marketing authorisation in this study as it will be administered alternately with AI treatment, and patients will not require prior anthracycline or taxane.

6.2.1. Supply, packaging and labelling

Eribulin (Halaven®) will be packaged and labelled by Catalent (UK) and distributed to sites by Catalent (UK). Labels will be prepared in accordance with Good Manufacturing Practice Annexe 13 requirements and local regulatory guidelines. Eribulin will only be dispatched to sites after receipt of confirmation that the regulatory checklist is complete.

6.2.2. Storage and Dispensing

The investigational products must be stored in a secure area with access limited to the Investigator and authorised site staff. Maintenance of a temperature log (manual or automated) is required. For further information investigators should refer to the investigator brochure.

The investigational product should only be dispensed and administered as directed in the protocol, and only by site staff authorised to do so i.e. pharmacist / trials technician. Only subjects enrolled in the trial may receive investigational product.

6.2.3. Dosage and Duration

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesilate). The recommended dose of eribulin in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin in patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

Eribulin will be administered in 3x3 weekly cycles starting at week 1 and at week 18, intravenously over 2-5 minutes on days 1 and 8 of every 21-day cycle.

Eribulin should be administered in units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

6.2.4. Dose Modifications for Eribulin

6.2.4.1. Dose delays

The administration of eribulin should be delayed, until resolved, for up to one month on Day 1 or Day 8 for any of the following:

- Absolute neutrophil count (ANC) < 1 x 10^9/l
- Platelets < 75 x 10^9/l
- Grade 3 or 4 non-haematological toxicities.

6.2.4.2. Dose reductions

Dose reduction recommendations for retreatment are shown in the following table. Do not re-escalate the eribulin dose after it has been reduced.

Table 5: Dose reduction recommendations

Adverse reaction after previous eribulin administration	Recommended dose of eribulin
Haematological:	
ANC < 0.5 x 10^9/l lasting more than 7 days	0.97 mg/m^2

ANC < 1 x 10^9/l neutropenia complicated by fever or infection Platelets < 25 x 10^9/l thrombocytopenia Platelets < 50 x 10^9/l thrombocytopenia complicated by haemorrhage or requiring blood or platelet transfusion	
Non-haematological:	
Any Grade 3 or 4 in the previous cycle	0.97 mg/m^2
Recurrence of any haematological or non-haematological adverse reactions as specified above	
Despite reduction to 0.97 mg/m^2	0.62 mg/m^2
Despite reduction to 0.62 mg/m^2	Discontinuation

6.2.5. Accountability

Accountability for the study drug at the study site is the responsibility of the investigator. This responsibility may be delegated to the pharmacist, or another appropriate person. The investigator will ensure that the study drug is used only in accordance with this protocol. Unused eribulin **may not** be used for any purpose other than that outlined in the protocol.

Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and disposal of the drug will be maintained by the clinical site. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable) and patient numbers.

All used, unused or expired study drug will disposed of at the study site and documented following authorisation by the Sponsor.

6.2.6. Drug interactions/Precautions

6.2.6.1. Restrictions

The following restrictions apply while the patient is receiving study treatment and for the 10 days before and after:

- Everolimus or any other mTOR inhibitor

The following should be administered with caution:

- Substances which are inhibitors of hepatic transport proteins such as organic anion-transporting proteins (OATPS) and multidrug resistant proteins (MRPs) etc. concomitantly with eribulin. Inhibitors of such transporters include but are not limited to: cyclosporine, ritonavir, saquinavir, lopinavir and certain other protease inhibitors, efavirenz, emtricitabine, quinine, quinidine, disopyramide.
- Concomitant treatment with inducing substances, such as carbamazepine, phenytoin, St John´s wort (Hypericum perforatum) could give rise to reduced plasma concentrations of eribulin, and co-administration with inducers should be carried out with caution considering a potential risk for reduced drug efficacy.
- No marked effects on eribulin exposure (AUC and C_{max}) were observed during treatment with the CYP3A4 inducer rifampicin. However, rifampicin may due to its transporter inhibitory property counteract its possible inducing effect on eribulin elimination. Therefore, the effect of rifampicin may not presently be extrapolated to other inducers

- In vitro data indicate that eribulin is a mild inhibitor of the important drug metabolising enzyme CYP3A4. No in vivo data are available. Caution and monitoring for adverse effects is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-medicated metabolism (e.g. alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

Eribulin may cause adverse reactions such as tiredness and dizziness which may lead to a minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

6.2.6.2. Concomitant treatments

Antiemetic prophylaxis including corticosteroids may be administered whilst patients are receiving eribulin, as per local policy.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the CRF.

6.2.7. Overdose of IMP

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations. If an overdose of eribulin occurs in the course of the study, then Investigators or other site personnel should inform the Sponsor **within one day** i.e. immediately and no later than **the end of the next business day** of when he or she becomes aware of it. For overdoses associated with a SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

For treatment of overdose with AI please refer to the local prescribing information. Overdose of AI with associated AEs / SAEs should be recorded in the relevant AE / SAE module of the eCRF and reported according to the standard timelines.

6.3. Permanent discontinuation of study medication and withdrawal from study

6.3.1. Permanent discontinuation of study medication

A patient may be permanently discontinued from study medication for the following reasons:

- Patient decision
- Significant adverse events or unacceptable toxicities
- Severe non-compliance to this protocol as judged by the Investigator
- Confirmed disease progression
- Allergic reaction to IMP

If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illnesses that develop after entering the study.

Once study medication is permanently discontinued it cannot be restarted.

6.3.2. Withdrawal from study

Withdrawal from the study refers to discontinuation of both study medication and study assessments; this can occur at any time according to the following reasons:

- Patient decision
- Lost to follow-up
- Death

6.3.3. Procedures for withdrawal from study

If the patient is withdrawn from the study the primary reason must be recorded in the CRF. If possible, the investigator should arrange for the post-study assessments to be completed. Where the patient has withdrawn due to an AE, the investigator should follow the procedures documented in section 7.0 in order to assess the safety of the IMP.

7. PHARMACOVIGILANCE

7.1. Definition of an adverse event (AE)

An AE is any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign including abnormal results of an investigation (e.g. laboratory finding, electrocardiogram), symptom(s) (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or disease temporally associated with the use of the trial medication.

7.1.1. Disease progression

Disease progression is a worsening of a patient's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or increase in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study**.

7.1.2. New cancers

The development of a new cancer should be regarded as an AE and reported accordingly. Generally, it will also meet at least one of the serious criteria.

7.2. Recording of adverse events

AEs will be collected throughout the study, from informed consent until the end of follow-up; they will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. SAEs will also be recorded throughout the study.

Any AEs which remain unresolved at the patient's last visit in the study should be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to eribulin, the Investigator should notify the trials unit.

The following details will be collected in the CRF for each AE:

- AE description / diagnosis

- Date of onset and date of resolution
- CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication
- Action taken with regard to study medication
- Outcome

7.3. Severity of adverse events

Severity is a measure of intensity whereas seriousness is defined by the criteria in section 7.6. Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 4.03 (June 2010) for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

7.4. Causality of adverse events

The Investigator will assess causal relationship between the investigational product and the combination treatment and each AE.

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.5. Abnormal laboratory test results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.6. Definitions of Serious Adverse Events (SAE)

An SAE is an AE occurring during any part of the study that meets one or more of the following criteria:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;

- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it were more severe.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.7. Reporting of SAEs

Rapid reporting, within 24 hours of the Principal Investigator or designee becoming aware of the event, of all SAEs occurring during the study or within 28 days following the completion of the study treatment by the subject, must be performed as detailed in the "SAE reporting instructions". If the investigator becomes aware of safety information that appears to be drug related, involving a subject who participated in the study, even after an individual subject has completed the study, this should also be reported to the Sponsor.

The SAE should be reported electronically to the study team at the Imperial Clinical Trials Unit – Section on Cancer via the ALERT study database as detailed in the Pharmacovigilance study manual.

All SAEs will be reviewed by the Chief Investigator or designated representative to confirm relatedness and expectedness.

Following documented assessment by the CI, the completed SAE form will be sent by email to the Sponsor by the study team at CCTS within the pre-specified timelines.

7.8. Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as an SAE that is judged to be related to any dose of study drug administered to the subject.

7.9. Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

7.10. Reporting of SUSARs

SUSARs will be notified to the appropriate regulatory authority, the relevant Independent Ethics Committee (IEC) / Institutional review board (IRB), Eisai Ltd, the Sponsor and the participating Principal Investigators by CCTS in accordance with regulatory requirements.

Any Suspected Unexpected Serious Adverse Reactions (SUSARs) and Serious Adverse Reactions (SARs) must be reported by CCTS immediately by email to EUMedInfo@eisai.net. If unable to scan and email report it should be faxed to 020 8600 1486/0845 676 1401.

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

7.11. Annual Reporting of Serious Adverse Reactions

Annual reports will be submitted to the MHRA and main REC by CCTS according to current requirements.

7.12. Pregnanacy

Due to the possible risks associated with the treatment, all women of childbearing potential (defined as women who have had any menstrual bleeding in the last 24 months and who have not had a hysterectomy) should be informed of the potential risks to their unborn child should they fall pregnant whilst receiving treatment. Any woman who is pregnant at the time of eligibility assessment or is unwilling to use medically approved contraception whilst receiving treatment will be ineligible for entry to the study. All women of childbearing potential must use appropriate medically approved contraception before, during and for 28 days after the end of study treatment.

Pregnancies occurring in participants of the study, or participants' partners during the study may represent a safety issue and must be reported via the eCRF. Site staff should notify CCTS of a pregnancy in a trial subject and the estimated due date. Where a pregnancy is known, this will be followed for outcome and any adverse outcome of pregnancy assessed for causality to the treatment received.

8. STATISTICAL ANALYSES

8.1. Sample size and power considerations

This study will be a pilot and due to feasibility constraints, we plan to recruit only 12 patients in this pilot proof of concept study. This will allow us to determine the PFS rate at the relevant time points of 3, 6 and 9 months and to validate these in an adequately powered study in the future.

8.2. Analysis Plan

The clinical data will be entered and stored in InFormTM database. Statistical analysis will be conducted using R version 3.0.1 and STATA 13 SE. Analysis of the data will occur only when the study is complete. There is no planned interim analysis. A separate statistical analysis plan will be prepared and finalised prior to database lock.

8.2.1. Deviations from the statistical plan

Any deviation(s) from the final statistical plan in the final analysis will be described and justification given in the final report.

8.2.2. Efficacy analysis

All efficacy data in the study will be analysed based on the Full Analysis Set (FAS) which consists of all patients who receive at least one dose of study treatment. If appropriate and required, a Per Protocol Analysis Set (PPS) will be defined prior to final analysis on which the efficacy analysis will be repeated.

The primary endpoint of PFS at 3, 6, and 9 months will be estimated by the Kaplan-Meier method. These rates estimate the proportion of patients who do not progress and are alive at a given time. The PFS is calculated from the start of treatment until the date of progression or death from any cause. Patients will be censored at the time of last follow-up if they are withdrawn or lost to follow-up before progression or death.

The secondary endpoint of CBR is defined as the proportion of patients whose best overall response, according to RECIST v1.1, is either a complete response (CR), partial response (PR) or stable disease (SD) for at least 6 months. The estimation of CBR and its 95% confidence interval will be reported.

8.2.3. Safety analysis

All patients who receive at least one dose of study treatment will be included in the safety analysis set. The frequency of AEs will be assessed for severity (NCI-CTCAE v4.03), expectedness, seriousness and causal relationship to study drugs(s). In addition, AEs will be summarised by toxicity type, impact on study drug(s) and by timing. The frequency of SAEs will be summarised by SAE reason, severity and causal relationship to study drug.

8.2.4. Translational analysis/ Exploratory Analysis

The exploratory analysis will measure alterations in CTCs and cfDNAs from baseline and at 9, 18 and 36 weeks after start of treatment, and associate these with clinical outcomes. Firstly, the alterations in CTCs and cfDNAs will be described at all time points through plots with appropriate repeated measures univariate tests run alongside. Subsequently, in order to determine whether CTCs and cfDNA, increase during hormonal therapy, levels of these biological measurements will be associated with timing of alternative erubulin and hormonal therapy through repeated measures ANOVA or another statistically appropriate repeated measures test such as its non-parametric version, the Friedman test, (depending on the final distribution of the biological measurements).

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1. Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions.

9.2. Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3. Independent Ethics Committee/Institutional Review Board Approval

9.3.1. Initial approval

Prior to the shipment of IMP and the enrolment of subjects, the IEC/IRB must provide written approval of: the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

9.3.2. Approval of amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the IEC/IRB for approval. Amendments requiring IEC/IRB approval may be implemented only after a copy of the IEC/IRB's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

9.3.3. Annual safety reports and end of trial notification

The IEC/IRB will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

9.4. Regulatory authority approval

The study will be performed in compliance with the regulatory requirements of the United Kingdom. Clinical Trial Authorisation from the appropriate Regulatory Authority must be sought/obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

9.5. Insurance

The Sponsor has civil liability insurance, which covers this study in the United Kingdom.

9.6. Informed consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation
- Ensure that each patient is notified that they are free to withdraw from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed sufficient time to read and understand the information sheet
- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure

- Ensure the original copy of the signed, dated Informed Consent Form is stored in the Investigator site file and a copy is also filed in the medical records
- Ensure that each patient receives a copy of the signed, dated Informed Consent Form

9.7. Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A template of the GP letter should be filed in the Investigator Site File.

9.8. Subject confidentiality

The investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a trial ID number only. Documents that are not submitted to the Sponsor (e.g. signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and Regulatory Authorities.

9.9. Data protection

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The Patient Consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

9.10. End of trial

The end of the trial is defined as the last visit of the last patient undergoing the study.

9.11. Study documentation and data storage

The investigator must retain essential documents until notified by the Sponsor (Imperial College London), and at least for ten years after study completion, as per Imperial College London policy. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA AND STUDY MANAGEMENT

10.1. Source data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as: original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2. Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

10.3. Data collection

In compliance with Good Clinical Practice (GCP), the medical records/medical notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial

The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the trial InForm electronic data collection (EDC) system.

10.4. Electronic recording of data

Full details for procedures for completion of eCRFs will be provided in the study manual.

10.5. Data management

Data management will be performed by the Imperial Clinical Trials Unit – Section on Cancer using the InForm electronic data capture (EDC) and management system. The system allows for real time oversight of trial activity including adverse event reporting, rapid data validation and data aggregation.

AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and CTCAE grade.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trial.

10.6. Study Management Structure

10.6.1. Trial Steering /Independent Data Monitoring Committee

As there is no planned interim analysis, a joint Trial Steering (TS) and Independent Data Monitoring Committee (IDMC) will be convened including as a minimum an independent Chair, an independent Statistician, independent clinician, the Chief Investigator and Trial Coordinator. The role of the

TS/IDMC will be to provide overall supervision of the trial progress and, as necessary, advice to the Trial Management Group on operational issues.

10.6.2. Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, Co-investigators and identified key collaborators, the Trial Statistician and Trial Coordinator. Principle Investigators and key study personnel may be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial.

Where possible, membership will also include a lay/consumer representative.

10.7. Monitoring

The study will be monitored periodically by monitors in the UK to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan. Monitoring will be proportionate to the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial. The appropriate level and nature of monitoring required for the clinical trial will be assessed by undertaking a formal risk assessment analysis of the study.

10.8. Quality Control and Quality Assurance

Quality Control will be performed according to Sponsor internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

10.9. Disclosure of data and publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting, should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) is completed.

Investigators may only present data separately to the total data available, with the permission of the TMG, and not less than 6 months after the publication of the main results.

Eisai has the right to review all abstracts, papers or other research communications prior to their submission to journals, meetings or conferences.

11. REFERENCES

1. Anon., 2010. *Cancer Stats Key Facts breast Cancer,* s.l.: Cancer Research UK.

2. Bidard, F. C. et al., 2014. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncology,* Volume 15, pp. 406-414.

3. Cortes , J. et al., 2011. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *The Lancet,* 12 March, 377(9769), pp. 914-923.

4. Giordano, S. H. et al., 2004. Is breast cancer survival improving?. *Cancer,* 100(1), pp. 44-52.

5. Shaw, J. A. et al., 2011. *A molecular portrait of circulating free DNA of patients with breast cancer: High-resolution analysis using SNP 6.0 arrays.* s.l., J Clin. Oncol..

6. Shaw, J. A. et al., 2012. Genomic analysis of circulating free DNA infers breast cancer dormancy. *Genome Research,* Volume 22, pp. 220-31.

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8. Stebbing, J. et al., 2014. The prognostic role of circulating tumour cells in heavily pre-treated individuals with a low life expectancy. *Future Oncology,* Volume 30, pp. 1-6.

9. Twelves, C. et al., 2010. Phase III Trials of Eribulin Mesylate (E7389) in Extensively Pretreated Patients With Locally Recurrent or Metastatic Breast Cancer. *Clinical Breast Cancer,* 10(2), p. 160–163.

12. SIGNATURE PAGES

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory.

I agree to the terms of this study protocol. I will conduct the study according to all stipulations of the protocol including all statements regarding confidentiality, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Study Title: ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer.

Protocol Number: C/31/2014

Signed: _____

Dr. Laura Kenny
Consultant Medical Oncologist
Imperial College London

Date: _____

SIGNATURE PAGE 2 (Sponsor)

The signature below constitutes approval of this protocol by the signatory.

Study Title: ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer.

Protocol Number: C/31/2014

Signed: _____

Gary Roper
Head of Regulatory Compliance
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signature below constitutes approval of this protocol by the signatory.

Study Title: ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer.

Protocol Number: C/31/2014

Signed: _____

Dr Xinxue Liu
Trial Statistician
Imperial College London

Date: _____

SIGNATURE PAGE 4 (INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: ALERT: A phase II study of alternating eribulin and hormonal therapy in pre-treated ER+ve breast cancer.

Protocol Number: C/31/2014

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

13. APPENDICES

Appendix A: Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

(ICTU-Cancer guidance document v2.0 dated 17 November 2014)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumour lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definition of Disease Parameters

Measurable disease Must be accurately measured in a least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5mm; when CT scans have slice thickness >5mm, the minimum size should be twice the slice thickness).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20mm by chest X-ray.

Note: Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measureable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Malignant lymph nodes Criteria for lymph nodes given as ≥15mm short axis for target lesions and 10mm to <15mm for non-target lesions. Nodes under 10mm to be considered non-pathological.

Non-measurable disease All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include; leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Note: Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

'Cystic lesions' thought to represent cystic metastases can be considered measurable 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.

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) and be representative of all involved organs, as well as their suitability for

reproducible repeated measurements. All measurements should be recorded in metric notation using calipers if clinically assessed. 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, which will be used as reference to further characterize any objective tumour regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target lesions All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

CT/MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g. for body scans but not for lung).

Chest x-ray Lesions on chest x-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial and ≥10mm in diameter as assessed using calipers. For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound (US) should not be used to measure tumour lesions.

Tumour markers Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology Can be used in rare cases (e.g. for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).

Endoscopy, Laparoscopy Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

New Lesions

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is no PD.

Response Criteria

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 may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker levels. 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) and/or maintenance of tumour marker level above the normal limits

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- When patient has measurable disease – to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- When patient has none-measurable disease – there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for

measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localised to widespread.

Evaluation of Best Overall Response

Summary of overall response status calculation at each time point, for patients who have measurable disease at baseline.

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**
Not all evaluated	Non-PD	No	Not evaluated	
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 manuscript 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.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, (taking as reference for PD the smallest measurements recorded on study).

Duration of stable disease: SD is measured from the start of the treatment (in randomised trials, from the date of randomization) until the criteria for disease progression are met, taking as reference the smallest sum on study (if baseline sum is the smallest, this is the reference for calculation of PD).The clinical relevance of the duration of SD varies for different studies and diseases. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Response Review

For trials where the objective response (CR and PR) is the primary endpoint it is recommended that all responses be reviewed by an expert(s) independent of the study. Simultaneous review of the patients' files and radiological images is the best approach.